INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

PAGE 159
2024 March; 30 (2): 159-162
p-ISSN 0854-4263 e-ISSN 2477-4685
Available at www.indonesianjournalofclinicalpathology.org

Analysis of NLR, PLR, and Carcinoembryonic Antigen in Colorectal Cancer Patients

Budi Parabang[1], Tenri Esa[1], Uleng Bahrun[1,2]

[1] Department of Clinical Pathology, Faculty of Medicine, Hasanuddin University/Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia. E-mail: budiparabang@yahoo.com
[2] Hasanuddin University Hospital, Makassar, Indonesia

ABSTRACT

Colorectal cancer (CRC) is the second leading cause of cancer death worldwide. The development and prognosis of CRC are affected by the tumor's appearance and the host's inflammatory response. A combination of several parameters, including the Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR), has been used as a cancer prognostic marker. Research needs to be performed to analyze its role in CRC. This study aimed to determine the differences in the NLR, PLR, and CEA values with the severity and site of CRC. Medical record data were collected from 246 CRC patients from January 2021 to June 2022 at Dr. Wahidin Sudirohusodo Hospital were used and grouped by severity (metastatic and non-metastatic) and site (left colon, right colon, rectum). This study collected the data on NLR, PLR, and CEA levels. The Mann-Whitney, Spearman Rho, and Kruskal-Wallis tests were used for statistical analysis by the research objectives (significant if $p<0.05$). There were differences in median PLR (194.47 vs. 201.18; $p=0.045$) and CEA (3.3 ng/mL vs. 11.95 ng/mL; $p<0.001$) between the metastatic and non-metastatic groups, whereas there was no significant difference of median NLR between the two groups (2.77 vs. 2.79; $p=0.438$). No correlation was found between the NLR, PLR, and CEA level values with the location of CRC (p-values 0.978, 0.511, and 0.419, respectively). PLR and CEA values were higher in metastatic CRC than in non-metastatic CRC, while NLR value was not significantly different. There was no correlation between the NLR, PLR, and CEA level values with the CRC site.

Keywords: Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, carcinoembryonic antigen, colorectal cancer

INTRODUCTION

Colorectal cancer (CRC) is a malignant condition that arises from the abnormal growth of cells originating from the large intestine and/or rectum. The incidence of colorectal cancer in Indonesia is ranked fourth with an incidence rate of 12.1 per 100,000 and ranked fifth as a cause of death after breast, cervical, lung, and liver cancer.[1–3]

The American Joint Committee for Cancer Executives (AJCC) classifies colorectal cancer into four stages such as Stages I, II (A, B, and C), III (A, B, and C), and IV (A and B). The higher stage generally has a lower survival rate. Early detection at an earlier stage of colorectal cancer is essential because it can be a prognostic factor in determining the survival rate of colorectal cancer patients.[1,4,5]

Increasing evidence suggests that cancer development and prognosis are influenced not only by tumor features but also by the inflammatory response of the host. The inflammatory response involves neutrophils, lymphocytes, monocytes, platelets, and acute-phase proteins such as albumin. A combination of several parameters, including Lymphocyte-Monocyte Ratio (LMR), Neutrophil-Lymphocyte Ratio (NLR), and Platelet-Lymphocyte Ratio (PLR), has been used in cancer prognosis, including colorectal cancer. There is increasing interest in CRC prognostics using clinical, inflammatory, and molecular biomarkers.[2,6–9]

Carcinoembryonic antigen (CEA), a serum glycoprotein secreted by tumors located in hollow organs, is the most commonly used biomarker in laboratory tests for screening, diagnosis, prognostics, and monitoring treatment and recurrence in patients with colorectal cancer. Increased CEA levels are reported in 72.4% of colorectal cancer patients. Toriyama *et al.* found that elevated CEA was a predictor of poor survival rates in colorectal cancer patients treated with neoadjuvant radiotherapy and chemotherapy. Other studies found that blood CEA levels were an independent predictive biomarker in patients with colorectal cancer.[1,9,10]

