

Research Article

Red Blood Cell Distribution Width as a Possible Predictor of Diagnosis and Survival in Gastric Cancer

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Abstract

Objectives: To compare the preoperative Red Cell Distribution Width (RDW) value in curatively-operated gastric cancer (GC) patients without receiving neoadjuvant chemotherapy (NACT) vs. control group, with the aim of investigating its preoperative prognostic effect.

Methods: Receiver Operator Characteristics (ROC) curve of RDW value was plotted for DFS. The area under curve (AUC) of the RDW was 0.714 with 73.5% sensitivity and >5.5 with 71.1% specificity. Patients were divided into 2 groups as RDW ≤15.5 and RDW >15.5.

Results: The study included 330 GC patients (37.7% female and 62.3% male) and 330 healthy controls (63.9% male and 36.1% female). ROC curves were used to confirm the predictive role of preoperative RDW value in predicting the presence of GC. For GC, the AUC of RDW was 0.665 with 61.3% sensitivity and 14.1 with 64% specificity. There was a positive correlation between disease stage and RDW in GC patients ($Rho=0.338$, $p<0.001$). Five-year DFS was 81.1% in the low-RDW group and 61.9% in the high-RDW group ($p=0.001$). Similarly, Corresponding 5-year overall survival (OS) rates were 74.4% and 57.7 ($p=0.001$). In multivariate analysis, male gender, stage III disease, high CEA, and RDW ≥ 15.5 were the factors associated with worse DFS, whereas adjuvant therapy ($p=0.036$) prolonged DFS significantly.

Conclusion: In our study, preoperative RDW was found to be both predictive and prognostic for GC.

Keywords: Biomarker, gastric cancer, inflammation, prognostic, red cell distribution width, survival

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Gastric cancer (GC) is one of the most common cancer-related deaths worldwide. The prevalence of advanced disease at the time of diagnosis reflects the high mortality rate. In addition to the development of new surgical techniques, GC is still a very fatal disease despite the use of chemotherapy and radiotherapy. The positive effect of these

treatments on survival in curatively resected-GC patients has become more pronounced over time; however, there is still no consensus on the best treatment approach. Therefore, determining the individual risk along with independent prognostic markers for follow-up procedures has become an important issue in this field of research for GC.^[1–4]

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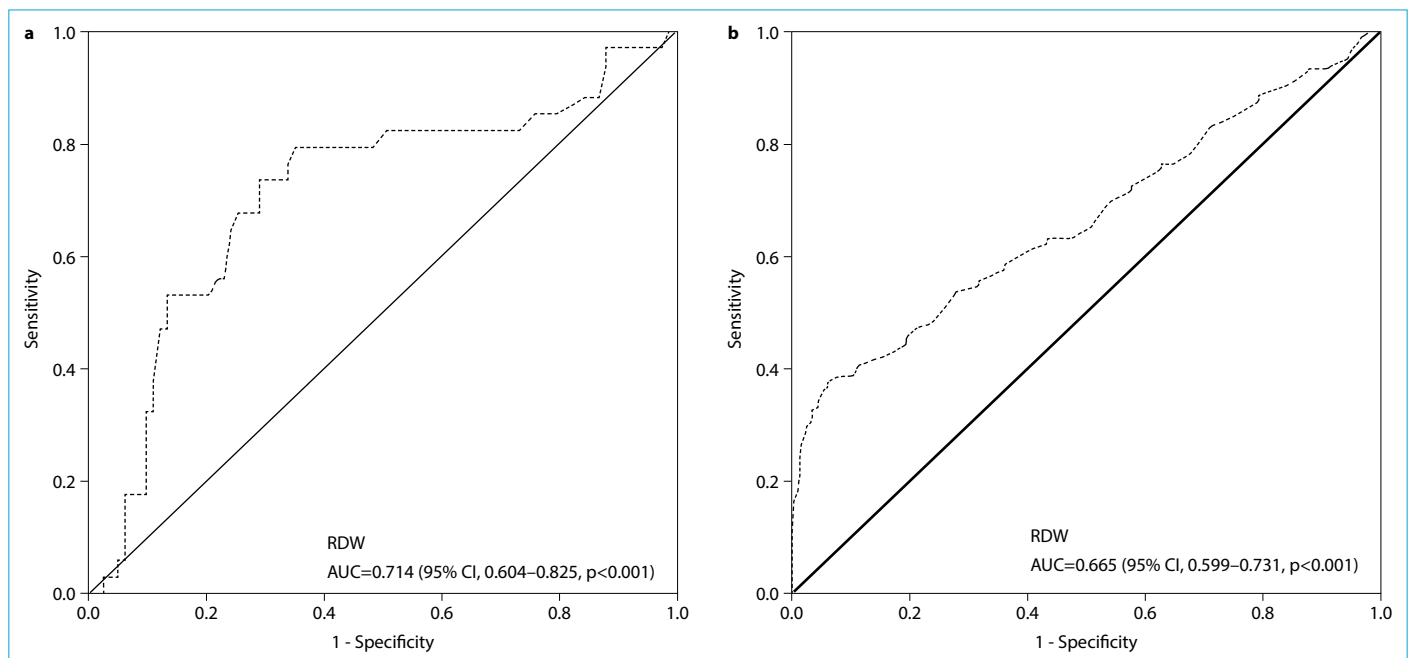


