Diagnosis and survival values of neutrophil-lymphocyte ratio (NLR) and red blood cell distribution width (RDW) in esophageal cancer

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ABSTRACT

Background: Recent studies have borne out claims that inflammation has a vital role in the development and progression of many diseases, including cancers. It has been reported that neutrophil-lymphocyte ratio (NLR) and red blood cell distribution width (RDW) could act as independent prognostic factors for several malignant tumors. We evaluated the diagnosis and prognosis values of preoperative inflammatory indicators, including NLR and RDW in esophageal cancer (EC).

Methods: We retrospectively analyzed the clinical data of 354 EC patients and 220 early esophageal cancer (EEC) undergoing potentially curative esophagectomy in Shandong Provincial Hospital Affiliated to Shandong University and chose 201 age and sex-matched healthy volunteers as the control group. We compared the clinicopathological features, survival curves and prognosis of the EC patients between the high and low groups according to the cutoff values of NLR and RDW.

Results: Significant higher preoperative NLR and RDW values were detected in patients with EEC and EC compared to the healthy controls (P < .001). A high RDW was significantly associated with an older age (P < .05). NLR and RDW values after surgery in EC group were significantly higher than those before surgery (P < .001 and P < .001, respectively). For EEC group, a higher RDW value showed a significantly worse overall survival (OS) and disease-free survival (DFS) (P = .040 and P = .013, respectively). For EC group, an increased NLR indicated a significantly association with poor overall survival (OS) (P = .004) and DFS (P = .001). Preoperative NLR can act as an independent prognostic indicator for EC.

Conclusion: The preoperative NLR and RDW are convenient, practical easily measured biomarkers of clinical diagnosis and prognostic assessment of patients with EC. Furthermore, NLR was more effective than RDW acting as an independent prognostic biomarker for EC.

1. Introduction

Esophageal cancer (EC) is the eighth most common tumor disease and sixth leading cause of cancer death worldwide [1]. An estimated 455,800 new cases of EC and 400,200 deaths occurred in 2012 worldwide [2]. EC is the most aggressive malignant tumor of the digestive tract, characterized by rapid development and poor prognosis and five-year survival of patients with EC < 20% [3]. Advanced surgical therapies and chemoradiation techniques did not significantly improve their survival. The reason for this fact may be the lack of early

symptoms, the relatively late diagnosis stage and the rapid development of tumor [4,5].

Recent studies have borne out claims that inflammation has a vital role in the development and progression of many diseases, including cancers [6,7], which might be usually accompanied by chronic irritation, infection, infiltrates of immune cells, secretion of cytokines and chemokines, endothelial dysfunction and platelet activation [8–13]. Moreover, substantial evidence indicates that the systemic inflammatory response is an important indicator of the prognosis of patients with various types of cancers, regardless of tumor stage [14].

Neutrophil-to-lymphocyte ratio (NLR) is a common index of systemic inflammation. NLR is defined as the absolute neutrophil count divided by the absolute lymphocyte count. It has been reported that an elevated NLR is a valuable predictive indicator of various cancer types, including pancreatic cancer, epithelial ovarian cancer, breast cancer and gastric cancer [15–18]. Red blood cell distribution width (RDW) is the coefficient of variation in red blood cell size, and elevated RDW generally corresponds to anisocytosis. RDW is also widely used laboratory parameter for inflammatory disease [19]. However, recent studies have reported that RDW can be used as laboratory parameter for inflammatory disease, such as atherosclerosis, ischemic cardiac diseases, inflammatory bowel diseases and prostate cancer [20–23]. Although whole blood count assay (WBC) have been routinely available to clinicians,the roles of several parameters in the diagnosis and management of patients, such as NLR and RDW, remains obscure. In recent years, there is a growing interest in establishing novel non-invasive predictive biomarkers from hematological and serologic parameters for various inflammatory diseases and cancers.

2. Materials and methods

2.1. Subjects and methods

In this study,we retrospectively analyzed the clinical data of 354 cases of EC patients in Shandong Provincial Hospital Affiliated to Shandong University between January 2011 and April 2015. In addition, we separately collected 220 cases of EEC patients. All cases underwent potentially curative esophagectomy. Meanwhile, we chose 201 age and sex-matched healthy volunteers as the control group. All the diagnosis were histopathologically confirmed by two pathologists after curative resection. Patients were selected for the present study according to the following inclusion criteria: confirmed histopathologic diagnosis; complete whole blood count before and after surgery; clinicopathological and follow-up data.

The patients with clinical signs of infection, hematologic disease, anemia, with blood transfusion made in the last three months, venous thrombosis detected in the last six months, severe coronary heart disease, autoimmune disease and a history of other malignancies were excluded from the study. Clinicopathological parameters were obtained from medical records. All patients were regularly followed up by telephone interviews and the last follow-up assessment was conducted in June 2016. As the primary study end point, overall survival (OS) was calculated from the initiation of treatment to death for any cause. The secondary end point was disease-free survival (DFS), which was defined as the time from the date of curative treatment to the date of identification of disease recurrence, either radiological or histological. Radiological recurrence was defined as a size increase of an existing lesion, new metastatic lesions, or disease-related symptoms. Histological recurrence was considered as cancerous cells, local invasion, vascular invasion, lymph node invasion by the repeat biopsy after treatment.

