Comprehensive Analysis of Red Blood Cell Distribution Width as a Preoperative Prognostic Predictor in Gastric Cancer

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Abstract. *Background/Aim:* The aim of the current study was to investigate the impact of the preoperative red cell distribution width (RDW) value on the overall survival (OS) and cancer-specific survival (CSS) of gastric cancer patients. *Patients and Methods:* A total of 366 gastric cancer patients who underwent curative gastrectomy were retrospectively reviewed. Among them, RDW was evaluated in 165 non-elderly and 201 elderly patients. *Results:* Multivariate analysis revealed that pathological stage (pStage), RDW, and carcinoembryonic antigen (CEA), were independent prognostic factors of OS, while pStage and RDW were independent prognostic factors of CSS. In non-elderly patients, based on the multivariate analysis, pStage, adjuvant chemotherapy, and RDW were identified as independent prognostic factors of OS. In elderly patients, RDW was identified as independent prognostic factors of OS and CSS. *Conclusion:* Preoperative RDW is a promising independent prognostic factor in gastric cancer.

Gastric cancer, one of the most common malignant tumors of the digestive tract, continues to be a major health problem worldwide. In 2012, gastric cancer was ranked fifth and third considering the worldwide incidence and mortality, respectively (1). Gastric cancer is either asymptomatic or causes nonspecific symptoms in its early stages. Therefore, screening for gastric cancer is not always effective, and it is often diagnosed at an advanced stage (2). The lack of specific, reliable tumor markers for gastric cancer is a primary cause of delay in its definitive diagnosis. To establish adequate treatment strategies for individual patients

with gastric cancer, precise patient stratification using reliable biomarkers is necessary.

Red cell distribution width (RDW) is an index of the heterogeneity in the size of circulating erythrocytes, and an elevated RDW is used to quantitate the extent of anisocytosis in peripheral blood. RDW is thus conventionally utilized for differentiating types of anemia in clinical practice. However, recent studies have demonstrated that RDW may also reflect the extent of patient's physiological reserve, tumor-associated inflammation, and poor nutritional status (3-7). Meanwhile, only a few studies have focused on RDW in the field of oncology (5, 6, 8, 9). In predicting the recurrence or prognosis of patients with gastric cancer, several tumor biomarkers, such as carcinoembryonic antigen (CEA), p53, programmed cell death-L1 (PD-L1), microsatellite instability (MSI), K-RAS, and BRAF, are used individually or in combination with each other. However, the use of these biomarkers is expensive and not well standardized, with limited availability (10-12). Therefore, there is a significant need to identify more valid, reliable, and accessible prognostic biomarkers for gastric cancer.

Thus, the aim of the current study was to investigate the impact of the preoperative RDW value on the overall survival (OS) and cancer-specific survival (CSS) of patients with gastric cancer.

Patients and Methods

Patients. This study was based on retrospective analysis of 366 patients with gastric adenocarcinoma who underwent curative laparoscopic (assisted) gastrectomy at our institute between January 2010 and December 2016. Gastric cancer patient who was operated without grasping the cancer site with forceps was regarded as indication for laparoscopic surgery. The inclusion criteria were as follows: 1) age 20-89 years, 2) histologically verified gastric adenocarcinoma, 3) no distant metastasis, 4) an Eastern Cooperative Oncology Group performance status of 0-2, and 5) curative gastrectomy with R0 resection. R0 resection was defined as a complete resection of the tumor with no microscopic margin involvement. Patients were excluded if they had remnant gastric cancer, an emergency gastrectomy for bleeding or perforation, and hematological, inflammatory, or autoimmune disorders. There was no patient who died of complications related to surgery within 30

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Key Words: Gastric cancer, red blood cell distribution width, prognostic factor.

days. The requirement for informed consent was waived, because this study was retrospective. All procedures were approved by the Institutional Review Board (IRB) (UMIN:000030472).

