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# Clinical significance of signet ring cells in surgical esophageal and esophagogastric junction adenocarcinoma: A systematic review and meta-analysis

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## Abstract

### BACKGROUND

The clinical significance of signet ring cells (SRCs) in surgical esophageal and esophagogastric junction adenocarcinoma (EEGJA) remains unclear now.

### AIM

To explore the association between the presence of SRCs and the clinicopathological and prognostic characteristics in surgical EEGJA patients by combining and analyzing relevant studies.

### METHODS

The PubMed, Web of Science, and EMBASE electronic databases were searched for the relevant literature up to March 28, 2021. The relative risk (RR) with 95% confidence interval (CI) was calculated to assess the relationship between SRCs and clinicopathological parameters of surgical EEGJA patients, and the hazard ratio (HR) with 95%CI was calculated to explore the impact of SRC on the prognosis. All statistical analyses were conducted with STATA 12.0 software.

### RESULTS

A total of ten articles were included, involving 30322 EEGJA patients. The pooled results indicated that the presence of SRCs was significantly associated with

and experimental

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tumor location (RR: 0.76, 95%CI: 0.61-0.96,  $P = 0.022$ ;  $I^2 = 49.4\%$ ,  $P = 0.160$ ) and tumor-node-metastasis stage (RR: 1.30, 95%CI: 1.02-1.65,  $P = 0.031$ ;  $I^2 = 73.1\%$ ,  $P = 0.002$ ). Meanwhile, the presence of SRCs in surgical EEGJA patients predicted a poor overall survival (HR: 1.36, 95%CI: 1.12-1.65,  $P = 0.002$ ;  $I^2 = 85.7\%$ ,  $P < 0.001$ ) and disease-specific survival (HR: 1.86, 95%CI: 1.55-2.25,  $P < 0.001$ ;  $I^2 = 63.1\%$ ,  $P = 0.043$ ).

#### CONCLUSION

The presence of SRCs is related with advanced tumor stage and poor prognosis and could serve as a reliable and effective parameter for the prediction of postoperative survival and formulation of therapy strategy in EEGJA patients. However, more high-quality studies are still needed to verify the above findings.

**Key Words:** Signet ring cells; Esophageal and esophagogastric junction adenocarcinoma; Clinicopathological characteristics; Prognosis; Systematic review; Meta-analysis

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**Core Tip:** Our manuscript indicated that the presence of signet ring cells (SRCs) was significantly associated with the tumor location ( $P = 0.022$ ) and tumor-node-metastasis stage ( $P = 0.031$ ). Meanwhile, the presence of SRCs in surgical esophageal and esophagogastric junction adenocarcinoma (EEGJA) patients predicted a poor overall survival ( $P = 0.002$ ) and disease-specific survival ( $P < 0.001$ ). The presence of SRC was related with advanced tumor stage and poor prognosis and could serve as a reliable and effective parameter for the prediction of postoperative survival and formulation of therapy strategy in EEGJA patients. However, more high-quality studies are still needed to verify the above findings.

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#### INTRODUCTION

Esophageal carcinoma is the eighth most common tumor worldwide with an estimated 456000 new cases in 2012 and an increasing incidence has been observed in recent decades (7.9/100000 in males and 1.4/100000 in females)[1-3]. Although great progress has been made in the surgical and adjuvant therapy of esophageal cancer in recent years, the survival of esophageal cancer patients remains poor due to the advanced stage at the time of diagnosis[4]. In Western countries, adenocarcinoma is the most common pathological subtype of esophageal cancer, although squamous cell carcinoma accounts for the highest proportion in Asian countries[5]. Signet ring cell (SRC) carcinoma is a rare mucinous subtype of adenocarcinoma that has been reported to be related with aggressive biology in gastrointestinal cancer[6,7].

