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Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR) And High Platelet Levels Before Therapy as Prognostic Factors of Colorectal Cancer Stage III & IV

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ABSTRACT

Background: Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR) and Platelets can reflect the balance between protumor inflammatory response and antitumor immune response. This examination is easily accessible, inexpensive, affordable and is known to be a prognostic predictor of CRC patients. ***Objective:*** to improve RNL, RTL and high platelet levels before therapy as prognostic factors for CRC stage III and IV at Prof. Dr IGNG Ngoerah Hospital Denpasar in 2017. ***Method:*** retrospective cohort analyzed descriptively, Chi-Square test, and Kaplan-Meier with the help of the Windows Statistical Package for the Social Sciences (SPSS) version 23 program. ***Results:*** Obtained as many as 144 respondents, 80 (55.6%) and 64 (44.4%) were alive, 26 were free from the disease, and 38 were still on treatment. The mean survival of 3 years overall survival was 24 months (95% CI 22-26 months; p<0.05). RNL> 2.2 obtained overall survival; RR 27.7 (95% CI 9.0 85.3; p<0.001) and 20-month mean survival (95% CI 17-22; p<0.001), disease-free survival RR 19.4 (95% CI 6.5-57.3; p<0.001). RTL > 130 obtained RR 92.4 (CI95% 20.5-415; p<0.001) and a mean survival of 19 months (95% CI 16-22; p<0.001), disease-free survival (95% CI 8.3-108.4; p<0.001). Platelet elevation >400,000 mm3 overall survival; RR 13.1 (95% CI 5.1-33.8; p<0.001) times and mean survival was 17 months (95% CI 14-19; p<0.001), disease-free survival 8.8 (95% CI 2-39.1; p=0.004). ***Conclusion:*** RNL, RTL, and high platelet levels before therapy are prognostic factors for CRC stage III and IV.

Keywords: colorectal cancer; platelets; RNL; RTL; survival

INTRODUCTION

Colorectal cancer (CRC) is a type of cancer that grows in the large intestine (colon) or in the lowermost part of the large intestine that connects to the anus (rectum). It can be called colon or rectal cancer, depending on where it grows. Cases of CRC are third most prevalent in men at 10.0% and second most prevalent in women at 9.2% of all cancer patients worldwide.[1] Almost 55 % of CRC cases occur in developed countries with Western cultures. There are geographical variations worldwide, with the highest incidence estimated to be in Australia and New Zealand, with an Age Standardized Rate (ASR) of 44.8 in men and 32.2 in women per 100,000.[2]

Colorectal cancer in Indonesia is the third malignancy, increasing from the sixth position.[3] At Prof. Dr IGNG Ngoerah Denpasar Hospital 2016-2017, there were 137 patients with colorectal cancer, with more men than women in the case group. The number of men in the case group sample was 73 people (53.3%), and 64 people (46.7%) were women.[4]

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 progression.

As a result of the complex interactions between mediators, host and tumor, it has been observed that there is an increased number of neutrophils and decreased number of lymphocytes in several different cancers, including colorectal cancer.[5] Increased neutrophils facilitate tumor proliferation, migration and vasculogenesis. Then, lymphocytes can increase cytotoxic cell activation and cytokine production, which inhibit tumor proliferation and migration.[1] Thus, low lymphocyte levels destroy the antitumor immune response and worsen the prognosis. Therefore, the Neutrophil-Lymphocyte Ratio (RNL) reflects the balance between the protumor inflammatory response and the antitumor immune response. [6,7]

Platelets and lymphocytes in cancer progression and metastasis comprise a cascade of steps involving interactions between the tumor and its microenvironment, including factors that support angiogenesis and inflammation. The capacity of tumor cells to invade, vascularize, and metastasize is initiated by signals from the primary tumor microenvironment, blood vessels, and new microenvironments (secondary sites). This provides the basis for researchers to determine RNL, RTL and high platelet levels before therapy as prognostic factors for stage III and IV CRC at Prof. Dr IGNG Ngoerah Denpasar Hospital in 2017.

METHODS

This study is an analytic observational study with the design used is a retrospective cohort. This study was conducted from June to July 2021 by taking medical record data for stage III and IV CRC patients from January 1 to December 31, 2017, at Prof. Dr IGNG Ngoerah Denpasar Hospital.

Inclusion Criteria: (1) All patients with KKR who have been diagnosed histopathologically at Prof. Dr IGNG Ngoerah Denpasar Hospital have stages III and IV, which will be performed surgery and or chemotherapy; (2) Complete medical record data; (3) Before giving therapy platelet levels (cut-off value > 400,000 mm3), RNL (cut-off value > 2.2) or RTL (cut-off value > 130). Exclusion Criteria: (1) Incomplete medical records (patient data such as address and phone number, laboratory results such as routine blood); (2) Metabolic disorders; (3) Hematologic and infectious disorders.

Data from the study will be analyzed statistically with the help of the Windows Statistical Package for the Social Sciences (SPSS) version 23 program. Data analysis was carried out by descriptive test, Chi-Square test, the significance level was expressed with p and Relative Risk (RR) with 95% Confident Interval (CI). Results were said to be statistically significant if $P < 0.05$. Data were then re-analyzed with Kaplan Meier to see the probability of survival.

