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THE CORRELATION BETWEEN THE LOCATION OF THE TUMOR TOWARDS HEMOGLOBIN LEVEL AND ERYTROCHYTE INDEX VALUE IN COLORECTAL CANCER PATIENTS AT RSUP PROF. DR. I.G.N.G. NGOERAH HOSPITAL

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ABSTRACT

One of the most often found clinical manifestation of colorectal cancer is anemia. If anemia is One of the most often found clinical manifestation of colorectal cancer is anemia. Worse response to the treatment, disease free period, locoregional control, and overall survival is predicted if anemia is present before the treatment. In elucidating the etiology of anemia, the erythrocytes index (MCV, MCH, MCHC) are useful. The hemoglobin level and erythrocyte index value in colorectal cancer patients is affected by a few factors. One of the most significant factor is the location of the tumor. The objective of this paper is to determine the correlation between location of the tumor towards hemoglobin level and erythrocyte index value in colorectal cancer patients at RSUP Prof. Dr. I.G.N.G. Ngoerah. The study design of this research was a cross sectional study. The data that used were taken from medical records of patients with colorectal cancer in RSUP Prof. Dr. I.G.N.G. Ngoerah from the period of January 2021 until December 2022. A total of 58 patients were met the inclusion criteria. The hemoglobin level and erythrocytes index value were obtained from the blood routine results of colorectal cancer patients. The hemoglobin level used to determine the severity of anemia, which classified into normal, mild anemia, moderate anemia, and severe anemia. Tumor location is divided into two, left-sided and right-sided. The chi square bivariate test is used as hypothesis test, and Kolmogorov-Smirnov test is used as alternative test. The majority of the age of the subjects are middle-age adults patient (41-60 years old), contributes 50% of all subjects. The colorectal cancer patients who experienced anemia were 74.1% (43/58). The colorectal cancer patients who had low MCV were 36.2% (21/58), low MCH 50% (29/58), and low MCHC 65.5% (38/58). The tumor location of the colorectal cancer is significantly correlated with hemoglobin level (p= 0.004). The tumor location is not significantly correlated with erythrocyte index; MCV, MCH, and MCHC (p=0.674, p=0.979, p=0.180).
Keywords : Colorectal Cancer., Tumor Location., Anemia

INTRODUCTION

Based on GLOBOCAN data, globally colorectal cancer (CRC) or also referred to as cancer of the colon or rectum, is the third most common cancer and the third leading cause of cancers related death in men and women.[1] In 2014, it has been predicted there are 96,830 new cases and 40,000 new cases of colon and rectal cancer, respectively. Jakarta, Central Java, and DIY Yogyakarta become the three provinces which have highest incidence for colorectal cancer in Indonesia.[2]Globally, the colorectal cancer incidence has been steadily rising. The increased in incident in developing countries correlated with the adoption of the "western" way of life.[3] Besides the external factors, colorectal cancer also has a significant genetic basis.[4]

One of the most often found clinical manifestation of colorectal cancer is anemia. Anemia may be present in 30%-75% of colorectal cancer patients and mostly due to the blood loss to the bowel, causing iron deficiency.[4,5] Besides due to chronic bleeding, anemia in colorectal cancer, especially normocytic anemia were correlated with the systemic inflammatory effects as the reaction of the cancer cells with the immune system.[4,6] Majority of colorectal cancer patients have anemia at the time of the diagnosis. Anemia also become one of the reasons colorectal cancer patients enter the primary care. Anemia has been discovered more commonly occured in colorectal cancer patients with proximal colon tumor and advanced stage 3–6. Several studies have appraised the prognostic value or predictive value of anemia in various colorectal subgroups. These studied also reported an association between anemia and adverse outcome.[4] Anemia that occurred before the treatment suggest Worse response to the treatment, disease

free period, locoregional control, and overall survival is predicted if anemia is present before the treatment.[7]

