Systematic Review and Meta-Analysis

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Laparoscopic gastrectomy for elderly patients with gastric cancer

A systematic review with meta-analysis

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Abstract

Background: Laparoscopic gastrectomy (LG) has been widely applied in patients with gastric cancer (GC). However, the safety and application value of LG in elderly patients with GC was still unclear. In this study, we aimed to evaluate the feasibility and safety of LG for elderly patients with GC using the meta-analysis.

Methods: Studies comparing elderly patients and nonelderly patients who underwent LG for GC were reviewed and collected from the PubMed, EBSCO, Cochrane Library, and EMBASE. Outcomes such as operative results, postoperative recovery, and morbidity were compared and analyzed. The Review Manager 5.3 was used to portray the weighted mean difference (WMD) and odds ratio (OR) with a 95% confidence interval (CI).

Results: Eleven observational studies with a total of 3275 patients were included. Compared with nonelderly patients, elderly patients had shorter operation time (WMD −10.46; 95% CI −17.06 to −3.86; $P=.002$), less retrieved lymph nodes (WMD −2.34; 95% CI −3.77 to −0.92; $P=.001$), delayed time to first flatus (WMD 0.31; 95% CI 0.10–0.51; $P=.003$), longer postoperative hospital stays (WMD 1.06; 95% CI 0.07–2.05; $P=.04$), higher risk for overall postoperative complication (OR 1.34; 95% CI 1.08–1.67; $P=.009$), nonsurgical postoperative complication (OR 1.98; 95% CI 1.24–3.15; $P=.004$), and postoperative pulmonary complication (OR: 3.09; 95% CI 1.68–5.68; $P<.001$). There was no significance between nonelderly patients and elderly patients regarding the estimated blood loss, incidences of surgical postoperative complication, surgical site infection, and ileus ($P>.05$).

Conclusion: Outcomes of LG for elderly patients were comparable to those in nonelderly patients. Age alone should not preclude LG in elderly patients.

Abbreviations: CI = confidence interval, GC = gastric cancer, LG = laparoscopic gastrectomy, OR = odds ratio, PPC = postoperative pulmonary complication, SD = standard deviation, WMD = weighted mean difference.

Keywords: elderly patients, gastric cancer, laparoscopic gastrectomy, meta-analysis

1. Introduction

Gastric cancer (GC) represents one of the leading causes of cancer-related death worldwide, especially in Japan, Korea, and China.[1–3] Gastrectomy with adequate lymph node dissection remains the mainstay of radical treatment for GC. Laparoscopic gastrectomy (LG) has been gradually accepted since first reported in 1994 by Kitano et al.[4] Several randomized trials and meta-analysis have proved the feasibility and surgical safety of LG, along with its advantages including milder surgical trauma, faster recovery, better cosmesis, etc.[5–8]

Amount of elderly patients diagnosed with GC continues increasing. For the elderly patients with GC, proper treatments are necessary to prong the survival time and improve the quality of life. Despite this, there was limited attention focused on the elderly patients with GC. Old age was considered as a risk factor for surgical safety. Opposed to the nonelderly patients, elderly patients usually suffer comorbidities and have poor functional capacities that may not allow them to endure the severe surgical trauma. Several studies have addressed gastrectomy could be carried out in elderly patients for GC safely. This should not be considered as a contraindication.[9–11] Although, the impact of old age on patients who underwent LG is still unclear. There are also a few of studies attempting to examine the feasibility and safety of the application of LG in the elderly patients, the majority of them were noncomparative or had sample sizes which were too small to transfer their evidence to an actual group.

In our study, we aimed to evaluate the feasibility and safety of LG for elderly patients with GC by comparing the nonelderly

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YP and KC equally contributed to this work.

Ethics statement: There is no need to seek informed consent from patients, since this is a meta-analysis based on the published data, without any potential harm to the patients.

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patients with respect to operative data, postoperative recovery, and postoperative morbidity.

2. Methods

2.1. Literature search

The meta-analysis was performed in accordance with the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses.[12] A comprehensive search was conducted in the PubMed, EBSCO, Cochrane Library, and EMBASE to identify articles comparing the elderly patients with nonelderly patients who underwent LG for GC. The latest search was conducted in September 2016. The search strategy was as following ((((gastric adenocarcinoma) OR gastric cancer)) AND ((laparoscopic) OR laparoscopy)) AND (((age) OR elderly) OR old). A manual search was also performed using "related artciles" and the reference lists of the retrieved articles to identify other potential studies. The language was limited to English.

2.2. Selection criteria

Eligibility criteria for the study included the following: all patients were confirmed to have GC, studies compared the elderly patients and nonelderly patients who underwent LG for GC, and availability of data on information of at least 3 outcome measures. Exclusion criteria included the following: open gastrectomy, hand-assisted gastrectomy, or robotic gastrectomy; including GC with distant metastasis or recurrent GC; abstracts presented at meetings, review articles, case report, or letters; and duplicated studies.

