



Review

Systematic review and meta-analysis of splenectomy in gastrectomy for gastric carcinoma

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ARTICLE INFO

Keywords:

Gastric cancer
Splenectomy
Morbidity
Long-term prognosis
Meta-analysis

ABSTRACT

Background: The role of splenectomy for patients with gastric cancer still remains controversial. We performed this meta-analysis to evaluate the safety and long-term oncological outcomes of splenectomy for patients with gastric cancer.

Methods: A systematic literature search was performed using PubMed, EMBASE, Cochrane Library, and Web of Science from January 1997 to October 2018. The results were analyzed according to predefined criteria. All statistical analyses were performed using RevMan 5.3 software.

Results: In total, 16 studies with 4457 patients, including 3 randomized controlled trials (RCTs) and 13 non-randomized controlled trials (nRCTs), were analyzed. The meta-analysis showed the splenectomy group was associated with higher rates of overall postoperative complication, anastomosis leakage, abdominal abscess, and pancreatic fistula. Regarding long-term oncological outcomes, the splenectomy group showed lower 5-year overall survival (OS) and higher recurrence rates on subgroup analysis for the nRCTs. No significant difference was observed in the 5-year OS and recurrence rates between the two groups on subgroup analysis for the RCTs.

Conclusions: Splenectomy increases postoperative complications without clearly improving long-term prognosis.

1. Introduction

Gastric cancer is a worldwide health concern and is the second leading cause of cancer-related deaths in China [1]. Recent years, the incidence of proximal gastric cancer has been increasing rapidly in Western and Asian countries [2]. Gastrectomy with proper perigastric lymph node dissection remains the cornerstone of radical resection for early and locally advanced gastric cancer (AGC) [3]. The metastatic rate of No. 10 lymph nodes in proximal gastric cancer is ranged from 8% to 27.9% and complete dissection is technical demanding without splenectomy [4–7]. According to the Japanese gastric cancer treatment guidelines 2014 (ver. 4), No. 10 lymph node dissection is recommend for middle and upper third AGC [8]. Splenectomy was performed for complete removal of the splenic hilar lymph nodes. Several studies reported that patients underwent gastrectomy with splenectomy had better long-term survival outcomes when compared with those underwent gastrectomy alone [9,10]. However, some studies demonstrated that splenectomy was associated with increased postoperative morbidity without survival benefit [11,12]. To date, the role of splenectomy

for patients with gastric cancer still remains controversial. Recently, a series of studies aimed to evaluate the role of splenectomy for gastric cancer have been published. Therefore, we performed this meta-analysis to evaluate the safety and long-term oncological outcomes of splenectomy for patients with gastric cancer.

2. Search strategy

2.1. Materials and methods

We conduct this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [13] and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines. A systematic literature search was performed using PubMed, EMBASE, the Cochrane Library, and Web of Science from January 1997 to October 2018. The language was restricted to English. The following search terms were used: (stomach neoplasm [MeSH] OR “gastric neoplasm” OR “gastric carcinoma” OR “gastric cancer”) AND (“splenectomy” OR “spleen

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<https://doi.org/10.1016/j.ijso.2019.06.018>

Received 19 March 2019; Received in revised form 5 June 2019; Accepted 24 June 2019

Available online 02 July 2019

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dissection” OR “splenic preservation”). The reference lists of articles obtained were also reviewed to find relevant literature. Two authors individually conducted the literature search and cross-checked their search results.

2.2. Study selection

Included criteria for this meta-analysis were as follows [1]: randomized controlled trials (RCTs) or non-randomized controlled trials (nRCTs) that compared the safety and long-term oncological outcomes of splenectomy to those of non-splenectomy [2]; patients should be confirmed adenocarcinoma by gastroscopy and pathological biopsy [3] studies that reported at least one outcome of interest, including postoperative complication, 5-year overall survival (OS) rate, recurrence rate, mortality, and reoperation rate; Exclusion criteria were as follows [1]: studies such as reviews, comments, letters, case reports or cohort studies including fewer than 20 cases [2]; patients with other gastric tumors except for gastric adenocarcinoma [3]. studies published in any language other than English.

2.3. Data extraction, outcome measures and bias assessment

Data were extracted independently by 2 reviewers, and discrepancies were adjudicated by a third reviewer. Primary outcomes included morbidity, 5-year OS, and recurrence rate. Secondary outcomes were mortality and reoperation rate. RCTs were evaluated using the Cochrane risk of bias tool [14]. Other studies were assessed using the Newcastle–Ottawa Scale (NOS), which has been widely used for the assessment of the quality of non-randomized studies in meta-analyses [15].

2.4. Statistical analysis

The risk ratio (RR) was used to calculate dichotomous variables and was reported with 95% confidence intervals (CI). Statistical heterogeneity among studies was evaluated using the Cochran Q statistic and quantified by I^2 statistics. Heterogeneity was graded as low ($I^2 < 25\%$), moderate ($I^2 = 25\%–75\%$), or high ($I^2 > 75\%$). The random-effects model was applied if low heterogeneity was considered, whereas the fix-effects model was used. Potential publication bias was tested by visual inspection of the funnel plot. This meta-analysis was carried out using the Review Manager software (RevMan version 5.3; Cochrane Collaboration). P value less than 0.05 was considered as statistically significant.

3. Results

3.1. Study selection

Finally, 16 studies [16–18] were eligible included in the pooled analysis, which contained 3 randomized controlled studies (16–18) and 13 retrospective cohort studies [19–31]. The detailed search steps are presented in Fig. 1.

3.2. The characteristics and quality of the studies

Table 1 summarizes the characteristics of included studies, which were published from 2001 to 2017. These articles are from 8 different countries, such as Japan, Chile, America, Greece, Korea, China, Italy, and Poland. A total of 4457 patients were included in the meta-analysis, among which 1748 cases in the splenectomy group and 2709 in the spleen preservation group. The 3 RCTs included 899 patients: 448 in the splenectomy group and 451 in the spleen-preservation group. The 13 retrospective cohort studies included 3558 patients: 1300 in the splenectomy group and 2258 in the spleen preservation group. Methodological assessment outcomes for RCTs are shown in Fig. 2. The

quality assessment outcomes of non-randomized studies are summarized in Table 2.

