



Clinical Significance of Pretreatment Red Blood Cell Distribution Width as a Predictive Marker for Postoperative Morbidity After Esophagectomy for Esophageal Cancer: A Retrospective Study

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ABSTRACT

Background. Clinical significance of red blood cell distribution (RDW) as a predictive marker for the incidence of postoperative morbidity after esophagectomy for esophageal cancer has not been established.

Methods. This study included 634 consecutive patients who underwent three-incisional esophagectomy with lymphadenectomy for esophageal cancer between April 2005 and November 2020. Correlation between pretreatment RDW and patient background, cancer background, and short-term outcome after esophagectomy were retrospectively investigated.

Results. Eighty patients (12.6%) had a high pretreatment RDW (> 14.2), which correlated with malnutrition estimated by body mass index, hemoglobin, total lymphocyte count, albumin, and total cholesterol. High pretreatment RDW was an independent risk factor for postoperative severe morbidity of grade IIIb or higher based on the Clavien–Dindo classification (hazard ratio [HR] 3.90, 95% confidence interval [CI] 1.707–8.887; $p = 0.0012$) and reoperation (HR 4.39, 95% CI 1.552–12.390; $p = 0.0053$) after open esophagectomy (OE). However, RDW was not

associated with postoperative morbidity incidence after minimally invasive esophagectomy (MIE).

Conclusions. Pretreatment RDW may be a surrogate marker for nutritional status and could be a predictive marker for postoperative severe morbidity, reoperation, and possibly pneumonia after OE. On the contrary, the lower invasiveness of MIE may have reduced the effect of pretreatment malnutrition on morbidity incidence, which could explain the insignificant relationship between RDW and poor short-term outcomes in MIE.

Esophagectomy for esophageal cancer is among the most invasive surgeries associated with frequent postoperative morbidity compared with other gastrointestinal cancer surgeries. The preoperative prediction of the incidence of postoperative morbidity is considered important because of its prophylactic value and the possible reduction of surgery-related mortality. Several predictive markers for postoperative morbidity have been previously reported.^{1–3} Notably, measurable markers based on common blood tests are useful because these could be performed at any institute and be objectively evaluated. To date, the mean corpuscular volume (MCV) and several nutritional markers are suggested as useful predictors of postoperative morbidity after esophagectomy.^{4–6}

Red blood cell distribution width (RDW) is a parameter in red blood cell size variability and is used for estimating the pathogenesis of anemia.⁷ High RDW may also be associated with several cardiovascular diseases^{8–10} and poor prognosis of inflammatory diseases.^{11–15} Recently, the

correlation between elevated RDW and high mortality in patients with coronavirus disease 2019 (COVID-19) has attracted increasing attention.¹⁶ However, the mechanism underlying the association of RDW with the incidence and prognoses of these diseases remains unclear.

RDW has been considered an indicator of inflammation, malnutrition, microvascular disorder, oxidative stress, and prothrombotic effect.¹⁷ Although the progression of these conditions could be a risk for postoperative morbidities after highly invasive surgery, there have been no studies regarding the effect of RDW on short-term outcomes after gastroenterological surgeries. Thus, this study aimed to clarify the correlation between pretreatment RDW and the short-term outcomes after esophagectomy for esophageal cancer. Moreover, the correlation between pretreatment RDW and patient and cancer backgrounds was also investigated to elucidate how high RDW reflects the frequent incidence of postoperative morbidities.

MATERIAL AND METHODS

Patients

A total of 803 consecutive three-incisional esophagectomies with lymphadenectomy were performed for esophageal cancer at the Kumamoto University Hospital between April 2005 and November 2020. Of these, 24 cases of two-stage esophagectomies, 43 cases of salvage esophagectomies after definitive chemoradiotherapy (CRT), and 102 cases with insufficient clinical data (70 data points for alcohol status, 1 for smoking status, 12 for pretreatment data of total cholesterol, 9 for RDW, 6 for C-reactive protein [CRP], and 4 for total lymphocyte count) were excluded. Eventually, 634 patients were enrolled in this study (Fig. 1). RDW examined in this study

