



PRETREATMENT PLATELET LYMPHOCYTE RATIO (PLR) AND NEUTROPHIL LYMPHOCYTE RATIO (NLR) AS PROGNOSTIC FACTORS OF STAGE III AND IV RECTAL CANCER PATIENTS IN H. ADAM MALIK MEDAN GENERAL HOSPITAL

Surgery

Uncok Ramses
Dody Simanjuntak

Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara, Medan

Adi Muradi Muhar*

Division of Digestive Surgery, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara, Medan *Corresponding Author

Aznan Lelo

Department of Pharmacology, Faculty of Medicine, Universitas Sumatera Utara, Medan

ABSTRACT

Introduction: Rectal cancer which included in colorectal cancer, is the third most common malignancy of all cancer and the fourth leading cause of death in all cancer patients in the world. Early detection of the lesions can decrease the morbidity and mortality. In the last few decades, pretreatment platelet and leukocyte count (including neutrophils and lymphocytes) has become the focus of the study in relation to the prognosis of various types of cancer.

Objective: To assess the role of pretreatment Platelet Lymphocyte Ratio (PLR) and Neutrophil Lymphocyte Ratio (NLR) as a prognostic factor in stage III and IV rectal cancer patients.

Methods: This was an observational analytic study with cross sectional and retrospective cohort design. The research sample was taken by consecutive sampling method based on registration data of rectal adenocarcinoma patients at H. Adam Malik Medan General Hospital from January 2011 until December 2013. Statistical analysis was did by SPSS Program Version 22.

Results: From a total of 55 patients, the mean age of the study subjects is 53.91 ± 1.72 years. The samples are 34 (61.8%) males and 21 (38.2%) females. Most cancer's lesions are found in 1/3 distal of the rectum (41.8%). Based on result of laboratory examination, mean of platelet count is 252.45 ± 77.83 , mean of lymphocyte count is 6.91 ± 21.21 , and mean of neutrophil count is 6.39 ± 3.44 . We determined a cut-off value of 2.2 for NLR and 130 for PLR in the whole group. From the Kaplan Meier test, overall survival in patients with low NLR is better than patients with high NLR (p value <0.001) and overall survival in patients with low PLR is also better than patients with high PLR (p value <0.001). While 5 years of disease free survival in patients with low NLR is better than patients with high NLR (p value = 0.018). Similarly, 5 years of disease free survival in patients with low PLR were compared with high PLR (p value = 0.035).

Conclusions: Our study found that high PLR and high NLR are the useful prognostic factors for predicting poor long-term outcomes in stage III and IV rectal cancer patients.

KEYWORDS

MLL - Morel-Lavallee Lesion

Introduction

Colorectal cancer in Indonesia is the third most common cancer diagnosed in both men and women after breast cancer and lung cancer (Globocan, 2012). Rectal cancer is also the third leading cause of death from all cases of mortality due to malignancy (Capple, 2005). In a previous study at RS H. Adam Malik it was found that rectum was the most common site of colorectal cancer.

Early detection in the early stages of the lesions can decrease the morbidity and mortality. Colonoscopy remains the gold standard for the early detection of rectal cancer. In addition, to assist the diagnosis requires the aid of non-invasive markers or markers to detect rectal cancer early. Recent studies explain the function and role of systemic inflammatory responses in increasing the chances of tumor metastasis and progression through apoptotic inhibition, promotion of angiogenesis and DNA damage (McMillan, 2009). Related to this, in the last few decades, platelet examination and arithmetic type of pre-therapy peripheral leukocytes (including neutrophils, lymphocytes and monocytes) became the focus of the study in relation to the prognosis of various types of cancer. Increased neutrophil lymphocyte ratio (NLR) has been shown to be associated with poor post-therapeutic outcomes in patients with gastrointestinal cancers (Walsh et al., 2005; Gomez et al., 2007; Yamanaka et al., 2007; Halazun et al., 2008; Halazun et al., 2009; Kishi et al., 2009; Bhatti et al., 2010). Several other studies have shown that platelet-lymphocyte platelet elevation (PLR) is associated with poor prognosis outcomes in oesophageal squamous cell carcinoma (Tanoglu et al. 2013, Feng et al., 2013, 2014), gastric cancer (Lee et al., 2013), liver cancer (Peng et al 2015).

