Prognostic impact of the red cell distribution width in esophageal cancer patients: A systematic review and meta-analysis

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Abstract

AIM
To clarify the previous discrepant conclusions, we performed a meta-analysis to evaluate the prognostic value of red cell distribution width (RDW) in esophageal cancer (EC).

METHODS
We searched the PubMed, EMBASE, Web of Science and Cochrane Library databases to identify clinical studies, followed by using STATTA version 12.0 for statistical
INTRODUCTION

Esophageal cancer (EC) is one of the most common digestive malignancies worldwide\(^{[1,2]}\), ranking as the fourth leading cause of cancer-related death\(^{[3]}\) and leading to approximately 400000 deaths in 2012\(^{[4]}\). The incidence of EC varies widely across different countries and regions\(^{[5]}\). According to the latest national statistics, EC is the fourth most common malignant tumor type in China\(^{[6]}\), with cancer-related morbidity and mortality rates of 11.1% and 13.3%, respectively, in 2015, which has emerged as a severe public health problem, particularly in some high-risk rural areas\(^{[6]}\). However, in 2012, the cancer-related morbidity and mortality rates of EC (3.41% and 2.98%, respectively) were lower in North America and Europe than those in China\(^{[6]}\).

EC is a highly aggressive digestive malignancy characterized by rapid growth and early metastasis. The rate of distant metastasis in EC patients is as high as 20%-30% at the time of initial diagnosis\(^{[7]}\). Despite the progress in radical resection and adjuvant therapy (radiation and chemotherapy), the 5-year overall survival (OS) rate of patients with EC remains approximately 20% in China\(^{[8]}\), emphasizing an urgent need to detect effective prognostic biomarkers which could guide personalized therapeutic strategy for EC patients\(^{[9,10]}\).

In recent years, accumulating evidence has shown that systemic inflammatory responses are closely associated with tumor initiation, progression and invasion\(^{[11-14]}\). Therefore, a variety of inflammatory indicators have been explored to assess their potential prognostic roles in various cancers. One such marker is the red blood cell distribution width (RDW), which is defined as the coefficient of variation in the red blood cell size. An elevated RDW indicates anisocytosis, which is considered as the basis for the clinical diagnosis of iron deficiency anemia\(^{[15]}\). However, fluctuations in the RDW have recently been reported as involved in many other pathophysiological conditions. For example, an elevated RDW is strongly associated with chronic inflammation, poor nutritional status, and age-associated diseases, which is indicative of changes in erythropoiesis. In addition, a number of studies have demonstrated a significant correlation between RDW and conventional inflammatory parameters, such as the C-reactive protein, interleukin-6 and tumor necrosis factor-\(\alpha\) levels and erythrocyte sedimentation rate. Cancer has been revealed to be associated with chronic inflammation, and the latter is a key determinant of disease progression and survival in various cancers\(^{[16,17]}\). In 2007, Felker et al\(^{[18]}\) found that RDW could serve as an independent predictor of morbidity and mortality in heart failure. Recent studies have revealed that RDW is associated with prognosis in several types of cancer, such as lung cancer\(^{[19]}\), prostate

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RDW is an important complete blood count parameter that is routinely monitored in cancer patients. Several studies conducted in recent years have investigated the relationship between EC prognosis and RDW due to the easy accessibility of obtaining blood samples and the low cost of analyzing RDW. However, the results of these studies show some discrepancies, which could be attributed to differences in the study design and relatively small sample sizes. To this end, in the present study, a meta-analysis was performed to identify the correlation between RDW and survival in EC patients.

MATERIALS AND METHODS
This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data sources and search strategies
A systematic review of studies that evaluated the prognostic value of RDW in EC patients was performed. Four databases were electronically searched: Medline (host: OVID) from 1946 to April 2017; EMBASE (host: OVID) from 1974 to April 2017; and Web of Science and Cochrane Database of Systematic Reviews from 2005 to June 2017. The search terms used in our study were “RDW”, “red cell distribution width with esophageal neoplasm”, “esophagus neoplasm”, “esophagus neoplasms”, “cancer of esophagus”, “cancer of the esophagus”, “esophageal cancer”, “esophageal cancers”, “esophageal squamous cancer”, “esophageal cancer”, “esophageal cancers”, “esophageal squamous cell cancer” (ESCC), and “esophageal adenocarcinoma”. Both free text and MeSH terms were used as keywords. The search strategy used for the PubMed database is shown in Table 1, and the presented search strategy was also used for the other electronic databases.

