

Relationship Between Postoperative Complications and the Prognosis of Gastric Carcinoma Patients Who Underwent Surgical Resection: A Systematic Review and Meta-Analysis

Guofeng Chen, MD¹, Jun Wang, MD^{1,2}, Kaibo Chen, MD¹, Muxing Kang, MD¹, Hang Zhang, MD¹, Xiaoli Jin, MD¹, Lele Lin, MD², and Jian Chen, MD^{1,2} 

Abstract

Background: Whether the presence of postoperative complications was associated with poor prognosis of gastric carcinoma (GC) patients remain controversial. This meta-analysis was designed and reported to compare the survival difference between patients with complications and non-complications.

Methods: Cochrane Library, PubMed and Embase databases were comprehensively searched for published literatures to review current evidence on this topic. The survival data were extracted, and a random-effect or fixed-effect model was used to analyze the correlation between postoperative complications and oncologic outcome of GC patients.

Results: Of all studies identified, 32 were eligible for this pooled analysis, with a total of 32,067 GC patients. The incidence of postoperative complications was approximately 12.5% to 51.0%. Among them, infectious complications varied from 3.0% to 28.6%, anastomotic leakage varied from 1.1% to 8.7% and postoperative pneumonia varied from 1.6% to 12.8%. The presence of postoperative complications resulted in a significant poorer overall survival (OS) of gastric carcinoma patients (hazard ratio [HR]: 1.49, 95% confidence interval [CI]: 1.33-1.67, $P < 0.001$). Additionally, the pooled results showed a significant correlation between infectious complications and decreased OS (HR: 1.61, 95%CI: 1.38-1.88, $P < 0.001$). Concerning specific postoperative complications, we found that both anastomotic leakage (HR: 2.36, 95%CI: 1.62-3.42, $P < 0.001$) and postoperative pneumonia (HR: 1.74, 95%CI: 1.22-2.49, $P = 0.002$) impaired the OS of gastric carcinoma patients.

Conclusion: Postoperative complications were significantly correlated to recurrence and poor survival in gastric carcinoma patients. To gain a better surgical outcome and long-term oncological outcome, postoperative complications should be minimized as much as possible.

Keywords

gastric carcinoma, postoperative complications, anastomotic leakage, postoperative pneumonia, survival, prognosis

Received October 24, 2020. Received revised March 05, 2021. Accepted for publication March 31, 2021.

¹ Department of Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

² Cancer Center, Zhejiang University, Hangzhou, Zhejiang, China

Corresponding Author:

Jian Chen, Department of Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China.

Email: zrchenjian@zju.edu.cn



Introduction

According to the 2018 Global Cancer Statistics, gastric carcinoma remains the common type of lethal malignancies around the world, although its prognostic outcome has been remarkably improved.¹ Surgical resection with adequate lymphadenectomy is the most effective treatment of choice for resectable gastric carcinoma. However, D2 lymphadenectomy is a complex and challenging task for the surgeons, resulting in a high incidence of postoperative complications.^{2,3}

Major and severe postoperative complications increase treatment costs, prolong the hospitalization time and have a negative effect on the quality of life. It has been reported that postoperative complications,^{4,5} especially for infection complications,^{6,7} anastomotic leakage,^{8,9} and postoperative pneumonia,^{10,11} are significantly related to a higher risk of local recurrence and worse long-term survival in gastric carcinoma patients. According to the analytic data of Wu et al,¹² the 3-year overall survival (OS) rate and 3-year relapse-free survival (RFS) rate of gastric carcinoma patients with postoperative complications were 56.8% and 43.5%, respectively. In contrast, the 3-year OS rate was 66.0% and 3-year RFS rate was 58.1% in those without postoperative complications. The survival curves revealed a significant survival difference.¹² However, other studies have shown that independent prognostic significance of postoperative complications is not significant in the adjusted multivariate regression analysis, although the prognosis of gastric carcinoma patients who had postoperative complications is inferior to that of those without postoperative complications.¹³ Understanding the prognostic significance of postoperative complications for gastric carcinoma patients is crucial to perioperative management and clinical treatment decision-making. In the current analysis, we systematically reviewed the current evidence and reported a meta-analysis to explore whether the presence of postoperative complications was associated with poor prognosis of gastric carcinoma patients who were treated with surgical resection.

Methods

Literature Search Strategy

Two investigators performed a systematic search for relevant literatures using the Cochrane Library, EMBASE (Ovid) and MEDLINE (Pubmed) databases. The search strategy included the following keywords and medical subject heading (MeSH) terms: “postoperative complication”, “anastomotic leakage”, “pneumonia” or “pulmonary infection”, “Clavien-Dindo”, “gastric cancer”, “gastric carcinoma” or “gastric adenocarcinoma”, “gastrectomy” and “prognosis”, “survival” or “prognostic”. The primary collection of studies was identified according to these combined keywords. What’s more, we scrutinized the reference lists of previously published literatures to ensure that all relevant studies were not missed. There is no language and publication date limitation for full-text index.

Eligibility Criteria

Eligible studies should report a comparison of survival outcome between gastric carcinoma patients who had and did not have postoperative complications. The original data from included studies, including OS, cancer-specific survival (CSS), disease-free survival (DFS) or RFS, were available. Hazard ratio (HR) and its 95% confidence intervals (CIs) were used as the summary statistics for survival data, and all data was extracted from the multivariate Cox regression analysis in order to control the effect of confounding variables on the pooled outcomes. The presence of postoperative complication was defined as an unusual course that occurred during within 30 days after surgery or the whole hospitalization. The studies assessed the severity of postoperative complications using the Clavien-Dindo classification, which was a treatment-oriented, objective criterion.¹⁴ Those studies that did not use the Clavien-Dindo classification to define the presence of postoperative complications or did not report at least 1 of long-term oncological outcomes should be excluded. In case of studies with overlapping data from the same populations, the most recent or the most informative study was included. Conference abstracts, letters to the editor, comments, review articles and case series were excluded.

Data Extraction and Assessment of Methodological Quality

The authors systematically reviewed the titles and abstracts of relevant literatures identified by the electronic search, and studies deemed potentially relevant were further selected for full-text screening. Relevant data and information extraction were independently conducted by 2 investigators using a standardized electronic form. In case of discordance, a collective discussion was made to reach a consensus. For non-randomized, observational reports, risk of bias for included study was evaluated by the Newcastle-Ottawa quality assessment scale (NOS),¹⁵ which scored each study based on the methodological items. Studies with a NOS score of 7 or more were thought of methodological high-quality. This systematic review and meta-analysis was conducted and reported according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.