Figure 1. (a) ROC curve analysis to verify the predictive power of preoperative RDW (%) in predicting presence of GC. **(b)** ROC curve of Preoperative RDW (%) for DFS.

Numerous studies and metaanalyses have proven potential prognostic values of many common tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), and CA 72-4 and these markers are still used routinely in the screening, diagnosis, and post-surgical follow-up of GC.^[5,6]

Systemic inflammatory response has been shown to induce tumor invasion and migration as a result of DNA damage and angiogenesis stimulation.^[7,8] It is quite interesting that some prognostic scoring systems such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, C-reactive protein/albumin ratio, prognostic nutritional index, and systemic immune-inflammatory index have been reported to play prognostic role in various types of cancer including GC.^[9–12]

Red cell distribution width (RDW) is a routine parameter of complete blood count and shows heterogeneity in erythrocyte size. It is widely used in the diagnosis of anemia. RDW has been reported to tend to increase in chronic inflammation and malnutrition. The close correlations of RDW with systemic inflammation and nutritional status suggest that RDW may be a useful prognostic indicator in cancer patients.^[13–16]

In the present study, we intended to compare the preoperative RDW value in non-metastatic GC patients who underwent curative surgery without receiving neoadjuvant therapy vs. healthy controls, with the goal of evaluating the prognostic effect of preoperative RDW in GC.

Methods

Study Population

The study group consisted of 330 patients who were followed up between 2007 and 2017 at the medical oncology department of Yüzüncü Yıl University Faculty of Medicine, Van, Turkey. A total of 330 healthy controls without any history of malignant disease or drug use were randomly selected from those who apply to the hospital outpatient clinics for routine control. Patients with any of the following criteria were excluded from the study; unoperated patients, metastatic stage, receiving neoadjuvant treatment, presence of benign or malignant hematologic disease, <18 years of age, acute or chronic infections, rheumatologic disease, history of a second primary cancer, histologic subtypes other than adenocarcinoma, and those with missing data. Patients were restaged according to the AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 8th edition.