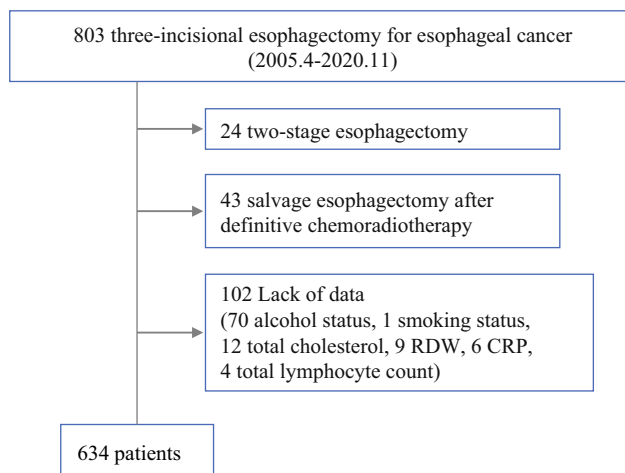


FIG. 1 Flow chart of analyzed patients. RDW red blood cell distribution width, CRP C-reactive protein

was measured before the administration of any treatments. Patients were divided into two groups according to the institutional standard value of pretreatment RDW—high ($14.2 <$) and normal (≤ 14.2). A retrospective investigation for the association between RDW and clinicopathological features, blood tests, and short-term outcomes after surgery was performed using a prospectively entered institutional clinical database. This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975. The institutional Ethics Committee approved the study procedures (registry number 2193). Written informed consent was waived for the patients because of the retrospective nature of this study.

Treatment Strategy

Treatment strategy details have been previously described.⁴ For non-T4 node-positive tumors, neoadjuvant chemotherapy has been administered since August 2008, whereas for T4 tumors, neoadjuvant CRT has been generally performed. The Union for International Cancer Control TNM staging (version 7) was used to classify the pretreatment clinical stage.¹⁸

Surgery

Esophagectomy was defined as three-incisional (in the neck, chest, and abdomen) esophagectomy with lymphadenectomy. The extent of lymphadenectomy was determined in accordance with the 2012 guidelines formulated by the Japan Esophageal Society.¹⁹ Regarding manipulation in the thorax, open esophagectomy (OE) was performed before April 2011. Minimally invasive esophagectomy (MIE) for clinical stage T1 and T2 cancers was initiated in May 2011. With progress in the operator's and team's skills, we have routinely performed MIE for cancers of all stages since September 2011. During MIE, chest manipulation was performed from the right thorax in the left semi-prone position.

Perioperative Management

Details regarding perioperative management have been previously described.²⁰ Bolus administration of methylprednisolone and continuous intravenous administration of neutrophil elastase inhibitors for 24 h were routinely conducted at the start of surgery. Moreover, precautionary antibiotics were administered every 4 h during surgery. Extubation was performed in the operating room shortly after surgery, and enteral nutrition was generally started on the first day after surgery.

Definitions of Morbidities

The morbidity details have been previously described.⁵ Severe morbidity was defined as a complication of grades IIIb or higher according to the Clavien–Dindo classification (CDc) system.²¹ Initial ventilatory support for > 48 h or reintubation for respiratory failure, need for tracheostomy, and pneumonia were defined as respiratory morbidities. Moreover, any respiratory morbidity requiring intervention or surgical treatment was included under this definition.

Statistical Methods

Statistical analyses were performed using the StatView™ version 5.0 software package (Abacus Concepts, Inc., Berkeley, CA, USA). The Chi-square test and Mann–Whitney *U* test were used to compare groups and unpaired samples, respectively. Fisher's exact test was used for the comparisons of groups containing a matrix with fewer than five patients. Data on pretreatment blood tests were divided into two groups according to the institutional standard value. Logistic regression analysis was performed to estimate the hazard ratio (HR) with a 95% confidence interval (CI) for each morbidity. The following data were adopted to analyze independent risk factors for the incidence of severe morbidity, reoperation, and pneumonia among patients who underwent OE: age (per 10 years), sex (male vs. female), body mass index (BMI; < 18.5 vs. \geq 18.5 kg/m²), performance status (PS; 0 vs. 1 and 2), American Society of Anesthesiologists physical status (ASAPS; 1 and 2 vs. 3), Brinkman index (tobacco number/day \times year, for a 100-point increase), chronic obstructive pulmonary disease (COPD; yes vs. no), neoadjuvant treatment (chemotherapy and CRT vs. none), dissection field (\leq 2 vs. 3), conduit (stomach vs. others), operative time (per 60 min increase), blood loss (per 100 g increase), clinical stage (II, III, and IV vs. I), and RDW (> 14.2 vs. \leq 14.2). Factors with a probability level of \leq 0.1 were adopted for subsequent multivariate analyses. Variables with a *p* value < 0.05 were presumed to be independent risk factors.