Statistical Analysis

The primary oncological outcomes of this pooled analysis included OS, CSS and RFS. Overall survival (OS) was defined as the time interval from the first surgery to the date of death from any cause or the last follow-up. Cancer-specific survival (CSS) was defined as the time interval from the date of surgery to the date of death related to gastric carcinoma or the last follow-up. Recurrence-free survival (RFS) was defined as the time interval from the date of surgery to the date of the first

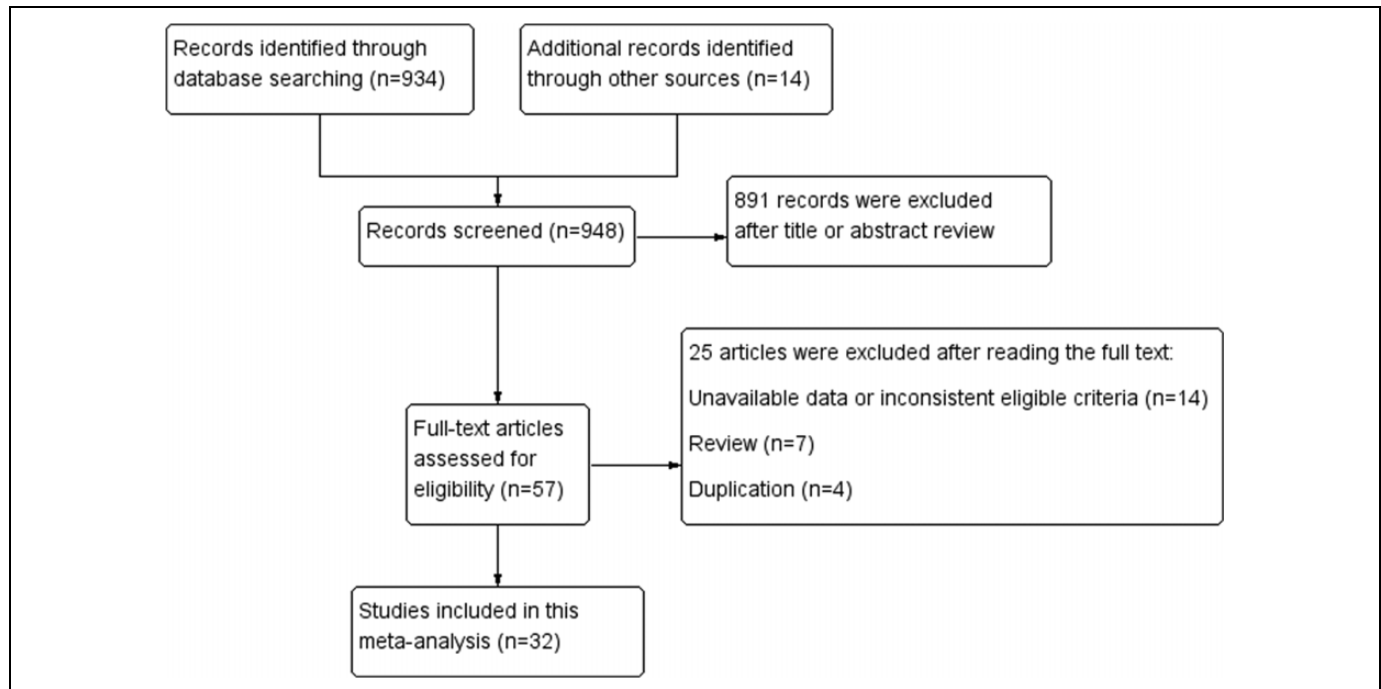


Figure 1. The flow diagram of study selection.

recurrence. In this meta-analysis, we used the HR estimates with 95% CIs as a summary statistical measure to calculate and weigh the correlation between postoperative complications and survival outcomes of gastric carcinoma patients. As time-to-event outcomes, a pooled HR more than 1 represented a worse prognosis in the experimental group (complication group) than in the contrast group (non-complication group). The Cochran Q test and the inconsistency (I^2) statistic were used to quantitatively evaluate the degree of heterogeneity among included studies, and I^2 statistic of greater than 50% and/or P value of less than 0.01 for Q test represented a considerable heterogeneity. In view of high clinical heterogeneity for the presence of postoperative complications, in this study, we selected a random-effect model to estimate the pooled HR of all outcomes.

Subgroup analyzes stratified by the study populations (Western versus Eastern), pathological stage (stage I-III versus stage I-IV), study size (≥ 450 versus < 450), the frequency of postoperative complications ($\geq 25\%$ versus $< 25\%$, based on the median of postoperative complication rates), Clavien-Dindo classification (\geq grade II vs \geq grade III) and assessment score of methodological quality (≥ 7 versus < 7 points) were performed to explore the clinical and methodological sources of heterogeneity. In addition, the publication bias for this meta-analysis was visually detected by the funnel plots via their symmetry. In this study, we used the Stata 13.0 software (Stata Corporation, College Station, TX, USA) to perform all data processing and statistical analyzes. The threshold of a 2-tailed P value for statistical significance was set at 0.05 for all analyzes.

Results

Search Results and Main Characteristics of Eligible Studies

Figure 1 showed the selection process of eligible studies. We initially identified 948 potentially relevant literatures from electronic databases through the predefined search strategy. 891 studies were considered to be irrelevant to this topic after scanning the titles and abstracts. Subsequently, the full texts of the remaining 57 articles were further screened to determine which studies met the eligibility criteria. Of these studies, 6 studies did not use Clavien-Dindo grade to describe the severity of postoperative complications, 8 studies did not present the prespecified outcomes, 4 were duplications, and 7 were review articles. Ultimately, a total of 32 published literatures were entered into qualitative or quantitative analysis.^{4-13,16-38}

Table 1 summarized the baseline characteristics of the included literatures. This meta-analysis involved 32,067 study participants who underwent gastrectomy for gastric carcinoma, which included 5,141 patients with postoperative complications and 26,926 patients without postoperative complications, with study sizes ranging from 101 to 5,327. The included studies were published between 2009 and 2020, of which all had a retrospective design. Among these studies, 17 were conducted in Japan, 7 were conducted in China, 4 were carried out in Europe, 2 were carried out in Korea and 2 were conducted in the USA. A total of 22 studies reported the data on comparing survival difference between overall postoperative complication and non-complication groups, and 7 studies and 3 studies specifically focused on the influence of anastomotic leakage and

Table 1. Clinicopathological Characteristics of Included Studies.

