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Research Article

The association of hypoxia-inducible factor-1 alpha expression, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio with three-year progression-free survival in locally advanced colorectal cancer patients

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Abstract

Introduction: Colorectal cancer (CRC) is the second leading cause of cancer-related death worldwide and ranks among the top three in Indonesia. Most patients were diagnosed in a locally advanced stage, with a high recurrence rate despite standard oxaliplatin-based chemotherapy. The hypoxic tumor microenvironment through activation of hypoxia-inducible factor-1 alpha (HIF-1α) and systemic inflammation reflected by the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) could be associated with the tumor progression.

Aim: To evaluate the association of HIF-1α expression, NLR, and PLR with three-year progression-free survival (PFS) in locally advanced CRC patients.

Methods: This retrospective cohort study included 50 patients with high-risk stage II and stage III CRC who underwent surgical resection and adjuvant oxaliplatin-based chemotherapy in Cipto Mangunkusumo National Hospital. HIF-1α expression was assessed by immunohistochemistry, while NLR and PLR were calculated from pre-treatment blood tests. Data were analyzed using Kaplan–Meier and Cox regression methods, with $p<0.05$ considered statistically significant.

Results: The median HIF-1α expression was 96.32%, with a cut-off value of 96.51% (AUC 0.472; $p=0.746$). There was no significant association between HIF-1α expression and three-year PFS (HR 1.274; $p=0.495$). The cut-off points for NLR and PLR were 3.46 (AUC 0.486; $p=0.872$) and 198.31 (AUC 0.505; $p=0.952$), respectively, and both were not significantly associated with three-year PFS (NLR: HR 0.947; $p=0.874$; PLR: HR 1.060; $p=0.869$).

Conclusions: HIF-1α expression, NLR, and PLR were not significantly associated with three-year progression-free survival in locally advanced CRC patients.

Keywords

colorectal cancer, HIF-1α, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, progression free survival

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Introduction

According to data from the Global Cancer Observatory (GLOBOCAN) in 2022, colorectal cancer (CRC) is the second highest mortality rate cancer in the world, with CRC cases reaching 1.9 million, representing 9.6% of all cancer diagnoses worldwide. In 2024, there were an estimated 106,590 new cases of colon cancer and 46,220 new cases of rectal cancer, with approximately 53,010 deaths from both. [1-4] Locally advanced stage cancer (ASCO) includes tumors measuring T3-T4 and/or non-metastatic nodal involvement. NCCN defines these stages as stages II and III. [1-4]

The tumor microenvironment (TME) consists of proliferating tumor cells, tumor stroma, blood vessels, infiltrating inflammatory cells, and various associated tissue cells.[5] The TME plays a role in CRC by being significantly involved in promoting or inhibiting these processes.[6] One of the important components of the TME is hypoxia-inducible factor-1 alpha (HIF-1α). HIF-1α is a transcription factor whose expression increases in hypoxia.[7] HIF-1α expression has been reported to play a role in tumor progression in terms of tumor proliferation, apoptosis, angiogenesis, immune escape, energy metabolism, and resistance to chemotherapy.[8]

Inflammation is also a major factor in tumorigenesis and the neoplastic process. The neutrophil-to-lymphocyte ratio has emerged as a promising, simple, inexpensive, and readily available serum inflammatory marker for predicting the prognosis of CRC patients.[9] In addition to NLR, the platelet-to-lymphocyte ratio is also an inflammatory marker that can predict the prognosis of CRC patients.[10]

Studies related to prognostic and predictive factors for therapy in advanced CRC patients are ongoing, as CRC cases that do not respond adequately to standard chemotherapy regimens are emerging. Therefore, this study aims to analyze HIF-1α expression, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio as prognostic factors in CRC patients, particularly in Indonesia, where research has not yet been conducted. This study also assessed PFS as the primary outcome, defined as the time when the patient first received therapy to progression or death from any cause.[11] A meta-analysis conducted by the Adjuvant Colon Cancer End Points (ACCENT) found that under three years of disease-free survival (DFS) is a predictor of five-year OS and can be an ideal primary endpoint for colon cancer research with adjuvant therapy.[1,12] Considering the research findings, researchers used a three-year follow-up period as a benchmark. PFS was assessed instead of DFS because the samples were collected in a government national hospital; consequently, delays occurred in giving treatment or in the radiology evaluation due to the high volume of patients. Therefore, PFS is more relatable for this study.

