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Systematic Review / Meta-analysis

Comparison of postoperative pancreatic fistula between open and laparoscopic surgery in patients with gastric cancer: A meta-analysis

Ahmed A.S. AL-Magedi, Rong Wu, Qingsong Tao *

Department of General Surgery, Affiliated Zhongda Hospital, School of Medicine, Southeast University, No. 87 dingjiaqiao, Nanjing, Jiangsu 210093, China

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ABSTRACT

Background: Open gastrectomy"OG" compared with laparoscopic gastrectomy"LG" in patients with gastric cancer"GC" has been widely discussed over the past years. However, the lack of comparative analysis in postoperative pancreatic fistula "POPF" hinders its severity as surgical procedures developed rapidly. Therefore, there are still moot on whether one of these surgical options is superior in POPF.

Objective: To compare the incidence of POPF in patients undergoing OG and LG for gastric cancer "GC".

Methods: Articles from January 2011 to August 2021 that compared LG and OG for GC were reviewed. Cohort studies were included in our study. The quality of enrolled studies was evaluated. Outcomes regarding POPF complication and relative operation results were analyzed. Statistical analysis portrayed the Weighted mean difference"WMD"and the odds ratio"OR"with a 95% confidence interval "CI". The curative effect was analyzed using RevMan 5.4.1 software.

Results: Totally 7 articles met the inclusion criteria, including 3194 patients with treatment of gastrectomy surgeries for gastric cancer "GC". There was no significant difference observed in POPF incidence (OR, 95% CI = 1.04 [0.74,1.46], P = 0.81) between OG group and LG group in patients undergoing GC gastrectomy.

Conclusion: We stringently explored the current incidence of POPF after GC gastrectomy, comparing its incidence during LG and OG, there was no significant difference between OG and LG in the incidence of POPF, and surgeons should give more concern for improvement in surgical techniques. Further research is still needed to explore the risk of causes and surgical techniques should be considered cautiously in a clinical procedure.

1. Introduction

Gastric cancer "GC" is the fourth leading cause of cancer-related death and the fifth of most common cancer worldwide. According to the Global Cancer Observatory 2020, it remains one of the most serious global health problems after breast cancer 11.7%, lung cancer 11.4%, colorectal cancers 10%, and prostate cancer 7.3% [1]. Surgical resection is still the preferred therapeutic option for patients diagnosed with GC. Over the years, gastrectomy (Open gastrectomy) for gastric cancer remains the cornerstone of the curative approach, however, the rapid development in minimally invasive strategies and medical technology has improved and created new techniques in gastric cancer surgeries. In 1994, Kitano et al. was firstly described the effectiveness of laparoscopic gastrectomy "LG" as a surgical instrument for GC, later on, LG has achieved rapid development and universalities due to minimal invasion, quicker recovery, less time of surgery and less blood loss [2–4].

In spite of the broad application of laparoscopic gastrectomy, whether postoperative complications can totally diminish from this minimally invasive approach as patients with gastric cancer remains controversial. While a good management of postoperative complications increase the opportunity of a faster recovery and alleviate the sufferings of the patient.

One of the complications that may lead a patient's condition to death due to sepsis or the rupture of pseudoaneurysms is Postoperative Pancreatic Fistula "POPF". Its incidence was different across various research centers and regions, and no consensus was reached. Many studies have identified risk factors for POPF, including the type of surgery and stage, pancreatic anatomy, pancreas injuries during

Abbreviations: POPF, Postoperative Pancreatic Fistula; LG, Laparoscopic gastrectomy; OG, Open gastrectomy; GC, Gastric cancer; CI, Confidence interval; HR, Hazard ratio; OR, odds ratio; MD, Mean difference; WMD, Weighted mean difference; RCT, Randomized controlled trials; PSM, Propensity score matching; LN, Lymph nodes.

* Corresponding author.
E-mail addresses: gedi@seu.edu.cn (A.A.S. AL-Magedi), rwu@seu.edu.cn (R. Wu), qstao@seu.edu.cn (Q. Tao).

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peripancreatic and suprapancreatic lymphadenectomy, and cardiovascular comorbidities [5–8].

