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Stage, Grade, and Pre-Operative Red Cell Distribution Width (RDW) Associated with Mortality of Colorectal Cancer Patients at Prof. Dr. I.G.N.G Ngoerah Hospital, Bali

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ABSTRACT

Background: Colorectal cancer is a world health problem with a high mortality rate and low survival rate. Previous studies have shown that factors such as age, histopathological type, TNM stage, and red cell distribution width (RDW) can influence patient mortality. This study aimed to evaluate the factors associated with the mortality of colorectal cancer patients at Prof. Dr. I.G.N.G Ngoerah Hospital, Bali.

Method: This is an analytical observational study with a case-control design in the Department of Digestive Surgery, Prof. Dr. I.G.N.G Ngoerah Hospital, Bali, from April to August 2023. This study included colorectal cancer patients aged > 18, within a study period, and with known clinical outcomes. Patients with incomplete medical records and severe comorbidity were excluded from this study. Statistical analysis was carried out with SPSS ver 20.0 for univariate, receiver operating characteristic (ROC) curve, bivariate, and multivariate tests.

Results: This study collected 118 samples, divided into 59 dead patients (cases) and 59 living patients (controls). Most of the colorectal cancer patients who died were stage IV patients (62.7%), had higher pre-operative RDW values (15.91 ± 4.14), and 20.3% were poorly differentiated. Multivariate analysis showed that stage IV (p = 0.04), poorly differentiated grade (p = 0.04), and pre-operative RDW > 13,575 (< 0.001) were independent factors of mortality in colorectal cancer patients.

Conclusion: Stage, grade, and pre-operative RDW affected the mortality of colorectal cancer patients at Prof. Dr. I.G.N.G Ngoerah Hospital, Bali.

INTRODUCTION

Colorectal cancer is the third most common cancer with the highest mortality rate in the world, and its number continues to increase in developing countries. According to GLOBOCAN data in 2018, the prevalence of colorectal cancer reached 6.1% of all cancer cases in the world, with a mortality rate of 9.2% or 800 thousand deaths per year [1]. Data in the United States in 2020 showed that there were more than 140 thousand new cases of colorectal cancer. Several developed countries with high incidences of colorectal cancer, such as Hungary, which reached 70.6 cases per 100,000 male population, and Norway, with an incidence of 29.3 cases per 100,000 female population [2].

Colorectal cancer also has a poor survival rate, as seen from the low survival rate. In some developed countries, the 5-year survival rate is only around 60%, and even < 50% in developing countries. In the United States, the 5-year survival rate for stage I colon cancer patients is around 93.2% and continues to decline to 82.5% for stage II, 59.5% for stage III, and 8.1% for stage IV [3].

Several previous studies have shown that several factors can affect the progression of colorectal cancer. Some of them are age, histopathology type, TNM stage,

and RDW [4–7]. The age of the patient is related to the risk of comorbid diseases, decreased functional status of the body, and response to the therapy to be given [8]. More aggressive histopathological types of colorectal cancer, such as signet ring cell carcinomas (SRCC) and mucinous adenocarcinoma, are known to have higher characteristics of lymph node metastasis, lymphovascular invasion, and perineural invasion than adenocarcinoma subtypes, and generally have a higher TNM stage than adenocarcinoma subtypes [9]. TNM stage of colorectal cancer is related to size, lymph node metastasis, and distant metastasis, which correlates with tumor aggressiveness. Increased RDW is in line with inflammation, malnutrition, and gastrointestinal bleeding that occur in colorectal cancer and affect patient survival [10]. Although there have been several studies that discuss the influence of several clinicopathological and hematological factors on the prognosis of colorectal cancer, until now there has been no study that examines the role of several prognostic factors such as age, histopathological type, TNM stage, RDW value on the mortality of colorectal cancer patients in the Balinese population. Therefore, this study aims to examine factors related to the mortality of colorectal cancer patients in Prof. Dr. I.G.N.G Ngoerah Hospital, Bali.

