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Correlation of High Eosinophil Count Levels in Blood with Metastasis in Colorectal Carcinoma

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ABSTRACT

Background: Eosinophils are bone marrow-derived granulocytes in peripheral blood and tissues primarily involved as effector cells in colorectal cancer metastasis. High levels of eosinophils correlate with poor prognosis in colorectal cancer. ***Aim:*** To prove the correlation between increased levels of eosinophils with clinical stage according to the TNM system and metastatic status in patients with colorectal carcinoma. ***Methods:*** An analytical cross-sectional study was conducted from July 2020 to June 2021 at Prof. Dr. IGNG Ngoerah Hospital. Data analysis in this study consisted of univariate analysis, bivariate analysis, and multivariate analysis using SPSS IBM version 23. ***Results:*** Obtained 40 subjects patient colorectal cancer where men were 25 (62.5%), mean age ± SD53.15 ± 12.5 years, normal nutritional status 29 (72.5%), most locations in the rectum 16 (40%), followed by descending colon 15 (37.5%), the most clinical-stage IVA 13 (32.5%), lung metastases 12 (30%) with adenocarcinoma type 34 (90%). The average level of eosinophils±SDobtained445.63±283.03. The correlation between eosinophil levels and the clinical stage is strongly positive ($r = 0.604$; $p < 0.001$), and with the incidence of distant metastases, a strong positive correlation ($r = 0.651$; $p<0.001$). ***Conclusion:*** There is a statistically significant correlation between increased levels of eosinophils in the blood in metastases and stages colorectal cancer patients, where the higher the eosinophil count levels, the higher the stage and an increase in the incidence of metastases.

Keywords: Eosinophil count levels; Colorectal Cancer; TNM stage; metastasis

INTRODUCTION

Eosinophil infiltration in the tumor area, also called tumor-associated tissue eosinophilia, is an easy parameter to assess in routine pathology. An increase in eosinophil count has been associated with disease recurrence and survival in patients with colorectal cancer.[1]The accumulation of eosinophils is associated with cell death and proliferation of CRCs, possibly due to a Th2 response. Eosinophils are said to be able to remodel tissue and stimulate tumor angiogenesis. In Loktionov 's study, in mice that had been implanted with KKR cells, IL33 expression was found in tumor cells, which induced the production of eotaxin 1, whose function is to summon eosinophils.[2]

Eosinophils have been detected in lymph node metastases in cancer patients and are known to produce lymphangiogenic factors (e.g., VEGF-C and VEGF-D). Human eosinophils produce matrix metalloproteinases (MMP-9) which regulate the digestion of extracellular matrix (ECM) and support the invasiveness and metastatic nature of cancer in the Tumor Microenvironment (TME).[3]

Prizment et al., (2016), where metastasis and stage were associated with increased eosinophil levels in 242 subjects (187 colon cancer and 56 rectal cancer) with $p = 0.003$ and reduced 5-year overall survival and resulted in decreased disease-free survival with $p <0.001$.[5]

Increased levels of high eosinophils with clinical stages are also known in Wei et al., (2018)in 569 subjects divided into three stages, namely stage 1 as many as 98 (17.2%), stage 2 252 (44.3%) and sodium III 219 (38.5%), expressed by p <0.001 there is a significant relationship where the higher eosinophil levels, the higher the stage of the patient.[6]

In Harbaum's (2014), it was found peritumoral eosinophil counts significantly impact the prognosis of colorectal cancer patients apart from the overall tumor-associated inflammatory response. Peritumoral eosinophil evaluation is an easy-to-assess tool that shows promise and should be performed routinely.[7]

Among the inflammatory cells involved in colorectal cancer immunity are eosinophils. It is known from an increasing number of studies demonstrating a role for eosinophils in carcinogenesis. Seeing this condition, Authors are interested in learning the relationship between eosinophils and clinical staging and distant metastases of colorectal carcinoma. Limited data in Indonesia is also why author want to do this study.

METHOD

This study is an analytic cross-sectional because this measures variables on subjects without any intervention. The study was conducted at the Department of Surgery, Prof. Dr. IGNG Ngoerah Hospital from July 2020 to June 2021.