Aim

The aim of this study was to assess the association of the expression of hypoxia-inducible factor-1 alpha (HIF-1α), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) with three-year progression-free survival (PFS) in patients with locally advanced colorectal cancer. The results of this study are expected to be useful in determining whether HIF-1 alpha expression, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio can be prognostic factors for locally advanced CRC patients by assessing three-year PFS, thereby assessing the benefits of administering the latest therapies for patients in the future.

Research methods

This study is a retrospective cohort study conducted at Dr. Cipto Mangunkusumo National Hospital in Jakarta after obtaining approval from the Research Ethics Committee of the Faculty of Medicine, University of Indonesia/RSCM. The study population included adult locally advanced CRC patients who received oxaliplatin-based combination chemotherapy at Cipto Mangunkusumo National Hospital from January 2021 to January 2024. The study sample was taken from the accessible population that met the inclusion criteria and did not meet the exclusion criteria. Inclusion criteria were patients aged 18 years and older with histopathologically diagnosed locally advanced CRC (high-risk stage II and stage III), who had undergone bowel resection and received oxaliplatin-based adjuvant chemotherapy; had disease progression based on radiological criteria; and had available paraffin blocks from the resected bowel for immunohistochemical staining. Exclusion criteria included patients with a history of other malignancies and patients with end-stage comorbidities based on the Charlson Comorbidity Index.

Sampling was conducted using the consecutive sampling method, and from the 230 patient records collected, 59 subjects met the inclusion criteria based on medical record data, including clinical, laboratory, and radiological data. A total of 171 subjects were excluded due to, among others, not meeting the criteria for locally advanced stage, having double primary cancer, not being given oxaliplatin-based chemotherapy, lack of radiological evaluation data, no bowel resection surgery, and being lost to follow-up and unable to be contacted. A total of 50 study subjects had FFPE that could be stained for HIF-1α and continued to statistical analysis.

HIF-1α expression was assessed using the immunohistochemical (IHC) staining method on resected tumor tissue with an anti-HIF-1α monoclonal antibody. HIF-1α IHC staining was performed on 50 formalin-fixed paraffin-embedded (FFPE) subjects, with the primary antibody being a concentrated rabbit monoclonal antibody from Biocare Medical®. The first step was to create positive and negative controls to serve as a reference for IHC readings. Reagent optimization was performed at a dilution of 1:250 with overnight incubation using Renoir diluent. Assessment of HIF-1α staining in tissue was by observing the nucleus

and/or cytoplasm of tumor cells that were stained brown. In this study, all FFPEs were stained in the cytoplasm of tumor cells. The percentage of HIF-1α was assessed by assessing the number of positive tumor cells divided by the total number of tumor cells assessed in five fields of view. HIF-1α immunohistochemical staining results were selected from well-stained malignant cells, and then the whole slides were scanned and counted in five fields of view at 400×magnification. The staining results were calculated using the ImageJ® program **(Fig. 1)**.

NLR and PLR were calculated from a complete blood count before chemotherapy. NLR was calculated as the ratio of neutrophil count (%) divided by lymphocyte count (%), while PLR was calculated as the ratio of platelet count divided by absolute lymphocyte count. Cut-off points for each variable were determined using Receiver Operating Characteristic (ROC) analysis of three-year PFS.

Data collected included demographic characteristics (age, sex), clinical data (disease stage, comorbidities), laboratory data, and immunohistochemistry results. The primary outcome was three-year PFS, defined as the time from the start of chemotherapy to disease progression or death from any cause observed within 3 years. Patients who did not experience progression by the end of follow-up were considered censored.

Data analysis was performed using SPSS software version 30.0. Univariate analysis was used to describe subject characteristics, while bivariate analysis used the Kaplan–Meier method to describe survival curves and the log-rank test to compare between groups. Multivariate analysis using the Cox proportional hazards regression model was performed to assess the association of HIF-1α, NLR, and PLR expression with three-year PFS, adjusting for confounding factors. A p-value <0.05 was considered statistically significant, and results are presented as a Hazard Ratio (HR) along with a 95% confidence interval (95% CI). All patient data is kep confidential and used only for scientific purposes in accordance with ethical principles of medical research.