RESULTS

This study used an analytic observational research design with a retrospective cohort design to prove that RNL, RTL and high platelet levels before therapy were prognostic factors for stage III and IV CRC at Prof. Dr. I.G.N.G. Ngoerah Denpasar Hospital in 2017. The results of this study involved 144 respondents with basic characteristics shown in Table 1.

TABLE 1: Characteristics of Research Subjects.

Variables		Frequency (N)	Percentage (%)
Age	≤ 50 years	52	36,1
	> 50 years	92	63,9
	Mean±SD	53,6±12,2	
Gender	Male	77	53,5
	Female	67	46,5
Location	Ascending colon	9	6,3
	Transverse colon	5	3,5
	Descendent Colon	3	2,1
	Sigmoid colon	10	6,9
	Secretary	2	1,4
	Rectum	91	63,2
	Sigmoid-rectum	24	16,7
Histopathology	Mucinous AdenoCa	25	17,4
	Well Differentiated AdenoCa	34	23,6
	Moderate Differentiated AdenoCa	59	41,0
	Poorly Differentiated AdenoCa	19	13,2
	Squamous cell carcinoma	7	4,9
Stadium	III	64	44,4
	IV	80	55,6
Lymphocytes (Mean±SD)		1,91±0,8	
Neutrophil (Mean±SD)		7,9±5,9	
RNL	Cut off≤ 2.2	42	29,2
	Cut off >2.2	102	70,8
	Mean RNL±SD	5,3±5,0	
RTL	Cut off≤ 130	47	32,6
	Cut off>130	97	67,4
	Mean RTL±SD	234,1±177,5	
Platelets	Cut off≤ 400,000 mm^3	92	63,9
	Cut off >400,000 mm^3	52	36,1
	Mean Platelets±SD	351,6±128,4	

The associations between RNL, RTL, and platelets with 3-year overall survival are described in Table 2.

TABLE 2: Associations of RNL, RTL, platelets with 3-year overall survival.

Variables		3-year overall survival		OR	95% IK	p-value*	Log-rank		Average survival	
		Died	Live				LRT	df	month	95% IK
RNL	Cut off≤ 2.2	4	38	27,7	9,0-85,3	<0,001†	44,792	1	35	33-36
	Cut off >2.2	76	26						20	17-22
RTL	Cut off≤ 130	2	45	92,4	20,5-415	<0,001†	65,146	1	35	34-36
	Cut off>130	78	19						19	16-22
Platelets	Cut off ≤400,000mm^3	34	58	13,1	5,1-33,8	<0,001†	43,003	1	28	26-30
	Cut off >400,000mm^3	46	6						17	14-19

Note: * chi-square test; † significant.

Table 2 shows that out of 144 respondents, 80 (55.6%) died, and 64 (44.4%) lived. Of the 64 living respondents, 26 were in the group with an RNL Cut-off point value> 2.2, 19 with RTL cut-off point> 130, and 6 with platelets> 400,000mm^3. In the results of statistical calculations, a significant relationship was found in all three variables with a p-value of <0.001. To see the occurrence of risk based on the results of the calculation of the relative risk between RNL and overall survival, it was found that the risk of patients dying was 27.7 times with 95% CI (9.0-85.3) in the RTL results with overall survival, it was found that the risk of patients dying was 92.4 times with 95% IK (20.5-415), and the increase in platelets >400,000mm^3 with overall survival, it was found that the risk of patients dying was 13.1 times with 95% IK (5.1-33.8).

The results of the Kaplan-Meier curve between RNL, RTL, platelets and 3-year overall survival are shown in Figure 1-3.