Approval for the study was granted by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong University. Informed consent was obtained from all study participants according to the Helsinki Declaration.

2.2. Laboratory data

WBC was routinely performed using an automated hematology analyzer XE-2100 (Sysmex Corp.) before surgery and three weeks after surgery. RDW was obtained directly from the whole blood cell count, while NLR was calculated as the ratio of neutrophils and lymphocytes.

2.3. Statistical Analysis

NLR and RDW are normally distributed and presented with mean ± SD and the differences were analyzed using student *t*-test. Differences between categories of each clinicopathological feature were analyzed using the χ^2 test or Fisher's exact test with one or more variables (< 5). The cutoff values of NLR and RDW in EC or EEC diagnosis were determined using receiver operating characteristic (ROC) curve analysis. Comparison of NLR and RDW values between before and after surgery used paired student's *t*-test. The association between these values and OS and DFS were calculated by the Kaplan–Meier method and survival curves were compared with the log-rank test. Significant predictors for survival in univariate analysis were incorporated into multivariate Cox proportional hazards model to determine independent prognostic factors. All statistical analysis was performed using SPSS statistical software (ver 19.0). P < .05 was considered statistically significant.

3. Results

3.1. Comparison of NLR and RDW in the three groups

The mean ± SD values of NLR in the EC group, EEC group and healthy group were 3.78 ± 4.160, 3.71 ± 4.935 and 1.79 ± 0.569, respectively. The mean ± SD values of RDW in the EC group, EEC group and healthy group were 13.03% ± 0.972, 12.97% ± 0.801 and 12.71% ± 0.493, respectively. NLR value in EC or EEC group was significantly higher than that in control group (P < .001), what's more, RDW value in EC or EEC group was also significantly higher than that in control group (P < .001). No significant differences were detected in NLR and RDW between EC and EEC group (P = NS)(Fig.1).

3.2. ROC curves analysis results

We used ROC curve analysis to verify the predictive power of NLR and RDW in predicting presence of EC and ECC. The optimal cutoffs of NLR and RDW for EC were determined to be 1.88(a sensitivity of 69.8% and a specificity of 65.7%) and 12.85% (a sensitivity of 50.3% and a specificity of 63.7%). The optimal cutoffs of NLR and RDW for EEC were determined to be 1.88(a sensitivity of 61.8% and a specificity of 65.7%) and 12.85% (a sensitivity of 51.4% and a specificity of 63.7%). For EC, the area under the curve (AUC) of NLR was 0.731 (95%CI = 0.690–0.772, P < .001) and the AUC of RDW was 0.589 (95%CI = 0.541–0.636, P = .001) for predicting the presence of EC, while for EEC, the AUCs of NLR and RDW were 0.659(95%CI = 0.607–0.711, P < .001) and 0.594(95%CI = 0.540–0.648, P = .001), respectively, for predicting the presence of EEC (Fig.2).

3.3. Associations between NLR, RDW and clinicopathological characteristics of 354 EC patients

A comparison between the clinicopathological characteristics with NLR and RDW in EC are exhibited in Table 1. A high RDW was significantly associated with older age (P = .015) while NLR was not related with any clinicopathological characteristic in EC.
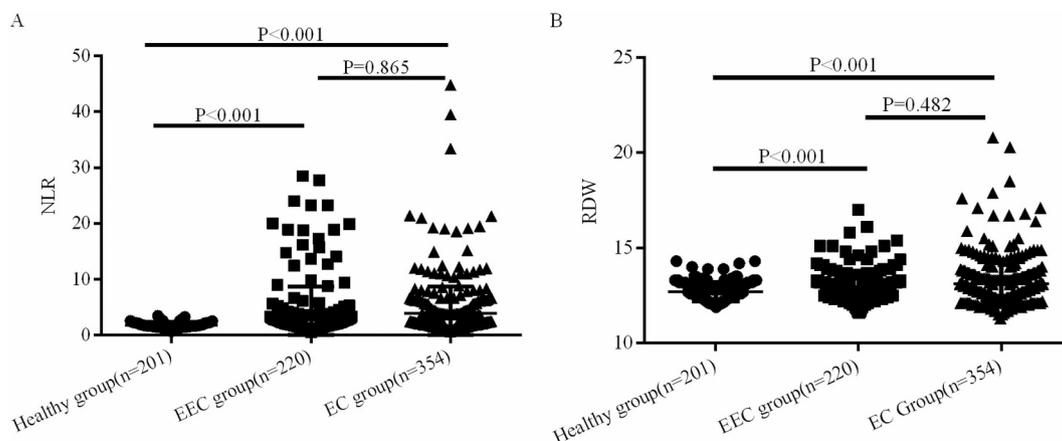
Fig. 1. Comparison of groups in terms of NLR(A) and RDW(B) values. Notes: Comparison between the groups using student *t*-test; Data are expressed as mean ± SD. Abbreviation: NLR, neutrophil-to-lymphocyte ratio; RDW, red blood cell distribution width. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. Comparison of NLR and RDW values of 354 EC patients before and after surgery

We compared the differences of NLR and RDW before and after surgery in 354 EC patients. The mean ± SD values of NLR and RDW were 3.72 ± 3.793 and 13.03% ± 0.972 before surgery, respectively, while 7.75 ± 5.547 and 13.38% ± 1.605 after surgery, respectively. The differences in NLR and RDW values between before and after surgery were analyzed in 354 patients with EC (Fig. 3). NLR and RDW values after surgery in EC group was significantly higher than those before surgery (P < .001 and P < .001, respectively).