In the present study, we reviewed 7 articles with open versus Laparoscopic surgery for GC, we stringently explored the current incidence of POPF after gastric cancer gastrectomy. Further sophistication of surgical techniques would give a great promise in reducing POPF after GC gastrectomy.

2. Methods

2.1. Literature search strategy and selection criteria

We searched PUBMED, Web of Science, EBSCO and EMBASE databases, Studies published from January 2011 to August 2021, using the following combined search terms: "Laparoscopic and Open Gastrectomy", "Gastric Cancer", "Gastrectomy", "Postoperative Pancreatic Fistula" and "Postoperative Complication".

Studies selection criteria was based on the following: (1) study design, prospective and retrospective cohort studies (meta-analysis, RCT, case-control studies and reviews studies were excluded); (2) if the same study group has published 2 or more articles, article with the largest sample size or the recent published was included; (3) studies published in English (other languages were excluded); (4) participants, patients undergoing gastric cancer gastrectomy; (5) interventions, surgical operation comparing LG with OG gastrectomy (studies reporting mixed data including pancreas tail resection, pancreaticosplenectomy and Robotic gastrectomy were excluded); and (6) outcomes, Primary outcomes are (a) postoperative pancreatic fistula, (b) number of lymph nodes harvested, and (c) total complications. Secondary outcomes are (d) intraoperative blood loss, and (e) operative time. Studies were excluded if no full text available or did not satisfy the inclusion criteria.

2.2. Data extraction and quality assessment

Two authors evaluated the included studies excluding duplication or irrelevant studies. Any divergences were solved by discussion. The data were extracted including: study type, gastrectomy type, number of cases in each group (OG and LG), mean age, primary and secondary outcomes include: POPF, total complications, number harvested lymph nodes in surgery, intraoperative blood loss, and operative time. Studies quality was estimated using Newcastle-Ottawa Scale assessment "NOS" [9] Table 1, while our study has been reported in line with the PRISMA criteria [10], and been evaluated using AMSTAR 2 criteria [11]. Also, it has been registered at Research Registry® with registration ID: reviewregistry1327 [12].

Table 1
Newcastle-Ottawa Scale assessment [9].

Article	1 Selection				2 Comparability	3 Outcome			Total
	A	B	C	D	E	F	G	H	
Etoh,T, 2018 [13]	*	*	*	*	**	*	–	*	8
Kinoshita, 2019 [14]	*	*	*	*	**	*	*	*	9
Yamamoto, 2019 [15]	*	*	*	*	**	*	*	*	9
Bofei Li, 2020 [16]	*	*	*	*	**	*	*	*	9
Panduro-Correa, 2020 [17]	*	*	*	*	**	*	*	*	9
Zhao, 2020 [18]	*	*	*	*	**	*	*	*	9
Kiudelis, 2021 [19]	*	*	*	*	**	*	*	*	9

1 Selection: A. Representativeness of exposed cohort; B. Selection of non-exposed cohort; C. Ascertainment of exposure; D. Demonstration that outcome of interest was not present at start of study.
2 Comparability: E. Comparability of cohorts on the basis of the design or analysis.
3 Outcome: F. Assessment of outcomes; G. Follow-up long enough for outcomes to occur; H. Adequacy of follow-up.

3. Statistical analysis

Statistical calculations were conducted using RevMan 5.4.1 version; statistical heterogeneity was evaluated using I^2 and P value. For the low heterogeneity ($I^2 \leq 50\%$ and $P \geq 0.1$), a fixed effects model was used, while a random effects model (M − H, Random,95%CI) was used in other outcomes with high heterogeneity ($I^2 > 50\%$ or $P < 0.1$). Weighted mean difference "WMD" with 95% confidence interval "CI" was calculated for continuous outcomes, while odds ratio "OR" with 95% CI for dichotomous variable. P value less than 0.05 ($P < 0.05$) was considered statistically significant.

