Systematic Review and Meta-Analysis

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Is it safe to perform gastrectomy in gastric cancer patients aged 80 or older?

A meta-analysis and systematic review

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Abstract

Background: Few studies have focused on octogenarian patients with gastric cancer (GC) who have undergone gastrectomy. This meta-analysis of published studies was performed to assess the safety of treating octogenarian GC patients with surgery.

Methods: Databases, including PubMed, Embase, Web of Science, and Cochrane Library were searched until January 2019. The incidence of preoperative comorbidities, postoperative complications, and mortality was assessed using odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Further, the hazard ratios (HRs) with 95% CIs were applied for survival outcomes.

Results: A total of 18,179 patients with GC in 21 studies were included. Our results demonstrated that octogenarian patients were associated with a higher burden of comorbidities (OR=2.79; 95% CI: 2.37, 3.28; P=.00), high incidences of overall postoperative complications (OR=1.48; 95% CI: 1.22, 1.81; P=.00), medical postoperative complications (OR=2.58; 95% CI: 1.91, 3.49; P=.00), in-hospital mortality (OR=3.24; 95% CI: 2.43, 4.31; P=.00) and poor overall survival (HR=1.96; 95% CI: 1.65, 2.27; P=.00).

Conclusions: Considering the high burden of comorbidities, high incidences of postoperative complications and mortality, surgery for extremely elderly patients with GC requires deliberation. Individualized treatment is recommended for such patients.

Abbreviations: ASA = American Society of Anesthesiologists, CI = confidence interval, DFS = disease free survival, GC = gastric cancer, HR = hazard ratio, NCCN = National Comprehensive Cancer Network, NOS = Newcastle–Ottawa scale, OR = odds ratio, OS = overall survival, RCT = randomized controlled trial.

Keywords: gastrectomy, gastric cancer, meta-analysis, octogenarian patients, systematic review

1. Introduction

Gastric cancer (GC) is one of the most common malignancies and is the fifth leading cause of death worldwide.[1] Due to a longer lifespan of the general population, the incidence of GC has increased in the elderly. In some western countries, the median age of GC patients is 66 to 69 years,[2] meaning most patients are elderly. While there is no standard definition of "elderly," the widely accepted classification includes patients aged 65 to 80 years. Therefore, patients enrolled in almost all randomized controlled trials (RCTs) must be 80 years and younger. The clinicopathological features, surgical outcomes and survival outcomes of octogenarian patients, especially those with GC, are still unclear. Compared to younger patients, octogenarians suffer from more comorbidities, complications, and mortality. Although surgery is the most effective method to treat GC, many clinicians and doctors are hesitant when recommending it to octogenarian patients, due to high risks of postoperative complications or mortality.[3]

With the steep increase in the number of elderly patients, especially octogenarians, it is necessary to report the most recent clinical findings and refine treatment options for octogenarian GC patients.[4–6] There is still controversy regarding the complications and mortality of octogenarian patients compared to younger patients. That is, some studies have revealed that the complications and mortality of octogenarian patients were similar to those of younger ones, while other studies have reported opposite results. To evaluate the safety of gastrectomy for octogenarian and young GC patients, we conducted a meta-analysis of retrospective studies regarding the preoperative comorbidities and postoperative outcomes after gastrectomy in patients 80 years or older and patients younger than 80 years.

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2. Methods

2.1. Literature search strategy

A systematic literature search was performed using PubMed, EMbase, Web of Science, and Cochrane Library (until January 1, 2019). In each database, the following terms were combined as Keywords: (gastric or stomach) and (tumor or cancer or carcinoma or adenocarcinoma or malignancy) and (surgery or operation or gastrectomy) and (octogenarian or "older than 80 years"). All article sections, including abstracts, studies, and references, were reviewed carefully. Articles in the reference list were screened to identify any potentially relevant studies.

This study was conducted in accordance with guidelines of the 1975 Declaration of Helsinki. The study and protocol were designed with approval from our institutional review board.

2.2. Inclusion criteria

The inclusion criteria were as follows:

(1) patients with GC;
(2) gastrectomy performed as the primary treatment method;
(3) patients enrolled in the studies were divided into octogenarian and younger groups; and
(4) preoperative comorbidities and/or postoperative complications and/or mortality and/or survival outcomes were mentioned.

2.3. Exclusion criteria

The exclusion criteria were as follows:

(1) articles that reported case reports, reviews, letters, and comments;
(2) studies that did not provide precise data about clinicopathological features;
(3) non-English publications; and
(4) studies with a sample size smaller than 50.

If 2 studies were reported by the same institution, the 1 with the smaller sample size was excluded.

2.4. Data extraction and quality assessment

All studies were carefully reviewed. Data were extracted from each study by 2 independent researchers, including study ID (first author's name and publication year), country, sample size, preoperative comorbidities, postoperative complications, in-hospital mortality, and long-term survival outcomes. Any inconsistencies between reviewers were resolved by a third investigator through discussion. If studies only provided Kaplan–Meier curve for overall survival (OS) and disease-free survival (DFS), the hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) were extracted using Engauge Digitizer version 4.1 (http://markummitchell.github.io/engauge-digitizer/).

The Newcastle–Ottawa scale (NOS) was used to assess the quality of retrospective studies. The NOS evaluates studies based on the selection of the study groups, comparability between the groups, and the determination of exposure/outcomes using a scale scoring from 0 to 9. Studies that scored ≥6 were deemed to be of high quality.[7]

2.5. Outcomes of interest

The primary outcome was postoperative complications. These postoperative complications were first examined and then divided into a surgical group and a medical group. Subgroup analysis was performed in both groups. The secondary outcome was in-hospital mortality. Besides, the burden of comorbidities of patients before operation was measured by the American Society of Anesthesiologists (ASA) score. The OS and DFS were also examined, when applicable.

2.6. Statistical analyses

We used STATA software version 14.0 (StataCorp., College Station, TX) to perform the meta-analysis. Heterogeneity among studies was tested using Cochran Q and Higgins' I^2 statistics. If there was no heterogeneity ($I^2 < 50\%$, $P > .10$), a fixed-effects model was used. Otherwise, a random-effects model was applied. Sensitivity analysis was carried out when the heterogeneity was higher than 50%. Studies were sequentially omitted at each step. If the result did not change, the pooled studies were considered stable. Publication bias was evaluated using the Egger test. Statistically significant values were defined as $P < .05$.

