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Review

# Laparoscopic versus open gastrectomy for high-risk patients with gastric cancer: A systematic review and meta-analysis

Zhengyan Li*,[1], Yan Zhao[1], Yezhou Liu, Deliang Yu, Qingchuan Zhao**

*Department of Surgery, Xijing Hospital of Digestive Diseases, The Fourth Military Medical University, No. 127 Changle West Road, Xi'an, 710032, China*

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ABSTRACT

*Background:* It is still remains unclear whether high-risk patients with gastric cancer can benefit from the application of laparoscopic gastrectomy (LG). The aim of this systematic review was to evaluate the surgical and long-term outcomes after LG and open gastrectomy (OG) for high-risk patients with gastric cancer.
*Methods:* We performed a systematic literature search in various databases from January 1994 to June 2018. Patients who had ≥ 1 of the following conditions were defined as high-risk patients: (1) age ≥ 70 years; (2) BMI ≥ 30 kg/m$^2$; (3) ASA (American Society of Anesthesiologists) grade ≥ 3; or (4) clinical T4 stage (cT4). The results were analyzed according to predefined criteria.
*Results:* In the present meta-analysis, the outcomes of 12 non-randomized controlled studies enrolling 1651 patients (873 in the LG group and 778 in the OG group) were pooled. The estimated blood loss was significantly lower in the LG group than those in the OG group ($P < 0.01$). There was no significant difference between two groups in operative time ($P = 0.17$) and number of harvested lymph nodes ($P = 0.21$). In the LG group, the time to flatus ($P < 0.01$), time to food intake ($P < 0.01$), and postoperative hospital stay ($P < 0.01$) were significantly shorter than those in the OG group. A lower overall postoperative complication rate was observed in the LG group ($P < 0.01$). The incidence of surgical ($P < 0.01$) and non-surgical ($P < 0.01$) complication was significantly lower in the LG group than that in the OG group. The pooled analysis showed no significant difference in overall survival (OS) between LG and OG groups ($P = 0.98$).
*Conclusions:* LG can be a safe and feasible procedure for high-risk patients with gastric cancer.

## 1. Introduction

Gastric cancer remains a world-wide cancer with high mortality and is the second leading cause of cancer-related deaths in China [1]. Gastrectomy with proper perigastric lymph node dissection remains the cornerstone of radical resection of potentially curable gastric cancer. Laparoscopic gastrectomy (LG) has been increasingly performed since it was first reported in 1994 by Kitano et al. [2]. Recently, several multicenter RCTs have reported LG is a safe and feasible surgical procedure for advanced gastric cancer (AGC) in terms of short-term outcomes [3–5]. With the development of society, the aging population and obesity have become increasingly prominent issues [6,7]. Additionally, in china, more than 80% of the gastric patients are diagnosed at advanced stages and cases with serosa-positive (T4a) gastric cancer account a large proportion. In clinical practice, patients with high body mass index (BMI), old age, T4 stage, and ASA grade ≥ 3 are always defined as high-risk patients [8–13]. To date, it is still remains unclear whether these patients can benefit from the application of LG.

Therefore, we conducted this meta-analysis to compare the surgical and long-term outcomes of LG with open gastrectomy (OG) for high-risk patients with gastric cancer in order to assess whether these patients can benefit from LG.

## 2. Methods

### 2.1. Literature search

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews)

* Corresponding author. Department of Digestive Surgery, Xijing Hospital of Digestive Diseases, The Fourth Military Medical University, No. 127 Changle West Road, Xian, 710032, China.
** Corresponding author.
*E-mail addresses:* lizhengyan01@sina.com (Z. Li), zhaoqc@fmmu.edu.cn (Q. Zhao).
[1] Zhengyan Li and Yan Zhao contributed equally to this work.

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Guidelines. A systematic literature was searched from PubMed, MEDILNE, EMBASE, the Cochrane Library, and Web of Science from January 1994 to June 2018. Search terms "gastric carcinoma", "gastric cancer", "laparoscopic", "laparoscopy", "age", "elderly", "old", "serosa-positive", "serous invasion", "T4a", "obese", "body mass index", and "high-risk" were used in combination with the Boolean operators AND or OR. 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. Inclusion and exclusion criteria

Included criteria for this meta-analysis were as follows: (1) histologically confirmed gastric cancer; (2) published studies comparing LG with OG for gastric cancer; (3) studies focusing on high-risk patients (age ≥ 70 years, pT4a stage, BMI ≥ 30 kg/m$^2$, or ASA grade ≥ 3); (4) studies that reported at least one of the following outcomes, including surgical outcome, postoperative complication, or the overall survival (OS). The excluded criteria were: (1) studies such as reviews, comments, letters, case reports, or cohort studies including fewer than ten patients; (2) studies published in a language other than English.

