Systematic Review and Meta-Analysis

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The safety and efficacy of chemotherapy combined with immunotherapy for pancreatic cancer

A meta-analysis

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Abstract

Background: Since the combination of chemotherapy and immunotherapy, such as new molecular targeted drugs or vaccines, is controversial in terms of survival advantages compared with chemotherapy therapy alone, we conducted a meta-analysis to compare the efficacy and safety of immunotherapy combined with chemotherapy and chemotherapy alone for advanced pancreatic cancer.

Methods: We searched PubMed, Embase, and Cochrane Library from the establishment of the database to November 2020. We included some studies that reported pancreatic cancer patients receiving immunotherapy, and we excluded duplicate publications, research without full text, incomplete information or inability to conduct data extraction, animal experiments, reviews, and systematic reviews.

Results: The risk ratio of the objective response rate and disease control rate was 1.10 (95% confidence interval [CI]: 0.88–1.38) and 1.17 (95% CI: 1.06–1.31), respectively, indicating that there was no significant difference between the objective response rate of combination therapy and chemotherapy alone, while the disease control rate of the combined treatment was higher than that of chemotherapy alone. The hazard ratio of overall survival and progression-free survival was 0.91 (95% CI: 0.82–1.01) and 0.87 (95% CI: 0.77–0.98), respectively, indicating that there was no significant difference between the overall survival of combination therapy and chemotherapy alone, while progression-free survival of the combined treatment was longer than that of chemotherapy alone. We also found that in addition to the combination treatment, the incidence of vomiting in pancreatic cancer was higher than that of chemotherapy alone, and the incidence of other complications was not significantly different from that of treatment alone.

Conclusion: Chemotherapy combined with immunotherapy for pancreatic cancer not only improves treatment efficiency but also does not cause serious adverse reactions. This treatment strategy should be widely used clinically.

Abbreviations: AEs = adverse events, CI = confidence interval, DCR = disease control rate, GEM = Gemcitabine, HR = hazard ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, RCTs = randomized controlled trials, RR = risk ratio.

Keywords: chemotherapy, combination therapy, immunotherapy, meta-analysis, pancreatic cancer

1. Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths worldwide, with a 5-year survival rate of <9%. Most patients with pancreatic cancer are diagnosed with unresectable advanced disease and die from the disease within 1 year.[1] Therefore, most patients require adjuvant therapy, such as radiotherapy and chemotherapy. Chemotherapy is known to prolong the survival of patients with advanced pancreatic cancer.[2,3] Although cytotoxic drugs are generally believed to have immunosuppressive effects, certain chemotherapies may enhance the effects of cancer vaccines.[4–8] Gemcitabine (GEM) and fluorouracil induce apoptosis of cancer cells, leading to the release of antigens, which can be absorbed by professional antigen-presenting cells and cross-presented to cytotoxic T cells.[9] The guidelines have recommended GEM monotherapy as the first-line treatment for unresectable locally advanced metastatic ductal carcinoma of the pancreas since 1997.[10] With the continuous emergence of single chemotherapy treatment failures, it is becoming increasingly important to explore new combination regimens.

Editor: Jianxun Ding.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

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How to cite this article: Huang Y, Yan X, Ren T, Yi F, Li Q, Zhang C. The safety and efficacy of chemotherapy combined with immunotherapy for pancreatic cancer: a meta-analysis. Medicine 2021;100:29(e26673).

Received: 14 December 2020 / Received in final form: 24 February 2021 / Accepted: 17 June 2021

http://dx.doi.org/10.1097/MD.0000000000026673

Several large clinical randomized controlled trials (RCTs) have been implemented to further observe the effectiveness and safety of GEM-based combination therapy.[11] In addition, FOLFIRINOX, 5-fluorouracil, Abraxane, and other chemotherapeutics other than GEM can also be used to treat pancreatic cancer. In recent years, immunotherapy, including PD1/PDL1 and CTLA-4 immune checkpoint inhibitors, has become more widely used in pancreatic cancer.[12] However, the combination of chemotherapy and immunotherapy, such as new molecular targeted drugs or vaccines, is controversial in terms of survival advantages compared with chemotherapy alone. Therefore, more representative results are needed to compare the efficacy and safety of immunotherapy combined with chemotherapy and chemotherapy alone, to provide guidance for current clinical treatment. In this meta-analysis, we compared the efficacy and safety of immunotherapy combined with chemotherapy and chemotherapy alone for advanced pancreatic cancer.