Actually, the clinical significance of SRCs in gastric and colorectal carcinomas has been widely verified. Nie *et al*[8] included 19 studies involving 35947 cases and demonstrated that gastric carcinoma patients with SRCs tended to be younger (weighted mean difference = -3.88,  $P = 0.001$ ) and predominantly female [odds ratio (OR): 1.60,  $P < 0.001$ ]. Besides, early-stage gastric cancer patients with SRCs were related with a better overall survival (OS) [hazard ratio (HR): 0.57,  $P = 0.002$ ], but advanced stage patients with SRCs were related with a worse prognosis (HR: 1.17,  $P < 0.001$ ); however, in the total population, no significant difference in OS between non-SRC and SRC patients was observed (HR: 1.02,  $P = 0.830$ ). Besides, after analyzing 2454 colorectal cancer patients, Tan *et al*[9] demonstrated that the presence of SRCs was an independent prognostic risk factor in colorectal cancer patients (SRC ratio < 50%: 2.182,  $P = 0.005$ ; SRC ratio > 50%: 1.699,  $P = 0.016$ ). Meanwhile, it has been reported that patients with an SRC ratio > 50% are more likely to experience an advanced stage



of disease and worse survival than patients with an SRC ratio < 50% [10]. However, these meta-analyses focused on the gastric and colorectal carcinomas which are more likely to be combined with SRCs and their results were inconsistent with the studies about esophageal and esophagogastric junction adenocarcinoma (EEGJA). Meanwhile, for EEGJA, the clinical significance of SRCs remains unclear because of the inconsistent reports [11-20].

Therefore, we conducted this systematic review and meta-analysis to explore the clinical significance of the presence of SRCs in EEGJA patients and the impact of SRCs on the clinicopathological and prognostic characteristics, which might contribute to the prediction of prognosis and formulation of treatment strategy for EEGJA patients.

## MATERIALS AND METHODS

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [21].

### **Inclusion criteria**

The inclusion criteria were as follows: (1) Patients were pathologically diagnosed with EEGJA; (2) All patients received surgical therapy; (3) Patients were divided into two groups according to the presence or absence of SRCs, and prospective randomized controlled trials (RCTs) or retrospective cohort studies were both available; (4) Clinicopathological parameters or prognosis between the two groups were compared and relevant data were provided; (5) Although the HRs with corresponding 95% confidence intervals (CIs) were not directly reported in articles, the Kaplan-Meier survival curves were provided to calculate them; and (6) The articles were published in English.

### **Literature retrieval**

The PubMed, Web of Science, and EMBASE electronic databases were searched from the establishment date to March 28, 2021. The following terms were used: "esophageal", "esophagus", "esophagogastric", "gastroesophageal", "adenocarcinoma", and "significance of signet ring cell". A combination of subject terms and free words was applied. Besides, the references cited in included studies were also reviewed for availability (Figure 1).

### **Exclusion criteria**

The exclusion criteria were as follows: (1) Duplicated studies or studies with severely overlapped data; (2) Case reports, reviews, meeting abstracts, and animal trials; and (3) Adenocarcinomas located in other sites like the stomach were also enrolled without subgroup analysis for EEGJA patients.

The titles and abstracts were screened first and irrelevant publications were excluded. Then full texts of potentially related studies were further reviewed for availability.

The literature retrieval and selection were conducted by two investigators (Wang YF and Xu SY).