In elucidating the cause of anemia, the erythrocytes index are useful. Erythrocytes index are used to define the size and hemoglobin content of red blood cells which include mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Iron deficiency anemia resulting in low MCV and MCH values in colorectal cancer patients.[6,8]Location of tumor in colorectal cancer is divided into two; right-sided and left-sided colorectal cancer. Right-sided colorectal cancer is defined as colorectal cancer which located on the caecum, ascendens, hepatic flexure, and transverse colon. Meanwhile, left-sided colorectal cancer is a colorectal cancer that located on the sphlenic flexure, descenden, sigmoid, and rectum.[9] Severe and life-threatening anemia are more commonly found in the right-sided colorectal cancer. On the contrary, mild and moderate anemia are more commonly found in left-sided colorectal cancer. In addition, from previous study that have been conducted, the prevalence of anemia was high when the tumor were located in the proximal colon and diminished gradually and linearly as the tumor were located more distal towards the rectum.[10]

There are some studies that have been conducted to study the correlation between the severity of anemia and the location of the tumor in colorectal cancer, involving the location of the tumor, MCV (Mean Corpuscular Volume) and/or hemoglobin levels as variables. Based on study that have been conducted by Rizqhan in RSUP Kariadi shows that there is a correlation between haemoglobin level and erytrochytes index (MCH and MCV) and tumor location at colorectal patients.[6] Research done by Aini ,also reported that there was a correlation between hemoglobin levels and tumor location of colorectal cancer. This study reported that moderate and severe anemia most commonly found on the right-sided colon compared to the left-sided colon.[11] However, study conducted at RSUP Dr. Soedarso reported another result. In this study, the severe anemia are most commonly found on the rectosigmoid, while the life-threatening anemia were most commonly found on the rectum. The rectosigmoid and rectum itself classified as left-sided colon.[12] In Indonesia, especially in Denpasar, study on the correlation between the location of the tumor and the severity of anemia in colorectal cancer patients is still rarely done. Therefore, researcher want to conduct a research about the correlation between the severity of anemia and erythrocyte index as predictive factors of tumor location in colorectal cancer patients at RSUP Prof. Dr. I.G.N.G. Ngoerah, Denpasar. This research is expected to help in estimating the possibility of a colorectal cancer and consider the appropriate examination for the estimated tumor location.

METHODOLOGY

This research was conducted in August until October 2022 at RSUP Prof. Dr. I.G.N.G. Ngoerah, Denpasar. The study design is analytical research that used a cross sectional study. The dependent variable in this research was the tumor location which categorized into right-sided and left-sided. Meanwhile, the dependent variables are the hemoglobin level and erythrocyte index. The hemoglobin level was categorized based on World Health Organization criteria. The hemoglobin was used to determine the severity of abemia, which categorized into normal (≥ 13 for men and ≥ 12 for non-pregnant women), mild anemia (11.0-12.9 for men and 11.0-11.9 for non-pregnant women), moderate anemia (8.0-10.9 for men and non-pregnant women), and severe anemia (< 8.0 for men and non-pregnant women). Index erythrocyte include MCV, MCH, and MCHC. The normal value for Mean Corspuscular Volume (MCV) are 87 ± 7 fl. Meanwhile the normal value for Mean Corpuscular Hemoglobin (MCH) are 29 ± 2 picograms (pg) per cell. The normal value for Mean Corpuscular Hemoglobin Concentration (MCHC) are 34 ± 2 g/dl.

The data that used were taken from medical records of patients with colorectal cancer in RSUP Prof. Dr. I.G.N.G. Ngoerah from the period of January 2021 until December 2022. The sample selection method in this study is cluster sampling. In this method, patient's medical record samples were grouped into female and male. Furthermore, in each group will be taken several samples using consecutive sampling method. In this method, sample selected by entering all samples that meet the inclusion criteria until the required number of samples is met. The chi square bivariate test is used as hypothesis test, and Kolmogorov-Smirnov test is used as alternative test. The Statistical Package for the Social Science (SPSS) software version 25 was used to processed the research data and data were presented in tables.