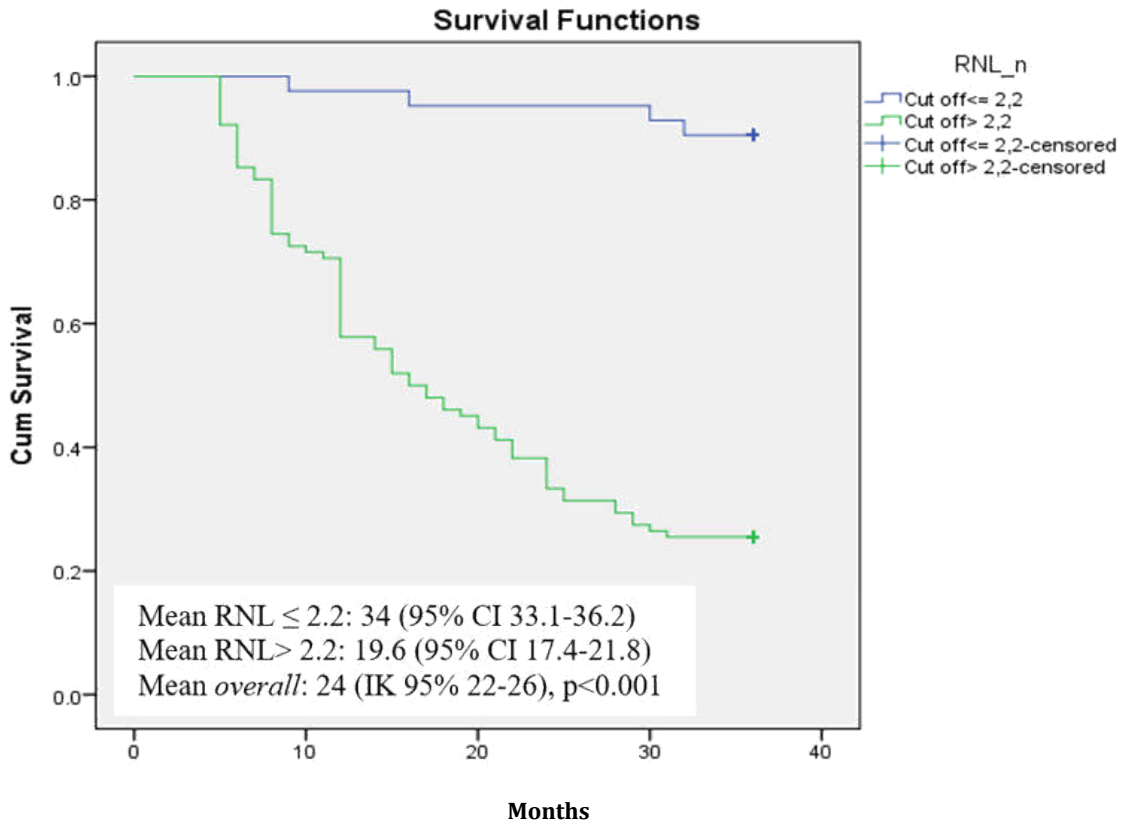

FIGURE 1: Kaplan-Meier curves for 3-year overall survival in CRC by RNL level.

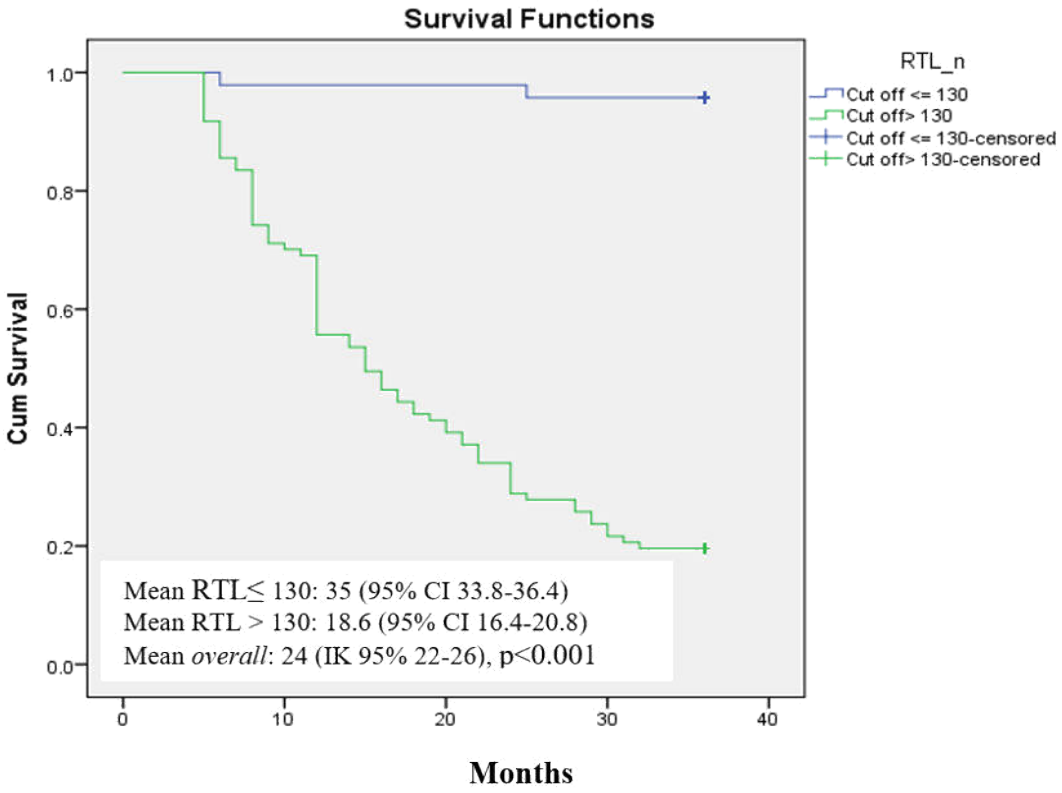

FIGURE 2: Kaplan-Meier curves for 3-year overall survival in CRCs by RTL level.

