

Research Paper

Clinicopathological Characteristics and Prognostic Value of Signet Ring Cells in Gastric Carcinoma: A Meta-Analysis

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Abstract

Background and Objectives: Previous studies of the prognostic value of the signet ring cell (SRC) type have yielded inconsistent results. Therefore, the aim of the present meta-analysis is to explore the clinicopathological characteristics and prognostic value of SRCs.

Methods: Relevant articles that compared SRC and non-SRC type in PubMed and Web of Science were comprehensively searched. Then, a meta-analysis was performed.

Results: A total of 19 studies including 35947 cases were analyzed. Compared with non-SRC patients, SRC patients tended to be younger (WMD: -3.88, P=0.001) and predominantly female (OR: 1.60, P<0.001). Additionally, SRC patients exhibited less upper third tumor location (OR: 0.62, P<0.001) and less frequent hematogenous metastasis (OR: 0.41, P<0.001). There was no difference in overall survival (OS) between SRC and non-SRC patients in the total population (HR: 1.02, P=0.830). Early gastric cancer with SRCs was associated with better OS (HR: 0.57, P=0.002), while advanced gastric cancer with non-SRCs was associated with a worse prognosis (HR: 1.17, P<0.001).

Conclusions: This meta-analysis revealed that SRC tends to affect young females and tends to be located in the middle and lower third of the stomach. Early SRCs are associated with better prognoses, while advanced SRCs are associated with worse prognoses.

Key words: signet ring cell; gastric cancer; prognosis; survival.

Introduction

Gastric cancer is the fourth most common malignancy and the third leading cause of cancer-related death worldwide, with an estimated 1.0 million new cases of gastric cancer and 723100 deaths due to gastric cancer in 2012 [1]. The burden caused by gastric cancer is growing worldwide,

particularly in developing countries [2].

The incidence of gastric cancer has decreased over the last 50 years. Meanwhile, differential trends have also occurred, such as an increase in the diffuse type, particularly signet ring cell (SRC). Henson et al. reported that SRC has increased on average 6.5% per

year from 1973 to 2000 in the United States [3]. SRC is a histological subtype of carcinoma with cells containing large amounts of intracytoplasmic mucins [4].

SRC was classified as one of the undifferentiated gastric carcinomas according to the Japanese Gastric Cancer Association [5]. It was reported that patients with SRC tend to be young females, and SRC patients tend to have more lymph node involvement and even peritoneal seeding [6], which indicates a more aggressive stage of SRC. However, the prognostic value of gastric cancer with SRC remains controversial. Several studies have reported that SRC is a poor prognostic factor for gastric cancer [6-11], while others have argued that gastric cancer patients with SRC have better survival [12-15]. Therefore, we aimed to perform a meta-analysis to evaluate the prognostic value of SRC in gastric cancer.

Methods

Search strategy and study selection

On July 1st, 2017, relevant articles were systematically and independently searched by two authors (RC, Nie and SQ, Yuan) in PubMed and Web of Science using the key words "gastric cancer", "gastric carcinoma", "gastric neoplasm", and "signet ring cell", limited to Abstract/Title. We also checked the reference lists of the articles retrieved manually to identify additional relevant articles.

According to the WHO criteria, SRC was defined by an adenocarcinoma with more than 50% of the tumor consisting of isolated or small groups of malignant cells containing intracytoplasmic mucins [4]. Studies were included if they compared SRC and non-SRC directly with more than 50 patients involved in the studies. Studies were excluded if they were basic studies about animals or cells, review articles, meta-analyses, abstracts, case reports, case series, letters, conference proceedings or non-English published articles. Studies were also excluded if they did not conform to or mention the WHO criteria. If multiple reports described the same population, the most recent or complete research was included.

Data extraction

The data from the included studies were extracted independently by two authors (RC, Nie and YQ, Yuan). The adjudicating senior authors (S, Chen and YB, Chen) were responsible for resolving any disagreements. The following information was extracted from each study: first author, year of publication, country, stage of disease, sample size and SRC/non-SRC ratio. We also extracted the following clinicopathological characteristics: age, gender, tumor location, tumor size, lymph node involvement,

lymphovascular invasion, perineural invasion, early disease ratio, gross type, peritoneal dissemination, hematogenous metastasis, and overall survival (OS).

Statistical analysis

The estimated odds ratio (OR) or weighted mean difference (WMD) was used to summarize the association between SRC pathological type and different clinicopathological characteristics. The hazard ratio (HR) was pooled to analyze the OS results as demonstrated by Parmar et al. [16]. All results were reported with 95% confidence intervals (CIs). Heterogeneity was assessed using the χ^2 test and quantified using the I^2 statistic, with the level of significance set at 10%.