3.3. Primary outcome measures

3.3.1. Morbidity

Postoperative complication was acquired from 15 studies (see Table 3). Our result showed that the splenectomy group had a higher postoperative complication rate (RR = 1.68, 95% CI = 1.41–2.01, $P = 0.00$) (Fig. 3), with a moderate heterogeneity between studies ($P = 0.01$, $I^2 = 51\%$). To assess the potential heterogeneity caused by different study designs, we perform a subgroup analysis. The result showed that the patients underwent splenectomy had higher postoperative complication rate in both the RCTs (RR = 1.74, 95%CI = 1.41–2.14, $P = 0.00$) and nRCTs (RR = 1.68, 95%CI = 1.33–2.12, $P = 0.00$) (Fig. 3). Regarding to specific postoperative complication, splenectomy group had higher incidence of anastomosis leakage (RR = 1.58, 95%CI = 1.08–2.33, $P = 0.02$) (Fig. 4A), abdominal abscess (RR = 3.16; 95%CI = 2.15–4.64; $P = 0.00$) (Fig. 4B), and pancreatic fistula (RR = 2.67, 95%CI = 1.57–4.56, $P = 0.00$) (Fig. 4C). There was no significant difference between two groups in terms of the incidence of pancreatitis (RR = 4.09, 95%CI = 0.55–30.35, $P = 0.17$) (Fig. 4D), wound infection (RR = 1.39; 95%CI = 0.87–2.23; $P = 0.17$) (Fig. 4E), and intestinal obstruction (RR = 1.79; 95%CI = 0.57–5.58; $P = 0.32$) (Fig. 4F).

3.3.2. Overall survival and recurrence

12 studies involving 3483 patients were identified to evaluate the 5-year OS outcomes. The pooled data analysis of these studies revealed that the splenectomy group had worse 5-year OS as compared with spleen preservation group (RR = 0.83, 95%CI = 0.72–0.95, $P = 0.01$), and high heterogeneity between these studies were observed ($P = 0.00$, $I^2 = 74\%$) (Fig. 5A). We performed subgroup analysis to evaluate the potential heterogeneity caused by study design. Our results showed that the 5-year OS were similar between the two groups in RCTs (RR = 1.01, 95% CI = 0.92–1.10, $P = 0.83$). However, splenectomy group had worse 5-year OS in nRCTs (RR = 0.75, 95% CI = 0.65–0.86, $P = 0.00$) (Fig. 5A). The stage-specific analyses demonstrated that the 5-year OS rates are comparable between the two groups in stage II, or III (Fig. 5B). For patients with proximal gastric cancer, the results showed that the 5-year OS were similar between the two groups (RR = 0.96, 95% CI = 0.79–1.17, $P = 0.69$) (Fig. 5C). 6 studies involving 1256 patients reported recurrence rate or cases experienced recurrence. Only one of these studies was RCT. The results showed that the splenectomy group had a higher recurrence rate (RR = 1.45, 95% CI = 1.02–2.07, $P = 0.04$) (Fig. 5D). However, high heterogeneity between studies was observed and random-effects model was applied. In addition, the only RCT reported that the recurrence rate was similar between the two groups ($P > 0.05$).

3.4. Secondary outcome measures

3.4.1. Mortality

7 studies involving 2017 patients reported data of mortality. In total, 18 (2.1%) patients in the splenectomy group and 27 (2.3%) patients in the spleen preservation group died. No significant difference was observed between the two groups (RR = 0.96, 95% CI = 0.54–1.70, $P = 0.88$) (Fig. 6A). Subgroup analysis demonstrated no significant difference in both RCTs (RR = 1.21, 95%CI = 0.41–3.54, $P = 0.73$) and nRCTs (RR = 0.87, 95%CI = 0.44–1.72, $P = 0.69$) (Fig. 6A).

3.4.2. Reoperation rate

2 RCTs and 2 nRCTs reported the number of patients who required reoperation. Of these studies, there was no significant difference between the splenectomy group and spleen preservation group (RR = 1.45, 95% CI = 0.91–2.33, $P = 0.12$) (Fig. 6B). Subgroup

