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Neutrophil to Hemoglobin Lymphocyte Ratio (NHLR) as a Novel Biomarker is Superior to Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) as Predictors of Advanced Colorectal Cancer

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ABSTRACT

Background: Neutrophils, Hemoglobin, and Lymphocytes are biological markers that may be related to the colorectal cancer stage. Neutrophils to Hemoglobin-Lymphocytes Ratio (NHLR) is a new biomarker that will be tested with Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) as common biomarkers that have been shown to have predictive value with colorectal cancer stage. This study aims to prove NHLR as a new biomarker that can predict advanced colorectal cancer in terms of staging and site of cancer compared to NLR and PLR.

Methods: This is a retrospective cross-sectional study. Data obtained from the medical records of colorectal cancer patients undergoing surgery at Dr Sardjito Hospital from 2020 until 2022.

Results: 386 patients enrolled in the study, and 62 patients met the inclusion criteria. Twenty-eight patients (45.16 %) were male, and 34 (54.84 %) were female. The mean age is 58.82 years. Bivariate analysis showed a significant relationship between NHLR, NLR, and PLR with colorectal cancer stage and significant differences between NHLR and NLR with early and advanced colorectal cancer, but not with PLR. There are also significant differences between NHLR, NLR, and PLR with colorectal cancer sites in the colon and rectum. Still, in locally advanced stages of colorectal cancer, there is no significant association between NLR and cancer sites. On the contrary, there are significant differences between colon and rectal cancer sites with NHLR and PLR.

Conclusions: NHLR is superior to NLR and PLR in predicting the stage and site of advanced colorectal cancer.

INTRODUCTION

Colorectal cancer is a malignancy that originates in the tissues of the colon, consisting of the colon and the rectum [1]. The incidence of colorectal cancer is in third place after breast cancer and lung cancer, at 10.2% of the total cancer in the world in men and women. In Indonesia, the incidence of colorectal cancer is fourth at 12.4%, with a mortality percentage of 6.7% [2].

Systemic inflammatory responses play an important role in cancer development through genetic mutations, genomic instability, tumor metastasis, and cancer cell proliferation [3]. Research shows that cancer cells proliferate and migrate in cancer patients after cancer cells release inflammatory mediators and inflammatory indicators can be used as stage prediction values for cancer [4]. Neutrophils and platelets signal the body's inflammatory state, and lymphocytes reflect the stressful state of body cells [5]. The changing proportion of leukocytes in the inflammatory environment is also meaningful in reflecting the anticancer immune response. A new set of prognostic indicators is set to enhance further predictive efficacy based on absolute lymphocyte count in colorectal cancer [6]. Lymphocytes are the most powerful component in the adaptive immune system in anticancer immune responses and some differences in research results may occur due to ethnic factors and comorbidities [7]. A combination of several parameters,

the ratio of neutrophils to lymphocytes (NLR) and the ratio of platelets to lymphocytes (PLR), has been used in predicting cancer prognosis [8]. Studies show high NLR in metastatic colorectal cancer (stage IV) or cancer with poorly differentiated cells [9]. High NLR in colorectal cancer is also due to lymphopenia due to impaired host immunity mediated by lymphocyte cells and neutrophilia due to response from systemic inflammation [10].

Anemia associated with stage T tumors, 21% of patients diagnosed at stage 0–1 were anemic, 39% at stage 2, 44% at stage 3, and 66% at stage 4 ($p = 0.001$), anemia also associated with advanced colorectal cancer at the preoperative stage. Once diagnosed with colorectal cancer, anemia of any severity is considered in determining prognosis in the preoperative stage [11]. Anemia classification for men (age 15 years and over) is mild anemia if Hb 11–12.9, moderate if Hb 8–10.9, and severe if Hb lower than 8. Anemia for women (age 15 years and over) is mild anemia if Hb 11–11.9, moderate if Hb 8–10.9, and severe if Hb lower than 8 [12]. Anemia was strongly associated with a higher TNM stage (OR = 1.84, $p < 0.05$) [13]. Decreased Hb levels were associated with advanced stages of TNM ($p < 0.001$), especially the higher T-stages ($p < 0.001$) [14].

Turhan et al. [15], reported a significant relationship between NLR values and colorectal cancer stage and no significant relationship between PLR values and colorectal cancer stage. In the research of Rohit Krishna and Anil Kumar [16], NLR values increase according to the stage of colorectal cancer, from stage I to stage II to stage III, but NLR values at stage IV are lower than stage III. PLR values were found to increase according to colorectal cancer stage from stage I to stage II to stage III, but PLR values at stage IV were lower than stage III. NLR and PLR are related to the stage of colorectal cancer, with the advantage of cost-effective and easily measurable screening. However, keep in mind that NLR and PLR values are influenced by various factors including ethnicity and comorbidities [17].

