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Role of red cell distribution width in colorectal cancer diagnosis and prognosis

Ahmet Karayiğit[1], Dursun Burak Özdemir[2], Hayrettin Dizen[3], Bülent Ünal[4], İlter Özer[5], Murat Ulaş[5]

[1]University of Health Sciences Adana City Training and Research Hospital, Department of Surgical Oncology, Adana, Turkey
[2]University of Health Sciences Samsun City Training and Research Hospital, Department of Surgical Oncology, Samsun, Turkey
[3]Acıbadem Eskişehir Hospital, Department of General Surgery, Eskişehir, Turkey
[4]Istanbul Aydın University Faculty of Medicine, Medical Park Florya Hospital, Department of Organ Transplantation, Istanbul, Turkey
[5]Eskişehir Osmangazi University Faculty of Medicine, Department of Surgical Oncology, Eskişehir, Turkey

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ABSTRACT

Objective: We aimed to assess whether red cell distribution width (RDW) was associated with pre-operative clinical features or post-operative clinicopathological outcomes in patients with colorectal cancer (CRC), and to determine the utility of RDW as a diagnostic or prognostic marker of CRC.

Material and Method: This retrospective cohort study was conducted between January 2018-May 2021 at a university hospital in Turkey. A total of 188 patients histologically diagnosed with CRC who had undergone surgery were included in the study.

Results: Our study included 118 (62.77%) male patients, and the mean age of the patients was 66.28±11.71 years. We found that RDW values were significantly higher in females compared to males (p=0.033), in patients with T3 or T4 tumors compared to those with T1 or T2 tumors (p<0.001), in patients with stage 2 and stage 3 tumors compared to stage 1 patients, those with early mortality (p=0.012), in patients with right or transverse colon tumors compared to those with descending colon or sigmoid colon or rectum tumors (p<0.001), and those that died during follow-up compared to survivors (p=0.001). Additionally, age (r=0.233, p<0.001), tumor size (r=0.229, p=0.002) and length of stay in hospital (r=0.167, p=0.022) were positively correlated with RDW values. RDW had 75.7% sensitivity and 67.5% specificity to predict mortality for the cut-off point of 15.7 (AUC: 0.704, 95.0%CI: 0.615-0.793, p<0.001).

Conclusion: These results show that RDW has a potential function as a biomarker for the diagnosis and prognosis of CRC.

Keywords: Colorectal cancer, RDW, prognosis, progression, overall survival

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, with more than 1 million new cases and 600.000 deaths annually (1). It is the second leading cause of cancer-related death among both men and women, and leads to increased healthcare expenditure (2).

Although the mechanisms underlying CRC are not fully understood, appropriate screening and accurate prognostic assessment can reduce deaths from CRC. Stool occult blood testing, stool DNA testing, colonoscopy, and computed tomography (CT) have long been used as screening tools in CRC, but these screening tools have many limitations, such as low sensitivity and specificity, invasiveness, and high cost. Thus, simple, inexpensive and readily available biomarkers for the diagnosis and prognosis of CRC are urgently needed (3). Red blood cell distribution width (RDW) is an important classical element of routine blood examination, mainly reflecting the uniformity of the volume and size of red blood cells. Relatively recent studies have focused on the identification of blood-derived biomarkers that could facilitate the early diagnosis of CRC, but there are currently no widely available markers that can be used to diagnose CRC (4). The RDW value has been shown to be associated with prognosis in various tumors such as renal cell carcinoma, gastric cancer, lung cancer, ovarian cancers, esophageal cancer, endometrial cancer, and breast cancer (3,5). Notably, Ay et al. (6) found that RDW was significantly higher in patients with colon cancer than those with colon

Corresponding Author: Ahmet Karayigit, drkarayigitahmet@gmail.com
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polyps, and that RDW could be used as an early indicator for solid colon tumors. Additionally, two recent studies showed that RDW was associated with cancer stage and survival in patients with CRC (7,8). Taken together, these results suggest that RDW may be useful in the diagnosis and prognosis of CRC (3).