To compare the relationship between the changes of NLR and RDW after surgery and clinicopathological characteristics, the EC patients were divided into two groups according to after surgery divided by before surgery —NLR < 1 and ≥ 1, RDW < 1 and ≥ 1. We found that a patient who is female or has a deeper tumor infiltration was inclined to have an elevated RDW after surgery, while the change of NLR after surgery was not related to the clinicopathological characteristics of the EC patients (Table 2).

3.5. Survival analysis of prognostic factors in EC or EEC patients

To investigate whether the NLR and RDW were associated with survival rates of EC and EEC, we performed Kaplan-Meier curves for OS and DFS. For the 220 EEC patients, the median follow-up duration was 26 months with a range of 2 to 80 months. A high RDW showed a significantly shorter OS and DFS (P = .040 and P = .013, respectively) (Fig.4). For the 354 EC patients, the median follow-up duration was

43 months with a range of 1 to 74 months. Elevated NLR might be associated with significantly poorer OS (P = .004) and DFS (P = .001), while RDW had no statistically significant difference in OS (P = .080) and DFS (P = .059) of EC patients(Fig.5).

To verify whether the NLR and RDW were the independent prognosis factors of EC, univariate and multivariate survival analysis for OS and DFS was performed. A univariate analysis showed that NLR, age, tumor location, tumor diameter, histotype, depth of tumor, lymph node metastasis, pStage were significantly associated with OS (P < .05). To identify the independent prognostic factors, significant factors according to a univariate analysis were included in a multivariate analysis. The multivariate analysis indicated that NLR, tumor diameter and lymph node metastasis could act as independent prognostic factors for OS (Table 3). Moreover, significant associations between NLR, age, tumor diameter, histotype, depth of tumor, lymph node metastasis, pStage and DFS was also observed in a univariate analysis (P < .05). The result of the multivariate analysis indicated that NLR, tumor diameter and lymph node metastasis could act as independent prognostic factors for DFS (Table 4). However, we have not yet found that RDW can act as an independent prognostic factor.

4. Discussion

Cancer is a leading cause of death in both more and less economically developed countries. In recent years, the fact that cancer may act as either a cause or a result of chronic inflammation aroused the attention to the connection between inflammation and malignancies. Studies have demonstrated that the cancer-associated inflammation
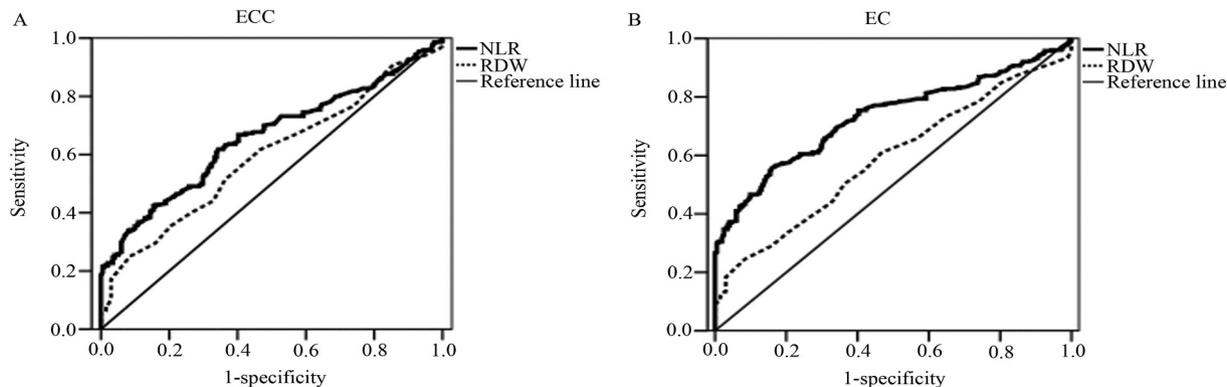

Fig. 2. The ROC curves grouped by NLR and RDW for EEC(A) and EC(B).

Table 1
Association of NLR and RDW with clinicopathological characteristics.