2.3. Data extraction and quality assessment

Data were independently extracted by (KC and WHY) using a standard form. Disagreements were discussed and a consensus was reached. The following data were extracted: study name, study period, sample size, mean age, mean body mass index, preoperative comorbidity, extent of lymph node dissection, tumor size, operation time, intraoperative blood loss, number of harvested lymph nodes, length of postoperative hospital stay, and postoperative complications. The qualities of studies were evaluated using the Newcastle-Ottawa Quality Assessment Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Studies with a score higher than 5 stars were included. Postoperative complications were classified into 2 categories, surgical and nonsurgical complication as defined by Jung et al.[13]

2.4. Statistical analysis

The means and standard deviations (SDs) were estimated using the method described by Hozo et al[14] in the studies with medians and ranges instead of means and SDs. Dichotomous variables were analyzed using the odds ratio (OR) with 95% confidence intervals (CIs). Continuous variables were assessed using weighted mean differences (WMDs) with a 95% CI. Statistical

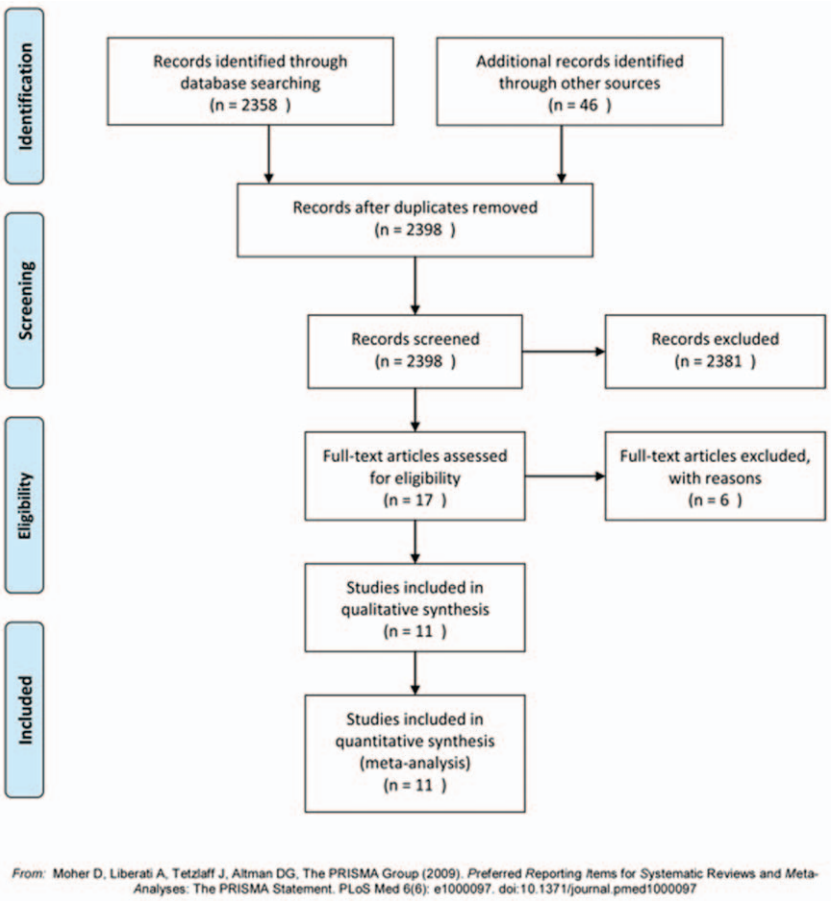

Figure 1. Flow chart of the studies included in the meta-analysis.

Table 1

The basic characteristics of included studies.

Study	Period	Country	Sample size		Gender (M/F)		Mean age, y		BMI, kg/m^2		Comorbidity, %		Extent of LND (D1 or D1+/D2), %		Age cutoff point
			E	NE	E	NE	E	NE	E	NE	E	NE	E	NE	
Cho et al	1998–2005	Korea	226	890	142/84	585/305	73.7	58.4	23.2	23.6	54.0	37.9	44.7/55.3	43.2/56.7	70
Fujisaki et al	2007–2014	Japan	70	123	44/26	79/44	80.1	64.8	22.3	22.6	NR	NR	65.7/34.3	62.6/37.4	75
Hwang et al	2003–2007	Korea	117	515	78/39	328/188	74.12	55.6	23.3	23.7	75.2	37.7	80.7/19.3	81.7/18.3	70
Kim EJ et al	2005–2010	Korea	93	223	61/32	137/86	70.2	51.3	22.7	22.9	65.6	39.0	62.5/37.5	60.0/40.0	65
Kosuga et al	2002–2013	Japan	55	237	35/20	145/92	79.5	60.5	22.2	22.8	61.8	43.0	98.2/1.8	92.0/8.0	75
Kouzu et al	2010–2014	Japan	25	77	20/5	56/21	NA	NA	20.4	22.3	84.0	41.6	72.0/28.0	50.6/49.4	75
Kunisaki et al	2000–2007	Japan	26	104	21/5	64/40	78.8	60.8	22.7	22.5	53.8	22.1	96.2/3.8	93.3/6.7	75
Mochiki et al	1998–2004	Japan	30	73	20/10	49/24	75.2	56.6	NA	NA	43.0	5.4	100/0	100/0	70
Mohri et al	1992–2011	Japan	71	139	52/19	84/55	76.6	58.5	22.9	22.6	63.4	35.2	85.9/14.1	78.2/20.2	70
Suzuki et al	2000–2011	Japan	38	41	28/10	27/14	78.5	58	22.5	22.6	73.7	29.3	94.7/5.3	91.2/9.8	75
Yasuda et al	1994–2003	Japan	45	57	26/19	33/24	75.7	59.5	NA	NA	55.6	28.1	100/0	100/0	70