The fixed-effects model was used when $P > 0.1$; otherwise, the random-effects model was used [17]. The publication bias was tested by Begg's linear regression [18]. A P value of < 0.05 was considered significant. Analyses were performed using STATA SE 12.0 (StataCorp, College Station, TX, USA).

Results

Study selection

Based on the inclusion and exclusion criteria, a total of 20 studies [6-15, 19-28] including 35947 cases were included in the final analysis (Fig. 1). The characteristics of the included studies are shown in Table 1. These studies were primarily from six countries (Japan, Korea, China, France, America, and Belgium) and were published from 1992 to 2017. The proportion of SRC ranged from 3.4% to 50.0% in the included studies.

Clinicopathological characteristics

The relationships between the clinicopathological characteristics and SRC were investigated. Compared with non-SRC patients, SRC patients tended to be younger (WMD: -3.88, 95% CI: -6.19- -1.56, $P=0.001$; $I^2=92.5\%$, $P<0.001$; Fig. 2A) and predominantly female (OR: 1.60, 95% CI: 1.34-1.91, $P<0.001$; $I^2=84.4\%$, $P<0.001$; Fig. 2B). Additionally, SRC patients exhibited less upper third tumor location (OR: 0.62, 95% CI: 0.47-0.81, $P<0.001$; $I^2=82.0\%$, $P<0.001$; Fig. 2C). There were no differences between SRC and non-SRC patients with regard to tumor size (WMD: -0.26 cm, 95% CI: -0.86- 0.33, $P=0.390$; $I^2=92.2\%$, $P<0.001$; Fig. 2D), early gastric cancer ratio (OR: 1.58, 95% CI: 0.87-2.86, $P=0.130$; $I^2=96.6\%$, $P<0.001$; Fig. 2E), lymph node involvement (OR: 0.83, 95% CI: 0.61-1.14, $P=0.247$; $I^2=93.2\%$, $P<0.001$; Fig. 2F), lymphovascular invasion (OR: 0.96, 95% CI: 0.66-1.40, $P=0.822$; $I^2=84.9\%$, $P<0.001$; Fig. 2G), or peritoneal dissemination (OR: 1.17, 95% CI: 0.97-1.42, $P=0.092$; $I^2=47.3\%$, $P=0.077$; Fig. 2H).

However, patients with SRC exhibited less frequent hematogenous metastasis (OR: 0.41, 95% CI: 0.27-0.64, $P<0.001$; $I^2=17.9%$, $P=0.294$; Fig. 2I).

With regard to early gastric cancer, there was no difference in tumor size (WMD: 0.15 cm, 95% CI: -0.25- 0.55, $P=0.460$; $I^2=77.2%$, $P=0.002$; Fig. 3A). However, patients with SRC had a higher frequency of the depressed gross type (OR: 2.11, 95% CI: 1.11-3.98, $P=0.022$; $I^2=76.7%$, $P=0.002$; Fig. 3B), more mucosal invasion (OR: 1.68, 95% CI: 1.24-2.29, $P=0.001$; $I^2=75.3%$, $P<0.001$; Fig. 3C), and marginally less lymph node metastasis (OR: 0.68, 95% CI: 0.46-1.01, $P=0.054$; $I^2=69.5%$, $P=0.001$; Fig. 3C).

The comparison of the major characteristics of advanced gastric cancer between SRC and non-SRC are shown in Figure 4. Compared with non-SRC, SRC was associated with marginally larger tumor size (WMD: 0.63 cm, 95% CI: -0.01- 1.13, $P=0.059$; $I^2=54.7%$, $P=0.039$; Fig. 4A) and increased Borrmann IV type (OR: 3.29, 95% CI: 2.02-5.34, $P<0.001$; $I^2=88.1%$, $P<0.001$; Fig. 4B). Although there were no differences in T4 invasion (OR: 0.88, 95% CI: 0.61-1.27, $P=0.497$; $I^2=85.6%$, $P<0.001$; Fig. 4C) and lymph node

metastasis (OR: 0.80, 95% CI: 0.58-1.11, $P=0.183$; $I^2=81.4%$, $P<0.001$; Fig. 4D) between SRC and non-SRC, patients with SRC tended to have more peritoneal dissemination (OR: 1.69, 95% CI: 1.41-2.02, $P<0.001$; $I^2=43.5%$, $P=0.115$; Fig. 4E).