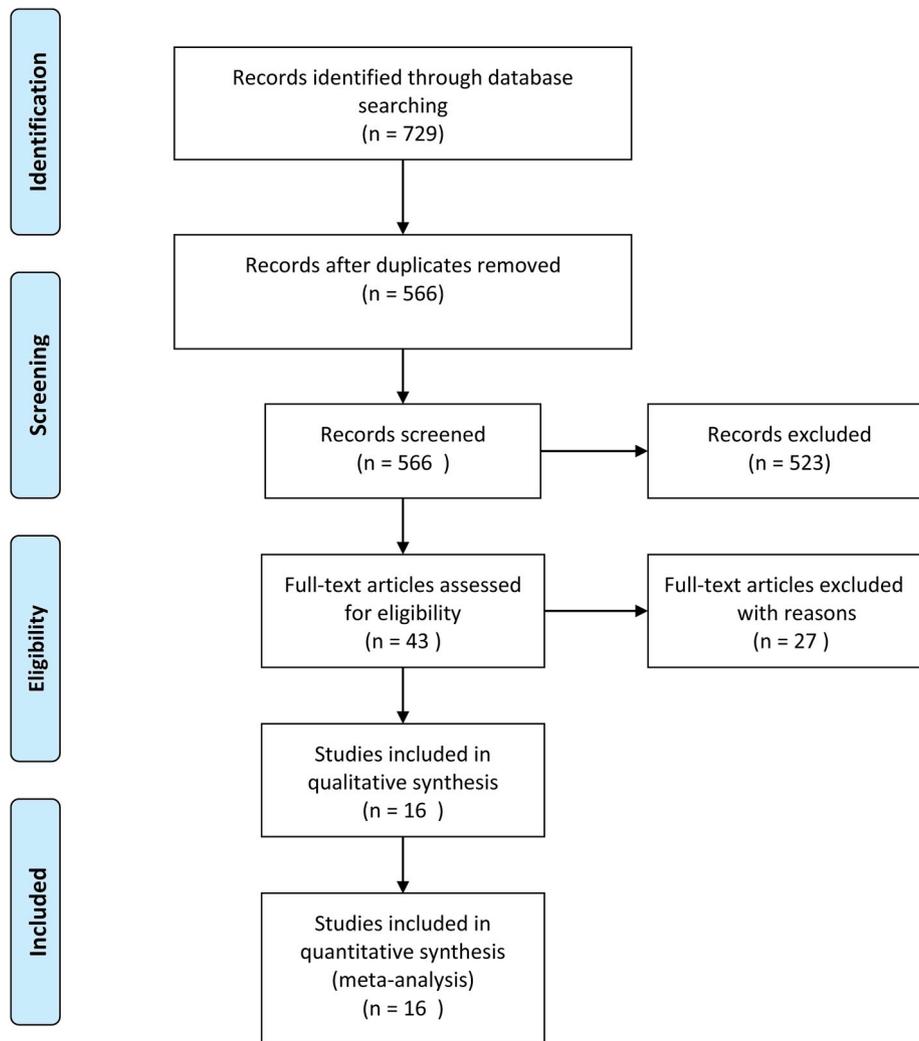


Fig. 1. The PRISMA flow diagram of the meta-analysis.

analysis of RCTs (RR = 1.05, 95% CI = 0.50–2.20, $P = 0.89$) and nRCTs (RR = 1.88, 95% CI = 1.01–3.48, $P = 0.05$) also showed no significant difference between the two groups (Fig. 6B).

3.4.3. Publication bias

Publication bias of this meta-analysis was assessed by visual inspection of the funnel plot. The funnel plot showed little publication

Table 1
Characteristics of included studies.

Study	Year	Country	Study Design	Study period	Patients		Resection extent	Age	Tumor stage	Median follow-up
					Splenectomy	Spleen Preservation				
Takeuchi et al.	2001	Japan	nRCT	1985–1999	65	98	TG	NR	T1-T4	NR
Csendes et al.	2002	Chile	RCT	1985–1992	90	97	TG	62 ^a	I-III	NR
Weitz et al.	2004	America	nRCT	1985–2001	105	230	PG,TG	65 ^b	I-IV	NR
Fatouros et al.	2005	Greece	nRCT	1986–1992	67	59	TG	65/66 ^b	I-III	55 months
Yu et al.	2006	Korea	RCT	1995–1999	104	103	TG	57 ^b	I-IV	5.4 years
Oh et al.	2009	Korea	nRCT	2000–2004	99	267	TG	NR	I-III	52 months
Yao et al.	2011	China	nRCT	NR	51	61	TG	57 ^a	I-IV	NR
Pacelli et al.	2011	Italy	nRCT	1990–2005	246	681	TG	NR	I-IV	NR
Nashimoto et al.	2012	Japan	nRCT	1994–2004	240	265	TG	NR	I-III	NR
Stojcev et al.	2013	Poland	nRCT	1997–2003	29	20	TG	58/60 ^a	I-IV	NR
Zhang et al.	2014	China	nRCT	1980–2003	100	114	TG,DG	NR	I-IV	NR
Wang et al.	2014	China	nRCT	1994–2008	172	291	TG	66/65 ^b	I-III	27.6 months
Usui et al.	2016	Japan	nRCT	2004–2014	19	59	LTG	61.9/64.6 ^a	I-III	NR
Ohkura et al.	2017	Japan	nRCT	1975–2015	63	45	PG,TG	64.0/65.6 ^b	I-III	135/189 months
Son et al.	2017	Korea	nRCT	2006–2012	44	68	LTG	54.7/60.3 ^a	I-III	40.9/43.4 months
Sano et al.	2017	Japan	RCT	2002–2009	254	251	TG	65 ^b	I-IV	71.8 months

RCT, randomized control trail; nRCT, non-randomized control trail; TG, total gastrectomy; DG, distal gastrectomy; PG, proximal gastrectomy; LTG, laparoscopic total gastrectomy; NR, no reported; a, mean age; b, median age.

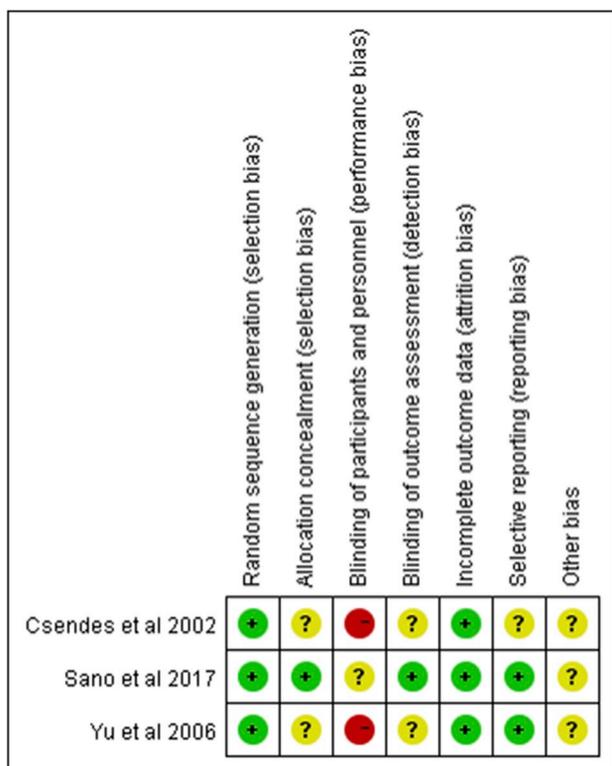


Fig. 2. Assessment of bias in RCTs. +: low risk of bias; -: high risk of bias; ?: unclear risk of bias.

Table 2
Newcastle-Ottawa Scale assessment of non-randomized studies.