Laparoscopic gastrectomy. As the basic procedure, early gastric cancer with lesions localized at the upper part of the stomach were treated by proximal gastrectomy and double-tract reconstruction, while early gastric cancer with lesions spreading in the upper and middle regions and advanced gastric cancer with lesions located at the upper region were subjected to total gastrectomy and Roux-en-Y reconstruction. Distal gastrectomy was selected when a satisfactory proximal resection margin can be obtained. The first choice of reconstruction was performed by Billroth I method, and when the residual stomach and duodenum was not reached, Roux-en Y method was performed. The extent of lymph node dissection was carried out according to the Japanese Gastric Cancer Treatment Guideline (version 3) (13); total gastrectomy was performed in 79 patients, proximal gastrectomy in 37 patients, and distal gastrectomy in 250 patients (Table I).

Outcome evaluation. OS and CSS were evaluated, and the cause of death determined from the hospital records. OS was calculated from the date of primary gastrectomy to the date of death from any cause or the last follow-up, and CSS was defined as the interval from the date of surgery to cancer-specific death. This retrospective study was conducted in accordance with the Declaration of Helsinki.

RDW. The RDW is a measurement derived from red blood cell distribution curves, which contains RDW-CV (RDW coefficient of variation) and RDW-SD (RDW standard deviation) values that reflect the extent of heterogeneity. The RDW-CV is calculated based on both the width of the distribution curve and the mean cell size, using the following formula: $RDW = (\text{one standard deviation of red cell volume} / \text{mean cell volume}) \times 100$. RDW-CV is reported as a % with a reference range of approximately 11.0%-15.0%. On the other hand, the RDW-SD is an actual measurement of the width of the red cell distribution curve in femtoliters (fL), and it is measured at the point that is 20% above the baseline. Since RDW-SD more accurately reflects the red cell size variance, RDW-SD was treated as the prognostic value of RDW for analysis (14). The routine reference cutoff value for RDW used in our hospital laboratory was <50.

Tumor staging. The pathological classification was determined according to the Japanese classification of gastric cancer (15).

Statistical analysis. Differences between the study groups were evaluated by using the Student's *t*-test, and differences in continuous variables among the three groups were assessed with the Kruskal-Wallis analysis for non-normally distributed variables. Differences between the clinicopathological features were analyzed by using the chi-square test. The routine reference cut-off value for RDW used in our hospital was 50. An RDW greater than 50 was considered to be high, while RDW of 50 or below was considered to be normal. OS and CSS were calculated according to the Kaplan-Meier method, and the differences between survival curves were assessed by the log-rank test.

Variables with a *p*-value <0.05 following the univariate analysis were subjected to multivariate logistic regression analysis. All statistical analyses were performed by using JMP software (version 11 for Windows; SAS Institute); *p*-values <0.05 were considered statistically significant.

Table I. Relationships between RDW and clinicopathological features in 366 patients with gastric cancer.

Characteristics	Total patients	RDW		<i>p</i> -Value
		<50 n=282 (%)	≥50 n=84 (%)	
Age (years old)		69.2±11.3	75.7±9.2	<0.0001
Gender				0.1103
Male	253	189 (67.0)	64 (76.2)	
Female	113	93 (33.0)	20 (23.8)	
BMI		22.39±3.42	22.52±3.64	0.7547
WBC (μl)		5826.5±1387.1	5550.0±1623.3	0.1244
RBC (×10 ⁴ μl)		440.1±215.7	419.1±500.9	0.5805
Location of tumor				0.2508
EGJ	11	7 (2.5)	4 (4.8)	
U	67	49 (17.4)	18 (21.4)	
M	163	133 (47.2)	30 (35.7)	
L	125	93 (33.0)	32 (38.1)	
Tumor size (cm)		4.45±3.01	5.56±3.36	0.0043
Procedure				0.0926
LTG	79	54 (19.1)	25 (29.8)	
LPG	37	31 (11.0)	6 (7.4)	
L(A)DG	250	197 (69.9)	53 (63.1)	
Tumor differentiation				0.1078
Well	133	97 (34.4)	36 (42.9)	
Moderate	162	124 (44.0)	38 (45.2)	
Poor	71	61 (21.6)	10 (11.9)	
Depth of tumor				<0.0001
T1a-1b	193	166 (58.9)	27 (32.1)	
2	48	38 (13.5)	10 (11.9)	
3	53	34 (12.1)	19 (22.6)	
4a-4b	72	44 (15.6)	28 (33.3)	
Lymph node metastasis				0.0003
N0	246	204 (72.3)	42 (50.0)	
N1	40	24 (8.5)	16 (19.0)	
N2	42	25 (8.9)	17 (20.2)	
N3	38	29 (10.3)	9 (10.7)	
Pathological stage				<0.0001
Ia-Ib	218	189 (67.0)	29 (34.5)	
Ila-IIb	66	40 (14.2)	26 (31.0)	
IIla-IIIc	82	53 (18.8)	29 (34.5)	
Operation time (min)		412.1±115.2	435.3±132.2	0.1173
Intraoperative blood loss (ml)		162.0±303.7	421.8±823.0	<0.0001
CEA (ng/ml)		4.46±8.33	7.09±19.29	0.0736
Albumin (g/dl)		4.03±0.51	3.52±0.711	<0.0001
CRP (mg/l)		0.288±0.815	0.626±1.444	0.0065
Adjuvant chemotherapy				0.4407
Yes	97	72 (25.5)	25 (29.8)	
No	269	210 (74.5)	59 (70.2)	