METHODS

Design and sample of the study

This study is an analytical observational study with a case-control design. The study was conducted at the Department of Digestive Surgery and the Medical Records Department of Prof. Dr. I.G.N.G Ngoerah Hospital, Bali, for six months starting from April to September 2023.

The sample in this study was all colorectal cancer patients undergoing treatment at Prof. Dr. I.G.N.G Ngoerah Hospital, Bali, in the period 2017-2021 who met the inclusion criteria and did not meet the exclusion criteria. The inclusion criteria in this study include: (1) colorectal cancer patients aged over 18 years; (2) colorectal cancer patients who came for treatment to the Digestive Surgery polyclinic Prof. Dr. I.G.N.G Ngoerah Hospital, Bali; and (3) colorectal cancer patients who died or were still alive after therapy. The case group is defined as the patients who died during or after therapy within this study time frame, meanwhile the control group is defined as the patients who still survive within this study time frame. The exclusion criteria in this study include: (1) patients with incomplete clinical and histopathological data in medical records; (2) colorectal cancer patients with a history of severe comorbidity; (3) patients with a history of hematological disorders, history of blood transfusion in the last 3 months, receiving iron deficiency anemia therapy. The minimum sample size in this study is 58 patients, collected using consecutive sampling techniques.

Variables and measurement

This study only evaluated the clinical, pathological, and hematological (pre-operative RDW value) parameters. This study did not evaluate the demography and socio-economic factors of the patients due to limited time and resources. Data regarding mortality, age, histopathology type, histological grade, stage, and preoperative RDW values were collected from medical records. The mortality of the patients was categorized into survivors or dead based on the patient's final status in the medical records. This study did not consider the treatment starting time since this study did not measure the mortality time of the patients. The histopathology type was based on the WHO category, the histological grade was divided into well-differentiated and poorly differentiated, and the stage was based on the American Joint Committee on Cancer (AJCC) 8th Edition. Preoperative RDW values were obtained from routine laboratory tests recorded in the medical records. The preoperative RDW values were then categorized into high and low based on the optimal cut-off value achieved from the receiver operating characteristic (ROC) test.

Statistical analysis

Statistical analysis was performed using SPSS software ver 25.0. Statistical analysis performed was in the form of univariate, bivariate, and multivariate analysis. For numeric data, we used the Independent T-Test as a bivariate analysis if the data was normally distributed. If the data were not normally distributed, we used the Mann-Whitney U Test. For categorical data, we used the Chi-Square test to determine the relationship between dependent and independent variables and obtain the odds ratio value. This study also conducted a Receiver operating characteristic (ROC) test to determine the optimal cut-off value of pre-operative RDW. Based on that optimal cut-off value, we can categorize the pre-operative value into high (above cut-off value) and low (below cut-off value); this test also shows its sensitivity and specificity. At the same time, the multivariate test used the logistic regression test. The level of statistical significance was set at a value of $p < 0.05$.

RESULTS

This study collected 118 samples, divided into 59 dead patients (cases) and 59 surviving patients (controls). The average age of colorectal cancer patients who died was slightly younger (59.47 ± 9.56 years) compared to patients who survived (59.86 ± 10.84 years), but not significantly different ($p = 0.836$). The gender of colorectal cancer patients who died was dominated by men (69.5%), as well as in patients who survived (64.4%), but not significant ($p = 0.557$). The location of the tumor, most often found in colorectal cancer patients who died, was in the rectum (39%), the same as in patients

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Table 1. Baseline characteristics of samples