Overall survival

In this meta-analysis, a total of 15 studies [6-15, 22, 24-28] were available for the pooled HR of OS. There was significant heterogeneity among the studies for the pooled HR of OS ($I^2=89.8%$, $P<0.001$; Fig. 5A); therefore, the random-effects model was used. The pooled HR was 1.02 (95% CI: 0.87-1.19, $P=0.830$), indicating no difference in OS between the SRC and non-SRC patients. In the subgroup analysis, early gastric cancer with SRC was associated with a better prognosis with a pooled HR of 0.57 (95% CI: 0.40-0.81, $P=0.002$), with significant heterogeneity ($I^2=70.6%$, $P<0.001$; Fig. 5B). However, the pooled HR for advanced gastric cancer with SRC was 1.17 (95% CI: 1.10-1.25, $P<0.001$), with no significant heterogeneity ($I^2=29.5%$, $P=0.214$; Fig. 5C).

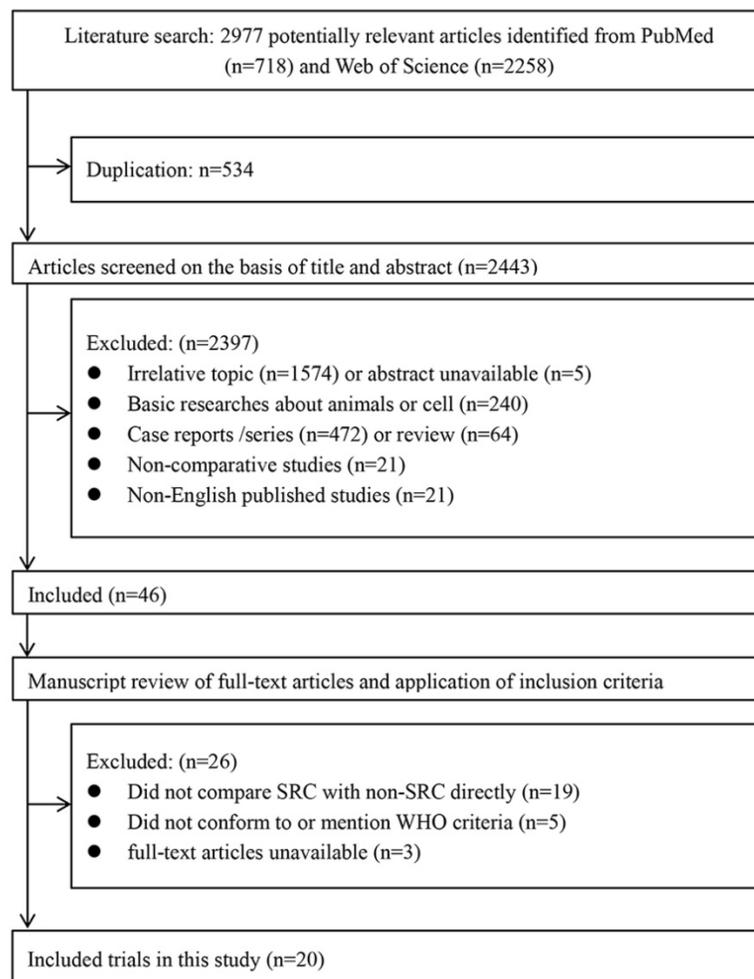


Figure 1. Flow diagram of the included studies.

Table 1. Characteristics of the included studies

Author	Year	Country	Stage	No. of patients	SRC/non-SRC (%)	HR for OS (SRC vs. non-SRC)
Maehara et al.	1992	Japan	all stage	1500	3.4% vs. 96.6%	NA
Otsuji et al.	1998	Japan	all stage	1498	10.3% vs. 89.7%	NA
Hyung et al.	2002	Korea	early stage	933	28.2% vs. 71.8%	0.58
Kim et al.	2004	Korea	all stage	2358	8.7% vs. 91.3%	NA
Kunisaki et al.	2004	Japan	all stage	1113	15.6% vs. 84.4%	0.20 ^a
Li et al.	2007	Korea&China	advanced stage	4759	13.9% vs. 86.1%	1.16
Piessen et al.	2009	France	all stage	215	32.5% vs. 67.5%	1.81 ^b
Lee et al.	2010	Korea	early stage	1326	33.8% vs. 66.2%	NA
Zhang et al.	2010	China	all stage	1439	15.1% vs. 84.9%	1.28
Chiu et al.	2011	China	all stage	2439	20.7% vs. 79.3%	1.01
Jiang et al.	2011	China	all stage	2315	9.1% vs. 90.9%	0.72
Gronnier et al.	2013	France	early stage	421	25% vs. 75%	0.56
Nafteux et al.	2014	Belgium	all stage	920	12.4% vs. 87.6%	1.60
Liu et al.	2015	China	all stage	1464	9.4% vs. 90.6%	1.45
Postlewait et al.	2015	America	all stage	768	40.6% vs. 59.4%	1.19
Wang et al.	2015	China	early stage	334	34.4% vs. 65.6%	0.40
Kong et al.	2016	China	N-stage ^c	480	18.8% vs. 81.2%	1.29
Lu et al.	2016	China	all stage	2199	16.1% vs. 83.9%	1.25
Voron et al.	2016	France	all stage	1799	50.0% vs. 50.0%	1.47
Chon et al.	2017	Korea	all stage	7667	21.5% vs. 78.5%	0.75