Results

Association between RDW and clinicopathological features. The relationship between preoperative RDW and clinicopathological features in 366 patients with gastric cancer is shown in Table I. RDW values were significantly

Figure 1. RDW values of all gastric cancer patients according to pStage. In each box plot, the lower and upper ends represent the 25th and 75th percentiles, respectively. Capped bars indicate the minimum and maximum values, respectively, and the line inside the box represents the median RDW value.

associated with age ($p < 0.0001$), tumor size ($p = 0.0043$), depth of tumor invasion ($p < 0.0001$), lymph node metastasis ($p = 0.0003$), pStage ($p < 0.0001$), intraoperative blood loss ($p < 0.0001$), serum albumin concentration ($p < 0.0001$), and C-reactive protein (CRP) ($p = 0.0065$).

RDW values and pStage. The Kruskal-Wallis one-way analysis indicated that there is a tendency for the proportion of patients with high RDW to be higher in Stage II and III than in Stage I gastric cancer patients. The percentages of high RDW patients were 13.3%, 39.4% and 35.4% for stage I ($n = 218$), stage II ($n = 66$), and stage III patients ($n = 82$), respectively (Figure 1).

Cox regression analysis for OS and CSS in all patients. As shown in Table II, univariate analyses revealed that age ($p = 0.0443$), pStage ($p < 0.0001$), tumor size ($p = 0.0003$), RDW ($p < 0.0001$), CEA ($p = 0.0072$), tumor differentiation ($p = 0.0119$), and adjuvant chemotherapy ($p = 0.0438$) were significantly associated with OS. Similarly, CSS was also found to be associated with pStage ($p < 0.0001$), tumor size ($p < 0.0001$), RDW ($p = 0.0015$), CEA ($p = 0.0266$), tumor differentiation ($p = 0.0317$), and adjuvant chemotherapy ($p < 0.0001$). Multivariate analysis revealed that pStage (hazard ratio [HR], 2.254; 95% confidence interval [CI]=1.258-4.069; $p = 0.0063$), RDW (HR=2.840; 95%CI=1.771-4.533; $p < 0.0001$), CEA

(HR=1.723; 95%CI=1.070-2.719; $p = 0.0259$), and tumor differentiation (HR=1.654; 95%CI=1.050-2.628; $p = 0.0297$) were independent prognostic factors of OS. Further, pStage (HR=5.292; 95%CI=2.203-13.519; $p = 0.0001$) and RDW (HR=2.281; 95%CI=1.156-4.040; $p = 0.0181$) were independent prognostic factors of CSS.

Survival analysis stratified by RDW in all patients. The median follow-up time was 2.8 years (range=0.3-8.1years). The log-rank test demonstrated that patients with a high RDW had a significantly poorer prognosis both in terms of OS ($p < 0.0001$) and CSS ($p = 0.0015$) when compared to patients with a normal RDW (Figure 2).