Data Collection

Demographic data of the patients including age, gender, type of surgery (e.g., total, subtotal, D1, or D2 dissection), primary tumor localization, tumor stage, adjuvant treatment, recurrence status, site of recurrence, preoperative/operative laboratory results, and final status were obtained from the written archive files. Gastric tumor localization was classified into 3 groups as upper 1/3 (gastroesophageal junction and cardia), middle 2/3 (corpus), and lower 1/3

Table 1. Demographic and laboratory data of patient and control groups

Characteristics	Control (n=330)		Patient (n=330)		p	RDW ≤15.5 (n=185)		RDW >15.5 (n=145)		p
	n	%	n	%		n	%	n	%	
Gender										
Female	119	36.1	113	37.7	0.676	74	40	45	31	0.117
Male	211	63.9	187	62.3		111	60	100	69	
Age										
Median	58.0		58.0		0.957	58		58		0.384
(min.-max.)	(19-87)		(24-97)			(24-84)		(29-97)		
<70			270	81.8		153	82.7	117	80.7	0.638
≥70			60	18.2		32	17.3	28	19.3	
Surgery										
Subtotal gastrectomy			158	47.9		91	49.2	67	46.2	0.590
Total gastrectomy			172	52.1		94	50.8	78	53.8	
D1 dissection			217	65.8		117	63.2	100	69.0	0.221
D2 dissection			113	34.2		68	36.8	45	31.0	
Margin status										
R0			316	95.8		180	97.3	136	93.8	0.168
R1			14	4.2		5	2.7	9	6.2	
Lauren										
Intestinal			185	56.1		108	58.4	77	53.1	0.324
Diffuse			125	37.9		64	34.6	61	42.1	
Mixt			20	6.1		13	7	7	4.8	
Localization										
1/3			59	17.9		30	15.7	21	14.5	0.367
2/3			246	74.6		139	75.2	107	73.8	
3/3			12	3.6		6	5.7	6	4.1	
linitis plastica			13	3.9		10	3.4	11	7.6	
Histology										
Adenocancer			247	74.8		136	73.5	111	76.6	0.561
TYH			67	20.3		38	20.5	29	20	
Mucinous			16	4.8		11	5.9	5	3.4	
Grade										
1			44	13.5		27	14.8	17	11.9	0.412
2			177	54.5		102	56	75	52.4	
3			104	32		53	29.1	51	35.7	
Stage										
I			77	23.3		52	28.1	25	17.2	0.067
II			123	37.3		64	34.6	59	40.7	
III			130	39.4		69	37.3	61	42.1	
Adjuvant therapy										
No			83	25.2		55	29.7	28	19.3	0.03
Yes			247	74.8		130	70.3	117	80.7	
Recurrence and localization										
Yes			82	24.8		31	16.8	51	35.2	0.001
Locoregional			12	14.8		3	9.7	9	18	
Liver			26	32.1		7	22.6	19	38	
Peritoneum			24	29.6		12	38.7	12	24	
Distant lymph node			2	2.5		2	6.5	0	0	
Lung			6	7.4		1	3.2	5	10	
Bone			5	6.2		2	6.5	3	6	
Others (ovary, breast, bladder)			6	7.4		4	7.9	2	4	
Last status										
Exitus			91	27.6		38	20.5	53	36.6	0.001

Table 1 (cont). Demographic and laboratory data of patient and control groups

Characteristics	Mean±SD	Mean±SD	p	Mean±SD	Mean±SD	p
CEA (ng/ml)		4.68±20.52		2.57±4.13	8.03±32.52	0.158
CA19-9 (U/ml)		86.50±373.17		102.48±118.10	61.36±290.07	0.557
Hb (g/dL)	13.81±1.63	12.35±2.05	0.041	12.72±2.18	11.82±1.72	0.032
RDW (%)	13.81±1.08	15.53±3.37	<0.001	13.99±1.75	18.35±2.76	<0.001
TPC (10 ³ /UI)	282.33±64.34	312.50±123.83	0.001	294.82±110.70	338.04±137.74	0.045
TNC (10 ³ /UI)	3.99±1.29	4.88±2.49	0.065	4.55±1.78	5.37±3.20	0.062
TLC (10 ³ /UI)	2.57±0.67	2.01±0.70	0.045	2.00±0.60	2.03±0.81	0.811
TMC (10 ³ /UI)	0.46±0.67	0.59±0.25	0.031	0.56±0.22	0.63±0.28	0.147
NLR		2.75±2.15		2.45±1.24	3.18±2.98	0.055

CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryogenic antigen; DFS: Disease-free survival; Hb: Hemoglobin; NLR: Neutrophil lymphocyte ratio; OS: Overall survival; RDW: Red blood cell distribution width; SD: Standard deviation; TLC: Total lymphocyte count; TMC: Total monocyte count; TNC: Total neutrophil count; TPC: Total platelet count.