Characteristics	NLR		P value	RDW		P value
	< 1.88	≥1.88		< 12.85	≥12.85	
Age			NS			0.015
< 60 y	31(28.7)	69(28)		60(34.1)	40(22.5)	
≥60	77(71.3)	177(72)		116(65.9)	138(77.5)	
Gender			NS			NS
Male	77(71.3)	190(77.2)		128(72.7)	139(78.1)	
Female	31(28.7)	56(22.8)		48(27.3)	39(21.9)	
Location			MS			MS
Upper	0(0)	3(1.2)		2(1.1)	1(0.6)	
Middle	98(90.7)	224(91.1)		162(92.0)	160(89.9)	
Lower	10(9.3)	19(7.7)		12(6.8)	17(9.6)	
Diameter			NS			NS
	41(38.0)	84(34.1)		63(38.9)	62(32.1)	
> 3	67(62.0)	162(65.9)		113(61.1)	116(67.9)	
Histotype			NS			NS
Squamous	103(95.4)	235(95.5)		170(96.6)	168(94.4)	
Adenocarcinoma	3(2.8)	7(2.8)		3(1.7)	7(3.9)	
Other	2(1.9)	4(1.6)		3(1.7)	3(1.7)	
Depth of tumor			NS			NS
T1	11(10.2)	21(8.5)		14(8.0)	18(10.1)	
T2	23(21.3)	39(15.9)		38(21.6)	24(13.5)	
T3	32(29.6)	81(32.9)		56(31.8)	57(32.0)	
T4	42(38.9)	105(42.7)		68(38.6)	79(44.4)	
Lymph node metastasis			NS			NS
N0	50(46.3)	135(54.9)		94(53.4)	91(51.1)	
N1	35(32.4)	69(28.0)		50(28.4)	54(30.3)	
N2	18(16.7)	26(10.6)		23(13.1)	21(11.8)	
N3	5(4.6)	16(6.5)		9(5.1)	12(6.7)	
Distance metastasis			NS			NS
M0	104(96.3)	234(95.1)		171(97.2)	167(93.8)	
M1	4(3.7)	12(4.9)		5(2.8)	11(6.2)	
pStage			NS			NS
I	8(7.4)	21(8.5)		13(7.4)	16(9.0)	
II	41(38.0)	79(32.1)		70(39.8)	50(28.1)	
III	55(50.9)	134(54.5)		88(50.0)	101(56.7)	
IV	4(3.7)	12(4.9)		5(2.8)	11(6.2)	

P values were calculated by χ^2 test.

plays an important role in carcinogenesis and tumor progression [24,25]. The possible mechanism may be that inflammation was associated with malnutrition, immune dysfunction, platelet activation, angiogenesis and activation of cytokines [7,26].

Previous studies have shown that carcinogenesis in the digestive tract is closely associated with chronic inflammation [27,28]. EC is the most aggressive malignant tumor of the gastrointestinal tract, characterized by rapid progress and poor prognosis and five-year survival of patients < 20% [3], and frequently results in local inflammatory fester and denutrition influenced by inappetence and feeding obstruction.

Advanced surgical and chemoradiation techniques did not substantially improve survival rate of EC. The reason of this fact might be lack of early symptoms, its specific biological features, the relatively late stage of diagnosis and the rapid progression of tumor [4,5]. Furthermore, the generally prognostic factors of EC including tumor stage, lymph node metastasis, and lymphatic vessel invasion were only obtained after surgery. These postoperative factors are not routinely available and severely limit their clinical application.

Despite scientific efforts, there are no suitable serum/plasma biomarkers of EC, which have high sensitivity and specificity for the
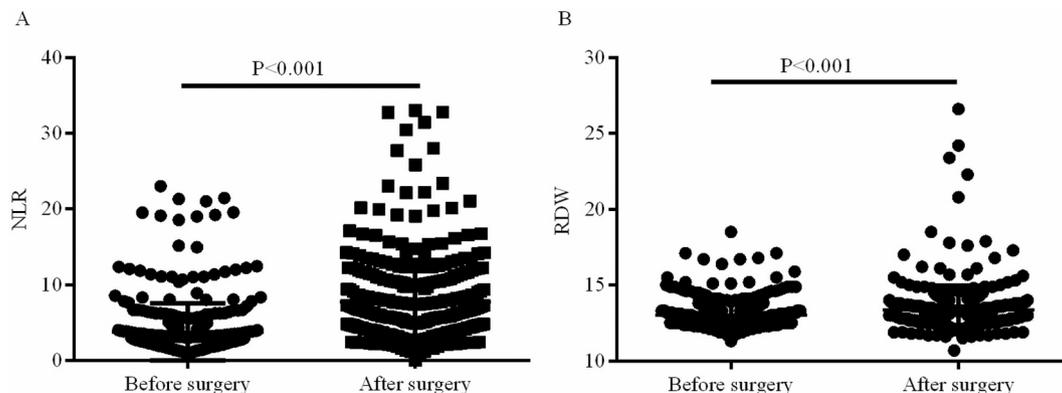

Fig. 3. Differences between before and after surgery in the NLR(A) and RDW(B). Notes: Comparison between before and after surgery in terms of NLR and RDW values used paired student *t*-test. Data are expressed as mean ± SD.

Table 2

Association of change in NLR and RDW values after surgery compared to before surgery with characteristics.

