ORIGINAL ARTICLE
Indonesia Surgical Journal (*INASJ*) 2024, Volume 1, Number 2 : 52-55

Platelet Indices as Potential Biomarkers for Detection and Monitoring of Colorectal Cancer after Resection

Ronald Erasio Lusikooy[1,2], Arham Arsyad[1*], Erwin Syarifuddin[1]

[1]Division of Digestive, Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia;
[2]Division of Digestive, Department of Surgery, Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia.

*Corresponding author:
Arham Arsyad;
Division of Digestive, Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia;
arham.arsyad@gmail.com

Received: 2024-08-22
Accepted: 2024-10-17
Published: 2024-11-23

ABSTRACT

Background: Colorectal cancer (CRC) is one of the most prevalent cancers worldwide. It is the second most common cause of cancer death in Western nations. In Europe, colorectal cancer is the third leading cause of cancer-related mortality. The current study set out to clarify the effectiveness of the platelet and hemoglobin (Hb) indices, including platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), and the platelet/lymphocyte ratio (PLR), as resources for the preoperative diagnosis of CRC and their value in CRC follow-up.
Methods: A total of 583 CRC patients, as diagnosed by colonoscopy, and 413 healthy participants were included in the study. To compare before and postoperative data, medical records were consulted including Hb, PLT, MPV, PDW, PCT and PLR. As the result MPV and PLR were significantly higher in CRC patients preoperatively, compared with healthy participants. Receiver-operating characteristic curve analysis suggested.
Results: The cut-off values for MPV and PLR are 8.46 fl and 142, respectively (AUC: 0.735, sensitivity: 53%, specificity: 74%, and AUC: 0.842, 71%, and 89%, respectively). Subgroup analysis revealed that nonanemic CRC patients had considerably greater levels of PC and MPV than the control group.
Conclusion: This finding has important theoretical and practical implications for the early diagnosis of CRC. Following surgical tumor excision, PLT, MPV, and PLR significantly decreased. Due to our findings, MPV and PLR could be utilized as simply accessed alternative biomarkers for CRC in both postoperative follow-up and general population screening.

Keywords: Colorectal cancer, platelet, hemoglobin, biomarkers.
Cite This Article: Lusikooy, R.E., Arsyad, A., Syarifuddin, E. 2024. Platelet Indices as Potential Biomarkers for Detection and Monitoring of Colorectal Cancer after Resection. *Indonesia Surgical Journal* 1(2): 52-55

INTRODUCTION

With 10% of all cases, colorectal cancer (CRC) is the third most frequent kind of cancer globally. Both the incidence and death rate from colorectal cancer have risen recently (Ferlay et al., 2010). According to 2011 – 2013 American Cancer Society Cancer Facts and Figures, About 5% of people will develop colon cancer throughout their lifetime. Additionally, 28% of cases start in the rectum and 70% of cases start in the colon. It is possible to avoid CRC-related mortality by using easily accessible screening. Regretfully, only 39% of malignancies receive an early diagnosis. The prognosis is particularly bad when the illness is at an advanced stage and there is evidence of metastatic involvement of lymph nodes or other organs. Comparably, 10% of patients with known distant metastases survive for five years.).

For years, CRC may not exhibit any clinical symptoms. When they do occur, symptoms frequently appear gradually over months or even years. The three primary signs of CRC are altered defecation habits, stomach pain, and rectal bleeding. For the majority of CRC patients, total excision of all malignant tissue is the preferred course of treatment because it is currently the only one that has a realistic possibility of success. Finding a potential curable relapse tumor or secondary primary tumor is one of the main objectives after curative excision of colorectal cancer. Numerous tumor factors, such as carcinoembryonic antigen (CEA), α-fetoprotein, carbohydrate antigen 19-9 (CA 19-9) and tumor specific growth factor, have been employed in the diagnosis and follow-up of colorectal cancer (CRC)[1,2] Their clinical utility is still debatable, though.