Inclusion criteria: 1) All patients listed in the medical records had colorectal carcinoma being treated at Prof. Dr. IGNG Ngoerah has been histopathologically proven through surgery from July 2020 to June 2021; 2) All patients listed in the medical record suffer from colorectal carcinoma being treated at Prof. Dr. IGNG Ngoerah General Hospital from July 2020 to June 2021, who have received chemotherapy and or radiotherapy; 3) All patients in the medical record suffer from colorectal carcinoma treated, complete clinical and histopathological data.Exclusion criteria were all patients listed in the medical record suffering from recurrent colorectal carcinoma. Data analysis in this study consisted of univariate analysis (descriptive statistics), bivariate analysis, and multivariate analysis. Statistical significance was assessed using the 95% CI (confidence interval). The entire process of data analysis above uses SPSS 24.0

RESULTS

The study involved 40 subjects patient colorectal cancer at Prof. Dr. IGNG Ngoerah Hospital took medical record data in the form of age, nutritional status, location of the pathology, clinical stage of TNM, distant metastases, and eosinophil levels. An overview of the characteristics of the data is in Table 1.

TABLE 1: Data Characteristics of Colorectal Cancer Patients.

Variable		n=40	%	Normality test*
Age	Mean ± SD	53.15 ±12.5		0.200†
Gender	Man	25	(62.5%)	<0.001
	Woman	15	(37.5%)	
Nutritional status	Obesity	11	(27.5%)	<0.001
	Not Obese	29	(72.5%)	
Pathology Location	Colon Ascendent	7	(17.5%)	<0.001
	Colon Descendent	15	(37.5%)	
	Rectosigmoid	5	(12.5%)	
	rectum	16	(40%)	
	Cecum	2	(5%)	
	Transverse Colon	4	(10%)	
Clinical Stage	IIIA	5	(12.5%)	<0.001
	IIIB	12	(30%)	
	IIIC	5	(12.5%)	
	IVAs	13	(32.5%)	
	IVB	5	(12.5%)	
Metastases	Lungs	12	(30%)	
	mesentery	3	(7.5%)	<0.001
	liver	7	(17.5%)	
	Peritoneal Carcinomatous	5	(12.5%)	
Types of Anatomical Pathology	Adeno Carcinoma	34	(90%)	<0.001
	Mucinous Adeno Carcinoma	4	(10%)	
Surgery Technical	Hemicolectomy	18	(45%)	0.113†
	Colostomy	3	(7.5%)	
	LAR	6	(15%)	
	Hartmann	4	(10%)	
	Miles Procedure	4	(10	
	Transverse colon resection	1	(2.5%)	
	Sigmoidectomy	2	(5%)	
	ULAR	2	(5%)	
Chemotherapy		30	(75%)	<0.001
Palliative		5	(12.5%)	<0.001
The mean eosinophil level ± SD		445.63±283.03		0.113†

Remarks: * Kolmogorov-Smirnov**; LAR: Low Anterior Resection;** ULAR: **Ultralow anterior resection;**†: means the distribution of data is normally distributed.

In this study, normality analysis was carried out with Shapiro Wilk because the number of subjects was < 50 (Table 2). After the Shapiro Wilk analysis was carried out, it turned out that the data on eosinophil levels were not normally distributed with a p-value <0.05; a different test would be carried out on eosinophil levels with clinical stage and distant metastases by Mann-Whitney analysis (Table 3), and to determine the correlation between increased eosinophil levels with metastases and staging, a correlation test was performed using Spearman rho (Table 4).

TABLE 2: Test for normality of eosinophil levels.

Variable	Shapiro-Wilk		
	Statistics	df	p-value
Eosinophil levels	0.785	40	<0.001

Description: p> 0.05: normal distribution

TABLE 3: The relationship between differences in eosinophil levels with clinical stages and distant metastases.

Variable		N	Serum eosinophil level Median [IQR] (min-max)]mg/dL	P*
Clinical Stage	IIIA	5	200 [60] 170-250	<0.001†
	IIIB	12	270 [308] 90-670	
	IIIC	5	230 [200] 150-450	
	IVAs	13	750 [523] 100-1700	
	IVB	5	650 [975] 300-2000	
Metastases	No Metastases	22	235 [170] 90-670	<0.001†
	Metastases	18	710 [514] 100-2000	

*Mann Whitney test; † significant

TABLE 4: Correlation between high eosinophil levels with clinical stage and distant metastases.