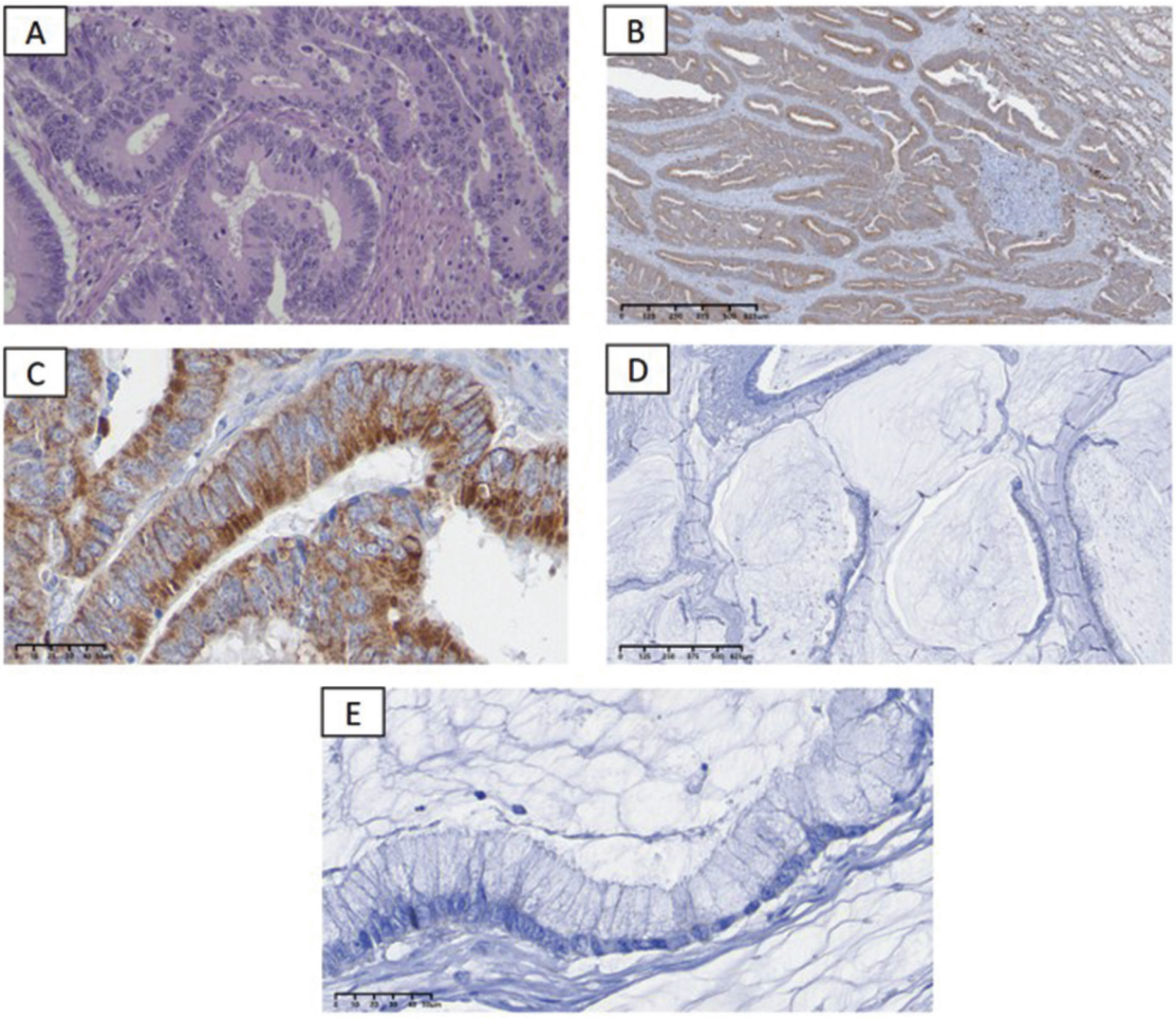

Figure 1. HIF-1α expression staining. (**A**) HE tumor mass 400×; (**B**) HIF-1α IHC (positive) 40×; (**C**) HIF-1α IHC (positive) 400×; (**D**) HIF-1α IHC Negative 40×; (**E**) HIF-1α IHC negative 400×.

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Results

The characteristics of the study subjects can be seen in **Table 1** below. The table shows that the median age of the subjects was 56 years, with a nearly equal proportion of men and women, at 46% and 54%, respectively. Seventy-five percent of subjects presented with stage III disease, and 80% had a good ECOG score of 0-1. Approximately 52% of subjects had comorbidities, with the most common being type 2 diabetes, hypertension, and coronary artery disease.