### 2.3. Data extraction and quality assessment

Data were extracted independently by two reviewer independently using predefined standards and cross-checked, and discrepancies were adjudicated by a third reviewer. The following data were extracted from each study: first author, publication year, country, study design, study period, median follow-up, postoperative complication (overall postoperative complication, surgical complication, non-surgical complication, wound problem, anastomotic leakage, abdominal abscess, and pneumonia), and OS. All included studies were methodologically 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 [14].

### 2.4. Statistical analysis

Odds ratio (OR) was used to calculated dichotomous variables. Weighted mean difference (WMD) was used to calculate continuous variables, and both were reported with 95% confidence intervals (CIs). Survival outcomes were summarized by adopting the generic inverse variance method. $I^2$ statistics were used to quantify the heterogeneity among studies. If data was not significantly heterogeneous ($P > 0.05$ or $I^2 < 50\%$), the pooled effects were calculated using a fixed model. Otherwise, the random effects analysis would be performed. Data analyses were performed with the Review Manager software (RevMan version 5.3; Cochrane Collaboration). Publication bias was evaluated by a funnel plot. The results were regarded as statistically significant at two-sided $P < 0.05$.

## 3. Results

### 3.1. Study selection

We conduct this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [15]. Finally, 12 non-randomized controlled studies [16–27] were eligibly included in the pooled analysis. 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 2004 to 2018. These articles are from Japan, Korea, and China. A total of 1651 patients were included in the meta-analysis, among which 873 cases in the LG group and 778 in the OG group. The quality assessment outcomes of non-randomized studies are summarized in Table 2.

### 3.3. Intraoperative outcomes and postoperative recovery

The estimated blood loss was significantly lower in the LG group than those in the OG group (WMD = −106.91 ml; 95%CI: -161.01 to −52.81, $P < 0.01$; Fig. 2A). There was no significant difference between two groups in operative time (WMD = 19.07 min; 95%CI: -8.11 to 46.26, $P = 0.17$; Fig. 2B) and number of harvested lymph nodes (WMD = 1.14; 95%CI: -0.66 to 2.94, $P = 0.21$; Fig. 2C). In the LG group, the time to first flatus (WMD = −0.79 d; 95%CI: -1.12 to −0.46, $P < 0.01$; Fig. 2D), time to food intake (WMD = −0.89 d; 95%CI: -1.09 to −0.70, $P = 0.00$; Fig. 2E), and postoperative hospital stay (WMD = −3.88 d; 95%CI: -5.57 to −2.19, $P < 0.01$; Fig. 2F) were significantly shorter than those in the OG group.

### 3.4. Postoperative complications

A lower overall postoperative complication rate was observed in the LG group (OR = −0.10; 95%CI: -0.14 to −0.07, $P < 0.01$; Fig. 3A). Subgroup Analysis also revealed a lower postoperative complication rate favoring LG in age ≥ 70 or 75 years (OR = −0.19; 95%CI: -0.28 to −0.11, $P < 0.01$; Fig. 3A), BMI ≥ 30 kg/m$^2$ (OR = −0.21; 95%CI: -0.38 to −0.04, $P = 0.02$; Fig. 3A), and mixed group. The incidence of surgical (OR = 0.57; 95%CI: 0.40 to 0.80, $P < 0.01$; Fig. 3B) and non-surgical complication (OR = 0.41; 95%CI: 0.28 to 0.61, $P < 0.01$; Fig. 3C) was significantly lower in the LG group than in the OG group. Further analysis revealed that the LG group was associated with a lower incidence in wound problem (OR = 0.37; 95%CI: 0.20 to 0.70, $P < 0.01$; Fig. 4A) and pneumonia (OR = 0.49; 95%CI: 0.32 to 0.77, $P < 0.01$; Fig. 4D). Incidences of anastomotic leakage (OR = 0.55; 95%CI: 0.30 to 1.01, $P = 0.05$; Fig. 4B) and abdominal abscess (OR = 0.61; 95%CI: 0.28 to 1.31, $P = 0.21$; Fig. 4C) were comparable in LG and OG.

### 3.5. Overall survival outcomes

The pooled analysis of the five studies showed no significant difference in OS between LG and OG (HR 1.00, 95% CI 0.83 to 1.21, $P = 0.98$; Fig. 5). For patients in pT4a stage, the subgroup analysis also showed that no significant difference in OS between the two groups (HR 0.93, 95% CI 0.67 to 1.27, $P = 0.64$; Fig. 5).