Variable	Clinical Stage		Distant metastases	
	rho	p-value	rho	p-value
Eosinophil levels cells/µL	0.604	<0.001*	0.651	<0001*

*Significant

In this study, it was found that high eosinophil levels had a strong positive correlation with clinical stage with the results r = 0.604; p <0.001, which can be concluded that the higher the eosinophil level, the higher the clinical staging as well as the results of correlation with metastases, the results of a strong positive correlation were obtained r = 0.651; p<0.001 that high eosinophil levels correlate with the presence of distant metastases in colorectal cancer.

The analytical test for confounding factors is found in Table 5, the results obtained were not statistically significant, but the results with a high eosinophil mean > 500cells/µL is present in the location results is Colon Descendent 816 cells/µLmen with an average height of 530cells/µL and pathological type of adenocarcinoma 515 cells/µL.

TABLE 5: Relationship between Confounding Variables and High Eosinophil Levels.

Variable		N	Average	std. Deviation	P value
Age	< 65 years	31	499,19	381,174	0.504*
	≥ 65 years	9	402,22	372,585	
Pathological Location	Colon Ascendent	7	374,29	291,711	0.205***
	Colon Descendent	15	816.67	540,987	
	Rectosigmoid	5	464.00	281,478	
	rectum	16	469.06	366,006	
	Cecum	2	445.00	431,335	
	Transverse Colon	4	215.00	36,968	
Gender	Man	25	530,40	399,317	0.240**
	Woman	15	389.00	329,568	
Nutritional status	Obesity	11	530,17	418,553	0.289**
	Not Obese	29	338,18	183,239	
Types of Anatomical Pathology	Adeno Carcinoma	34	515.00	372,657	0.946**
	Mucinous Adeno Carcinoma	4	473,19	471,911	

*Independent t-test; ** Mann-Whitney, ***Kruskal Wallis

In this study, a multivariate test was carried out to determine the independent factor of eosinophils; the results were obtained in Table 6. The results of the Poisson test showed that eosinophil levels were statistically significant for metastases, with the result p = <0.001.

TABLE 6: Multivariate Analysis of Poisson Regression Test.

Model	Unstandardized Coefficients		Standardized Coefficients	Sig.	95.0% Confidence Interval for B	
	B	std. Error	Betas		LowerBound	Upper bound
Clinical stage	21,565	93,478	0.074	0.819	-169,084	212,215
Metastases	455,783	96,156	0.610	<0.001*	261,125	650,441

*significant

DISCUSSION

The prevalence of CRC patients in Indonesia is 8.6% of all cancers, with a majority of 19.1 per 100,000 men and 15.6 per 100,000 population in women, with most cases occurring in elderly individuals.[8] But in this study known age mean age ± SD 53.15 ± 12.5 years old, thus proving that the age tends to be younger, the risk of becoming an advanced stage increases sharply according to the Abad et al., 2003 dan Sutrisna, 2018 where the tendency of change towards an increase in staging starts at the age of 40 years. Statistical test results found no difference in patients aged <65 years and ≥65 years with p=0.281. [9,10] The results are the same in Prizment et al., (2011), where there is no difference in patient eosinophil results with a mean age of 54.[4] This study's results differ from the study Wei et al., (2018). A significant increase in eosinophil levels occurred at 61 years and over, yielding 1,397 cells/µL with a range (0.844-2.207) with p = 0.081. [6]The results of increasing eosinophils with age are also known in study Prizment et al., (2016)with p=0.02. [4]

The results of this study are also in accordance with Sitorus, (2010), where the most age was also at the age of 40-60 years, 47 patients (59.49%), and Dianti's study also stated that the most age was <60 years as many as 22 (66.7%).[11,12]The results are also the same in Prizment et al., (2016), where the median age (IQR) is 55(69). [4]

The results differ fromPestana, 2016 CRC, a common disease of the elderly and occur more frequently in the sixth and seventh decades of life. However, an increased incidence has been observed in younger individuals in recent decades.[13] Nielsen, 1999; Harbaum et al., 2014and Fernandez, 2000 also stated that colorectal cancer occurs at an advanced age; in Harbeum's study, the median was 68.5 years, Nielsen's median age (IQR) was 61 (49.75), and Fernandez's median (IQR) was 67.35 (32.87)). [7,14,15]. Myers studyed young patients. In his study, Myers used a sample of 180 patients under 50 years.[16].