Study	Selection				Comparability	Outcome			Total
	1	2	3	4	5	6	7	8	
Takeuchi et al.	*	*	*	*	-	*	*	-	6
Weitz et al.	*	*	*	*	-	*	*	-	6
Fatouros et al.	*	*	*	*	*	*	*	*	8
Oh et al.	*	*	*	*	*	*	*	*	8
Yao et al.	*	*	*	*	**	*	*	*	9
Pacelli et al.	*	-	*	*	-	*	*	*	6
Nashimoto et al.	*	*	*	*	*	*	*	-	7
Stojcev et al.	*	*	*	*	*	*	*	-	7
Zhang et al.	*	*	*	*	**	*	-	-	7
Wang et al.	*	*	*	*	*	*	*	*	8
Usui et al.	*	*	*	*	*	*	-	-	6
Son et al.	*	*	*	*	*	*	*	*	8
Ohkura et al.	*	*	*	*	**	*	*	*	9

1. Representativeness of exposed cohort; 2. Selection of non-exposed cohort; 3. Ascertainment of exposure; 4. Outcome of interest was not present at start of study; 5. Comparability of cohorts on the basis of the design or analysis; 6. Assessment of outcomes; 7. Follow-up long enough for outcomes to occur; 8. Adequacy of follow-up.

bias existed in our analysis (Fig. 7).

4. Discussion

In the classification of the Japanese Gastric Cancer Association (JGCA), the No. 10 lymph node dissection means the dissection or lymphadenectomy of splenic hilar lymph nodes [8,32]. The metastatic rate of No. 10 lymph nodes in advanced proximal gastric cancer is ranged from 8% to 27.9% [4–7]. Splenectomy was performed for complete removal of the splenic hilar lymph nodes [18,30]. In clinical practice, some surgeons hold the opinion that a survival benefit can be achieved with an extend lymph node dissection. However, the survival

benefit of splenectomy still remains unclear. Till date, limited number of high-quality RCTs on this topic has been reported. This meta-analysis aimed to evaluate the safety and long-term oncological outcomes of splenectomy and spleen-preservation for gastric cancer based on all available evidence. Our results showed that splenectomy in gastrectomy associated with increased postoperative complication rate without improving survival rate. Additionally, no significant difference was observed between the two groups in terms of mortality and reoperation rate.

Postoperative complication is always regarded as one of the major concern in clinical practice. A previous meta-analysis showed the morbidity did not occur more in splenectomy group than those in splenic preservation group [33]. However, some studies have showed that gastrectomy combined with splenectomy increase the risk of morbidity which had an adverse effect on postoperative the recovery of patients [16–18]. Our results also demonstrated that patient underwent splenectomy in gastrectomy was associated with higher overall complication rate when compared with those underwent gastrectomy alone. In addition, the subgroup analysis based on different study designs (RCTs or nRCTs) also confirmed this result. Previous studies demonstrated that the pancreatitis, anastomotic leakage, abdominal abscess, wound infection, and intestinal obstruction were the common postoperative complications after splenectomy [33]. In this meta-analysis, the splenectomy group showed higher incidence of anastomosis leakage, abdominal abscess, and pancreatic fistula. Regarding postoperative mortality, no significant difference was observed between the splenectomy and spleen preservation groups. Additionally, the present study failed to go against splenectomy in terms of reoperation rate.

Long-term survival outcome is a key index to assess oncological safety. The effect of splenectomy in gastrectomy on long-term survival outcomes is a very controversial subject. A randomized trial conducted by Csendes et al. [16] showed that splenectomy has no effect on survival after total gastrectomy in early gastric cancer, and therefore splenectomy can be avoided. The result was also consistent with the study conducted by Yu et al. [17]. A recent randomized trial in Japan demonstrated that splenectomy associated with increased morbidity without improving survival for proximal gastric cancer not invading the greater curvature. The 5-year OS was 75.1% in splenectomy group and 76.4% in spleen-preservation group [18]. Hartgrink et al. [34] reported no survival benefit of pancreatectomy and splenectomy for patients with metastasis in No.10 lymph nodes during a longfollow up period. Our meta-analysis suggested that splenectomy was associated with worse 5-year OS and higher recurrence rates as compared with spleen preservation group regardless of study design. However, further analysis based on RCTs revealed that the two groups had similar 5-year OS and recurrence rates. This may attributed to the limitations of retrospective study, such as selection bias and potential confounding factors. We also found that the patients in the splenectomy group were always in more advanced stage and larger tumor size, indicating a poor prognosis for these cases. Regarding the OS in different tumor stage, Oh et al. [22] reported that the 5-year OS rates were comparable between the two groups for patients in stage I to III. Nashimoto et al. [25] did not find the superiority of splenectomy in gastrectomy when considering the 5-year OS rate for patients in stage II, IIIA, and IIIB. A randomized study also showed that the splenectomy in gastrectomy did not bring survival benefit for patients in stage II, IIIA, and IIIB [16]. In the present meta-analysis, we could not perform stage-specific analysis due to the varied staging system among included studies. Therefore, further studies in uniform staging standard are necessary to provide more solid evidence on this topic.

With the development of surgical techniques, some experienced laparoscopic surgeons attempt to preform laparoscopic spleen-preserving No.10 lymph node dissection [35]. Several studies suggests that experienced surgeons can safely perform laparoscopic spleen-preserving No.10 lymph node dissection [36–38]. However, it is still a challenging and technically demanding procedure even for experienced

Table 3
Pooled short-term outcomes of meta-analysis.