During the 36-month observation period, 32 of 50 patients with locally advanced colorectal cancer (64.0%) progressed. Kaplan–Meier estimates showed a cumulative PFS probability at 28 months of 36.0% (SE 0.68). The median time without progression was limited to 36 months, with a mean PFS of 22.32 months (95% CI 18.962–25.681). Median survival was not estimated because the curve did not cross 0.50 during the observation period. Visually, the curve showed the sharpest decline in the first 6–28 months and tended to level off thereafter **(Fig. 2)**.

Table 2 shows the expression characteristics of HIF-1α, NLR, and PLR in the study subjects. The median NLR value was 3.44 and the median PLR value was 204.26.

From **Fig. 3**, the AUC was 0.472 (95% CI 0.299 – 0.646) with p=0.746, and it was found that the cut-off point for HIF-1α expression based on 3-year PFS was 96.51 with a sensitivity of 50% and a specificity of 55.6%.

Based on **Table 3**, there was no difference in the proportion between subjects with HIF-1α overexpression and underexpression of 66.7% and 61.5%, respectively at 3 years with p=0.495.

From **Fig. 4**, the AUC was 0.486 (95% CI 0.314 – 0.658) with p=0.872, and the cut-off point of NLR was 3.464 with a sensitivity of 46.9 and a specificity of 50%.

Based on **Table 4**, there was no difference in the proportion between subjects with high and low NLR of 57.1% and 66.7% for the 3-year event with p=0.894.

From **Fig. 5**, the AUC was 0.505 (95% CI 0.333 – 0.678)

Table 1. Characteristics of research subjects

Subject characteristics	Total (N=50)	3-year event	
		Yes (n=32)	No (n=18)
Age, median (IQR)	56 (44.75 – 61.25)	51 (43.25 – 60)	58 (49.75 – 64.5)
Sex, n (%)			
Men	23 (46.0)	16 (50.0)	7 (38.9)
Women	27 (54.0)	16 (50.0)	11 (61.1)
Education, n (%)			
Junior high school	4 (8.0)	3 (9.4)	1 (5.6)
Senior high school	35 (70.0)	21 (65.6)	14 (77.8)
Diploma/Bachelor/Master degree	11 (22.0)	8 (25.0)	3 (16.7)
Comorbidities, n (%)			
Yes	26 (52.0)	16 (50.0)	10 (55.6)
Type 2 DM, n (%)	6 (12.0)	3 (9.4)	3 (16.7)
Hypertension, n (%)	12 (24.0)	6 (18.8)	6 (33.3)
CAD, n (%)	5 (10.0)	4 (12.5)	1 (5.6)
No	24 (48.0)	16 (50.0)	8 (44.4)
Timeliness of chemotherapy, n (%)			
No	4 (8.0)	4 (12.5)	0 (0.0)
Yes	46 (92.0)	28 (87.5)	18 (100.0)
Cycle completeness, n (%)			
No	8 (16.0)	7 (21.9)	1 (5.6)
Yes	42 (84.0)	25 (78.1)	17 (94.4)
Stage, n (%)			
II High Risk	12 (24.5)	5 (16.1)	7 (38.9)
III	38 (75.5)	27 (83.9)	11 (61.1)
Initial ECOG, n (%)			
0-1	40 (80.0)	25 (78.1)	15 (83.3)
2	10 (20.0)	7 (21.9)	3 (16.7)

IQR: interquartile range; DM: diabetes mellitus; CAD: coronary artery disease; ECOG: Eastern Cooperative Oncology Group

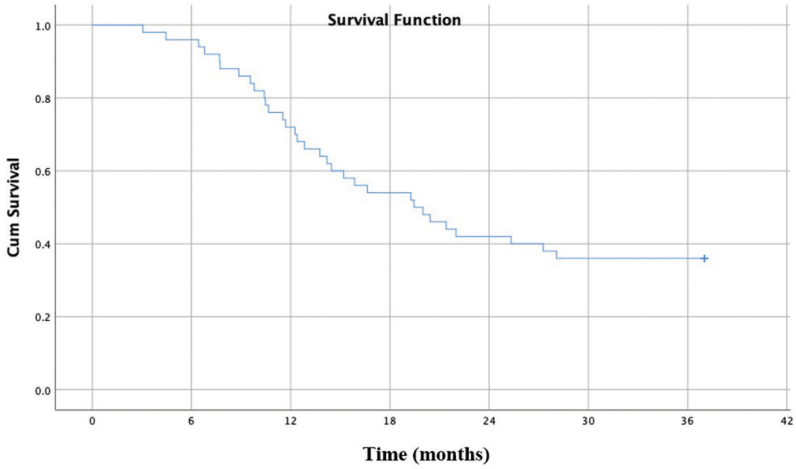

Figure 2. Kaplan–Meier 3-year PFS in patients with locally advanced colorectal cancer.