The aim of the study was to assess the prognostic value of NLR and PLR as a predictor of prognosis in patients with stage III and IV rectal cancer.

Methods

This was an analytic observational study with cross sectional in pediatric retrospective cohort. The aim of this study is to know the role of Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio

(PLR) pretreatment as prognostic factor of stage III and IV rectal cancer patients in RSUP H. Adam Malik Medan. The sampling method was consecutive sampling based on registration data in Department of Surgery Division of Digestive Surgery of Haji Adam Malik General Hospital Medan from January 2011 to December 2013. The inclusion criteria of this study were patients who had examination with histopathology examination of well to poorly degree of differentiation, had complete data, information, tumor, examination result before tumor, tumor histopathology stage and tumor stage, and informed consent were distributed. Samples excluded when there were other malignancies, other chronic diseases, and have synchronous tumors or there are other gastroenteric inflammations. The data collected from the secondary data is by recording the status of medical record and special status in the Department of Surgery of RSUP H. Adam Malik Medan in 2011-2013, then recorded according to the variables in the reading. The data obtained are then presented descriptively in the form of narrative, proportion distribution tables, and statistical analysis of SPSS ver.20.

Result

Data used in this research is secondary data. Data were taken from patient's medical record with rectal cancer at RSUP H. Adam Malik Medan, which were 55 patients with the following characteristics:

Table 1. Patients Characteristic

Characteristic	Frequency (n)	Percentage (%)
Mean age (Mean \pm SD)	53,91 \pm 1,72	
Sex		
Male	34	61,8
Female	21	38,2
Tumor site		
1/3 proximal of rect	17	30,9
1/3 distal of rect	23	41,8
1/3 medial of rect	15	27,3
Mortality		
Alive	20	36,4
Dead	35	63,6
Stadium		
Stadium II	24	43,6
Stadium IV	31	56,4
Mean Platelet	252,45 \pm 77,83	
Mean Lympho	6,91 \pm 21,21	
Mean Neutro	6,39 \pm 3,44	
Mean NLR	2,87 \pm 2,05	
Cut off < 2.2	15	27,3
Cut off > 2.2	40	72,7

Based on the table above it was found that the mean age of the subjects was 53.91 ± 1.72 years. The table also shows that the number of rectal cancer patients was 34 (61.8%) male and 21 (38.2%) women. We found the most prevalent site of the tumor was in 1/3 lower of the rectum, 23 (41.8%) cases. Based on laboratory test result, mean platelet was $252,45 \pm 77,83$, mean lymphocyte was $6,91 \pm 21,21$, mean neutrophil was $6,39 \pm 3,44$, mean of NLR was $2,87 \pm 2,05$. The cut-off point $NLR > 2.2$ group accounted for 40 (72,7%) patient while cut-off point $NLR < 2.2$ group accounted for 15 (27,3%) patient. The mean PLR was $116,72 \pm 54,71$ with cut-off point $PLR > 130$ group were 35 (63,6%) patients and with PLR cut off point < 130 were 20 (36,4%) patients.

testing was analyzed by Kaplan Meier test and looked at the p value. Figure 1 and 2 show the Kaplan Meier Curve of 5 years overall survival. The overall survival in patients with low NLR was better than patients with high NLR ($p < 0.001$) and in patients with low PLR was also better than patients with high PLR ($p < 0.001$).

Figure 3 and 4 showed 5 years of disease free survival in patients with lower NLR better than patients with high NLR (pValue: 0.018). The same result for patients with low PLR compared to high PLR (pValue: 0.035).