Complete blood count (CBC) analyzers commonly measure parameters such as lymphocyte count, mean platelet volume (MPV) and platelet count. By dividing the total number of platelets by the total number of lymphocytes, platelet/lymphocyte ratio (PLR). It has been demonstrated that in operable colorectal cancers, a complex interplay between the tumor's local features and the host inflammatory response may indicate cancer recurrence and mortality at an earlier age[1,3]. PLR are biomarkers of the systemic inflammatory response, and numerous studies have shown a correlation between elevated levels and the advancement of colorectal cancer (CRC)[2,3]. The average thrombocyte volume, or MPV, is a measure of the stimulation and rate of platelet formation. A number of studies have reported an association between increased MPV and the existence of various solid tumors, including gastric cancer, lung cancer, hepatocellular carcinoma, endometrial

cancer, and pancreatic cancer.[2,3,4] However, investigation has not yet been done on the predictive value or efficacy of hemoglobin platelet indicators, such as PLT, PDW, PCT, MPV, and PLR, in the diagnosis and follow-up of colorectal cancer.

The present investigation has set out to evaluate the efficacy of platelet indices as a diagnostic tool for colorectal cancer (CRC) in preoperative diagnosis and follow-up, as well as to look into possible associations between these indicators and disease stage.

PATIENTS AND METHODS

All of the CRC patients' medical records at Wahidin sudirohusodo Hospital were reviewed. The period of time window that was examined was January 2012–December 2022. We retrospectively analyzed the clinical and demographic data from the records of CRC patients who underwent colorectal resection after receiving a colonoscopy diagnosis for a variety of conditions. Exclusions from the study were patients with coexisting hematological illnesses, renal disease, chronic infections, cerebrovascular or arterial coronary disease, and other malignancies. Individuals with postoperative infections, including wound infections, and those who had received chemotherapy or radiation therapy prior to surgery were also not included. The study only included participants whose adenocarcinomas were confirmed histologically. In following the recommendations of the American Joint Committee on Cancer, the staging of colorectal cancer was carried out based on the tumor–nodes metastases (TNM) classification[5,6]. The study comprised 413 healthy subjects who were determined to be normal by colonoscopy and 583 CRC patients overall. Hemoglobin (Hb) levels, PLT, PDW, PCT, MPV, and PLR were among the preoperative and postoperative data that was recorded. Hb levels of less than 13.0 g/dl in men and less than 12.0 g/dl in women were used to determine anemia. Before the procedure, a colonoscopy was used to obtain preoperative data. After the procedure, two weeks later, postoperative data were collected. PLR were computed straight from the CBC. Using the Siemens Healthcare Diagnostic Item ADVIA 2120i (Siemens Healthcare, Malvern, England), CBCs of blood treated with ethylenediamine tetraacetic acid were measured.

Statistical analysis

For statistical analysis, SPSS software (SPSS 22.0, Chicago, Illinois, USA) was utilized. The data was shown as mean±SD. Preoperative CRC patient and control parameters were compared using an independent t-test. The categorical variables were compared using the $\chi 2$-test. The preoperative and postoperative variables were compared using the paired sample test. An examination of the receiver-operating characteristic (ROC) curve was performed to determine the best PLR and MPV cutoff values. More than a P-value of 0.05 was regarded as statistically significant.

RESULTS

In all, 583 CRC patients and 413 healthy individuals from the control group were included in the study. Table 1 displays the patient and control groups' demographics, CBCs, tumor location, grade differentiation, and TNM staging. Age and sex differences between the groups were not statistically significant. When comparing preoperative CRC patients to healthy participants, MPV and PLR were considerably greater in patients with CRC regardless of TNM stage (9.72 vs. 7.23, P < 0.001; 231.0 vs. 119.6, P < 0.001; 9.44 vs. 7.92 fl, P < 0.001; Tables 1 and 2). According to ROC analysis, the cutoff values for MPV (AUC: 0.735, sensitivity: 53%, specificity: 74%;) and PLR (AUC: 0.842, sensitivity: 71%, specificity: 89%) were respectively 142 and 8.46 fl. There were 227 nonanemic patients in the patient group. A review of individuals demonstrated that nonanemic CRC patients had considerably larger MPV and PLR when compared to healthy individuals (9.25 vs. 7.23, P < 0.001; 172.0 vs. 111.6, P < 0.001; Table 3). MPV and PLR significantly decreased with surgical tumor removal (231.0 vs. 121.3, P < 0.001; 9.72 vs. 7.52 fl, P < 0.001; Table 4). In accordance with TNM stage, we looked at PLR and MPV in more detail. A statistically significant distinction was observed between the PLR, MPV, and TNM.

