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Surgery

KEY WORDS: PLR, NLR, Prognostic Factors, Colon Cancer

PRETREATMENT PLATELET-TO-LYMPHOCYTE RATIO (PLR) AND PRETREATMENT NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) AS A PROGNOSTIC FACTOR OF COLON CANCER AT H. ADAM MALIK MEDAN HOSPITAL IN 2011-2013

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ABSTRACT

Introduction: Colorectal cancer is a malignancy of the colon and rectum epithelial cells and ranks third in malignancy. Colorectal cancer has a high mortality rate and can be prevented by knowing and avoiding risk factors. The Neutrophil-to-Lymphocyte Ratio (NLR) is associated with poor life expectancy in patients with colon cancer. Similarly, Platelet-to-Lymphocyte Ratio (PLR) is a method that can be used to predict the prognosis of patients with colon cancer. High pretreatment PLR can predict poor prognosis in patients suffering from tumors. The aim of this study was to determine pretreatment of Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) as a prognostic factor of colon cancer at H. Adam Malik Medan Hospital in 2011-2013.

Methods: This research is an analytical study with cross sectional design. During the period of 2011 to 2013, 33 colonic cancer patients who had been diagnosed histopathologically at Adam Malik Hospital Medan were included in this study. Patients who have metabolic, hematological and infection disorders and do not have a complete medical record were excluded from this study. In this study, survival analysis was analyzed by proportional cox test to assess the PLR and NLR as prognostic factors for colonic cancer patients.

Results: Of the 33 colon cancer patients, 23 (69.7%) of male were found, mean age 52.34 ± 11.15 years, with age group <60 years were 22 (66,7%) people. Ascending colon is the most common site of colon tumor, with the most histopathologic features in colon cancer patients is moderate differentiated as many as 16 (48.5%) patients. Based on the result of laboratory test, the average of platelet is 302,56 ± 139,12, mean of lymphocyte is 1,84 ± 0,49, mean of neutrophil is 3,8 ± 0,95, mean of NLR is 2,29 ± 1,2 with cut off point NLR is 2,2 and 19 (57,6%) patient at cut off point NLR <2,2, and mean of PLR is 185,19 ± 93,2 with cut off point PLR is 130 and 20 (60,6%) the patient was at PLR cutoff point > 130. Based on survival analysis with cox proportional regression model, there was a significant correlation between NLR value (pValue: 0.016; OR: 1.9; 95% CI: 46.5-54.0) and PLR (pValue: 0.001; OR: 1.9; 95% CI: 46.5-54.0) with 5 years of overall survival of colon cancer patients. Based on survival analysis with cox proportional regression model, there was a significant correlation between PLR value (pValue: 0.018; OR: 3.0; 95% CI: 35.1-47.2) with 5 years disease free survival of colon cancer patients. While at the value of NLR (pValue: 0.053; OR: 3.0; 95% CI: 35.1-47.2) no significant relationship was found.

Conclusion: Of the 33 study subjects who had colon cancer, the mean platelet count was 302.56 ± 139.12, lymphocyte mean was 1.84 ± 0.49, neutrophil mean was 3.8 ± 0.95, NLR mean was 2.29 ± 1.2 and PLR mean was 185.19 ± 93.2. Hypothesis test in this study using proportional cox test to assess the survival analysis showed a significant relationship between PLR values (pValue: 0.018; OR: 3.0; 95% CI: 35.1-47.2) with 5 years of disease free survival of colon cancer patients. While at the value of NLR (pValue: 0.053; OR: 3.0; 95% CI: 35.1-47.2) no significant relationship was found.

INTRODUCTION

According to the American Cancer Society, colorectal cancer is one of the most common malignancies in the world, ranks the third most frequently diagnosed malignancy in the United States and most often causes death in both men and women (Japaries et Desen, 2013). In 2002 there were more than 1 million incidences of colorectal cancer with a mortality rate of over 50%. 9.5 percent of men with cancer have colorectal cancer, while in women the number reaches 9.3 percent of the total number of cancer patients (Kastomo et Soemardi, 2005).