### 3.6. Publication bias

Publication bias of our meta-analysis was assessed using funnel plots. No evidence of significant publication bias was found (Fig. 6).

## 4. Discussion

LG has been widely adopted because its advantage of minimally invasiveness as compared to open gastrectomy [28–30]. However, it is still remains unclear whether high-risk gastric patients can benefit from the application of LG. Meanwhile, the clinical efficacy of LG for these patients is a major concern of surgeons. Therefore, the surgical and long-term outcomes of LG for high-risk gastric cancer were important and necessary for the wide application of LG in gastric cancer. To our knowledge, this is the first meta-analysis to give an overview of the clinical efficacy of LG for high-risk patients with gastric cancer.

Extensive research has confirmed that LG is associated with better short-term outcomes, such as less intraoperative blood loss and earlier postoperative recovery [31–33]. For high-risk patients with gastric cancer, the results of our study showed that the LG group had superior short-term outcomes in terms of estimated blood loss, time to first

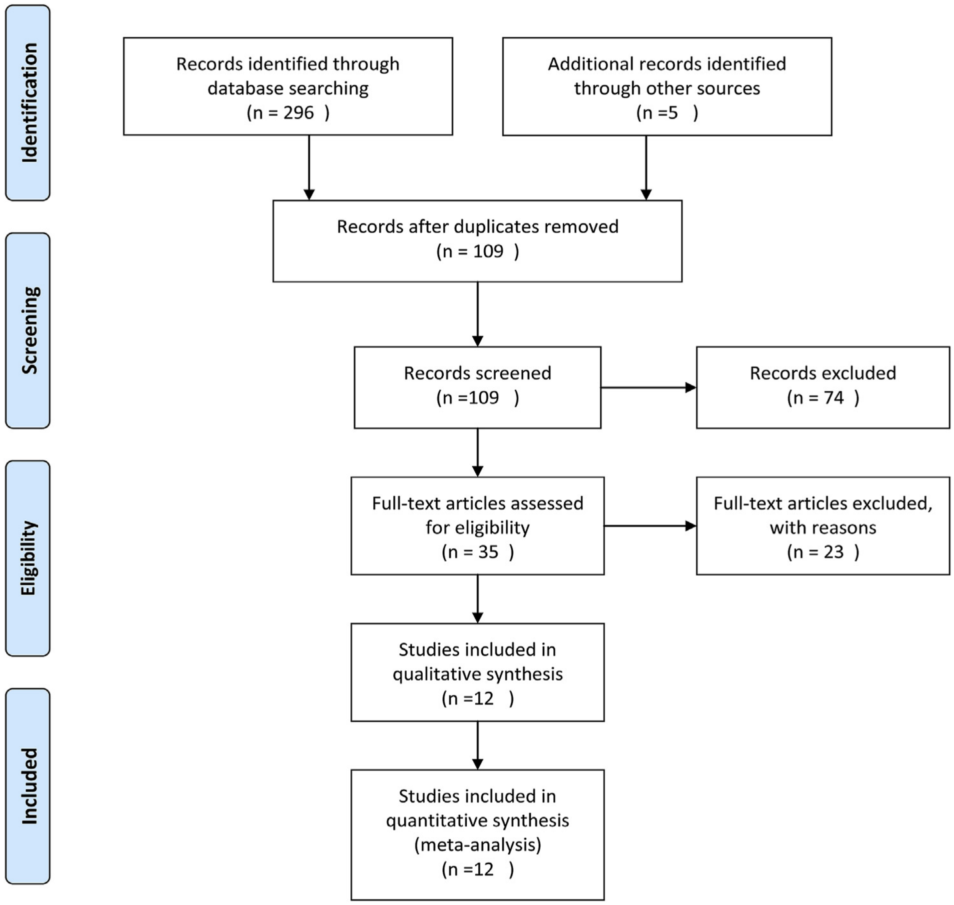


**Fig. 1.** PRISMA flow diagram of the meta-analysis.

flatus, time to first oral intake, and postoperative hospital stay. These indicated that the benefits of LG still exist even for high-risk patients.