Outcomes	No. of studies	Sample size		Heterogeneity (<i>P</i> , <i>I</i> ²)	Overall effect size	<i>P</i> value
		Splenectomy	Spleen Preservation			
Overall complications	15	1502	2028	0.01, 51%	RR = 1.68	0.00001
Anastomosis leakage	9	1088	1460	0.45, 0%	RR = 1.58	0.02
Abdominal abscess	4	578	673	0.28, 21%	RR = 3.26	0.00001
Pancreatic fistula	9	1040	1512	0.06, 46%	RR = 2.67	0.0003
Pancreatitis	2	164	365	0.17, 48%	RR = 4.09	0.17
Wound infection	6	560	887	0.94, 0%	RR = 1.39	0.17
Intestinal obstruction	6	753	1066	0.15, 39%	RR = 1.79	0.32
Mortality	7	851	1166	0.63, 0%	RR = 0.96	0.88
Reoperation rate	4	548	845	0.59, 0%	RR = 1.45	0.12
Hospital stay (days)	2	118	326	0.25, 24%	RR = 2.62	0.002

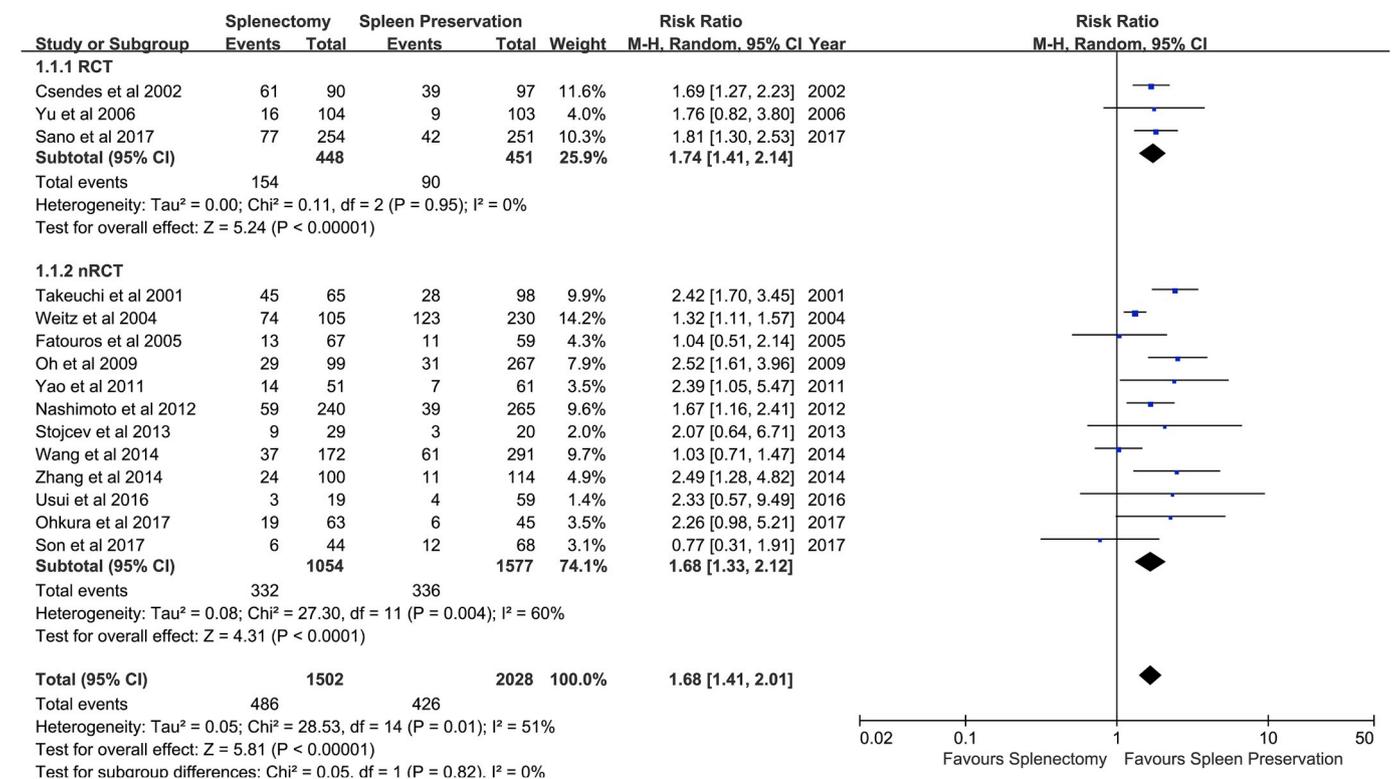


Fig. 3. Forest plot of pooled risk ratio of overall postoperative complication.

surgeons [39,40]. Meanwhile, the surgical safety and oncologic efficacy have only been reported in nRCT with relatively small sample size [31]. Therefore, large cohort and prospective multicenter RCTs are still needed to clarify the real benefits of this procedure. At present, a randomized trial to evaluate the clinical efficacy of laparoscopic spleen-preserving No.10 lymph node dissection for advanced upper or middle third gastric cancer is ongoing (No. NCT02333721). We believe the ongoing RCT will provide definitive evidence in the near future.

In current meta-analysis, most of the included studies evaluated all patients regardless of tumor location. Lack of the control of tumor location may provide limited clinical value because it is a major concern to identify the patient which may benefit from splenectomy. Recently, the result of JCOG 0110 showed that the splenectomy is no superior to spleen preservation for proximal gastric cancer not invading the greater curvature in terms of OS and recurrence [18]. However, it still remains unclear whether patients will benefit from splenectomy regarding tumors involving the greater curvature. Watanabe et al. [10] conducted a retrospective analysis and found that patients underwent splenectomy may have a survival benefits when tumors was located in the greater curvature. But Ohkura et al. [30] reported that the rate of No.10 lymph

node metastasis was only 6% for patients with tumors invading the greater curvature, and their results suggested that prophylactic splenectomy may not have significant impact on prognosis of patients. At present, for AGC involving the greater curvature of the upper stomach, splenectomy is recommended in 2014 guideline of the Japanese Gastric Cancer Association based on some retrospective studies. Therefore, high-quality RCTs are required to provide definitive evidence on whether splenectomy is needed or not in patients with advanced proximal gastric cancer involving the greater curvature of the upper stomach. In recent years, the preservation of organ function is being accepted by more and more surgeons in clinical practice. What's more, several studies have demonstrated that the spleen-preservation could boost immunity, reduce early recurrence, and enable immune therapy for patients with gastric cancer [41,42]. Therefore, future studies should also investigate whether spleen-preserving splenic hilar lymphadenectomy may replace splenectomy for advanced proximal gastric cancer involving the greater curvature of the upper stomach.