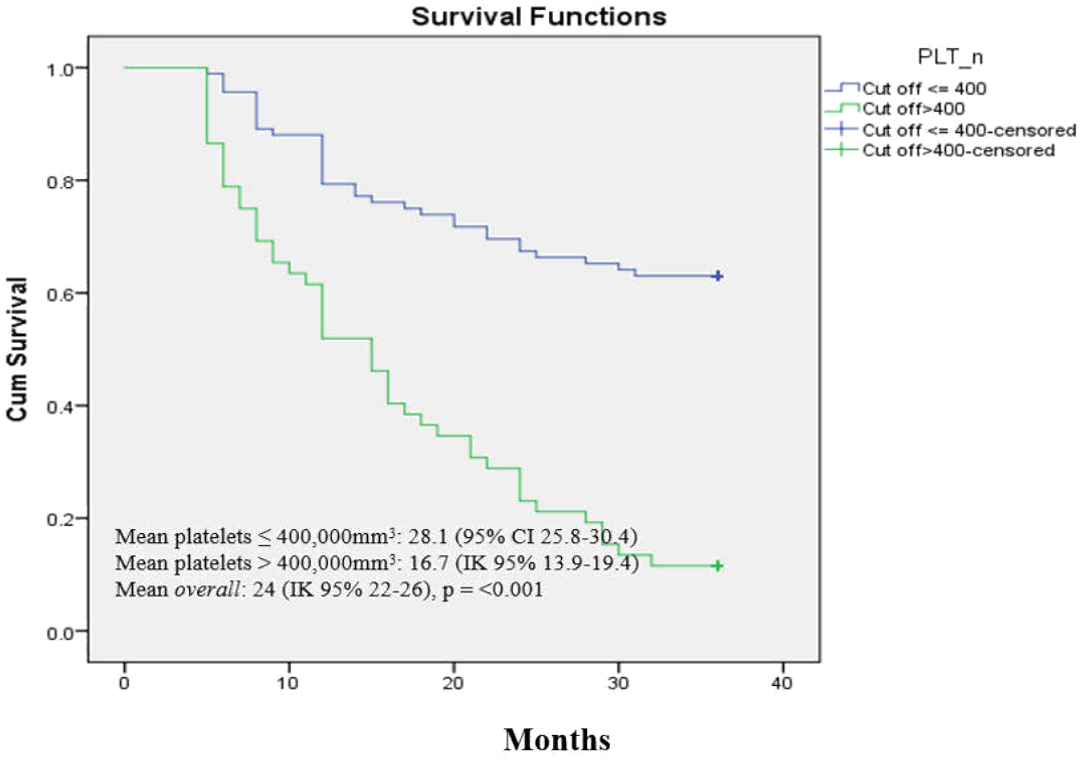

FIGURE 3: Kaplan-Meier curves for 3-year overall survival in CRCs by RTL level.

Based on the analysis of 3-year overall survival with Kaplan Meier, there was a significant relationship between the value of RNL, RTL and platelet increase with the exact p-value of <0.001, while for survival with a mean of 3-year overall survival known to be 24 months (IK 95% 22-26 months). The results of RNL obtained at Cut off point ≤ 2.2 survival with a mean 3-year overall survival of 34 months (IK 95% 33.1-36.2), and the results of RNL Cut off point> 2.2 survival with a mean 3-year overall survival of 18.6 months (IK 95% 16.4-20.8) months.

The results of RTL were obtained at Cut off point ≤ 130 known survival with a mean 3-year overall survival of 35 months (IK 95% 33.8-36.4) months and at RTL with Cutoff point> 130 18.6 months (IK 95% 16.4-20.8) months. As well as the results of platelets with Cutoff point ≤ 400,000mm3 known survival with a mean 3-year overall survival of 28.1 months (IK 95% 25.8-30.4) months and platelets with Cutoff point > 400,000mm3 known survival with a mean 3-year overall survival of 16.7 (IK 95% 13.9-19.4).

This study also conducted a Cox non-proportional hazard regression test to determine the factors influencing 3-year overall survival in SCI with age, gender, location, histopathologic features, stage, RNL, RTL, and platelets obtained in Table 3.

This test showed that the independent risk factors for survival to death in patients with SCI that were statistically significant were RNL, RTL and platelets.

TABLE 3: Test analysis of the Cox regression method of non-proportional hazard.

Variables	OR	95% IK	p
Location	1,142	0,995-1,310	0,059
RNL	10,187	3,634-28,560	< 0,001†
RTL	20,526	4,898-86,022	< 0,001†
Platelets	2,087	1,318-3,303	0,002 †

Notes: † significant

The association between RNL, RTL, platelets and disease-free survival is shown in Table 4.

TABLE 4: Association between RNL, RTL, platelets and disease-free survival.

Variables		disease-free survival		OR	95% IK	p-value*
		With disease	Disease-free			
RNL	Cut off≤ 2.2	17	21	19,4	6,5-57,3	<0,001†
	Cut off >2.2	21	5			
RTL	Cut off≤ 130	22	23	30	8,3-108,4	<0,001†
	Cut off>130	16	3			
Platelets	Cut off ≤400,000mm^3	34	24	8,8	2-39,1	0,004†
	Cut off >400,000mm^3	4	2			

Notes: * chi square test; † significant.

Table 4 shows that out of 64 (44.4%) living respondents, 26 (41%) were declared disease-free. Of these 26 patients, as many as 17 respondents with NLR < 2.2, as many as 22 patients were in the group who had RTL values < 130, and 24 respondents had platelets ≤ 400,000 mm^3. Meanwhile, out of 38 (59%) respondents of KKR patients who had up to 3 years of follow-up were still with the disease, 21 patients were in the group with NLR> 2.2, 23 of them were in the RTL>130 group, and four respondents had platelets> 400,000 mm^3.