Study selection
The search was performed by two investigators (Xu and Wang) who also evaluated the titles and abstracts of all candidate articles. Full-text was reviewed when the articles could not be categorized based on the title and abstract. Articles were included and excluded in accordance with the corresponding criteria defined in this study. Any disputes during the selection period were discussed with and resolved by a third investigator (Xiong). A flowchart demonstrating the details of the study selection according to the PRISMA guidelines is shown in Figure 1.

Inclusion and exclusion criteria
Studies that met the following criteria were considered eligible: (1) A study of EC patients who underwent radical esophagectomy; (2) a study of patients with localized disease without distant metastasis; (3) a study of patients without preoperative neoadjuvant therapy; (4) a study of patients without previous antiinflammatory therapies and with available preoperative laboratory outcomes; (5) a study of the association between the preoperative RDW and OS/disease-free survival (DFS)/cancer-specific survival (CSS); and (6) a complete paper published in English. Studies that met the following criteria were excluded: (1) Letters, case reports, reviews or preclinical studies; (2) studies describing a repeated analysis or duplicate data; (3) studies lacking key information for further analysis; and (4) nonhuman studies.

Data extraction
We used predesigned extraction forms for data collection. The following information was extracted from each study: first author's name, year of publication, country of the patients, research type, number of male/female patients included in the study, pathological types, RDW cut-off value, hazard ratio (HR) of elevated RDW for OS, CSS and DFS with 95% confidence interval (CI) and P-value. Assuming that most of the deaths were related to cancer, in the case of unavailability of OS information, data for CSS were extracted. HRs from multivariable analyses were extracted when available; otherwise, HRs from univariable analyses were extracted or estimated from Kaplan-Meier survival curves as described by Parmar and colleagues. HRs for subgroups were compared defined by different markers.

Data synthesis and statistical analyses
HRs and the corresponding 95% CIs were directly obtained from each publication. If the values were not directly reported, the values were calculated according to the method described by Parmar and colleagues. The meta-analysis was performed with STATA software version 12.0 (STATA Corporation, College Station, TX, United States) to combine the HRs with 95% CIs for categorical data and the weighted mean difference or standardized mean difference with 95% CIs for continuous data. All statistical tests were bilateral, and a P value < 0.05 was considered as statistical significance. If the data were not suitable for pooling, a systematic narrative synthesis of the information was performed.
which was presented in the text to understand and to summarize the findings as well as characteristics of the included studies.

**Heterogeneity analysis**
The heterogeneity of the pooled results was assessed through Cochran’s Q test and Higgins I-squared statistic. Significant heterogeneity was identified by $P < 0.05$ and/or $I^2 > 50\%$, and the random-effects model (DerSimonian-Laird method) was used to combine the data. Otherwise, the fixed-effects model (Mantel-Haenszel method) was employed. To explore the potential source of heterogeneity among studies, subgroup analyses were performed according to various variables, such as the RDW cut-off value, the patient number in each study, and the study type and quality.

**Assessment of study quality**
The quality of the included studies was assessed by using the Newcastle-Ottawa quality scale (NOS)\(^{(28)}\). Three aspects, namely, selection, comparability and outcomes, were assessed on this scale, which had a maximum score of 9. Studies with scores $\geq 7$ were considered to be of high quality.

**Sensitivity analysis**
If significant heterogeneity was observed, a sensitivity analysis was performed after data extraction and subgroup analyses. This sensitivity analysis, which included the sequential omission of each study using the “metaninf” STATA command, aimed to validate the findings of this meta-analysis.