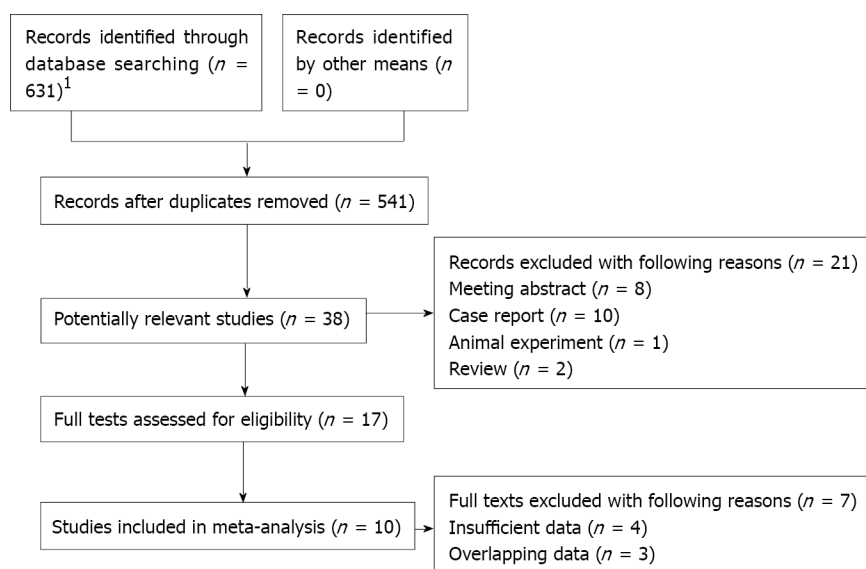
### **Data extraction**

The data extraction was conducted by two authors (Wang YF and Xu SY) through the Microsoft Excel sheet independently. The following information was extracted from each included studies: The author, publication year, country where the study was conducted, sample size, tumor location (esophageal *vs* esophagogastric), tumor-node-metastasis (TNM), SRC ratio, sex, smoking, family history, lymph node metastasis status, relative risk (RR), and HR with 95% CI or corresponding data for their calculation.

The association of SRCs with sex, smoking, family history, tumor location, lymph node metastasis, and TNM stage were measured in this study. For the prognostic role of SRCs in EEGJA, the primary outcome was the OS and the second outcomes included the disease-free survival (DFS) and disease-specific survival (DSS).

### **Quality assessment**

The Newcastle-Ottawa Scale (NOS) was applied to evaluate the quality of included studies [22]. This scale includes object selection, comparability, and exposure assessment and objectively evaluates the risk of bias with the maximum score of 9, and



**Figure 1** Flow diagram of this meta-analysis. <sup>1</sup>PubMed ( $n = 175$ ), EMBASE ( $n = 169$ ), and Web of Science ( $n = 287$ ).

studies with a score  $\geq 6$  were considered to have high quality. The quality assessment was performed by two authors (Wang YF and Xu SY) independently. Any disagreement was solved by team discussion.

### Statistical analysis

All statistical analyses were conducted with STATA 12.0 software. The RR and HR with corresponding 95%CI were calculated to assess the association between the presence of SRCs and clinicopathological characteristics and prognosis of EEGJA patients, respectively. If the HR with 95%CI was not reported in articles directly, they would be calculated from Kaplan-Meier curves[23]. The heterogeneity among the included studies was evaluated by  $I^2$  statistics and  $Q$  test. When significant heterogeneity was observed [ $I^2 > 50\%$  and (or)  $P < 0.1$ ], the random effects model was applied; otherwise, the fix effects model was used. The sensitivity analysis and meta-regression analysis were performed to detect the source of heterogeneity and evaluate the stability of pooled results. Besides, the Begg's funnel plot and Egger's test were conducted to detect publication bias[24,25]. Significant publication bias was defined as  $P < 0.05$ .

## RESULTS

### Literature retravel

Initially, 631 records were searched and then 90 duplicated records were excluded. After reviewing the titles and abstracts, 503 records without any relativity were excluded. Then, 17 full texts were assessed for eligibility after eliminating 21 publications according to our exclusion criteria. Finally, ten retrospective articles were included in this systematic review and meta-analysis[11-20].

### Basic characteristics

Among the ten included articles, Chirieac *et al*[11] and van Hootegem *et al*[17] enrolled two different subgroups of patients, which were regarded as two studies separately. Thus, a total of 12 retrospective cohort studies from ten publications were included, involving 30322 EEGJA patients. Most cases were from America and the sample size ranged from 163 to 14224. Three studies only enrolled esophageal adenocarcinoma patients. All studies were high-quality studies with an NOS score of 6 or higher. Detailed information is presented in Table 1.