BMI = body mass index, E = elderly, F = female, LND = lymph node dissection, M = male, NE = nonelderly, NA = not available.

heterogeneity was evaluated using methods described by Higgins et al.[15] I^2 values between 0% and 25% suggest low heterogeneity, values above 25% suggest moderate heterogeneity, and values above 75% suggest high heterogeneity. Pooled effects with low heterogeneity were calculated by using the Mantel–Haenszel test for fixed-effects models,[16] while those with moderate or high heterogeneity used the DerSimonian and Laird test for random-effects models.[17] The potential publication bias based on the overall postoperative complications was assessed by conducting the funnel plots. Subgroup analysis was performed based on the cutoff of ages. Data analysis was performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). $P < .05$ was considered statistically significant.

3. Result

3.1. Study characteristics

The search strategy initially retrieved 2358 hits. After exclusion of irrelevant studies by screening abstracts, full texts of 17 potentially relevant articles were obtained for assessment. Six studies were excluded due to overlapping data, statistical data unavailable, or noncomparative studies. Eleven studies were included eventually.[18–28] The PRISMA flowchart of literature review is shown in Fig. 1.

The characteristics of the included studies were summarized in Table 1. A total of 3275 patients from Japan and Korea were pooled in this meta-analysis: 796 patients were in the elderly group and 2479 in the nonelderly group. Patients who were more than 70 years old were categorized as elderly patients in 5 studies,[19,21,23,26,28] more than 65 years old in one studies,[25] and more than 75 years old in 5 studies.[18,20,22,24,27] According to the Newcastle-Ottawa Quality Assessment Scale, all 11 studies were achieved no less than 6 stars, Table 2.

3.2. Intraoperative outcomes

All 11 pooled studies reported the operation time. Compared with nonelderly patients, elderly patients had shorter operation time (WMD −10.46; 95% CI −17.06 to −3.86; $P = .002$; Fig. 2A). According to 10 studies reporting estimated blood loss, our meta-analysis found there was no difference between elderly and nonelderly patients (WMD: −6.05; 95% CI: −42.18–30.07; $P = .74$; Fig. 2B). Moreover, elderly patients achieved less lymph nodes compared with nonelderly patients (WMD −2.34; 95% CI −3.77 to −0.92; $P = .001$; Fig. 2C).

3.3. Postoperative outcomes

The first flatus postoperatively in elderly patients was delayed (WMD.31; 95% CI 0.10–0.51; $P = .003$; Fig. 3A). Longer postoperative hospital stays were observed in elderly patients (WMD 1.06; 95% CI 0.07–2.05; $P = .04$; Fig. 3B).

Table 2

The qualities of included studies evaluated using the Newcastle-Ottawa Quality Assessment Scale.

Study	Selection 1. Representativeness of exposed cohort 2. Selection of nonexposed cohort 3. Ascertainment of exposure 4. Outcome not present at the start of the study	Comparability	Outcomes 1. Assessment of outcomes 2. Length of follow-up 3. Adequacy of follow-up	Total
Cho et al	****	*	*	******
Fujisaki et al	****	**	*	*******
Hwang et al	****	**	*	*******
Kim et al	****	*	*	******
Kosuga et al	****	**	*	*******
Kouzu et al	****	*	*	******
Kunisaki et al	****	*	***	********
Mochiki et al	****	*	***	********
Mohri et al	****	*	***	********
Suzuki et al	****	**	**	********
Yasuda et al	****	*	*	******

* 1 Score.