Although our meta-analysis draws a reasonable conclusion, there were still several limitations need to be noted. First, 13 of 16 studies were nRCTs, which may limit the statistical power of this study. Second,

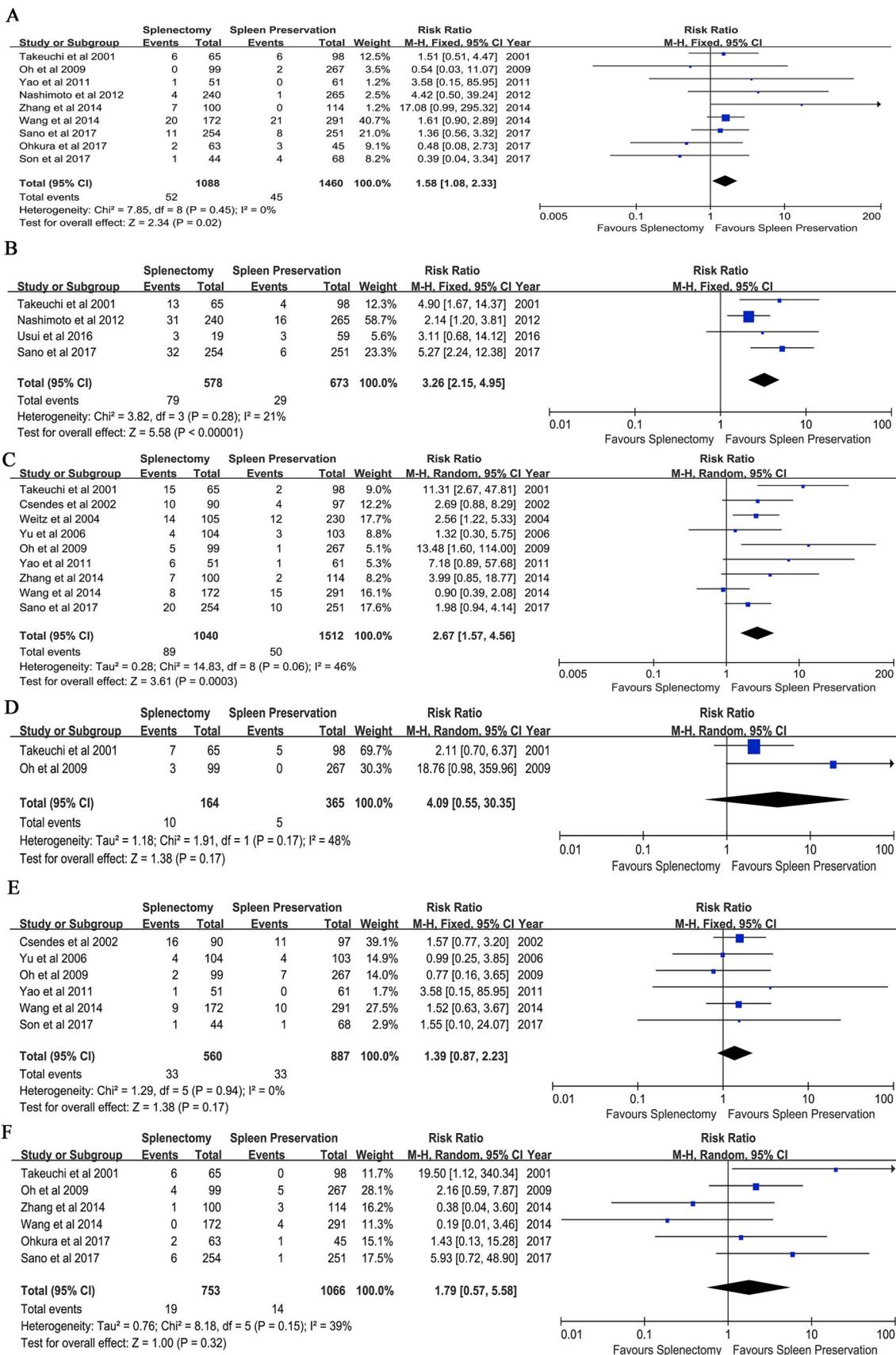


Fig. 4. Forest plot of pooled risk ratio of specific postoperative complication. A Anastomotic leakage; B Abdominal abscess; C Pancreatic fistula; D Pancreatitis; E Wound infection; F Intestinal obstruction.