Study	Country	Inclusion period	Sample size (C/ NC)	PC (%)	IC (%)	AL (%)	PP (%)	C-D grade	Follow-up, median (range)	Resection stage	TNM stage	Survival data (C group vs NC group)	Quality
Vicente et al ²¹	Japan	1995-2015	421 (215/206)	51.0%	-	-	-	≥II	N/A	R+	I-III	OS, HR:1.42 (1.05-1.91); DFS, HR:1.19 (0.91-1.56)	7
Takeuchi et al ²²	Japan	2002-2012	993 (392/1845)	39.5%	-	1.7%	3.6%	I-IV	N/A	R+	I-IV	OS, HR:1.23 (0.73-2.08); CSS, HR:1.02 (0.54-1.94)	6
Fujiya et al ⁷	Japan	2002-2009	1541 (174/1367)	25.8%	11.3%	3.2%	3.8%	≥II	63.5 mo	R0	I-III	OS, HR:1.41 (1.08-1.92); RFS, HR:1.39 (1.03-1.88)	8
Powell et al ⁵	UK	2004-2016	373 (127/246)	34.0%	19.8%	4.8%	6.9%	I-IV	60 mo (6-60)	R+	I-III	OS, HR:2.25 (1.04-4.85); DFS, HR:1.63 (1.06-2.50)	7
Tu et al ^{1,25}	China	1996-2014	5327 (767/4560)	14.4%	-	-	7.2%	I-IV	35 mo	R0	I-III	5-OS:49.0% vs 60.0%; CSS, HR:1.19 (1.05-1.36)	6
Li et al ²³	China	2008-2015	571 (102/469)	17.9%	-	1.1%	1.6%	≥II	N/A	R0	I-III	5-CSS:65.2% vs 76.2%; OS, HR:1.07 (0.60-1.90)	8
Kader et al ¹⁸	Japan	1991-2010	265 (38/227)	-	14.3%	5.7%	-	≥II	N/A	R0	II-III	5-OS:34.5% vs 70.7%; CSS, HR:2.63 (1.61-4.31)	7
Hayashi et al ⁶	Japan	2000-2005	502 (52/450)	-	10.4%	1.2%	4.1%	≥II	61 mo (1-110)	R0	I-IV	5-RFS:58.0% vs 83.0%; HR:2.82 (1.75-4.54)	7
Kubota et al ⁴	Japan	2005-2008	1395 (207/1188)	14.8%	-	2.4%	-	≥II	37.2 mo	R0	I-III	OS, HR:1.88 (1.26-2.80); CSS, HR:1.90 (1.19-3.02)	7
Li et al ¹⁶	China	2005-2006	432 (54/378)	12.5%	3.0%	1.2%	2.5%	I-IV	N/A	R0	I-IV	5-OS:21.8% vs 39.9%; HR:2.5 (1.8-3.6)	6
Watanabe et al ²⁶	Japan	1992-2010	430 (134/296)	31.2%	28.6%	6.3%	2.3%	≥III	N/A	R0	I-III	OS, HR:0.97 (0.69-1.34); RFS, HR:0.98 (0.70-1.36)	7
Saito et al ¹³	Japan	2001-2012	305 (86/219)	28.2%	-	3.6%	-	≥II	N/A	R0	I-III	RFS, HR:1.10 (0.70-1.73)	6
Climent et al ¹⁹	Spain	1990-2009	271 (116/155)	42.8%	22.5%	-	7.0%	≥II	149.9 mo (140-1159.7)	R0	I-III	OS, HR:0.72 (0.41-1.26); RFS, HR:0.99 (0.49-1.26)	8
Tokunaga et al ¹⁷	Japan	2002-2006	765 (81/684)	-	10.6%	2.4%	-	≥II	63 mo	R0	I-IV	OS, HR:2.45 (1.48-4.06); RFS, HR:2.22 (1.33-3.41)	7
Mohri et al ²⁴	Japan	2000-2011	404 (103/301)	25.5%	17.6%	3.2%	4.7%	N/A	52.0 mo	R0	I-III	OS, HR:2.34 (1.24-4.42); CSS, HR:2.27 (1.21-4.24)	6
Jiang et al ²⁰	China	2002-2006	751 (305/446)	40.6%	-	-	-	I-III	N/A	R0	I-IV	OS, HR:1.46 (1.34-1.58)	6
Jin et al ²⁹	USA	2000-2012	824 (336/488)	40.7%	-	-	-	I-IV	35 mo	R0	I-IV	5-RFS:23.0% vs 40.0%; OS, HR:1.3 (1.1-1.6)	7
Suzuki et al ³⁵	Japan	2000-2014	250 (32/218)	-	-	-	12.8%	≥II	30.5 mo (0-157)	R0	I-III	OS, HR:1.40 (0.90-2.14); PP, HR:2.06 (1.05-3.75)	7
Nagasako et al ³²	Japan	1997-2008	400 (14/386)	-	-	3.5%	-	≥II	62.0 mo (3-146)	R0	I	5-OS:81.0% vs 94.2%; HR:2.45 (1.08-5.58)	6
Yoo et al ⁹	Korea	2000-2005	478 (32/446)	-	-	6.7%	-	N/A	62.5 mo (4-121)	R0	II-III	OS, HR:3.58 (2.29-5.59); CSS, HR:4.06 (2.55-6.45)	7
Sierzega et al ⁸	Japan	1999-2004	690 (41/649)	33.0%	-	5.9%	-	N/A	34 mo (5-101)	R+	I-IV	OS, HR:3.14 (1.51-6.53)	6
Andreou et al ³¹	Germany	2005-2012	471 (41/430)	-	-	8.7%	-	≥II	35 mo (1-101)	R+	I-III	OS, HR:2.29 (1.43-3.69); DFS, HR:1.74 (1.03-2.96)	7
Kiuchi et al ¹⁰	Japan	1997-2013	1413 (31/1382)	-	-	-	2.2%	≥II	N/A	R0	I-III	OS, HR:2.32 (1.168-4.145)	6
Kim et al ³³	Korea	2003-2012	3827 (72/3755)	-	-	1.9%	-	N/A	58.5 mo (0-136)	R+	I-IV	Median OS:97.6 vs 109.5 mo; HR:0.81 (0.51-1.31)	6
Liu et al ³⁴	China	2012-2015	1254 (31/1223)	-	-	2.5%	-	N/A	18 mo (3-40)	R0	I-III	3-OS:41.1% vs 53.9%; HR:2.722 (1.598-4.635)	6

(continued)

Table 1. (continued)

Study	Country	Inclusion period	Sample size (C/ NC)	PC (%)	IC (%)	AL (%)	PP (%)	C-D grade	Follow-up, median (range)	Resection stage	TNM stage	Survival data (C group vs NC group)	Quality
Eto et al ²⁷	Japan	2005-2015	101 (35/66)	34.7%	-	3.0%	3.0%	≥II	33.7 mo	R0	I-IV	3-RFS:41.7% vs 47.0%; HR:1.18 (0.67-2.02)	7
Tsujimoto et al ³⁰	Japan	1986-2005	1332 (141/1191)	-	10.6%	3.6%	3.8%	N/A	68.5 mo (3-211)	R0	I-IV	OS, HR:1.88 (1.50-2.94); CSS, HR:1.84 (1.13-2.99)	7
Zhuang et al ²⁸	China	2008-2013	937 (227/710)	24.2%	-	-	-	≥II	62.3 mo	R0	I-III	OS, HR:1.57 (1.09-2.26); DFS, HR:1.43 (0.93-2.20)	6
Kamarajah et al ³⁶	UK	1997-2016	969 (58/911)	-	-	6.0%	-	I-IV	N/A	R+	I-III	OS, HR:3.96 (2.11-7.44); DFS, HR:0.65 (0.09-4.81)	7
Kanda et al ³⁷	Japan	2010-2014	2954 (664/2290)	22.5%	-	4.0%	3.0%	≥II	51.1 mo	R0	I-III	OS, HR:1.60 (1.32-1.94); RFS, HR:1.48 (1.18-1.84)	6
Tokunaga et al ³⁸	Japan	2010-2015	1191 (408/783)	23.0%	13.4%	2.8%	2.7%	I-IV	3.6 mo	R+	I-IV	OS, HR:1.42 (1.05-1.91); RFS, HR:1.22 (0.94-1.57)	6
Wu et al ¹²	China	2006-2016	230 (66/164)	28.7%	-	-	-	I-IV	25.7 mo	R0	I-III	OS, HR:1.35 (0.82-2.21); DFS, HR:2.13 (1.24-3.65)	6

Abbreviations: C, complication group; NC, no complication group; PC(%), overall incidence of overall postoperative complication; IC(%), the incidence of postoperative infectious complication; AL(%), the incidence of anastomotic leakage; PP(%), the incidence of postoperative pneumonia; C-D, Clavien-Dindo classification; OS, overall survival; CSS, cancer-special survival; DFS, disease-free survival; RFS, recurrence-free survival; HR, hazard ratio.