Variables	Patient outcome (n =1 18)		p
	Died (n = 59)	Survived (n = 59)	
Age (years), mean ± SD	59.47 ± 9.56	59.86 ± 10.84	0.836[a]
Gender, n (%)			
Male	41 (69.5%)	38 (64.4%)	0.557[c]
Female	18 (30.5%)	21 (35.6%)	
Tumor site, n (%)			
Caecum	1 (1.7%)	0 (0%)	0.108[c]
Ascending colon	14 (23.7%)	3 (5.1%)	
Transversum colon	2 (3.4%)	2 (3.4%)	
Descending colon	3 (5.1%)	4 (6.8%)	
Sigmoid colon	7 (11.9%)	13 (22%)	
Rectum	23 (39%)	27 (45.8%)	
Rectosigmoid	9 (15.3%)	10 (16.9%)	
Stage, n (%)			
II	2 (3.4%)	3 (5.1%)	0.632[c]
III	33 (55.9%)	28 (47.5%)	
IV	24 (40.7%)	28 (47.5%)	
T stage, n (%)			
2	1 (1.7%)	6 (10.2%)	0.002[c]
3	28 (47.5%)	40 (67.8%)	
4	30 (50.8%)	13 (22.0%)	
N stage, n (%)			
0	15 (25.4%)	13 (22%)	0.523[c]
1	27 (45.8%)	30 (50.8%)	
2	13 (22.0%)	15 (25.4%)	
3	4 (6.8%)	1 (1.7%)	
Metastasis status, n (%)			
Metastasis	29 (49.2%)	25 (42.4%)	0.460[c]
Non-metastasis	30 (50.8%)	34 (57.6%)	
Histological grade, n (%)			
Well-differentiated	6 (10.2%)	13 (22.0%)	0.037[c]
Moderately differentiated	41 (69.5%)	42 (71.2%)	
Poorly differentiated	12 (20.3%)	4 (6.8%)	
Histopathological type n (%)			
Adenocarcinoma	52 (88.1%)	59 (100%)	0.013[c]
Non-adenocarcinoma	7 (11.9%)	0 (0%)	
Type of surgery, n (%)			
Resection	43 (72.9%)	40 (67.8%)	0.545[c]
Biopsy	16 (27.1%)	19 (32.2%)	
Chemotherapy, n (%)	10 (16.9%)	9 (15.3%)	0.802[c]
None	49 (83.1%)	50 (84.7%)	
Yes			
Comorbidity, n (%)			
Yes	3 (5.1%)	3 (5.1%)	1.000[c]
None	56 (94.9%)	56 (94.9%)	
Pre-operative RDW value (%), median (min-max)	15.914.14	13.051.41	< 0.001[b]

RDW: red-cell distribution width, [a]Independent T-Test, [b]Mann-Whitney U Test, [c]Chi-square

who survived (45.8%), but not significantly different (p = 0.108) **(Table 1).**

The most common stage of patients found in colorectal cancer patients who died was stage III (55.9%), while in patients who survived, the proportion between stages III and IV was balanced (47.5%), but not significantly different (p = 0.632). Colorectal cancer patients who died and survived were equally more likely not to experience metastasis (50.8% and 57.6%), but not significantly different (p = 0.460). The histological grade of patients who died and survived was dominated by the moderately differentiated type (69.5% and 71.2%) and was significantly different (p = 0.037). Likewise, the histopathological type in both the dead and survived patients was dominated by the adenocarcinoma type (88.1% and 100%), which was significantly different (p = 0.013). The type of surgery, chemotherapy, and patient comorbidities in this study did not differ significantly between the dead and surviving patient groups (p > 0.05). Meanwhile, the pre-operative RDW value was found to be lower in surviving patients, compared to the dead patients, which was significantly different (p < 0.001) **(Table 1).**

Receiving operating curve (ROC) analysis was performed to determine the most optimal preoperative RDW cut-off value in differentiating the outcomes of colorectal cancer patients in this study **(Figure 1).** The results of the ROC curve analysis found that with a cut-off of 13.575%, the preoperative RDW value had an area under the curve (AUC) of 0.753 with sensitivity and specificity of 71.2% and 64.4%, respectively (p < 0.001) **(Table 2).**

Bivariate analysis was conducted to determine whether the differences found in each were significantly different from the outcome of colorectal cancer patients. The age of colorectal cancer patients who died (58.02 ± 11.03 years) was found to be lower than patients who survived (61.15 ± 9.16 years), although this difference was not significant (p = 0.096). Based on the stage, colorectal cancer patients who died were more patients with stage IV (62.7%), meanwhile, in patients who survived, most of them were stages II–III (55.9%), where this result was significantly different (p = 0.042).