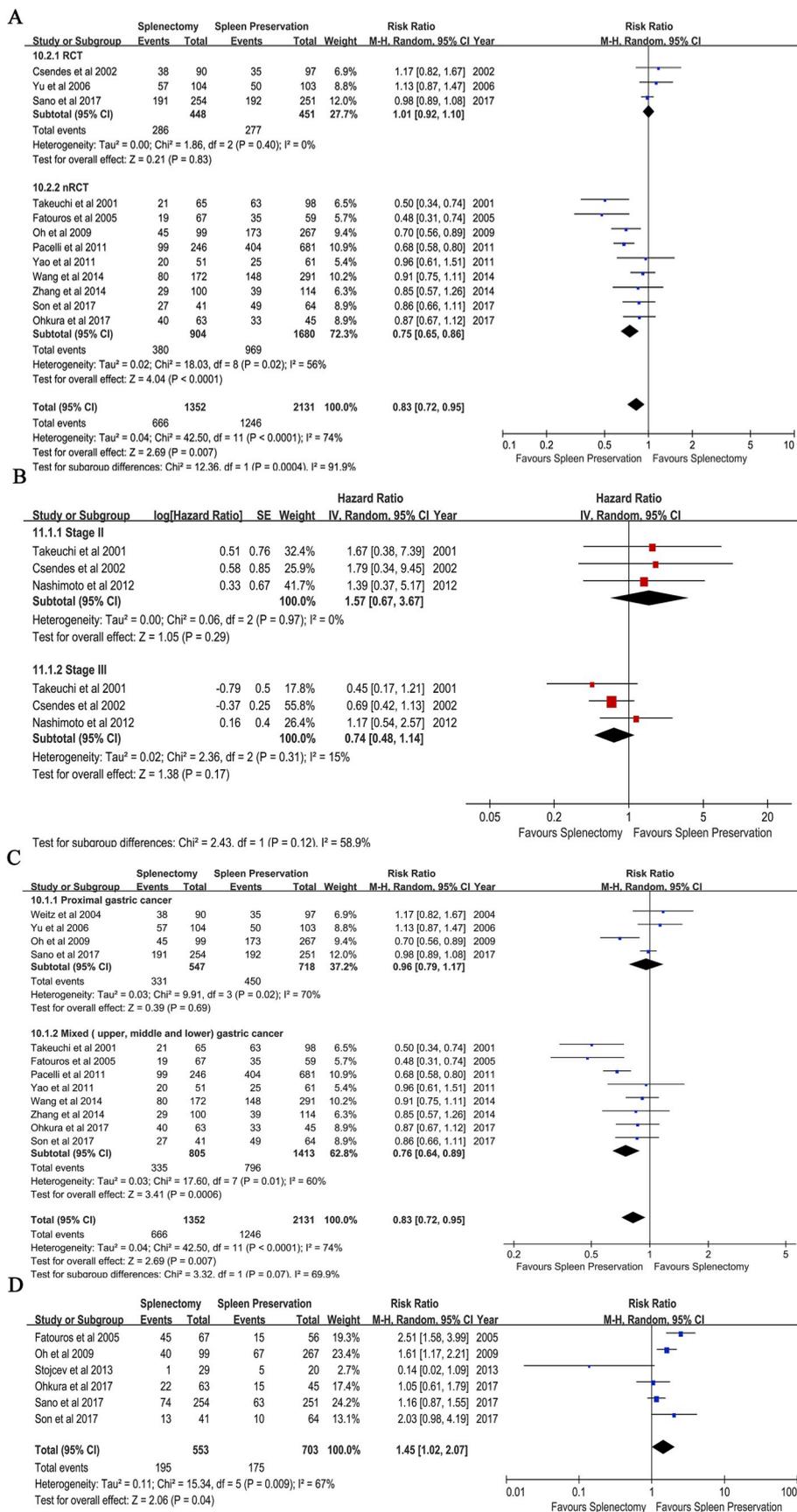
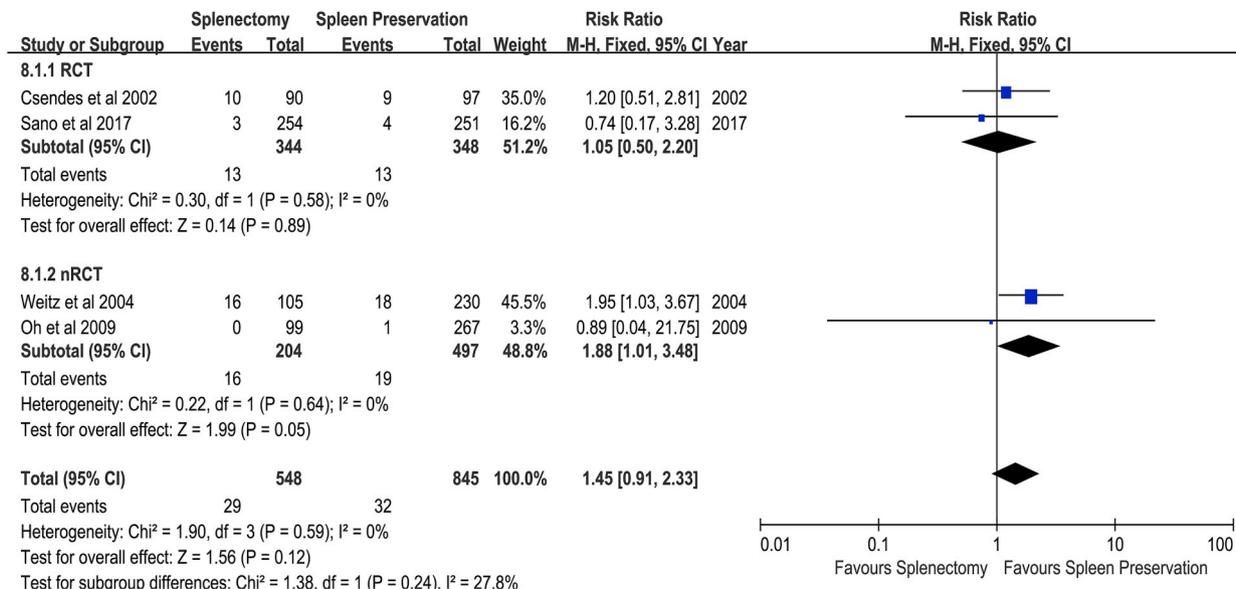
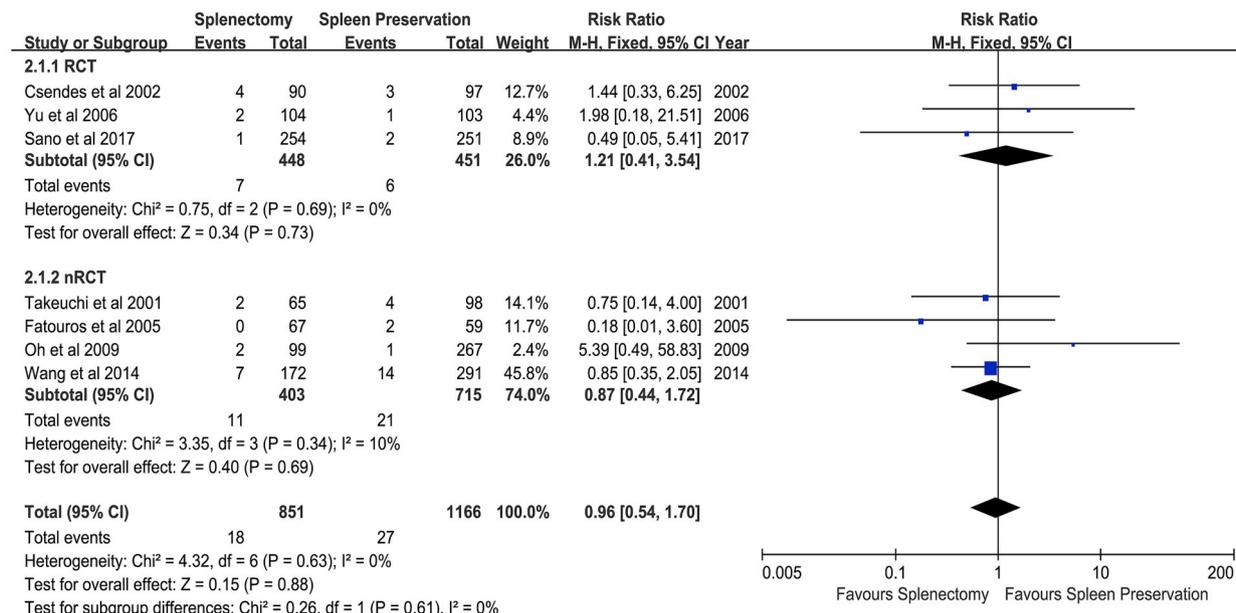