The aim of the present study was to assess whether RDW level was associated with pre-operative clinical features and post-operative clinicopathological outcomes of patients with CRC, and to determine the possible utility of RDW as a diagnostic and/or prognostic parameter in CRC.

MATERIAL AND METHOD

This was a retrospective single center study conducted between January 2018-May 2021 at Department of General Surgery, Eskişehir Osmangazi University. The protocol of this study was approved by the Non-Interventional Clinical Researches Ethics Committee of Eskişehir Osmangazi University (Date:15.06.2021, Decision No: 09), and carried out in accordance with the ethical standards stated in the Declaration of Helsinki and its amendments. As the study has a retrospective nature, the Medical Ethics Committee of the Eskişehir Osmangazi University did not require written informed consent from patients. All samples and information were recorded anonymously.

Study Population and Follow-up

A total of 188 patients histologically diagnosed with CRC who had undergone surgery were included in the study. Other inclusion criteria were: being aged older than 18 and younger than 90 years, having a complete blood count result obtained and studied two weeks before the surgery, and being followed for at least 12 months after surgery. Patients who received neoadjuvant chemotherapy and/or radiotherapy, had an active infection when the blood sample was taken, those in which necessary data were incomplete, patients who were lost to follow-up, subjects with a history of other serious diseases that affect survival outcomes (such as cardiovascular and cerebrovascular diseases, pulmonary diseases, blood diseases, infectious diseases, other malignant tumors, cerebral infarction, pulmonary infarction, uncontrolled hypertension, HIV infection etc.) were excluded from the study.

The following information of each patient was acquired from hospital records: demographic characteristics including age and gender; tumor characteristics including location, size, pathological diagnosis, number of lymph nodes, number of metastatic lymph nodes, differentiation, surgical margin positivity, perineural invasion, lymphovascular invasion, TNM stage and clinical stage (reported according to the pathological classification criteria of the 7th Edition of the American Joint Committee on Cancer guidelines and the Union International Contre Le Cancer criteria for CRC), liver metastasis. Additionally, surgical characteristics including type and extent of surgery, whether ostomy was opened, laboratory measurements (including complete blood count; CBC) length of stay in hospital, follow-up time; complications including leakage, infection and recurrence, and finally, mortality state (early mortality was defined as death occurring within 30 days of surgery).

Patients were called for check-up at regular intervals for an average of 21 months (0-40) postoperatively, and necessary examinations were performed. All outcomes such as leakage, infection, recurrence and death were recorded.

Laboratory Analysis

Blood samples were acquired from the antecubital vein for the measurement of the CBC before the operation. CBC, including hemoglobin and hematocrit values, white blood cell, neutrophil, lymphocyte, platelet counts, and MPV and RDW values were measured via use of routine devices (Sysmex XE-5000, Japan and Roche, Cobas E601, Switzerland) within 2 weeks prior to the date of surgery.

Pathological Analysis

All of the specimens obtained from fully resected tumors were sent to the pathology unit of the Eskişehir Osmangazi University for pathological examinations. Lymph node metastasis, depth of infiltration and tumor size, pathological type and degree of differentiation, radial surgical margin positivity, distal surgical margin positivity, perineural invasion, and lymphovascular invasion were reported by qualified pathologists.

Statistical Analysis

All study data were entered into an SPSS v25 (SPSS Inc., Chicago, IL, USA) database and analyses were performed. Q-Q plots and histograms were used to assess quantitative variable distributions. Quantitative variables were depicted with mean±standard deviation or median (1st quartile - 3rd quartile) values with regard to normality of distribution (normal and non-normal, respectively), and as frequency (percentage) for categorical data. Between-group comparisons were done with the Mann-Whitney U test or the Kruskal-Wallis test depending on the number of groups being compared, and subsequent post-hoc analyses after Kruskal-Wallis tests were performed with the Bonferroni correction method. Spearman correlation coefficients were calculated to evaluate relationships between quantitative variables. Mortality prediction performance of the RDW was assessed by using Receiver Operating Characteristic (ROC) curve analysis. Optimal cut-off point was determined by using Youden index. Two-tailed p values were calculated and values of $p<0.05$ were considered to show statistical significance.