3. Results

3.1. Search strategy

Three hundred thirty-three articles were identified after searching PubMed, Embase, Web of Science, and Cochrane Library. After duplicates were removed, 63 articles were screened. Thirty-three articles were excluded because they

(1) were non-English publications,
(2) contained irrelevant subjects,
(3) included other treatment methods (ie, chemotherapy or radiotherapy), or
(4) used grouping standards that were different from the studies under consideration.

After reading the full-text articles, those that could not provide a precise number of outcomes of interest were excluded. Finally, 21 articles were included in this meta-analysis (Fig. 1).

3.2. Cohort characteristics and quality of the studies

Twenty-one studies were finally included in our analysis.[5,6,8–26] Sample sizes varied from 60 to 3637 participants. Regarding location where the studies were performed, 9 studies were from Japan, 3 from China, 3 from Korea, 3 from the USA, 1 from the UK, and 1 from Switzerland. The publication date ranged from 2012 to 2018 and all studies were retrospective in nature. Eighteen studies provided comorbidities and/or ASA score. All studies provided postoperative complications except 1.[16] Six articles reported survival outcomes. According to the NOS, 4 articles received a score of 5, 9 were scored 6, and all others received a score of 7. The characteristics and quality assessment scores of the included studies are presented in Table 1.

3.3. Preoperative comorbidities

Several articles provided detailed descriptions of patients' preoperative comorbidities. However, extremely old patients usually had 2 or more comorbidities. Therefore, it was not appropriate to calculate and analyze these comorbidities together. Therefore, we used the ASA score to measure the number of comorbidities of the patients before surgery. Thirteen articles with 9253 patients provided ASA score data. Analysis of ASA scores revealed that octogenarian patients had a higher prevalence of comorbidities (OR = 2.79; 95% CI: 2.37, 3.28; $P = .00$) (Fig. 2).

3.4. Overall postoperative complications

Twenty-one articles with 18,549 patients reported postoperative complications. Due to significant heterogeneity ($I^2 = 63.2\%$; $P = .000$), the random-effects model was used. We found that,

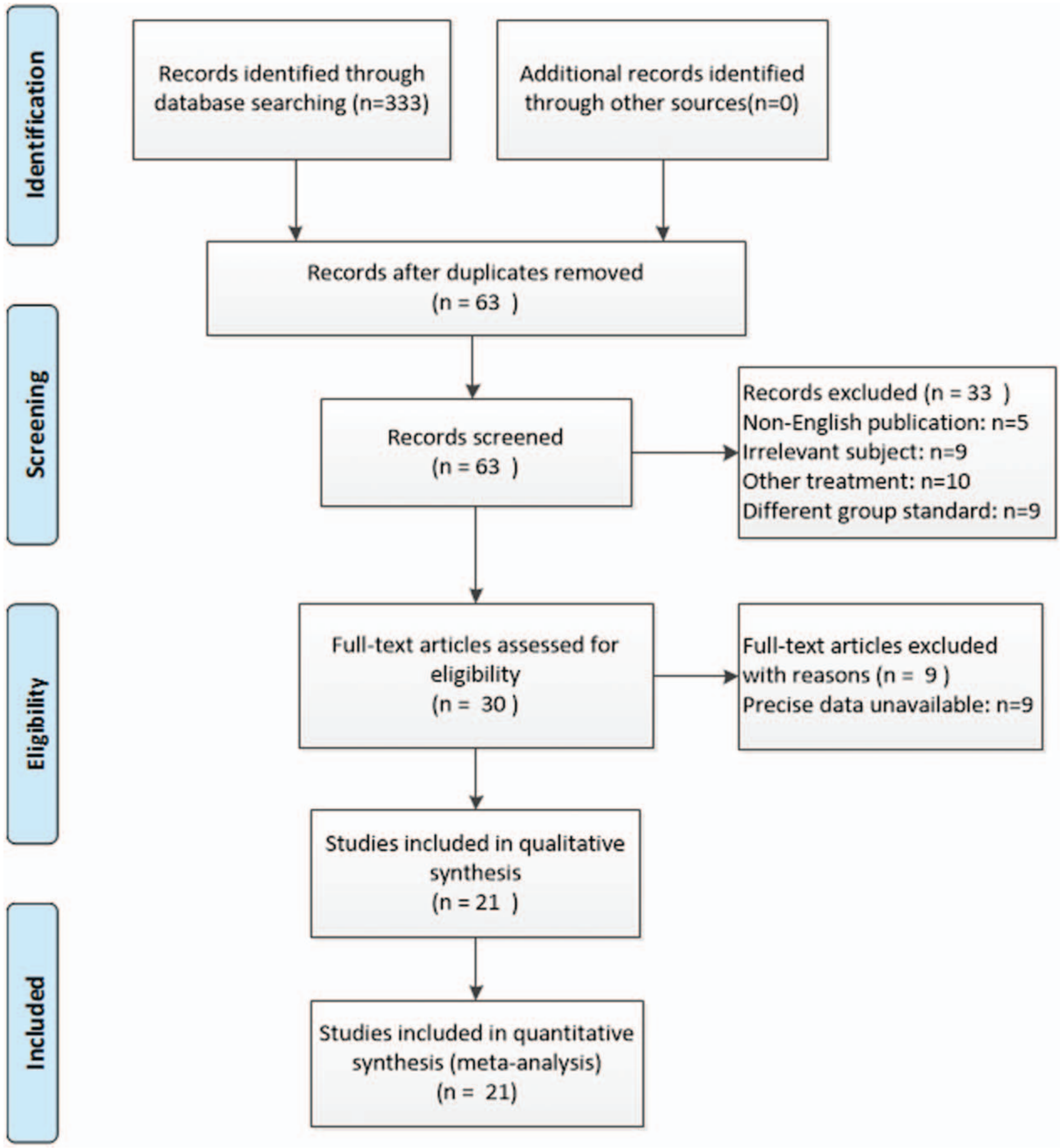

Figure 1. Flow diagram for study selection.

compared to younger patients, octogenarian patients had more complications (OR=1.48; 95% CI: 1.22, 1.81; P=.00) (Fig. 3).