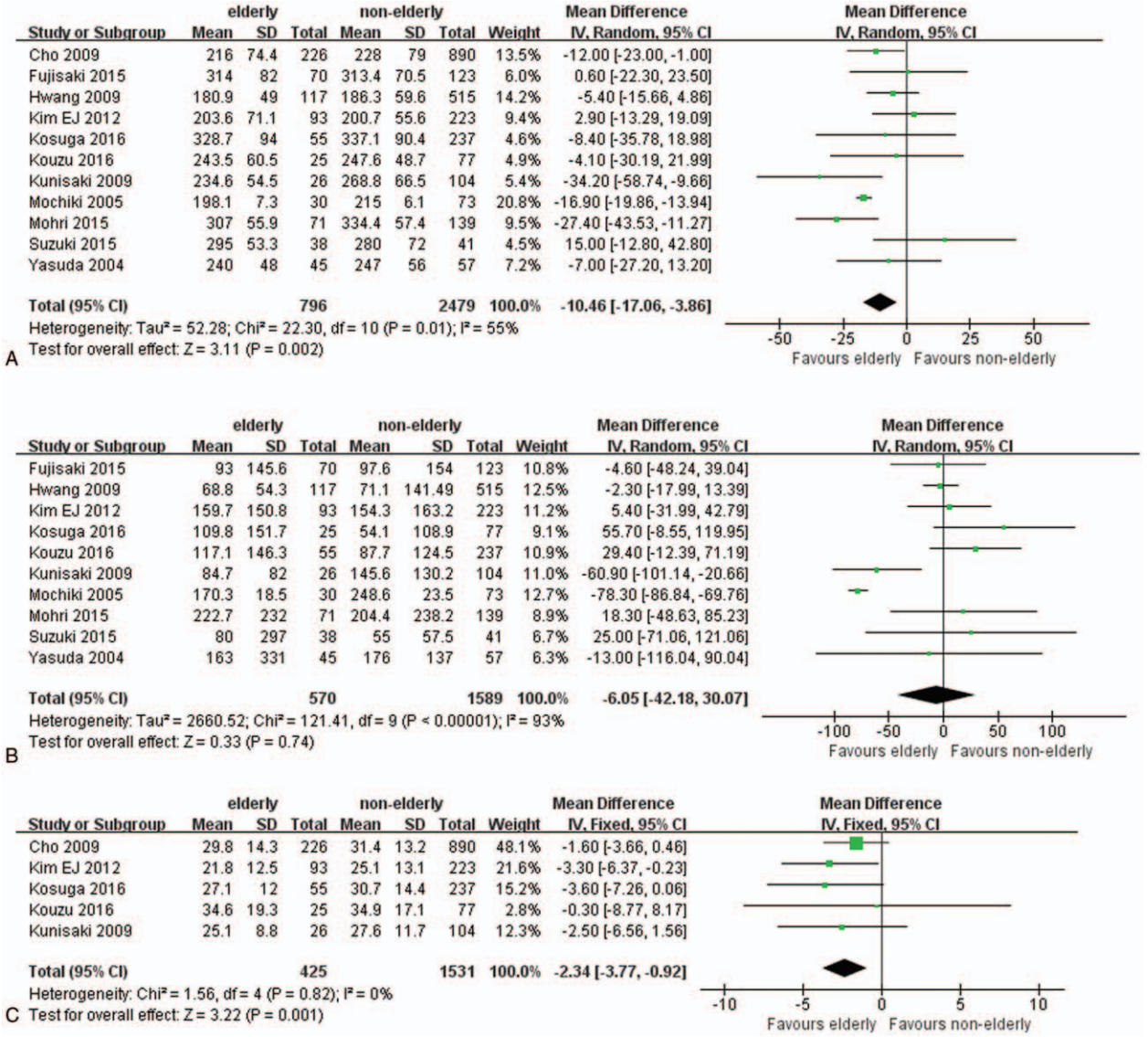

Figure 2. Forest plots of operative outcomes: (A) operation time, (B) estimated blood loss, and (C) number of retrieved lymph nodes.

Postoperative complications were recorded in all studies, Table 3. Elderly patients had higher risk for overall postoperative complication (OR 1.34; 95% CI 1.08–1.67; $P=.009$; Fig. 4A). As for surgical complications, there were no significant differences between 2 groups (OR: 1.20; 95% CI 0.94–1.53; $P=.14$; Fig. 4B). Nonsurgical postoperative complication significantly increased in elderly patients (OR 1.98; 95% CI 1.24–3.15; $P=.004$; Fig. 4C). Further analysis revealed an association between higher postoperative pulmonary complication (PPC) rate and the elderly patients (OR: 3.09; 95% CI 1.68–5.68; $P<.001$; Fig. 4D). Incidences of surgical site infection (OR: 1.47; 95% CI 0.98–2.21; $P=.06$; Fig. 4E) and ileus (OR: 1.24; 95% CI 0.44–3.51; $P=.68$; Fig. 4F) were comparable in elderly patients and nonelderly patients.

The extents of lymph node dissection were comparable between elderly and nonelderly patients in each included studies, as showed in Table 3. Moreover, 3 included studies reported the long-term outcomes, which revealed similar overall survival rates and disease-free survival rate between elderly and nonelderly patients (Table 3).

3.4. Sensitivity analysis, subgroup analysis, and publication bias

Sensitivity analyses were conducted by excluding the highest weighted study in each pooled analysis. In addition, further analyses were conducted by exclusion of the studies by due to the unbalance of surgical extent between the elderly patients and nonelderly patients.[21,27] These exclusions did not alter the results obtained in cumulative analyses. Subgroup analysis based on the cutoff of age showed similar trends as the overall effects. Details of subgroup analysis were showed in Table 4. A funnel plot based on the overall postoperative complication was performed to assess publication bias. No significant publication bias was detected by visual inspection of the funnel plot in which the pooled studies were almost symmetry and none of them were outside the 95% CI (Fig. 5).