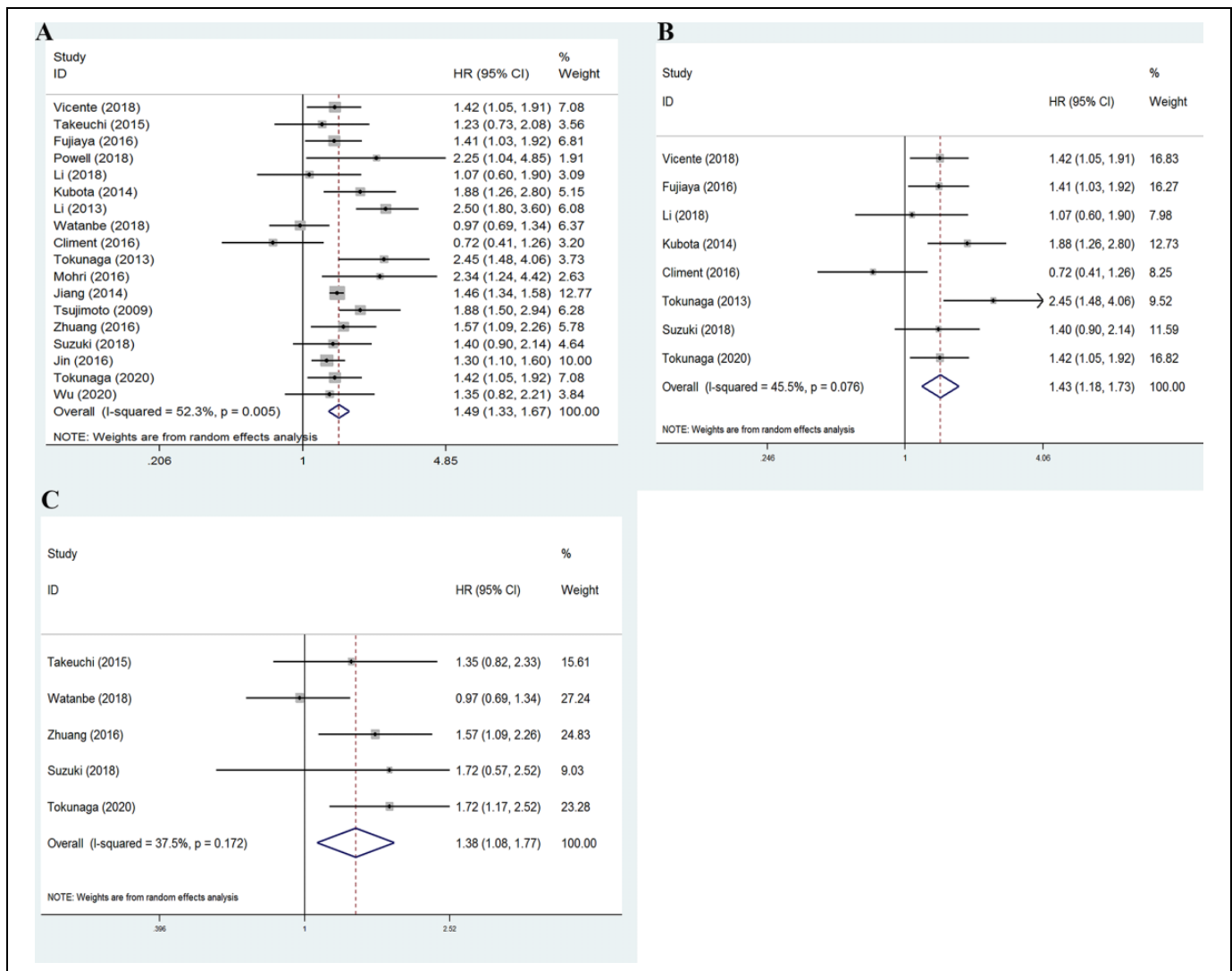


Figure 2. A, Forest plots evaluating the impact of postoperative complications on the OS of gastric carcinoma patients. B and C, Forest plots evaluating the impact of the severity of postoperative complications on the OS of gastric carcinoma patients. (B) For Clavien-Dindo grade \geq II; (C) for Clavien-Dindo grade \geq III.

postoperative pneumonia on survival outcomes in gastric carcinoma patients, respectively. The median follow-up period ranged from 3.6 to 149.9 months. According to included studies, the incidence of overall postoperative complications varied from 12.5% to 51.0% across gastric carcinoma patients who underwent surgical resection. The frequency of overall postoperative complications ranged from 14.8% to 39.5% in Japan, ranged from 12.5% to 40.6% in China and ranged from 34.0% to 51.0% in Western countries, respectively. In terms of the postoperative complication category, the incidence of infectious complications, anastomotic leakage and postoperative pneumonia varied from 3.0% to 28.6%, 1.1% to 8.7% and 1.6% to 12.8%, respectively.

Overall Postoperative Complications

In total, 18 reports compared the OS between postoperative complication and non-complication groups, and 12 of these

studies showed a significant survival difference. Meta-analysis of the pooled data demonstrated a pooled HR of 1.49 for OS (95% CI: [1.33, 1.67], $P < 0.001$), and heterogeneity I^2 was significant at 52.3% ($P = 0.005$) (Figure 2A). Next, we performed the sensitivity analysis and the result showed that the study of Li et al (2013)¹⁶ might be a potential source of heterogeneity for OS. The pooled result remained significant and heterogeneity was markedly decreased when this study was removed (HR: 1.43, 95% CIs: [1.29, 1.59], $P < 0.001$; $I^2 = 38.6%$) (Figure S1).

Table 2 shows the results of the subgroup analysis for prognostic effect of postoperative complications. The results demonstrated that the sample size, tumor stage, Clavien-Dindo grade, the frequency of postoperative complications, occurrence time of postoperative complications, and study quality could not affect the pooled results except for geographic area. In addition, we also conducted a meta-

Table 2. Subgroup Analysis for the Impact of Postoperative Complications on Survival Outcome of Gastric Cancer Patients.

Subgroup analysis	Studies	Patients	Pooled results		Heterogeneity	
			Effect size (95%CI)	P value	I ²	P value
Region			HR			
Eastern	15	11,643	1.54 (1.36-1.73)	<0.00	47.1%	0.023
Western	3	1,468	1.23 (0.75-2.01)	0.410	67.2%	0.047
TNM stage			HR			
I-III	11	6,823	1.38 (1.16-1.64)	<0.001	42.1%	0.068
I-IV	7	6,288	1.61 (1.36-1.91)	<0.001	64.8%	0.009
Sample size			HR			
≥450	10	10,300	1.48 (1.35-1.62)	<0.001	17.7%	0.281
<450	8	2,811	1.46 (1.09-1.96)	0.011	71.6%	0.001
Complication rate			HR			
≥25%	10	6,238	1.34 (1.17-1.52)	<0.001	43.1%	0.071
<25%	8	6,873	1.73 (1.44-2.08)	<0.001	41.9%	0.099
Clavien-Dindo			HR			
Grade ≥II	8	6,405	1.44 (1.26-1.65)	<0.00	45.5%	0.076
Grade ≥III	5	3,801	1.36 (1.13-1.64)	0.001	37.5%	0.172
Occurrence time of complications			HR			
within 30 d	8	6,336	1.60 (1.28-2.01)	<0.001	67.5%	0.003
the whole hospitalization	10	6,775	1.44 (1.26-1.64)	<0.001	35.5%	0.124
Study quality			HR			
≥7	11	8,173	1.42 (1.19-1.68)	<0.001	55.9%	0.012
<7	7	4,938	1.60 (1.34-1.90)	<0.001	48.5%	0.070

regression analysis based on the stratified variables (eg: sample size, the frequency of postoperative complications, TNM stage and study quality), but the results did not show any significant sources of heterogeneity (Supplemental material).