In their study, Agusrly *et al.* showed a significant relationship between increasing serum CEA levels

and increasing stages of colorectal cancer. Xia *et al.*, in their research, stated that patients with high NLR and PLR showed a 3-year Overall Survival (OS) rate that was much worse than patients with low NLR and PLR. Patients with high NLR and PLR also have a 3-year Disease Free Survival (DFS) rate much lower than those with low NLR and PLR. In line with these results, a study by Sheng *et al.* on 330 colorectal cancer patients stated that high NLR, PLR, and CEA had worse OS. The site of cancer in the colon and rectum to determine the prognosis of CRC remains debatable. Research by Salem *et al.* states that cancer located in the right colon has a worse prognosis compared to cancer located in the left colon and rectum due to differences in genetic mutations in the three tumor locations. In addition, the tumor of the right colon is usually large, has poor histopathological differentiation, and frequently metastasizes to other organs.[11] With this background, authors were interested in further analyzing the correlation between NLR, PLR, and tumor marker CEA with the severity and site of colorectal cancer through a retrospective study.[1,8,12,13]

METHODS

This research was a retrospective study using a cross-sectional method. It used secondary data from medical records of patients diagnosed with colorectal cancer by clinicians at KSM Surgery Dr. Wahidin Sudirohusodo Hospital, Makassar, from January 2021 to June 2022. The research sample was an accessible population that met the inclusion criteria of age >18. Patients without routine blood results, CEA, and histopathology data were excluded from this study.

Variables used in this study were age, gender, severity (metastatic and non-metastatic), site of cancer (left colon, right colon, and rectum), CEA levels, NLR, and PLR values based on blood cell count results using Sysmex XN-1000 hematology analyzer (flow cytometry method). The samples were then analyzed statistically using SPSS version 25. The Kolmogorov-Smirnov test was used to assess the normality of data, whereas Mann-Whitney, Spearman Rho, and Kruskal-Wallis tests were used for further analysis. Test results with p-values <0.05 were reported as significant.

Approval for ethical permission was obtained from the Health Research Ethics Commission (KEPK) Faculty of Medicine, Hasanuddin University/ Hasanuddin University Hospital (RSUH)/Dr. Central General Hospital. Wahidin Sudirohusodo with number 439/UN4.6.4.5.31/PP36/2022.

RESULTS AND DISCUSSIONS

The research results showed that from a total of 246 subjects, there were more females (51.2%), with an age range of 23–81 years. The most common site of colorectal cancer was the rectum (48%), with the highest level of severity, such as non-metastatic (58.5%) (Table 1).

Table 1. Characteristics of research subjects

Criteria	n (%)	Mean±SD
Gender		
Male	120 (48.8)	
Female	126 (51.2)	
Age (years)		53.6±12.5
Site of cancer		
Rectum	120 (48.8)	
Left colon	102 (41.5)	
Right colon	24 (9.8)	
Severity		
Non-metastatic	144 (58.5)	
Metastatic	102 (41.5)	
NLR		3.53±3.4
PLR		216.25±144.3
CEA (ng/mL)		47.19±74.6

Based on the data normality test using Kolmogorov-Smirnov, it was found that continuous data were not normally distributed; therefore, Mann-Whitney, Kruskal-Wallis, and Spearman Rho statistical analysis tests were used. Based on the Kruskal-Wallis difference test (data not normally distributed), it was found that there were no significant differences in NLR, PLR, and CEA levels among three different sites of colorectal cancer with a p-value of 0.532; 0.058 and 0.568 (p > 0.05), respectively. Based on the Spearman rho correlation test (data were not normally distributed), it was found that there was no significant correlation between NLR, PLR, and CEA levels with the location of colorectal cancer with a p-value of 0.978; 0.511 and 0.419, respectively (p > 0.05) (Table 2).

Based on the Mann-Whitney difference test (data were not normally distributed), it was found that there was no significant difference in the NLR value between non-metastatic and metastatic with a p-value of 0.438 (p > 0.05). However, there was a significant difference in the PLR and CEA levels with p-values of 0.045 and <0.001, respectively (p <0.05) (Table 3).

Table 2. Difference and correlation in NLR, PLR, and CEA with site of colorectal cancer

Variable	Site of Cancer			p	r
	Rectum	Left Colon	Right Colon		
NLR	2.42 (0.61-14.3)	3.07 (0.83–20.35)	3.27 (1.26-6.40)	0.532*	-
				0.978**	0.002
PLR	198.65 (54.95-662.16)	232.72 (86.27-557.14)	225.42 (119.1-428.2)	0.058*	
				0.511**	0.042
CEA (ng/mL)	3.02 (0.44-201)	8.65 (0.64-201)	3.63 (0.56-240.02)	0.568*	-
				0.419**	0.052

*Kruskal-Wallis test **Spearman Rho test

Table 3. Difference in NLR, PLR, and CEA between non-metastatic and metastatic colorectal cancer

