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ORIGINAL ARTICLE

Elevated neutrophil-to-lymphocyte ratio predicts poorer histopathological differentiation in colorectal cancer: a study from a Southeast Asian Tertiary Hospital

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ABSTRACT

Aim To evaluate the correlation between pre-treatment NLR and histopathological differentiation in colorectal cancer, and to assess the diagnostic accuracy of NLR as a predictive biomarker.
Methods A retrospective study was conducted at Adam Malik Haji Centre General Hospital Medan, North Sumatera. Medical records of 45 colorectal cancer patients treated between January and December 2024 were reviewed. Pre-treatment NLR values were calculated from peripheral blood counts. Receiver operating characteristic (ROC) curve analysis was performed to determine diagnostic performance, and correlation analysis was used to assess the relationship between NLR and tumour grade.
Results The mean NLR was 6.33±4.92. ROC analysis yielded an area under the curve (AUC) of 0.874, indicating excellent diagnostic ability. An NLR cutoff value of 6.25 provided a sensitivity of 87.5% and specificity of 72.5% for predicting poor histopathological differentiation. A moderate positive correlation ($r=0.612$; $p<0.001$) was found between higher NLR values and poorer differentiation.
Conclusion Pre-treatment NLR correlated with histopathological grade and showed promise as a simple, non-invasive biomarker for assessing tumour aggressiveness in colorectal cancer.
Keywords: biomarkers, tumour, inflammation, prognosis, survival analysis

INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent malignancies worldwide and remains a major cause of cancer-related mortality. Its incidence continues to rise in many low- and middle-income countries, including Indonesia, partly due to lifestyle transitions and delayed diagnosis (1,2). Despite advances in treatment, prognosis in many regions remains poor, largely because of late presentation and limited access to molecular prognostic tools (3).

In recent years, systemic inflammation has gained attention as a driver of cancer progression, influencing tumour initiation, invasion, and metastasis (4). Inflammation-based biomarkers derived from routine blood tests, such as the neutrophil-to-lymphocyte ratio (NLR), have shown promise as prognostic indicators in solid tumours. Multiple studies and recent meta-analyses have consistently reported that elevated pretreatment NLR is associated with tumour aggressiveness, recurrence, and reduced survival in patients with colorectal cancer (5–7). Importantly, the prognostic role of NLR remains in focus of current research, with clinical studies from the past five years reinforcing its relevance in modern oncology practice, particularly due to its low cost and accessibility (8,9).

Although the relationship between NLR and colorectal cancer outcomes has been explored previously, significant knowledge gaps remain. First, the association between NLR and histopathological differentiation, a key determinant of tumour biology and survival, has not been well established across diverse populations. A 2017 study from China reported a correlation between high NLR and poor differentiation in colorectal cancer (10). However, most available evidence originates from East Asian and Western cohorts, and data from Southeast Asia, particularly Indonesia, are scarce. Second, population-specific variations in immune response, tumour biology, and healthcare access may influence the prognostic value of NLR (11,12). Therefore, it is important to validate NLR as a biomarker in different ethnic and clinical settings before recommending its routine application in clinical practice.

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The aim of this study was to evaluate the association between preoperative NLR and the degree of histopathological differentiation among colorectal cancer patients treated at a tertiary hospital in Southeast Asia. Given that NLR is inexpensive, minimally invasive, and routinely available, confirming its prognostic value may support its integration into risk stratification strategies, particularly in resource-limited healthcare settings.

PATIENTS AND METHODS

Patient and study design

This observational analytic study employed a cross-sectional design to examine the association between the neutrophil-to-lymphocyte ratio (NLR) and histopathological differentiation in patients with colorectal cancer. Secondary data were retrospectively collected from medical records at Haji Adam Malik General Hospital, a tertiary referral centre in North Sumatra, Indonesia.

The study population consisted of all patients diagnosed with colorectal cancer and treated at the hospital between January and December 2024. A consecutive sampling technique was used to include all eligible patients who met the inclusion criteria until the required sample size was achieved.

Inclusion criteria were as follows: histopathologically confirmed colorectal cancer, age >18 years, no history of prior chemotherapy or radiotherapy, and absence of metastatic disease. Exclusion criteria included: a history of inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease), concurrent malignancies, medical conditions or medications known to affect leukocyte counts (e.g., bacterial infections, systemic inflammation, metabolic disorders, or use of corticosteroids or lithium), myeloproliferative disorders, and incomplete clinical or laboratory data.

Ethical approval for this study was obtained from the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara.

Methods

Demographic, clinical, and laboratory data were extracted from electronic medical records. Laboratory results were obtained from routine preoperative blood tests, including total white blood cell count, absolute neutrophil count, and absolute lymphocyte count.

The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count from preoperative complete blood count results. A predefined NLR cut-off value of 3.0 was applied to categorize patients into low NLR (<3.0) and high NLR (≥3.0) groups. This cut-off has been widely reported in previous colorectal cancer studies as clinically relevant for prognostic stratification (13,14).