Postoperative complication is one of the major concerns in clinical practice. Our previous study demonstrated that the occurrence of complications adversely affected long-term survival outcomes after LG with D2 lymph node dissection for gastric cancer [34]. Extensive studies have demonstrated that patients who underwent LG are always has lower postoperative complications rate when compared with OG [31,35–37]. For high-risk patients with gastric cancer, the result of our study confirmed that the LG group was also associated with lower overall complication rate as compared with OG. Further analysis also revealed that the LG group had less surgical and nonsurgical complications. In the future, the proportion of aged patients with a diagnosis of gastric cancer is expected to increase gradually over the world [7]. Characteristics of elderly patients such as declining physiological function, poor nutritional status, and reduced ability to tolerate surgical stress have been identified as surgical risk factors [38–40]. Previous studies have confirmed that old age is not only an independent risk factor for postoperative mortality and longer hospital stay, but also for the occurrence of postoperative complication [34,40,41]. For elderly patients, the result of subgroup analysis showed that the LG group had a lower overall postoperative complication rate. The elderly patients are usually accompanied with comorbidities. Pneumoperitoneum during LG has been reported to be correlated with the deterioration of

**Table 1**
Characteristics of included studies.

| Study | Year | Country | Study Design | Study period | Patients | | Risk factor | Median follow-up |
|---|---|---|---|---|---|---|---|---|
| | | | | | LG | OG | | |
| Yasuda et al. | 2004 | Japan | nRCT | 1994–2003 | 45 | 28 | Age ≥ 70 years | NR |
| Mochiki et al. | 2005 | Japan | nRCT | 1998–2004 | 30 | 16 | Age ≥ 70 years | 40 months |
| Li et al. | 2014 | China | nRCT | 2008–2009 | 54 | 54 | Age ≥ 70 years | 36 months |
| Qiu et al. | 2014 | China | nRCT | 2012–2013 | 30 | 34 | Age ≥ 70 years | NR |
| Son et al. | 2014 | Korea | nRCT | 2003–2009 | 39 | 22 | pT4a stage | 64 months |
| Suzuki et al. | 2015 | Japan | nRCT | 2000–2011 | 38 | 28 | Age ≥ 75 years | 42 months |
| Son et al. | 2015 | Korea | nRCT | 2003–2012 | 62 | 19 | BMI ≥ 30 kg/m2 | LG:37.8; OG:47.9 |
| Zheng et al. | 2016 | China | nRCT | 2013–2014 | 23 | 27 | Age ≥ 70 years | 19 months |
| Xu et al. | 2017 | China | nRCT | 2007–2011 | 67 | 67 | pT4a stage | 22 months |
| Zhang et al. | 2017 | China | nRCT | 2006–2008 | 111 | 119 | pT4a stage | 36 months |
| Chen et al. | 2018 | China | nRCT | 2009–2016 | 33 | 23 | BMI ≥ 30 kg/m2 | NR |
| Xu et al. | 2018 | China | nRCT | 2007–2014 | 341 | 341 | Mixed | 42 months |

RCT, randomized control trail; nRCT, non-randomized control trail; NR, no reported.

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

| Study | Selection | | | | Comparability | Outcome | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| Yasuda et al. | * | * | * | * | * | * | * | – | 7 |
| Mochiki et al. | * | * | * | * | * | * | * | * | 8 |
| Li et al. | * | * | * | * | ** | * | * | * | 9 |
| Qiu et al. | * | * | * | * | * | * | * | – | 7 |
| Son et al. | * | * | * | * | ** | * | * | * | 9 |
| Suzuki et al. | * | * | * | * | * | * | * | * | 8 |
| Son et al. | * | * | * | * | ** | * | * | * | 9 |
| Zheng et al. | * | * | * | * | * | * | – | – | 6 |
| Xu et al. | * | * | * | * | ** | * | – | – | 7 |
| Zhang et al. | * | * | * | * | ** | * | * | * | 9 |
| Chen et al. | * | * | * | * | * | * | * | – | 7 |
| Xu 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.

pulmonary comorbidities and increased respiratory complications [22,42]. Therefore, whether LG is suitable for elderly patients with pulmonary comorbidity still remains controversial. However, Li et al. [18] reported the respiratory complication rate was lower in the LG group, although there was no significant difference between the two groups. This result was consistent with the study conducted by Qiu et al. [19]. In a study by Suzukiet al et al. [22], they found the transitory cardiopulmonary adverse effects due to pneumoperitoneum could normalize during the intraoperative period even among decrepit elderly patients with cardiopulmonary disease. Chen et al. [26] reported that the pain caused by a large incision after OG can make it difficult for patients to cough. The reduced pain obtained by LG could also prevent specific pulmonary complications. In the present study, the LG group showed a superior in the incidence of pulmonary complication as compared with OG, but these differences were not statistically significant in the subgroup analysis for elderly group.

To date, it has been unclear whether LG is suitable for patients with pT4a gastric cancer. The surgical and long-term survival outcomes of LG for pT4a gastric cancer have been seldom reported. A retrospective study reported that postoperative complication rate did not differ between the LG and OG groups for patients with confirmed pT4a gastric cancer [20]. Recently, Zhang et al. [25] reported that the postoperative complication rate was 7.2% for patients with pT4a gastric cancer, which is lower than those in the OG group. In this study, our results revealed that LG group was associated with lower overall postoperative complication rate for patients pT4a gastric cancer.