RESULTS

In order to determine the correlation between location of the tumor towards hemoglobin level and erythrocyte index in this research, data were obtained at RSUP Prof. Dr. I.G.N.G. Ngoerah. Data were collected from patient's medical records, start from Agustus until October 2022. Cluster sampling were choosen as sampling technique. From 58 samples that had met the inclusion criteria, 29 samples were taken from the female group and 29 samples were taken from the male group.

Research Subjects Characteristics

Charateristic of the subjects include age, hemoglobin level, eritrochyte index, and tumor location were presented at tables as follows.

Tabel 1. Age characteristics of the subjects

Characteristic	Frequency (n %) (N = 58)
Age	
Young adults (≤ 40 years old)	6 (10.3)
Middle-age adults (41-60 years old)	29 (50.0)
Old Adults (> 60 years old)	23 (39.7)
Tumor Location	
Right-sided	13 (22.4)
Left-sided	45 (77.6)
Anemia Severity	
Normal	15 (25.9)
Mild Anemia	19 (32.8)
Moderate Anemia	17 (29.3)
Severe Anemia	7 (12.1)
Index Eythrocyte	
MCV	
Normal	34 (58.6)
Increased	3 (5.2)
Decreased	21 (36.2)
MCH	
Normal	26 (44.8)
Increased	3 (5.2)
Decreased	29 (50.0)
MCHC	
Normal	19 (32.8)
Increased	1 (1.7)
Decreased	38 (65.5)

From the Table 1, the majority of research subjects who have colorectal cancer are middle-age adults (50%). The youngest age of the subjects were 25 years old, while the oldest were 78 years old. Patients with right-sided colon cancer were 22.4%, meanwhile patients with left-sided colon cancer were 77.6%. Colorectal cancer patients who had anemia are 74.1 %, while 25.9% colorectal cancer patients were normal. The majority of the subjects had mild anemia (32.8%). The majority of the patients had normal MVC (58.6%), decreased MCH (50%), and decreased MCHC (65.5%).

The Correlation of the Tumor Location towards Hemoglobin Level

Tabel 2. The Correlation of Tumor Location towards Hemoglobin Level

	Anemia Severity Classification				P
	Normal	Mild	Moderate	Severe	
Right-sided	0	2	5	6	0.004
Left -sided	15	17	12	1	
Total	15	19	17	7	

The Chi Square were not used because there were 4 cells with expected count more than 5 (>20% cells). As the alternative, the correlation between tumor location and hemoglobin level were tested by using Kolmogorov Smirnov test. From the test, the significance value (p value) were 0.004 or $p<0.05$, so it can be concluded that there is significant correlation between tumor location and hemoglobin level or severity of the anemia in colorectal cancer patients.

The Correlation of the Tumor Location towards MCV Value

Tabel 2. The Correlation of the Tumor Location towards MCV Value

	MCV Value			P
	Decreased	Normal	Increased	
Right- sided	7	6	0	0.674
Left-sided	14	28	3	
Total	21	34	3	

The Chi Square were not used because there were 3 cells with expected count more than 5 (>20% cells). As the alternative, the correlation between tumor location and MCV value were tested by using Kolmogorov-Smirnov Test. From the test, the significance value (p value) were 0.674 or p> 0.05, therefore it can be concluded that tumor location were not signicantly correlated with MCV value.

The Correlation of the Tumor Location towards MCH Value

Table 3. The Correlation of the Tumor Location towards MCH Value

	MCH Value			P
	Decreased	Normal	Increased	
Right-sided	8	5	0	0.979
Left-sided	21	21	3	
Total	29	26	3	

The Chi Square were not used because there were 2 cells with expected count more than 5 (20%). As the alternative, the correlation between tumor location and MCH value were tested by using Kolmogorov-Smirnov Test. From the test, the significance value (p value) were 0.979 or p> 0.05, therefore it can be concluded that tumor location were not signicantly correlated with MCH value.