In the results of statistical calculations, there was a significant relationship between RNL and 3-year disease-free survival with a p-value <0.001 and a relative risk of 19.4 times and 95% CI (6.5-57.3) times. In RTL to 3 years, disease-free survival with p-Value <0.001 and a relative risk of 30 times and IK 95% (8.3-108.4) times. And the results of platelets on 3-year disease-free survival with a p-value of 0.004 and a relative risk of 8.8 times and IK 95% (2-39.1) times.

The results of the Kaplan-Meier curves between RNL, RTL, platelets and 3-year disease-free survival are shown in Figures 4, 5 and 6.

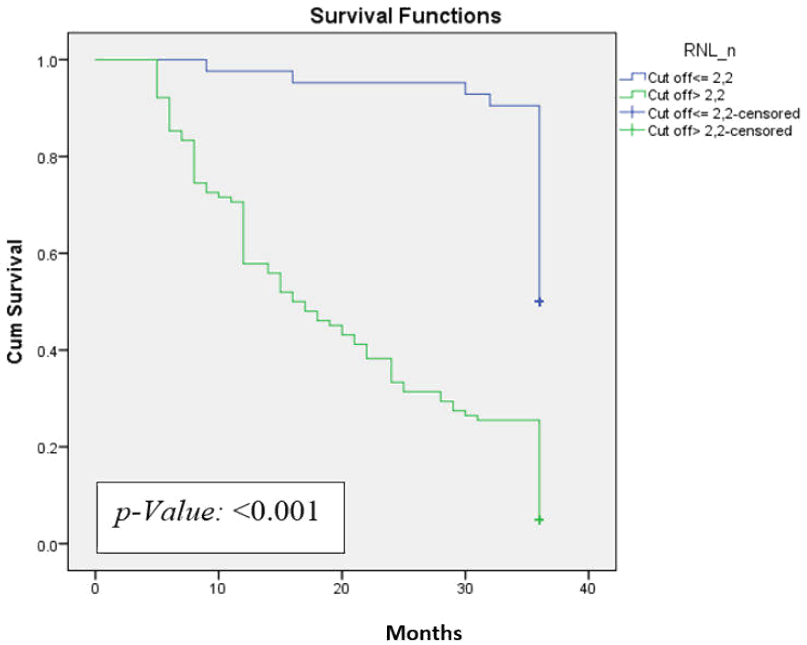

FIGURE 4: Kaplan-Meier curves for 3-year disease-free survival in CRC based on RNL level.

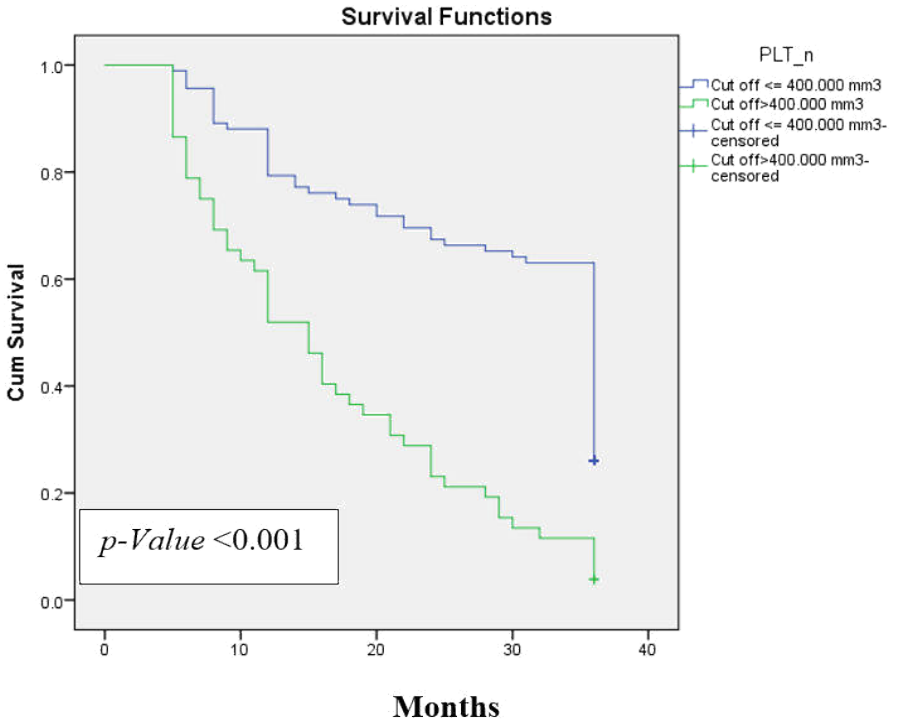

FIGURE 5: Kaplan-Meier curves for 3-year disease-free survival in CRCs by RTL level.