SRC, signet ring cell carcinoma; HR, hazard ratio; OS, overall survival; NA, not available;

a, HR was only available for early stage;

b, HR for resected patients;

c, Study including only node-negative gastric cancer.

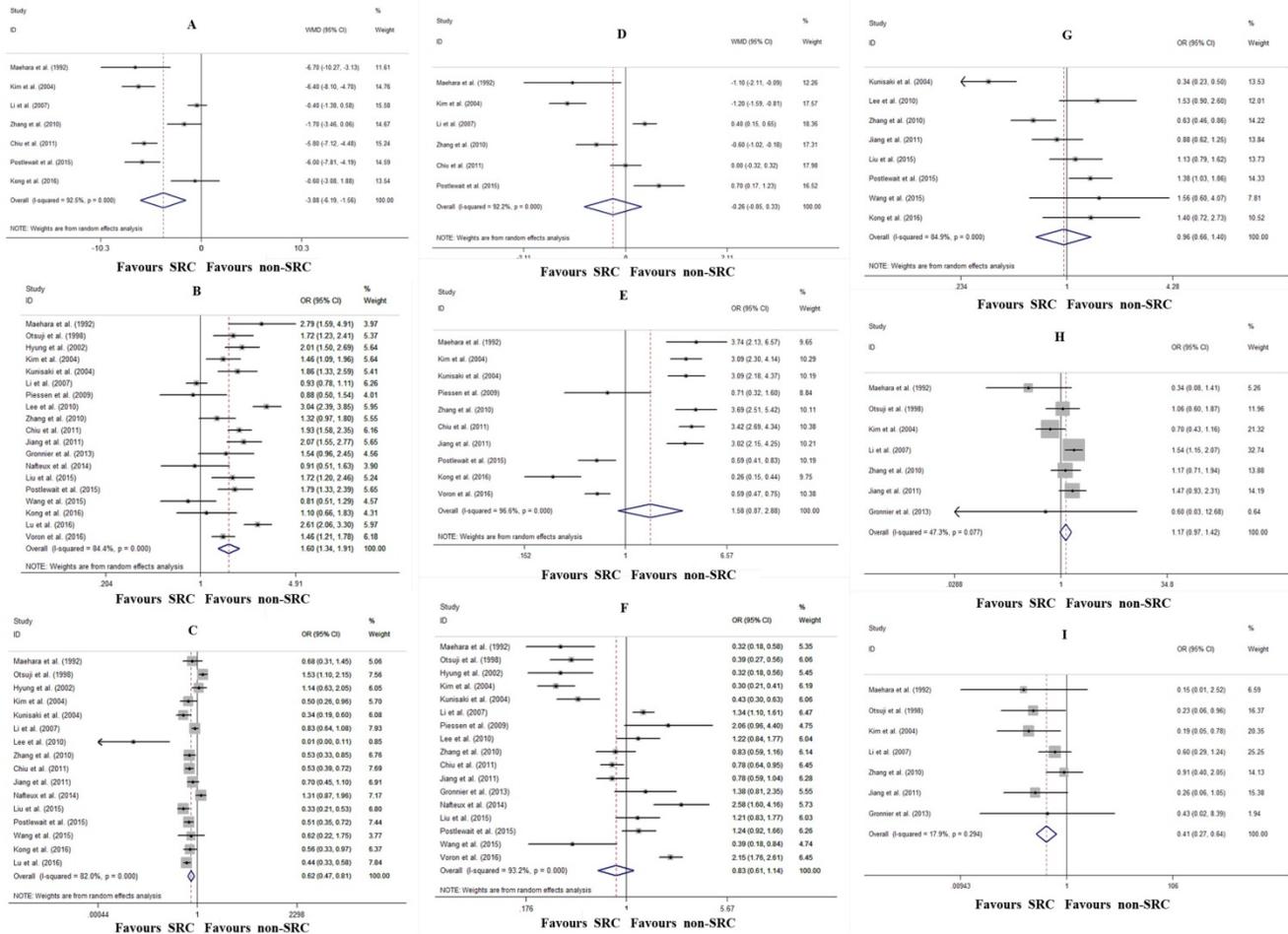


Figure 2. Forrest plot assessing different clinicopathological characteristics following SRC and non-SRC gastric cancer in the total population. A, age; B, female; C, tumor location; D, tumor size; E, early gastric cancer ratio; F, lymph node involvement; G, lymphovascular invasion; H, peritoneal dissemination; and I, hematogenous metastasis