RESULTS

Association Between Pretreatment Red Blood Cell Distribution Width and Clinicopathological Features

Among all patients, 80 (12.6%) had a high pretreatment RDW (> 14.2). High RDW significantly correlated with lower BMI (*p* = 0.045); however, high RDW was not related to any other clinicopathological factors, such as age, sex, past smoking and drinking, PS, ASAPS, comorbidity, clinical stage, and histological type of cancer

(Table 1). The blood test revealed that high RDW was significantly associated with lower hemoglobin (*p* < 0.0001) and total lymphocyte count (*p* = 0.012). Moreover, high RDW exhibited a trend toward lower serum albumin and total cholesterol. Nevertheless, high RDW was also irrelevant to inflammation, as suggested by white blood cell count and CRP (Table 2).

Short-Term Outcomes After Surgery

Because the distribution of OE and MIE was considerably different between the high and normal RDW groups, the short-term outcomes for OE and MIE were separately investigated. Table 3 shows the short-term outcomes in patients who underwent OE, according to pretreatment RDW. Operative time and blood loss were significantly higher in the high RDW group, possibly due to frequent use of the colon conduit (high RDW, 19%; normal RDW, 6%; *p* = 0.0046). Moreover, postoperative severe morbidity, pneumonia, and reoperation were significantly frequent in the high RDW group. The association of high RDW with frequent severe morbidity, reoperation, and pneumonia was also seen in patients who underwent reconstruction using a gastric conduit (electronic supplementary Table 1). By contrast, short-term outcomes in patients who underwent MIE were statistically equivalent between the high and normal RDW groups (Table 4).

Risk Factors for Postoperative Morbidities of Grades IIIb or Higher According to the Clavien–Dindo Classification, Reoperation, and Pneumonia in Patients who Underwent Open Esophagectomy

Table 5 shows the results of multivariate analyses for postoperative morbidities in patients who underwent OE. High pretreatment RDW was an independent risk factor for postoperative severe morbidity of CDc grade IIIb or higher (HR 3.90, 95% CI 1.707–8.887; *p* = 0.0012) and reoperation (HR 4.39, 95% CI 1.552–12.390; *p* = 0.0053). It also exhibited a trend toward frequent incidence of pneumonia, although it was not statistically significant (HR 2.70, 95% CI 0.995–7.351; *p* = 0.051).

DISCUSSION

In this study, several interesting results were obtained for the clinical value of pretreatment RDW in esophagectomy for esophageal cancer. First, high RDW may be a surrogate marker for malnutrition estimated by BMI, hemoglobin, total lymphocyte count, albumin, and total cholesterol. Second, high RDW was not relevant to factors other than nutrition, such as age, sex, past smoking and

TABLE 1 Association between pretreatment red blood cell distribution width and patient characteristics

Clinical, epidemiological, and pathological feature	Total <i>N</i>	Pretreatment red blood cell distribution		<i>p</i> value
		≤ 14.2	14.2 <	
All cases	634	554	80	
Age, years [mean ± SD]	66.5 ± 8.3	66.7 ± 8.2	65.2 ± 8.7	0.14
Male patients	556 (88)	483 (87)	73 (91)	0.30
Body mass index [mean ± SD]	21.9 ± 3.1	22.0 ± 3.1	21.3 ± 3.1	0.045
Estimated ethanol consumption ^a [mean ± SD]	2450 ± 2040	2450 ± 2060	2450 ± 1900	0.98
Brinkman index ^b [mean ± SD]	770 ± 570	770 ± 580	800 ± 460	0.64
Performance status				0.82
0	565 (89)	495 (89)	70 (88)	
1	64 (10)	55 (10)	9 (11)	
2	5 (1)	4 (1)	1 (1)	
ASA physical status				0.24
1	125 (20)	111 (20)	14 (18)	
2	483 (76)	423 (76)	60 (75)	
3	26 (4)	20 (4)	6 (8)	
Comorbidity				
Diabetes mellitus	133 (21)	117 (21)	16 (20)	0.82
Chronic obstructive pulmonary disease	196 (31)	167 (30)	29 (36)	0.27
Cardiovascular	334 (53)	295 (53)	39 (49)	0.45
Clinical stage				0.25
0, I	276 (44)	248 (45)	28 (35)	
II	113 (18)	94 (17)	19 (24)	
III	204 (32)	178 (32)	26 (33)	
IV	41 (6)	34 (6)	7 (9)	
Pathology				0.70
Squamous cell carcinoma	577 (91)	505 (91)	72 (90)	
Adenocarcinoma	36 (6)	30 (5)	6 (8)	
Others	21 (3)	19 (3)	2 (3)	
Neoadjuvant treatment				0.83
None	359 (57)	315 (57)	44 (55)	
Chemotherapy	208 (33)	182 (33)	26 (33)	
Chemoradiotherapy	67 (11)	57 (10)	10 (13)	
Surgical procedure, MIE	355 (56)	318 (57)	37 (46)	0.060