4. Results

4.1. Characteristics of included studies

Our search yielded 153 articles, searched PUBMED, Web of Science, EBSCO and EMBASE databases. We excluded 146 articles with reasons e.g.: (22 Studies with duplicate, 15 reviews, 27 Meta-analysis, 4 RCT, 10 articles written in Chinese, and 46 articles with only one type of gastrectomy (OG or LG) data. Finally, 7 original articles compared OG with LG for patients with GC gastrectomy were eligibly included in this analysis [13–19]. Fig. 1 present search steps detail.

Table 2 Shows the characteristics of articles included in our study, which were published from January 2011 to August 2021. A total of 3194 cases with gastric cancer undergoing gastrectomy surgeries were included in our study, distributed as 1669 cases in OG group and 1525 cases in LG group.

4.2. POPF

The pooled analysis of the seven studies showed no significant difference in POPF incident in two groups (OG and LG) (OR, 95% CI = 1.04 [0.74, 1.46], P = 0.81) Fig. 2. A.

4.3. Overall outcomes

Overall postoperative complication rate and intraoperative blood loss were significantly lower in LG group than OG group (OR, 95% CI = 1.45 [1.02, 2.06], P = 0.04; Fig. 2 B) and (WMD, 95% CI = 203.62 [87.25, 320.00], P = 0.0006; Fig. 2. C) respectively.

Operative time (WMD, 95% CI = −62.46 [-118.62, −6.29]; P = 0.03; Fig. 2. D) and number of harvested lymph nodes intraoperative (WMD, 95%CI = −3.72 [-7.08, −0.36], P = 0.03; Fig. 2. E) were superior in OG group.

5. Discussion

As compared to open gastrectomy, laparoscopic gastrectomy has been adopted widely due to its advantages in minimal invasiveness [20–22]. Many research has confirmed that laparoscopic surgery was found to be contributed to less intraoperative blood loss, earlier recovery after surgery, lower postoperative complications, and less overall hospital stay as compared with OG [23,24]. However, it remains unclear if the application of LG for Advanced gastric cancer (TNM stage II B and above) and/or high-risk patients can be safe and efficient [17,25]. Meantime, the surgical efficacy of LG is still a major concern of surgeons.

Since our study was aimed to compare the incidence of POPF in patients undergoing OG and LG for GC, we decided to analyze total, subtotal and distal gastrectomy altogether, due to the small number of cases in each type of gastrectomy and the shortage of reported data on