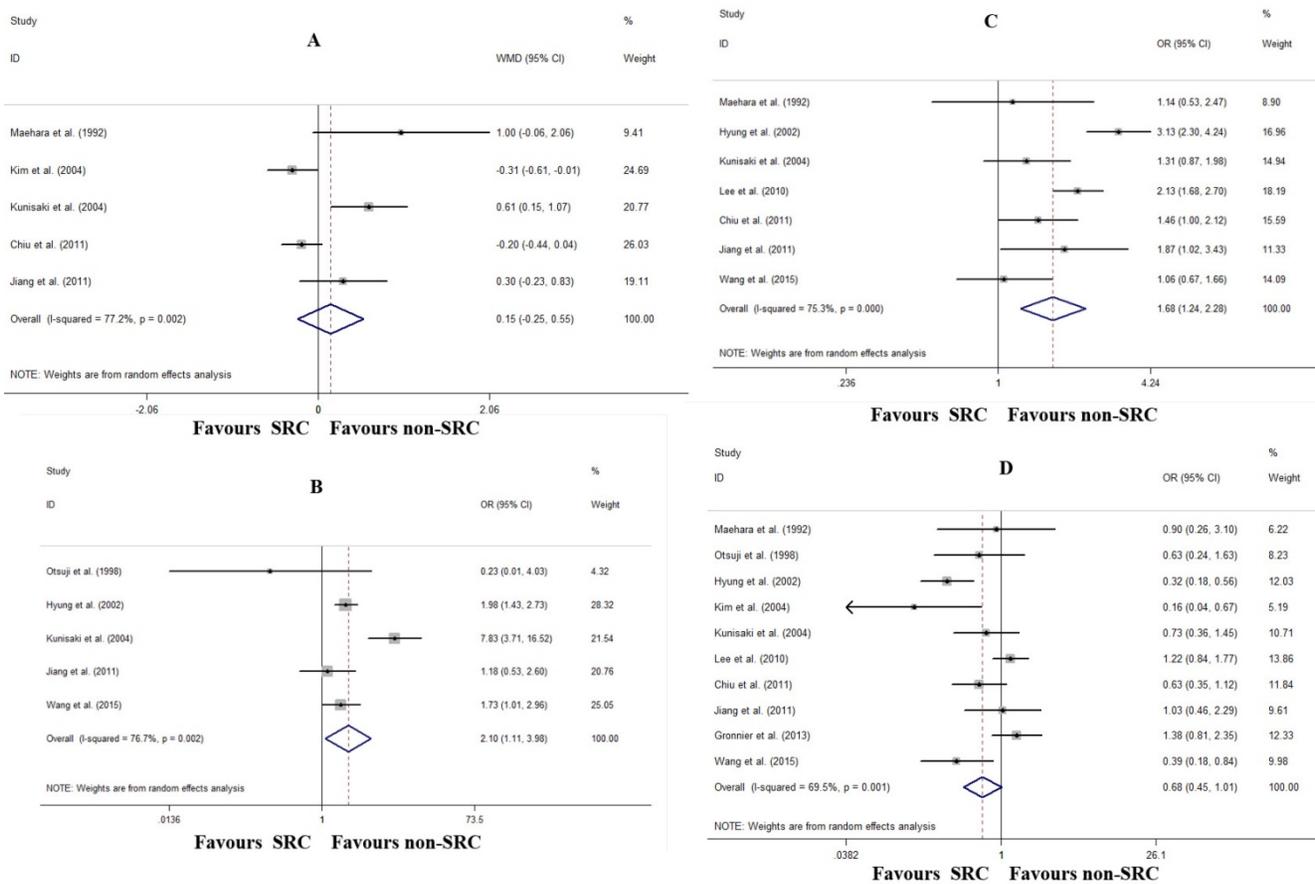


Figure 3. Forrest plot assessing different clinicopathological characteristics following SRC and non-SRC in early gastric cancer. A, tumor size; B, depressed gross type; C, mucosal invasion; and D, lymph node involvement

Publication bias

In the present meta-analysis, Begg’s linear regression was performed to assess the publication bias of OS. There was no publication bias detected for OS (P=0.374) (Fig. 6).