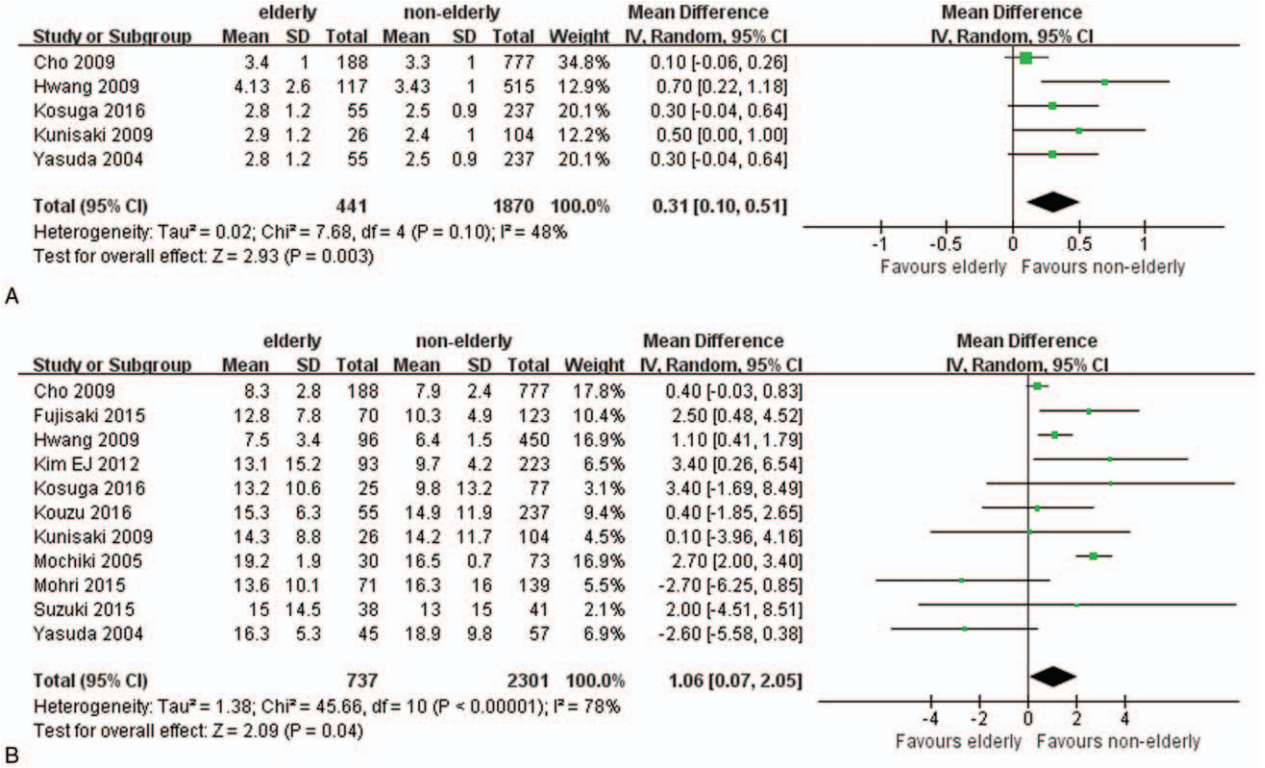

Figure 3. Forest plots of postoperative recovery: (A) time to first flatus, (B) length of postoperative hospitalization.

4. Discussion

Nowadays LG has been widely adopted owning to its minimally invasiveness as compared to open gastrectomy. Increasing elderly patients with GC accepts operation to achieve better prognosis with the improvement of surgical techniques and perioperative care. Till now, results of randomized studies and reviews focus on the elderly patients underwent LG have not yet been reported. To evaluate the feasibility and safety of LG in elderly patients, we conducted this study by reviewing and analyzing the previous studies using the meta-analysis method.

Pronged operation time and elevated blood loss were reported to increase surgical stress and risks of postoperative complications. Huang et al[29] reviewed 2170 patients who underwent LG and identified intraoperative blood loss more than 75 mL as an independent risk factor for major complications. Park et al[30] also reported pronged operation time was an important risk factor for the 30-day mortality rate. Characteristics of LG

Table 3

Surgical and long-term outcomes of included studies.