Microscopically, colorectal cancer has different degrees of differentiation, not only from one tumor with another tumor but also from the area to the same tumor, they tend to have heterogeneous morphology (Shah, 2002). The histopathological picture of colorectal cancer is 96% in the form of adenocarcinoma, 2% other carcinomas (including carcinoid tumors), 0.4% epidermoid carcinoma, and 0.08% in the form of sarcomas. Adenocarcinoma is often found with a moderate degree of differentiation and has not metastasized at the time of diagnose, signet ring cell carcinoma is found with a bad degree of differentiation and has distant metastatic at the time of diagnosis, while small cell carcinoma does not have a degree of differentiation and often has distant metastatic at the time of diagnosis (Stewart et al, 2006).

Two thirds of colorectal cancers appear in the left colon and one third appear in the right colon. Mostly in the rectum (51.6%), followed by sigmoid colon (18.8%), descending colon (8.6%), transverse colon (8.06%), ascending colon (7.8%), and multifocal (0.28%). Data from statistical cancers in the United States show that about 60% of colorectal cancers are found in the rectum, it is also seen in China that about 80% of colorectal cancers are found in the rectum, with> 60% of colorectal cancers present only in the rectum (Soeripto et al, 2007).

Signs and symptoms of colon cancer are very varied and not specific. The main complaints of patients with colorectal cancer relate to the size and location of the tumor. A slight tendency to cause obstruction because the intestinal lumen is larger and the stool is still watery. Clinical symptoms are often full of feeling, abdominal pain, bleeding and symptomatic anemia (causing weakness, dizziness and weight loss). Tumors in the left colon tend to lead to changes in the pattern of defecation as a result of irritation and reflex response, bleeding, shrinking of the size of the stool, and constipation because left-leaning tendonous lesions lead to obstruction (Price et Wilson, 2006).

Metastasis to the regional lymph nodes is found in 40-70% of cases at resect. Invasion of a vein is found in more than 60% of cases. Metastasis is often to the liver, peritoneal cavity, lungs, followed by the adrenal glands, ovaries and bones. Metastasis to the brain is very rare, due to the lymphatic and venous pathways from the rectum to the inferior cava vein, the rectal cancer metastasis is more common first in the lungs. In contrast to the colon where the lymphatic and venous pathways go to the portal vein, colon cancer metastases are first most common in the liver (Casciato et al., 2012).

Confirmation of malignancy with a biopsy examination is very important. If there is an obstruction so that biopsy is not possible then the cytology brush will be very useful (Casciato et al., 2012). Other investigations such as CEA, a glycoprotein present on the cell surface entering the bloodstream, are used as serological markers to monitor the status of colorectal cancer and to detect early recurrence and metastasis to the liver. CEA is too insensitive and nonspecific to be used as a screening for colorectal cancer. Increased serum CEA values, however, relate to several parameters. High CEA values are associated with grade 1 and 2 tumors, advanced stage of disease and presence of metastasis to internal organs. Although serum CEA concentrations are independent prognostic factors. New serum CEA values can be said to be meaningful in ongoing monitoring after surgery. Despite the limited specificity and sensitivity of the CEA test, however, these tests are often proposed to recognize early recurrences. Preoperative CEA testing is very useful as a prognostic factor and whether the primary tumor is associated with increased CEA values. Improved preoperative CEA values are useful for early identification of metatases because metastatic tumor cells often result in elevated CEA values (Casciato et al., 2012).

Imaging techniques such as MRI, CT scan, transrectal ultrasound are part of the imaging techniques used for evaluation, staging and follow-up of patients with colon cancer, but this technique is not a screening test. CT scans can detect metastases to the liver, adrenal glands, ovaries, lymph glands and other organs in the pelvis. CT scans are useful for detecting recurrences in patients with elevated CEA values after colon cancer surgery. CT sensitivity reaches 55%. CT scan plays an important role in patients with colon cancer because of the difficulty in determining the stage of the lesion before surgery. Pelvic CT scans can identify tumor invasion of the intestinal wall with accuracy up to 90%, and detect lymph node enlargement> 1 cm in 75% of patients. The use of CT with contrast of the abdomen and pelvis can identify metastases in the liver and intraperitoneal areas (Chen et al, 2006). MRI is more specific for tumors in the liver than with CT scans and is often used in unidentified clarification of lesions using CT scans. Because of its higher sensitivity than CT scan, MRI is used to identify metastases to the liver (Casciato et al, 2012).