The Correlation of the Tumor Location towards MCHC Value

Table 4. The Correlation of the Tumor Location towards MCHC Value

	MCHC Value			P
	Decreased	Normal	Increased	
Right-sided	12	1	0	0.180
Left-sided	26	18	1	
Total	38	19	1	

The Chi Square were not used because there were 3 cells with expected count more than 5 (>20% cells). As the alternative, the correlation between tumor location and MCHC value were tested by using Kolmogorov-Smirnov test. From the test, the significance value (p value) were 0.180 or p> 0.05, therefore it can be concluded that tumor location were not signicantly correlated with MCHC value.

DISCUSSION

In this research, it was found that the majority of the colorectal cancer patients were middle-aged adults patients (41-60 years old), which constitutes 50% of all cases. Old adults patients (≥ 60 years old) contributes 39.7%, meanwhile young adults patients (≤ 40 years old) contributes 10.3% of all cases. The results was in accordance with research that have been conducted at RSUP Prof. Dr. I.G.N.G. Ngoerah in 2010-2014 that the highest number of cases was found at the age of 40-60 years old patient, followed by age > 60 years old, and age <40 years old.[13] The same results were also obtained in research at RSUP Kariadi Semarang in 2009-2010 which showed that the largest age population was 51-60 years old.[6] The incidence of colorectal cancer in old populations is associated with decreasing function of the immune system, acumulation of carcinogenic agents, and genetic events in ageing tissues.[14] Colorectal cancer which were located on the left (77.6%) were more common than those on the right (22.4%). The result was in accordance with research that have been conducted at RSU DR Soedarso Pontianak which reported left-sided colorectal cancer were more common (70%) than the right-sided colorectal cancer. The same results were also obtained in research at RSUP Kariadi Semarang that showed left-sided colorectal cancer were more common than those on the right (59.3% and 40.7%), respectively. However, this result contradicts the study conducted by Jennifer M. Weiss *et al* which showed that right-sided colorectal cancer were more common than the left-sided colorectal cancer, 67% and 33%, respectively.[15] The difference in results may be due to differences in demographic characteristics of the subjects. Specifically, location of the tumor mostly found on the rectosigmoid colon, comprising 53.44% of all cases. This result was different from previous researches. Colorectal cancer mostly located on the rectum, contributes 57.14% from all cases,

based on research that have been done by Yogi *et al* at RSUP Prof. Dr. I.G.N.G. Ngoerah in 2010-2014.[13] The difference in results may be due to the difference in the number of samples and subjects studied. In the research by Yogi *et al* involved 435 subjects during 2010-2014. Meanwhile this research involved 58 subjects as respresentation of the colorectal cancer patients during 2021-2022. In this study, 72.4 % colorectal cancer patients were anemia, while the remaining 27.6% were normal. Research that have been done at RSUP Prof. Dr. I.G.N.G. Ngoerah in 2016 by Ariesta *et al* also found similar results that colorectal cancer patients who had anemia were 69.2%.[16] In addition, research at RSUP Kariadi obtained that 85.3% colorectal cancer patients had anemia.[6] Frequently, colorectal cancer patients have anemia at the time of diagnosis and become one of the reasons colorectal cancer patients enter the primary care. Decreased in hemoglobin level are associated with systemic inflammation and mechanistically related to the bleeding.[4]