RESULTS

Seventy female and 118 male patients were included in our study, and the mean age of the patients was 66.28±11.71 (range 36 - 87) years. Patients and tumor characteristics, laboratory measurements and data obtained throughout clinical follow-up studies are depicted in **Table 1**.

The median RDW value of patients with T3 or T4 tumors was found to be significantly higher than that of patients with T1 or T2 tumors ($p < 0.001$). We also found a significant relationship between RDW and gender (female > male, p=0.033), tumor stage (stage 1 values lower than stage 2 and 3 values, p=0.010) and mortality. A total of 7 patients had early mortality (postoperative days 0, 2, 3, 5, 14, 22 and 29). The preoperative RDW values of patients who died during this period were significantly higher compared to the other patients (p=0.012). There were no relationships between RDW and any other parameters analyzed (**Table 2**)

When tumor localizations were evaluated, a significant difference was found between the RDW values of patients with right colon tumor (n=67, 35.64%) and patients with rectal tumor (n=74, 39.36%) (p=0.004). Since the number of patients with tumors in other localizations such as the transverse colon (n=15, 7.98%), descending colon (n=16, 8.51%), sigmoid colon and rectosigmoid region (n=16, 8.51%) was insufficient, reliable statistical evaluations could not be performed with respect to specific sites (**Figure 1a**, **Table 1**). However, when tumor localizations were grouped, the median RDW values of patients with tumors in the right or transverse colon were significantly higher than that of patients with tumors in the descending or sigmoid colon or the rectum (p<0.001) (**Figure 1b**).

In addition, the median RDW value of patients who died was significantly higher compared to those who survived (p=0.001) (**Figure 2**).

There were significant weak positive correlations between RDW and several continuous variables, including age (r=0.233, p<0.001), tumor size (r=0.229, p=0.002) and length of stay in the hospital (r=0.167, p=0.022). There were no significant correlations between RDW values and the number of lymph nodes or the number of metastatic lymph nodes (**Table 3**).

Mortality prediction success of the RDW was found to be statistically significant (AUC: 0.704, 95.0% CI: 0.615 - 0.793, p<0.001) (**Figure 3**). RDW had 75.7% sensitivity, 67.5% specificity, 69.1% accuracy, 36.4% positive predictive value and 91.9% negative predictive value to predict mortality for the cut-off point of 15.7 (equal or higher values predict mortality) (**Table 4**).

Table 1. Summary of patients and tumor characteristics and laboratory measurements