5-years survival rate reflects the prognosis of disease staging. In stage dukes A> 90% of patients survived within 5 years. In stage B stage dukes decreased prognosis to 60-80%. If there is regional lymph node involvement (stage C dukes) the prognosis is 20-50%, and if there is metastasis (dukes stage D) the prognosis is only <5%. Recommended using TNM staging system with dukes system modified by Astler Coller (Casciato et al, 2012). Patients with well differentiated carcinomas (grades 1 and 2) have better 5-year survival compared to poor differentiated carcinomas (grades 3 and 4). And tumors in the transverse colon and descending colon have a worse prognosis when compared to tumors in the ascendant colon and rectosigmoid colon (Casciato et al., 2012).
Surgery is the only way that has been widely accepted as curative handling for colorectal cancer. Curative surgery should fill with a broad boundary and maximum regional lymphadenectomy while retaining the function of the colon as much as possible. For lesions above the rectum, tumor resection with a minimum margin of 5 cm is tumor free. Excision of tumors located in the right colon should include branches of the colic media artery as well as all right artery ileocolica and artery colonies. Excision of the tumor in the hepatic flexure or splenic flexure should include the entire artery of the colica medium (Casciato et al, 2012).

Radiation therapy is the treatment of cancer by using high-energy x-rays to kill cancer cells. There are two ways of administering radiation therapy, namely with external radiation and internal radiation. The choice of the way radiation is given depends on the type and stage of the cancer. External radiation (external beam therapy) is a treatment where high levels of radiation are precisely directed at cancer cells. Internal radiation (brachytherapy, implant radiation) uses radiation given into the body as close as possible to cancer cells. Internal radiation provides a higher level of radiation with a relatively short time when compared with external radiation, and some internal handling of radiation is temporarily settled within the body (William et al., 2013).

Chemotherapy is very effective when it is used in the presence of very few tumors and the fraction of malignant cells that are in many growth phases. Chemotherapy drugs may be used as single agents or by combination, eg 5-fluorouracil (5FU), 5FU + levamisole, 5FU + leucovorin. The combined use of such chemotherapy drugs is associated with increased survival when postoperatively administered to patients without coexisting illness. 5FU + levamisole therapy reduced the recurrence of cancer by 39%, reducing deaths from cancer by 32% (Brunicardi et al, 2005).

The Neutrophil-to-lymphocyte ratio (NLR) is associated with poor life expectancy in patients with colon cancer. Similarly, Platelet-to-lymphocyte Ratio (PLR) is a method that can be used to predict the prognosis of patients with colon cancer, but is still rarely used throughout the world (Lu et al, 2017).

Platelets are anucleated small cell fragments derived from bone marrow megakaryocytes and are reactive cellular effectors of hemostasis, inflammation and immunity. Platelets are one of the largest reservoirs of angiogenic and oncogenic growth factors in the human body. The concept by which platelets play a role in tumor invasion and metastasis is quite long. Studies that assess thrombocytosis occur in patients with solid cancer have been done more than 100 years ago. Nearly 40% of patients with malignancy in the gastrointestinal, pulmonary, breast and ovarian, and prostate cells are found to have a platelet count of more than 400,000 mm3. The most important thing that triggers thrombocytosis in cancer is the secretion of a derived-cytokines tumor such as IL-1, G-CSF and IL-6 that will stimulate thrombopoesis through thrombopoetic-dependent mechanisms, affect massive growth and differentiation of megakaryopoetes. Megacariopoietics also have the same ability to produce inflammatory cytokines, which also affect bone marrow endothelial cells to support megakariocytopenia.