As the heterogeneity was significant, sensitivity analysis was performed to evaluate the stability of pooled studies. The results did not substantially change when studies were omitted 1 at each step, meaning the results were stable (Fig. 4).

3.5. Surgical and medical complications

Surgical complications were defined as related complications directly caused by surgical procedures. Meanwhile, the medical complications were defined as cardiovascular, respiratory or other organ dysfunction caused by surgery.

To distinguish surgical and medical complications, we stratified the groups. The results indicated that the incidence of surgical complications was similar between the 2 groups (OR=1.06; 95% CI: 0.91, 1.23; P=.45) (Fig. 5A). According to the random-effects model (I^2=67.3%; P=.00), there was a close association between octogenarian patients and a high incidence of medical complications (OR=2.58; 95% CI: 1.91, 3.49; P=.00) (Fig. 5B).

3.6. Subgroup analysis of surgical complications and medical complications

In the subgroup analysis, abscess (OR=1.27; 95% CI: 1.05, 1.54; P=.01), anastomotic leakage (OR=1.37; 95%

Table 1

Characteristics of studies included in the analysis.

Study	Year	Country	No. of patients	Patients younger than 80	Patients older than 80	Type of surgery	Neoadjuvant therapy (<80/>80)	Adjuvant therapy (<80/>80)	Minimally invasive surgery	Characteristics reported	NOS score
Mengardo	2018	UK	507	432	75	TG,STG,PG	175/2	201/4	N/A	1,2,3,4,5,6	5
Fujiwara	2017	Japan	448	333	115	DG,TG,PG,PPG	N/A	N/A	No	3,5,6	6
Hamilton	2017	USA	3637	3086	551	TG,STG	N/A	N/A	No	1,2,3,5	7
Casella	2017	Italy	60	34	26	TG,STG	N/A	14/0	No	1,2,3,6	7
Yoshida	2017	Japan	69	38	31	DG	N/A	N/A	Yes	1,2,3,4,6	6
Kim	2016	Korea	478	446	32	TG,STG	N/A	N/A	No	2,3,5,6	5
Ceccarelli	2016	Switzerland	63	52	11	TG	N/A	N/A	Yes	2,4	6
Kitano	2016	Japan	413	341	72	TG,DG,PG	N/A	N/A	No	2,3,4	5
Yang	2015	Korea	824	756	68	DG,PPG,PG,TG	N/A	97/14	No	2,3,5	6
Yoshikawa	2015	Japan	402	358	44	TG,DG	N/A	N/A	Yes	1,3	7
Zhou	2015	China	729	690	39	TG,STG	N/A	291/8	No	1,2,3,4,5	6
Tran	2015	USA	953	826	127	TG,STG	179/6	442/24	Yes	2,3,5	7
Sakurai	2015	Japan	461	366	95	DG,TG,PG	16/3	106/9	No	1,2,3,4,5	6
Nakanoko	2015	Japan	471	430	41	DG,TG,PG	N/A	N/A	Yes	1,3	6
Mikami	2014	Japan	441	394	47	TG,STG	N/A	N/A	Yes	2,3,5	5
Mita	2013	Japan	396	336	60	TG,STG	N/A	N/A	No	2,3,5,6	7
Takeshita	2013	Japan	1193	1089	104	DG,TG,PG	N/A	N/A	Yes	3	6
Hsu	2012	China	2422	2258	164	TG,STG	N/A	1284/76	No	1,3,5	7
Liu	2017	China	359	279	80	TG,STG	N/A	N/A	Yes	3	6
Kim	2015	Korea	1262	1187	75	TG,STG	N/A	N/A	No	3,5,6	7
Teng	2017	USA	2591	2104	487	TG,STG	222/12	N/A	No	2,3,5,6	7

1. Comorbidities; 2. ASA score; 3. Postoperative complication; 4. Clavien–Dindo score; 5. Postoperative mortality; 6. Long-term survive outcome.
DG = distal gastrectomy, PG = partial proximal gastrectomy, PPG = pylorus-preserving gastrectomy, STG = subtotal gastrectomy, TG = total gastrectomy.