Long-term survival outcome is a key indicator for assessing patients' prognosis. Currently, some retrospective studies have reported that the long-term survival outcomes of patients underwent LG are similar with those treated with OG [30,36,37,43,44]. However, few of them reported the stage-specific survival outcomes of patients in pT4a stage. In this study, 5 included studies reported the OS after LG and OG, and 3 of them performed specific analysis for patients with pT4a stage gastric cancer. The result of our analysis proved the comparable long-term survival outcome between LG and OG for high-risk patients with gastric cancer, especially for patients in pT4a stage.

Obesity has become a serious health problem worldwide [7]. Obese patients were always associated with higher incidence of several surgical complications and it has been confirmed as a risk factor for postoperative complications in patients undergoing gastric cancer surgery [45,46]. Obesity is a challenging issue for LG because of technical difficulties and high conversion rates [21]. Up to now, only two published studies that directly compared LG with OG in obese patients [21,26]. In this meta-analysis, LG group showed lower overall complication rate when compared with OG. Additionally, LG group showed superior in estimated blood loss and postoperative recovery outcomes. These results demonstrated that LG could be safely performed in obese patients.

There are several limitations in the present study. First, all the included studies were retrospective and conducted in single center, which may had bias in patients selection, surgeons experience, and regional differences, etc. Second, high heterogeneity was observed in some outcomes such as estimated blood loss, operative time, time to first flatus, and postoperative hospital stay. Additionally, limited data was available on disease free survival and recurrence outcomes, so we cannot perform further analysis in terms of long-term prognosis. Therefore, Well-designed multicenter RCTs are warranted to reach more definitive conclusions on this topic.

In conclusion, LG has better short-term outcomes and comparable long-term survival when compared with OG. Our study suggests that LG can be a safe and feasible procedure for high-risk patients with gastric cancer.

## Ethical approval

No need Ethical Approval.


## Funding

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## Author contribution

Zhengyan Li, Yan Zhao and Qingchuan Zhao conceived the study and drafted the manuscript. Zhengyan Li and Yan Zhao identified and screened the search findings for potentially eligible studies of the meta-analysis. Yezhou Liu and Deliang Yu independently extracted the data using a unified datasheet, and the Qingchuan Zhao was consulted when controversial issues were presented. Yezhou Liu and Zhengyan 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.

## Conflicts of interest

The authors declare that they have no conflict of interest.

## Research registration number

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## Guarantor

Zhengyan Li.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## Data statement

No data to be made available.