Histopathological differentiation was determined from postoperative pathology reports and classified according to the World Health Organization (WHO) criteria. Tumours were categorized as well-differentiated adenocarcinoma (>95% gland formation, minimal cellular atypia, and preserved glandular architecture), moderately differentiated adenocarcinoma (50–95% gland formation, increased nuclear atypia, and irregular glandular structure), and poorly differentiated adenocarcinoma (<50% gland formation, marked pleomorphism, high mitotic activity, and a solid growth pattern indicative of aggressive behaviour) (15).

Disease staging was defined using the American Joint Committee on Cancer (AJCC) Tumor–Node–Metastasis (TNM) 8th edition system. Tumour invasion depth (T), regional lymph node involvement (N), and presence of distant metastasis (M) were extracted from surgical and imaging records to classify patients into stages I–IV (16).

Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD) or median (interquartile range, IQR), depending on data normality. The association between NLR and histopathological differentiation was assessed using the ANOVA test. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curve analysis to determine the optimal NLR cut-off value, sensitivity, and specificity. A $p<0.05$ was considered statistically significant. Results were presented in tables with descriptive summaries to support interpretation. A bivariate analysis was used to evaluate the relationship between the Neutrophil-to-lymphocyte ratio (NLR) and the degree of histopathological differentiation in colorectal cancer. Prior to the analysis, a normality test was performed to assess the distribution of the data. Given that the sample size was below 50, the Shapiro-Wilk test was utilized.

RESULTS

A total of 75 patients were initially identified during the study period. However, 30 patients were excluded for not meeting the inclusion criteria: 12 had undergone chemotherapy, radiotherapy, or presented with metastatic disease; three had diabetes mellitus; one had an autoimmune disorder; one had chronic kidney disease; one had heart failure; two had concurrent malignancies (endometrial and ovarian cancer); and 10 presented with acute infections. After applying the eligibility criteria, 45 patients remained in the final analysis, meeting the minimum sample size requirements determined by prior calculations.

Regarding sex distribution, 24 (53.3%) patients were male and 21 (46.7%) were female. The mean age of the cohort was 56.67 ± 14.6 years, with a median age of 57 years; the youngest patient was 26 years old and the oldest was 87 years.

Analysis of tumour localization revealed that the rectum was the most common site of malignancy, accounting for 28 (62.2%) patients, followed by the sigmoid colon in 11 (24.4%) patients. Histopathological examination showed that adenocarcinoma was the predominant tumour type, observed in 41 (91.1%) patients. Regarding disease staging, stage IIb was most frequently diagnosed, affecting 21 (46.7%) patients (Table 1).

The mean NLR across the study population was 6.33 ± 4.92, reflecting substantial variability in systemic inflammatory response among patients. The median NLR was 4.01, with values ranging from 1.03 to 18.3 (Table 2). Based on histopathological classification, 26 (57.8%) patients had well-differentiated tumours, 11 (24.4%) had moderately differentiated tumours, and 8 (17.8%) had poorly differentiated tumours (Table 2).

The diagnostic performance of NLR for distinguishing histopathological differentiation was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was 0.874, indicating excellent discriminatory ability (AUC > 0.5), which was statistically significant ($p < 0.001$). The optimal NLR cut-off value was 6.25, yielding a

Table 1. Baseline clinicopathological characteristics of the study population

Variable	Values
Age (years)	
Mean±SD	56.67 ± 14.6
Median (min.-max.)	57 (26-87)
Sex (No; %)	
Man	24 (53.3)
Woman	21 (46.7)
Tumor size (cm)	
Mean+SD	5.2 ± 2.1
Median (min.-max.)	5.0 (2.0–11.5)
	No (%) of patients
Location	
Rectum	28 (62.2)
Sigmoid	11 (24.4)
Cecum	1 (2.2)
Ascending Colon	3 (6.7)
Transverse Colon	1 (2.2)
Descending Colon	1 (2.2)
Histopathological overview	
Adenocarcinoma	41 (91.1)
Mucinous adenocarcinoma	3 (6.7)
Signet ring carcinoma	1 (2.2)
Stage	
I	1 (2.2)
IIa	9 (17.8)
IIb	21 (46.7)
IIc	6 (13.3)
IIIa	1 (2.2)
IIIb	4 (8.9)
IIIc	4 (8.9)
Histopathological degree differentiation	
Well-differentiated	26 (57.8)
Moderately-differentiated	11 (24.4)
Poorly-differentiated	8 (17.8)
NLR	
Mean ± Standard Deviation	6.33±4.92
Median (min-max)	4.01 (1.03–18.3)

sensitivity of 87.5% and a specificity of 72.5%. The positive likelihood ratio (LR+) was 4.5, and the negative likelihood ratio (LR−) was 0.125, further supporting the robustness of NLR as a predictive biomarker (Table 2, Figure 1).