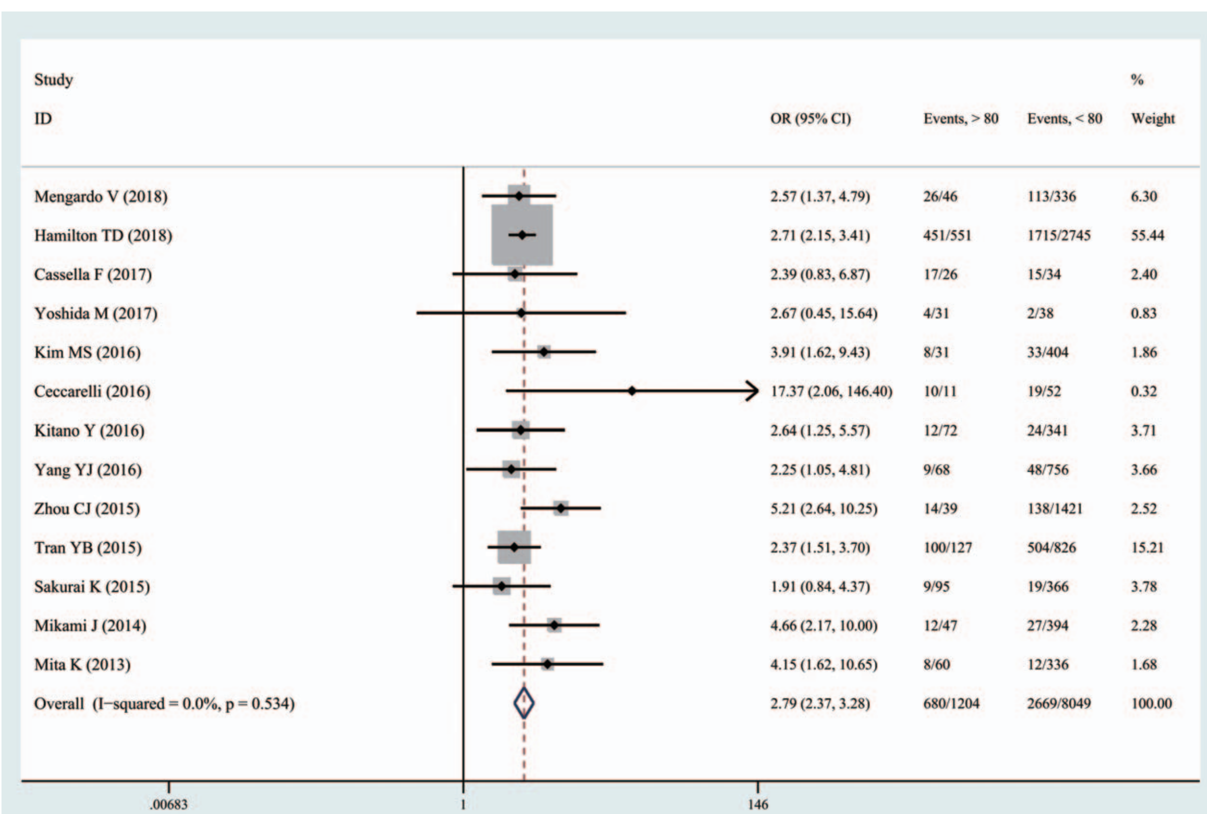

Figure 2. Meta-analysis forest plots of comparison of patients who had ASA score from 3 to 4 between both groups. ASA = American Society of Anesthesiologists.

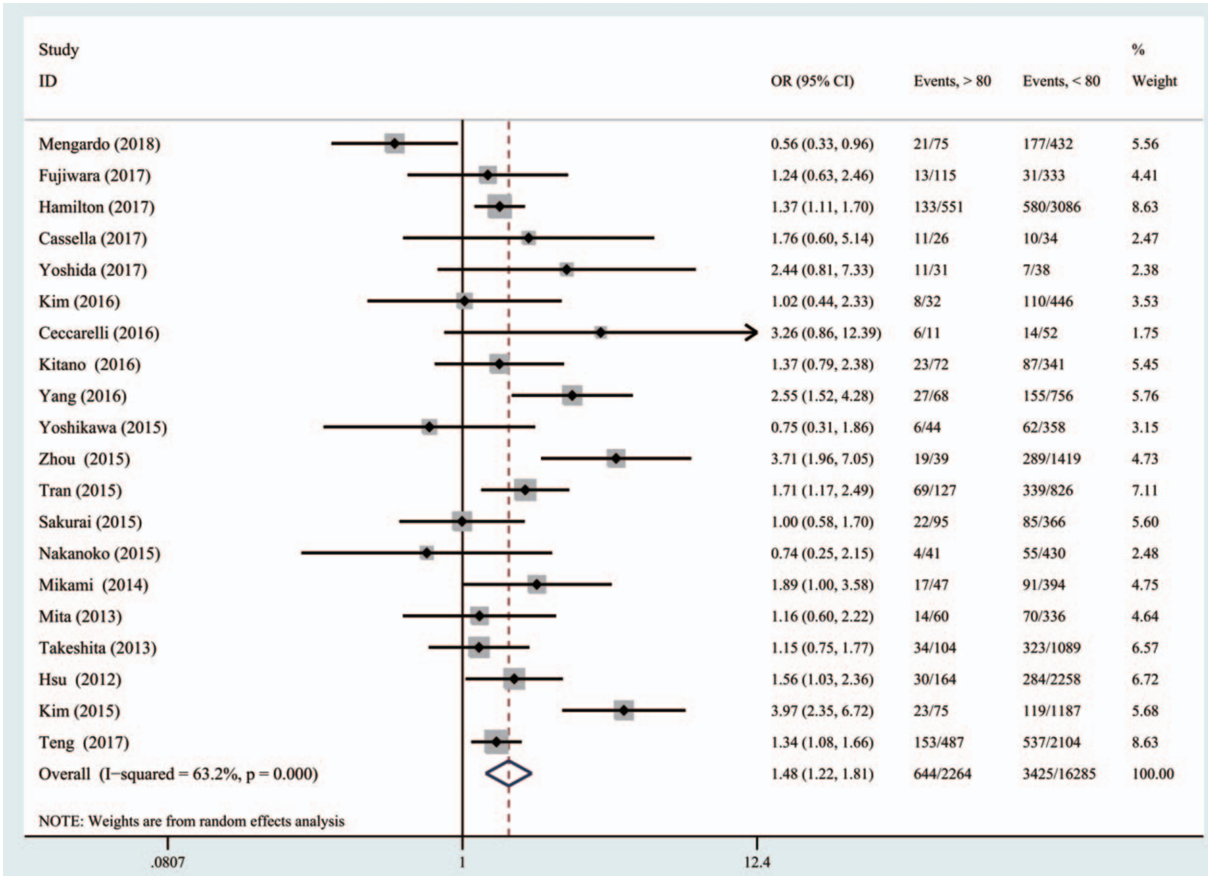

Figure 3. Meta-analysis forest plots of comparison of overall postoperative complications between both groups.