**Assessment of publication bias**
Begg’s funnel plot and Egger’s linear regression test were performed to evaluate publication bias, and a $P$ value of $< 0.05$ was considered statistically significant.

**RESULTS**

**Search results and study characteristics**
Initially, 17 studies were selected from the electronic databases, and 10 studies remained after the removal of duplicates. After reading the titles and/or abstracts, four unrelated studies were excluded, and six full-text articles\(^{(21-26)}\) were further assessed. None of these studies were excluded after thorough review of full-text. These six studies\(^{(21-26)}\), which included 3826 patients, were included in this meta-analysis. The detailed search method and a flowchart representing the selection process are shown in Figure 1. These studies included five retrospective studies and one prospective study. The sample sizes varied from 144 to 2396, with a median value of 638. All six studies were conducted in Asian countries. The cut-off values for the RDW ranged from 12.2% to 15.3%. All six studies reported a correlation between RDW and OS/CSS, and two of the studies also investigated the association between RDW and DFS.
Impact of the RDW on OS and DFS in EC

The HRs and 95%CIs from the six studies involving 3826 patients were extracted and then pooled. The pooled results showed that the RDW was not associated with OS or CSS (HR = 1.27, 95%CI: 0.97-1.57, P = 0.056; Figure 2), with significant heterogeneity among the six studies (I² = 53.6%, P = 0.056; Figure 2); thus, the random-effects model was adopted for further analyses. The correlation between the RDW and DFS in EC patients were further investigated based on the pooled HRs and 95% CIs from two studies comprising 647 patients. As a result, RDW was not associated with DFS (HR = 1.42, 95%CI: 0.96-1.88, P = 0.000; Supplementary Figure 1), and no heterogeneity was observed (I² = 0.0%, P = 0.423; Supplementary Figure 1). In consideration of the significant heterogeneity of the pooled results regarding the effect of the RDW on OS/CSS, subgroup analyses, sensitivity analyses and Begg's funnel plot and Egger's linear regression analyses were conducted to further identify the heterogeneity source.

Sensitivity analyses was carried out by sequentially omitting each study to investigate its influence on results, indicating that the study conducted by Hu et al was the primary source of heterogeneity (Figure 3). After exclusion of this study, the heterogeneity was effectively reduced or eliminated (I² = 0.0%, P = 0.926; Supplementary Figure 2). Surprisingly, the corresponding pooled HR varied with the inclusion (HR = 1.27, 95%CI: 0.97-1.57, P = 0.000; Figure 2) and omission of this study (HR = 1.42, 95%CI: 1.16-1.69, P = 0.000; Supplementary Figure 2). After reviewing the six studies included in our meta-analysis, we found that the study conducted by Hu et al was the only prospective study, whereas the other five studies were retrospective ones. The sensitivity analyses indicated that the study type might be a source of heterogeneity. Therefore, we performed a subgroup analysis based on the study type (Supplementary Figure 3) and found that a high RDW is significantly associated with poor OS/CSS in patients with EC.

Furthermore, when the subgroups were stratified by patient number (< 400 or > 400), the heterogeneity was effectively reduced or eliminated after excluding the studies with > 400 patients (I² = 0.0%, P = 0.850; Supplementary Figure 4), and the corresponding pooled HR was 1.45, 95%CI: 1.13-1.76, P = 0.000; Supplementary Figure 4). Therefore, the subgroup analyses indicated that the patient number might also be a source of heterogeneity. For studies involving > 400 patients, the RDW cut-off value > 13% was significantly associated with poor OS/CSS in patients with EC.