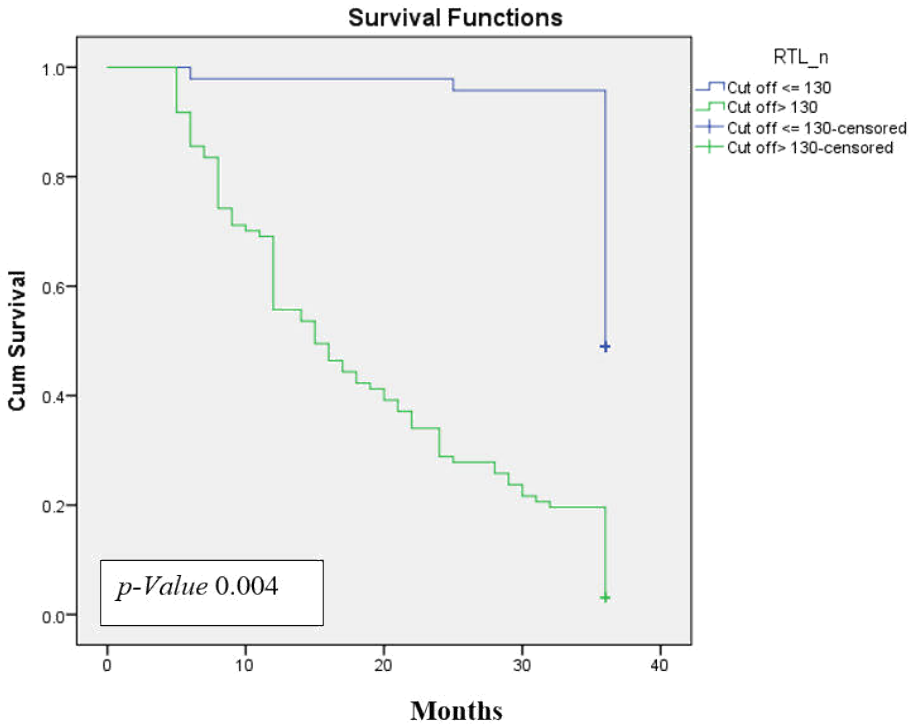

FIGURE 6: Kaplan-Meier curves for 3-year disease-free survival in CRC by platelet level.

Based on survival analysis with Kaplan Meier, there was a significant relationship between the value of RNL (p-Value: 0.004) and RTL (p-Value: 0.009) with 3-year disease-free survival, but for the result of increasing platelets> 400,000 mm3, there was no significant relationship with p = 0.705.

This study also conducted a Cox non-proportional hazard regression test to determine the factors influencing 3-year disease-free survival in SCI with age, gender, location, histopathological features, stage, RNL, RTL, and platelets obtained in Table 5. The results of this test showed that the independent risk factors for 3-year disease-free survival in respondents with SCI were RNL, RTL, platelet elevation, histopathologic features and stage.

TABLE 5: Test analysis of Cox regression method of non-proportional hazard.

Variables	OR	95% IK	p
Histopathology	1,356	1,116-1,649	0,002
RNL	3,298	1,990-5,465	0,000
RTL	3,282	1,993-5,406	0,000
Platelets	1,812	1,181-2,779	0,006

In this study, the factors of age, gender, location of the SCI, histopathology results and stage were analyzed with 3-year overall survival and 3-year disease-free survival, shown in Tables 6 and 7.

TABLE 6: Associations between age, gender, site of CRC, histopathologic result and stage 3-year overall survival.

Variables		3-year overall survival		RR	95% IK	p-value*	Log-rank		Mean Survival	
		Died	Live				LRT	df	Month	95% IK
Age	≤ 50 years	29	23	0,9	0,5-2	0,969	0.008	1	24	21-27
	> 50 years	51	41						24	21-27
Gender	Male	42	35	1,1	0,6-2,1	0,794	0,074	1	24	21-27
	Female	38	29						24	21-27
Location	Colon	16	13	1	0,5-2,3	0,963	0,06	1	24	21-29
	Rectum	64	51						24	22-26
Histopathology	AdenoCa	75	62	2,1	0,4-11	0,395	1,394	1	24	22-26
	Non-AdenoCa	5	2						19	10-29
Stadium	III	23	41	4,4	2,1-8,9	<0,001	0,045	1	28	25-31
	IV	57	23						20	18-32

Note: * Chi-square test.

The results of age, gender, location of SCI, histopathology results and stage with 3-year overall survival showed that none of these factors was significant with p>0.05, the respective p-values of age (0.969), gender (0.794), location of SCI (0.963), histopathology results (0.395),

Significant results were obtained at stage (<0.001), which means that stage IV is three years worse overall survival compared to stage III, namely with a relative risk of 4.4 times with a life span of only 20 months with months (IK 95% 18-32 months) while in stage III is 28 months (IK 95% 25-31 months) while in stage IV.

TABLE 7: Associations between age, gender, location of CRC, histopathologic results and stage 3 years of disease-free survival.

Variables		disease-free survival		RR	95% IK	p-value*
		With disease	Disease-free			
Age	≤ 50 years	15	8	0,7	0,2-2	0,477
	> 50 years	23	18			
Gender	Male	22	13	0,7	0,3-2	0,534
	Female	16	13			
Location	Colon	13	2	0,2	0,04-1	0,052
	Rectum	51	14			
Histopathology	AdenoCa	36	26	0,6	0,5-0,7	0,235
	Non-AdenoCa	2	0			
Stadium	III	20	21	3,7	1,2-12,1	0,025
	IV	18	5			

Note: * Chi-square test.