DISCUSSION

Thrombocytosis has been found to be related to prognosis in individuals with a range of malignancies in recent decades. Increased platelet counts have been shown in numerous studies to facilitate the growth, invasion, and metastasis of tumors.[6,7] While the precise nature of the association between thrombocytosis and cancer remains unclear, there is enough data at now to suggest a plausible mechanism. Initially, platelets may mix with cancer cells in the bloodstream, and a venous thrombus may form more quickly in the presence of a larger concentration of platelets. Furthermore, there would be a little increase in the formation of metastatic emboli, which would facilitate the implantation of cancer cells. Second, by protecting circulating cancer cells from the lethal effects of natural killer cells, platelets serve as "cloaks" for these cells.[8,9,10]

In addition to their physiological function in hemostasis, platelets also have a role in inflammation, atherosclerosis, and cancer metastasis through the release of chemokines and cytokines as well as the expression of several adhesion receptors[11]. Many bioactive mediators that contribute to platelet activation are secreted by tumor cells, such as IL-6, ADP and cysteine proteinases[12]. The synthesis of thrombin, which is increased by tissue factor and elevated in the tumor microenvironment's oxidative stress, can activate platelets. Numerous tumor development and proangiogenic factors, such as platelet-derived growth factor, transforming growth factor β, epidermal growth factor, vascular endothelial growth factor, and angiopoietin, are secreted by activated platelets and are involved in the carcinogenesis.[6] Because they are covered in blood, circulating tumor cells evade immune monitoring and encourage the development of metastases.[13]

It functions as a measurement for platelet volume in relation to MPV. A subpopulation of adolescents, metabolically and enzymatically more active platelets participating in the homeostasis process is shown by increased MPV (Mangalpally et al., 2010). Our hypothesis is that greater MPV in a group of patients who have just received

Table 1. Preoperative demographic characteristics of patients and controls

Variables	CRC patients n = 583	Control group n = 413	*P*-value
Age (mean ± SD)	64.5 ± 13.2	59.5 ± 10.2	0.62
Sex (Male/female)	313/270	213/200	0.73
Tumor location (n/%)			
Right colon	117 (30)		
Left colon	221 (38)		
Rectum	245 (42)		
TNM staging (n/%)			
I	24 (4)		
II	128 (22)		
III	251 (43)		
IV	180 (31)		
Grade differentiation			
Well	192 (33)		
Moderate	257 (44)		
Poor	134 (23)		
Anemia (n/%)			
Yes	356 (61)		
No	227 (39)		
Hb (mean, SD)	11.3 ± 2.8	14.3 ± 1.3	0.036*
PLT (mean, SD)	291.5 ± 110.2	241.7 ± 102.3	0.011*
PDW (mean, SD)	16.3 ± 7.2	13.7 ± 9.1	0.232
PCT (mean, SD)	0.35 ± 0.08	0.22 ± 0.09	0.153
MPV (mean, SD)	9.72 ± 0.87	7.23 ± 0.42	0.0001*
PLR (mean ± SD)	231 ± 152.1	119.6 ± 12.9	0.002*

Table 2. Preoperative patient MPV and PLR levels and control based on Staging TNM

	MPV (fl) (mean ± SD)	PLR (mean ± SD)	*P*-value
TNM staging (n/%)			
I (n = 24)	8.91 ± 0.43	239 ± 142.3	0.001*
II (n = 128)	9.12 ± 0.35	247 ± 132.6	0.001*
III (n = 251)	9.50 ± 0.24	269 ± 112.3	0.001*
IV (n= 180)	9.44 ± 0.31	258 ±108.2	0.001*
Control group			
n = 413	7.92 ± 0.52	119 ± 101.7	