Table 2 Main characteristics of included studies in meta-analysis

| Order number | Author       | Year of publication | Country | Research type | Patients number | Male | Female | Pathological types | RDW, cut-off value, % | CSS/OS/DFS | HR, U | LCI, U | UCI, U | P-value, U | HR, M | LCI, M | UCI, M | P-value, M | NOS score |
|--------------|--------------|---------------------|---------|---------------|----------------|------|--------|-------------------|----------------------|-------------|-------|--------|--------|-----------|-------|--------|--------|-----------|-----------|
| 1            | Chen et al   | 2015                | China   | Retrospective | 277            | 240  | 37     | ESCC              | 14.5                 | CSS         | 1.719 | 1.268  | 2.331  | < 0.001   | 1.396 | 1.022  | 1.908  | 0.036     | 6         |
| 2            | Wan et al    | 2016                | China   | Retrospective | 179            | 150  | 29     | ESCC (133), EAC (46) | 15                   | OS          | 3.087 | 1.85   | 5.152  | < 0.001   | 1.895 | 1.023  | 3.508  | 0.042     | 7         |
| 2            | Wan et al    | 2016                | China   | Retrospective | 179            | 150  | 29     | ESCC (133), EAC (46) | 15                   | DFS         | 3.208 | 1.922  | 5.353  | < 0.001   | 1.907 | 1.02  | 3.565  | 0.043     | 7         |
| 3            | Hirahara et al | 2016              | Japan   | Retrospective | 144            | 129  | 15     | ESCC              | 15.3                 | CSS         | 2.332 | 1.704  | 3.919  | 0.005     | 1.684 | 0.929  | 3.071  | 0.03       | 6         |
| 4            | Sun et al    | 2016                | China   | Retrospective | 362            | 268  | 94     | ESCC              | 13.6                 | OS          | 1.381 | 0.946  | 2.016  | 0.094     | 1.356 | 0.948  | 1.94   | 0.095     | 5         |
| 5            | Zhang et al  | 2016                | China   | Retrospective | 468            | 376  | 92     | ESCC              | 12.2                 | OS          | 1.505 | 1.068  | 2.122  | 0.02      | 1.356 | 0.948  | 1.94   | 0.095     | 7         |
| 5            | Zhang et al  | 2016                | China   | Retrospective | 468            | 376  | 92     | ESCC              | 12.2                 | DFS         | 1.474 | 1.046  | 2.077  | 0.027     | 1.349 | 0.943  | 1.929  | 0.101     | 7         |
| 6            | Hu et al     | 2017                | China   | Prospective   | 2396           | 1822 | 574    | ESCC (133)        | 12.70 (men)          | OS          | 0.85  | 0.76   | 0.94   | 0.02      | 0.84  | 0.75   | 0.93   | 0.091     | 8         |
| 6            | Hu et al     | 2017                | China   | Prospective   | 2396           | 1822 | 574    | ESCC (133)        | 12.70 (women)        | OS          | 1.02  | 0.89   | 1.18   | 0.73      | 1.01  | 0.88   | 1.17   | 0.994     | 8         |

With the exception of one study, the NOS scores of all the other studies were > 5. The general characteristics of the six included studies are summarized in Table 2.
with patient number $\leq 400$, a high RDW was significantly associated with poor OS/CSS in patients with EC.

Finally, when the subgroups were stratified by NOS scores ($\leq 6$ or $> 6$), heterogeneity was effectively reduced or eliminated after omitting the studies with NOS scores $> 6$ ($I^2 = 0.0\%$, $P = 0.876$; Supplementary Figure 5), and the corresponding pooled HR was increased (HR $= 1.42$, 95%CI: 1.09-1.74, $P = 0.000$; Supplementary Figure 5). Thus, the study quality might be another source of heterogeneity.

### Publication bias

Begg's funnel plot and Egger's linear regression analyses were performed to estimate the potential publication bias.
in the present meta-analysis. The P values regarding OS/CSS were 0.133 (Begg’s test; Supplementary Figure 6) and 0.005 (Egger’s test; Supplementary Figure 7). Due to the small sample sizes of the included studies, there was significant publication bias in our study, which was also demonstrated by the funnel plot (Funnel plot; Supplementary Figure 8). Therefore, publication bias might be another source of heterogeneity.