Association between RDW and clinicopathological features in non-elderly and elderly patients. In non-elderly patients, significant associations were found between RDW and factors such as lymph node metastasis ($p = 0.0006$), operation time ($p = 0.0106$), and serum albumin concentration ($p < 0.0001$) (Table III). In elderly patients, RDW values were significantly associated with tumor size ($p = 0.0167$), depth of tumor invasion ($p = 0.0001$), lymph node metastasis ($p = 0.0312$), pathological tumor, node, metastasis (pTNM) stage ($p < 0.0001$), intraoperative blood loss ($p = 0.0005$), and serum albumin concentration ($p < 0.0001$) (Table IV).

RDW values and pStage in non-elderly and elderly patients.

The Kruskal-Wallis one-way analysis showed that there is a tendency the proportion of non-elderly patients with high RDW to be higher in Stage II and III than in Stage I gastric cancer patients. The percentages of high RDW patients were 8.4%, 18.2% and 19.4% for stage I (n=107), stage II (n=22), and stage III patients (n=36), respectively (Figure 3a). Similarly, there was a tendency the proportion of elderly patients with high RDW is higher in Stage II and III than in Stage I gastric cancer patients. The percentages of high RDW patients were 18.0%, 50.0% and 47.8% for stage I (n=111), stage II (n=44), and stage III patients (n=46), respectively (Figure 3b).

Cox regression analysis for OS and CSS in non-elderly patients. Univariate analyses revealed that pStage ($p<0.0001$), tumor size ($p=0.007$), RDW ($p=0.0022$), and adjuvant chemotherapy ($p=0.0034$) were significantly associated with OS. Similarly, pStage ($p<0.0001$), tumor size ($p=0.0019$), and adjuvant chemotherapy ($p<0.0001$) were significantly associated with CSS. Based on the multivariate analysis, pStage (HR=11.856; 95%CI=3.791-38.066; $p<0.0001$) and RDW (HR=3.400; 95%CI=1.339-8.154; $p=0.0114$) were identified as independent prognostic factors of OS, while pStage (HR=25.871; 95%CI=5.958-118.999; $p=0.0001$) was found as the only independent prognostic factor of CSS (Table V).

Cox regression analysis for OS and CSS in elderly patients. Univariate analyses revealed that while OS was significantly associated with pStage ($p=0.0262$), tumor size ($p=0.0289$), RDW ($p=0.0003$), and tumor differentiation ($p=0.0057$), CSS was associated with pStage ($p=0.0004$), tumor size ($p=0.0014$), RDW ($p=0.0041$), and adjuvant chemotherapy ($p=0.023$). Based on a multivariate analysis, RDW (HR=2.562; 95%CI=1.447-4.547; $p=0.0014$) and differentiation (HR=1.971; 95%CI=1.128-3.467; $p=0.0173$) were identified as independent prognostic factors of OS, while RDW was the only prognostic factor for CSS (HR=2.832; 95%CI=1.069-7.958; $p=0.0363$) (Table VI).

Survival analysis stratified by RDW in non-elderly patients.

The log-rank test demonstrated that patients with a high RDW had a significantly poorer prognosis in terms of both OS ($p=0.0190$) and CSS ($p=0.0278$) when compared to patients with normal RDW (Figure 4).

Survival analysis stratified by RDW in elderly patients. The log-rank test demonstrated that patients with a high RDW had a significantly poorer prognosis in terms of both OS ($p=0.0003$) and CSS ($p=0.0042$) when compared to patients with normal RDW (Figure 5).

Discussion

With accumulating evidence supporting the role of inflammation in carcinogenesis and tumor progression, several serum parameters for systemic inflammation have been shown to be potential predictors of survival in a variety of cancers (3, 4, 16). Although the exact mechanisms remain unknown, recent studies have suggested that cytokines secreted by inflammatory cells in the tumor microenvironment influence tumor cell proliferation and migration (17, 18). RDW is a routinely analyzed parameter in clinical laboratories as a component of the complete blood count to gather information on the heterogeneity in the size of circulating erythrocytes. It essentially reflects the nutritional status of patients, including iron, folate, or vitamin B12 deficient anemia, which are frequently detected in patients with cancer. Furthermore, recent growing evidence indicates that high RDW is a potential predictor of poor survival in various cancers due to close association with tumor-related systemic inflammation (5-9). However, these findings have not been confirmed uniformly, and the impact of routine blood-test markers in the prognosis of gastric cancer is still an ongoing subject of debate. Therefore, the present study aimed to clarify the prognostic value of RDW in gastric cancer patients.