Age	66.28±11.71
Gender	
Female	70 (37.23%)
Male	118 (62.77%)
Location	
Right colon	67 (35.64%)
Transverse colon	15 (7.98%)
Descending colon	16 (8.51%)
Sigmoid colon & rectosigmoid region	16 (8.51%)
Rectum	74 (39.36%)
Pathological diagnosis	
Non-mucinous adenocarcinoma	138 (73.40%)
Mucinous adenocarcinoma	50 (26.60%)
Tumor size	40 (27.5 - 60)
Number of lymph nodes	23 (16 - 34.5)
Number of metastatic lymph nodes	0 (0 - 1)
Differentiation	
Poor	20 (10.64%)
Moderate	144 (76.60%)
Well	24 (12.77%)
Radial surgical margin positivity	4 (2.13%)
Distal surgical margin positivity	3 (1.60%)
Perineural invasion	42 (22.34%)
Lymphovascular invasion	66 (35.11%)
T stage	
T1	6 (3.19%)
T2	33 (17.55%)
T3	118 (62.77%)
T4	31 (16.49%)
N stage	
N0	117 (62.23%)
N1	48 (25.53%)
N2	23 (12.23%)
Stage	
Stage 1	31 (16.49%)
Stage 2	85 (45.21%)
Stage 3	72 (38.30%)
Liver metastasis	1 (0.53%)
Type of surgery	
Laparoscopy	33 (17.55%)
Open surgery	155 (82.45%)
Operation	
Right hemicolectomy	53 (28.19%)
Transverse hemicolectomy	10 (5.32%)
Left hemicolectomy	21 (11.17%)
Anterior resection	24 (12.77%)
Low anterior resection	62 (32.98%)
Abdominoperineal resection	17 (9.04%)
Other	1 (0.53%)
Ostomy	76 (40.43%)
Hemoglobin	12.32±2.12
Hematocrit	37.89±5.56
White blood cell (x1000)	7.34 (5.90 - 9.60)
Neutrophil (x1000)	4.83 (3.91 - 6.71)
Lymphocyte (x1000)	1.48 (1.05 - 2.01)
Platelet (x1000)	279 (223 - 372)
MPV	9.56±1.15
RDW	14.65 (13.30 - 17.55)
Length of stay in hospital, days	6 (5 - 9)
Follow-up time, months	21 (12.5 - 28)
Leakage	7 (3.72%)
Infection	30 (15.96%)
Recurrence	12 (6.38%)
Mortality	37 (19.68%)
Early mortality (≤30 days)	7 (3.72%)

Data are given as mean±standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

Table 2. Summary of RDW with regard to patients and tumor characteristics

	Median (1st quartile-3rd quartile)	p
Gender		0.033
Female	15.5 (13.7 - 17.9)	
Male	14.55 (13.2 - 17.2)	
Location		<0.001
Right colon & Transverse colon	16.25 (14.0 - 19.1)	
Descending colon & Sigmoid colon & Rectum	14.2 (13.3 - 16.6)	
Pathological diagnosis		0.149
Non-mucinous adenocarcinoma	14.9 (13.5 - 17.8)	
Mucinous adenocarcinoma	14.35 (13.2 - 17.2)	
Differentiation		0.477
Poor	13.95 (13.1 - 17.4)	
Moderate	14.65 (13.4 - 17.35)	
Well	16.1 (13.5 - 17.65)	
Perineural invasion		0.504
No	14.65 (13.4 - 17.8)	
Yes	14.65 (13.3 - 17.2)	
Lymphovascular invasion		0.211
No	14.9 (13.3 - 17.8)	
Yes	14.4 (13.3 - 17.1)	
T stage		0.001
T1 & T2	13.8 (13.2 - 15.2)	
T3 & T4	15.3 (13.5 - 18.1)	
N stage		0.586
N0	14.8 (13.5 - 17.7)	
N1	14.85 (13.3 - 16.9)	
N2	14.3 (13.1 - 18.4)	
Stage		0.010
Stage 1	13.9 (13.2 - 15.3)	
Stage 2 & 3	15.1 (13.5 - 17.9)	
Leakage		0.271
No	14.6 (13.3 - 17.2)	
Yes	17.9 (13.2 - 19.4)	
Infection		0.263
No	15.1 (13.3 - 17.8)	
Yes	14.35 (13.5 - 15.7)	
Recurrence		0.086
No	14.6 (13.3 - 17.2)	
Yes	17.2 (15 - 18.75)	
Status		<0.001
Alive	14.4 (13.3 - 17.2)	
Exitus	17.1 (15.7 - 19.1)	
Early mortality (≤30 days)		0.012
No	14.6 (13.3 - 17.2)	
Yes	18.6 (17.1 - 20.2)	

Same letters denote the lack of statistically significant differences between groups