Table 2. Characteristics of HIF-1α, NLR, and PLR expression in research subjects

Subject characteristics	Total (N=50)	3 year event	
		Yes (n=32)	No (n=18)
NLR, median (IQR)	3.44 (2.41 – 4.60)	2.98 (2.45 – 4.42)	3.47 (2.26 – 4.67)
PLR, median (IQR)	204.26 (143.19 – 293.42)	198.31 (156.14 – 300.21)	213.83 (133.49 – 284.95)
Leukocytes, median (IQR)	8520 (7310 – 11305)	8640 (7440 – 11740)	7930 (6495 – 10432)
Platelets, median (IQR)	380000 (307750 – 450500)	386000 (312750 – 450500)	343000(253250 – 472000)
Neutrophils, mean (SD)	67.49 (9.73)	68.14 (9.29)	66.35 (10.66)
Lymphocytes, mean (SD)	21.76 (8.46)	21.69 (8.22)	21.89 (9.29)
HIF-1α expression, median (IQR)	96.32 (93.56 – 97.37)	96.39 (93.68 – 97.32)	96.32 (92.33 – 97.58)
HIF-1α category, n (%)			
3+ (51-80%)	4 (8.0)	2 (6.3)	2 (11.1)
4+ (81-100%)	46 (92.0)	30 (93.8)	16 (88.9)
Absolute lymphocyte count, mean (SD)	1888.49 (605.53)	1936.05 (557.92)	1803.96 (690.94)

IQR: interquartile range; SD: standard deviation. Quantitative assessment of HIF-1α expression showed a median value of stained cells of 96.32%.

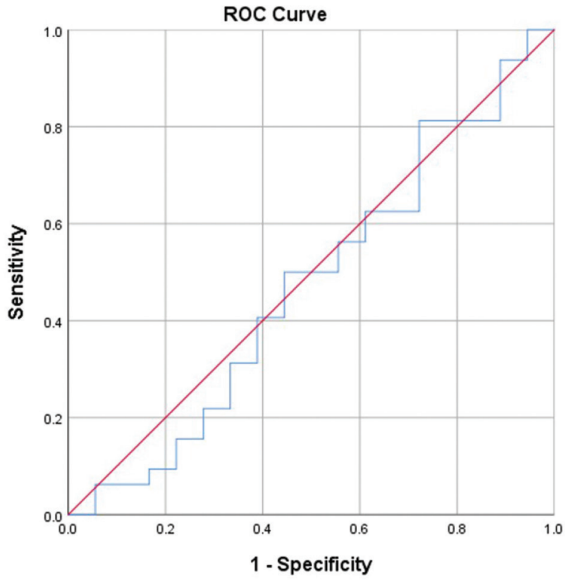

Figure 3. ROC curve of HIF-1α expression based on 3-year PFS.

with p=0.952, and the cut-off point of PLR was 198.306 with a sensitivity of 50% and a specificity of 55.6%.

Based on **Table 5**, there is no difference in the proportion between subjects with high and low PLR of 61.5% and 66.7% for the 3-year event with p=0.869.

Discussion

In this study, the median NLR value was 3.44, and the PLR value was 204.26. These values are within a relatively similar range to the results of previous studies on colorectal cancer. In a study by Liu et al.[13], it was found that a pre-treatment NLR cut-off of 3 differentiated the group of patients with a longer PFS compared to the group with NLR≥3 (PFS 9.1 months vs. 6.1 months) in CRC patients receiving chemotherapy with the FOLFOX regimen. In addition, the median PLR value of 204.26 in this study is also in accordance

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Table 3. Association of HIF-1α expression and 3-year events

Variables	3 year event		HR (95% IK)	*p*-value
	Yes (N=32)	No (N=18)		
HIF-1α expression, n (%)				
≥96.51 (overexpression)	16 (66.7)	8 (33.3)	1.274 (0.636 – 2.549)	0.495
<96.51 (underexpression)	16 (61.5)	10 (38.5)		