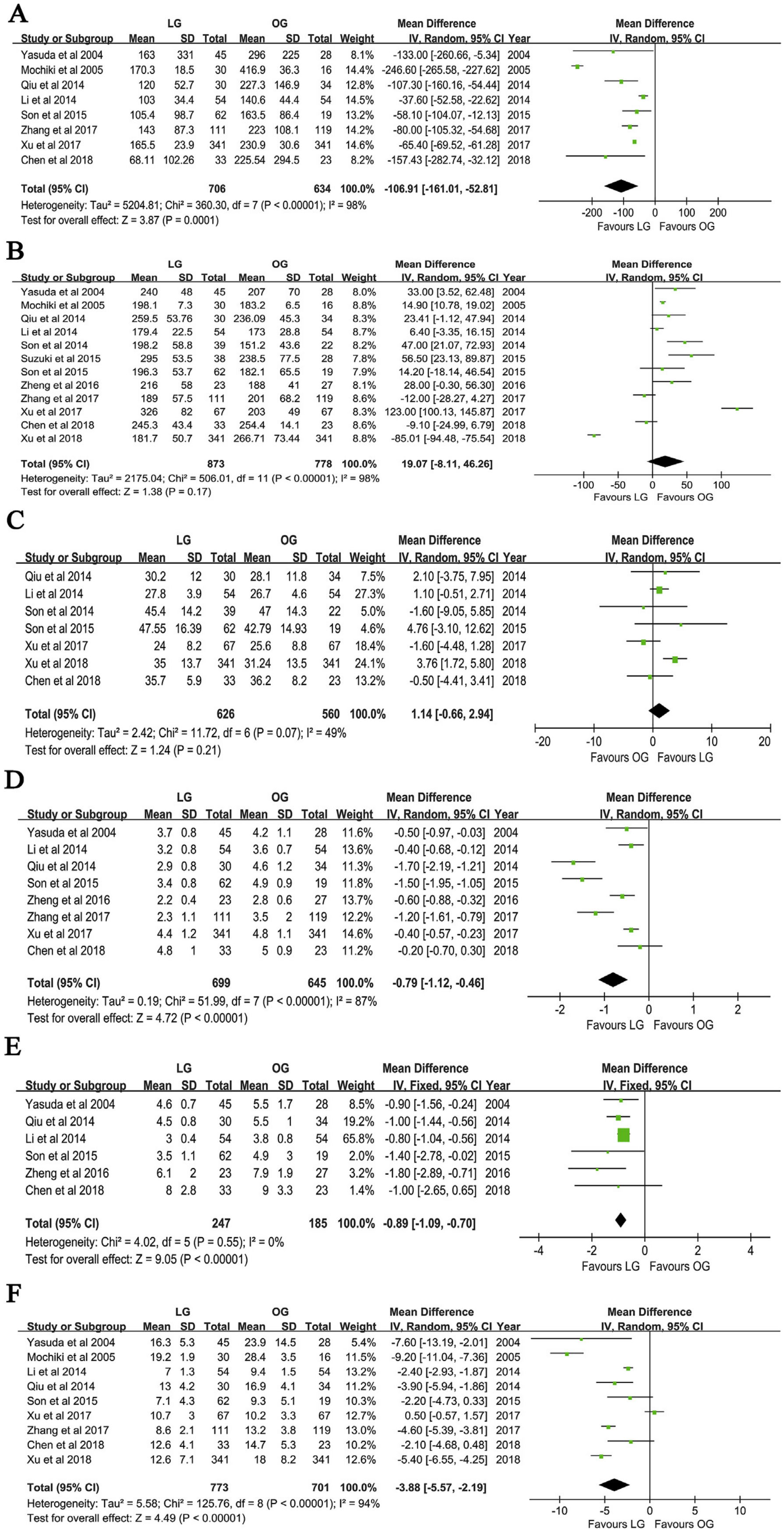


**Fig. 2.** Forest plots for intraoperative outcomes and postoperative recovery. A Estimated blood loss; B operative time; C Number of harvested lymph nodes; D Time to first flatus; E Time to food intake; F Postoperative hospital stay.