Variable	Non-Metastatic	Metastatic	p
NLR	2.77 (0.61-14.3)	2.79 (0.79–34)	0.438*
PLR	194.47 (54.95–1443.75)	201.18 (63.81–801.92)	0.045*
CEA (ng/mL)	3.3 (0.44–201)	11.95 (0.64–201)	< 0.001*

* Mann-Whitney test

The most common site of colorectal cancer found in this study was the rectum (48.8%), in line with a study by Song *et al.*, which also reported that the rectum was the most common site of cancer (57.6%) compared to the colon. The rectal mucosa has at least four times higher risk of malignant transformation than the colonic mucosa, presumably depending on different susceptibility to carcinogens or carcinogenic processes between the colon and rectum. The median age in this study was 55 years (23-81 years), contrary to the findings of Song *et al.*, which reported a median age of 62 years (range 13-86).[6,14]

It was also discovered in this study that there was no difference or correlation between the NLR, PLR, CEA levels, and the site of colorectal cancer ($p>0.05$). This study was in line with a study by Liu *et al.*, which reported no significant differences in NLR and PLR values observed in age, gender, tumor site, and differentiation level. In addition to NLR and PLR variables, d-NLR was also analyzed. TNM stage criteria were used to classify the severity of subjects in a study by Liu *et al.*, indicating a slight difference from this study. Differences between right- and left-sided colon tumors in terms of clinical symptoms, incidence, molecular pathways involved, oncological outcome, as well as embryological origin have been reported. A study by Mazaki *et al.* evaluating the prognostic value of NLR based on tumor side found that the 5-year OS and 5-year Relapse-Free Survival (RFS) rates were significantly lower in patients with left-sided colon cancer who had a higher NLR.[15,16]

There was a significant difference between PLR, CEA levels, and the severity of colorectal cancer. PLR and CEA levels were higher in the metastatic group compared to the non-metastatic group but not in the NLR value. This study differed from a study by Woo *et al.*, which proved that NLR was related to the depth of CRC infiltration, Tumor Node Metastasis (TNM) stage, and clinical manifestation. Neutrophils release prostaglandin E2 (PGE2) to enhance inflammation and create a tumor microenvironment, which can promote colon tumorigenesis, suppress natural killer cell activity, and increase tumor cell exudation through the secretion of IL-1β and Matrix Metalloproteinase (MMP). In addition, neutrophils can release extracellular traps to promote liver metastasis in CRC by trapping tumor cells. In contrast, lymphocytes produce cytokines that inhibit cancer cell proliferation and metastatic spread and trigger cytotoxic cell death. Increased neutrophils and decreased lymphocytes in circulation have been reported in the process of carcinogenesis.[3,8,9,17]

The PLR can indicate the balance between the anti-cancer activity of platelets and the anti-tumor immunity of lymphocytes. High platelet counts can promote cancer progression by increasing angiogenesis through the production of Vascular Endothelial Growth Factor (VEGF); its overexpression has been associated with disease progression and metastasis in patients with colorectal cancer. Platelets can also secrete cellular growth factors such as platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor-beta, and platelet factor 4, stimulating angiogenesis and tumor growth. Lymphocytes play an important role in cytotoxic cell death and inhibition of tumor cell proliferation and metastatic spread.[8,9]

Recent studies reported that CEA correlated with

the TNM stage in CRC and showed better potential to estimate metastasis and recurrence. The mechanism of CEA elevation in advanced colorectal cancer is still not fully understood. However, according to previous studies, CEA can activate Kupffer cells in the liver to induce cytokine overexpression and change the liver microenvironment to allow circulating colorectal tumor cells to survive in the liver. According to research by Li *et al*., combining PLR with CEA shows a higher diagnostic value than using PLR or CEA alone. Therefore, this combination can also be a simple but effective marker to identify tumor development in colorectal cancer surveillance.[1,4,16]

The use of secondary data and single-centered retrospective design in this research, leading to limited information, remained the limitation of this study.

CONCLUSIONS AND SUGGESTIONS

There was no correlation between NLR, PLR, and CEA levels and the site of CRC. PLR and CEA values were higher in metastatic CRC than in non-metastatic CRC, whereas the NLR value was not significantly different.

It was recommended that a further study be performed using cancer classification according to stage of disease (I, II, III, and IV) to analyze PLR, NLR, and CEA levels to obtain more specific prognosis results. Confounding factors, such as other comorbid diseases, must be excluded in future research to avoid interfering with research results.