(antrum and pyloricum). Disease-free survival (DFS) was calculated as the time from the initiation of treatment to the progression. Overall survival (OS) was calculated as the time from the date of diagnosis to the date of death or last follow up control. Receiver Operator Characteristics (ROC) curve was plotted to estimate the optimal cut-off value of RDW for DFS. The Area under the curve (AUC) of RDW was 0.714 (95%CI =0.604–0.825, $p=0.013$) with 73.5% sensitivity and >15.5 with 71.1% specificity (Fig. 1a). Patients were grouped as RDW ≤ 15.5 and RDW >15.5 .

Ethics Committee Approval

This study was conducted in accordance with the Declaration of Helsinki and it was reviewed and approved by the Ethics Committee of the Yüzüncü Yıl University Faculty of Medicine (2020/01-16).

Statistical Analysis

Statistical Package for Social Sciences 22.0 for Windows software (Armonk NY, IBM Corp. 2013) was used for all statistical analysis. Descriptive statistics were presented as mean, standard deviation, minimum, and maximum for numerical variables and as numbers and percentages for categorical variables. Student's t test was used when the numerical variable provided the normal distribution condition in two independent groups, whereas Mann Whitney U test was used when the normal distribution condition was not provided. Chi-square analysis was used to compare the ratios in the groups. Monte Carlo simulation was applied when the conditions were not met. Survival analyzes were performed by Kaplan Meier Analysis. The determinant factors were examined by Cox Regression Analysis. Forward stepwise model was used for the factors with $p<0.150$ which were determined in univariate analysis. Cut-off value was determined with ROC curve analysis. An overall 5%

alpha error level was used to infer statistical significance. Statistical significance level was accepted as $p<0.05$.

Results

This study included 330 (37.7% female and 62.3% male) GC patients and 221 (63.9% male and 36.1% female) healthy controls. The median age was 58 (range, 24-97) years in patient group and 58 (range, 19-87) years in the control group, with no significant difference between the groups in terms of age and gender ($p=0.676$, $p=0.957$, respectively) demographic data are presented in Table 1.

The mean hemoglobin value was 12.3 ± 2.0 in the patient group and 13.8 ± 1.6 in the control group ($p=0.041$). The mean RDW value was 15.4 ± 3.3 in the patient group and 13.8 ± 1.0 in the control group ($p<0.001$). The laboratory data of both groups and RDW subgroups in GC group are summarized in Table 1.

We used ROC curve to confirm the decisive strength of preoperative RDW value in predicting the presence of GC. For GC, the AUC of RDW was 0.665 (95% CI=0.599–0.731, $p<0.001$) with 61.3% sensitivity and 14.1 with 64% specificity (Fig. 1b).

During the median follow-up time of 50 months, 82 (24.8%) patients developed recurrence and 91 (27.6%) patients died (Table 1). RDW values according to the tumor stage in GC patients are shown in Figure 2. There was a positive correlation between stage and RDW ($Rho=0.338$, $p<0.001$) (Figure 2).

In survival analysis, 1-, 2-, 3-, 5-, and 10-year DFS rates were 91.5%, 82.6%, 76.4%, 72.7%, and 70.5%, respectively, with corresponding OS rates of 92.0%, 84.5%, 75.6%, 65.2%, and 58.9%. DFS and OS rates by RDW groups are given in Table 2.