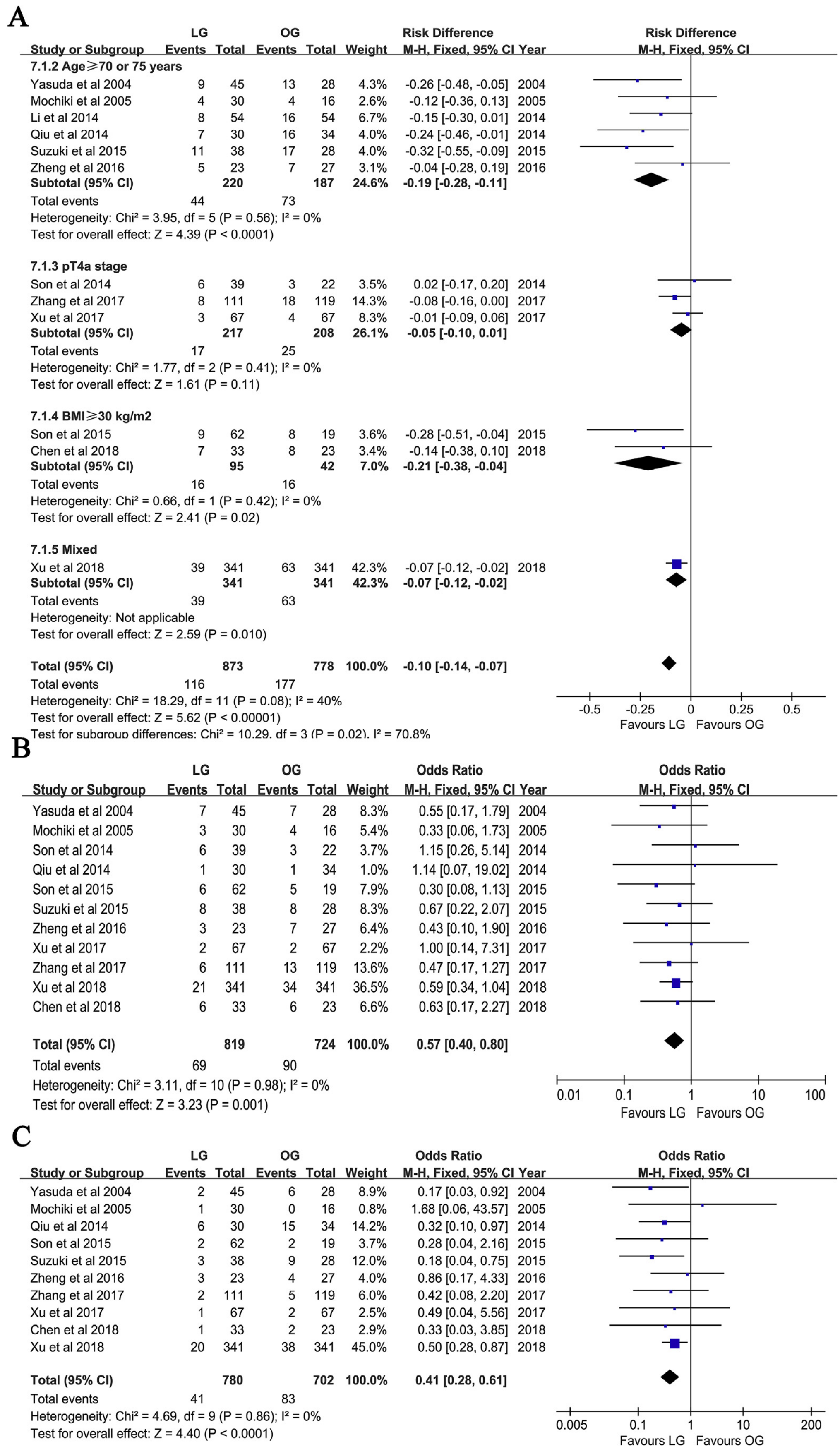


**Fig. 3.** Forest plots for intraoperative outcomes and postoperative recovery. A Estimated blood loss; B operative time; C Number of harvested lymph nodes; D Time to first flatus; E Time to food intake; F Postoperative hospital stay.