The results of age, gender, location of the CRC and histopathology results with three years of disease-free survival showed that none of these factors was significant with p>0.05, the results of each p-value of age (0.477), gender (0.534), location of the CRC (0.052), histopathology results (0.235).

Significant results were obtained at stage (0.025), which means that stage IV is worse disease-free survival compared to stage III, with a relative risk of 3.7 times (IK 1.2-12.1).

DISCUSSION

This study was conducted by Fauza (2018), where it was found that NLR was related to overall survival with a p-Value of 0.02 and RR 2.1 times.[8] The increase in RNL in this study indicates an increase in mortality and a decrease in survival in patients with SCI. Research by Zhang et al. (2017) showed poor survival in RNL with the results of RR 1.92 (IK 95% 1.57-2.34; p<0.00001) and found a significant relationship between NLR with DFS and OS where the results of p < 0.00001 but results of Fauza where

the value of NLR with 5-year disease-free survival (pValue: 0.204) did not find a significant relationship.[8,9] This is different because the studies' subjects, numbers and locations differ.

Neutrophils play a significant role in the acute phase of inflammation and resistance to pathogen invasion. In recent developments, it has been argued that neutrophils are integrated into innate and adaptive immune responses. Neutrophils are a component of the tumor-inflammatory microenvironment.[10] Elevated pretreatment RNL was first described by Walsh et al. (2005) as a useful prognostic indicator in colorectal cancer.[11] After that, evidence emerged from several studies showing that RNL has prognostic value in patients with pancreatic, breast, lung, and gastric cancer.[12] RNL, calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, has been proposed as a prognostic index of systemic inflammatory response easily achieved in various diseases, including colorectal cancer.[13] The study is also consistent with Kim (2016), who stated that NLR is a valuable marker for predicting overall survival in patients with colon cancer. RNL can be used as a non-invasive serum biomarker in predicting poor prognosis related to the overall survival of patients with SCI.[9]

Recent studies have demonstrated mechanisms of neutrophil recruitment and roles in the tumor microenvironment, such as extracellular matrix upregulation, enhanced angiogenesis, and interactions with other cells, including epithelial, stromal, and other immune cells. In the tumor microenvironment, neutrophils play a role in inducing pro-inflammation and promoting tumor cell development.[14]

High neutrophil counts are associated with poor prognosis in many cancers. Although the cause is still complex, further studies are being conducted with several hypotheses. Neutrophils may inhibit the immune system. Neutrophils suppress the cytolytic activity of lymphocytes, natural killers and T cell activation.[15]

Tumor-associated T lymphocytes and neutrophils do not act on each other directly. Instead, they cooperate and determine cancer progressivity together. Elevated white blood cell counts can be a valuable addition to the current prognostic markers of systemic immune response. In recent studies, the peripheral ratio of neutrophils to lymphocytes has been found to correlate with cancer disease progression.[16] Tumor-infecting RNL values have been reported as a marker of systemic inflammatory response, able to predict clinical outcomes in patients with colorectal carcinoma metastases. Therefore, the question arises whether tumor-infiltrating RNL is more advantageous than using either of the two parameters alone. Until now, the prognostic value of tumor-infiltrated RNL in colorectal cancer was unclear. The results of this study clearly showed that increased tumor-infiltrating RNL was associated with lymph node metastasis and a trend toward advanced TNM stage.[17]

Increased RNL is associated with increased peritumoral macrophage infiltration and interleukin (IL). Other studies have reported increased markers of systemic inflammatory response, increasing the concentration of many types of cytokines (IL-1, IL-6, IL-7, IL-8, IL-9, IL-12, Interferon-gamma) in the circulation. Acquired neutrophils and other cells, such as macrophages, can secrete tumor growth factors, including vascular endothelial growth factor, hepatocyte growth factor, IL-6, IL-8, matrix metalloproteinase, elastase which contribute to stimulating the tumor microenvironment.[15]

Neutrophil to lymphocyte ratio is an inexpensive biomarker for various tumor types, including lung cancer, hepatocellular carcinoma, nasopharyngeal carcinoma, colorectal cancer, melanoma, and breast cancer. RNL is generally elevated in patients with aggressive disease, as indicated by increased tumor size, nodules, and many metastatic lesions. Also, high RNL correlates with adverse patient survival in many solid tumors. Despite the clinical evidence from the various studies, neutrophilia (a more significant number of neutrophils in the blood) is not always a bad indicator of cancer.[18]

The results of RTL this study similar with Fauza (2018), where RTL (p-Value: 0.024) with 5-year overall survival of colon cancer patients and in the analysis of Zhang et al., 2017 with the results of RR = 1.56 [95% CI 1.04-2.33; P = 0.03].[8,9] Lymphocytes are cells that circulate in the blood and tissues. It is related to the existence between immune infiltration and breast cancer. T cells, T cells, Natural Killer and Macrophages infiltrate tumors. Infiltrating T cells are helper (CD4+) and cytotoxic (CD8+) (Gisterek et al., 2008). Low lymphocytes are associated with poor outcomes (Noh et al., 2013). The importance of lymphocytes has been investigated in several studies. Lymphocytes are associated with their cytotoxic function. A good response is when many lymphocytes infiltrate tumor cells.[15]