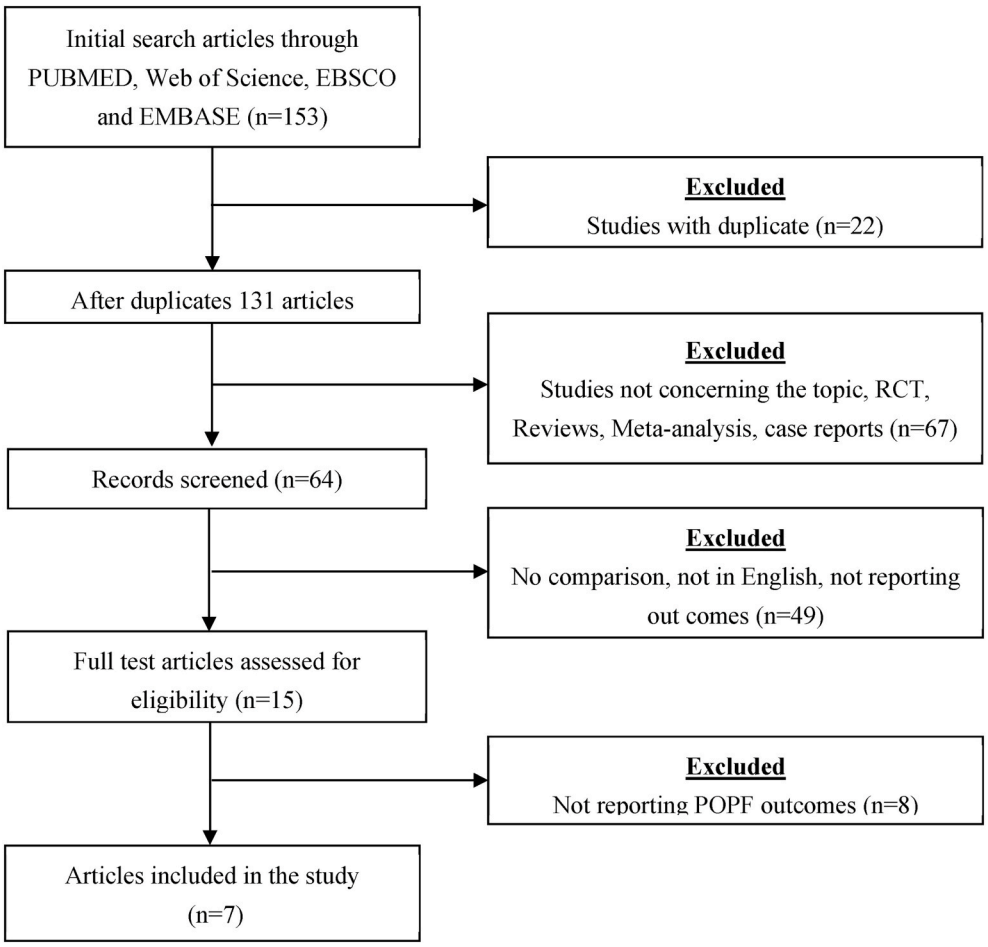

Fig. 1. Study's Flow diagram

POPF.

We found that LG did not seem to differ significantly from the OG regarding POPF parameters and this result might have been influenced by surgeons' experience, intraoperative harvesting of lymph nodes, and technical constrains. However, postoperative pancreatic fistula is mainly caused due to invasive operative procedures. Many studies are still discussing whether LG can dissect the peripancreatic and supra-pancreatic lymph nodes safely, more importantly, improvement of lymphadenectomy procedures for preventing pancreas injury which might lead to POPF as gastrectomy with D2 lymphadenectomy is presently the recommended procedure for gastric cancer patients [22, 25–29].

In other words, the utmost caution should be paid to prevent pancreas injury during lymph node dissection or by forceps and energy devices compression while expanding the operative field or displacing the pancreas. Also, we believe that a high-skilled laparoscopic surgeon with high-quality laparoscopic instruments and a magnified view is a remarkable factor to achieve the aim of gastric resection favorably.

In addition, our study verified that overall postoperative complication favored LG over OG for patients with GC, as a result of the improvement and refinement of laparoscopic surgical techniques in recent years. Also, a lower blood loss of LG was significantly superior to OG, and that may be related to the meticulous hemostasis and dissection under a magnified view of laparoscopic surgical instruments, which promotes effective prevention of excessive disruptions or unexpected bleeding.

However, operative time was shorter in OG than LG, as it was reported in many studies previously [23,30], which maybe related to the type of gastrectomies, operation process, technically challenging, surgeon's level of proficiency and lymph node dissection, etc. Although we found that the number of harvested lymph nodes during OG was superior to LG, this result is different from the data by N.A.G. Hakkenbrak et al. [31] and M. Chen et al. [32] that reported similar harvested number of lymph nodes, but it is similar to the study by C.-D. Zhang et al. [33] and Y. Liang et al. [34] that reported significant reduction in lymph nodes harvested. In this meta-analysis, the number of harvested lymph nodes was >30 in both OG and LG, which may be sufficient for gastric cancer but it is still unclear whether it was related to the high incidence of POPF [13–15]. Further studies are still needed for verification, while laparoscope may be favored in lymph nodes retrieval due to the magnified view that it provides.

6. Limitations

The present study has certain limitations. First, all studies we used were prospective and retrospective cohort studies and no RCTs, which may cause patients selection bias and/or surgeons' experience bias. Second, heterogeneity ($I^2 > 50\%$ or $P < 0.1$) was high in some outcomes analyses e.g. intraoperative blood loss and operative time. Additionally, some data was in median and significantly skewed away from normality after converting the median percentile range to Mean ± SD, which could cause bias against the outcomes, hence were excluded from the analysis. Therefore, surgical RCT articles are recommended for such topics.