Discussion

Rectal cancer is one of the most common malignant neoplasms in humans and is the second most common cancer (28%) in the colon after proximal colon cancer (42%) (Fazeli et Keramati, 2014). The American Cancer Society (ACS) estimates 43,030 new cases of rectal cancer will occur in 2018. In this study, we found the average age of patients with rectal cancer 53.91 ± 11.15 years. The incidence of colorectal cancer began to increase after the age of 35 and increased rapidly after the age of 50 years, the peak in the seventh decade. More than 90% of colon cancers occur after the age of 50 years (American Cancer Society, 2018). However, the rate of rectal cancer in younger people has increased. In those aged (40 to 54 years) incidence has increased 2.3% every year since the 1990s. Currently, adults born around 1990 have a fourfold risk of developing rectal cancer compared with those born around 1950 (Siegel et al, 2017). This study found the number of rectal cancer patients in men more than in women (61.8% and 38.2%, respectively). Colon and rectal cancer is the third most common cancer in women and men. According to the ACS survey, in 2018, 25,920 cases of rectal cancer are estimated to occur in men and 17,110 cases in women. This may be related to the habits of most men who smoke and consume alcohol, which are factors that may increase the risk of colorectal cancer (American Cancer Society, 2018). Rectal cancer is categorized by location as low (up to 5 cm), center (from > 5 to 10 cm) and high (from > 10 to 15 cm) (Jones et al, 2017). This study found that the most common site was in the lower third of the rectum. A study by Wijenayake et al in 2011 found that 60% of rectal cancers located in the distal rectum were between 0-6 cm from anal verge. For estimates of death, ACS combines colon and rectal cancer; about 50,630 deaths from colorectal cancer are estimated to occur in 2018 (American Cancer Society, 2018)

For estimates of death, about 50,630 deaths from colorectal cancer are estimated to occur in 2018 (American Cancer Society, 2018). In this study we used cutoff point 130 in accordance with the research Lu et al in 2017. From the analysis, we found overall survival for rectal cancer patients with low lymphocyte platelet ratio better than those with high lymphocyte platelet ratio and disease free survival for rectal cancer patients with platelet lymphocyte ratio low group is also better than those with high lymphocyte platelet ratio group. This is in line with research by Kim et al (2017) conducted in stage III and IV rectal cancer patients (Kim et al, 2017). In another study conducted in China in 2017, patients with colorectal cancer found a lower overall survival value in the high PLR group than in the low PLR group ($P = 0.001$). This suggests that increased PLR is a predictive indicator of poor prognosis and is significantly associated with advanced tumor features in patients with colorectal cancer. (Lu et al, 2017)

Platelets play an important role in the development and progression of malignancy. Great interest has been given in the prognostic role of thrombocytosis in patients with recent malignancies. There are several possible explanations for explaining the relationship between platelet and poor malignancy. First, platelets protect tumor cells from cytotoxicity, thereby increasing metastasis, by protecting the surface from the detection of the body's immune system, and this seems to be the main mechanism for platelet protection. Second, proteins that regulate angiogenesis are involved in tumor growth and invasion. In patients with colorectal cancer, PDGF, PF4 and VEGF levels increase the platelets, and elevated levels of these three proteins correlate with cancer status. Platelets can stimulate the growth of angiogenic vessels and prevent bleeding from angiogenic vessels, promoted by adhesion function of platelets, as mediated by Iba glycoprotein (GP), and this process can stimulate and potentiate tumor cells to form distant metastases.