In this study, analysis of patients with gastric cancer revealed a positive association between RDW and tumor size, depth of tumor, lymph node metastasis, pathological stage, intraoperative blood loss, serum albumin concentration, and CRP. These results support the hypothesis that a high RDW reflects tumor-related systemic inflammation and malnutrition induced by more aggressive or progressive cancers. Since there was a tendency for advanced cancer patients to have a low RDW value, possibly there is an association between preoperative RDW and operation time and intraoperative blood loss. Propensity score matched analysis will be necessary in the future. In line with this hypothesis, a significant association between high RDW and unfavorable OS and CSS was also found. Furthermore, Cox multivariate analysis suggested that RDW is an independent prognostic indicator of gastric cancer after curative resection. The mechanism underlying the association between RDW and patient's survival has not been elucidated, but recent studies have revealed that RDW correlates with systemic inflammatory response and malnutrition. Elevated RDW has been reported to be correlated with inflammatory cytokines, such as interleukin-6, tumor necrosis factor- α , hepcidin, and other circulating cytokines (19, 20). Inflammatory cytokines have been shown to play a role in suppressing the stimulating effect of erythropoietin on bone marrow erythrocyte stem cells, its antiapoptotic effect, and its role in red blood cell maturation. Therefore, more immature red blood cells are released into the peripheral blood circulation, consequently increasing their heterogeneity and

Figure 2. Kaplan-Meier curves of postoperative survival based on RDW of 366 patients with gastric cancer. (a) Overall survival, (b) cancer-specific survival.

Table II. Univariate and multivariate analyses for prognostic factors in overall gastric cancer patients.

Variables	Overall survival						Cancer-specific survival					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95%CI	p-Value	HR	95%CI	p-Value	HR	95%CI	p-Value	HR	95%CI	p-Value
Gender												
Female/Male	1.451	0.891-2.467	0.1381				1.432	0.725-3.086	0.3119			
Age												
<70/≥70	1.594	1.012-2.571	0.0443	1.18	0.720-1.968	0.516	0.681	0.361-1.269	0.2264			
pStage												
I, II/III	3.373	2.163-5.234	<0.0001	2.254	1.258-4.069	0.0063	10.212	5.250-21.370	<0.0001	5.292	2.203-13.519	0.0001
Tumor size												
<5/≥5	2.247	1.443-3.545	0.0003	1.371	0.785-2.379	0.2653	3.975	2.044-8.317	<0.0001	1.418	0.646-3.302	0.3921
RDW												
<50/≥50	3.411	2.171-5.330	<0.0001	2.84	1.771-4.533	<0.0001	2.922	1.531-5.472	0.0015	2.281	1.156-4.040	0.0181
CEA												
<5.0/≥5.0	1.927	1.200-3.027	0.0072	1.723	1.070-2.719	0.0259	2.129	1.096-3.995	0.0266	1.742	0.893-3.283	0.1012
Diff.												
Well & mod /poor	1.762	1.133-2.766	0.0119	1.654	1.050-2.628	0.0297	1.982	1.061-3.803	0.0317	1.482	0.769-2.925	0.2407
BMI												
≥18.5/<18.5	1.574	0.787-2.853	0.1871				0.707	0.303-2.060	0.4869			
Adjuvant												
No/Yes	1.613	1.014-2.522	0.0438	0.906	0.530-1.527	0.7128	4.384	2.337-8.515	<0.0001	1.608	0.774-3.449	0.2055

Diff.: Tumor differentiation; Adjuvant: adjuvant chemotherapy.

elevating RDW (21). In addition, the tumor microenvironment is characterized by a state of tumor-related systemic inflammation, thus accelerating tumor progression (22). As RDW reflects progressive cancer and tumor-related systemic inflammation, it was found to be associated with malnutrition, which has been shown to be correlated to poor response to treatment and worse prognosis (23).