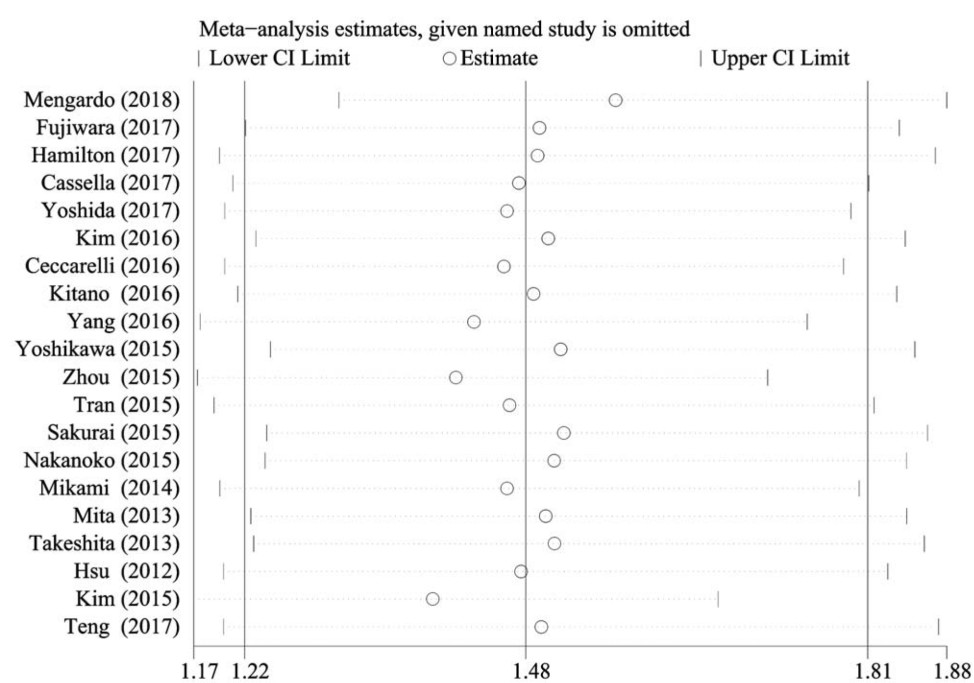

Figure 4. Sensitivity analysis for the pooled odds ratios of overall complications of patients.

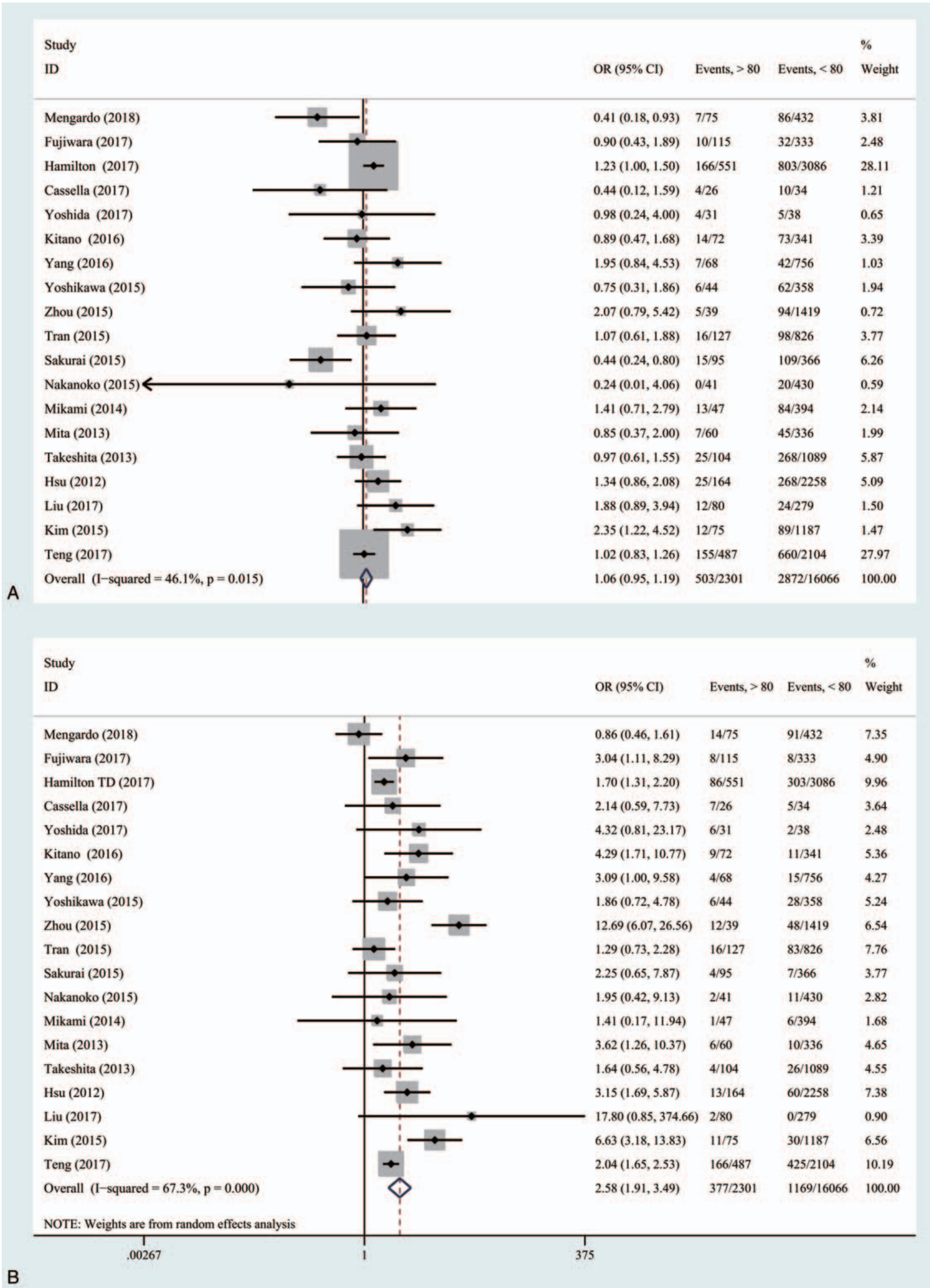

Figure 5. (A) Meta-analysis forest plots of comparison of surgical postoperative complications between both groups. (B) Meta-analysis forest plots of comparison of medical postoperative complications between both groups.

CI: 1.01, 1.86; $P=.04$), respiratory events (OR=2.34; 95% CI: 1.89, 2.89; $P=.00$), and cardiac events (OR=2.19; 95% CI: 1.59, 3.01; $P=.00$) were found more frequently in octogenarian patients (Table 2).

3.7. In-hospital mortality

A total of 12 studies reported in-hospital mortality between octogenarian versus younger patients. The in-hospital mortality of octogenarian patients was 3 times higher than that of

Table 2

Subgroup analysis of surgical and medical complications.