Characteristics	NLR(After/Before)		P value	RDW(After/Before)		P value
	< 1 (*n* = 61)	≥1 (*n* = 293)		< 1 (*n* = 100)	≥1 (*n* = 254)	
Age			NS			NS
< 60 y	17(27.9)	83(28.3)		31(31.0)	69(27.2)	
≥60 y	44(72.1)	210(71.7)		69(69.0)	185(72.8)	
Gender			NS			0.001
Male	48(78.7)	219(74.7)		88(88.0)	179(70.5)	
Female	13(21.3)	74(25.3)		12(12.0)	75(29.5)	
Location			NS			NS
Upper	1(1.6)	2(0.7)		2(2.0)	1(0.4)	
Middle	54(88.5)	268(91.5)		87(87.0)	235(92.5)	
Lower	6(9.8)	23(7.8)		11(11.0)	18(7.1)	
Diameter			NS			NS
≤ 3	18(29.5)	107(36.5)		32(32.0)	93(36.6)	
> 3	43(70.5)	186(63.5)		68(68.0)	161(63.4)	
Histotype			NS			NS
Squamous	60(98.4)	278(94.9)		99(99.0)	239(94.1)	
Adenocarcinoma	1(1.6)	9(3.1)		1(1.0)	9(3.5)	
Other	0(0)	6(2.0)		0(0)	6(2.4)	
Depth of tumor			NS			NS
T1	7(11.5)	25(8.5)		11(11.0)	21(8.3)	
T2	10(16.4)	52(17.7)		17(17.0)	45(17.7)	
T3	25(41.0)	88(30.0)		41(41.0)	72(28.3)	
T4	19(31.1)	128(43.7)		31(31.0)	116(45.7)	
Lymph node metastasis			NS			NS
N0	36(59.0)	149(50.9)		55(55.0)	130(51.2)	
N1	16(26.2)	88(30.0)		27(27.0)	77(30.3)	
N2	6(9.8)	38(13.0)		15(15.0)	29(11.4)	
N3	3(4.9)	18(6.1)		3(3.0)	18(7.1)	
Distance metastasis			NS			NS
M0	59(96.7)	279(95.2)		96(96.0)	242(95.3)	
M1	2(3.3)	14(4.8)		4(4.0)	12(4.7)	
pStage			NS			NS
I	7(11.5)	22(7.5)		11(11.0)	18(7.1)	
II	25(41.0)	95(32.4)		36(36.0)	84(33.1)	
III	27(44.3)	162(55.3)		49(49.0)	140(55.1)	
IV	2(3.3)	14(4.8)		4(4.0)	12(4.7)	

P values were calculated by χ^2 test.

screening or surveillance of this malignancy, especially in comparison with other gastrointestinal neoplasms [29,30]. Although recent clinical and laboratory studies have indicated that hematologic parameters including NLR, RDW and other blood parameters were significantly correlated with host inflammation and nutrition status induced by various types of cancers, partially predicting the progression or survival [31–33], the mechanism is unclear. Whole blood count assay have been routinely available to clinicians for some time and can give information about the patient's formed blood contents such as the red and white cells, the platelets, the count and dimensions of the subgroups of cells and parameters such as the distribution weights and mean platelet volume. In this study, we retrospectively analyzed the values of NLR and RDW and the clinical data of EC patients to determine whether these parameters could be used for assessment of disease diagnosis and prognosis.

As everyone knows, bacterial infections and steroid treatments can increase neutrophil counts, as well as viral infections may cause increase in lymphocyte counts. Consequently, inflammation conditions like bacterial or viral infections or drug might make the ratio of these two parameters changed. Especially when white blood cells are in normal range, their subtypes may reflect the degree of inflammation and predict cardiovascular mortality [34]. In recent years, NLR has been proposed as a surrogate marker for endothelial dysfunction and inflammation in distinct populations and has prognostic and predictive values [34,35]. Moreover, numerous studies have reported that increased preoperative NLR may reflect enhanced inflammation, advanced stage, poor survival of patients with colon cancer, lung cancer, and hepatocellular carcinoma by suppressing lymphokine-activated

killer cells and increasing the propensity to metastasis [36–39]. Thereinto, neutrophils may constitute a significant fraction of immune cells involved in the inflammatory process and play a key role in tumor proliferation, producing a number of ligands that induce tumor cell proliferation and invasion, and promoting tumor vascularization by releasing proangiogenic chemokines and other factors. In the context of cancer, neutrophils were shown to exert both pro- and antitumor activities suggesting a dual mode of activation. On the other hand, the function of lymphocytes is to induce cytotoxic cell death and cytokine production that inhibits the proliferation and metastatic activity of cancer cells. In brief, NLR can be considered to reflect the balance between the pro-tumor inflammatory status and the antitumor immune status [40].