### Association between presence of SRCs and clinicopathological characteristics of EEGJA patients

The pooled results indicated that SRCs were more likely to occur in esophageal adenocarcinoma rather than esophagogastric junction adenocarcinoma (RR: 0.76,

**Table 1 Basic characteristics of included studies**

| Author                          | Year | Country                        | Sample size | Location         | TNM   | SRC ratio              | Endpoint     | NOS |
|---------------------------------|------|--------------------------------|-------------|------------------|-------|------------------------|--------------|-----|
| Chirieac <i>et al</i> [11]      | 2005 | United States (ACC: 1985-2003) | 193         | Esophageal + EGJ | I-IV  | > 0%                   | OS           | 7   |
| Chirieac <i>et al</i> [11]      | 2005 | United States (ACC: 1985-2003) | 219         | Esophageal + EGJ | I-IV  | > 0%                   | OS           | 7   |
| Yoon <i>et al</i> [12]          | 2010 | United States (MCTR)           | 796         | Esophageal + EGJ | NR    | > 0%                   | OS, DSS, DFS | 6   |
| Yendamuri <i>et al</i> [13]     | 2013 | United States (SEER)           | 11825       | Esophageal       | I-IV  | > 0%                   | OS,          | 7   |
| Nafteux <i>et al</i> [14]       | 2014 | Belgium                        | 779         | Esophageal + EGJ | I-IV  | 1%-50%, > 50%          | DSS          | 7   |
| Patel <i>et al</i> [15]         | 2014 | United States (ACC: 2000-2012) | 723         | Esophageal + EGJ | II-IV | > 0%                   | OS, DFS      | 7   |
| Chen <i>et al</i> [16]          | 2017 | China                          | 671         | Esophageal       | I-III | 1%-50%, > 50%          | OS           | 8   |
| Van Hooitegem <i>et al</i> [17] | 2019 | Australia                      | 298         | Esophageal + EGJ | NR    | > 0%                   | OS, DFS      | 7   |
| Van Hooitegem <i>et al</i> [17] | 2019 | Australia                      | 391         | Esophageal + EGJ | NR    | > 0%                   | OS, DFS      | 7   |
| Corsini <i>et al</i> [18]       | 2020 | United States (ACC: 2006-2018) | 819         | Esophageal       | NR    | 1%-10%, 11%-49%, ≥ 50% | OS           | 8   |
| Sathe <i>et al</i> [19]         | 2020 | United States (NCD: 2004-2015) | 14224       | Esophageal + EGJ | I-III | NR                     | OS           | 7   |
| Solomon <i>et al</i> [20]       | 2021 | Israel                         | 163         | Esophageal + EGJ | I-III | > 0%                   | OS           | 6   |

SRC: Signet ring cell; NOS: Newcastle-Ottawa Scale; EGJ: Esophagogastric junction; Surg: Surgery; nCT: Neoadjuvant chemotherapy; OS: Overall survival; DSS: Disease-specific survival; DFS: Disease-free survival; SEER: Surveillance, Epidemiology, and End Results; R: Recurrence; ACC: Anderson Cancer Center; MCTR: Mayo Clinic Tumor Registry; RTCT: Response to chemotherapy; NCD: National Cancer Database; DS: Downstaging; TNM: Tumor-node-metastasis; NR: Not reported.

95%CI: 0.61-0.96,  $P = 0.022$ ;  $I^2 = 49.4\%$ ,  $P = 0.160$ ) and TNM stage III/IV EEGJA patients (RR: 1.30, 95%CI: 1.02-1.65,  $P = 0.031$ ;  $I^2 = 73.1\%$ ,  $P = 0.002$ ). However, no significant relation was observed between SRCs and the sex (RR: 0.99, 95%CI: 0.87-1.13,  $P = 0.917$ ;  $I^2 = 39.4\%$ ,  $P = 0.105$ ), smoking (RR: 0.86, 95%CI: 0.55-1.35,  $P = 0.507$ ;  $I^2 = 86.9\%$ ,  $P = 0.006$ ), family history (RR: 1.157, 95%CI: 0.762-1.757), and lymph node metastasis (RR: 1.05, 95%CI: 0.92-1.20,  $P = 0.488$ ;  $I^2 = 7.2\%$ ,  $P = 0.340$ ) (Table 2).