Outcome	No. of studies	Patients aged 80 or over	Patients younger than 80	Odds ratio (95% CI)	Statistics difference
Surgical complications					
Abscess	12	1438	11,272	1.27 (1.05–1.54)	0.012
Anastomotic leakage	14	1125	10,408	1.37 (1.01–1.86)	0.041
Anastomotic stenosis	5	390	2929	1.08 (0.47–2.49)	0.852
Bleeding	10	729	7212	1.22 (0.66–2.25)	0.520
Pancreatic fistula	8	492	4341	0.89 (0.55–1.45)	0.644
Surgical site infection	8	1096	9754	0.93 (0.69–1.24)	0.601
Delayed gastric empting	5	402	4691	1.72 (0.88–3.35)	0.112
Ileus	10	802	7761	0.90 (0.48–1.67)	0.731
Medical complications					
Respiratory	16	1713	13,496	2.34 (1.89–2.89)	0.000
Cardiac events	11	1763	13,131	2.19 (1.59–3.01)	0.000
Others	8	1133	7665	1.18 (0.80–1.74)	0.391

CI = confidence interval.

younger patients (OR = 3.24; 95% CI: 2.43, 4.31; P = .00) (Fig. 6).

3.8. Survival outcomes

Six articles reported the OS and DFS in GC patients who had undergone gastrectomy. The difference in OS was statistically significant, showing that OS was poorer in the octogenarian group than in the younger group (OR = 1.96; 95% CI: 1.65, 2.27; P = .00) (Fig. 7A). Alternately, the rate of DFS was not statistically different between the 2 groups (OR = 1.09; 95% CI: 0.85, 1.32; P = .08) (Fig. 7B).

3.9. Publication bias

We assessed the publication bias in the primary and secondary outcomes (overall complications and in-hospital mortality) according to the Begg and Egger tests. In the overall complication

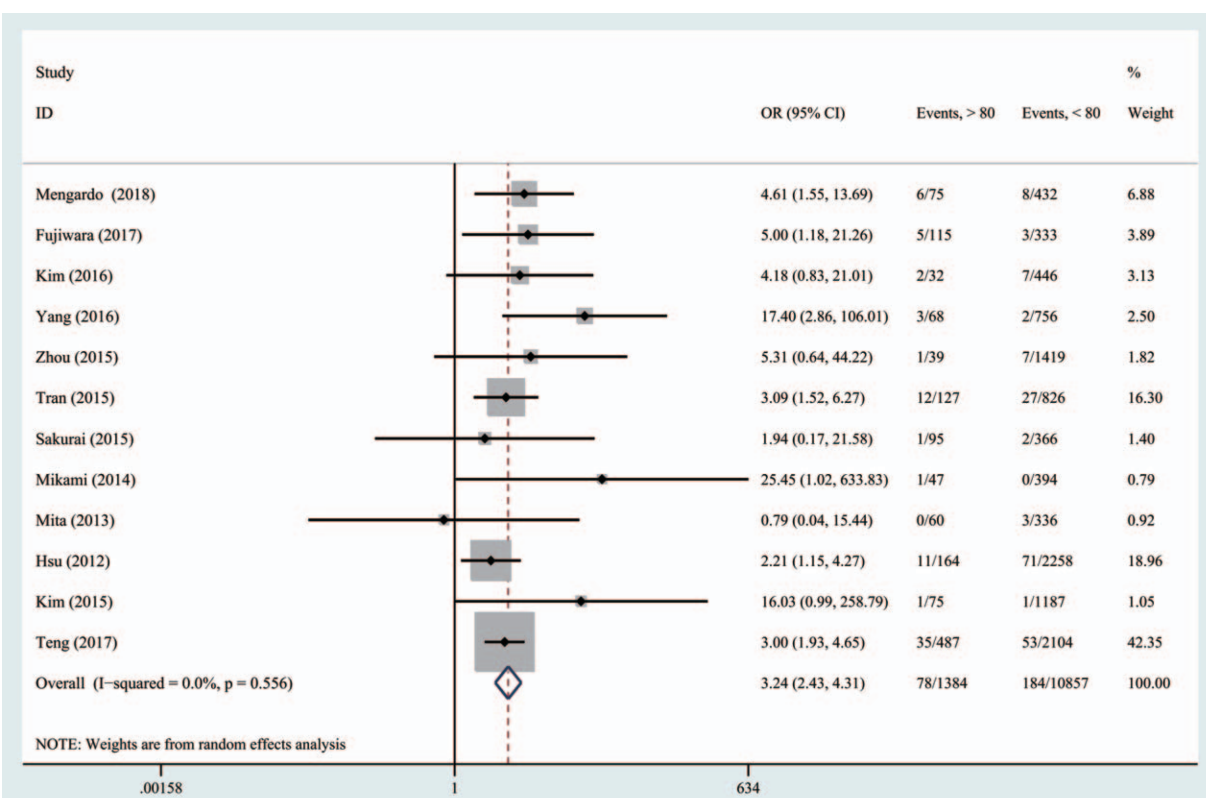

Figure 6. Meta-analysis forest plots of comparison of in-hospital mortality between both groups.