The available data on RFS and CSS measures were extracted from 11 studies and 7 studies, respectively. Meta-analysis of recurrence and cancer-specific survival also indicated that the presence of postoperative complications resulted in a worse long-term oncological outcomes of gastric carcinoma patients (HR for RFS: 1.36, 95% CIs: [1.17, 1.58], $P < 0.001$; $I^2 = 38.3%$; HR for CSS: 1.63, 95% CIs: [1.24, 2.13], $P < 0.001$; $I^2 = 66.0%$) (Figure S2).

Clavien-Dindo Grader

In the analysis of the severity of postoperative complications, we found that Clavien-Dindo grade II or higher had a negative impact on both OS (HR: 1.43, 95% CIs: [1.18, 1.73], $P < 0.001$; $I^2 = 45.5%$) (Figure 2B) and RFS (HR: 1.28, 95% CIs: [1.10-1.49], $P = 0.002$; $I^2 = 35.0%$) (Figure S3A). Similarly, postoperative complications with Clavien-Dindo grade ≥III significantly reduced the OS of gastric carcinoma patients (HR: 1.38, 95% CIs: [1.08, 1.77], $P = 0.009$; $I^2 = 37.5%$) (Figure 2C).

Infection Complications

In included studies, infection complications were defined as being present in patients who received antibiotic therapy for an infection or suspected infection and had at least 1 of the

following: body temperature $\geq 38.0^\circ\text{C}$, white blood cell count $> 10,000/\mu\text{L}$ and positive blood or fluid culture.^{6,24} In general, infectious complications included wound infection, intra-abdominal abscess, pancreatic fistula, anastomotic leakage, pneumonia, cholecystitis, catheter-related sepsis, urinary tract infection and so on. The results of this meta-analysis also revealed a negative relevance between infection complications and OS in gastric carcinoma patients (HR for OS: 1.62, 95% CI: [1.34, 1.95], $P < 0.001$; $I^2 = 28.3%$), as illustrated in Figure 3A. Similarly, the presence of infection complications was significantly associated with worse RFS (HR for RFS: 1.59, 95% CI: [1.34, 1.89], $P < 0.001$; $I^2 = 1.5%$) (Figure S3B).

Intra-abdominal infection complications included pancreatic fistula, anastomotic leakage, and intra-abdominal abscess without leakage. Our results suggested that there was a significant decrease in OS (HR: 1.48, 95% CIs: [1.14, 1.93], $P = 0.004$; $I^2 = 42.5%$) (Figure 3B) and RFS following intra-abdominal infection complications (HR: 1.44, 95% CIs: [1.11, 1.87], $P = 0.006$; $I^2 = 38.5%$) (Figure S3C).

Anastomotic Leakage and Postoperative Pneumonia

Concerning the specific postoperative complications, we found that both anastomotic leakage (HR: 2.36, 95% CIs: [1.62, 3.42], $P < 0.001$; $I^2 = 73.6%$) and postoperative pneumonia (HR: 1.74, 95% CI: [1.22, 2.49], $P = 0.002$; $I^2 = 64.5%$) had a correlation to poor OS of gastric carcinoma patients (Figure 3C and D). Moreover, the presence of anastomotic leakage was significantly associated with worse CSS of these

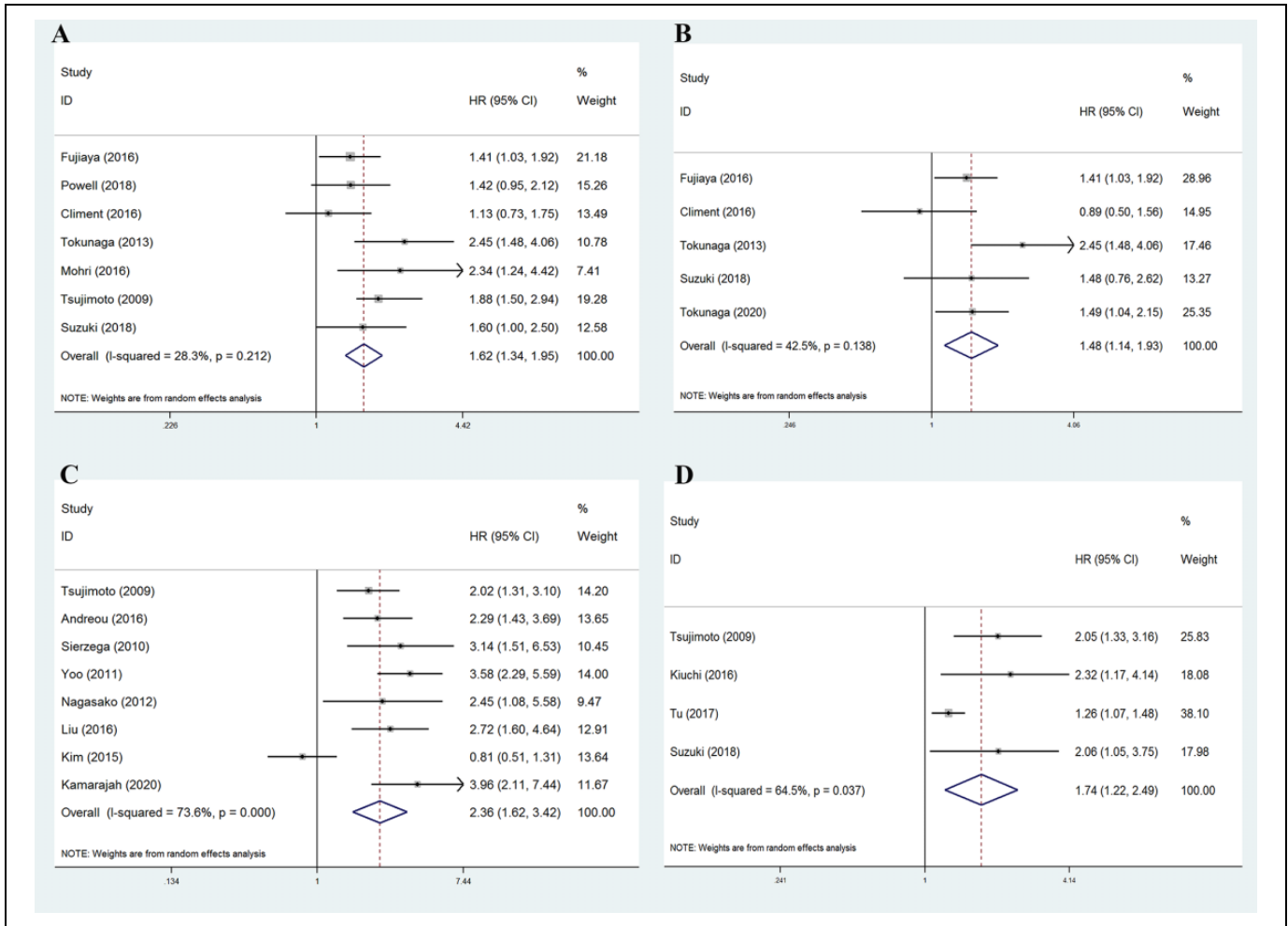


Figure 3. Forest plots evaluating the impact of different types of postoperative complications on the OS of gastric carcinoma patients. (A) For infectious complications; (B) for intra-abdominal infectious complications; (C) for anastomotic leakage; (D) for postoperative pneumonia.