The pre-operative RDW value of deceased colorectal cancer patients (15.91 ± 4.14) was found to be higher than that of living patients (13.05 ± 1.41); this finding was significantly different (p ≤ 0.001). When grouped based on the cut-off, deceased colorectal cancer patients were dominated by patients with RDW values > 13.575 (71.2%), while living patients were dominated by patients with values ≤ 13.575 (64.4%); this finding was significantly different (p ≤ 0.001). Based on the histological grade, 20.3% of deceased colorectal cancer patients were found to be poorly differentiated, while only 6.8% of living patients were poorly differentiated, which was significantly different (p = 0.031). Based on histopathology type, in colorectal cancer patients who

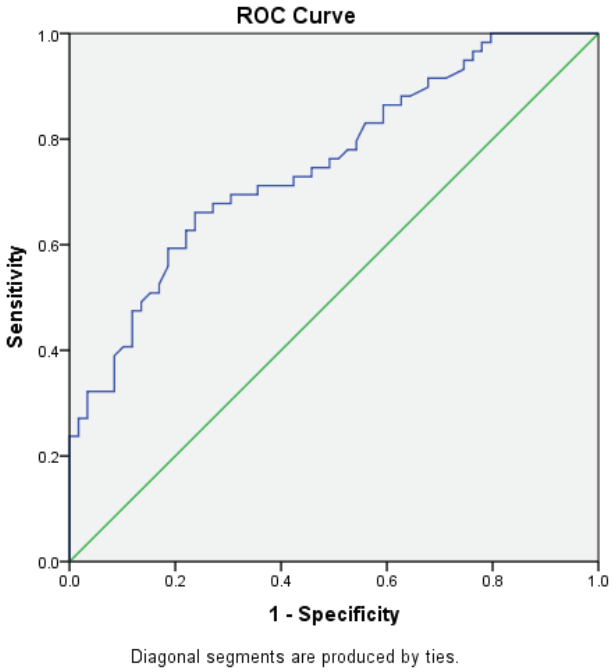

Figure 1. ROC of pre-operative RDW value

died, the dominant type was adenocarcinoma (88.1%), and the rest were non-adenocarcinoma. Meanwhile, in patients who lived, all were adenocarcinoma and none were non-adenocarcinoma (p = 0.013) **(Table 3).**

Multivariate analysis was performed to determine whether the relationship between each variable was independent and not influenced by other variables. Multivariate analysis was performed using a logistic regression test. It was found that stage IV (p = 0.044; OR: 2.135; 95%CI: 1.022–4.459), poorly differentiated grade (p = 0.040; OR: 3.511; 95%CI: 1.061–11.617), and pre-op RDW > 13.575 (p ≤ 0.001; OR: 4.471; 95%CI: 2.059–9.709) were independent factors that increased the risk of colorectal cancer patients dying. Meanwhile, the results of multivariate analysis showed that the type of histopathology was not an independent factor in the mortality of colorectal cancer patients (p = 0.999) **(Table 4).**

DISCUSSION

The stage is the tumor progression parameter in colorectal cancer. At least 35% of colorectal cancer patients are diagnosed with stage IV and have metastasized. Meanwhile, 20%–50% are diagnosed when they are already in stage II or III and can develop into stage IV as the disease progresses. Regarding patient prognosis, stage IV has the worst prognosis among other stages in colorectal cancer cases, with a 5-year survival rate of less than 10%, with a median survival of stage IV patients who have been given optimal supportive care, without chemotherapy, only reaching 5 years [11].