Table 3. PLT, MPV, and PLR levels of nonanemic preoperative patients are compared with control groups

Variable	CRC (nonanemic)	Control	*P*-value
PLT (Mean + SD)	312.6 ± 121.4	241.7 ± 102.3	0.033*
MPV (Mean + SD)	9.25 ± 0.53	7.23 ± 0.42	0.001*
PLR (Mean + SD)	172 ± 167.1	111.6 ± 12.9	0.001*

Table 4. Comparison of CRC patients' preoperative and postoperative Hb, PLT, MPV, and PLR

Variable	Preoperative	Postoperative	*P*-value
Hb (mean ± SD)	11.3 ± 2.8	11.8 ± 2.6	0.075
PLT (Mean + SD)	291.5 ± 110.2	232.1 ± 172.3	0.003*
MPV (Mean + SD)	9.72 ± 0.87	7.52 ± 0.54	0.001*
PLR (Mean + SD)	231 ± 152.1	121.3 ± 16.9	0.001*

a colorectal cancer (CRC) diagnosis may indicate persistent colonic inflammation and be associated with increased cytokine levels, especially IL-6. Furthermore, our findings showed a significant decrease in MPV following a CRC operation, indicating that surgically removing colon cancer efficiently reduces the tumor burden and the inflammatory process associated with the disease. Therefore, we propose that MPV, independent of TNM staging, may be utilized to track CRC recurrence following surgical resection.[11,13,14]

Inflammation is a critical and vital factor in the initiation and spread of cancer (Balkwill and Coussens, 2004). Angiogenesis, the suppression of apoptosis, and a growth in the number of tumor cells proliferate while the inflammatory process inside the tumor continues. The prognosis of colorectal cancer (CRC) has been linked to a number of systemic inflammation markers, such as Glasgow Prognostic Score, NLR, PLR, cytokines and C-reactive protein.[10,13] Therefore, it appears that colorectal cancer (CRC) carcinogenesis is triggered by inflammation.

PLR is a representative systemic inflammatory indicator. A higher preoperative NLR than 140 has been linked to a worse prognosis in cases of ovarian, gastric, and non-small cell lung cancer, according to research.[11,13,15] Additionally, it was demonstrated that increased PLR was a distinct poor prognostic factor for CRC.[10] Leukocytes and platelets are necessary for the host's systemic inflammatory response. Our research unequivocally shows that a tumor-induced nonspecific systemic inflammatory response is responsible for an increase in circulating platelets and a higher PLR.

One characteristic of CRC that has been identified is iron-deficiency anemia. According to Fjørtoft et al. (2013), it is found in 57% of CRC patients and is especially predictive of cecal malignancies. The majority of physicians agreed that in order to rule out colonic cancer, individuals with iron deficiency anemia who don't know why should think about getting a colonoscopy. Even though iron-deficiency anemia is frequently linked to colorectal cancer (CRC), the condition is not always excluded in its absence. As a result, those without anemia may

experience a delay in receiving a CRC diagnosis. Anemia was not present in 227 of the CRC patients in our research when they were diagnosed. PLR and MPV significantly differed between nonanemic CRC patients and controls, which may have clinical implications for the early detection of CRC.[15,16,17]

Our study has certain limitations. First off, the data for this investigation were acquired retrospectively and the design was single-center. Secondly, it's possible that the elevated PLR and MPV in our cohort of recently diagnosed CRC patients represent an unspecific inflammatory reaction brought on by the disease. Therefore, a rise in these parameters may result from any inflammatory or malignant activity. In actuality, these indicators could not screen for asymptomatic individuals very well if they are utilized alone. In order to verify the diagnostic value of PLR and MPV, prospective studies involving a greater number of asymptomatic individuals are required to compare their performance with that of other diagnostic and monitoring assays.