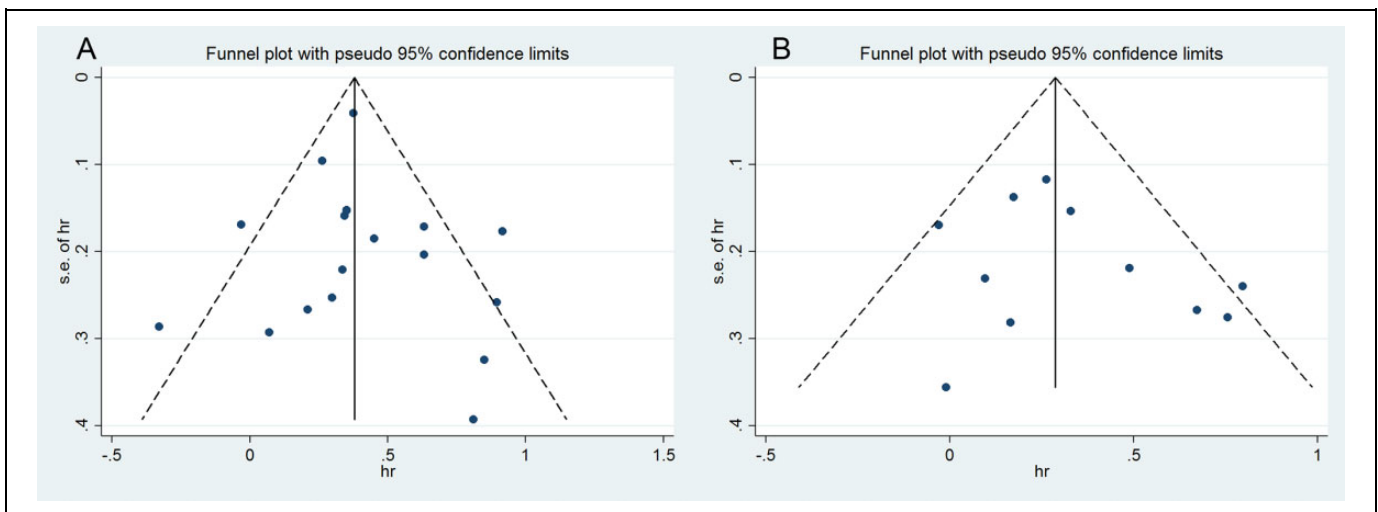


Figure 4. Funnel plot for the association between postoperative complications and the prognosis of gastric carcinoma patients. (A) For overall survival (OS); (B) for recurrence-free survival (RFS).

patients (HR: 2.46, 95% CI: [1.41, 4.31], $P < 0.001$; $I^2 = 69.1\%$) (Figure S3D).

Publication Bias

The funnel plots of pooled analysis for the impact of postoperative complications on the prognosis of gastric carcinoma patients revealed no significant asymmetry, suggesting a low possibility of publication bias (Figure 4).

Discussion

Infectious complications, including duodenal stump leakage, pancreatic fistula, anastomotic leakage, intra-abdominal infection/abscess, wound infection and pneumonia, are the most common postoperative complications after gastrectomy with curative intent. The adverse impacts of postoperative complications, especially for infectious complications, on recurrence and long-term survival have been reported previously.^{6-8,10} By comparing the survival outcomes of gastric carcinoma patients, Hayashi et al showed that the 5-year RFS rates were 58% and 83% in those with and without infectious complications, respectively.⁶ Similarly, Kubota et al assessed the prognostic significance of postoperative complications for gastric carcinoma patients using the propensity-score matching analysis, and the results revealed a significant and independent correlation between infectious complications and poor survival outcomes (HR for OS: 1.88, 95% CIs: [1.26, 2.80], $P < 0.001$; HR for CSS: 1.90, 95% CIs: [1.19, 3.02], $P < 0.001$).⁴ These findings suggested that the presence of postoperative complications, especially infectious complications, was significantly correlated to disease recurrence and poor survival. However, a few studies reported a conflicting finding with regard to the prognostic effect of postoperative complications.^{13,19,26} In the current study, we systematically searched relevant literatures and evaluated the correlation between postoperative complications and oncological outcomes of gastric carcinoma patients. The results of meta-analysis indicated that the presence of postoperative complications, including infectious complications, intra-abdominal infectious complications, anastomotic leakage and postoperative pneumonia were predictors of recurrence and poor long-term survival.

The following several possible reasons may explain why there was a negative correlation between postoperative complications and prognostic outcomes. First, inflammatory responses to severe postoperative complications may result in immune suppression. The cell-mediated immune response, particularly involving cytotoxic T lymphocytes and natural killer cells, is compromised by systemic inflammation and surgical stress, promoting the immune escape of micrometastatic carcinoma cells.^{39,40} Second, a large amount of activated leukocytes and cytotoxic mediators such as interleukin-1(IL-1), IL-6 and TNF- α released from the inflammatory response could accelerate the proliferation and invasion ability of residual cancer cells, which promotes the development of tumor recurrence and metastasis.^{13,41}

Consequently, reducing surgical stress and postoperative inflammatory responses may be helpful to improve short-term and long-term outcomes. Recent evidence have demonstrated that laparoscopic surgery for gastric carcinoma has more advantages over open gastrectomy in the field of surgical trauma, intraoperative blood loss and postoperative recovery.^{42,43} With the advancement in laparoscopic technique and accumulation of surgical experience, laparoscopic gastrectomy has increasingly become an alternative surgical procedure for gastric carcinoma patients, and surgical trauma and the incidence of postoperative complications would be further reduced in the future.

Another possible explanation for the adverse impact of postoperative complications on survival outcome is the delayed initiation of adjuvant chemotherapy or the omission of adjuvant chemotherapy caused by severe postoperative complications. In general, adjuvant chemotherapy should be initiated as soon as possible after full recovery from surgery. It has been demonstrated that advanced, resectable gastric carcinoma patients could benefit from perioperative chemotherapy.⁴⁴ However, Kubota et al revealed that the initiation time of adjuvant chemotherapy for gastric carcinoma patients who had postoperative complications was later by at least a median of 1 week than that for those who had no postoperative complications.⁴ A previous report demonstrated that at least half of gastric carcinoma patients who had postoperative complications were unlikely to be treated by adjuvant chemotherapy.²⁹ The data revealed that the combination of postoperative complications and no adjuvant chemotherapy increased the risk of death by more than 200% in comparison to patients who did not experience postoperative complications and received adjuvant chemotherapy. However, the overall survival of gastric carcinoma patients with postoperative complications could be improved by adjuvant chemotherapy.²⁹ In other words, delayed initiation or the failure to receive adjuvant chemotherapy may play an intermediate role in decreased survival of patients with postoperative complications.