The increased lymphocyte platelet ratio or lymphocyte neutrophil ratio shows a relative reduction in lymphocytes and immune responses mediated by lymphocytes, which play an important role in cytotoxic

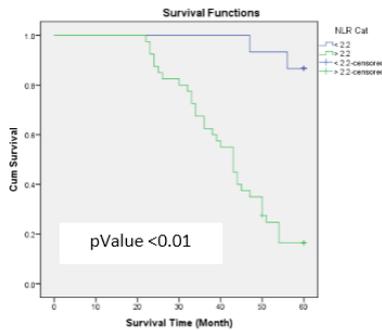


Figure 1. Kaplan Meier 5 years overall survival curve for NLR

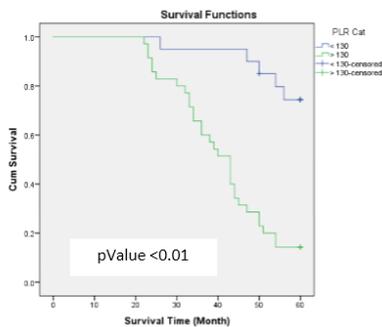


Figure 2. Kaplan Meier 5 years overall survival curve for PLR

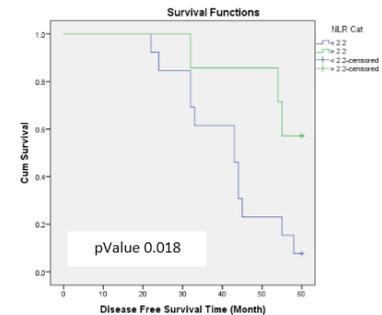


Figure 3. Kaplan Meier 5 years disease free survival for NLR

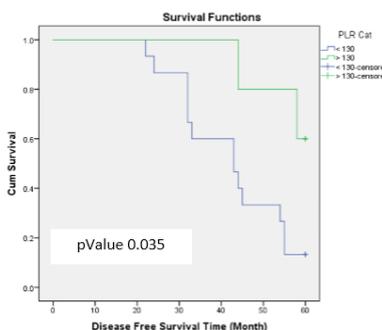


Figure 4. Kaplan Meier 5 years disease free survival for PLR

Analysis of research data assessed in this study includes NLR, PLR and 5 years of overall survival and diseases free survival. Hypothesis

cell death (Kim et al, 2017). In this study, We used cutoff point 2.2 in accordance with Ozdemir et al research in 2014. From the analysis, We found overall survival for patients with low lymphocyte neutrophil ratio better than those with high lymphocyte neutrophil ratio and disease free survival for patients with low lymphocyte neutrophil ratio is better than those with high lymphocyte neutrophil ratios. This is in line with previous research (Kim et al, 2017). Other studies showed high NLR pretreatment ($p = 0.001$) predicted shorter survival, and in multivariate analysis, high NLR pretreatment remained independently associated with poor overall survival after adjustment for known prognostic factors (Ozdemir, 2014).

Many cancers arise from the site of infection, chronic irritation, and inflammation. It is now clear that the tumor microenvironment, which is largely regulated by inflammatory cells, is an important role in neoplastic processes, which promotes the proliferation, survival, and migration of cancer cells (Ozdemir, 2014).

Increased neutrophil counts resulting in tumor growth and metastasis by remodeling the extracellular matrix, releasing reactive oxygen species, and suppressing lymphocyte activity (Kim et al, 2017). Inflammation affects all stages of tumor development and inflammatory cell infiltration and increased expression of pro-inflammatory mediators has been reported in rectal cancer. For example, transformed epithelial cells produce and secrete inflammatory mediators such as chemokines and pro-inflammatory cytokines (for example, IL-1b, TNF- α) to maintain leukocyte recruitment and activation. In colorectal cancer in humans, it was recently explained that T lymphocyte infiltration correlates with a better prognosis in rectal cancer, this finding is consistent with the protective function of adaptive immune responses in these tumors (Galdiero et al, 2016).

Conclusion

Our study showed that high platelet lymphocyte ratio and high lymphocyte neutrophil ratio were useful prognostic factors for predicting poor long-term outcomes in stage III and IV rectal cancer patients. This study can be developed by examining the change in platelet lymphocyte ratio and the ratio of neutrophil lymphocyte during the follow-up period in rectal cancer patients to see its role as a surveillance marker.