### Association between presence of SRCs and prognosis of EEGJA patients

A total of 11 studies explored the relationship of SRCs with the OS of EEGJA patients (16-18, and 20-25), and the pooled results demonstrated that the presence of SRCs predicted a much poor OS (HR: 1.36, 95%CI: 1.12-1.65,  $P = 0.002$ ;  $I^2 = 85.7\%$ ,  $P < 0.001$ ) (Figure 2). Meanwhile, four studies assessed the impact of SRCs on the DFS of EEGJA patients[12,15,17] and the pooled results did not predict a significant association between SRCs and DFS (HR: 1.21, 95%CI: 0.94-1.57,  $P = 0.145$ ;  $I^2 = 63.1\%$ ,  $P = 0.043$ ) (Figure 3). Besides, after combining two studies[17,19], a significant relationship was observed between the presence of SRCs and poor DSS (HR: 1.86, 95%CI: 1.55-2.25,  $P < 0.001$ ;  $I^2 = 0.0\%$ ,  $P = 0.323$ ) (Table 3).

### Sensitivity analysis and publication bias

According to Figure 4, the sensitivity analysis revealed that the pooled results were stable and reliable.

Besides, the Begg's funnel plot was symmetrical (Figure 5) and the  $P$  value of Egger's test was 0.572, which indicated nonsignificant publication bias.

### Meta-regression analysis

Due to the significant heterogeneity of the OS, meta-regression analysis was conducted based on some variables including the publication year, country, sample size, location, SRC ratio, TNM stage, and NOS score. Unfortunately, none of these parameters were

**Table 2 Association between signet-ring cells and clinicopathological characteristics**

| Study                                | Sex (male)                   | Smoking                      | Family history      | Tumor location (esophageal)  | Lymph node metastasis        | TNM stage (III/IV)           |
|--------------------------------------|------------------------------|------------------------------|---------------------|------------------------------|------------------------------|------------------------------|
| Chirieac <i>et al</i> [11] 2005      | 0.722 (0.254-2.053)          | -                            | -                   | -                            | -                            | 0.895 (0.522-1.532)          |
| Chirieac <i>et al</i> [11] 2005      | 0.730 (0.341-1.564)          | -                            | -                   | -                            | -                            | 1.855 (0.997-3.454)          |
| Yoon <i>et al</i> [12] 2010          | -                            | -                            | -                   | -                            | -                            | -                            |
| Yendamuri <i>et al</i> [13] 2013     | 0.975 (0.783-1.214)          | -                            | -                   | -                            | -                            | 1.267 (1.060-1.513)          |
| Nafteux <i>et al</i> [14] 2014       | 0.882 (0.558-1.395)          | -                            | -                   | 0.636 (0.451-0.896)          | -                            | 1.048 (0.702-1.563)          |
| Patel <i>et al</i> [15] 2014         | 0.518 (0.309-0.867)          | -                            | -                   | -                            | 1.357 (0.907-2.028)          | -                            |
| Chen <i>et al</i> [16] 2017          | 1.461 (0.945-2.258)          | 0.667 (0.495-0.899)          | 1.157 (0.762-1.757) | -                            | -                            | 1.095 (0.811-1.480)          |
| Van Hooitegem <i>et al</i> [17] 2019 | 1.138 (0.662-1.956)          | -                            | -                   | 0.888 (0.649-1.216)          | 0.929 (0.677-1.275)          | -                            |
| Corsini <i>et al</i> [18] 2020       | 0.771 (0.460-1.292)          | 1.061 (0.923-1.219)          | -                   | -                            | 1.038 (0.888-1.215)          | -                            |
| Sathe <i>et al</i> [19] 2020         | 1.164 (0.912-1.485)          | -                            | -                   | -                            | -                            | 1.832 (1.542-2.177)          |
| Solomon <i>et al</i> [20] 2021       | -                            | -                            | -                   | -                            | -                            | -                            |
| Overall                              | 0.99, 0.87-1.13, $P = 0.917$ | 0.86, 0.55-1.35, $P = 0.507$ | 1.157 (0.762-1.757) | 0.76, 0.61-0.96, $P = 0.022$ | 1.05, 0.92-1.20, $P = 0.488$ | 1.30, 1.02-1.65, $P = 0.031$ |

TNM: Tumor-node-metastasis.