Anastomotic leakage is a major and serious surgical-related complication, and its incidence varies from 1.1% to 8.7% in gastric carcinoma patients who underwent surgical resection.^{7,8,23,31} Despite the low incidence, anastomotic leakage prolongs the length of hospital stay and increases the risk of hospital mortality. The results of the current study indicated that anastomotic leakage had a detrimental impact on the long-term survival outcome of gastric carcinoma patients. Based on these findings, meticulous surgical techniques and intensive perioperative care should be encouraged to minimize the morbidity rate and improve long-term oncological outcomes. Postoperative pneumonia was another common complication after surgical resection for gastric carcinoma, and its frequency has been reported to be 1.6% to 12.8%.^{5,23,35} Our study also investigated the influence of postoperative pneumonia on oncological outcomes, indicating that it is responsible for worse overall survival of gastric carcinoma patients who underwent curative-intent resection. Concerning the occurrence of postoperative pneumonia, it has been shown that elder age (≥ 65 years), poor

nutritional status, advanced tumor stage (\geq stage II), comorbid disease, total gastrectomy and extended lymphadenectomy are its independent risk factors.^{10,35} To prevent the occurrence of postoperative pneumonia, active preoperative interventions such as respiratory function training and sufficient nutritional support should be considered.

In the current study, we confirmed the negative correlation between postoperative complications and poor survival in gastric carcinoma patients who underwent gastrectomy. Based on current evidence, however, it is difficult to determine whether the systemic inflammatory response or postoperative complications themselves have a direct effect on the survival outcomes of these patients. Saito et al reported that the 5-year RFS of patients who had postoperative complications was significantly worse than that of those who did not experience postoperative complications, but adjusted multivariate analysis indicated that the level of serum C-reactive protein (CRP) rather than postoperative complication could independently affect the prognostic outcome of gastric carcinoma patients.¹³ The researchers believed that systemic inflammatory response induced by surgical trauma and tissue damage resulted in poor prognostic outcome even if postoperative complications did not occur. In addition, it is also hard to determine that the negative correlation should be ascribed to patient-specific conditions or postoperative complications. It has been reported that combined multiorgan resection, extended lymphadenectomy, a high body mass index (BMI) (≥ 25 kg/m²) and prolonged operation time are independent predictors for the presence of postoperative complications.^{16,17,45} In addition to surgery-related factors, postoperative complications can occur as a result of other factors such as advanced age, poor performance status and severe comorbidities,²³ which also can significantly affect the oncological evaluation of gastric carcinoma patients, especially in the case of death unrelated to gastric carcinoma.

Several limitations may still exist in this study and need to be further underlined. First, the level of current evidence from this meta-analysis is relatively limited. All data and conclusions were based on retrospective design, which inevitably introduces a potential source of bias. Moreover, the studies that did not provide data on HR and its 95% CIs had to be excluded from this meta-analysis, which might also result in a potential bias. Second, although all studies used the Clavien-Dindo grade to assess the severity of postoperative complications, its definition was inconsistent across studies. Not all studies classified patients with grade II or more severe postoperative complications into the research group. Moreover, the occurrence time of postoperative complications were not clearly defined by a few studies. These differences may become a potential source of high heterogeneity and limit the comparison between postoperative complication and non-complication groups. However, we further performed a subgroup analysis for the severity and the occurrence time of postoperative complications to determine their impacts on the prognosis of gastric carcinoma patients, and the results still showed a significant finding. Third, although we used adjusted HR and 95% CIs to perform the pooled analysis, there may be several covariates or

unknown factors (e.g., physical status, comorbidities and surgical quality) that were not included in multivariate Cox regression analysis. On the other hand, the baseline characteristics, such as surgical procedures, the extent of lymphadenectomy and the administration of adjuvant chemotherapy, were not comparable among the included studies. However, it is unlikely to design and carry out a RCT for evaluating the prognostic significance of postoperative complications for gastric carcinoma patients since their occurrence could not be controlled or adjusted. This systematic review and meta-analysis was helpful for understanding the prognostic significance of postoperative complications in gastric carcinoma patients and guiding subsequent treatment strategies.

Conclusions

Postoperative complications including infectious complications, intra-abdominal infectious complications, anastomotic leakage and postoperative pneumonia were significantly associated with poor survival outcomes and tumor recurrence in gastric carcinoma patients. Although the exact mechanism underlying this negative correlation was unclear, the establishment of perioperative management aimed at minimizing complications was necessary for the improvement of short-term and long-term outcomes of resectable gastric carcinoma patients.

Authors' Note

Guofeng Chen, MD, and Jun Wang, MD, are equal contributors to this work. All data and materials related to this manuscript can be accessed via e-mail to the corresponding author. No ethical approval and informed consent were required for this systematic review and meta-analysis.


Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Zhejiang Provincial Key Project of Research and Development (2019C03043).

ORCID iD

Jian Chen, MD  <https://orcid.org/0000-0002-2542-9669>

Supplemental Material

Supplemental material for this article is available online.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.
2. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of