7. Conclusion

In conclusion, OG and LG have no significant difference in POPF after gastrectomy, while LG has better and comparable overall outcomes

Table 2
Summarizes the characteristics of included articles.

Author, Year	Country	Type of study	Participants					Surgical procedure	
			Total	(after PSM)	OG, n (%)	LG, n (%)	age	Type of gastrectomy	D2 Lymphadenectomy, n(%)
Etoh,T, 2018 [13]	Japan	PSM, prospective cohort study	2494	1024	512	512	68 ± 11.1	Total G	–
Kinoshita, 2019 [14]	Japan	PSM, multicenter historical noninferiority cohort study.	1824	610	305	305	67.1 ± 4.6	Distal G, Total G, other	130 (42.6)/138 (45.2)
Yamamoto, 2019 [15]	Japan	Single-institution PSM, prospective study	1131	690	345	345	60.4 ± 9.8	Distal G or Total G, other	–
Bofei Li, 2020 [16]	Hong Kong	PSM, prospective cohort study	294	108	54	54	69.1 ± 9.11	Distal G, Total G, Proximal G	95 (87.96)
Panduro-Correa, 2020 [17]	Peru	Retrospective cohort study	482	475	236	239	66.7 ± 8.1	Total G, Subtotal G	315 (66.3)
Zhao, 2020 [18]	China	Retrospective study	175	151	121	30	66.1 ± 10.6	Distal G, Total G, Proximal G	–
Kiudelis, 2021 [19]	Lithuania	Retrospective non-randomized, single-centre, cohort study	175	136	96	40	67.4 ± 11.1	Total G, Subtotal G	–

Author, Year	no. of complications, n(%)			POPF Incidence rate, n (%)		Other outcomes (Mean ± SD)		
	Total	OG	LG	OG	LG	Operative time(min) OG/LG	Blood loss (mL) OG/LG	LN retrieved OG/LG
Etoh,T, 2018 [13]	230 (22.46)	128 (25)	102 (19.9)	19 (3.7)	14 (2.7)	[a] 254 (178–369) /352 (255–517)	[a] 342 (100–961) /80 (10–460)/	[b] 40.4 ± 44.54 /41.7 ± 40.09
Kinoshita, 2019 [14]	179 (29.34)	92 (30.16)	87 (28.52)	18 (5.9)	27 (8.9)	[b] 228 ± 82.6/ 365 ± 134.5	[b] 396 ± 362.8 /140 ± 219.	[b] 34 ± 14.86/ 43.7 ± 17.83
Yamamoto, 2019# [15]	88 (15.9)	47 (17.0)	41 (15.0)	14 (5.1)	13 (4.7)	322.3 ± 102.5/336.7 ± 85.6	423.4 ± 329.8/153.0 ± 187.0	34.92 ± 18.24/40.65 ± 19.89
Yamamoto,2019* [15]	35 (25.36)	20 (29.0)	15 (21.7)	0	0	312.4 ± 114.0/337.6 ± 67.0	477.8 ± 489.8/137.0 ± 134.9	30.09 ± 16.06/37.42 ± 19.42
Bofei Li, 2020 [16]	41 (37.96)	22 (40.7)	19 (35.2)	0	1 (1.9)	231.8 ± 61.2 /294.7 ± 96.4	351.0 ± 264.3/191.6 ± 235.1	47.6 (18.4) /46.9 (20.4)
Panduro-Correa, 2020 [17]	143 (30.1)	103 (43.64)	40 (16.74)	18 (7.63)	12 (5.02)	280.0 ± 40.0 /430.0 ± 40.0	–	–
Zhao, 2020 [18]	31 (20.53)	24 (19.8)	7 (23.3)	1 (0.83)	0	211.3 ± 66.7 /211.6 ± 52.1	168.5 ± 80.1 /132.3 ± 98.5	19.6 ± 7.7/ 21.4 ± 6.8
Kiudelis, 2021 [19]	45 (33.1)	34 (35.42)	11 (27.5)	2 (2.1)	0	234.4 ± 50.9 /279.0 ± 78.2	–	25.9 ± 11.6/ 25.1 ± 9.6