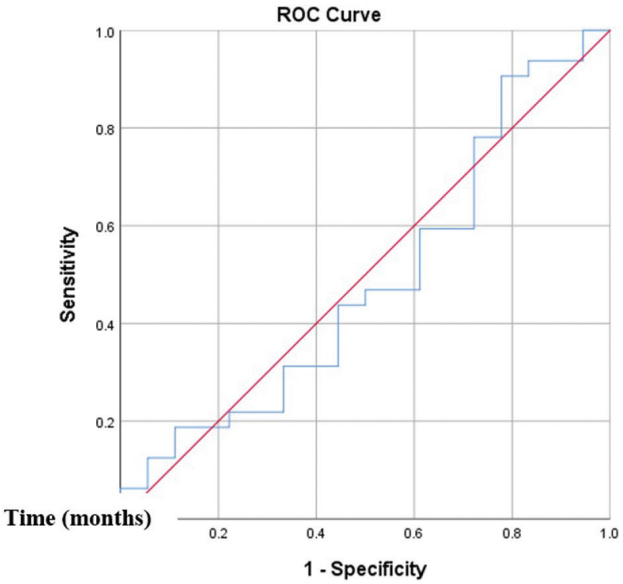

Figure 4. ROC curve of NLR expression based on 3-year PFS.

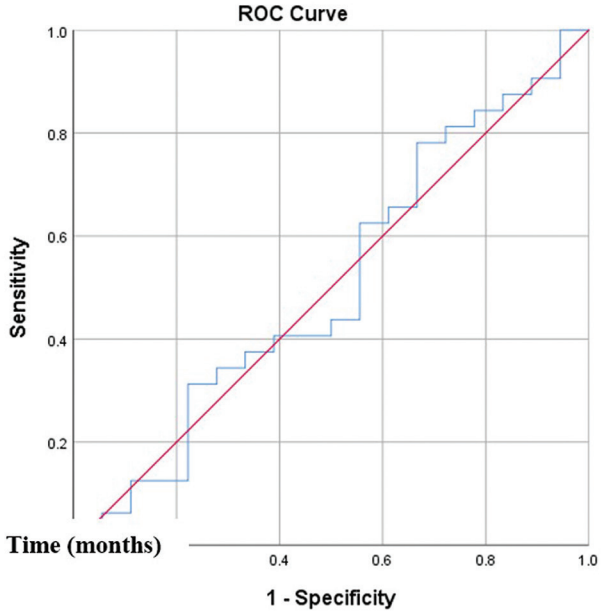

Figure 5. ROC curve of PLR expression based on 3-year PFS.

Table 4. Association of NLR with 3-year PFS

Variables	3 year event		HR (95% IK)	*p*-value
	Yes (N=32)	No (N=18)		
NLR, n (%)				
≥3.46 (high)	8 (57.1)	6 (42.9)	0.947 (0.425 – 2.109)	0.894
<3.46 (low)	24 (66.7)	12 (33.3)		

Table 5. Association of PLR and 3-year PFS

Variables	Event 3 years		HR (95% IK)	*p*
	Yes (N=32)	No (N=18)		
PLR, n (%)				
≥198.31 (high)	16 (61.5)	10 (38.5)	1,060 (0.530 – 2,121)	0.869
<198.31 (low)	16 (66.7)	8 (33.3)		

with the cut-off range values widely reported in various colorectal cancer studies, which generally range from 130 to 200.[14] The study by Jia et al.[15] found that a PLR cut-off of 154.31 significantly differentiated patient groups with different prognoses, where high PLR was associated with worse OS in colorectal cancer patients undergoing curative resection.

In this study sample, the median HIF-1α expression was 96.32, with 92% being categorized as 4+. HIF-1α expression was assessed by assessing the percentage of nuclei and/or cytoplasm stained with the reagent. Determination of HIF-1α expression using immunohistochemistry was also used in a study by Baba et al.[16], which showed that HIF-1α was significantly higher in tumor tissue than in normal

tissue. In that study, a cutoff of expression >10% of cells with moderate to strong intensity provided 70% sensitivity and 100% specificity in differentiating tumor tissue from normal tissue, with an area under the curve (AUC) of 0.833 (p<0.001).[16] These results confirm that HIF-1α expression can serve as a sensitive diagnostic indicator of hypoxic activity and tumor progression.