Platelets release inflammatory mediators such as chemokines and cytokines. When there is tumor growth, endothelial damage occurs so that platelets adhere to close the damaged blood vessels. Hemostasis begins with platelet adhesion when the von Willebrand factor closes the collagen exposed to platelets. This is followed by aggregation, inflammation and maturation. RTL is one of the markers for increased inflammation caused by platelet-derived mediators. High platelet levels and low lymphocytes are also said to contribute to increased mortality and morbidity.[9] RTL is a ratio; it is said that RTL is more stable when compared to blood parameters that can change with several variables (dehydration, over-hydration and specimen handling).[19]

In this study, the value of platelets was similar to the research of Zhang et al., 2017 with RR = 1.89, 95% CI 1.58-2.25; P < 0.00001.[9] Platelets are small anucleated 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 the human body's angiogenic and oncogenic growth factors. The concept that platelets play a role in tumor invasion and metastasis is long. Studies assessing thrombocytosis in patients with solid cancers were conducted more than 100 years ago. Nearly 40% of patients with gastrointestinal, lung, breast and ovarian, and prostate malignancies had platelet counts greater than 400,000 mm^3. The most important thing that triggers thrombocytosis in cancer is the secretion of tumor-derived cytokines such as IL-1, G-CSF and IL-6, which will stimulate thrombopoiesis through thrombopoietin-dependent mechanisms, affecting the growth and differentiation of megakaryopoiesis to a large extent. Megakaryopoetics also have the same ability to produce inflammatory cytokines, which also affect bone marrow endothelial cells to support megakaryocytopoiesis. Platelet adhesion with tumor cells can help tumor cells form intravascular colonies or extravasate to target organs. The platelet membrane contains a thick layer of glycoprotein integrins and selectins that mediate platelet adhesion and aggregation. Platelet adherence with tumor cells in vivo experimental lung metastasis studies enhances tumor cells' interaction with monocytes and increases tumor cell lysis by natural killer cells.

Platelet adherence also protects tumor cells from the immune system, supporting cell survival, proliferation and invasion. In addition, platelets can also release pro-angiogenic factors that stabilize tumor vascularization [9].

Platelets trigger bone marrow migration and adherence at sites of angiogenesis and cause differentiation of endothelial cell progenitors into mature endothelial cells. Furthermore, activated platelets are regulators of tumor vascular hemostasis by preventing tumor bleeding through selective disassembly of their granule content.[16] This, in particular, makes an essential contribution to tumor angiogenesis characterized by abnormal, immature, dilated and fragile vascular morphology.[20] The relationship between inflammation, coagulation and cancer progression has been frequently researched. While the exact pathophysiological mechanisms governing the cycling between coagulation parameters, inflammation and tumor cells remain unclear, there are novel biomarker studies in oncology that test the interaction of the three. These biomarkers link the proinflammatory and pre-coagulation status of cancer with the endogenous residual ability of anticancer, where platelet elevation can be used to determine poor prognosis and a reliable and inexpensive novel biomarker.[21]

There are three main theories underlying the relationship between platelets and colon cancer. In patients with thrombocytosis, tumor progression may be enhanced by platelet-released pro-angiogenic cytokines; the mechanism may be platelet protection against tumor cells to promote metastasis, or tumor-secreted cytokines may independently increase platelet count.

The advantage of this study is that it uses a cohort research design where by using this method, it can prove prognostic factors in CRC patients for 3 years of overall survival and 3 years of disease-free survival with a simple laboratory examination in the form of complete blood which is relatively cheap and available in health facilities from level 1 and independent laboratories (private) in which the results of the description of RNL, RTL and high platelet levels are obtained. This study has also been matched by design on confounding variables so that it is expected to minimize the influence of other variables. In addition, the Cox non-proportional hazard regression method was also analyzed to determine independent factors affecting 3-year overall survival and 3-year disease-free survival. The weakness of this study is that it uses subjects in specific populations and is conducted in certain places; secondary data are available, so the results of this study cannot describe the same conditions in different populations and areas.

CONCLUSION

Based on the results of this study, it is concluded that:

(1) RNL, RTL and high platelet levels before therapy as prognostic factors of CRC with stage III and IV in digestive surgery clinic of Prof. Dr IGNG Ngoerah Denpasar Hospital in 2017 with the result of $p<0.001$.

(2) Patients CRC with stage III and IV with RNL Cut off point > 2.2 have a risk of death 27.7 times in 3 years overall survival with a range of 9.0-85.3 times and an average survival of 20 months with a range of 17-22 months and have a risk of morbidity 19.4 times in 3 years with a range of 6.5-57.3 times.

(3) Patients with CRC stage III and IV with RTL Cut off-point results> 130 have a risk of death 92.4 times in 3 years overall survival with a range of 20.5-415 times and an average survival of 19 months with a range of 16-22 months and have a risk of 30 times in 3 years with a range of 8.3-108.4 times.

(4) Patients with CRC stage III and IV with platelet cut-off point> 400,000 mm^3 have a risk of death 13.1 times at 3 years overall survival with a range of 5.1-33.8 times and mean survival obtained 17 months with a range of 14-19 months, and have a risk of morbidity 8.8 times in 3 years with a range of 2-39.1 times.

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