**DISCUSSION**

To the best of our knowledge, this study constitutes the first meta-analysis investigating the prognostic value of the RDW in EC. The most notable finding is that RDW is not associated with the prognosis of EC patients, including both OS/CSS and DFS. This novel finding is inconsistent with previous conclusions regarding the prognostic value of RDW in EC. Significant heterogeneity was observed across the included studies. After investigating the source of this heterogeneity by subgroup and sensitivity analyses, we derived four major conclusions. (1) In the retrospective studies, an elevated RDW was associated with poor OS/CSS, which did not affect DFS. (2) In the included prospective study, an elevated RDW was associated with a favorable prognosis in male ESCC patients, which is contradictory to the conclusions of most previous studies on cancers.[20,29-32]

Additionally, RDW was not associated with prognosis in female patients. (3) When the patient number was < 400, an elevated RDW was associated with poor OS/CSS, but this prognostic correlation was not observed when the number of patients was > 400. And, finally, (4) an elevated RDW was significantly associated with poor OS/CSS when the RDW cut-off value was > 13%, but this association was not observed when the cut-off value was ≤ 13%.

The role of the RDW is being increasingly appreciated due to its close correlation with the risks of cardiovascular diseases and systemic inflammation[33,34]. Previous studies have identified RDW as an accurate predictor of inflammation in hepatitis B infection, mortality due to acute pancreatitis, and activity of inflammatory bowel disease[34-36]. Moreover, an elevated RDW has been found to be a risk factor and progression indicator in multiple malignancies[19,31,37,38].

In the last 2 to 3 years, studies concerning the correlation between RDW and EC prognosis have become increasingly prominent. However, the conclusions of these studies are varied and sometimes even conflicting. Four small-scale retrospective studies[21-24] included in this meta-analysis concluded that an elevated RDW was significantly associated with worse OS in EC patients. In addition, one intermediate-scale retrospective study[25] concluded that the RDW was not associated with OS at all. Moreover, one large-scale prospective study[26] concluded that an elevated RDW was associated with better OS in male but not female EC patients. Considering that men are three to four times more likely to suffer from EC than women[37], this finding harbors important clinical implications in guiding therapeutic strategies for EC.

There are several reasons for the discrepant conclusions from diverse studies. Four small-scale retrospective studies[21-24] demonstrated that an elevated RDW was a predictor of unfavorable prognosis in EC patients, and the underlying mechanism might be one of the following. First, since Rudolf Virchow noted the presence of leucocytes within tumor tissues approximately 150 years ago and suggested that cancer might be initiated as a result of chronic inflammation[11,39], numerous preclinical and population-based studies have verified his observation. Inflammation might contribute to increased RDW levels by not only impairing iron metabolism but also inhibiting the production of or response to erythropoietin or by reducing red blood cell survival[40,41]. Second, chronic inflammation has also been associated with poor response to chemotherapy[42]. Third, RDW has been found to be correlated with malnutrition, which is an independent risk factor for nosocomial infections associated with poor therapeutic response, an increased rate of treatment-related toxicity, reduced survival rates, and poor quality of life[43,44].

In contrast, one large-scale prospective study[26] concluded that an elevated RDW was a positive predictor of prognosis in male EC patients, however the actual mechanism remains largely undefined. This finding is consistent with the results of another cohort study[49] with data from 26709 nondiabetic adults with more than 14 years of follow-up, which indicated that a low RDW was significantly associated with an increased incidence of diabetes mellitus independent of traditional risk factors. The underlying mechanism might be as follows. Aerobic glycolysis has been proposed as a hallmark of cancer, and the acidic environment caused by aerobic glycolysis is a necessary component of carcinogenesis[42]. Due to the significant association between a low RDW and an increased incidence of diabetes mellitus, it is reasonable to speculate that an elevated RDW might be a surrogate indicator of improved glucose metabolism, which is a key factor for prolonged survival in EC patients. Nevertheless, further clinical evidence and preclinical experiments are warranted to support and verify the accurate mechanism and to identify the real prognostic significance of the RDW in EC.