With the steady increase in average life expectancy due to advances in medical sciences, gastric cancer is still the third leading cause of cancer-related deaths worldwide (24). It occurs predominantly in elderly people, with a peak incidence between 70 and 75 years of age. Because age-specific prognostic factors in patients with gastric cancer have not yet been described, patients were divided into two

Table III. Relationships between RDW and clinicopathological features in 165 non-elderly patients with gastric cancer.

Characteristics	Total patients	RDW		p-Value
		<50 (n=145)	≥50 (n=20)	
Age (years old)		60.3±7.6	62.6±5.7	0.2027
Gender				0.1122
Male	115	98 (67.6)	17 (85.0)	
Female	50	47 (32.4)	3 (15.0)	
BMI		22.44±3.62	22.46±4.80	0.9886
WBC (μl)		5927.0±1370.2	5782.0±1299.9	0.6559
RBC (×10 ⁴ μl)		464.3±295.2	386.8±73.3	0.2447
Location of tumor				0.6691
EGJ	4	4 (2.8)	0 (0)	
U	32	28 (19.3)	4 (20.0)	
M	79	71 (49.0)	8 (40.0)	
L	50	42 (29.0)	8 (40.0)	
Tumor size (cm)		4.15±2.82	4.30±3.29	0.8326
Procedure				0.3867
LTG	35	29 (20.0)	6 (30.0)	
LPG	21	20 (13.8)	1 (5.0)	
L(A)DG	109	96 (66.2)	13 (65.0)	
Tumor differentiation				0.3552
Well	25	24 (16.6)	1 (5.0)	
Moderate	51	45 (31.0)	6 (30.0)	
Poor	89	76 (52.4)	13 (65.0)	
Depth of tumor				0.3045
T1a-1b	97	88 (60.7)	9 (45.0)	
2	18	16 (11.0)	2 (10.0)	
3	18	16 (11.0)	2 (10.0)	
4a-4b	32	25 (17.2)	7 (35.0)	
Lymph node metastasis				0.0006
N0	115	106 (73.1)	9 (45.0)	
N1	13	11 (7.6)	2 (10.0)	
N2	16	9 (6.2)	7 (35.0)	
N3	21	19 (13.1)	2 (10.0)	
Pathological stage				0.1385
Ia-Ib	107	98 (67.6)	9 (45.0)	
IIa-IIb	22	18 (12.4)	4 (20.0)	
IIIa-IIIc	36	29 (20.0)	7 (35.0)	
Operation time (min)		411.8±117.0	487.9±163.3	0.0106
Intraoperative blood loss (ml)		164.3±359.0	314.5±436.2	0.0897
CEA (ng/ml)		4.16±7.57	5.96±6.10	0.313
Albumin (g/dl)		4.16±0.49	3.61±0.830	<0.0001
CRP (mg/l)		0.227±0.678	0.411±0.666	0.2562
Adjuvant chemotherapy				0.0577
Yes	52	42 (29.0)	10 (50.0)	
No	113	103 (71.0)	10 (50.0)	

Table IV. Relationships between RDW and clinicopathological features 201 elderly patients with gastric cancer.