Data are expressed as *n*(%) unless otherwise specified

MIE minimally invasive esophagectomy, *SD* standard deviation, *ASA* American Society of Anesthesiologists

^aEthanol consumption was calculated as follows: estimated daily ethanol consumption [(0.4 × whisky + 0.2 × distilled spirit + 0.15 × wine and sake + 0.04 × beer) × year]

^bBrinkman index was calculated as follows: number of cigarettes/day × smoking duration (year)

drinking, comorbidities, cancer stage, and histological type. Third, high RDW was an independent risk factor for severe morbidity, reoperation, and possibly pneumonia after OE, but not after MIE.

RDW is an indicator of variation in red blood cell size. In patients with anemia, RDW increases because of the mixture of different erythrocyte sizes via erythrocyte turnover. In patients with chronic anemia, the size of

erythrocytes is uniform, irrespective of macrocytic or microcytic anemia; hence, RDW becomes normalized. RDW also reflects bone marrow function and is used in estimating the pathogenesis of anemia.⁷ RDW could also reflect inflammation and may be a predictive marker for activity level and survival in several inflammatory diseases, such as inflammatory bowel disease,¹¹ chronic hepatitis,¹² COPD,¹³ acute pancreatitis,¹⁴ acute respiratory distress

TABLE 2 Association between pretreatment red blood cell distribution width and blood parameter test results

Blood test	Total <i>N</i>	Pretreatment red blood cell distribution		<i>p</i> value
		≤ 14.2	14.2 <	
All cases	634	554	80	
Hemoglobin, g/dL [mean ± SD]	13.6 ± 1.5	13.8 ± 1.4	12.7 ± 1.7	< 0.0001
Hemoglobin, <11.6 g/dL	50 (8%)	33 (6%)	17 (21%)	< 0.0001
White blood cell count, /μL [mean ± SD]	6490 ± 2740	6540 ± 2830	6110 ± 1940	0.19
White blood cell count, < 3300 /μL	11 (2%)	10 (2%)	1 (1%)	> 0.99
Total lymphocyte count, /μL [mean ± SD]	1740 ± 630	1770 ± 640	1580 ± 550	0.012
Total lymphocyte count, <1600 /μL	282 (44%)	229 (43%)	43 (54%)	0.074
C-reactive protein, mg/dL [mean ± SD]	0.45 ± 0.97	0.47 ± 1.02	0.32 ± 0.44	0.21
C-reactive protein, ≥ 1.00 mg/dL	72 (11%)	67 (12%)	5 (6%)	0.12
Serum albumin, g/dL [mean ± SD]	4.04 ± 0.39	4.05 ± 0.39	3.97 ± 0.39	0.074
Serum albumin, < 3.5 g/dL	45 (7%)	38 (7%)	7 (9%)	0.54
Total cholesterol, mg/dL [mean ± SD]	197 ± 35	197 ± 35	193 ± 39	0.33
Total cholesterol, < 180 g/dL	212 (33%)	178 (32%)	34 (43%)	0.071

SD standard deviation

TABLE 3 Pretreatment red blood cell distribution width, surgical feature, and short-term surgical outcomes of patients who underwent open esophagectomy