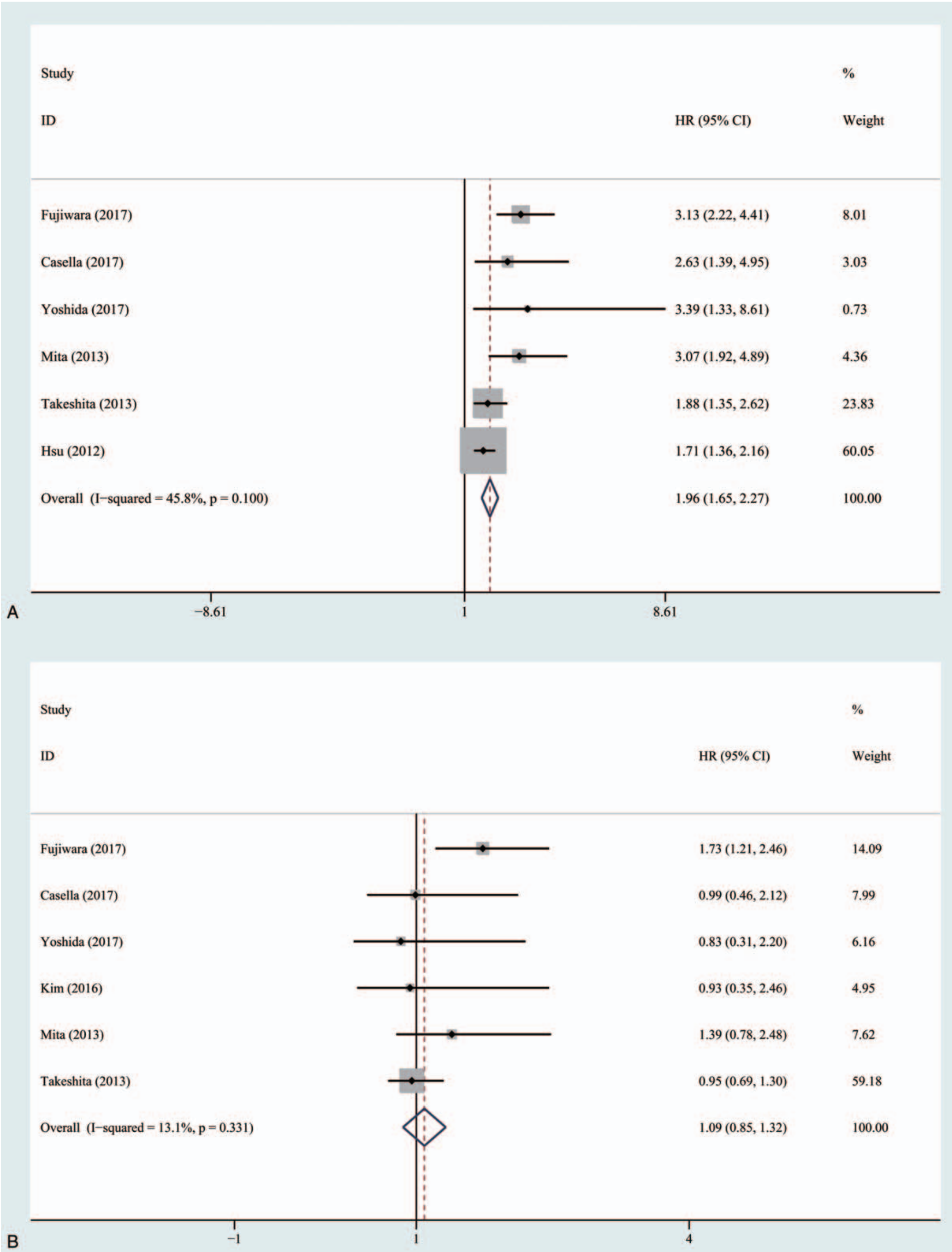

Figure 7. (A) Meta-analysis forest plots of comparison of OS between both groups. (B) Meta-analysis forest plots of comparison of DFS between both groups. DFS = disease-free survival, OS = overall survival.

analysis, the Begg test ($P=.92$) and Egger test ($P=.66$) showed there was no publication bias (Fig. 8A). The result was similar in the mortality analysis: Begg test ($P=.24$) and Egger test ($P=.09$) (Fig. 8B).

4. Discussion

According to the National Comprehensive Cancer Network (NCCN) guidelines, the recommended treatment method for GC is surgery. Most RCTs have focused on GC with a restricted age