**Table 3 Results of meta-analysis**

|                           | No. of studies  | HR   | 95%CI     | $P$ value | $I^2$ | $P$ value |
|---------------------------|-----------------|------|-----------|-----------|-------|-----------|
| Overall survival          | 11[11-13,15-20] | 1.36 | 1.12-1.65 | 0.002     | 85.7  | < 0.001   |
| Disease-free survival     | 4[12,15,17]     | 1.21 | 0.94-1.57 | 0.145     | 63.1  | 0.043     |
| Disease-specific survival | 2[12,14]        | 1.86 | 1.55-2.25 | < 0.001   | 0.0   | 0.323     |

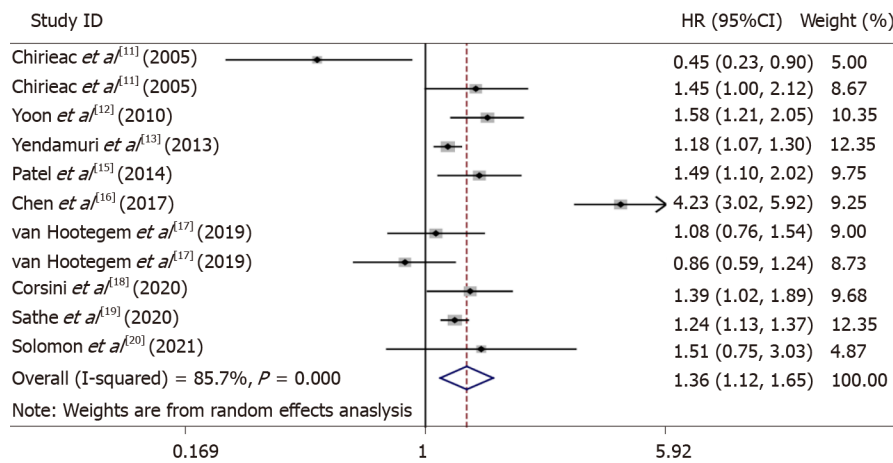
HR: Hazard ratio; CI: Confidence interval.

the causes of heterogeneity.

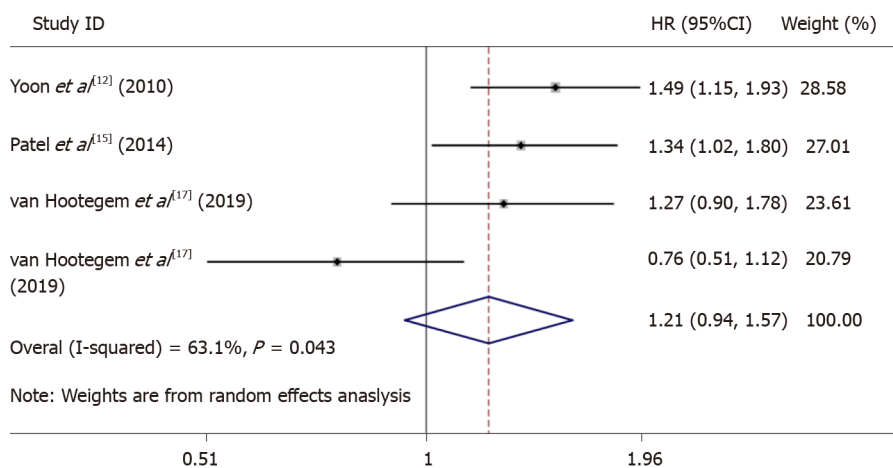
## DISCUSSION

The current systematic review and meta-analysis demonstrated that the presence of SRCs was significantly associated with tumor location (RR: 0.76,  $P = 0.022$ ) and TNM stage (RR: 1.30,  $P = 0.031$ ). Meanwhile, the presence of SRCs in surgical EEGJA patients predicted a poor OS (HR: 1.36,  $P = 0.002$ ) and DSS (HR: 1.86,  $P < 0.001$ ). The presence of SRCs might be an independent prognostic factor in EEGJA patients and contribute to the evaluation of prognosis and decision making.