2. Methods

2.1. Literature inclusion and exclusion criteria

Inclusion criteria were limited to RCTs and language was limited to English.

Exclusion criteria include as follows: repetitive publication; study without full text, incomplete information, or data extraction is impossible; and the definition of exposure is quite different from most of the literature and the incomplete ethics review.

2.2. Search strategy

We searched PubMed, Embase, and Cochrane Library. The search period was from the establishment of the database until November 2020. The combination of subject words and free words was used to search for the search terms. Search terms included "pancreatic neoplasms" "pancreas cancers" "pancreatic carcinoma" "pancreatic cancers," and "immunotherapy" "pembrolizumab" "tremelimumab" "avelumab" "cetuximab" "bevacizumab" "erlotinib," and "chemotherapy" "FOLFIRINOX" "5-FU," and "Abraxane."

2.3. Literature screening and data extraction

The literature search, screening, and information extraction were independently completed by 2 researchers. When there were doubts or disagreements, the decision or consultation with a third party was made after discussion. The content of data extraction included author, year, country, research type, number of cases, objective response rate (ORR), disease control rate (DCR), overall survival (OS), and progression-free survival (PFS).

2.4. Literature quality assessment

Two researchers independently conducted the literature quality assessment according to the Cochrane risk assessment scale. When opinions are inconsistent, it is decided through a discussion or consultation with a third person. The meta-analysis was performed based on the items related to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (PRISMA statement).[13]

2.5. Statistical methods

The data were analyzed using Review Manager version 5.3. Risk ratio (RR) was used to compare the ORR and DCR of the 2 groups, and hazard ratio (HR) (95% confidence interval [CI]) was used to assess PFS and OS. If the heterogeneity test was $P \geq .1$, $I^2 \leq 50\%$, the fixed-effect model was used for the combined analysis; if $P < .1$, $I^2 > 50\%$, the random effect model was used for the combined analysis, and sensitivity analysis and meta-regression were used to explore sources of heterogeneity when necessary. Since the number of articles in this study was less than 10, no publication bias was discussed.

3. Results

3.1. The results of the literature search

In this study, 1177 studies were retrieved from the database. After eliminating duplicate studies, a total of 837 patients were obtained. After browsing the titles and abstracts, 681 studies were conducted. Finally, after the full-text reading, 8 articles were included in the meta-analysis (Fig. 1).

3.2. Baseline characteristics and quality assessment of the included studies

3.2.1. Baseline characteristics. Eight RCT studies were included in this meta-analysis. The sample size ranged from 84 to 743, and a total of 2547 patients were included in the present meta-analysis. Patients in 2 studies were from Asia, while the others were from Europe and America (Table 1).

3.2.2. Quality assessment of the included studies. The quality assessment of these included studies are shown in Figures 2 and 3

3.3. Results of meta-analysis

3.3.1. Efficacy analysis. Six studies, including 2223 patients, reported the RR of the ORR. Since there was no significant heterogeneity ($I^2 = 0.0\%$, $P = .55 > .1$), a meta-analysis was conducted using a fixed-effects model. The RR of ORR was 1.10 (95% CI: 0.88–1.38), indicating that there was no significant difference between the ORR of combination therapy and chemotherapy alone (Fig. 4A).

Five studies, including 1554 patients, reported the RR of DCR. Since there was no significant heterogeneity ($I^2 = 0.0\%$, $P = .51 > .1$), a meta-analysis was conducted using a fixed-effects model. The RR of DCR was 1.17 (95% CI: 1.06–1.31), indicating that the DCR of the combined treatment was higher than that of chemotherapy alone (Fig. 4B).