The results of the study showed that HIF-1α expression was not significantly associated with 3-year PFS, with a HR of 1.274 (95% CI 0.636–2.549) in the ≥96.51% score group. There was also no difference in proportion between subjects with HIF-1α overexpression and underexpression, amounting to 66.7% and 61.5% for the 3-year event with p=0.495. In this study, it was found that positive results from HIF-1α staining did not affect the PFS level of locally advanced CRC patients (HR 1.274 (95% CI 0.636–2.549); p=0.495). This is different from the study by Baba et al.[17] that found that HIF-1α overexpression was significantly associated with higher colorectal cancer-specific mortality in univariate Cox regression (HR=1.84; 95% CI, 1.37–2.47; p<0.0001) and multivariate analysis (adjusted HR=1.72; 95% CI, 1.26–2.36; p=0.0007). This difference may be explained by Baba et al.[17] recruiting subjects from all stages of CRC, not just locally advanced stages in this study. This inclusion allowed analysis of the influence of HIF-1α in stages I and IV, which were not examined in this study. Subgroup analysis conducted by the study also found that HIF-1α only significantly affected CRC-related mortality in stage IV both univariately (HR 1.94, 95% CI 1.23–3.06) and multivariately (HR 1.88; 95% CI 1.17–3.02), and no other significant associations were found in stages I, II, and III. A similar finding was observed in the study of Cao et al.[18] who found that HIF-1α affected the overall survival of CRC patients. Cao et al.[18] in their study also included patients with CRC stages III and IV, so this study differed. The study of Liu et al.[19] showed that HIF-1α expression in CRC patients had different levels and distributions in each stage.

The results of this study indicate that NLR is not significantly associated with 3-year PFS and there is no difference in the proportion between subjects with high and low NLR with values of 57.1% and 66.7% for 3-year PFS with a p value of 0.894. Based on the analysis results, a HR of 0.947 (95% CI 0.425–2.109) was found in the group with values ≥3.46. The HR value close to one and the high p value indicate that systemic inflammation represented by NLR does not directly affect disease progression in this population. Biologically, an increase in the number of neutrophils and a decrease in the number of lymphocytes reflect an inflammatory state that can facilitate tumor growth and inhibit the immune response to cancer cells. Many previous studies have reported that high NLR before therapy is associated with a poor prognosis in various solid cancers, including colorectal cancer. However, these findings are not always consistent.[20-22]

In a study by Yang et al.[23] assessing stage III/IV colorectal cancer patients after adjuvant chemoradiotherapy, NLR was analyzed alongside other inflammatory indices such as PLR and systemic immune-inflammation index (SII) to determine its association with PFS. The NLR cut-off value was set at 2.88 based on ROC curve analysis. Univariate analysis showed that patients with high NLR (≥2.88) had a significantly shorter PFS compared to patients with low NLR (p=0.016), indicating that increased neutrophils relative to lymphocytes are associated with a greater risk of disease progression. However, in multivariate Cox regression analysis, after accounting for clinical factors such as ECOG performance status, CA19-9 levels, and SII, NLR was no longer an independent predictor of PFS (p>0.05).[23] Biologically, an increase in NLR reflects a predominance of pro-tumor neutrophils and a decrease in lymphocytes involved in antitumor immunity, but because this index involves only two components, it does not fully capture the complexity of the broader inflammatory and immune responses. Another study by Liu et al.[13], examining patients with metastatic colorectal cancer treated with the FOLFOX chemotherapy regimen, found that changes in NLR were significantly associated with PFS. This study assessed not only basal NLR values but also the dynamics of their changes during treatment. The results showed that patients with high baseline NLR and those who experienced an increase in NLR after two cycles of FOLFOX had a significantly shorter PFS than patients with low NLR or those who experienced a decrease in NLR during therapy. Specifically, the median PFS of patients with a continuously increasing NLR reached approximately 6 months, while in the group with a decreasing NLR it reached approximately 10 months, with a statistically significant difference (p<0.05). Multivariate analysis showed that dynamic changes in NLR were an independent prognostic factor for PFS, even after controlling for other clinical variables such as age, performance status, and metastatic location. These findings confirm that not only the single NLR value, but also the direction of its change during chemotherapy, reflects the balance between the inflammatory response and antitumor immunity, although the association between NLR and PFS remained statistically insignificant.