However, when the data from female patients were included in the present study, the RDW was not found to be associated with OS (HR = 0.92, 95%CI: 0.75-1.08, P = 0.000; Supplementary Figure 9), which is consistent with the conclusions of an intermediate-scale retrospective study[25] included in this meta-analysis. Further analyses revealed that the two above studies have some common characteristics-the sample size was relatively large (468 vs 2396) and the RDW cut-off values were 13%. This finding is consistent with the results of a study[47] conducted in 2012, which revealed that the RDW was elevated (> 14.8%) in 31.6% of benign biliary obstruction cases and 68.4% of malignant biliary stricture cases, whereas the RDW was reduced (< 14.8%) in
72.9% of benign cases and 27.1% of malignant cases (these differences were statistically significant, \( P < 0.001 \)). Therefore, an RDW cut-off of 14.8% was the most suitable for predicting a malignant biliary stricture, with a sensitivity of 72% and a specificity of 69% (area under the curve = 0.755, 95%CI: 0.649-0.810). The conclusions of the two studies might be partly attributed to the lower RDW cut-off value. Thus, more large-scale studies exploring the actual relationship between RDW and the prognosis of EC patients are urgently needed in the future. Furthermore, it is necessary to establish a reasonable method for identifying the appropriate RDW cut-off value for predicting the prognosis of EC patients.

However, in contrast to the findings obtained from male EC patients, an elevated RDW was not associated with the prognosis of female EC patients\(^{[26]}\). Despite the prospective nature of the study demonstrating these results, we cannot neglect a potential correlation between the RDW and sex due to the large sample size in that study. Moreover, however, studies are needed to investigate and confirm this correlation and to explore the underlying mechanisms.

There are certain limitations that should be acknowledged in this meta-analysis. First, most of the studies included in this meta-analysis were retrospective in nature, and the numbers of patients in these retrospective studies were relatively small. Only one study was prospective, which might prevent generalization of the results. Second, this meta-analysis was performed based on the pooled HRs and 95%CIs from eligible studies, rather than detailed individual information. We were unable to exclude uncontrolled or unmeasured risk factors from the original studies, which might have confounded the true association, resulting in potential bias. Third, the cut-off values for the RDW varied across the included studies due to differences in the study populations and experimental methods. Although the patients were divided into RDW-high and RDW-low populations, the stratification might change depending on the cut-off values. Therefore, a standard and uniform cut-off value is needed to accurately define high versus low RDW. Fourth, all of the included articles were in English, most of the included studies included a small number of patients, and potential publication bias cannot be neglected. Thus, more large-scale, well-designed and high-quality prospective studies are required to elucidate the precise mechanisms linking the RDW to survival in EC patients.

In conclusion, an elevated RDW is not associated with the prognosis of EC patients, including both OS/CSS and DFS. This finding is contrary to previous knowledge regarding the prognostic value of the RDW in malignant tumors, particularly in EC. However, when the RDW cut-off value is \( \leq 400 \), the patient number is \( \leq 400 \), and the study type is retrospective, an elevated RDW is indeed significantly associated with worse OS/CSS in EC patients.

**ARTICLE HIGHLIGHTS**

**Research background**

Esophageal cancer (EC) was the eighth most common cancer globally, with about half of all cases occurring in China. Prominent symptoms usually do not appear until the cancer has infiltrated over 60% of the circumference of the esophageal tube, by which time the tumor is already in an advanced stage and the prognosis generally tends to be fairly poor. Therefore, finding a simple and effective prognostic indicator is particularly urgent for individualized treatment of EC patients. Recently, red blood cell distribution width (RDW), as an important complete blood count parameter which has a close correlation with cancer-related inflammation, has been investigated as an important prognostic factor for EC patients in more and more studies, but the conclusions of these studies have not been consistent. Therefore, we conducted this meta-analysis to explore and verify the real role of RDW in the prognosis of patients with EC.

**Research motivation**

We systematically reviewed the existing studies regarding the role of RDW in the prognosis of EC patients and performed a meta-analysis with the extracted data to clarify the real impact of RDW on the outcomes of the EC patients. Identifying the real role of RDW in the prognosis of patients with EC and the defects existing in the previous and current studies can guide the future researchers to conduct more well-designed related studies on this topic and the upstream or downstream research related to RDW.