In the Kaplan Meier analysis, DFS was significantly longer in the patients with RDW <15.5 than that in the patients with RDW >15.5 (log rank $p=0.001$). In stage I, II, and III patients,

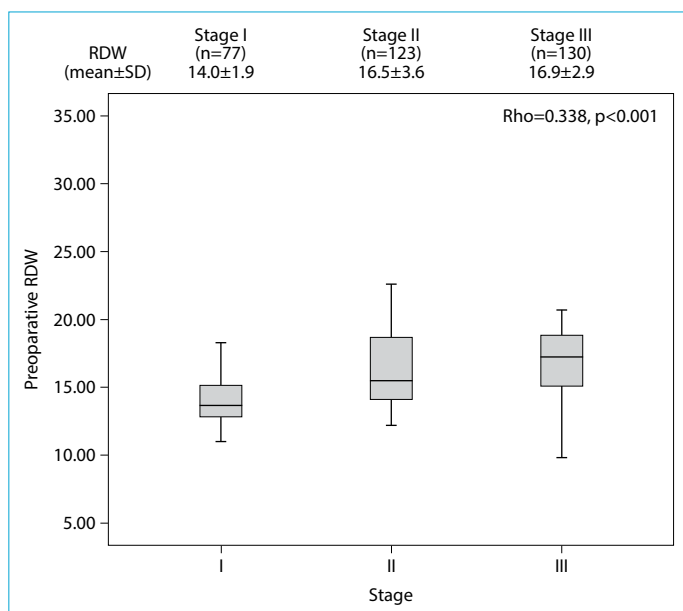


Table 2. 1-, 2-, 3-, 5-, and 10-year survival rates of all patients according to RDW groups

Years	Patients (%)	RDW ≤15.5 (%)	RDW >15.5 (%)
DFS			
1	91.5	95.5	85.9
2	82.6	86.4	73.3
3	76.4	83.5	66.3
5	72.7	81.1	61.9
10	70.5	80.0	58.3
OS			
1	92.0	93.4	90.2
2	84.5	87	81.4
3	75.6	83.3	67.8
5	65.2	74.4	57.7
10	58.9	69.1	52.5

Figure 2. RDW values according to stages and correlation of RDW with stage.

RDW: Red blood cell distribution width; DFS: Disease-free survival; OS: Overall survival.