Neutrophils, hemoglobin, and lymphocytes are the influential components in the process of advanced colorectal cancer, so it is possible to make a ratio between the three in predicting the location and advanced stage of colorectal cancer better than existing biomarkers. Therefore, This study aims to prove NHLR as a new biomarker that can predict advanced colorectal cancer, in terms of stage and site of cancer compared to NLR and PLR from local population samples and strict inclusion criteria to suppress comorbid factors. In addition, this study is also expected to determine the cut-off value of NHLR, NLR, and PLR between early and advanced cancer, as well as with the sites of cancer, if a significant difference is obtained.

Prediction of the early or advanced stage and location of colorectal cancer prepares surgical tools, positions, and techniques more planned, as well as education about the surgery plan to patients and their families.

METHODS

Study Design

A retrospective, cross-sectional research study. Data were taken from the medical records of colorectal cancer patients who underwent surgery at RSUP Dr. Sardjito Yogyakarta between 1 January 2020 and 31 December 2022. Data collection has been carried out in April 2023. Minimum Sample Calculation Using Mean Difference T Test and obtained the results of 62 research samples [18]. According to the protocol in Dr. Sardjito Hospital, all patients have full hematology parameters before the operation. Routine blood tests ≤ 2 weeks before surgery. Preoperative Hemoglobin in units g/dl with spectrophotometer methods, lymphocytes in units 103/µl with flow cytometry methods, neutrophils in units 103/µl flow cytometry methods, and platelets in units 103/µl with impedance methods are noted. NHLR is the value of neutrophils multiplied by ten divided by hemoglobin and lymphocyte (NHLR = (Nx10)/(HxL)), NLR is the value of neutrophils divided by lymphocytes (NLR = N/L), and PLR is the value of platelets divided by lymphocytes (PLR = P/L).

Colorectal cancer stage according to the criteria of the 2017 AJCC TNM System [19]. Stage I consists of T1 and T2 (Tumor invades the submucosa and Propia muscular), Stage II consists of T3 and T4a,b (Tumor invades peri colorectal tissue and penetrates visceral peritoneum or adherent to other organs or structure), stage III means tumor with regional lymph metastases, stage IV means tumor with distant metastasis. The early stage consists of stages I and II, and the advanced stage consists of stages III and IV. The colon tumor site consists of ascending, transverse, descending, and sigmoid colon. The rectum tumor site consists of the proximal, media, and distal rectum, according to histopathological results The early stage is stage I+II, the advanced stage is stage III+IV, and the locally advanced colorectal stage is stage III.

Patients Selection

Inclusion and exclusion criteria were used for the study sample to reduce patient bias and comorbidity. Inclusion criteria are Colorectal cancer patients of Javanese ethnicity confirmed by postoperative histopathology examination and colorectal cancer patients who undergo cancer resection. Taking lymph ≥ 12 so that stage N can be known histopathologically; for N2b criteria, if there are already ≥ 7 regional lymph that is positive for tumors, research can be included even though the lymph taken is less than 12, For N1c Criteria, if regional lymph ≥ 9 is taken which is tumor negative, with tumor deposit (+), then research can be

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included even though the lymph taken is less than 12, and Leukocyte value ≤ 12,000 /µl. The exclusion criteria are Colorectal cancer patients who only have a biopsy, Stage N cannot be determined histopathologically, Laboratory values after blood transfusion, the patient suffers from another malignancy, Residual or recurrent colorectal cancer, and the patient has undergone chemotherapy and radiotherapy.

Data Analysis

The statistical software IBM SPSS Statistics version 22 was used to analyze this study. The normality test was performed by the Shapiro-Wilk test. Data analysis using the Kruskal Wallis and Mann Whitney Test if the data distribution is abnormal, when the data distribution is normal using the T-test. The statistical test results are significant if the p-value < 0.05 and the confidence interval is 95%.

RESULTS

The study included 386 patients, with 62 patients meeting the inclusion criteria. All obtained data were tested for their normality by using the Shapiro-Wilk test, abnormal data distribution with $p < 0.05$ data analysis using a non-parametric test (Kruskal Wallis test and Mann Whitney test), and normal data distribution with $p > 0.05$ data analysis using a parametric test (T-test).

Table 1 shows gender, age (average age 58.82 years), tumor site, histopathological results, TNM stage, and early or advanced stage. **Table 2** shows the mean variable and bivariate analysis for stage I-IV, which means a significant relationship exists between NHLR, NLR, and PLR in the colorectal cancer stage. Mann Whitney test and T-test show a relationship between each stage of the variable, The results found significant differences between NHLR, NLR, and PLR with stages I-IV, stage II-IV, and III-IV colorectal cancer.