Platelet adhesion with tumor cells can help tumor cells form intravascular colonies or extravasation to target organs. Platelet membranes contain a thick layer of glycoprotein integrins, and selectin which mediates platelet adhesion and aggregation. The adherence of platelets with tumor cells in in vivo experimental studies of pulmonary metastases, increased tumor cell interaction with monocytes, and increased tumor cell lysis by natural killer cells. Platelet adherence also protects tumor cells from the immune system, supports cell resistance, proliferation and invasion. In addition, platelets can also release pro-angiogenic factors that stabilize tumor vascularization. Active platelets are released by a number of bioactive molecules including chemokines, cytokines, growth factors, coagulation factors and metalloproteinases from 3 types of secretory vesicles: alpha granules, dense granules and lysosomes. In particular, platelet apha granules are rich in pro- and antiangiogenic factors. The granule contains a number of proteins that are released during platelet activation. Recent studies suggest that pro- and antiangiogenic factors can be selectively differentiated when platelets bind to specific surface receptors, such as protease-activated receptors. VEGF is a pro-angiogenic protein found in the formation of tumors, which causes blood vessels to become hyperpermabeled in circulating macromolecules. VEGF is known for its presence in platelet megakariocytes or proteomes and is released by thrombin stimulated megakaryocytes and platelets in vitro. In a recent study, VEGF was reported to be present in platelet -granules, which showed almost complete colocalization with the -granule fibrinogen protein through immunostaining and fluorescence miscroscopes. Bambace et al demonstrated in his research that ADP dependent platelet aggregation triggered by cancer cells would lead to platelet activation which would subsequently release VEGF as a pro-angiogenic factor, but not endostatin (antiangiogenic) in vitro. Platelet residues and microparticles found in angiogenic growth and in vitro showed a dose-response relationship between platelet counts and angiogenic growth rates. Platelets trigger bone marrow migration and adherence at the site of angiogenesis and cause differentiation of endothelial cell

progenitors into mature endothelial cells. Furthermore, active platelets are a regulator of tumor vascular hemostasis by preventing tumor bleeding through selective demolition of the granule content. This specifically makes an important contribution to tumor angiogenesis characterized by abnormal, immature, dilated and fragile vascular morphology. The relationship between inflammation, coagulation and cancer progression has been a frequently studied problem. When the exact pathophysiological mechanisms that regulate cycles between coagulation, inflammation and tumor cell parameters remain unclear, there are novel biomarker research in the field of oncology that tests all three interactions. The biomarker connects the pre-inflammatory status and pre-coagulation in cancer with the ability of the endogenous anticancer residues; where NLR and PLR are specifically examined as reliable and inexpensive novel biomarkers (Peng et al, 2016).

Inflammatory state can accelerate tumor growth, invasion, angiogenesis, and even metastasis. Increased markers of inflammation (reactive protein C) are associated with decreased survival of patients. There is also a link between simple inflammatory markers (such as neutrophils, lymphocytes, and peripheral blood platelets) and carcinoma outcomes. The relationship between the high ratio of neutrophils to lymphocytes and the poor prognosis is very complex (Lu et al, 2017).

In neutrophil and lymphocyte culture experiments from donors of carcinoma, tumor-linked neutrophils through enzymatic reactions trigger the formation of new extracellular matrices that result in the release of basic fibroblas growth factors, endothelial cell migration, and cell carcinoma dissociation. In addition, the reactive oxygen species produced by neutrophils decrease the adhesion and promotional properties of the extracellular matrix and inhibit tumor cell apoptosis through nuclear factor (NK) - B activation. These events result in increased angiogenesis, tumor growth, and progression to metastatic phenotype. The presence of lymphocytes that infiltrate tumors is associated with better life rates, and better responses to anthracycline-based chemotherapy (Pedrazzani et al., 2017)