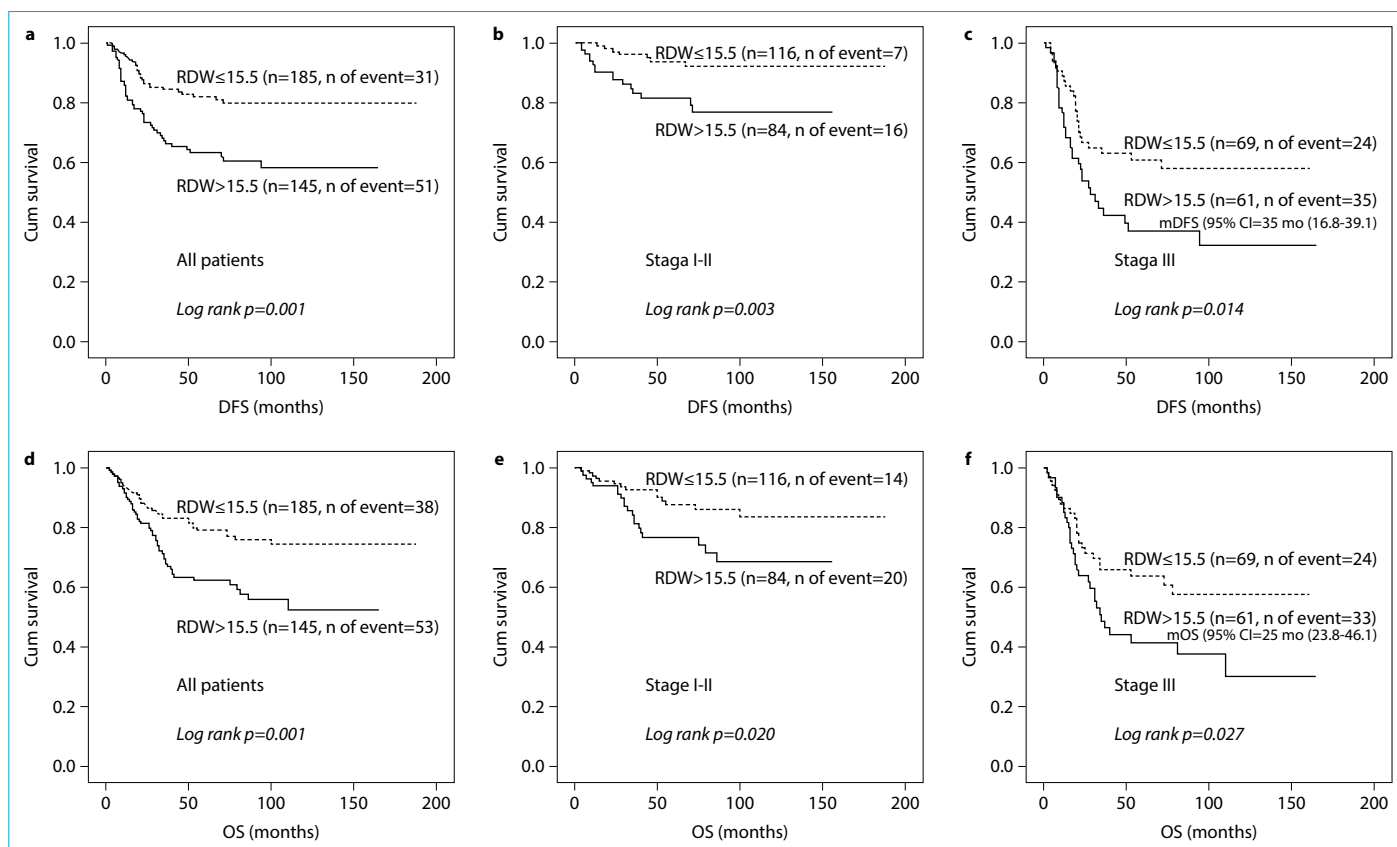


Figure 3. DFS and OS according to stages and RDW groups. **(a)** DFS according to RDW groups in all patients. **(b)** DFS according to RDW groups in Stage I and II patients. **(c)** DFS according to RDW groups in Stage III patients. **(d)** OS according to RDW groups in all patients. **(e)** OS according to RDW groups in Stage I and II patients. **(f)** OS Stage according to RDW groups in III patients.

DFS was found to be significantly longer in those with RDW ≤15.5 compared to that in the patients with RDW >15.5 (log rank $p=0.003$). In stage III patients with RDW >15.5, the median

DFS was 28 months (Fig. 3a–c). In all patients, OS was found to be significantly longer in those with RDW ≤15.5 than that in patients with RDW >15.5 (log rank $p=0.001$).