Six studies, including 1777 patients, reported the HR of OS. Since there was no significant heterogeneity ($I^2 = 6\%$, $P = .380.1$), a meta-analysis was conducted using a fixed-effects model. The HR of OS was 0.91 (95% CI: 0.82–1.01), indicating that there was no significant difference between the OS of combination therapy and chemotherapy alone (Fig. 4C).

Four studies, including 1022 patients, reported the HR of PFS. Since there was no significant heterogeneity ($I^2 = 50\%$, $P = .110.1$), a meta-analysis was conducted using a fixed-effects model. The HR of PFS was 0.87 (95% CI: 0.77–0.98), indicating that the PFS of the combined treatment was longer than that of chemotherapy alone (Fig. 4D).

3.3.2. Incidence of adverse events. Among all studies, 7 were included in the analysis of grade ≥3 adverse events. Moreover,

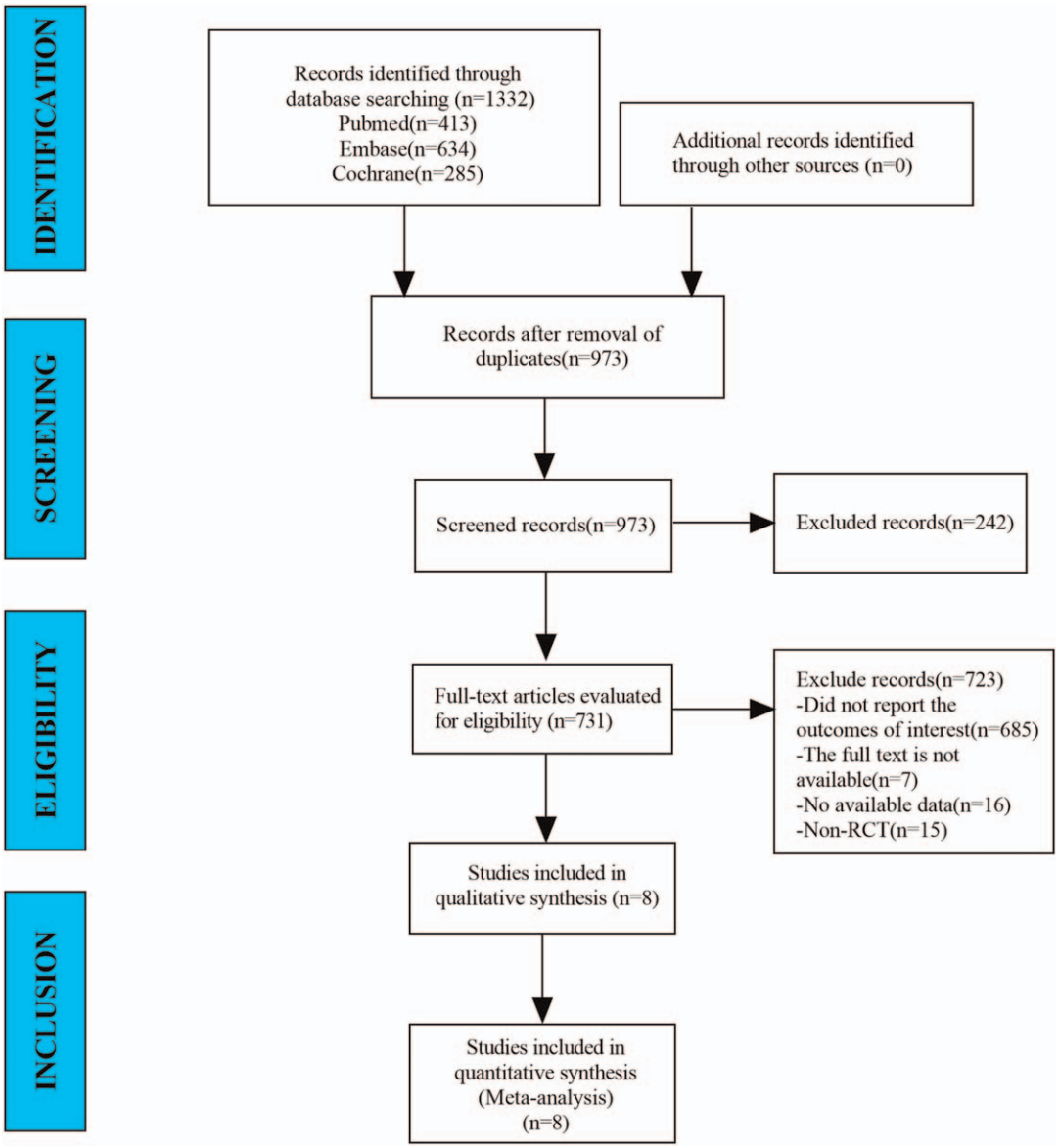

Figure 1. Flow diagram for selection of studies.

Table 1

Baseline characteristics of the included studies.

					Number of cases		Age		Gender		