Fig. 5. Forest plot of pooled risk ratio of long-term prognosis. A 5-year OS; B. Subgroup analyses of 5-year OS in different tumor stage; C Subgroup analyses of 5-year OS in different resection extents; D Recurrence.

A



B



C

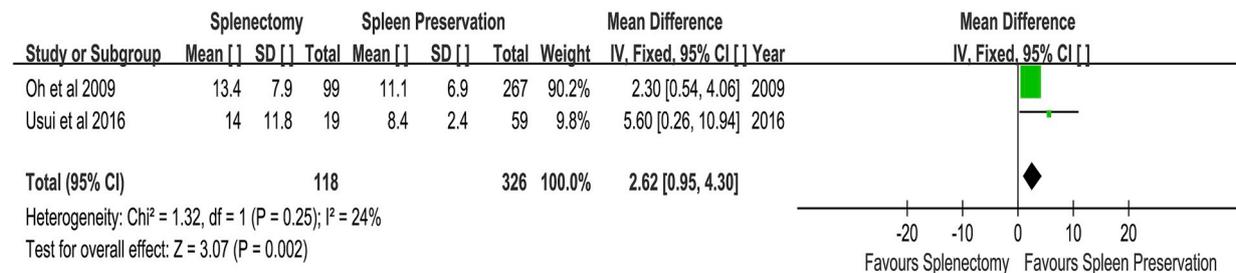


Fig. 6. Forest plot of pooled risk ratio of: A Mortality; B Reoperation rate.

considerable heterogeneity among included studies cannot be neglected due to the inherent differences of regional, characteristics of patients, surgeon experience, type of surgical procedure, and length of follow-up period. Finally, the staging standard and tumor location are varied

among included studies. Therefore, we were unable to perform subgroup analysis based on different TNM stage and tumor location.

In conclusion, splenoctomy in gastrectomy increases postoperative complications without clearly improving long-term prognosis.

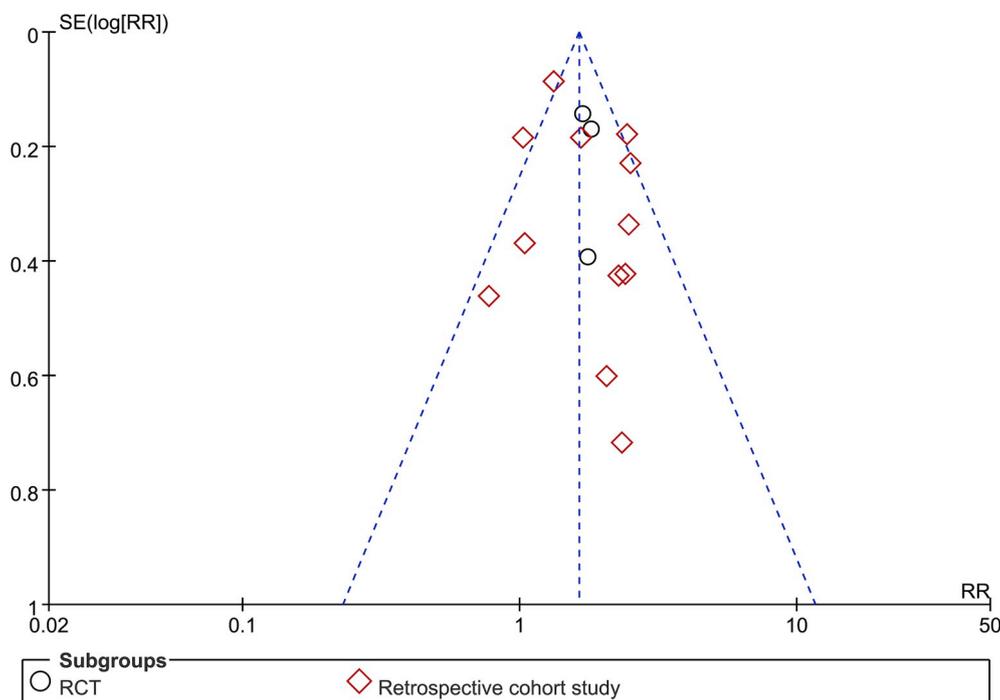


Fig. 7. Funnel plot of the overall postoperative complications.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijso.2019.06.018>.

Ethical Approval

No need Ethical Approval.

Sources of funding

This study was supported by the National Key Basic Research Program of China (No. 2014CBA02002). The National Key Research and Development Program of China (2017YFC1311002, 2017YFC1311004); The National Key Research and Development Program of Shan'xi province, China (2017ZDXM-SF-053)

Author contribution

Zhengyan Li conceived the study and drafted the manuscript. Zhengyan Li and Bo Lian identified and screened the search findings for potentially eligible studies of the meta-analysis. Jie Chen and Dan Song independently extracted the data using a unified datasheet, and the Qingchuan Zhao was consulted when controversial issues were presented. Dan Song and Zhengyan Li performed the statistical analyses and gave an interpretation of the results. Zhengyan Li and Qingchuan Zhao revised and supervised the study. All authors read and approved the final manuscript.

Guarantor

Zhengyan Li.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Disclosures

The authors declare that they have no conflict of interest.

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