Due to non-normal data distribution, the Kruskal-Wallis test was performed, revealing mean NLR values of 3.93 ± 4.03 in the well-differentiated group, 7.98 ± 4.77 in the moderately differentiated group, and 11.09 ± 2.9 in the poorly differentiated group ($p < 0.001$). NLR values were highest in poorly

Table 2. Neutrophil-lymphocyte ratio (NLR) bivariate analysis of histopathological degrees

Histopathological degree	NLR average±SD	p*	r†
Well-differentiated	4.28 ± 4.37		0.612
Moderately-differentiated	7.91 ± 4.63	< 0.001	
Poorly-differentiated	10.83 ± 3.21		

*Kruskal Wallis test; †Spearman's Rho test

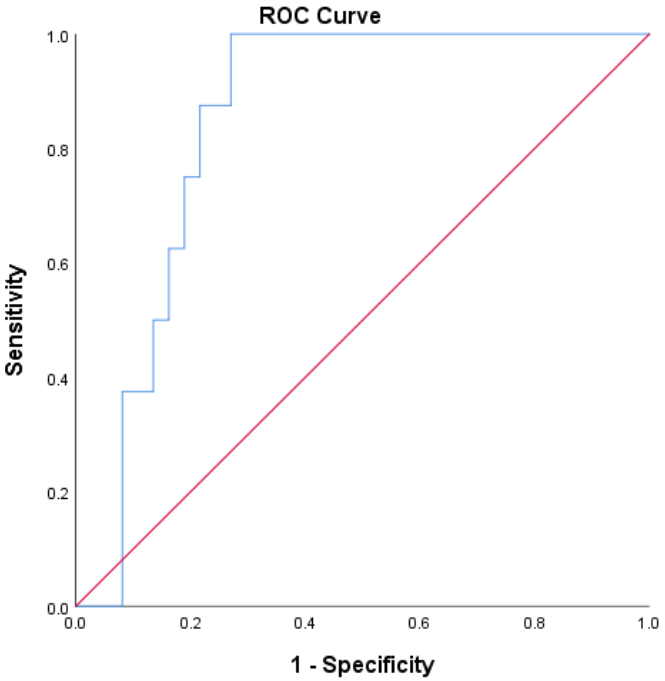

Figure 1. Neutrophil-lymphocyte ratio (NLR) and receiver operating characteristics (ROC) curve to histopathological degree

differentiated tumours, followed by moderately and well-differentiated tumours. Spearman's rho correlation analysis indicated a moderate positive correlation between NLR and histopathological differentiation ($r = 0.612$), suggesting that higher NLR values are associated with poorer tumour differentiation.

DISCUSSION

This study observed a higher prevalence of colorectal cancer among males, consistent with global data suggesting greater male susceptibility (9). This sex disparity may be attributed to both biological and lifestyle factors, including higher visceral fat accumulation, increased consumption of red and processed meats, higher rates of smoking and alcohol use, and pro-inflammatory metabolic profiles (9).

Age remains an important factor in colorectal cancer risk. The study population reflects the typical middle-aged to older adult demographic, aligning with previous reports highlighting regional variability in age at diagnosis (10). Given the rising incidence of colorectal cancer in younger populations, earlier screening protocols for individuals under 50 years have been suggested (11).

A central finding of this study is the significant association between systemic inflammation, as measured by the neutrophil-to-lymphocyte ratio (NLR), and histopathological differentiation. Elevated NLR was associated with poorer tumour differentiation, supporting previous evidence linking systemic inflammation with aggressive tumour biology (19,20). Mechanistically, neutrophils promote tumour angiogenesis and facilitate dissemination via secretion of factors such as vascular endothelial growth factor (VEGF), while lymphocytes mediate anti-tumour immunity through activation of CD8+ cytotoxic and CD4+ helper T cells, inducing tumour apoptosis and suppressing proliferation and metastasis (21,22). A high NLR thus reflects an imbalance between pro-tumour inflammatory activity and impaired anti-tumour immune response.

The clinical implications of this finding are significant. NLR is a simple, cost-effective biomarker that could be integrated into routine preoperative evaluation to aid in risk stratification, guide treatment planning, and identify patients who may require more intensive management or closer follow-up. Unlike some previous studies that assessed NLR only as a prognostic marker, this study additionally evaluated its diagnostic performance in relation to histopathological differentiation, highlighting its potential utility in clinical decision-making (23).

Histopathological differentiation itself remains a key determinant of treatment response and prognosis. Poorly differentiated tumours often show reduced responsiveness to neoadjuvant chemotherapy and radiotherapy, emphasizing the need for reliable preoperative markers of tumour aggressiveness (24). By linking NLR to differentiation, this study provides further evidence for its potential role in guiding individualized therapeutic strategies.

Several limitations should be acknowledged. The study was conducted at a single tertiary referral centre, which may bias the sample toward more advanced or complex cases. The relatively small sample size and the one-year study period may limit the generalizability of the findings and the robustness of statistical analyses. Additionally, the retrospective design relying on medical record data introduces the possibility of information and observer bias.

In conclusion, systemic inflammation, as reflected by NLR, is closely linked to tumour aggressiveness in colorectal cancer. Its incorporation into routine clinical assessment may facilitate early risk stratification and individualized treatment planning. Future large-scale, prospective, multicentre studies are warranted to validate these findings and to explore the integration of NLR with other inflammatory and molecular biomarkers to optimize prognostic and therapeutic decision-making.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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