A study by Kulendran et al., (2011)states that colon cancer is divided into familial cancers syndrome (FAP and HNPCC), ranging from 5-15% of the total incidence and occurs at a younger age, while most of the rest are non-hereditary sporadic cancers. [17] Familial cancers syndrome causes hundreds of adenomas at the age of 16 years and will form colon cancer at 25-30 years.[18] The highest incidence is at the age of 50 years; early detection of colon cancer, early detection begins at the age of 30-40 years. Because the formation of colon cancer from normal colon cells takes 10-20 years. Generally, only about 3% - 5% of these malignancies are under 40 [9,10].

As you get older, the body becomes more susceptible to cancer. The most vulnerable age for colorectal cancer is at more than 60 years compared to less than 60 years. Old age is prone to genetic mutations and decreased organ function. The transformations that occur cause activation of the proto-oncogene B-catenin, inactivation of tumor suppressor genes such as APC and TP53, and down-regulation of K-RAS gene expression, which regulates apoptosis, thus triggering the uncontrolled proliferation of colon cells. Nonetheless, cases of colorectal cancer at the age of under 60 years continue to increase.[12]. Pal (2006)in India looked at the incidence of colorectal cancer at the age of fewer than 40 years to get more than 20% of cases of colorectal cancer occur at the age of fewer than 40 years. [19]Individuals younger than 40 years who develop colorectal cancer have a poor prognosis. Dukes and Bussey estimate that metastases to lymph nodes are higher in patients younger than 40 years, so the disease progression is faster in young patients.[6].

Colorectal cancer cases are in third place, primarily affecting men with a percentage of 10.0%, and the second most in women with 9.2% of all cancer patients worldwide.[20]this study men are 62.5%, nearly 55% of cases of CRC occur in developed countries with Western culture. There is geographic variation worldwide, with the highest incidence estimated in Australia and New Zealand, with an Age Standardized Rate (ASR) of 44.8 in males and 32.2 in females per 100,000.[21] Colorectal cancer in Indonesia is the third malignancy, increasing from the sixth position.[22]At Prof. Hospital Dr. IGNG Ngoerah Hospital 2016-2017, there were 137 patients with colorectal cancer, with more males than females in the case group. The number of men in the case group sample was 73 people (53.3%) and 64 people (46.7%) women[10].

The results of this study are the same as Sitorus where men are 44 (55.7%),Fernanda & Wisnaningsih (2018)41 men (58.6%). [11] In Fauzia (2018), 23 men (69.7%) and data from previous study at Prof. Dr. IGNG Ngoerah Hospital CRC patients in 2016-2017 were also dominated by 73 men (53.3%)[24,25]. Study Prizment et al., (2011, 2016); Harbaum et al., (2014); Saraiva, (2018)also stated that there were more men than women, with the results of statistical analysis showing that there was no significant difference between increased eosinophil levels and gender according to this study where gender was not associated with increased eosinophil levels with p = 0.854. [4,5,7,26]

In this study, it was known that nutritional status was still within normal limits, and it was known that the mean ± SD of eosinophils was more in patients with obesity, namely 530.40 ± 399.317. However, statistically, there was no significant difference with p = 0.330. It is also known that eosinophil levels are not statistically related to nutritional status in colorectal cancer patients[4].