Table 3. Relationships between RDW and continuous variables

	r	p
Age	0.233	0.001
Tumor size	0.229	0.002
Number of lymph nodes	0.048	0.516
Number of metastatic lymph nodes	-0.059	0.420
Length of stay in hospital	0.167	0.022

r: Spearman correlation coefficient

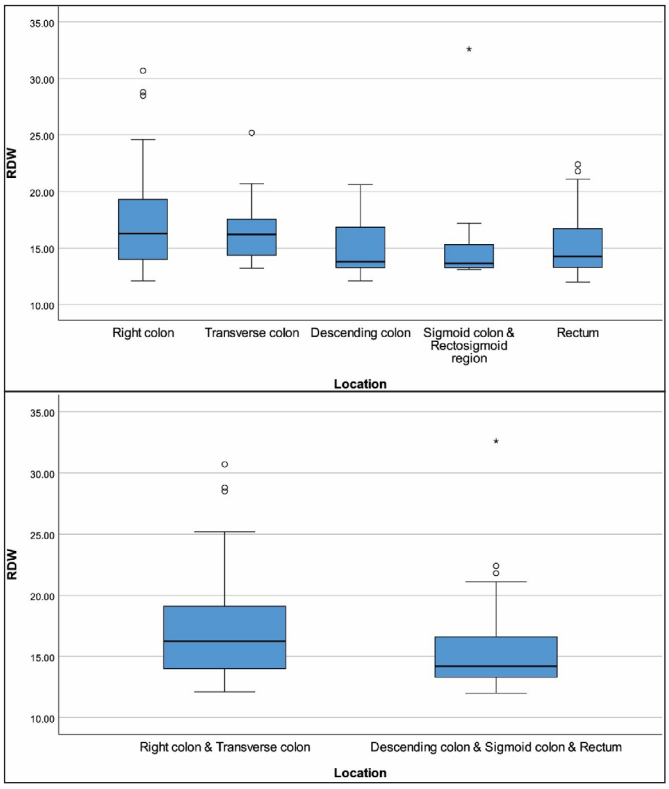

Figure 1a, 1b. Relationships between RDW and tumor site

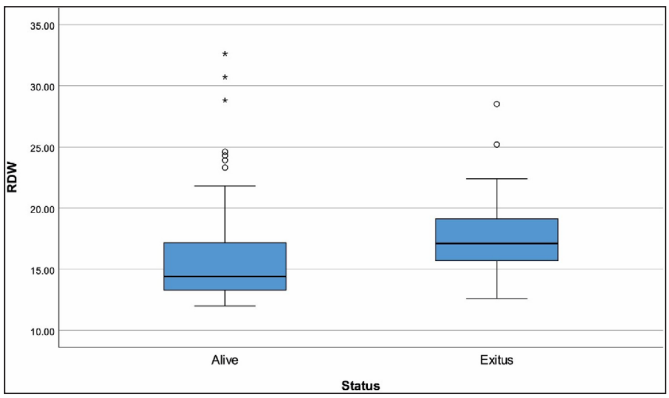

Figure 2. Relationship between RDW and mortality

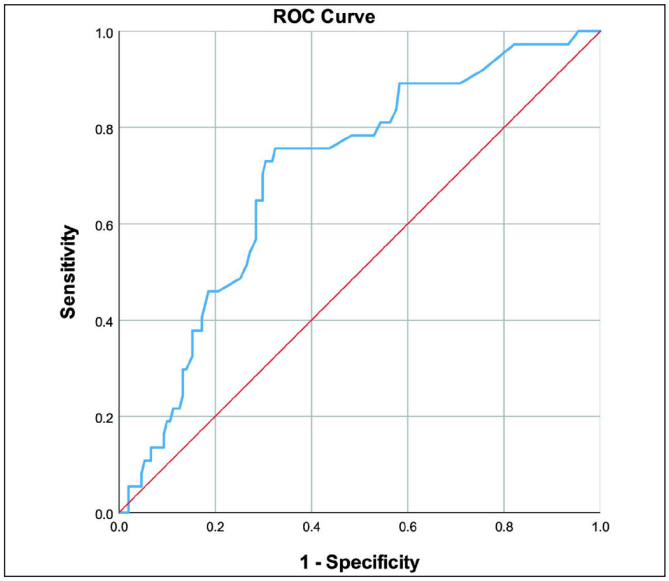

Figure 3. ROC curve of the RDW to predict mortality

Table 4. Performance of the RDW to predict mortality	
Cut-off	≥15.7
Sensitivity	75.7%
Specificity	67.5%
Accuracy	69.1%
PPV	36.4%
NPV	91.9%
AUC (95.0% CI)	0.704 (0.615 - 0.793)
p	<0.001

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals

DISCUSSION

According to the results we obtained, it was found that the RDW values showed significant differences with respect to gender, age, tumor localization, T stage, clinical stage, duration of post-operative hospitalization, tumor size, early death, and death during follow-up.

CRC is the third most common cancer in both men and women and the second leading cause of cancer-related death (2,9,10). For these reasons, early diagnosis, proper treatment and prognostic assessment of CRC are critical. Blood tests are of great importance for diagnosis, treatment and prognosis, and help clinicians in assessing patients. In addition, the fact that blood tests are easier and less costly supports the focus of interest in the search for new markers associated with the diagnosis, treatment and prognosis of CRC (11-14). RDW is an indicator of the heterogeneity of red blood cell volume and is used in the diagnosis and prognosis of several diseases like anemia, some cardiovascular and infectious diseases and some types of cancer including lung, stomach, esophageal, hepatocellular, breast cancers, and, in recent years, CRC (15-23). In some studies, it has been shown that the RDW level of patients with CRC is higher than that of controls (3,4,7,8,24). The underlying cause of the relationship between RDW and cancer is unknown (1,25), but several possible mechanisms have been considered. The first is the hypothesis that inflammation and oxidative stress around the tumor