Author	Year	Country	Research type	Median follow-up time (months)	Combined therapy	Chemotherapy	Combined therapy	Chemotherapy	Combined therapy	Chemotherapy	Measures of combined therapy
Cascinu et al[14]	2008	Italy	RCT	11.8	42	42	61.0 (38.0–78.0)	64.0 (40.0–76.0)	29/13	22/20	Gemcitabine + Cetuximab
Philip et al[15]	2010	Canada	RCT	/	372	371	63.7	64.3	51/79	54/46	Gemcitabine + Cetuximab
Kindler et al[16]	2010	United States	RCT	12	302	300	63.7 (26.0–88.0)	65.0 (35.0–86.0)	175/127	168/162	Gemcitabine + Bevacizumab
Wang et al[17]	2013	China	RCT	/	28	30	50.25	50.22	15/13	16/14	S-1 + CIK
Middleton et al[18]	2014	United Kingdom	RCT	6	354	358	62.0 (55.0–69.0)	63.0 (57.0–69.0)	196/158	209/149	Gemcitabine + GVAX
Yamaue et al[19]	2015	Japan	RCT	3.7	100	53	63.5 (38.0–80.0)	65.0 (36.0–80.0)	62/38	31/22	Gemcitabine + Elpamotide
Dalgleish et al[20]	2016	United Kingdom	RCT	6.7	75	35	68.0 (45.0–88.0)	66.0 (53.0–83.0)	38/37	21/14	Gemcitabine + IMM-101
Nishida et al[21]	2018	Japan	RCT	12	42	43	66.0 (37.0–77.0)	65.0 (43–77)	26/16	25/18	Gemcitabine + WT1

RCTs = randomized controlled trials.

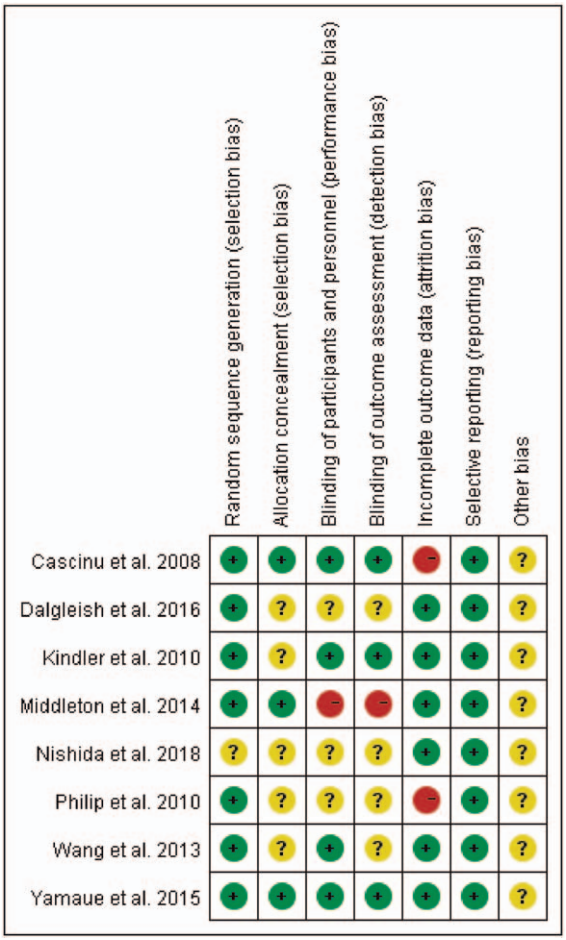

Figure 2. Risk of bias summary.