Table 3 shows that there are significant differences between NHLR and NLR with early and advanced stages of colorectal cancer, otherwise, there are no significant differences between PLR with early and advanced stages of colorectal cancer, with better NHLR sensitivity than NLR and NLR specificity is better than NHLR. **Table 4** shows the mean variable and significant relationship between NHLR, NLR, and PLR with colorectal cancer sites (stage I-IV) with the best cut-off value specificity in NHLR and the best sensitivity in PLR. **Table 5** shows the mean variable and significant difference between NHLR and PLR in the sites of local advanced colorectal cancer (stage III). At the same time, there is no significant difference between NLR and local advanced colorectal cancer sites, with PLR sensitivity better than NHLR and NHLR specificity better than PLR.

The study results showed a significant difference between NHLR and NLR with early and advanced stages of colorectal cancer but not with PLR. There were also significant differences between NHLR, NLR, and PLR with colorectal cancer sites in the colon and rectum. Still, in locally advanced stages of colorectal cancer, only significant differences were found between NHLR and PLR with colon and rectal cancer sites, but not NLR.

Table 1. Characteristics of the patients

Variable	N (%)
Gender	
Male	28 (45.16%)
Female	34 (54.84%)
Age (years)	
< 60	29 (46.77%)
≥ 60	33 (53.23%)
Tumor Site	
Rectum	41 (66.13%)
Colon	21 (33.87%)
Histopathological Adenocarcinoma Results	
Well Differentiated	16 (25.81%)
Moderately Differentiated	42 (67.74%)
Poor Differentiated	4 (6.45%)
TNM Stage	
Stage I	10 (16.13%)
Stage II	10 (16.13%)
Stage III	33 (53.22%)
Stage IV	9 (14.52%)
Early or advanced Stage	
Early Stage (stage I+II)	20 (32.26%)
Advanced Stage (stage III+IV)	42 (67.74%)

Table 2. Mean variable and variable bivariate analysis for stages I–IV

Variable	Mean ± SD	Mean ± SD Early stage	Mean ± SD Advanced stage	p-value
NHLR	3.42 ± 2.01	2.71 ± 1.57	3.76 ± 2.12	0.043*
NLR	3.56 ± 1.75	2.94 ± 1.43	3.85 ± 1.82	0.030*
PLR	236.65 ± 126.27	195.62 ± 80.24	256.19 ± 139.73	0.040*

D = standard of deviation; NHLR = Neutrophil to Hemoglobin Lymphocyte Ratio; NLR = Neutrophil Lymphocyte Ratio; PLR = Platelet Lymphocyte Ratio; *significant at p<0.05 by Kruskal Wallis Test; p = Probability.

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Table 3. Bivariate analysis of variables for early and advanced stages

Variable	p-value	Cut off point	Sn	Sp
NHLR	0.032*	2.44	73.8 %	65.0%
NLR	0.030*	3.01	71.4 %	70.0%
PLR	0.098	-	-	-

*significant at p<0.05 by Mann Whitney Test; p = Probability; NHLR = Neutrophil to Hemoglobin Lymphocyte Ratio; NLR = Neutrophil Lymphocyte ratio; PLR = Platelet Lymphocyte Ratio; Sn = Sensitivity; Sp = Specificity

Table 4. Mean and variable bivariate analysis for tumor site (stage I–IV)

Variable	Mean ± SD Colon	Mean ± SD Rectum	p-value	Cut off point	Sn	Sp
NHLR	4.58 ± 2.32	2.82 ± 1.54	0.001*	3.12	65.9%	76.2%
NLR	4.25 ± 1.78	3.21 ± 1.64	0.014*	3.20	61.0%	71.4%
PLR	308.76 ± 157.83	199.72 ± 87.92	0.001*	239.46	78.0%	66.7%

SD = Standard of Deviation; *significant at p<0.05 by Mann Whitney Test; p = Probability; NHLR = Neutrophil to Hemoglobin Lymphocyte Ratio; NLR = Neutrophil Lymphocyte ratio; PLR = Platelet Lymphocyte Ratio; Sn = Sensitivity; Sp = Specificity

Table 5. Mean and variable bivariate analysis for tumor site (stage III)

Variable	Mean ± SD Colon	Mean ± SD Rectum	p-value	Cut off point	Sn	Sp
NHLR	4.65 ± 2.34	2.77 ± 1.07	0.034*	3.12	65.2%	90.0%
NLR	3.90 ± 1.08	3.13 ± 1.09	0.069	-	-	-
PLR	287.69 ± 140.88	198.57 ± 79.36	0.031*	231.79	73.9%	70.0%

SD = Standard of Deviation; *significant at p<0.05 by Mann Whitney Test; p = Probability; NHLR = Neutrophil to Hemoglobin Lymphocyte Ratio; NLR = Neutrophil Lymphocyte ratio; PLR = Platelet Lymphocyte Ratio; Sn = Sensitivity; Sp = Specificity

DISCUSSION

A significant relationship was obtained between NHLR, NLR, and PLR with colorectal cancer stages, significant differences were obtained between NHLR, NLR, and PLR with stages I-IV, stage II–IV, and stage III–IV colorectal cancer. There was also a significant difference between NHLR and NLR with early and advanced stages of colorectal cancer with better NHLR sensitivity than NLR. Still, there was no significant relationship between PLR with early and advanced colorectal cancer.