Table 2. ROC analysis

Variable	AUC	Cut-off Value	Sn	Sp	p	CI 95%
pre-op RDW	0.753	13.575	71.2%	64.4%	< 0.001*	0.667–0.839

AUC: area under the curve, Sn: sensitivity, Sp: specificity, RDW: red-cell distribution width

Table 3. Bivariate analysis

Variables	Patient outcome		OR	p
	Died (n=59)	Survived (n=59)		
Age (years), mean ± SD	59.47 ± 9.56	59.86 ± 10.84	-	0.836[a]
Stage, n (%)				
Stage IV	37 (62.7%)	26 (44.1%)	2.135	0.042[c]
Stage II–III	22 (37.3%)	33 (55.9%)		
Pre-operative RDW (%), mean ± SD	15.91 ± 4.14	13.05 ± 1.41	-	< 0.001[b]
Pre-operative RDW (%), n (%)				
≥ 13,575	42 (71.2%)	21 (35.6%)	4.471	< 0.001[c]
< 13,575	17 (28.8%)	38 (64.4%)		
Histological grade, n (%)				
Poorly differentiated	12 (20.3%)	4 (6.8%)	3.511	0.031[c]
Well, to moderate differentiated	47 (79.7%)	55 (93.2%)		
Histopathological type				
Adenocarcinoma	52 (88.1%)	59 (100%)	-	0.013[c]
Non-adenocarcinoma	7 (11.9%)	0 (0%)		

RDW: red-cell distribution width, [a]Independent T-Test, [b]Mann-Whitney U Test, [c]Chi-square

Table 4. Multivariate analysis

Variables	B	SE	p	Adjusted OR	95% CI
Stage IV	0.758	0.376	0.044	2.135	1.022–4.459
Grade poorly differentiated	1.256	0.611	0.040	3.511	1.061–11.617
Pre-op RDW > 13,575	1.498	0.396	< 0.001	4.471	2.059–9.709
Histopathological type adenocarcinoma	-21.329	15191.505	0.999	0.000	-

RDW: red-cell distribution width, SE: standard error, OR: odds ratio, CI: confidence interval

This study found that colorectal cancer patients who died were dominated by patients with stage IV (62.7%), meanwhile, in patients who survived, the proportion of patients with stage IV was lower than the proportion of patients with stages II and III, and was significantly different (p = 0,042). These results are in line with several previous studies, such as Oh et al. [12] in 2007. The study found that patients with stage I had a 5-year stage-specific survival rate of 91%, and continued to decline in stage II by 82%, stage III by 51%, and stage IV by only 4% [12]. Another study by Zacharakis et al. [13] in 2010 in Greece showed that patients with stage IV colorectal cancer with metastasis who were physically fit had low C-reactive protein (CRP) levels, and were still able to tolerate combination chemotherapy, had better outcomes than those who were not.

Colorectal cancer patients with stage IV generally have a worse prognosis when compared to patients with lower stages. This is because patients with stage IV generally have a worse performance status, which is positively correlated with disease progression and worse patient outcomes. In addition, patients with stage IV also generally have several other complaints, such as anorexia, weakness, and a low tolerance for drug toxicity [13]. Furthermore, stage IV patients generally come with metastatic presentations, worsening the patient's prognosis. Stage IV patients also generally have limited therapeutic options, especially surgical therapy [7].

Poor histological grade is one of the factors that play a major role in poor outcomes in colorectal cancer patients. Until now, the histopathological grade of colorectal cancer has been based on the percentage of

glandular differentiation in the tumor based on WHO criteria. This classification system is based on the calculation of five or more cells with low glandular structure (poorly differentiated), and the amount of tumor stroma or the presence of invasive edges in colorectal cancer tissue. Poorly differentiated histopathological grade is one of the important prognostic factors in colorectal cancer cases [14].