Interestingly, Chirieac *et al*[11] demonstrated that the presence of SRCs predicted a much poor prognosis in patients who received surgery alone ( $P = 0.05$ ), but for patients who received neoadjuvant chemotherapy and surgery, the presence of SRCs predicted a better prognosis ( $P = 0.02$ ). This phenomenon indicated that SRCs might play an essential role in the response to chemotherapy. In the study by Corsini *et al* [18], EEGJA patients with usual type had a much higher pathologic complete response than patients with SRCs (25% *vs* 10%,  $P = 0.006$ ). Meanwhile, Solomon *et al*[20] also revealed that patients with SRCs were less sensitive to neoadjuvant chemoradiotherapy (OR: 6.118, 95%CI: 1.299-28.821,  $P = 0.022$ ) and less likely to experience downstaging after neoadjuvant chemotherapy (OR: 0.306, 95%CI: 0.099-0.946,  $P = 0.040$ ). The presence of SRCs may predicted a poor response to chemotherapy, which is opposite to the results reported by Chirieac *et al*[11]. Thus, more relevant studies are



**Figure 2** Forest plot of association between presence of signet ring cells and overall survival<sup>[11-13,15-20]</sup>. HR: Hazard ratio; CI: Confidence interval.



**Figure 3** Forest plot of association between presence of signet ring cells and disease-free survival<sup>[12,15,17]</sup>. HR: Hazard ratio; CI: Confidence interval.

still needed to identify the clinical role of SRC in the chemotherapy and radiotherapy of EEGJA patients.

Although the pooled results indicated that there was no significant association between the presence of SRCs and DFS of EEGJA patients (HR: 1.21, 95%CI: 0.94-1.57, *P* = 0.145), Yoon *et al*<sup>[12]</sup> and Patel *et al*<sup>[15]</sup> both reported that patients with SRCs were more likely to experience a worse DFS (HR: 1.49, 95%CI: 1.15-1.93, *P* = 0.001; HR: 1.34, 95%CI: 1.02-1.80, *P* = 0.048). Therefore, we believed that SRCs might also predict a poor DFS in EEGJA patients, which needs more studies to further verify.

Besides, Naftoux *et al*<sup>[14]</sup> demonstrated that the presence of SRCs was significantly associated with a higher recurrence rate (56% *vs* 42% for usual type adenocarcinoma, *P* = 0.003). In their multivariate analysis, SRC ratio > 50% was an independent risk factor for recurrence (OR: 2.070, 95%CI: 1.159-3.696, *P* = 0.014), which also indicated that the presence of SRCs was related with a poor prognosis in EEGJA patients.

Actually, there are still several valuable fields about the clinical significance of SRCs in EEGJA patients that are worth further investigation. First, as mentioned above, the role that SRCs play in the chemotherapy and radiotherapy is unclear, and more studies comparing the clinical outcomes between EEGJA patients with and without neoadjuvant chemoradiotherapy or postoperative chemoradiotherapy are needed. Second, it is necessary to identify whether SRCs could serve as a reliable predictor for the selection of therapeutic strategies. Third, to explore the role of the proportion change of SRC during chemotherapy in predicting the prognosis of EEGJA patients might be significative. Fourth, according to previous reports, the proportion of SRCs may also be related with the prognosis of EEGJA patients and patients with different ratios of SRCs might have different survival rates.