RDW, which is a measure of heterogeneity in erythrocyte size, is a sensitive and specific indicator of iron deficiency anemia. Recently, emerging evidence has suggested a role for high RDW which is frequently influenced by inflammation and oxidative stress in predicting an increased overall and disease-specific mortality across patients with chronic or progressive inflammation diseases [20–23]. Many studies have shown that it was closely related to the inflammation markers such as CRP, IL-6 and TNF-α [22,41]. It was also shown that RDW increased in the inflammatory intestinal disease in which chronic and active inflammation increased [20]. A growing body of evidence has suggested that RDW might have a role as diagnostic or prognostic marker in various solid cancers. In particular, most published studies focused on RDW at the time of diagnosis as an independent predictor of cancer patient survival. Seretis et al. showed that RDW was significantly higher in patients with breast cancer compared to the patients with
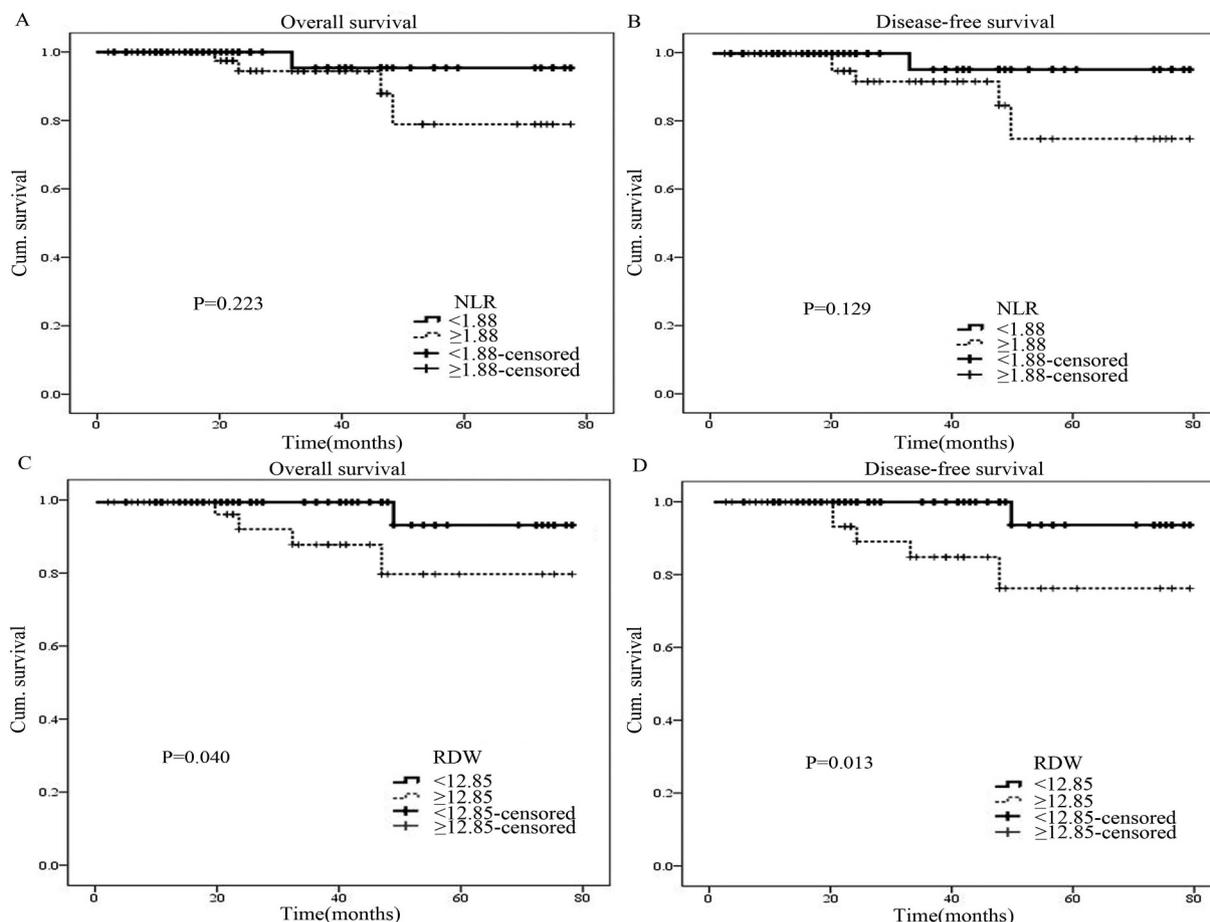
Fig. 4. Kaplan-Meier curves for OS and DFS of patients with EEC based on NLR (A and B) and RDW(C and D).

fibroadenomas. RDW showed a high correlation with the size of primary tumor, the number of metastatic axillary lymph glands and overexpression of HER2 [42]. Warwick et al. showed that preoperative RDW in patients undergoing pulmonary resections for non-small-cell lung cancer could predict mortality and long-term survival [43]. Potential mechanisms may be that RDW in cancer patients is usually accompanied by increased inflammation or malnutrition, which was induced by impaired iron release from reticuloendothelial macrophages, inhibited response to erythropoietin, and decreased red blood cell survival via production of inflammatory markers. Up-expression of cytokines such as CRP, tumor necrosis factor-α, and interleukin-6 has been repeatedly demonstrated to play a vital role in induction of chronic inflammation in cancer patients. Moreover, RDW was found to be correlated to malnutrition which has been shown to be an independent risk factor for nosocomial infections and associated with lower efficacy and increased toxicity of treatment, lower survival rates, and poorer quality of life [44,45].

As we mention above, the interaction between inflammation and carcinogenesis remain obscure. Therefore, in the present study, firstly, we detected whether the preoperative NLR and RDW values could distinguish the patients of EC and EEC from the healthy controls. Secondly, we analyzed the association of NLR, RDW with the clinicopathological features of patients with EC. Thirdly, the existence of any differences in NLR and RDW before and after radical surgery resection was assessed. Fourthly, we evaluated the predictive effect of NLR and RDW on progression and prognosis of EC and EEC. Our results are listed as following.

Through the comparison between groups, we found that the values of NLR and RDW in 354 patients with EC were significantly higher than those in healthy group (P < .001), which are consistent with the

results of other studies [20–23].

In addition to, in order to validate whether the NLR and RDW can become the differential diagnosis indicators of EEC, we collected 220 patients with EEC to compare with the healthy group, finding that the differences were also statistically significant(P < .001). The results enlightened us that the NLR and RDW can be used as screening indicators of EC. Although there have been several studies on NLR, RDW and esophageal cancer published in recent years, most of them have studied the role of NLR and RDW in the prognosis of esophageal cancer [46–48]. However, in these studies, the value of NLR and RDW in the early diagnosis and differential diagnosis of esophageal cancer has not been mentioned. In the present study, we detected that the values of NLR and RDW in patients with EC or EEC were significantly higher than those in healthy controls, which indicated that NLR and RDW can act as screening indicators to distinguish the patients with EC or EEC from the healthy controls. Therefore, the diagnostic value of NLR and RDW is of great significance for clinical applications.