- the randomised nationwide Dutch D1D2 trial. *Lancet Oncol.* 2010;11(5):439-449.
3. Mocellin S, McCulloch P, Kazi H, Gama-Rodrigues JJ, Yuan Y, Nitti D. Extent of lymph node dissection for adenocarcinoma of the stomach. *Cochrane Database Syst Rev.* 2015;2015(8)..
 4. Kubota T, Hiki N, Sano T, et al. Prognostic significance of complications after curative surgery for gastric cancer. *Ann Surg Oncol.* 2014;21(3):891-898.
 5. Powell A, Coxon AH, Patel N, Chan D, Christian A, Lewis W. Prognostic significance of post-operative morbidity severity score after potentially curative D2 gastrectomy for carcinoma. *J Gastrointest Surg.* 2018;22(9):1516-1527.
 6. Hayashi T, Yoshikawa T, Aoyama T, et al. Impact of infectious complications on gastric cancer recurrence. *Gastric Cancer.* 2015;18(2):368-374.
 7. Fujiya K, Tokunaga M, Mori K, et al. Long-term survival in patients with postoperative intra-abdominal infectious complications after curative gastrectomy for gastric cancer: a propensity score matching analysis. *Ann Surg Oncol.* 2016;23(suppl 5):809-816.
 8. Sierzega M, Kolodziejczyk P, Kulig J, Polish Gastric Cancer Study Group. Impact of anastomotic leakage on long-term survival after total gastrectomy for carcinoma of the stomach. *Br J Surg.* 2010;97(7):1035-1042.
 9. Yoo HM, Lee HH, Shim JH, Jeon HM, Park CH, Song KY. Negative impact of leakage on survival of patients undergoing curative resection for advanced gastric cancer. *J Surg Oncol.* 2011;104(7):734-740.
 10. Kiuchi J, Komatsu S, Ichikawa D, et al. Putative risk factors for postoperative pneumonia which affects poor prognosis in patients with gastric cancer. *Int J Clin Oncol.* 2016;21(5):920-926.
 11. Tu RH, Lin JX, Li P, et al. Prognostic significance of postoperative pneumonia after curative resection for patients with gastric cancer. *Cancer Med.* 2017;6(12):2757-2765.
 12. Wu C, Wang N, Zhou H, et al. Effects of neoadjuvant chemotherapy toxicity and postoperative complications on short-term and long-term outcomes after curative resection of gastric cancer. *J Gastrointest Surg.* 2020;24(6):1278-1289.
 13. Saito T, Kurokawa Y, Miyazaki Y, et al. Which is a more reliable indicator of survival after gastric cancer surgery: postoperative complication occurrence or C-reactive protein elevation? *J Surg Oncol.* 2015;112(8):894-899.
 14. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205-213.
 15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25(9):603-605.
 16. Li QG, Li P, Tang D, Chen J, Wang DR. Impact of postoperative complications on long-term survival after radical resection for gastric cancer. *World J Gastroenterol.* 2013;19(25):4060-4065.
 17. Tokunaga M, Tanizawa Y, Bando E, Kawamura T, Terashima M. Poor survival rate in patients with postoperative intra-abdominal infectious complications following curative gastrectomy for gastric cancer. *Ann Surg Oncol.* 2013;20(5):1575-1583.
 18. Abdul KATM, Murakami Y, Yoshimoto M, et al. Intra-abdominal complications after curative gastrectomies worsen prognoses of patients with stage II-III gastric cancer. *Yonago Acta Med.* 2016; 59(3):210-216.
 19. Climent M, Hidalgo N, Vidal O, et al. Postoperative complications do not impact on recurrence and survival after curative resection of gastric cancer. *Eur J Surg Oncol.* 2016;42(1):132-139.
 20. Jiang N, Deng JY, Ding XW, et al. Effect of complication grade on survival following curative gastrectomy for carcinoma. *World J Gastroenterol.* 2014;20(25):8244-8252.
 21. Vicente D, Ikoma N, Chiang YJ, et al. Preoperative therapy for gastric adenocarcinoma is protective for poor oncologic outcomes in patients with complications after gastrectomy. *Ann Surg Oncol.* 2018;25(9):2720-2730.
 22. Takeuchi D, Koide N, Suzuki A, et al. Postoperative complications in elderly patients with gastric cancer. *J Surg Res.* 2015; 198(2):317-326.
 23. Li Z, Bai B, Zhao Y, et al. Severity of complications and long-term survival after laparoscopic total gastrectomy with D2 lymph node dissection for advanced gastric cancer: a propensity score-matched, case-control study. *Int J Surg.* 2018;54(Pt A):62-69.
 24. Mohri Y, Tanaka K, Toiyama Y, et al. Impact of preoperative neutrophil to lymphocyte ratio and postoperative infectious complications on survival after curative gastrectomy for gastric cancer: a single institutional cohort study. *Medicine (Baltimore).* 2016;95(11):e3125.
 25. Tu RH, Lin JX, Li P, et al. Comprehensive complication index predicts cancer-specific survival of patients with postoperative complications after curative resection of gastric cancer. *Gastroenterol Res Pract.* 2018;2018..
 26. Watanabe M, Kinoshita T, Tokunaga M, Kaito A, Sugita S. Complications and their correlation with prognosis in patients undergoing total gastrectomy with splenectomy for treatment of proximal advanced gastric cancer. *Eur J Surg Oncol.* 2018; 44(8):1181-1185.
 27. Eto K, Hiki N, Kumagai K, et al. Prophylactic effect of neoadjuvant chemotherapy in gastric cancer patients with postoperative complications. *Gastric Cancer.* 2018;21(4):703-709.
 28. Zhuang CL, Huang DD, Pang WY, et al. Sarcopenia is an independent predictor of severe postoperative complications and long-term survival after radical gastrectomy for gastric cancer: analysis from a large-scale cohort. *Medicine (Baltimore).* 2016;95(13):e3164.
 29. Jin LX, Sanford DE, Squires MH, et al. Interaction of postoperative morbidity and receipt of adjuvant therapy on long-term survival after resection for gastric adenocarcinoma: results from the U.S. gastric cancer collaborative. *Ann Surg Oncol.* 2016;23(8):2398-2408.
 30. Tsujimoto H, Ichikura T, Ono S, et al. Impact of postoperative infection on long-term survival after potentially curative resection for gastric cancer. *Ann Surg Oncol.* 2009;16(2):311-318.
 31. Andreou A, Biebl M, Dadras M, et al. Anastomotic leak predicts diminished long-term survival after resection for gastric and esophageal cancer. *Surgery.* 2016;160(1):191-203.
 32. Nagasako Y, Satoh S, Isogaki J, Inaba K, Taniguchi K, Uyama I. Impact of anastomotic complications on outcome after laparoscopic gastrectomy for early gastric cancer. *Br J Surg.* 2012; 99(6):849-854.
 33. Kim SH, Son SY, Park YS, Ahn SH, Park DJ, Kim HH. Risk factors for anastomotic leakage: a retrospective cohort study in a

- single gastric surgical unit. *J Gastric Cancer*. 2015;15(3):167-175.
34. Liu J, Hong L, Yang X, et al. Analysis of risk factors and prognosis of esophagojejunal anastomotic leakage in gastric cancer patients after curative total gastrectomy. *Zhonghua Wei Chang Wai Ke Za Zhi*. 2016;19(7):756-762.
35. Suzuki S, Kanaji S, Matsuda Y, et al. Long-term impact of postoperative pneumonia after curative gastrectomy for elderly gastric cancer patients. *Ann Gastroenterol Surg*. 2018;2(1):72-78.
36. Kamarajah SK, Navidi M, Griffin SM, Phillips AW. Impact of anastomotic leak on long-term survival in patients undergoing gastrectomy for gastric cancer. *Br J Surg*. 2020;107(12):1648-1658.
37. Kanda M, Ito S, Mochizuki Y, et al. Multi-institutional analysis of the prognostic significance of postoperative complications after curative resection for gastric cancer. *Cancer Med*. 2019;8(11):5194-5201.
38. Tokunaga M, Kurokawa Y, Machida R, et al. Impact of postoperative complications on survival outcomes in patients with gastric cancer: exploratory analysis of a randomized controlled JCOG1001 trial. *Gastric Cancer*. 2020;24(1):214-223.
39. Lerut T, Moons J, Coosemans W, et al. Postoperative complications after transthoracic esophagectomy for cancer of the esophagus and gastroesophageal junction are correlated with early cancer recurrence: role of systematic grading of complications using the modified Clavien classification. *Ann Surg*. 2009;250(5):798-807.
40. Roxburgh CS, Horgan PG, McMillan DC. The perioperative immune/inflammatory insult in cancer surgery: time for intervention? *Oncoimmunology*. 2013;2(12):e27324.
41. Okamura A, Takeuchi H, Matsuda S, et al. Factors affecting cytokine change after esophagectomy for esophageal cancer. *Ann Surg Oncol*. 2015;22(9):3130-3135.
42. Kim W, Kim HH, Han SU, et al. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer: short-term outcomes from a multicenter randomized controlled trial (KLASS-01). *Ann Surg*. 2016;263(1):28-35.
43. Bo T, Peiwu Y, Feng Q, et al. Laparoscopy-assisted vs. open total gastrectomy for advanced gastric cancer: long-term outcomes and technical aspects of a case-control study. *J Gastrointest Surg*. 2013;17(7):1202-1208.
44. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393(10184):1948-1957.
45. Xiao H, Xiao Y, Quan H, Liu W, Pan S, Ouyang Y. Intra-abdominal infection after radical gastrectomy for gastric cancer: incidence, pathogens, risk factors and outcomes. *Int J Surg*. 2017;48:195-200.