This study found that histopathology grade is significantly associated with the mortality of colorectal cancer patients (p = 0.031). This is in line with several other studies, such as the O'Connell et al. [3] study in 2004 found that patients who were classified as poorly differentiated in the study had a significant relationship with patient survival in stages II, III, and I. Similar results were also found in the Ueno et al. [11] study found that patients with well-differentiated had the best prognosis with a 5-year survival rate reaching 99.3%. Meanwhile, patients who were classified as moderately differentiated and poorly differentiated only had a 5-year survival rate of 86% and 68.9%, respectively.

Tumors classified as poorly differentiated have characteristics of gland formation or mucin production, small gland size, irregular, and complex architecture. In addition, tumors classified as poorly differentiated also have high tumor heterogeneity. It was recorded that 72.5% of colorectal cancers classified as poorly differentiated have mismatch repair (MMR) deficiency, which disrupts clonality and molecular aspects of the tissue. In addition, tumors with MMR deficiency also have high levels of BRAF gene mutations and fusions, and TP53 and KRAS gene amplification also increase, causing tumor instability [16]. In addition, colorectal cancer tissue with a poorly differentiated grade is more often found to have microsatellite instability (MSI) and tends to have a mucinous appearance. This is the basis for the poorly differentiated grade to correlate with poor prognosis in colorectal cancer.

In general, colorectal cancer is dominated by adenocarcinoma type as much as 90%, and only a small portion of the rest is mucinous and signet ring adenocarcinoma type. Mucinous and signet ring adenocarcinoma types only have a proportion of 10% and 2.4% of all colorectal cancer cases. The mucinous type is categorized based on the presence of extracellular mucin in large amounts (> 50%). While the signet ring adenocarcinoma type is characterized by the presence of mucin that presses the nucleus to one side to form a ring. The mucinous and signet ring adenocarcinoma types are categorized as non-adenocarcinoma types. This type affects the prognosis of colorectal cancer due to being associated with advanced stages, metastasis, and higher recurrence [17].

In this study, it was found that the histopathology type of adenocarcinoma was not an independent factor affecting the outcome of colorectal cancer patients (p = 0.999). The findings of this study are slightly different from several previous studies. Wu et al. [18] found that non-adenocarcinoma histopathology types, such as mucinous (50.7%) and signet ring adenocarcinoma (26.8%), had worse 5-year overall survival compared to patients with adenocarcinoma histopathology (58%) (p < 0.001). Hosseini et al. [19] found that the 5-year disease-free survival of colorectal cancer patients with mucinous histopathology type was only 39.7%, compared to patients with non-mucinous histopathology type, which could reach 57.6% (p < 0.001).

Non-adenocarcinoma type, especially mucinous type, is associated with microsatellite instability (MSI) in both sporadic and hereditary non-polyposis syndromes, which causes it to have a high degree of methylation. This is also found in the signet ring adenocarcinoma type, which is associated with high microsatellite instability (MSI) and its characteristics, such as old age, female gender predominance, location in the right colon, and high lymphocyte infiltration, although it is not a significant predictor of mortality [17].

Red blood cell distribution width (RDW) is one of the parameters in laboratory examination in the form of complete blood. RDW provides an overview of the heterogeneity of the size of red blood cells circulating in the blood vessels. Under normal conditions, the diameter of red blood cells ranges from 6–8 µm, but in some pathological cases, the size of the diameter of red blood cells can vary. A higher RDW value indicates a higher variation in the size of the red blood cell diameter as well. Several recent studies have shown that the RDW value can act as a prognostic marker in several types of cancer, such as gastric, lung, ovarian, and colorectal cancer. This is supported by the characteristics of the RDW examination, which is simple, inexpensive, and minimally invasive [20].