Furthermore, other factors such as patient status, disease stage, and the presence of comorbidities may also influence the association between NLR and PFS. Therefore, although NLR may be an indicator of systemic inflammation, its use as a single prognostic biomarker in colorectal cancer requires further consideration and confirmation through further studies with more robust designs and larger sample sizes.[22]

The results of this study indicate that PLR also has no significant association to PFS for three years, and there is no difference in the proportion between subjects with high and low PLR of 61.5% and 66.7% with respect to 3-year PFS with p=0.869. Based on the analysis results, HR was found to be 1.060 (95% CI 0.530–2.121) in the group of values ≥198.31. The HR value close to one indicates that variations in PLR values among patients are not directly related to the risk of disease progression, so that both patients with high and low PLR have a relatively similar probability of progression. A high PLR ratio theoretically indicates

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a predominance of processes that support tumor growth over immunoprotective mechanisms, and could therefore hypothetically be associated with a poorer prognosis.[24,25]

However, findings from various studies have shown inconsistent results, similar to those related to NLR. In a meta-analysis conducted by Guo et al.[26], of 27 studies with a total of 13,330 colorectal cancer patients, it was shown that a high PLR ratio was significantly associated with a worse prognosis. Patients with a high PLR had a higher risk of overall survival with a hazard ratio HR=1.40 (95% CI: 1.21–1.62; $p<0.00001$), as well as a greater risk of disease recurrence or progression as reflected by disease-free survival (HR=1.44; 95% CI: 1.09–1.90; $p=0.01$) and recurrence-free survival (HR=1.48; 95% CI: 1.13–1.94; $p=0.005$). However, the association of PLR and progression-free survival (HR=1.14; 95% CI: 0.84–1.54; $p=0.40$) and cancer-specific survival (HR=1.16; 95% CI: 0.88–1.53; $p=0.28$) was not significant.[26] This indicates that although PLR can predict certain long-term outcomes, its role in determining PFS is not always reliable.

Furthermore, Li et al.[6] conducted a meta-analysis involving various types of advanced cancer and found that PLR can act as a negative prognostic factor for overall survival and PFS. However, the effect of PLR on PFS and other outcomes varies widely, depending on the type of cancer, disease stage, method of PLR measurement, and patient clinical characteristics.[7] These findings suggest that although PLR may reflect systemic inflammatory status and potential tumor support by platelets, its use as a single biomarker to predict PFS in colorectal cancer patients requires cautious interpretation and needs to be confirmed by larger follow-up studies.[24,25]

Limitation of the study

This study has several implications and suggestions for future development. High HIF-1α expression in patients with locally advanced colorectal cancer suggests potential as a basis for the development of future targeted therapies. However, there is currently no standard method for assessing HIF-1α expression in colorectal cancer, so further research using more standardized and validated methods is needed.

Assessment of the neutrophil-to-lymphocyte Ratio (NLR) and platelet-to-lymphocyte Ratio (PLR) in retrospective studies has many limitations because their values can be influenced by various factors at the time of sampling. Based on this, it is recommended to conduct studies with other designs, such as prospective ones, to obtain more accurate and representative results in the future.

In this study, the lack of a significant association between NLR and PLR with PFS over three years of follow-up may be due to several other factors and subject characteristics that need to be considered. First, most patients in this study were in good condition and underwent complete adjuvant therapy. This condition may result in a smaller variation in the response to systemic inflammation, thus reducing the ability of NLR and PLR to predict PFS. Overall, the results of this study indicate that although NLR and PLR have potential as biomarkers of systemic inflammation that may influence PFS, factors such as population homogeneity, retrospective study design, and the influence of non-malignant conditions need to be considered in interpreting the results. Therefore, further research is needed to confirm the role of NLR and PLR in predicting PFS in colorectal cancer patients.

Conclusion

Colorectal carcinoma involves multiple tumorigenic pathways, including HIF-1α expression and some inflammation markers such as NLR and PLR values. This analysis provides information that can be critical to appropriate patient treatment and prognosis assessment, including progression-free survival, particularly in locally advanced stages. Although this study found no association among HIF-1α expression, NLR values, and PLR values with three-year PFS in locally advanced CRC due to several limitations, further development of this research will certainly lead to improved outcomes.

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Additional information

Ethical statement

- The authors declared that no clinical trials were used in the present study.
- The authors declared that no experiments on humans or human tissues were performed for the present study.
- All patients included in the study gave their informed consent before they were included in the study.
- This retrospective cohort study was conducted in accordance with the Declaration of Helsinki. The study received ethical approval from the Research Ethics Committee of the Faculty of Medicine, University of Indonesia.
- The authors declared that no experiments on animals were performed for the present study.
- The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

Conflict of interest

The authors have declared that no competing interests exist.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI. No AI tools were used in the preparation of this manuscript.

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Data availability

All of the data that support the findings of this study are available in the main text.