Surgical data and morbidities	Total <i>N</i>	Pretreatment red blood cell distribution		<i>p</i> value
		≤ 14.2	14.2 <	
All cases	279	236	43	
Operation time, min [mean ± SD]	540 ± 110	540 ± 110	570 ± 100	0.034
Blood loss, g [mean ± SD]	580 ± 440	560 ± 380	740 ± 670	0.012
Postoperative morbidity				
Any morbidity, CDc grade II or higher	111 (40)	89 (38)	22 (51)	0.097
Severe morbidity, CDc grade IIIb or higher	33 (12)	20 (8)	13 (30)	<0.0001
Respiratory morbidity	48 (17)	37 (16)	11 (26)	0.11
Pneumonia	21 (8)	14 (6)	7 (16)	0.018
Cardiovascular morbidity	14 (5)	13 (6)	1 (2)	0.70
Leak	32 (11)	25 (11)	7 (16)	0.28
Reoperation	19 (7)	10 (4)	9 (21)	<0.0001

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *CDc* Clavien–Dindo classification

syndrome,¹⁵ and several cardiovascular diseases.^{8–10} Recently, several studies on the significance of RDW as a predictive marker for COVID-19 mortality have been attracting increasing attention.¹⁶ Moreover, RDW could be a prognostic marker for several malignancies, including esophageal cancer.^{22,23} However, the mechanism behind the significant association between high RDW and the prognosis of the aforementioned diseases has not been established.

To date, no previous studies regarding the association of pretreatment RDW and short-term outcomes after gastroenterological surgery are available. To the best of our knowledge, this is the first study to disclose that high RDW may correlate with the incidence of postoperative morbidity after esophagectomy. In this study, RDW seemed a mere surrogate marker of nutritional status. Although a huge cohort study suggested that smoking habit may affect RDW level,²⁴ no such associations were observed in this study. Other factors that could affect the incidence of

TABLE 4 Pretreatment red blood cell distribution width, surgical features, and short-term surgical outcomes of patients who underwent minimally invasive esophagectomy

Surgical data and morbidities	Total <i>N</i>	Pretreatment red blood cell distribution		<i>p</i> value
		≤ 14.2	14.2 <	
All cases	355	318	37	
Operation time, min [mean ± SD]	580 ± 100	580 ± 100	570 ± 100	0.54
Blood loss, g [mean ± SD]	230 ± 290	240 ± 300	190 ± 230	0.36
Postoperative morbidity				
Any morbidity, CDc grade II or higher	121 (34)	108 (34)	13 (35)	0.89
Severe morbidity, CDc grade IIIb or higher	46 (13)	42 (13)	4 (11)	0.80
Pulmonary morbidity	49 (14)	44 (14)	5 (14)	0.96
Pneumonia	31 (9)	29 (9)	2 (5)	0.76
Cardiovascular morbidity	26 (7)	26 (8)	0	0.092
Leak	46 (13)	40 (13)	6 (16)	0.53
Reoperation	24 (7)	22 (7)	2 (5)	>0.99

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, CDc Clavien–Dindo classification

TABLE 5 Logistic regression analysis (backward stepwise elimination) for morbidities of grades IIIb or higher according to the Clavien–Dindo classification, reoperation, and pneumonia in patients who underwent open esophagectomy

Morbidity	Characteristics	Univariate analysis		Multivariate analysis	
		HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
CDc grade IIIb or higher	Dissection field ≤ 2 (vs. 3)	0.42 (0.157–1.139)	0.089	0.45 (0.159–1.262)	0.13
	Conduit stomach (vs. others)	0.24 (0.090–0.646)	0.0046	0.33 (0.103–1.061)	0.063
	Operation time (for 60 min increase)	1.17 (0.979–1.401)	0.085	1.03 (0.823–1.277)	0.82
	Red blood cell distribution 14.2 < (vs. ≤ 14.2)	4.68 (2.111–10.373)	0.0001	3.90 (1.707–8.887)	0.0012
Reoperation	Conduit stomach (vs. others)	0.11 (0.036–0.305)	<0.0001	0.17 (0.047–0.590)	0.0055
	Operation time (for 60 min increase)	1.28 (1.031–1.589)	0.026	1.06 (0.803–1.387)	0.70
	Blood loss (for 100 g increase)	1.08 (0.997–1.179)	0.059	1.03 (0.934–1.138)	0.54
	Red blood cell distribution 14.2 < (vs. ≤ 14.2)	5.98 (2.268–15.78)	0.0003	4.39 (1.552–12.390)	0.0053
Pneumonia	Operation time (for 60 min increase)	1.17 (0.979–1.401)	0.085	1.03 (0.823–1.277)	0.82
	Red blood cell distribution 14.2 < (vs. ≤ 14.2)	3.08 (1.165–8.161)	0.023	2.70 (0.995–7.351)	0.051