**Research objectives**

The main objectives of this article were to perform a meta-analysis of the data provided in these studies with inconsistent conclusions about the prognostic effect of RDW on EC patients, and to verify the real impact of RDW on the prognosis of EC patients by increasing the sample size. In the end, we could determine whether we need to conduct further studies on this topic according to the conclusion of this systematic review and meta-analysis.

**Research methods**

First, we searched four related electronic databases (PubMed, EMBASE, Web of Science and Cochrane Library) using the identified MESH terms, and finally identified six studies which met the standards based on the inclusion and exclusion criteria of the selected literature, then we assessed the quality of the included studies according to Newcastle-Ottawa quality scale. Second, we used the electronic EXCEL table to collect the data from the included studies that we needed and utilized statistical software (STATA version 12.0) to conduct statistical analysis of the related data. Third, we performed the sensitivity analysis, subgroup analysis, Begg’s funnel plot and Egger’s linear regression test to explore the potential source of heterogeneity among studies, to find the influencing factors that affect the role of RDW in the prognosis of EC patients and point out the directions for further related research in the future. Different from the traditional review, we used meta-analysis methods to synthesize data and perform statistical analysis relevant to the literature and quantify the effect of RDW on the prognosis of EC patients. Moreover, in addition to sensitivity analysis and subgroup analyses to find sources of heterogeneity, we also used the Begg’s funnel plot and Egger’s linear regression test to query publication bias rather than just using the traditional funnel plot for qualitative analysis. These were the characteristics and indicate the novelty of the research methods used in our study.

**Research results**

This systematic review and meta-analysis indicated that elevated RDW was not an independent risk factor for the worse outcome of EC patients overall, whether it’s for overall survival/cancer-specific survival [hazard ratio (HR) \( = 1.27, 95\% \text{ CI}: 0.97-1.67, P = 0.000 \)] or disease-free survival (HR = 1.42, 95\% CI: 0.86-1.86, P = 0.000). The prognostic value of RDW in patients with EC is only reflected in the retrospective study (HR = 1.42, 95\% CI: 1.16-1.69, P = 0.000) of small samples (sample size \( \leq 400 \), HR = 1.45, 95\% CI = 1.13-1.76, P = 0.000) currently, and there is a need to choose the appropriate RDW cutoff value (RDW > 13\%, HR = 1.45, 95\% CI: 1.13-1.76, P = 0.000) as a prerequisite. Therefore, the actual effect of RDW on the prognosis...
of EC patients needs further prospective multicenter large-sample studies to be validated in the future.

Research conclusions
Different from the traditional viewpoints, our systematic and meta-analysis demonstrated that RDW had no correlation with the prognosis of EC patients, no matter favorable or unfavorable. Therefore, such traditional ideas and assumptions that cancer-related inflammation leads to an increased RDW in the blood, and elevated RDW in turn suggests the occurrence of cancer, were challenged and questioned by the results of our meta-analysis. At the same time, it also suggests that we could perform the meta-analysis to statistically analyze the inconsistent result data of different types of small-sample studies and achieve a conclusion that is completely different from our previous understanding. This leads to the emergence of new theories and assumptions and provides direction for our future research design and potential mechanism research. Our systematic reviews and meta-analysis suggest that we should be more cautious and rational to see the impact of increased RDW on the prognosis of EC patients in our future clinical work.

Research perspectives
From our study, we could learn that we can’t blindly believe in traditional ideas that already exist. When the opinions of previous studies are inconsistent and chaotic, we should use statistical methods to perform statistical clustering analysis on various data, and draw a scientific conclusion to guide our clinical work and indicate the future research direction. Moreover, through the systematic analysis of the previous research, we should carry out more multicenter, large-sample prospective studies in the future to overcome the defects of the current research in the study design to further verify the role of RDW in the prognosis of EC patients. In addition, we also need to conduct further basic experiments based on the results of such above-mentioned optimized research to uncover its underlying mechanisms.

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