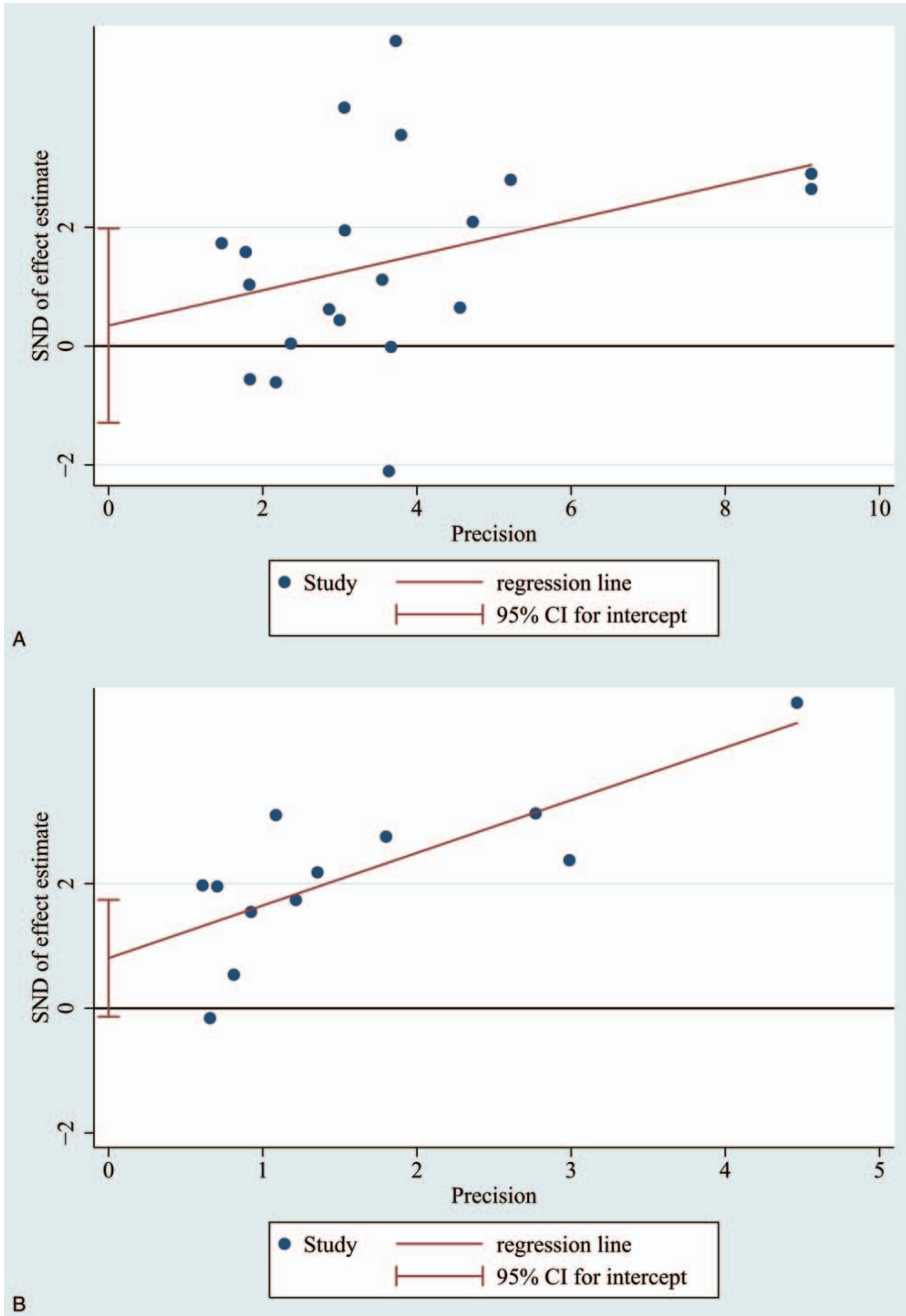

Figure 8. (A) The graph of Egger test in overall complication analysis. (B) The graph of the Egger test in mortality in hospital analysis.

of 80 years and younger for enrolled patients. As a result of these previous RCTs, the burden of comorbidities, complications, mortality, and survival outcomes among octogenarian and younger patients remained elusive. This meta-analysis was performed to fill this gap in the research.

The size of the elderly population, especially octogenarians, has steeply increased in the past decades, according to the United Nations 2015 report. If this trend continues, in 2050, octogenarians will account for 20% of the world's population.[27] The World Health Organization stratified the "old" as follows: "elderly" was older than 65 years, "young-old" was 65 to 75 years old and "old-old" was older than 75 years; however, the optimal cut-off age for patients undergoing gastrectomy has remained controversial. In the present study, Fujiwara found that a cut-off value of 79.2 years precisely predicted mortality according to the survival receiver operating characteristic curve.[18]

When clinicians and doctors develop therapeutic regimens for old patients, they are confronted with "aging," poor nutritional status and many comorbidities. Fried defined "frailty" as a clinical phenotype associated with a high risk of falls, disabilities, comorbidities, hospitalization, and mortality.[28] The age of patients is directly proportional to the incidence of frailty phenotype. As a result, the octogenarian patients may suffer from a higher risk of malnutrition, comorbidities, disabilities, and deterioration of organs or organ function. As we found in this research, the burden from comorbidities of octogenarian patients was 2-fold poorer than that of younger patients. The poor preoperative status may partly explain the high risk of postoperative complications.

Takama reported that postoperative complications in patients 80 years and older occurred more frequently compared to younger patients.[29] Hayashi found that octogenarian patients who underwent D2 or modified D2 lymphadenectomy had a higher risk of severe complications (16%) than younger patients, suggesting that standard surgery for GC should be limited in extremely old patients. In contrast, Ruspi showed that the incidence of morbidities and mortalities were similar between old patients and patients of other ages.[30] Our findings indicated that octogenarian patients were associated with a high incidence of overall postoperative complications and in-hospital mortality. These results imply that radical surgery methods should be limited. However, considering the benefits for long-term survival, these methods may be suitable for octogenarian patients in good health.

Interestingly, the risk of surgical postoperative complications for octogenarian patients was the same as the risk for younger patients, except for abscess and anastomotic leakage. This may benefit the technical development of surgery and anesthesia. Laparoscopy and robotic surgery have significantly reduced bleeding and trauma of patients, despite having a longer operation time. Therefore, the surgical complications were significantly reduced. The risk of medical postoperative complications, including cardiac and respiratory events, was significantly higher in octogenarian patients. These patients might have a higher incidence of preoperative comorbidities. Lee suggested the high rate of respiratory complications in elderly patients, especially pneumonia, was closely associated with long-term tobacco use and a possible high prevalence of chronic obstructive pulmonary disease.[31]

Recently, many studies have revealed the OS of octogenarians was significantly lower than that of younger patients. On the other hand, the DFS between the 2 groups has been found to be quite similar.[9,13] Surgical type and extent of node dissection could not influence DFS in extremely old patients with GC. Another study reported by Kim also found the same result. In addition, the tumor, node, metastasis stage was the independent predictor of OS, rather than sex, comorbidities, surgical types, and complications.[25] Our study consistently illustrated that the OS was poorer in the octogenarian patients, while the DFS was comparable between the 2 groups. According to the NCCN guidelines, patients who are clinically diagnosed as T2 or higher should receive neoadjuvant therapies. However, we found that the rate of neoadjuvant therapies received by patients was quite lower in the elderly group than in the younger group. This may be caused by a variety of factors, including a heavy burden of comorbidities, poor tolerance of radiotherapy and chemotherapy, and lower life expectation. However, interestingly, the DFS between the 2 groups was not statistically different, suggesting that standard therapies may be not suitable for octogenarian patients. Personalized therapies, including neoadjuvant therapies or palliative surgeries, may be the optimal choice for these patients.

Finally, we concluded that it is not feasible to set up a unified guideline, because statuses are quite different among the patients, especially octogenarian patients. Many surgeons suggested that the assessments and decisions regarding optimal treatment should be prepared before surgery. For the patients who had a good general status and few comorbidities, regardless of "aging" itself, the radical surgery with R0 resection and extended lymphadenectomy was recommended. Apart from that, conservative treatment regimens should be performed.

There are some limitations to our meta-analysis that should be addressed. First, all the included studies were retrospective, which may have led to additional selection and information bias. Second, comparing the incidence of postoperative complications without similar physical histories always results in a significant selection bias.

In conclusion, this meta-analysis consistently indicated that octogenarian GC patients had a heavy burden of comorbidities and high incidence of postoperative complications and mortality. According to the survival outcomes analysis, the OS was significantly lower in octogenarian patients, but the DFS in patients 80 years and older was similar to that of younger patients. Considering the heavy burden of comorbidities and high rate of complications, radical surgery may be not the optimal choice for all elderly patients. Some may benefit more from conservative treatments or palliative surgery.

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Author contributions

Conceptualization: Xuezhong Xu.
Validation: Yibo Wang, Nianyuan Ye.
Visualization: Yixin Xu.
Writing – original draft: Yixin Xu, Cheng Xi.
Writing – review and editing: Xuezhong Xu.

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