Significant differences also exist between NHLR, NLR, and PLR with colorectal cancer sites in the colon and rectum, with the highest specificity of cut-off point in NHLR and highest sensitivity of cut-off point in PLR. but in the locally advanced stage of colorectal cancer, there was no significant relationship between NLR and cancer site, instead, there was a significant difference between colon and rectal cancer site with NHLR and PLR, with the cut-off point value NHLR is better in specificity and PLR is better in sensitivity.

NLR and PLR research results are the same as those of Rohitt Krishna and Anil Kumar [16] and Song et al. [20], who reported a significant relationship between NLR and PLR values in the colorectal cancer stage. NLR research obtained the same results as Turhan et al. [15], who reported a significant relationship between NLR and colorectal cancer stage. In the post hoc test, there was a significant difference between NLR values with stages I and III colorectal cancer. It was also reported that there was a significant difference between NLR values with early and advanced stages of colorectal cancer with a p-value of 0.034, with a cut-off value of 3.7 (sensitivity 40.8%, specificity 40.1%) and no significant difference between PLR values with early and advanced stages of colorectal cancer with a p-value of 0.099.

NHLR can be used as a new biomarker of colorectal cancer by the theory that lymphocytes, neutrophils, and hemoglobin are associated with colorectal cancer. Lymphocytes are the main component of the immune system in response to colorectal cancer. Research shows that lymphocytes produce cytokines, which inhibit the proliferation, and metastasis of cancer cells and trigger cytotoxic cell death [21]. Lymphocyte values tend to be high in tumors with good differentiation, and an increase in lymphocytes indicates a smaller tumor size [22].

Neutrophils and macrophages are involved in developing various solid tumors. In particular, it is infiltrated by NK cells, macrophages, and neutrophils. Tumor-associated macrophages (TAMs) and chemokines (CXC) secreted by tumor cells recruit neutrophils to the tumor site, and the presence of these tumor-associated neutrophils (TANs) is associated with tumor progression. Vascular endothelial growth factor (VEGF) derived from neutrophils is associated with angiogenic activity [23].

Goubran et al. [24] explain that elevated VEGF, PDGF, and PF4 likely indicate increased platelet counts in colorectal cancer patients, assuming that platelets can trigger the formation of new blood vessels and prevent bleeding from new blood vessels, leading to tumor cell development.

Colorectal cancer stage and Hb were independent risk factors for predicting progression-free survival (PFS) and overall survival (OS) [25]. Anemia is associated with a larger tumor diameter (> 3 cm) and cancer of the right colon. The causes of anemia in colon cancer are mostly caused by iron deficiency and correspond to chronic blood loss by chronic bleeding from tumors [26]. This is in accordance with the relationship between T-stage and anemia. Advanced T stage is associated with a higher prevalence of anemia [27]. Preoperative hemoglobin in colorectal cancer patients obtained inversely correlated with primary tumor size (R: 0.71, R2: 1.55, P = 0.0001) and nodal status (R: 0.02, R2: 0.05, P = 0.01), preoperative anemia and thrombocytosis is found mainly in right-sided, advanced and lymph positive stages of colorectal cancer [28]. This study of the relationship between NHLR and tumor site showed that colon cancer has a higher NHLR and higher NHLR means lower Hb levels in the colon according to the research of Sadahiro et al. [29] which showed that cancer of the cecum, ascending colon, and transverse colon is a factor associated with a high incidence of anemia.

NHLR is superior in predicting the sites and stages of advanced colorectal cancer because it is linked to three components: Hemoglobin value, which has differences between colon and rectal cancer neutrophils and lymphocytes associated with advanced stages of colorectal cancer [28]. NLR only links neutrophils and lymphocytes associated with advanced stages of colorectal cancer but not with tumor sites in advanced local colorectal cancer [15,16]. PLR only links platelets and lymphocytes, platelets are more associated with bleeding reactions and can distinguish the location of the tumor but cannot determine the early and advanced stages of colorectal cancer [15,28].

CONCLUSIONS

NHLR, as a new biomarker, proved superior to NLR and PLR associated with advanced colorectal cancer in terms of predicting the stage and site of cancer. However, large-scale studies are still needed to validate our results due to the limitations of this study.

DECLARATIONS

Competing interest

The authors declare no competing interest in this study.

Ethics Approval

The Ethical Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada / Dr. Sardjito General Hospital, approved this study (KE/FK/0199/EC/2023).

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