METHODS

This research is an analytic research using cross sectional method. During the period of 2011 to 2013, 33 patients suffering from colon cancer who had been diagnosed histopathologically in H. Adam Malik General Hospital Medan were included in this study. Patients who have metabolic, hematological and infection disorders and do not have a complete medical record were excluded from this study. Sampling is done by simple random sampling. Minimum sample number calculated based on the formula:

$$n = \left[\frac{(z_\alpha + z_\beta)}{0{,}5\ln\,(1 + r/1 - r)}\right]^2 + 3$$

$$n = \left[\frac{(1{,}645 + 0{,}842)}{0{,}5\ln\,(1 + 0{,}5/1 - 0{,}5)}\right]^2 + 3$$

$$n = \left[\frac{2{,}487}{0{,}5\ln\,(3)}\right]^2 + 3$$

$$n = 32{,}85$$

Information:

n: large sample

zα: The default derivative α (type I error) = 5%, then zα 1.645.

zβ: The standard derivative β (type II error) = 20% then zβ is 0.842.

r: correlation coefficient value = 0.5.

Then get the sample amount of at least 33 people.

The collected data will be presented descriptively in the frequency distribution table. In this study survival analysis using cox proportional regression model to assess PLR and NLR as prognostic factors of colon cancer in the form of overall survival and disease free survival.

RESULTS

Sample Characteristics

The mean age of the study subjects was 52.34 ± 11.15 years with male colon cancer cases of 69.7% and women 30.3%. In patients it was found that the descending colon (36.4%) was the most common site of colon cancer. The most histopathologic picture of colon cancer patients in this study was moderate differentiated as many as 16 (48.5%) patients. Based on the result of laboratory test, the average of platelet is 302,56 ± 139,12, mean of lymphocyte 1,84 ± 0,49, mean of neutrophil 3,8 ± 0,95, mean of NLR 2,29 ± 1,2 with cut off point NLR 2 , 2 and got 19 (57,6%) patient at cut off point NLR <2,2, and PLR average equal to 185,19 ± 93,2 with PLR 130 cut off point and 20 (60,6%) sufferers are at the cut off point of PLR> 130.

Table 1. Subjects Characteristics

Characteristics	Frequency (n)	Percentage (%)
Age (Mean ± SD)	52,34 ± 11,15	
Age < 60 years old	22	66,7
Age < 60 years old	11	33,3
Gender		
Male	23	69,7
Female	10	30,3
Colon Tumor Location		
Ascenden Colon	12	36,4
Descenden Colon	11	33,3
Sigmoid Colon	9	27,3
Caecum	1	3
Histopathology		
Mucinous AdenoCa	5	15,2
Well Differentiated	11	33,3
Moderate Differentiated	16	48,5
Poorly Differentiated	1	3,0
Mean of Platelet	302,56 ± 139,12	
Mean of Lymphocyte	1,84 ± 0,49	
Mean of Neutrophil	3,80 ± 0,95	
Mean of NLR	2,29 ± 1,2	
Cut off< 2,2	19	57,6
Cut off > 2,2	14	42,4
Mean of PLR	185,19 ± 93,2	
Cut off < 130	13	39,4
Cut off > 130	20	60,6

Data Analysis Results

Relation of NLR and PLR related 5 years of overall survival of colon cancer patients Based on survival analysis with cox proportional regression model, there was a significant correlation between NLR value (pValue: 0.016; OR: 1.9; 95% CI: 46.5-54.0) and PLR (pValue: 0.001; OR: 1.9; 95% CI: 46.5-54.0) with 5 years of overall survival of colon cancer patients.

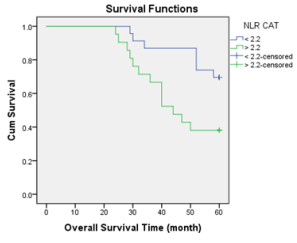

Figure 1. Kaplan-Meier curve for overall survival of colon cancer based on NLR levels

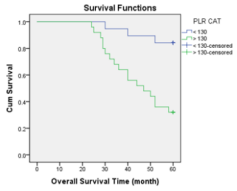

Figure 2. Kaplan-Meier curve for overall survival of colon cancer based on PLR level

Relation of NLR and PLR related 5 years disease free survival of colon cancer patients

Based on survival analysis with cox proportional reflex model, there was a significant correlation between PLR value (pValue: 0.018; OR: 3.0; 95% CI: 35.1-47.2) with 5 years disease free survival of colon cancer patients. While at the value of NLR (pValue: 0.053; OR: 3.0; 95% CI: 35.1-47.2) no significant relationship was found.