Discussion

Although the incidence of gastric cancer is decreasing, the proportion of SRC in gastric cancer has tended to increase [3]. The definition of gastric SRC is not based on biological behavior but on microscopic features of the cancer. SRC was classified as a diffuse type by the Lauren classification [29], as an infiltrative type by the Ming classification [30], and as an undifferentiated type by the WHO classification criteria [4]. Previous studies of the characteristics and prognostic value of SRC in gastric cancer have yielded inconsistent results [6-15, 19-28, 31, 32] and, therefore, remain controversial. Therefore, we performed the present meta-analysis to investigate the characteristics and prognostic value of SRC in gastric cancer. The pooled results of OS demonstrated that there was no difference in OS between SRC and non-SRC patients in the total population. However, SRC was associated

with a better prognosis in early gastric cancer but worse survival in advanced gastric cancer.

Our results showed that SRC tended to affect younger female patients, and SRC tended to be located in the middle and lower third of the stomach. The association between sex and SRC may be due to sex hormones. It has been reported that levels of the estrogen receptor were higher in young women and in patients with poorly differentiated gastric cancer [33].

Early gastric cancer is defined as a lesion confined to the mucosa or submucosa, regardless of the status of lymph node metastasis [34]. The prognostic value of SRC in early gastric cancer is debatable. Wang et al. reported that early gastric cancer with SRC was associated with a lower incidence of lymph node involvement and a longer 5-year survival (93.9% vs. 85.8%, P=0.027) [15], in accordance with several studies [13, 14, 22, 24, 25, 27]. However, other studies showed that there was no difference in survival between SRC and non-SRC patients [7, 10, 26]. The present meta-analysis revealed that SRC is a better prognostic factor for early gastric cancer (HR: 0.57, P=0.002), which is characterized by a higher proportion of the depressed gross type (OR:

2.11, $P=0.022$), more mucosal invasion (OR: 1.68, $P=0.001$), and marginally less lymph node metastasis (OR: 0.68, $P=0.054$). A higher percentage of the depressed type and the distinct feature of enriched intracytoplasmic mucins with the nucleus compressed peripherally may lead to early detection of the tumor by gastroscopy and biopsy [20]. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been associated with excellent

prognoses [35, 36]. EMR and ESD are recommended for early-stage gastric cancer lesions smaller than 2 cm in diameter without relevant ulcer formation [37]. Therefore, considering the lower incidence of lymph node metastasis and better prognosis, less invasive gastric surgery, such as EMR, ESD, or gastrectomy with D1 lymphadenectomy, is highly recommended for patients with early SRC.