may increase RDW. The second is that the tumor may indirectly cause changes in erythropoiesis by causing malnutrition, which may increase RDW. Finally, it is also possible that iron deficiency anemia due to bleeding seen in patients with CRC may increase RDW (26-28). All these results show that high RDW may be an independent risk factor for CRC (13).

In some studies, it has been shown that high RDW values might be a negative predictors of survival in several types of malignancies including lung, gastric, esophageal, hepatocellular cancers and breast cancer (1,15,17-20,29). A similar relationship has been suggested to exist between elevated RDW and CRC (8,30). Prior studies have also reported that RDW can independently assess the prognosis of patients with colorectal cancer (13). Pedrazzani et al. (1) have shown that CRC patients with high RDW have a lower 10-year overall survival compared to those with lower RDW. Zhang et al. (30) found high RDW to be associated with poorer overall and disease-free survival in their study of 625 patients with rectal cancer who underwent curative surgery without neoadjuvant therapy. Li et al. (13), in a retrospective analysis of 168 colorectal cancer patients, found a positive relationship between RDW values and both 3- and 5-year overall and disease free survival. Similarly, high RDW was found to be associated with worse overall survival by Kust et al. (7) in a retrospective study of 90 patients with CRC; however, this relationship was only present in subjects with stage II cancer. Several other studies have also shown similar results (1,4,31). In this study, we also showed that the preoperative mean RDW values of patients who died during postoperative follow-up were significantly higher than those who survived. Also, interestingly, we found that patients who died within the first 30 days after surgery had higher RDW values. Additionally, it was observed that patients with high RDW had longer hospital stay after surgery. This significant relationship between high RDW and CRC-related deaths may be due to chronic inflammation due to cancer, iron deficiency anemia due to chronic blood loss in CRC, folate deficiency, changes in erythropoiesis, dyslipidemia and other metabolic abnormalities (32-36).