Characteristics	Total patients	RDW		p-Value
		<50 (n=137)	≥50 (n=64)	
Age (years)		78.7±5.3	79.8±5.4	0.1714
Gender				0.318
Male	138	91 (66.4)	47 (73.4)	
Female	63	46 (33.6)	17 (26.6)	
BMI		22.33±3.20	22.54±3.24	0.66
WBC (μl)		5720.1±1401.9	5477.5±1714.6	0.2893
RBC (×10 ⁴ μl)		414.4±50.5	429.2±573.1	0.7641
Location of tumor				0.2237
EGJ	7	3 (2.2)	4 (6.3)	
U	35	21 (15.3)	14 (21.9)	
M	84	62 (45.3)	22 (34.4)	
L	75	51 (37.2)	24 (37.5)	
Tumor size (cm)		4.78±3.18	5.95±3.31	0.0167
Procedure				0.1833
LTG	141	101 (73.7)	40 (62.5)	
LPG	16	11 (8.0)	5 (7.8)	
L(A)DG	44	25 (18.2)	19 (29.7)	
Tumor differentiation				0.1201
Well	46	37 (27.0)	9 (14.1)	
Moderate	82	52 (38.0)	30 (46.9)	
Poor	73	48 (35.0)	25 (39.1)	
Depth of tumor				0.0001
T1a-1b	96	78 (56.9)	18 (28.1)	
2	30	22 (16.1)	8 (12.5)	
3	35	18 (13.1)	17 (26.6)	
4a-4b	40	19 (13.9)	21 (32.8)	
Lymph node metastasis				0.0312
N0	131	98 (71.5)	33 (51.6)	
N1	27	13 (9.5)	14 (21.9)	
N2	26	16 (11.7)	10 (15.6)	
N3	17	10 (7.3)	7 (10.9)	
Pathological stage				<0.0001
Ia-Ib	217	91 (66.4)	20 (31.3)	
IIa-IIb	65	22 (16.1)	22 (34.4)	
IIIa-IIIc	86	24 (17.5)	22 (34.4)	
Operation time (min)		412.3±113.7	418.9±117.7	0.7056
Intraoperative blood loss (ml)		159.6±232.5	455.3±911.1	0.0005
CEA (ng/ml)		4.78±9.08	7.44±21.87	0.2244
Albumin (g/dl)		3.90±0.50	3.49±0.67	<0.0001
CRP (mg/l)		0.353±0.937	0.694±1.611	0.0608
Adjuvant Chemotherapy				0.8073
Yes	45	30	15	
No	156	107	49	

age groups to determine the age-specific prognostic values of the RDW (25). In non-elderly patients, a significant association was found between high RDW and unfavorable OS, but not with CSS. On the other hand, elderly patients showed a significant association between high RDW and

unfavorable OS and CSS. This difference was possibly due to the positive association between RDW and TNM pStage in elderly but not in non-elderly patients. Because RDW has been reported to be more closely associated with all-cause mortality, including chronic lower respiratory tract infection-

Figure 3. RDW values of all gastric cancer patients according to pStage. (a) Non-elderly patients (n=165). (b) Elderly patients (n=201). In each box plot, the lower and upper ends represent the 25th and 75th percentiles, respectively. Capped bars indicate the minimum and maximum values, respectively and the line inside the box represents the median RDW value.

Figure 4. Kaplan-Meier curves of survival based on RDW of 165 non-elderly patients with gastric cancer. (a) Overall survival, (b) cancer-specific survival.

related deaths and cardiovascular mortality, RDW could be a surrogate for poor physical condition of elderly patients (26-28). In this study, RDW cut off value set at >50 by our hospital laboratory routine use. Although RDW has shown to be one of the prognostic factors of esophageal cancer, it was not in elderly patients (5). This is the first report suggesting that RDW could have a prognostic value in elderly patient with gastric cancer. However, because the number of people with high RDW in the non-elderly group is small (only 20 people), there is a possibility that this consideration is subject to a large bias. To define the

significance of RDW according to age, studies with larger sample size are required.

This study had several limitations that should be discussed. First, the main limitation of the present study was its retrospective nature and the fact that some of the patient characteristics may have been biased since only 20 patients had RDW-SD of >50 in the non-elderly group. Second, this study was a single center study, and the number of analyzed patients was relatively low. Third, this trial had a short follow-up of survival, therefore there were many early censored cases in survival analysis. Despite these limitations,

Table V. Univariate and multivariate analyses for prognostic factors in non-elderly gastric cancer patients.