In this study, it was found that the pre-operative RDW value of patients who died was higher than that of patients who lived and was significantly different. Furthermore, after analyzing based on the cut-off value obtained from the ROC curve, it was found that colorectal cancer patients who died were dominated by patients with pre-operative RDW values ≥ 13.575 (p < 0.001). These findings are consistent with several previous studies. A study by Lu et al. [21] in 2022 in China evaluated the role of preoperative RDW values on the prognosis of colorectal cancer patients. The study found that with a cut-off value of 13.5%, high preoperative RDW values were associated with worse OS (HR = 1.52; 95%CI: 1.11–2.08; p < 0.01). In addition, the study also found that changes in RDW values (ΔRDW) were positively correlated with poor OS in colorectal cancer patients (HR = 1.65; 95%CI: 1.19–2.28; p < 0.01). Song et al. [13] research found that the RDW value with a cut-off of 13.95 had a good area under the curve (AUC) value of 0.643 in distinguishing between colorectal cancer patients

and healthy patients, with a sensitivity and specificity of 41% and 94%, respectively. Another study by Pedrazzani et al. [15] found that with a cut-off of 14.1%, patients with high RDW values had lower overall survival (OS) compared to patients with low RDW values (< 14.1%), although it was not an independent prognostic factor. A meta-analysis by Wen et al. [16] found that RDW-SD value was an independent prognostic factor for OS (HR = 1.99, I2 = 0%, 95% CI = 1.59–2.49, P < 0.01) and DFS (HR = 1.77, I2 = 56%, 95% CI = 0.91-3.43, P = 0.09 < 0.10) of colorectal cancer patients.

RDW values are related to inflammatory conditions in the body because high RDW values are positively correlated with several inflammatory markers. In conditions of active cancer cell proliferation, there is an increase in inflammatory reactions reflected by an increase in several inflammatory markers such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), IL-6, and TNF-α. This chronic inflammatory condition causes decreased erythropoietin production, which affects the effectiveness of erythropoiesis which causing an increase in variations in RDW values due to anemia [24].

Furthermore, the presence of chronic inflammation in cancer patients, especially in advanced stages, causes iron metabolism disorders. This condition causes suppression of erythropoiesis and shortens the life span of erythrocytes in the blood, thereby increasing the incidence of anisocytosis. This picture causes an increase in RDW values. RDW values can also describe several general conditions in the body, such as oxidative stress, malnutrition, erythrocyte fragmentation, and erythropoietin disorders. Often in patients with cancer, cancer cachexia occurs, which causes patients to experience weight loss and malnutrition. In colorectal cancer patients, malnutrition may occur due to deficiencies of vitamin B12, iron, or folic acid, which can cause several types of anemia. In the case of colorectal cancer patients, gastrointestinal bleeding can also occur continuously. This condition can cause changes in the erythropoiesis process, which is reflected in the RDW value. This can cause a decrease in the patient's hemoglobin levels, which can also be reflected through the RDW value [25].

Best of our knowledge, this study is the first to evaluate the association of pre-operative RDW value, clinical, and pathological data with the mortality of colorectal cancer patients in Bali, Indonesia. However, this study still possesses some limitations, first, this study does not evaluate the effect of these variables on disease-free survival or progression-free survival due to the limited time frame of this study. Second, this study is limited to the Balinese population, so it needs further study that includes other populations. Nevertheless, these results still showed the potential of staging, grading, and pre-operative RD value in predicting the mortality of colorectal cancer patients.

CONCLUSIONS

Age, gender, tumor site, nodal status, metastasis status, type of surgery, chemotherapy history, adenocarcinoma type, and comorbidity were not associated with the mortality of colorectal cancer patients. Meanwhile, stage IV, poorly differentiated grade, and pre-operative RDW > 13,575 are significantly associated with the mortality of colorectal cancer patients at Prof. Dr. I.G.N.G Ngoerah Hospital, Bali.

DECLARATIONS

Competing interest

The author(s) declare no competing interest in this study.

Ethics approval and consent to participate

This study has obtained ethical clearance from the Research Ethics Commission of the Faculty of Medicine, Udayana University, with number No/1698/UN/14.2.2.VII/14/LT/2023.

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