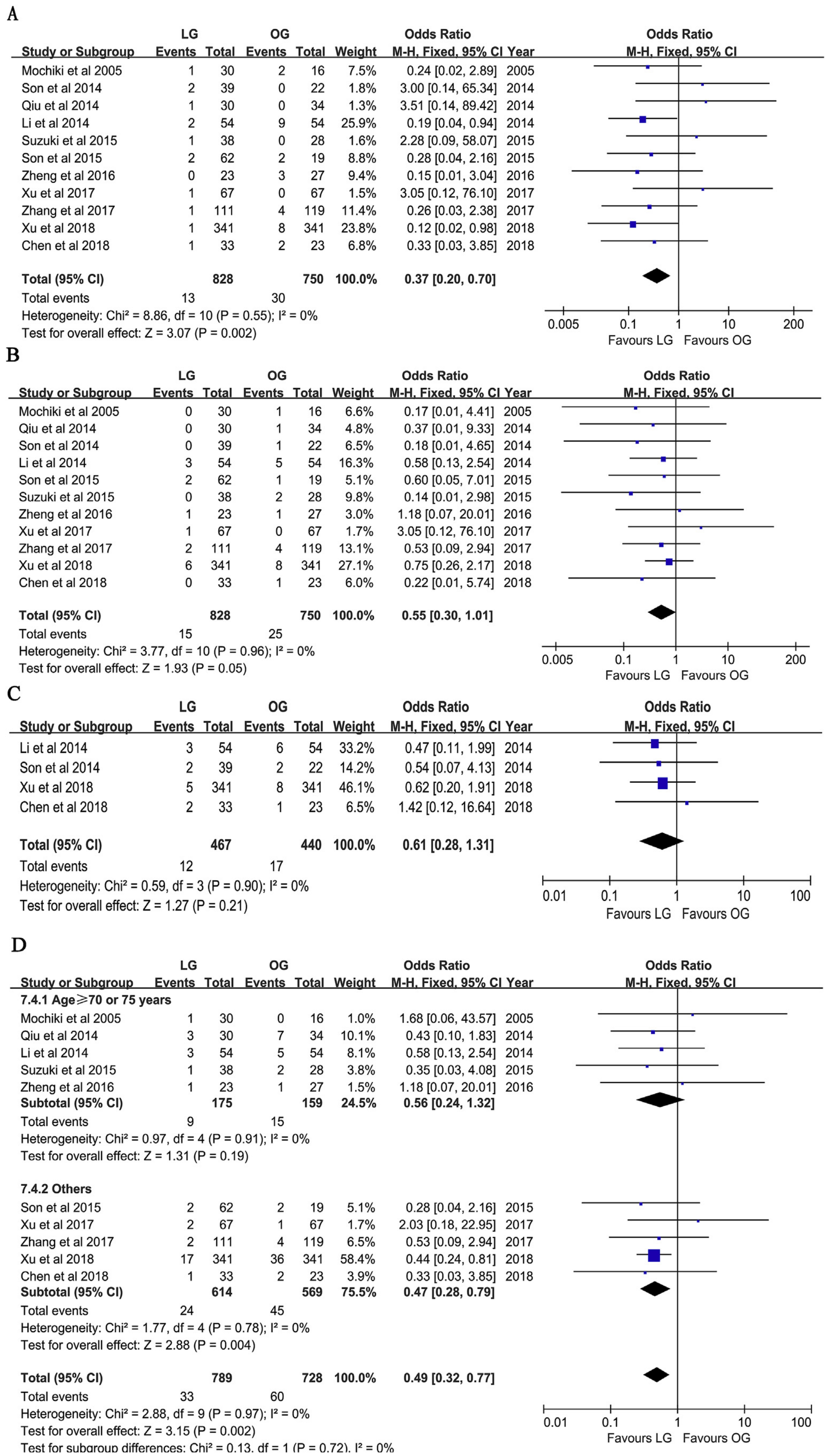


**Fig. 4.** Forest plots for specific complication. A Wound problem; B Anastomotic leakage; C Abdominal abscess; D Pneumonia.

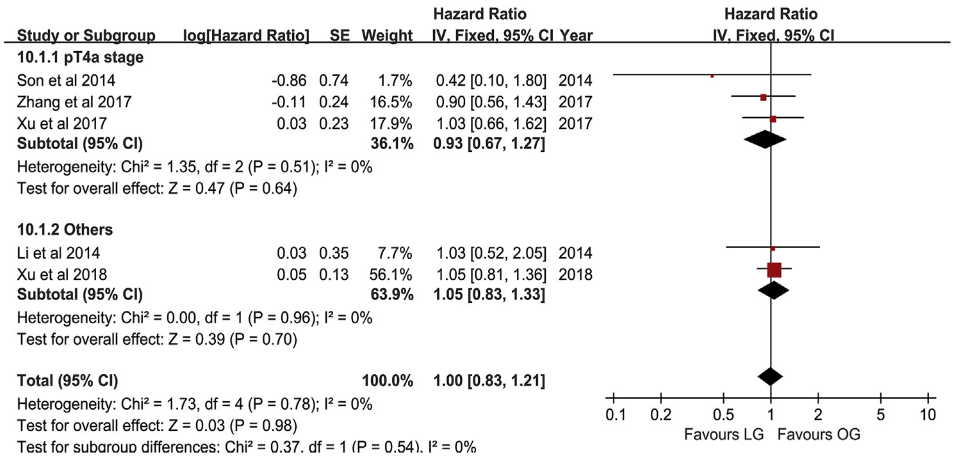


**Fig. 5.** Forest plot for overall survival.

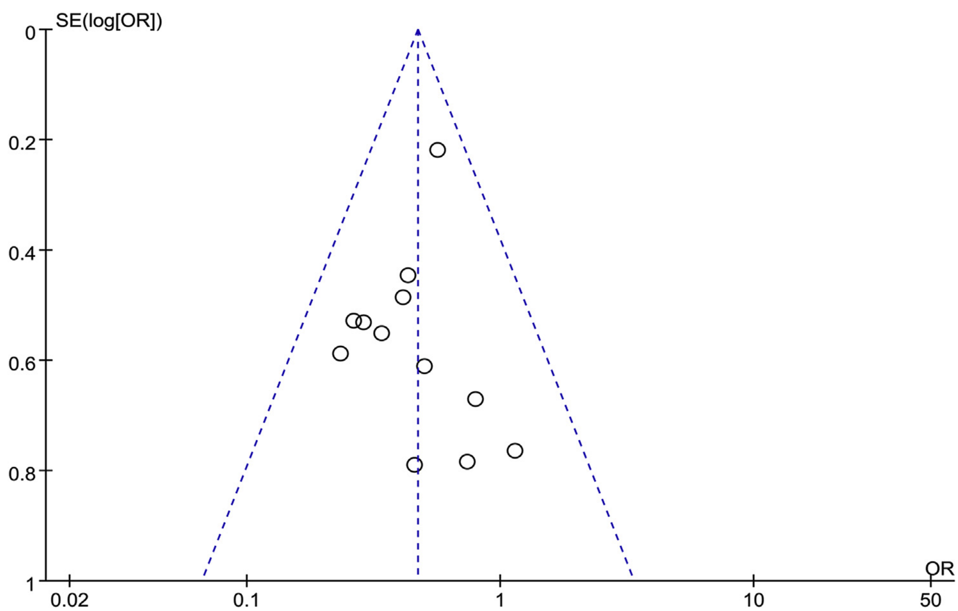


**Fig. 6.** Funnel plots of meta-analysis.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.03.003.

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