Variables	Overall survival						Cancer-specific survival					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95%CI	p-Value	HR	95%CI	p-Value	HR	95%CI	p-Value	HR	95%CI	p-Value
Gender												
Female/male	2.466	0.947-8.416	0.0661				1.485	0.586-4.523	0.4221			
pStage												
I, II/III	10.383	4.675-24.802	<0.0001	11.856	3.791-38.066	<0.0001	21.656	7.983-75.612	<0.0001	25.871	5.958-118.999	
Tumor size												
<5/≥5	2.866	1.339-6.267	0.007	2.106	0.901-5.044	0.0857	3.827	1.637-9.590	0.0019	1.669	0.677-4.398	0.2697
RDW												
<50/≥50	4.088	1.718-9.150	0.0022	3.4	1.339-8.154	0.0114	2.785	0.989-6.900	0.0523			
CEA												
<5.0/≥5.0	2.077	0.887-4.530	0.0895				1.972	0.749-4.701	0.1597			
Diff.												
Well & mod/poor	1.565	0.727-3.554	0.2551				1.946	0.819-5.105	0.1341			
BMI												
≥18.5/<18.5	0.445	0.1815-1.331	0.1348				0.661	0.225-2.814	0.5261			
Adjuvant												
No/Yes	3.184	1.472-7.053	0.0034	0.513	0.184-1.513	0.2218	6.598	2.668-18.714	<0.0001	1.53	0.381-5.003	0.527

Diff.: Tumor differentiation; Adjuvant: adjuvant chemotherapy.

Table VI. Univariate and multivariate analyses for prognostic factors in elderly gastric cancer patients.

Variables	Overall survival						Cancer-specific survival					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95%CI	p-Value	HR	95%CI	p-Value	HR	95%CI	p-Value	HR	95%CI	p-Value
Gender												
Female/male	1.192	0.675-2.205	0.553				1.295	0.488-4.041	0.6168			
pStage												
I, II/III	1.941	1.085-3.369	0.0262	1.16	0.603-2.273	0.6595	5.503	2.166-14.964	0.0004	2.114	0.689-7.411	0.1959
Tumor size												
<5/≥5	1.84	1.064-3.263	0.0289	1.36	0.714-2.629	0.3517	5.6	1.848-24.179	0.0014	2.704	0.681-13.243	0.1597
RDW												
<50/≥50	2.794	1.616-4.844	0.0003	2.562	1.447-4.547	0.0014	3.939	1.549-10.722	0.0041	2.832	1.069-7.958	0.0363
CEA												
<5.0/≥5.0	1.79	0.999-3.117	0.0503				2.462	0.940-6.244	0.0658			
Diff.												
Well & mod/poor	2.165	1.255-3.764	0.0057	1.971	1.128-3.467	0.0173	1.862	0.726-4.773	0.1911			
BMI												
≥18.5/<18.5	0.758	0.350-1.982	0.5383				0.806	0.229-5.098	0.78			
Adjuvant												
No/Yes	1.16	0.615-2.073	0.634				2.996	1.170-7.675	0.023	1.685	0.608-4.685	0.3114

Diff.: Tumor differentiation; Adjuvant: adjuvant chemotherapy.

the present study provides useful information about not only non-elderly but also elderly gastric cancer patients. In addition, this study was focused on just the preoperative RDW values and did not evaluate the dynamic changes in

RDW during the course of the disease, since postoperative value may depend on many factors such as measurement timing. Finally, the biological and molecular mechanisms that can explain the prognostic ability of systemic

Figure 5. Kaplan–Meier curves of survival based on RDW of 201 elderly patients with gastric cancer. (a) Overall survival, (b) cancer-specific survival.

inflammatory factors are yet to be elucidated. Thus, Large-scale multicenter collaborative studies should be conducted to confirm our preliminary findings.

Despite the above limitations, RDW is easy to measure routinely because of its low cost, convenience, and reproducibility. The present study provides evidence that the preoperative RDW is a promising independent prognostic factor in patients with gastric cancer. Nevertheless, further studies are required on the role of RDW values in the identification of patients at high risk of recurrence accurately, selection-appropriate treatment strategies, and treatment outcomes in gastric cancer patients.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

NH was the lead author and conceived this study. YF, SK, TY, RH, TT and YK collected data and performed analysis. YT reviewed paper. All authors read and approved the final manuscript.

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Received April 9, 2019

Revised April 30, 2019

Accepted May 2, 2019