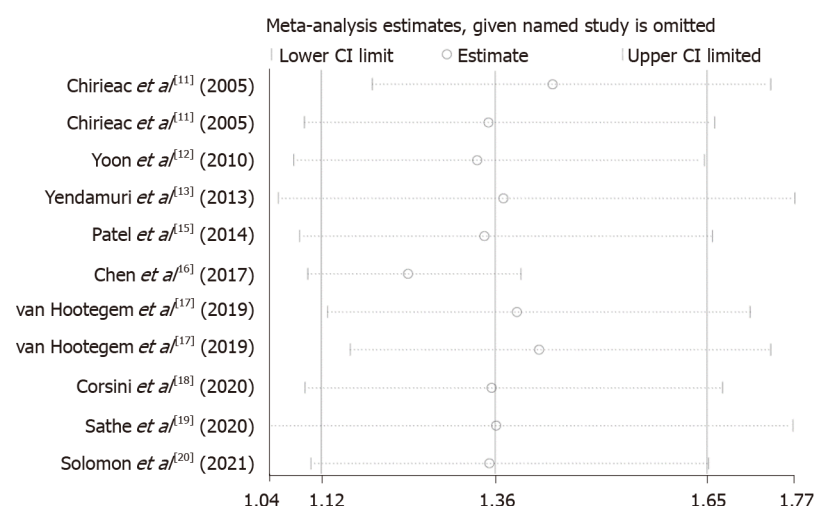


Figure 4 Sensitivity analysis of association between presence of signet ring cells and overall survival[11-13,15-20]. CI: Confidence interval.

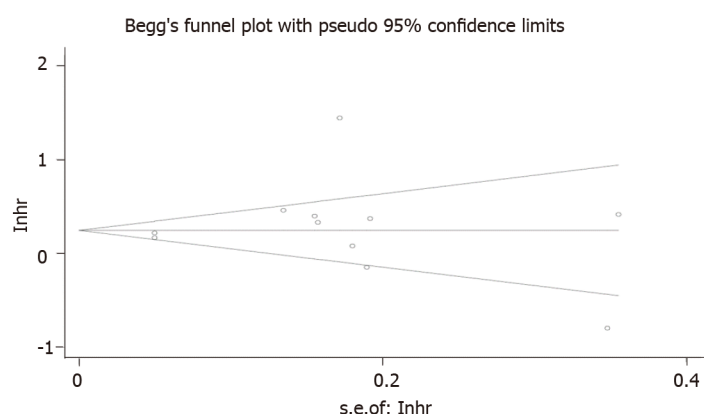


Figure 5 Begg's funnel plot of association between presence of signet ring cells and overall survival.

There were some limitations in this study. First, all included studies were retrospective, which may cause some bias. Second, the association of SRCs with other parameters such as alcohol drinking, differentiation status, *Helicobacter pylori* infection, and age was not explored due to the lack of relevant data. Third, we failed to conduct subgroup analysis based on the clinicopathological parameters such as age, sex, and TNM stage because the detailed data were not available even if we contacted the authors of included studies.

## CONCLUSION

The presence of SRCs is related with advanced tumor stage and poor prognosis and could serve as a reliable and effective parameter for the prediction of postoperative survival and formulation of therapy strategy in EEGJA patients. However, more prospective high-quality studies are still needed to verify our findings.

## ARTICLE HIGHLIGHTS

### Research background

The clinical role of signet ring cells (SRCs) in surgical esophageal and esophagogastric junction adenocarcinoma (EEGJA) remains unclear now.

**Research motivation**

To explore the clinical role of the presence of SRCs in surgical EEGJA patients.

**Research objectives**

To explore the association between the presence of SRCs and the clinicopathological and prognostic characteristics in surgical EEGJA patients.

**Research methods**

Several electronic databases were searched to identify the relevant articles. The relative risks and hazard ratios with their corresponding 95% confidence intervals were estimated, respectively.

**Research results**

The presence of SRCs was significantly associated with the tumor location ( $P = 0.022$ ) and tumor-node-metastasis stage ( $P = 0.031$ ). Meanwhile, the presence of SRCs in surgical EEGJA patients predicted a poor overall survival ( $P = 0.002$ ) and disease-specific survival ( $P < 0.001$ ).

**Research conclusions**

SRC was significantly related with advanced tumor stage and poor prognosis in EEGJA patients.

**Research perspectives**

The presence of SRCs could serve as a reliable and effective parameter for the prediction of postoperative survival and formulation of therapy strategy in EEGJA patients.

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