Table 3. Univariate and multivariate analysis for DFS

Characteristics	Univariate			Multivariate		
	HR	95% CI for HR	Sig.	HR	95% CI for HR	Sig.
Gender						
Men vs. women	1.704	1.037–2.798	0.035	3.240	1.147–3.146	0.046
Age (years)						
≥70 vs. <70	1.106	0.816–3.606	0.652			
Margin status						
Positive vs. negative	3.713	1.783–7.730	0.001			
LN dissection						
D1 vs. D2	1.945	1.231–3.071	0.004			
Surgery						
Total vs. subtotal	1.031	0.644–1.652	0.898			
Stage						
III vs. I+II	4.962	3.094–7.958	<0.001	15.497	2.306–104.115	0.005
Localization						
1/3	Ref.		0.007	Ref.		0.094
2/3	0.811	0.466–1.412	0.459	1.355	0.292–18.982	0.421
3/3	0.255	0.033–1.921	0.185	0.904	0.211–19.176	0.360
Linitis plastica	2.967	1.217–7.233	0.017	8.773	2.144–20.376	0.016
Lauran						
Intestinal	Ref.		0.402			
Diffuse	0.864	0.546–1.365	0.531			
Mixt	0.469	0.146–1.504	0.203			
Histology						
Adenocancer	Ref.		0.398			
Ring-cell	0.788	0.440–1.408	0.421			
Mucinous	1.522	0.66	0.326			
Grade						
3 vs. 1+2	1.399	0.892–2.194	0.143			
Adjuvant treatment						
Yes vs. no	0.585	0.398–0.745	0.005	0.710	0.511–0.862	0.036
CEA (ng/m)	1.011	1.002–1.019	0.008	1.015	1.002–1.028	0.022
CA-19.9 (U/ml)	1.000	0.999–1.001	0.615			
Hb (g/dL)	0.828	0.6920.989	0.038			
TPC (10 ³ /UI)	1.000	0.997–1.003	0.813			
TNC (10 ³ /UI)	1.064	0.920–1.231	0.400			
TLC (10 ³ /UI)	0.996	0.597–1.661	0.989			
TMC (10 ³ /UI)	2.398	0.343–6.722	0.378			
NLR	1.038	0.841–1.281	0.726			
RDW (%)						
<15.5 vs ≥15.5	3.887	1.812–8.332	<0.001	5.795	1.885–11.322	0.001

CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryogenic antigen; DFS: Disease-free survival; Hb: Hemoglobin; NLR: Neutrophil lymphocyte ratio; OS: Overall survival; RDW: Red blood cell distribution width; SD: Standard deviation; TLC: Total lymphocyte count; TMC: Total monocyte count; TNC: Total neutrophil count; TPC: Total platelet count.

In patients with stage I, II, and III disease, OS was found to be statistically significantly longer in those with RDW ≤15.5 compared to the patients with RDW >15.5 group (log rank p=0.020). In stage III patients with RDW >15.5, the median OS was 35 months (Fig. 3d–f).

In univariate analysis; gender, surgical margin status, type of lymph node dissection, stage, tumor localization, adjuvant therapy, CEA, hemoglobin level, and RDW were the factors affecting DFS (p=0.035, p=0.001, p=0.001, p<0.001, p=0.007, p=0.005, p=0.008, p=0.038, p<0.001, respective-

ly). The parameters with $p \leq 0.150$ determined in univariate analysis were subsequently evaluated in multivariate analysis with forward stepwise model. Male gender, stage III disease, high CEA value, and $RDW \geq 15.5$ were the factors associated with poor DFS ($p=0.046$, $p=0.005$, $p=0.016$, $p=0.022$, $p=0.001$, respectively), whereas adjuvant treatment ($p=0.036$) significantly prolonged DFS (Table 3).

Discussion

In this study, we compared the preoperative RDW value in the curatively-operated GC patients without neoadjuvant therapy vs. healthy controls and found the RDW value to be 14.1, with 61.3% sensitivity and 64% specificity in predicting the presence of GC. In addition, we evaluated the prognostic effect of preoperative RDW value in GC patients and found the RDW value to be greater than 15.5, with 73.5% sensitivity and 71.1% specificity for DFS. In our study, we found that high RDW value in all stages significantly reduced both DFS and OS.

Studies have shown that high RDW is strongly associated with increased risk of death and cardiovascular disease.^[17–19] In addition, the relationship between RDW and cancer has been investigated.^[20–22] Seretis et al.^[20] compared the patients with benign lesions to those with breast cancer and showed that RDW was significantly higher in breast cancer patients compared to those with fibroadenoma. They also found that RDW was associated with tumor stage. Likewise, in a study by Beyazit et al.^[21] investigating the value of RDW in patients with biliary obstruction, RDW level was reported to play a role in the differential diagnosis of malignant biliary disease. Supportingly, in our study, the RDW value in patient group was significantly higher than that in the healthy controls.