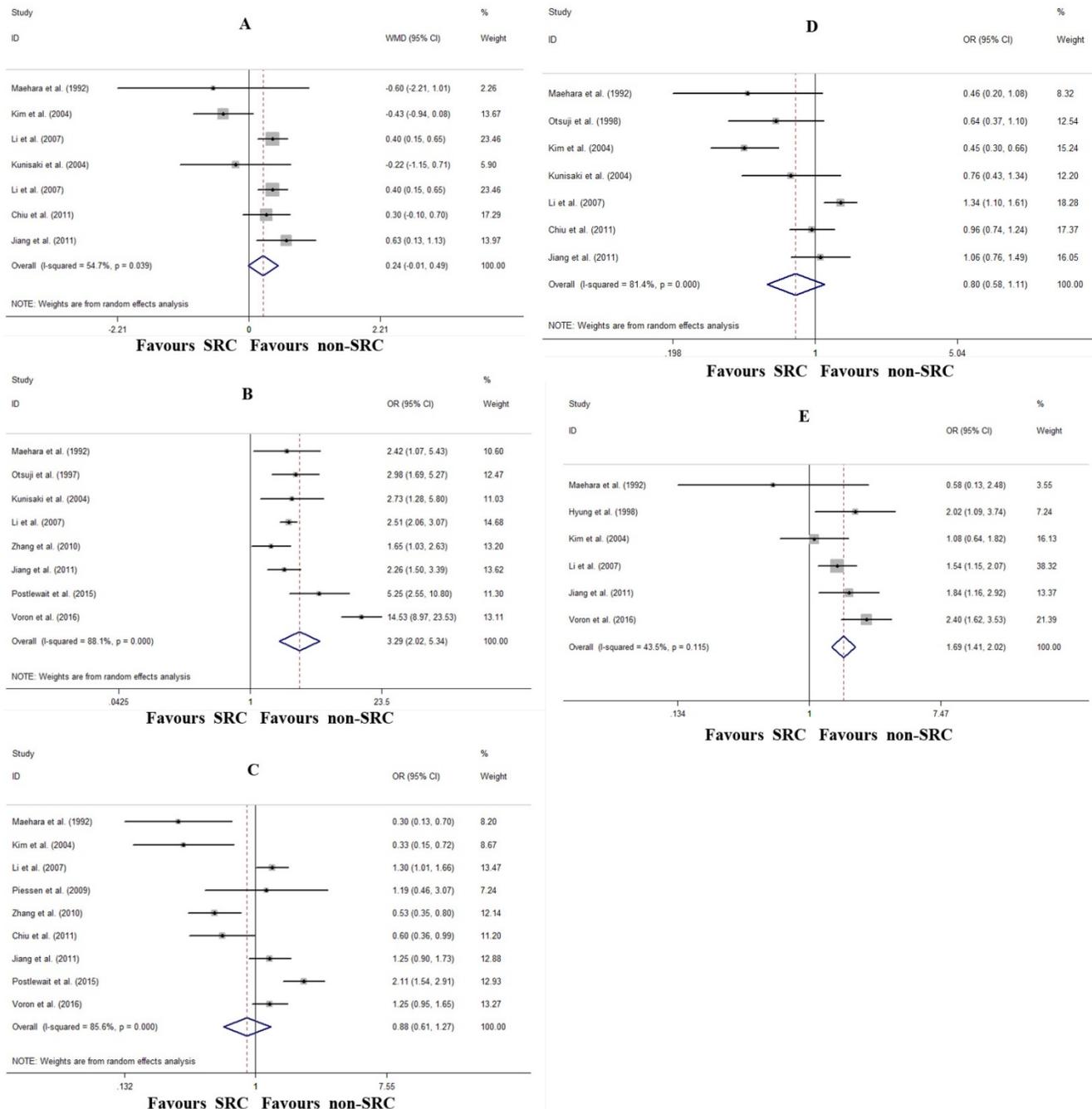


Figure 4. Forrest plot assessing different clinicopathological characteristics following SRC and non-SRC in advanced gastric cancer. A, tumor size; B, Borrmann IV type; C, T4 invasion; D, lymph node involvement; and E, peritoneal dissemination