Study	Extent of LND (D1 or D1+/D2), %		Postoperative morbidity, %		Postoperative mortality, %		Length of follow-up	OS	DFS
	E	NE	E	NE	E	NE		E	NE
Cho et al	44.7/55.3	43.2/56.7	16.8	12.7	0.9	0.8	NA	NA	NA
Fujisaki et al	65.7/34.3	62.6/37.4	11.4	8.1	1.4	0	NA	NA	NA
Hwang et al	80.7/19.3	81.7/18.3	17.9	12.6	0	0	NA	NA	NA
Kim et al	62.5/37.5	60.0/40.0	14.0	13.0	NA	NA	NA	NA	NA
Kosuga et al	98.2/1.8	92.0/8.0	21.8	16.5	0	0	NA	NA	NA
Kouzu et al	72.0/28.0	50.6/49.4	20	14.3	NA	NA	NA	NA	NA
Kunisaki et al	96.2/3.8	93.3/6.7	11.5	3.8	0	0	Mean: 28.4 m	E, 5y: 98%, NE, 5y: 95%	E, 5y: 100%, NE, 5y: 100%
Mochiki et al	100/0	100/0	13.3	13.6	0	0	Median: 40 m	E, 5y: 95.7%, NE, 5y: 98.4%	E, 5y: 96%, NE, 5y: 97.6%
Mohri et al	85.9/14.1	78.2/20.2	18.3	21.6	0	0	NA	Significantly lower in E than NE	No difference between E and NE
Suzuki et al	94.7/5.3	91.2/9.8	29	9.8	0	0	Median: 42 m	NA	NA
Yasuda et al	100/0	100/0	20	17.5	0	0	NA	NA	NA

DFS = disease-free survival, E = elderly, LND = lymph node dissection, NA = not available, NE = nonelderly, OS = overall survival.

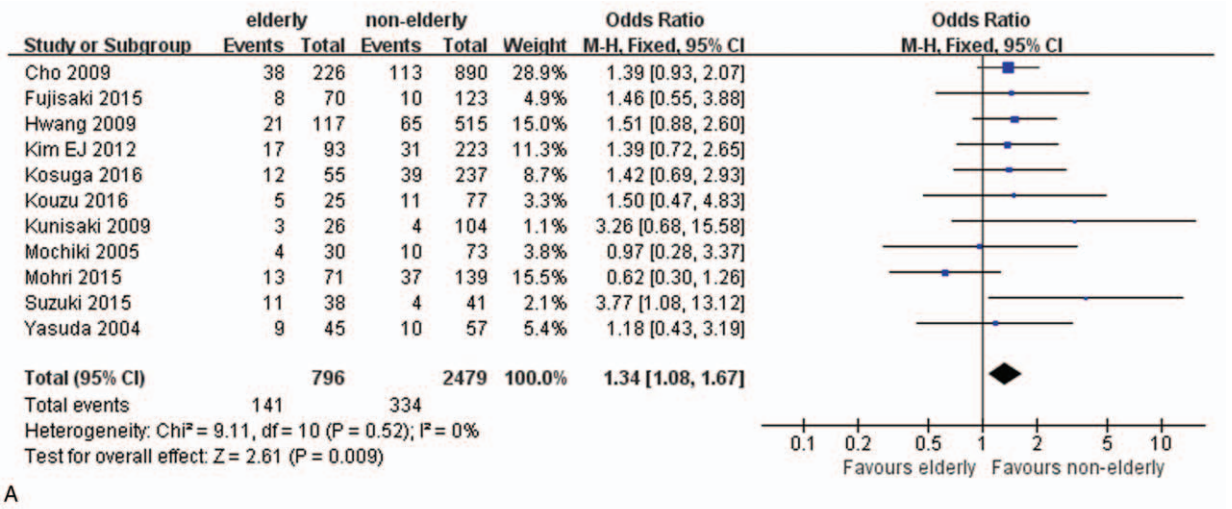

Figure 4. Forest plots of postoperative complications: (A) overall complication, (B) surgical complication, and (C) nonsurgical complication.

including amplified operating view and meticulous manipulation helped to reduce the blood loss, which also led to longer operation time. Many surgeons had gradually overcome this drawback as they passed the learning curves and utilized more advanced instruments. In our analyses, the operation time and estimated blood loss of elderly patients was comparable with that of nonelderly patients. In fact, the operation time was slightly less in elderly patients (nearly 10 minutes). Operation time and estimated blood loss might not be specific disadvantages accompanied with the elderly patients.

Postoperative complications of LG are the major concern among the elderly. Elderly patients usually have increased severity of associated comorbidities and decreased functional reservation. Malignancies like GC could damage the balanced

Table 4

Subgroup analysis of outcomes based on the cutoff ages.