Today, TNM stage is accepted as the most significant prognostic factor for CRC (3). Many researchers have shown that RDW was significantly associated with clinical stage, T stage, N stage, M stage and tumor size in subjects with CRC. For instance, Song et al. (32) found that RDW values were associated with TNM stage, pT stage, and pM stage, similar to the results put forth by Yang and colleagues (8). Importantly, they also found that the level of RDW was associated with tumor size. However, there was a difference between the two studies with regard to the relationship between pN stage and RDW level. While the study by Yang et al. (8) found a significant positive correlation between RDW and pN stage, the study by Song et al. (32) did not. Moreover, Yang et al. (8) showed that RDW values in stage 3 and 4 CRC were higher compared to stage 1 and 2, similar to our results. In another research, RDW values were found to be associated with clinical stage, and T status, but not N or M status (4). Consistent with the results by Yang et al. (8), RDW values of CRC patients at the T3 and T4 stages in our study were found to be significantly higher than those with disease stages T1 and T2. We found similar results with regard to comparisons based on clinical staging. That is, the RDW levels of stage 1 patients were lower compared to patients with stage 2 or 3 disease. Likewise, we found that, as the tumor size increases, the RDW value also increases. Taking into

account these studies and our findings, it appears that increased tumor burden in CRC patients is associated with RDW elevation. Despite the fact that there are various studies showing the aforementioned relationship, the underlying causes for said relationship is not known exactly, but the increase in inflammatory activity around the tumor is likely a primary factor.

The relationship between the site of the CRC tumor and RDW has also been an interesting subject. In a study, RDW level was found to be significantly higher in right sided CRC tumors than left sided CRC tumors, similar to the present study (37). We also found higher RDW in patients with CRC tumors localized in the right or transverse colon compared to those with tumors in the descending colon, sigmoid colon or rectum. This interesting association may be a consequence of iron deficiency anemia. Right colon tumors are known to have a greater frequency of demonstrating bleeding and associated symptoms. As a result, anemia is a relatively more common symptom in tumors of the right colon compared to other regions of the colon (38).

Additionally, significant positive correlations between age and RDW levels have been reported previously (1,34,39), and we found supportive results in the current study. The relationship between gender and RDW is still unclear. Some studies have shown that the RDW is slightly higher in females (40), while others have found no significant association between RDW and gender. In our study, we also found that the RDW values of females were significantly higher than that of males; however, current data is not sufficient to draw conclusions regarding this matter.

Although our study showed significant relationships between RDW and various CRC characteristics that were largely consistent with previous studies, it has several limitations that must be noted. First, this is a single center and retrospective cohort study and has relatively few patients. Additionally, a control group was not included in this study, and therefore, comparisons with data from healthy patients were not possible. These may have led to various types of bias. Second, the number of patients in several sub-group analyses could have limited statistical reliability, and therefore, comparisons based on parameters such as tumor localization, pathological diagnosis, differentiation, T stage and N stage should be cautiously evaluated. Considering the presence of various studies showing some degree of relationship between elevated RDW and CRC prognosis, it appears that there is a need for further prospective, long-term multicenter studies with a larger number of patients to accurately assess the diagnostic and/or prognostic value of RDW in patients with CRC.

CONCLUSION

Both our study and similar studies have shown that CRC patients with high RDW levels have shorter postoperative survival or greater likelihood of death. Furthermore, elevated RDW seems to be associated with greater tumor size and more advanced clinical and TNM stages. All these relationships indicate a positive correlation between RDW values and the severity of CRC, and suggest that RDW may have a potential function as a diagnostic or prognostic marker in patients with CRC. For instance, it will not be surprising to suspect higher tumor burden in subjects with relatively elevated RDW –which could potentially be used to make decisions on surgical approach. However, in order for RDW to be accepted as a molecular marker associated with prognosis and survival in CRC, more comprehensive studies which can perform longer-term follow-up are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The protocol of this study was approved by the Non-Interventional Clinical Researches Ethics Committee of Eskişehir Osmangazi University (Date:15.06.2021, Decision No: 09).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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