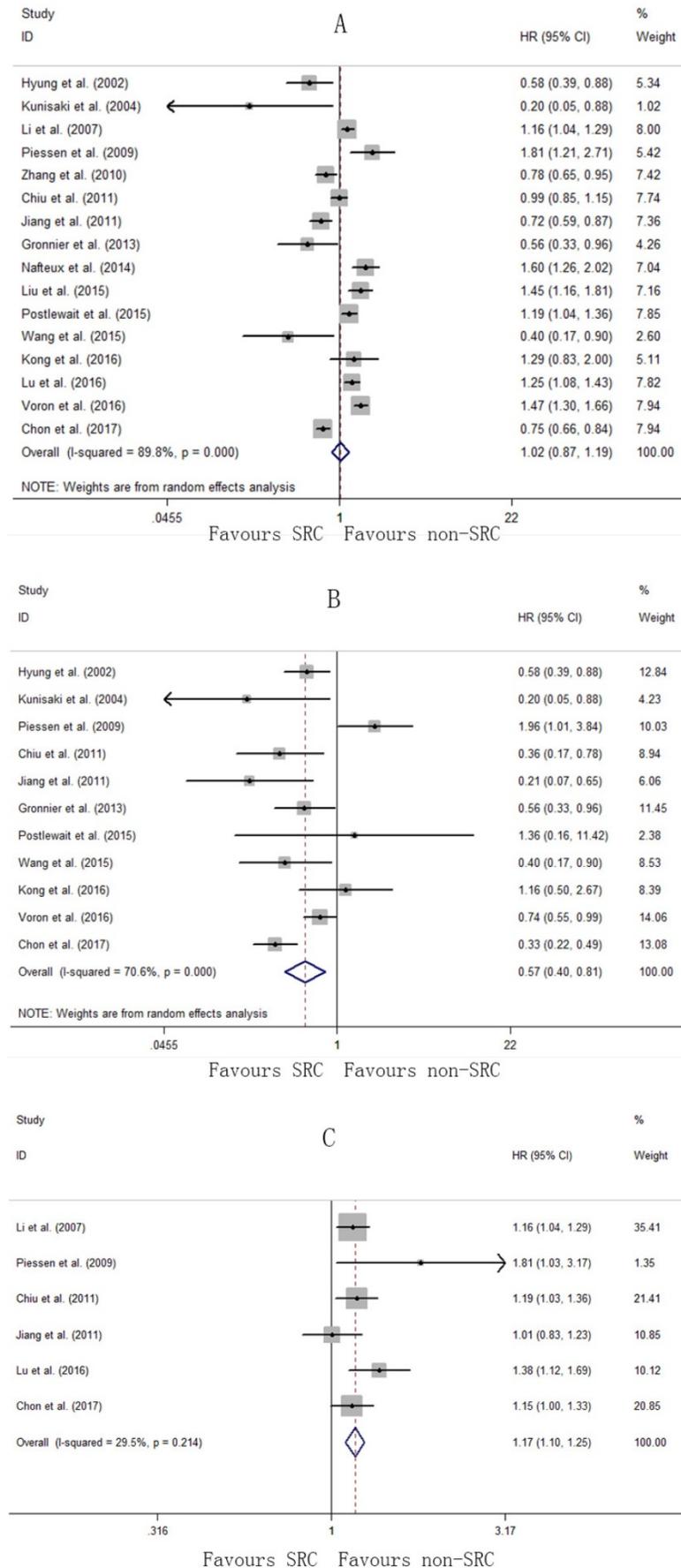
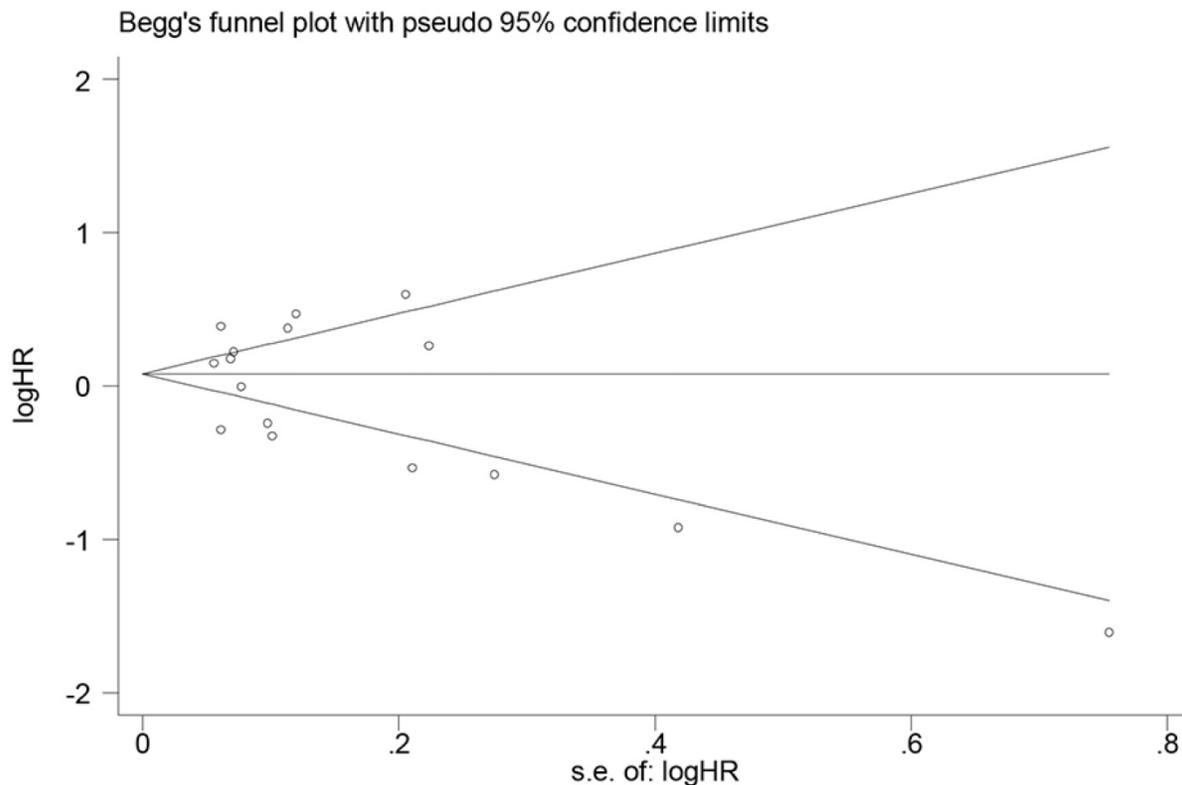


Figure 5. Forrest plot assessing overall survival following SRC and non-SRC in the total population (A), in early gastric cancer (B), and in advanced gastric cancer (C)



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