CONCLUSIONS

Taking consideration of the obvious statistical significance, we may initially assume that increased PLT, MPV and PLR may be closely associated with a worse prognosis in patients with colorectal cancer, despite the many variations and influencing factors. For the purpose of early identification of CRC patients with a poorer prognosis, elevated PLT, MPV and PLR may be utilized as three prognostic indicators. They are could be a useful diagnostic biomarker for colorectal cancer because readily accessible and affordable as well.

REFERENCES

1. Mezouar S, Frere C, Darbousset R, Mege D, Crescence L, Dignat-George F, et al. Role of platelets in cancer and cancer-associated thrombosis: experimental and clinical evidences. Thrombosis Res 2016;139:65–76.
2. Liu Y, Jiang P, Capkova K, Xue D, Ye L, Sinha SC, et al. Tissue factoractivated coagulation cascade in the tumor microenvironment is critical for tumor progression and an effective target for therapy. Cancer Res 2011;71: 6492–502.
3. Timp, J.F.; Braekkan, S.K.; Versteeg, H.H.; Cannegieter, S.C. Epidemiology of cancer-associated venous thrombosis. *Blood* **2013**, *122*, 1712–1723. [CrossRef] [PubMed]
4. Sevestre, M.A.; Soudet, S. Epidemiology and risk factors for cancer-associated thrombosis. *J. Med. Vasc.* **2020**, *45*, 6S3–6S7. [CrossRef]
5. M. Kreidieh, D. Mukherji, S. Temraz, and A. Shamseddine, "Expanding the scope of immunotherapy in colorectal cancer: current clinical approaches and future directions," BioMed Research International, vol. 2020, Article ID 9037217, 24 pages, 2020.
6. R. Ward, A. Meagher, I. Tomlinson et al., "Microsatellite instability and the clinicopathological features of sporadic colorectal cancer," Gut, vol. 48, no. 6, pp. 821–829, 2001.
7. Z. Gatalica, S. Vranic, J. Xiu, J. Swensen, and S. Reddy, "High microsatellite instability (MSI-H) colorectal carcinoma: a brief review of predictive biomarkers in the era of personalized medicine," Familial Cancer, vol. 15, no. 3, pp. 405–412, 2016.
8. Yang Y, Zhu H, Li Q. Partial response of donafenib as the third-line therapy in metastatic colon cancer: a case report. Medicine (Baltimore). 2021;100(37):e27204. doi: 10.1097/md.0000000000027204.
9. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, et al. Colon cancer, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19(3):329-59. doi: 10.6004/jnccn.2021.0012.
10. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91. doi: 10.1136/ gutjnl-2015-310912.
11. Kim IH, Lee JE, Yang JH, et al. Clinical significance of changes in systemic inflammatory markers and carcinoembryonic antigen levels in predicting metastatic colorectal cancer prognosis and chemotherapy response. Asia Pac J Clin Oncol. 2018,14(3):239-46. 2
12. Olsen RS, Nijm J, Andersson RE, et al. Circulating inflammatory factors associated with worse long-term prognosis in colorectal cancer. World J Gastroenterol. 2017,23(34):6212-9.
13. Passardi A, Scarpi E, Cavanna L, et al. Inflammatory indexes as predictors of prognosis and bevacizumab efficacy in patients with metastatic colorectal cancer. Oncotarget. 2016,7(22):33210-9.
14. Masson-Lecomte A, Rava M, Real FX, et al. Inflammatory biomarkers and bladder cancer prognosis: A systematic review. EUR UROL. 2014; 66:1078-1091.
15. Dolan RD, McSorley ST, Horgan PG, et al. The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: Systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017; 116:134-146.
16. Templeton AJ, McNamara MG, Seruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: A systematic review and meta-analysis. J Natl Cancer Inst. 2014;106: u124. [30] Mancuso ME, Santagostino E. Platelets: Much more than bricks in a breached wall. Br J Haematol. 2017; 178:209-219.
17. Thomas MR, Storey RF. The role of platelets in inflammation. Thromb Haemost. 2015; 114:449-458.