In our previous work, we drew the ROC curves using a relatively small sample cases (101 healthy controls and 284 EC patients) and analyzed that the cutoff values of NLR and RDW were 1.89(a sensitivity of 63.7% and a specificity of 73.3%) and 12.85 (a sensitivity of 49.3% and a specificity of 74.3%), respectively. We got the values of cut off in small number patients and then we tested them in considerable number patients. So we collected more EC patients and healthy controls, and the number of EC patients was added to 354 and healthy controls to 201.When 1.89 was the cutoff value of NLR, the true positive rate (sensitivity) of NLR in the larger samples was 69.2%, and the true negative rate(specificity) was 66.2%. When 12.85 was the cutoff value of RDW, the true positive rate (sensitivity) of RDW in the larger samples was 51.1%, and the true negative rate (specificity) was 63.7%. The
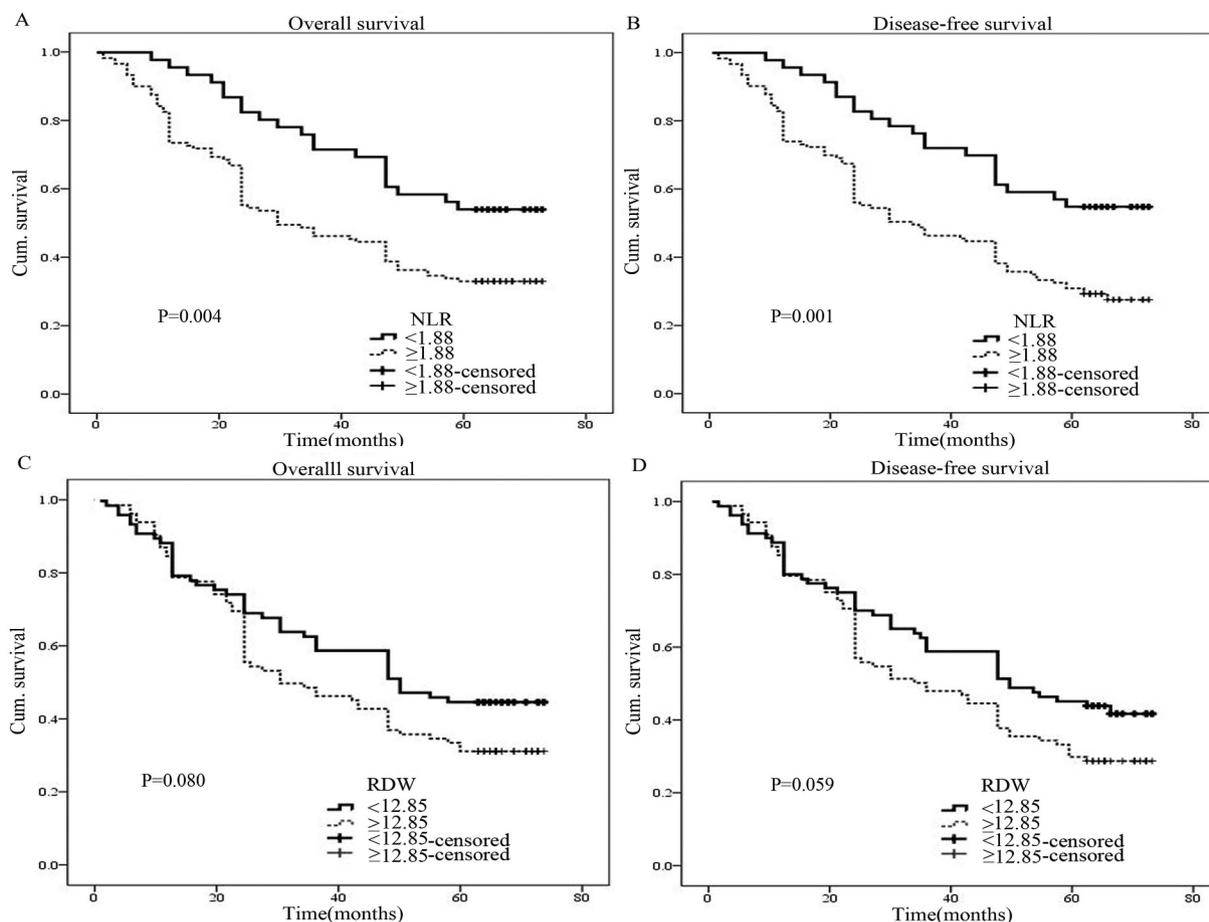
Fig. 5. Kaplan-Meier curves for OS and DFS of patients with EC based on NLR (A and B) and RDW(C and D).

sensitivity and specificity of diagnosis did not change significantly in large samples using the cutoff values calculated by small samples. This indicated that the cutoff values calculated from small samples had the same sensitivity and specificity in the diagnosis of large samples, and the cutoff values were stable in diagnosis regardless of large or small samples (Date was not shown).

According to ROC curve analysis in the large samples, the cutoff values of NLR and RDW were determined to be 1.88 and 12.85% for predicting EEC or EC which were consistent with the cutoff values calculated by small samples. Furthermore, in this study, a higher RDW was detected in these EC patients who had clinicopathologic

characteristics related to advanced cancers such as older age (P < .05). However, we found no correlation between NLR and any pathological parameter.