PSM: Propensity score matching; LN: Lymph nodes.
Same study with two subgroups, #aged<75 years (non-E group), *aged<75 years (E group).
[a] **Data were excluded**, the data were significantly skewed away from normality after changed median percentile range (10–90) to Mean ± SD [35–37].
[b] **Data were included** after converted median percentile range (10–90) to Mean ± SD, The data were no significant evidence to show that the data are skewed [35–37].

when compared with OG, thus the application of laparoscopy has attracted more and more attention. A prospective trial is currently underway from our department to establish the incidence of POPF after gastrectomy for patients with gastric cancer. Further high-quality meta-analysis of surgical RCTs is still needed, and surgical techniques should be considered cautiously in the future clinical procedure.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Ethical approval

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Author contribution

The three authors participated in the study. Conception and design of the research, acquisition analysis and interpretation of the data, statistical analysis.

Author A.A.S.A contributed to the drafting of the manuscript.

Author Q.S.T contributed to the revision of the manuscript.

Registration of research studies

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Corresponding author: **Qingsong Tao** (E-mail: qstao@seu.edu.cn), Department of General Surgery, Affiliated Zhongda Hospital, School of Medicine, Southeast University, 87 Dingjiaqiao Road, Nanjing, Jiangsu 210093, China.

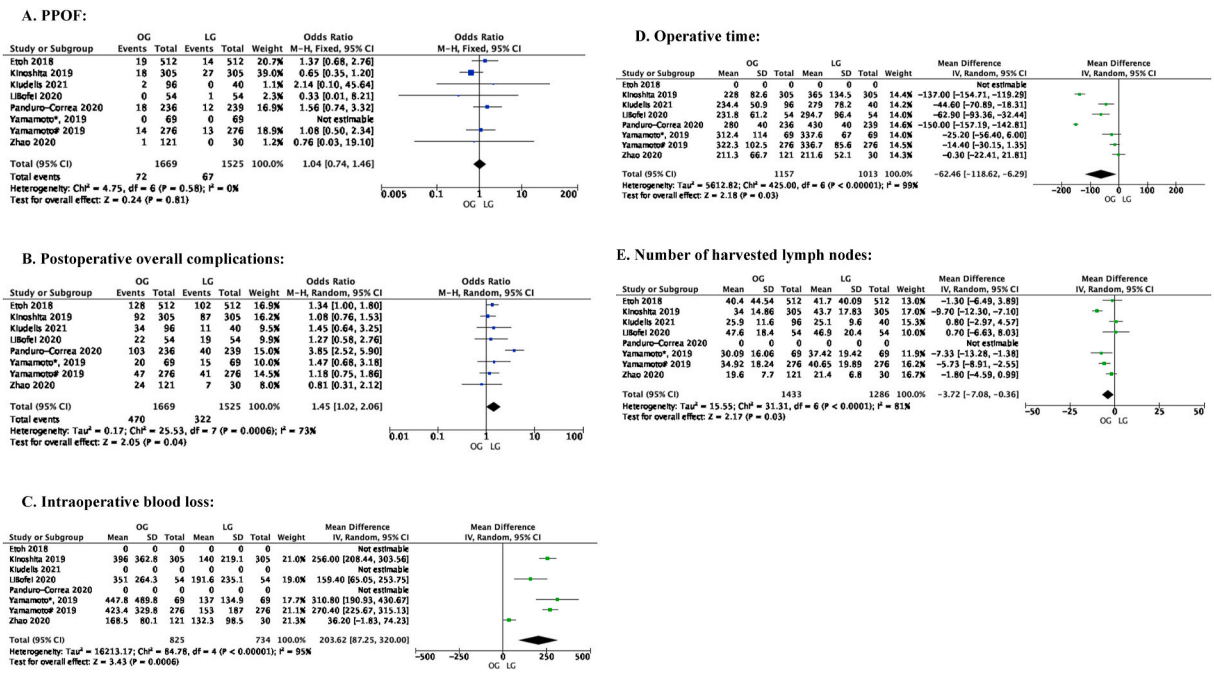

Fig. 2. Forest plots for outcomes.

Consent

NA.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103558.

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