Mild anemia were more commonly found on the left-sided colorectal cancer (37.7%) compared to the right sided colorectal cancer (15.3%). Meanwhile, moderate anemia on the right-sided colorectal cancer contributes 38.5%, while left-sided colorectal cancer contributes 26.7%. On the contrary, severe anemia were more commonly occurred on the right sided colorectal cancer (46.15%) compared to those on the left-sided (2.2%). This correlation between tumor location and hemoglobin level have been statistically significant with significance value p=0.004, therefore it can be established that there is a correlation between tumor location of the colorectal cancer towards hemoglobin level. The likelihood of anemia increased when the tumor was in the proximal colon and decreased progressively and linearly as it moved further distally towards the rectum.[10] Due to the tendency of blood to mix with feces and disintegrate during colonic transit, severe rectal bleeding is infrequently brought on by proximal malignancies. This occult blood loss causes the insidious signs of anemia that is gradually getting worse. These signs are significantly less concerning than the overt bleeding that is more typical in distant tumors. Additionally, this might delay the detection of the cancer and perhaps explain why patients with proximal tumors appear with anemia more frequently and more severed .[6] In addition, right-sided colorectal cancer is also tend to present with a more advanced stage tumor and larger tumor size, lead to the worse prognosis.[17] The larger tumor size were associated with anemia cases and also associated with the worse progmosis. Moreover, in predicting the highly advanced cancer, anemia as a whole, spesifically severe anemia is important.[7]This result were in line with research that have been done by Luluk Qurrota Aini which showed that moderate and severe anemia were more commonly found on the right-sided colorectal cancer.[11] The research that have been conducted at RSUP Kariadi Semarang also showed similar results, that mild anemia were more commonly occurred on the left-sided colorectal cancer and on the contrary, severe anemia were more commonly occurred on the right-sided. However, this research showed different results. Research conducted at RSUP Kariadi showed that moderate anemia had been discovered more common on the left-sided compared to those on the right-sided.[6] The difference in results can be caused by the difference of the cut-off point that have been used in determining the severity of the anemia. Cut off point in determining the severity anemia based on National Cancer Institute (NCI) were used in research at RSUP Kariadi. Meanwhile, cut off point in determining the severity of the anemia that have been used in this research based on World Health Organization (WHO) that have been used on research at RSUP Kariadi Semarang, which is also used by Kemenkes as a reference. Moderate anemia based on NCI describes as hemoglobin level between 8.0-10 g/dL. While based on WHO, moderate anemia characterized as hemoglobin level between 8.0-10.9 g/dL.

Erythrocyte Index includes MCV, MCH, and MCHC were used in this research in elucidating type of anemia in colorectal cancer patients. However, in this research, there is no significant correlation between tumor location towards erythrocyte index. The results were different from previous researchers. Research that have been conducted at RSUP Kariadi showed that there was a significant correlation between tumor location and erythrocyte index. The same results also reported by Sadahiro *et al* that right-sided colorectal cancer was a factor that caused microcytic and hypochromic anemia with MCH and MCHC value below normal.[4] The difference in total number of samples and proportion of the MCV, MCH and MCHC among studies may results in difference of the results. In this research, without considering the location of the colorectal cancer, it has been discovered that among patients, 58.6% patients had normal MCV (normocytic), followed by 36.2% patients had decreased MCV (microcytic), and 5.2% patients had increased MCV (macrocytic). Another research that have been conducted by Väyrynen et al that stated anemia is common in colorectal cancer patients and it is most commonly normocytic, then followed by microcytic anemia.[4]Anemia in colorectal cancer, especially normocytic anemia were correlated with the systemic inflammatory effects, reaction of the cancer cells with the immune system.[4,6] Both immune and cancer cells synthesize proinflammatory cytokines such as IL-1, TNF-α, and IL-6 causing the condition of chronic inflammation, leading to anemia through several mechanisms; shortened erythrocyte survival due to the increased erythrocyte destruction, decreased erythropoiesis in bone marrow, erythropoietin production, and change in iron metabolism, leading to iron-restricted erythropoiesis. The chronic inflammation were linked with advanced stage cancer.[18] While the normocytic anemia are associated with the systemic inflammation, the microcytic anemia associated with chronic bleeding, more commonly occurred on the proximal tumor location.[4](30%).

CONCLUSION AND RECOMMENDATION

Based on the results of the research that have been conducted at RSUP Prof. Dr. I.G.N.G. Ngoerah based on the medical record 2021-2022, it can be concluded There is a significant correlation between tumor location towards hemoglobin level at colorectal cancer patients at RSUP Prof. Dr. I.G.N.G. Ngoerah. However, there is no significant correlation between tumor location towards erythrocytes index at colorectal cancer patients at RSUP Prof. Dr. I.G.N.G. Ngoerah.The researcher suggest further research regarding the correlation of anemia with other variables, such as tumor stage and age of the patient.

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