The high RDW observed in cancer patients is thought to result from an increased inflammation caused by cancer cells or cancer microenvironment. Increased inflammation inhibits the response to erythropoietin and hence shortens erythrocyte life, leading to elevation in RDW. Therefore, elevation in RDW in cancer patients may reflect an increased inflammation. It is widely accepted that inflammation plays an important role in tumor pathogenesis and inflammatory microenvironment of all tumors.^[23]

The determination of non-invasive hematologic and serological prognostic predictors for various cancers has long been under intense investigation. Some serum markers that reflect inflammation, immunity, and nutritional status have been reported to be associated with the prognosis of many cancer types, including GC. Previous studies have shown that RDW is associated with the prognosis of different types of cancer such as lung cancer, prostate cancer,

and esophageal cancer.^[9–12,24–26] In a study of 177 curatively-operated GC patients by Yazici et al.,^[27] the cut-off value for RDW was found to be 16.0, with the greater RDW value having correlation with stage and grade. In addition, the author reported that high RDW was significantly associated with postoperative mortality and disease prognosis. Similarly, Shota et al.^[28] investigated the relation of pre- and post-operative RDW with survival in 221 GC patients and found the cut-off value for pre- and post-operative RDW value to be 14.85 and 14.05, respectively, with 5-year OS rates being 78% in the low-RDW group vs. 52.4% in the high-RDW group. They found post-operative RDW value as the only factor affecting OS.

Cheng et al.^[29] reported that pre-operative RDW value was associated with tumor diameter as an independent prognostic factor for DFS. Wei et al.^[30] analyzed 144 GC patients and showed RDW value to be significantly higher in the patient group than that in the control group, indicating bilirubin and RDW as the potential prognostic factors for survival. Another recent study advocated that RDW can be used as an independent prognostic factor for survival in both elderly and young GC patients.^[31] Similar to the previous studies, RDW was significantly correlated with survival in our study and this correlation was also maintained when we analyzed the patient population according to disease stage. The 5-year survival rate was 57.7% in patients with high-RDW and 74.4% in those with low-RDW, with the RDW value >15.5 augmenting the risk of recurrence by 5.7 times.

Unlike the other studies, our study also included the healthy controls and the number of cases was far greater than those in the other studies. Furthermore, follow-up period was much longer and a subgroup analysis according to the stages was also performed.^[27–30] However, there were some limitations in our study. Although we tried to choose a more homogenous group to prevent bias, our study had a retrospective nature. Secondly, since the follow-up period was far longer, we could not determine the disease-specific survival because we could not identify those who died due to reasons out of GC. Although we found that RDW had a predictive value in patient group compared to healthy controls, the control group in our study consisted of healthy individuals and we do not exactly know the its value in GC patients in whom anemia was due to benign causes. Therefore, our results need to be supported by larger studies.

In conclusion, we found that RDW, which is routinely examined and easily obtained from peripheral blood, can be a predictive marker for the presence of GC in operated-GC patients compared to healthy controls and can be used as a prognostic marker for recurrence and survival in this patient population. However, further studies are needed on

the role of RDW in the screening, diagnosis, and treatment outcomes of GC patients as well as identifying patients at high risk for recurrence.

Disclosures

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and it was reviewed and approved by the Ethics Committee of the Yuzuncu Yil University Faculty of Medicine (2020/01-16).

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declare no conflicts-of-interest related to this article.

Authorship Contributions: Concept – A.S., S.S., M.A., Ab.S.; Design – A.S., O.A., A.A., R.E.; Supervision – S.S., M.N.A., M.C.K., Ab.S.; Resources – A.S., O.A., M.A., M.N.A.; Materials – S.S., A.A., R.E., Ab.S.; Data collection and/or processing – A.S., O.A., M.N.A., Ab.S.; Analysis and/or interpretation – S.S., M.A., M.C.K., R.E.; Literature search – O.A., A.A., M.N.A., Ab.S.; Writing manuscript – A.S., S.S., M.N.A., Ab.S.; Critical review – S.S., A.A., M.C.K., Ab.S.; Other – M.A., A.A., M.N.A., R.E.

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