Hormonal factors are said to have little effect, although external use, such as estrogen and progestin, have a protective effect against colorectal cancer. Many studies state that the risk of colorectal cancer increases in people with obesity, a high-fat diet (fat is associated with the

development of bacterial flora that degrades bile salts into a potentially carcinogenic N-nitroso component), high in calories, and lacks fiber, consuming lots of red mea, (meat cooked at high temperatures triggers the production of heterocyclic amine and polycyclic aromatic hydrocarbons, which are carcinogenic substances), consumes less fruit, rarely exercises, and smokes.[12]

In men, there is an increase in the incidence of CRC, one of which is caused by obesity; in the Agung et al., (2019), It is known that men have an increase in BMI of 5 kg/m^2, which is closely related to CRC (RR 1.24; p<0.001). [24]

In this study, most locations were in the rectum area 16 (40%). The eosinophil levels were insignificant with the statistical analysis results, where p = 0.709. This same with Sitorus (2010) where is the location of the rectum 47 (59.49%) results Fernanda & Wisnaningsih (2018) also stated that most location was in the rectum area 67%. [11,23] Prizment stated that most locations were in the distal colon/rectum area, resulting in no difference in increased eosinophil levels at pathological locations.[4]The more distal the location of colonic tumors, the more often they are found due to mucosal contact with inflammatory processes and infections that last longer in the rectum compared to the colon.[9]. This differs from the Wei et al., (2018), where there is a difference in the increase in eosinophil levels in the right colon location compared to the left colon location with p = 0.028.

The study results in the Anatomical Pathology Section of Al-Islam Hospital Bandung for January 2012-December 2017 found that the most common location for colorectal cancer was in the rectum, with a frequency of 37 cases (60.66%). The results of this study are from previous studies conducted at Immanuel Hospital Bandung for the period January 2009-December 2011, which stated that the highest preference for colorectal cancer was the rectum (68.2%). The influencing factor is diet. Certain types of food, such as low fiber and high protein and fat, will make the stool transit time longer. This can trigger the occurrence of colorectal cancer, especially in the rectum area because the function of the rectum is a place of transit and defecation[12]

In Sutrisna, Sudartana & Widiana, 2018) where the location of colon tumors that were most often found was in the sigmoid and rectosigmoid, namely 52 people (59.09%) with statistical data obtained a comparison of colon cancer and rectal cancer was 1 in 2. The location of this malignancy was most commonly found in the rectum, ascending colon, sigmoid, descending colon, and transverse colon.[10]

This study is different from Widhasih's results, where most locations are in the ascending colon 12 (36.4%), which is in line with a survey conducted by Myers et al. in 2013, which stated that the right colon, including the ascending colon, is the most common location for colon tumors with a percentage of 19%.[25,27]

In colorectal carcinoma, there is a change in the normal colonic epithelium to become metastatic. The stage of this change goes through two phases of the process, namely the formation of a tumor that has not pressed the surrounding tissue, which is known as a benign adenoma, and the stage of cancer that has encouraged the surrounding tissue, which is known as a malignant adenocarcinoma. Histopathology is the gold standard examination in CRC. Macroscopically, adenocarcinoma is divided into four variants, namely ulcerative adenocarcinoma, the variant that is often found mainly found in the descending and sigmoid colon, exophytic adenocarcinoma (polypoid or fungating), tumors that protrude into the lumen, located in the ascending colon and caecum, annular adenocarcinoma (scirrhous), tumors that grow circumferentially in the intestinal lumen produce an apple core appearance on barium contrast images and the rare variant of submucosal infiltrative [28].

Adenocarcinoma is a malignant cell from the glandular epithelium of the colorectal mucosa with a tubular and irregular structure and multiple lumens with a scanty stroma. Sometimes these cells are separated from one another and secrete mucus called mucinous/colloid adenocarcinoma. If the mucus is still inside the cell and pressing the cell nucleus to the periphery, it is said to be a signet ring cell[28,29]

Tumors create inflammation within their microenvironment and the host. Many different cytokines and other inflammatory mediators are released into the tumor microenvironment and circulation during tumor development. As a result of the complex interaction between mediators, host, and tumor, it has been observed that there is an increase in eosinophil levels.[26]