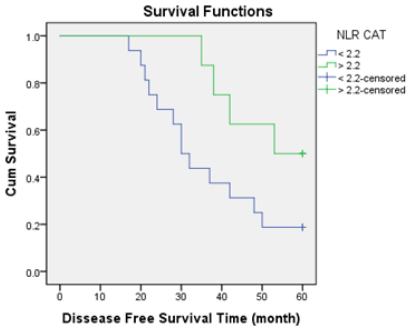

Figure 3. Kaplan-Meier curve for disease free survival in colon cancer based on NLR level

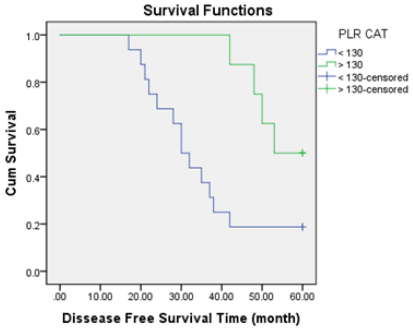

Figure 4. Kaplan-Meier curve for disease free survival in colon cancer based on PLR levels

DISCUSSION

Colorectal cancer is a common disease in the elderly, occurring more frequently in the sixth and seventh decades of life, although it has been observed an increased incidence in younger individuals in recent decades (Pestana et Martin, 2016). In the study the mean age of colon cancer patients was 52.3 years. Based on the location of the tumor, this study found that the commonest location of colon cancer was in ascending colon, this is in line with some previous studies, one of which is a study conducted by Myers et al in 2013 where mentioned right colon including colon ascenden is the most common location the occurrence of colon tumor with percentage of 19%.

There are three main theories underlying the relationship between platelets and colon cancer. In patients with thrombocytosis, tumor progression may be enhanced by proangiogenic cytokines released by platelets; its mechanism by protecting platelets against tumor cells to increase tumor-secreted metastases or cytokines can independently increase platelet counts. These three processes can occur simultaneously (Bailey et al, 2017). In this study PLR has been shown to have an effect on overall survival and diseasefree survival in colon cancer patients. Previously, Zhang et al. In his research has also mentioned that PLR can be a non-invasive serum biomarker in predicting a poor prognosis associated with overall survival and diseasefree survival in colon cancer patients (Zhang et al., 2017).
Neutrophils play a very significant role in the acute phase of inflammation and resistance to pathogenic invasion. In recent developments, it is said that neutrophils are integrated in the innate and adaptive immune response. Neutrophils are a component of the tumor microenvironment of tumor (Galdiero et al, 2016). The increased NLR pretreatment was first described by Walsh et al. (2005) as a useful prognostic indicator of colorectal cancer. Thereafter, various evidence emerged from several studies shows that NLR has a prognostic value in the patient with pancreatic cancer, breast cancer, lung cancer and stomach cancer (Ozdemir et al, 2014). NLR, which is calculated by dividing absolute neutrophil counts by absolute lymphocyte counts, has been proposed as a prognostic index of systemic inflammatory responses that are easily achieved in a variety of diseases including colorectal cancer (Leitch et al., 2007). In this study it was found that NLR was related to overall survival but not related to disease free survival of patients which is in line with previous studies in 2016 by Kim who stated that NLR is a useful marker for predicting overall survival in patients with colon cancer (Kim et al., 2016). In several other studies NRL proved to be influential with disease free survival which is different from the findings in this study, this occurs because of differences in the number of samples with previous studies.

CONCLUSION

Based on data analysis, there was a significant correlation between PLR value with 5 years of overall survival (pValue: 0.001; OR: 1.9; 95% CI: 46.5-54.0) and 5 years of disease free survival (pValue: 0.018; OR: 3.0 ; 95% CI: 35.1-47.2) and NLR values with 5 years of overall survival (pValue: 0.016; OR: 1.9; 95% CI: 46.5-54.0) in colon cancer patients.

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