	Pooled studies	Sample size	Pooled estimates	95% CI	*P*
Operation time	11	3275	−10.46	−17.06, −3.86	<.01
65 y	1	316	2.90	−13.29, 19.09	.73
70 y	5	2163	−14.02	−20.27, −7.78	<.01
75 y	5	796	−6.65	−22.47, 9.16	.41
EBL	10	2159	−6.05	−42.18, 30.07	.74
65 y	1	316	5.40	−31.99, 42.79	.78
70 y	4	1047	−23.17	−81.22, 34.88	.43
75 y	5	796	4.42	−38.91, 47.75	.84
Retrived lymph nodes	5	1956	−2.34	−3.77, −0.92	<.01
65 y	1	316	−3.30	−6.37, −0.23	.03
70 y	1	1116	−1.60	−3.66, 0.46	.13
75 y	3	524	−2.84	−5.43, −0.25	.03
Postoperative hospital stays	11	3038	1.06	0.07, 2.05	.04
65 y	1	316	3.40	0.26, 6.54	.03
70 y	5	1926	0.55	−0.77, 1.87	.41
75 y	5	796	1.55	0.22, 2.88	.02
Overall postoperative complication	11	3275	1.34	1.08, 1.67	<.01
65 y	1	316	1.39	0.72, 2.65	.32
70 y	5	2163	1.20	0.91, 1.58	.19
75 y	5	796	1.78	1.14, 2.80	.01
Surgical complication	11	3275	1.20	0.94, 1.53	.14
65 y	1	316	1.29	0.64, 2.58	.48
70 y	5	2163	1.12	0.83, 1.52	.47
75 y	5	796	1.40	0.85, 2.33	.19
Nonsurgical complication	10	3172	1.98	1.24, 3.15	<.01
65 y	1	316	1.82	0.40, 8.32	.44
70 y	4	2060	1.46	0.78, 2.71	.23
75 y	5	796	3.58	1.52, 8.44	<.01
Surgical site infection	10	3173	1.47	0.98, 2.21	.06
65 y	1	316	7.25	0.29, 179.57	.23
70 y	4	2061	1.35	0.86, 2.13	.19
75 y	5	796	1.82	0.70, 4.75	.22
Pneumonia	9	2963	3.09	1.68, 5.68	<.01
65 y	1	316	2.43	0.34, 17.50	.38
70 y	3	1851	2.50	1.12, 5.58	.02
75 y	5	796	4.73	1.56, 14.34	<.01
Ileus	9	2057	1.24	0.44, 3.51	.68
65 y	1	316	1.61	0.26, 9.81	.60
70 y	3	945	0.69	0.11, 4.19	.69
75 y	5	796	2.08	0.30, 14.19	.46

CI = confidence interval, EBL = estimated blood loss.

immune and nutrient status in elderly patients. In the study, we found elderly patients had more postoperative complications than the nonelderly patients (17.7% vs 13.5%). Hager et al[11] reported the overall complication in elderly patients who underwent open gastrectomy was 27.6% with an in-hospital mortality of 12%. In a study including 2014 patients (ranged from 12 to 91 years) underwent LG, Lin et al[31] revealed that 13.6% of the patients suffered postoperative complications. Thus, the overall complication rate in elderly patients was acceptable as compared with historical reports. We also demonstrated there was no difference between elderly patients and nonelderly patients in surgical complications, while elderly patients had more nonsurgical complications. In detail, elderly patients had comparable surgical site infections rate and ileus rate, but a higher pulmonary complications rate. Further analysis also showed in subgroup elder cutoff age (75 years), elderly patients suffered higher risk of pneumonia, nonsurgical complications, and subsequently overall complications. These results also corroborated the point that elderly patients were associated with higher pulmonary complications rate.

Pneumoperitoneum during LG was considered as an adverse factor, which may exacerbate the preexistent pulmonary comorbidities and bring new pulmonary complications including pneumonia, atelectasis, pleural effusion, etc. Cho et al[28] reported higher incidence of postoperative respiratory complications were observed among elderly patients with preoperative pulmonary diseases who underwent LG. Conversely, Suzuki et al[20] argued the transitory cardiopulmonary adverse effects by pneumoperitoneum could normalize during the intraoperative period even among decrepit elderly patients with cardiopulmonary disease. In a study by Hamakawa et al,[32] chronic obstructive pulmonary disease was significantly associated with the occurrence of postoperative complications. Thus, we speculated the severity of the preoperative comorbidities and the patients' physiological statuses were the main risk factors for PPCs. Proper interventions are recommended for preventing