Eosinophils are granulocytes originating from the bone marrow in the peripheral blood and tissues primarily involved as effector cells in colorectal cancer metastases.[30]. High levels of eosinophils correlate with poor prognosis in colorectal cancer because it is significantly associated with response to chemoradiation therapy, operability, staging, and metastasis. These findings suggest that the degree of eosinophilia can be used as a prognostic marker. Among studies on eosinophils and neoplastic conditions, trends of increasing and decreasing eosinophil counts in colorectal neoplasms have been reported concerning tumor development. A histopathological study of tissue eosinophilia in colorectal neoplasms has revealed that the degree of eosinophilia differs according to the malignant potential of the lesion; the number of eosinophils infiltrating the tissues increases in low-grade dysplasia, decreases in high-grade lesions, and decreases even more in cases of cancer, show significant and rapid changes compared to the surrounding normal tissue. As previously mentioned, more prominent eosinophilia in colorectal cancer is associated with a poorer prognosis.[4,30,31]

In this study, it was found that high eosinophil levels had a strong positive correlation with clinical stage with the results r = 0.604; p <0.001, which can be concluded that the higher the eosinophil level, the higher the clinical stage as well as the results of correlation with metastases, the results of a strong positive correlation were obtained r = 0.651; p<0.001 that high eosinophil levels correlate with the presence of distant metastases in colorectal cancer. Harbaum (2014), the number of peritumoral eosinophils correlated strongly with the number of intratumoral eosinophils (R=0.69; P<0.001) and with the intensity of the overall inflammatory cell reaction (R=0.318; P<0.001).[7]In Prizment et al., (2016)where metastasis and stage were associated with increased eosinophil levels in 242 subjects (187 colon cancer and 56 rectal cancer) with p = 0.003 and reduced 5-year overall survival and resulted in decreased disease-free survival with p <0.001.[5]

Increased levels of high eosinophils with clinical stages are also known in Wei et al., (2018)in 569 subjects divided into three stages, namely stage 1 as many as 98 (17.2%), stage 2 252 (44.3%) and sodium III 219 (38.5%), expressed by p <0.001 there is a significant relationship where the higher eosinophil levels, the higher the stage of the patient. [6]

In Harbaum et al., (2014), the classification of stages T, N, American Joint Committee on Cancer(AJCC)/Union

Internationale Contre le Cancer (UICC), histological appearance, lymphatic invasion, venous invasion and growth of tumor size statistically affected by increased eosinophil levels with p<0.01 in 381 subjects.[7]In Prizment et al., (2016)also stated that the stage of increased eosinophils was related to the clinical stage with p=0.03 and was not associated with the chemotherapy or radiation carried out.[4]In Nielsen, (1999)Obtained significant statistical analysis on the degree of Dukes AD with eosinophil levels with p<0.0001. [14]

Different on Fernandez, (1999), where the increase in eosinophil levels is more than 300 cells/μL, had no significant effect on Dukes stage, histological grade, tumor size, lymph node enlargement, vascular invasion, and vascularization in 126 subjects. [15]Results Associated peripheral blood eosinophilia with a better prognosis was found in metastatic colon cancer with a relatively small sample (n = 21).[32] This can be different for author due to other sampling subjects.

This study uses designed cross-sectional from data in one year with complete data and detailed information from medical records. Author have also excluded the presence of acute illness, which could reflect an increase in the number of eosinophils during blood sampling. Eosinophil laboratory examination is part of a simple laboratory examination, namely a complete blood count, which is relatively cheap and available at health facilities from level 1 and independent (private) laboratories.

The limitation of this study is that eosinophils have not been taken periodically after surgery, chemotherapy, or radiotherapy, which can be considered a prognostic evaluation of colorectal cancer patients. However, in previous Prizment et al., (2016), there is no relationship between increased levels of eosinophils with surgery, chemotherapy, and radiotherapy.[4]This study also did not evaluate overall survival or disease-free survival.

CONCLUSION

1. There is a relationship between eosinophil levels and the clinical stage of colorectal cancer, namely the higher the eosinophil level, the higher the clinical staging of the patient, with a strong positive correlation (r = 0.604; p <0.001)
2. There is a relationship between eosinophil levels and the incidence of distant metastases, i.e., the higher the eosinophil level, the higher the incidence of distant metastases in colorectal cancer with the results strong positive correlation (r = 0.651; p<0.001)

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DECLARATIONS

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