It is important to explore the risk factors for postoperative complications after esophagectomy, because they are more likely to cause complications when comparing esophagectomy with other gastrointestinal surgery. There are few studies in respect to comparing the changes of NLR and RDW values before surgery and after surgery. We found that the mean values of NLR and RDW after surgery were significantly higher than before surgery, and the patients who are female or have deeper tumor infiltration were inclined to detect a higher RDW

Table 3
Univariate and multivariable Cox regression analyses for OS in 354 patients with EC.

Variables	Univariate[a]		P value	Multivariate[b]		P value
	HR	95% CI		HR	95% CI	
NLR (< 1.88/≥1.88)	1.960	1.212–3.171	0.006	2.083	1.283–3.3811.699	0.003
RDW (< 12.85/≥12.85)	1.405	0.948–2.084	NS			
Gender (Male/Female)	1.031	0.638–1.666	NS			
Age (< 60 y/≥60 y)	1.594	1.001–2.539	0.049			
Tumor location (Upper/Middle/Low)	2.306	1.257–4.228	0.007			
Tumor diameter (≤3/ > 3)	2.102	1.351–3.270	0.001	1.799	1.147–2.822	0.011
Histotype (Squamous/Adenocarcinoma/Other)	1.663	1.056–2.619	0.028			
Depth of tumor (T1/T2/T3/T4)	1.283	1.036–1.589	0.022			
Lymph node metastasis (N0/N1/N2/N3)	1.413	1.176–1.699	< 0.001	1.394	1.155–1.683	0.001
Distance metastasis (M0/M1)	1.442	0.700–2.970	NS			
pStage (I/II/III/IV)	1.733	1.295–2.319	< 0.001			

[a] Performed using the Kaplan–Meier analysis model and the log-rank test; values of P < .05 in the univariate analysis were entered into a multivariate analysis.
[b] performed using Cox proportional hazards models with the forward likelihood method.

Table 4
Univariate and multivariable Cox regression analyses for DFS in 354 patients with EC.

Variables	Univariate[a]		Pvalue	Multivariate[b]		P value
	HR	95% CI		HR	95% CI	
NLR ($< 1.88/\geq 1.88$)	2.202	1.367–3.550	0.001	2.377	1.469–3.845	< 0.001
RDW ($< 12.85/\geq 12.85$)	1.426	0.974–2.088	NS			
Gender (Male/Female)	0.995	0.623–1.588	NS			
Age ($< 60/\geq 60$)	1.673	1.062–2.635	0.026			
Tumor location (Upper/Middle/Low)	1.801	0.955–3.394	NS			
Tumor diameter ($\leq 3/ > 3$)	1.985	1.306–3.017	0.001	1.672	1.090–2.565	0.018
Histotype (Squamous/Adenocarcinoma/Other)	1.654	1.050–2.605	0.030			
Depth of tumor (T1/T2/T3/T4)	1.239	1.013–1.514	0.037			
Lymph node metastasis (N0/N1/N2/N3)	1.443	1.207–1.725	< 0.001	1.439	1.199–1.727	< 0.001
Distance metastasis (M0/M1)	1.768	0.922–3.393	NS			
pStage (I/II/III/IV)	1.679	1.270–2.221	< 0.001			

[a] Performed using the Kaplan–Meier analysis model and the log-rank test; values of P < .05 in the univariate analysis were entered into a multivariate analysis.
[b] Performed using Cox proportional hazards models with the forward likelihood method.

after surgery than before surgery. The results reminded us that an elevated postoperative RDW might be associated with a poor prognosis of EC patients.

We carried out the follow-up and analyzed the survival rates in patients with EC and EEC. A high preoperative RDW predicted a poorer OS and DFS in patients with EEC (P = .040, P = .013, respectively). A high NLR might be associated with poor OS (P = .223) and DFS (P = .129), although the difference was not statistically significant, at least it showed that the NLR had an impact on unfavorable OS and DFS of patients with EEC. A high NLR exhibited an unfavorable OS and a worse DFS in patients with EC, which were both statistically significant (P = .004, P = .001, respectively). A high RDW might be associated with poor OS (P = .080) and DFS (P = .059), which indicated that the RDW had an impact on unfavorable survival rate of patients with EC. These results testified that NLR and RDW could be used to estimate the survival of the patients with EC. Furthermore, we conducted univariate and multivariate analysis to predict the independent factors of EC. We found that preoperative NLR could be an independent prognostic factor for disease progression or death in EC patients, which was consistent with previous research [40,41]. Although high RDW lost its independent prognostic significance for OS and DFS in multivariate analysis, it still offered considerable information on RDW for clinical prognosis.

An assessment of NLR and RDW levels to predict clinical outcomes in patients with EC has advantages. It can be acquired immediately when the patient is suspected of EC to assess the patient's general condition objectively such as infectious condition and malnutrition, contribute to diagnosis and prognosis evaluation. However, we have not yet found that RDW can act as independent prognostic indicator, this may be related to the limitations of the present study. First, our study was a retrospective study, so there may be potential bias and inaccuracy in data collection as in most retrospectively designed studies. Second, the sample size was small. Third, the follow-up duration was not long enough. Therefore, the study needs to be validated in further investigation with a larger sample size and longer follow-up duration.

5. Conclusion

Preoperative NLR and RDW are convenient, practical easily measured biomarkers of clinical diagnosis and prognostic assessment of patients with EC.

Acknowledgements

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