References

1. Arnold, Christian N. Ajay Goel, et al. 2005. Molecular Pathogenesis of Colorectal Cancer Implications for Molecular Diagnosis. American Cancer Society.
2. American Cancer Society. 2018. American Cancer Society. Cancer Facts & Figures 2018. Available at: <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf>
3. Bailey, H. Randolph. Richard P. Billingham. Michael J. Stamos. Michael J. Snyder. Colorectal Surgery. Philadelphia: Elsevier Saunders; 2013. Chapter 1, Anatomy and Physiology; P. 3-16. Chapter 2, Diagnostic Evaluation, P. 17-40. Chapter 12, Screening for Colorectal Cancer; P. 207-217. Chapter 14, Colon Cancer Evaluation and Staging; P. 234-242. Chapter 17, Colorectal Cancer; Adjuvant Therapy and Surveillance; P. 287-296.
4. Bhatti, I., Peacock, O., Lloyd, G., Larvin, M., Hall, R.I. 2010. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus plateletlymphocyte ratio. *Am J Surg*. 200;197-203.
5. Cappelle M. S. 2005. The pathophysiology, clinical presentation, and diagnosis of colon cancer and adenomatous polyps. *Med Clin N Am*, 89, 1-42.
6. Chang, KH, Johnson, JA, Waldron, D, et al. 2015. A comparison of the usage of anal verge and dentate line in measuring distances within the rectum, *International Journal of Surgery Open*. Elsevier Ltd, 1(2015), pp. 18-21. doi: 10.1016/j.ijso.2016.02.004.
7. Cormann, M. L. 2005. *Colon and Rectal Surgery* (5th Edition). USA: Lippincott Williams&Wilkins.
8. Cummings J. Colorectal Cancer. 2016. Retrieved from: [https://d1n1luoi1dd30v.cloudfront.net/C20130126979/B9780323280471001943/main.pdf?Expires=1439814210&Key-Pair-Id=APKAICLNFGBCWVYGVIZQ&response-content-disposition=attachment; filename="download.pdf"&Signature=F3s0er2W2kdPZ114fYEV0HxCNBbCsYdG0O8p829ngkDUdhhl](https://d1n1luoi1dd30v.cloudfront.net/C20130126979/B9780323280471001943/main.pdf?Expires=1439814210&Key-Pair-Id=APKAICLNFGBCWVYGVIZQ&response-content-disposition=attachment; filename=)
9. Fazeli MS, et Keramati MR. (2015). Rectal cancer: a review. *Medical Journal of the Islamic Republic of Iran*. Vol.29:171
10. Feng, J.F., Huang, Y., Zhao, Q., Chen, Q.X. 2013. Clinical significance of preoperative neutrophil lymphocyte ratio versus platelet lymphocyte ratio in patients with small cell carcinoma of the esophagus. *ScientificWorldJournal*, 2013:1-7.
11. Glynne-Jones R, Wyrwicz L, Tiret E et al. 2017. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. doi:10.1093/annonc/mdx224
12. Guthrie, G.J.K., Charles, K.A., Roxburgh, C.s.d., Horgan, P.G., McMillan, D.C., Clarke, S.J. 2013. The systemic inflammation based neutrophil lymphocyte ratio: Experience in patients with cancer. *Critical Review in Oncology/Hematology*. 88: 218-230
13. Hamilton & Aaltonen. 2000. *Pathology and Genetics of Tumours of the Digestive System*. Lyon: IARC Press.
14. Kim JH, Lee JY, Kim HK et al. 2017. Prognostic significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with stage III and IV colorectal cancer. *World J Gastroenterol*. doi: 10.3748/wjg.v23.i3.505
15. Kokki I, Papan A, Campbell H, Theodoratou E. 2013. Estimating the incidence of colorectal cancer in South East Asia. *Croat Med J*. 2013 Dec;54(6):532-40.
16. Lee, S., Oh, S.Y., Kim, S.H., Lee, J.H., Kim, M.C., Kim, K.H. 2013. Prognostic

- significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. *BMC cancer*, 13(1):350-361.
17. Lu C, Gao P, Yang Y, Yu D, et al. (2017). Prognostic evaluation of platelet to lymphocyte ratio in patients with colorectal cancer. *Oncotarget*, 8(49): 86287-86295.
 18. Matthew F. 2012. Colorectal carcinoma: Pathologic aspects. *J Gastrointest Oncol*, 3(3): 153-173.
 19. McMillan, D.C. 2009. Systemic inflammation, nutritional status and survival in patients with cancer. *Curr Opin Clin Nutr Metab Care*. 12:223-6.
 20. Miglani, R.K., Bhateja, N., Bhat, R.S., Kumar, K.V. 2013. Diagnostic role of platelet lymphocyte ratio (PLR) in pancreatic head masses. *Indian J Surg* 75(1):4-9.
 21. Ozdemir Y, Akin ML, Sucullu I, et al. (2014). Pretreatment Neutrophil/Lymphocyte Ratio as a Prognostic Aid in Colorectal Cancer. *Asian Pacific Journal of Cancer Prevention*. Vol.15:2647-2649. DOI:<http://dx.doi.org/10.7314/APJCP.2014.15.6.2647>
 22. Peng, W., Li, C., Zhu, W.J., Wen, T.F., Yan, L.N., Li, Bo., et al. 2015. Prognostic value of the platelet to lymphocyte ratio change in liver cancer. *J Surg Res*, 194(2):464-470.
 23. Polat E., Duman U., Duman M., Atici E., Reyhan E., Dalgic T., et al. 2014. Diagnostic value of preoperative serum carcinoembryonic antigen and carbohydrate antigen 19-9 in colorectal cancer. Retrieved from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3921033&tool=pmcentrez&rendertype=abstract>
 24. Samsuhidajat R., Jong W.D. 2005. *Buku Ajar Ilmu Bedah*. Jakarta: EGC.
 25. Schaebybroeck S. V., Lawler M., Johnston B., Salto T. M., Lee J., Loughlin P., et al. 2013. Colorectal Cancer. Retrieved from Elsevier website: <http://dx.doi.org/10.1016/B978-1-4557-2865-7.00077-1>
 26. Siegel RL, Fedewa SA, Anderson WF, et al. (2017). Colorectal Cancer Incidence Patterns in the United States, 1974-2013. *Journal of the National Cancer Institute*. Vol.109(8). Available at: <https://doi.org/10.1093/jnci/djw322>
 27. Siegel R., & Jemal A. 2016. Colorectal Cancer Facts & Figures 2014-2016. *Am Cancer Soc*, 1-32.
 28. Smith Gillian, Francis A, et al. 2002. Mutations in APC, Kirsten-ras, and p53—alternative genetic pathways to colorectal cancer.
 29. Takagawa R., Fujii S., Ohta M., Nagano Y., Kunisaki C., Yamagishi S., et al. (2008). Preoperative serum carcinoembryonic antigen level as a predictive factor of recurrence after curative resection of colorectal cancer. *Ann Surg Oncol*, 15(12):3433-9.
 30. Tanoglu, A., Karagoz, E., Yiyit, N., Berber, U. 2013. Is combination of neutrophil to lymphocyte ratio and platelet lymphocyte ratio a useful predictor of postoperative survival in patients with esophageal squamous cell carcinoma? *Oncol Target Ther*, 7(4):433-434.
 31. Walsh, S.R, Cook, E.J., Goulder, F., Justin, T.A, Keeling, N.J. 2005. Neutrophil lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol*. 91(3):181-184.