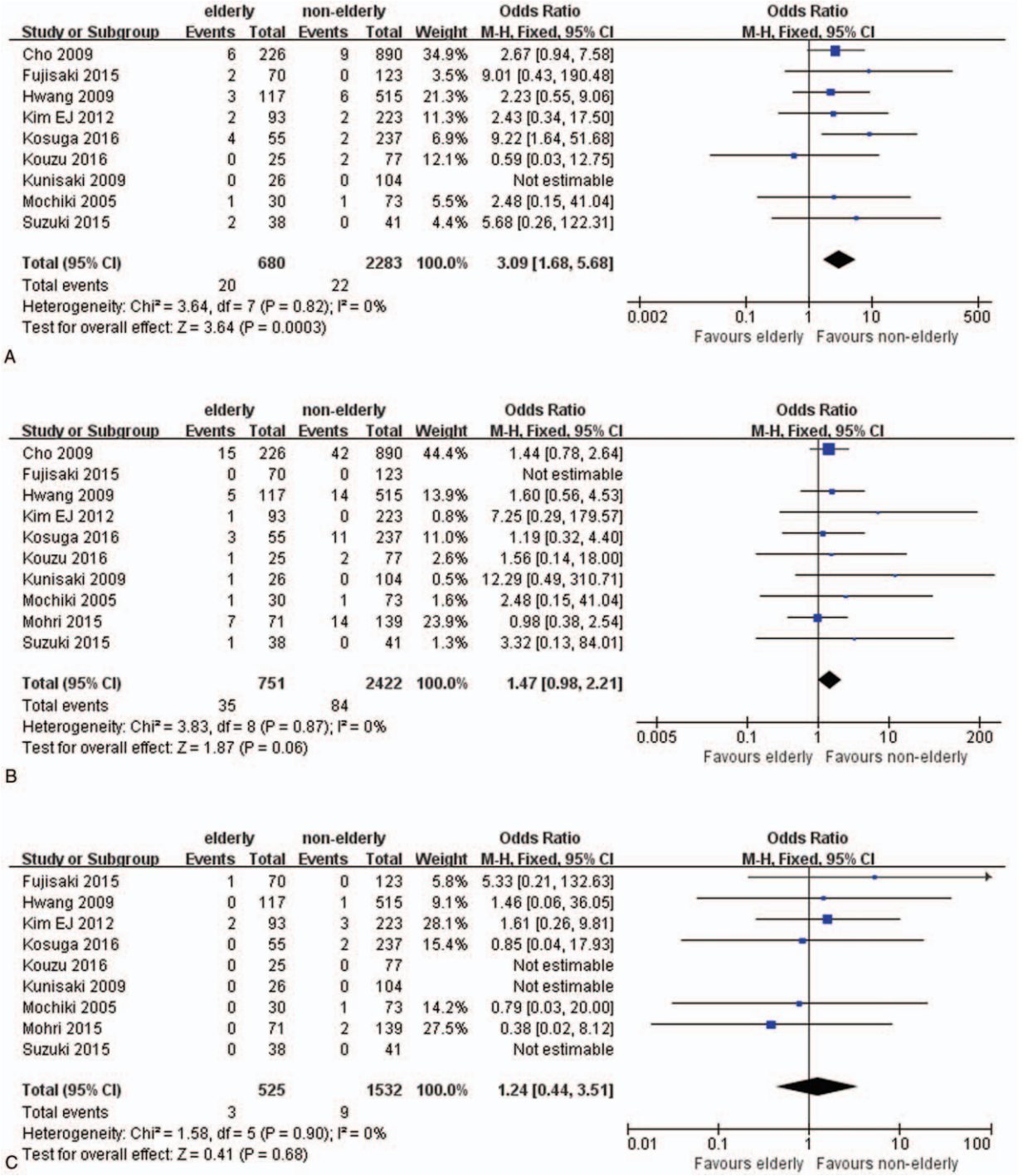

Figure 5. Details of postoperative complications: (A) postoperative pulmonary complications, (B) surgical site infections, and (C) ileus.

PPCs including medicine, nutrient-supporting treatment, and inspiratory muscle training.[33,34]

Our study also found elderly patients had delayed first flatus, which indicated the bowel function recovery of elderly patients was slower than younger patients. In consistent with this, elderly patients had a longer length of hospitalization, which was likely a result of slower recovery and higher postoperative morbidity.

An unexpected result of our study was that the retrieved lymph nodes in elderly patients were less than younger patients. In some pooled studies, elderly patients were less likely to undergo D2 or even D1+ lymphadenectomy. Performing extended lymph node resection meant a higher risk of postoperative complications. Previous studies reported that there were no significant survival benefits of D2 over D1 in elderly patients.[35] Furthermore, Takeshita et al[36] reported that limited lymph node dissection on elderly patients may reduce life expectancy, especially in stage I and II patients. For this population gastrectomy with limited lymph node dissection is recommended. In the present study, the oncological outcomes as reported by several pooled studies showed no differences between the elderly and nonelderly

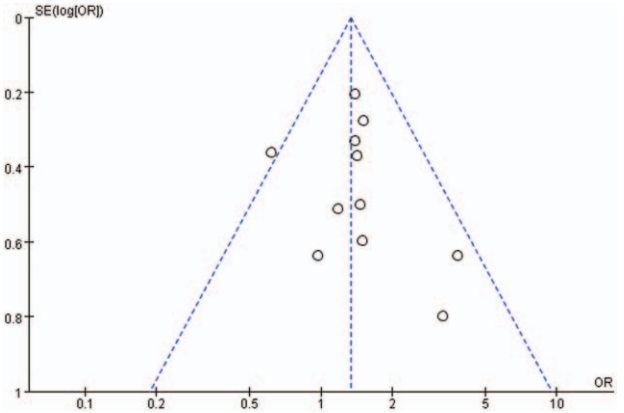

Figure 6. Funnel plots of overall postoperative complication.

patients. The residual life expectancy of elderly patients is short. The true value of extended lymphadenectomy in this population needs more well-designed studies to evaluate.

Our studies also had some limitations needed to be noted. First, all the pooled studies were retrospective, which had bias in patients selection, surgeons techniques, surgical extents and regional differences, etc. Second, heterogeneity in the studies with different cutoff ages of elderly patients may also bring the bias. Third, the inclusion of some studies not reporting the means and SDs and estimate the data using the method described by Hozo et al may also result in bias.

5. Conclusion

In conclusion, LG for elderly patients is a feasible and safe approach for GC. Despite of delayed recovery and higher risks of postoperative complications, old age should not be considered as the absolute contraindication for LG.

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