REFERENCES

1. Agusrly C, Sungkar T, Siregar GA. Relationship between staging and carcinoembryonic antigen serum levels in colorectal cancer patients. J Endocrinol Trop Med Infect Dis, 2020; 2(3): 118-23.
2. Zhang F, Qiao S. Research progress on the relationship between inflammation and colorectal cancer. Ann Gastroenterol Surg, 2022; 6(2): 204-11.
3. Chan JCY, Chan DL, Diakos CI, Engel A, Pavlakis N, *et al.* The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. Ann Surg, 2017; 265(3): 539-46.
4. Li X, Guo D, Chu L, Huang Y, Zhang F, *et al.* Potential diagnostic value of combining inflammatory cell ratios with carcinoembryonic antigen for colorectal cancer. Cancer Manag Res, 2019; 11: 9631-40.
5. Yamamoto T, Kawada K, Obama K. Inflammation-related biomarkers for the prediction of prognosis in colorectal cancer patients. Int J Mol Sci, 2021; 22(15): 8002.
6. Song Y, Yang Y, Gao P, Chen X, Yu D, *et al.* The preoperative neutrophil to lymphocyte ratio is a superior indicator of prognosis compared with other inflammatory biomarkers in resectable colorectal cancer. BMC Cancer, 2017; 17(1): 744.
7. Tsai P-L, Su W-J, Leung W-H, Lai C-T, Liu C-K. Neutrophil-lymphocyte ratio and CEA level as prognostic and predictive factors in colorectal cancer: A systematic review and meta-analysis. J Cancer Res Ther, 2016; 12(2): 582-9.
8. Ming-Sheng F, Mei-Ling D, Xun-Quan C, Yuan-Xin H, Wei-Jie Z, Qin-Cong P. Preoperative neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and cea as the potential prognostic biomarkers for colorectal cancer. Nakamura M, editor. Can J Gastroenterol Hepatol, 2022; 2022: 1-9.
9. Stojkovic Lalosevic M, Pavlovic Markovic A, Stankovic S, Stojkovic M, Dimitrijevic I, *et al.* Combined diagnostic efficacy of Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Mean Platelet Volume (MPV) as biomarkers of systemic inflammation in the diagnosis of colorectal cancer. Dis Markers, 2019; 2019: 1-7.
10. Temur AA, Rashid FA. Irisin and carcinoembryonic antigen (CEA) as potential diagnostic biomarkers in gastric and colorectal cancers. Reports Biochem Mol Biol, 2021; 10(3): 488-94.
11. Salem ME, Weinberg BA, Xiu J, El-Deiry WS, Hwang JJ, *et al.* Comparative molecular analyses of left-sided colon, right-sided colon, and rectal cancers. Oncotarget, 2017; 8(49): 86356-68.
12. Bhattacharjee D, Quirke P. What is the role of the neutrophil: lymphocyte ratio in colorectal cancer?. Turkish J Color Dis, 2021; 31(1): 1-12.
13. Xia L, Li W, Zhai J, Yan C, Chen J, Yang H. Significance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and prognostic nutritional index for predicting clinical outcomes in T1-2 rectal cancer. BMC Cancer, 2020; 20(1): 208.
14. Paschke S, Jafarov S, Staib L, Kreuser E-D, Maulbecker-Armstrong C, *et al.* Are colon and rectal cancer two different tumor entities? A proposal to abandon the term colorectal cancer. Int J Mol Sci, 2018; 19(9): 2577.
15. Mazaki J, Katsumata K, Kasahara K, Tago T, Wada T, *et al.* Neutrophil-to-lymphocyte ratio is a prognostic factor for colon cancer: A propensity score analysis. BMC Cancer [Internet], 2020; 20(1): 922.
16. Liu X-C, Dai Y-L, Huang F, Zhong Z-J, Liu X-F. Diagnostic value of carcinoembryonic antigen combined with multi-inflammatory cell ratios in colorectal cancer. Belardinilli F, editor. Dis Markers, 2022; 2022: 1-6.
17. Choi WJ, Cleghorn MC, Jiang H, Jackson TD, Okrainec A, Quereshy FA. Preoperative neutrophil-to-lymphocyte ratio is a better prognostic serum biomarker than platelet-to-lymphocyte ratio in patients undergoing resection for non-metastatic colorectal cancer. Ann Surg Oncol, 2015; 22(S3): 603-13.