HR hazard ratio, CI confidence interval, CDc Clavien–Dindo classification

postoperative morbidities were equivalent between the high and normal RDW groups. The same result was obtained in several studies reporting that pretreatment malnutrition increased postoperative morbidities in highly invasive gastroenterological procedures, such as esophagectomy,^{25–27} pancreatoduodenectomy,²⁸ and rectal surgery.²⁹

The Controlling Nutritional Status (CONUT) score is one indicator for the nutritional status estimation and could be a predictive marker for postoperative morbidity after several gastroenterological surgeries.^{5,30,31} In this study, the CONUT score in the high RDW group was significantly

higher than that in the normal RDW group (high RDW, 1.6 ± 1.6 ; normal RDW, 1.2 ± 1.3 ; $p = 0.0096$). Moreover, the percentage of patients with malnutrition estimated by the CONUT score was significantly higher in the high RDW group (high RDW, 41%; normal RDW, 32%; $p = 0.025$) [data not shown]. The Prognostic Nutritional Index (PNI) is the first identified nutrition-related indicator and could predict complications after esophagectomy.⁶ In this study, the PNI was also significantly worse in the high RDW group than in the normal RDW group (high RDW, 47.5 ± 5.1 ; normal RDW, 49.3 ± 5.3 ; $p = 0.0050$) [data

not shown]. These results support that RDW reflected nutritional status and affected short-term outcomes after esophagectomy.

RDW reportedly increases in several diseases, such as heart failure, atrial fibrillation, peripheral vascular disease, coronary artery disease, stroke, and pulmonary hypertension.^{8–10} Li et al. have reviewed the effects of high RDW on cardiovascular disease.¹⁷ This study discussed how high RDW reflected microvascular disorder, high inflammatory cytokine, oxidative stress, and prothrombotic effects. Thus, patients with high RDW may have several latent disadvantages other than malnutrition, which could have influenced the frequent incidence of postoperative morbidities.

OE is considered more invasive and associated with more frequent postoperative morbidities than MIE.^{1,32,33} No studies have clarified the correlation between preoperative malnutrition and poor short-term outcomes in MIE to date. In general, poor preoperative conditions could severely affect the incidence of postoperative morbidity as the surgery becomes more invasive. The lower invasiveness of MIE may have reduced the effect of pretreatment malnutrition on the incidence of morbidities, which could explain the irrelevance between high RDW and poor short-term outcomes in MIE.

We previously reported that high MCV was associated with low BMI and higher frequency of habitual alcohol and tobacco use, which significantly increased pulmonary morbidities after esophagectomy.⁴ We investigated the association of MCV with patient's backgrounds and short-term outcomes using the current cohort. Consequently, high MCV was correlated with lower BMI ($p = 0.040$) and more frequent habitual alcohol ($p < 0.0001$) and tobacco use ($p = 0.0002$); however, MCV was not related to total lymphocyte count ($p = 0.74$), serum albumin ($p = 0.13$) and cholesterol ($p = 0.13$) levels, and malnutrition in CONUT ($p = 0.47$). Although RDW could reflect malnutrition based on the blood test, CONUT, and PNI, it was not related to habitual alcohol and tobacco use. Thus, we consider that both MCV and RDW reflect different backgrounds. Finally, we conducted multivariate analysis to calculate the incidence of postoperative pneumonia, including both MCV and RDW, as an element. Only RDW was identified as an independent risk factor for pneumonia after OE (HR 2.94, 95% CI 1.079–7.988; $p = 0.035$). Based on the result, RDW may be superior to MCV in the prediction of postoperative pneumonia in patients with OE.

Nevertheless, this study has several limitations. First, this was a retrospective study at a single institute and with a comparatively long study period; hence, there could have been historical bias regarding treatment strategy and

perioperative management. Second, many patients had to be excluded due to insufficient data, which could be a selection bias.

CONCLUSION

Pretreatment RDW may be a surrogate marker for nutritional status and could be a predictive marker for postoperative severe morbidity, reoperation, and possibly pneumonia after OE; however, further multi-institutional investigation with a large cohort is necessary to establish the importance of pretreatment RDW for predicting short-term outcomes after esophagectomy.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1245/s10434-021-10719-2>.

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