studies with insufficient data were excluded from the analysis. The pooled RR of diarrhea, nausea, vomiting, and increased ALT and AST between the combined treatment group and chemotherapy group were 1.09 (95% CI: 0.64–1.88; $I^2=0$), 1.31 (95% CI: 0.91–1.88; $I^2=0$), 1.54 (95% CI: 1.02–2.31; $I^2=21$), 1.36 (95% CI: 0.72–2.56; $I^2=0$), and 1.52 (95% CI: 0.54–4.27; $I^2=0$), respectively (Fig. 5). The results showed that the incidence of vomiting in combination therapy was higher than that in the chemotherapy alone, and the incidence of other complications was not significantly different from that of chemotherapy alone.

3.4. Publication bias

A funnel plot of this study is shown in Figure 6. It can be seen that the funnel plot is basically symmetrical, indicating that there is no obvious publication bias in this study.

3.5. Sensitivity analysis

Sensitivity analysis eliminates each included study one by one and performs a summary analysis on the remaining studies to assess whether a single included study has an excessive impact on the results of the entire meta-analysis. The results showed that none of the studies had an excessive impact on the results of the meta-analysis, indicating that the results of the remaining studies were stable and reliable.

3.6. Discussion

GEM, FOLFIRINOX, 5-fluorouracil, Abraxane, and other chemotherapeutics have been commonly used to treat pancreatic cancer. In recent years, immunotherapy, including PD1/PDL1 and CTLA-4 immune checkpoint inhibitors, has become more widely used in pancreatic cancer.[12] However, the combination of chemotherapy and immunotherapy, such as new molecular targeted drugs or vaccines, is controversial in terms of survival advantages compared with chemotherapy alone, and we conducted a meta-analysis to compare the efficacy and safety of immunotherapy combined with chemotherapy and chemotherapy alone for advanced pancreatic cancer. In this meta-analysis, we included 8 articles involving 2547 patients.

Pancreatic cancer is characterized by early local regional spread and distant metastasis. Most patients cannot be cured by surgical resection when they are diagnosed, and without effective treatment, the overall median survival time is 4.6

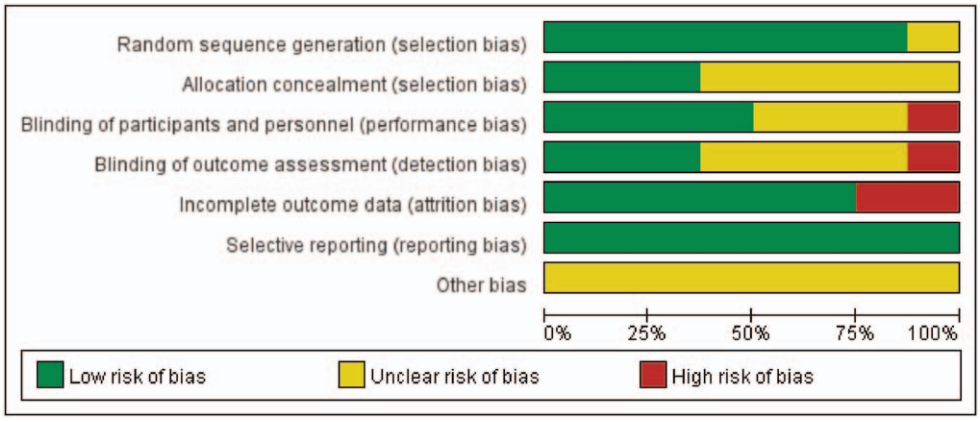

Figure 3. Risk of bias items.

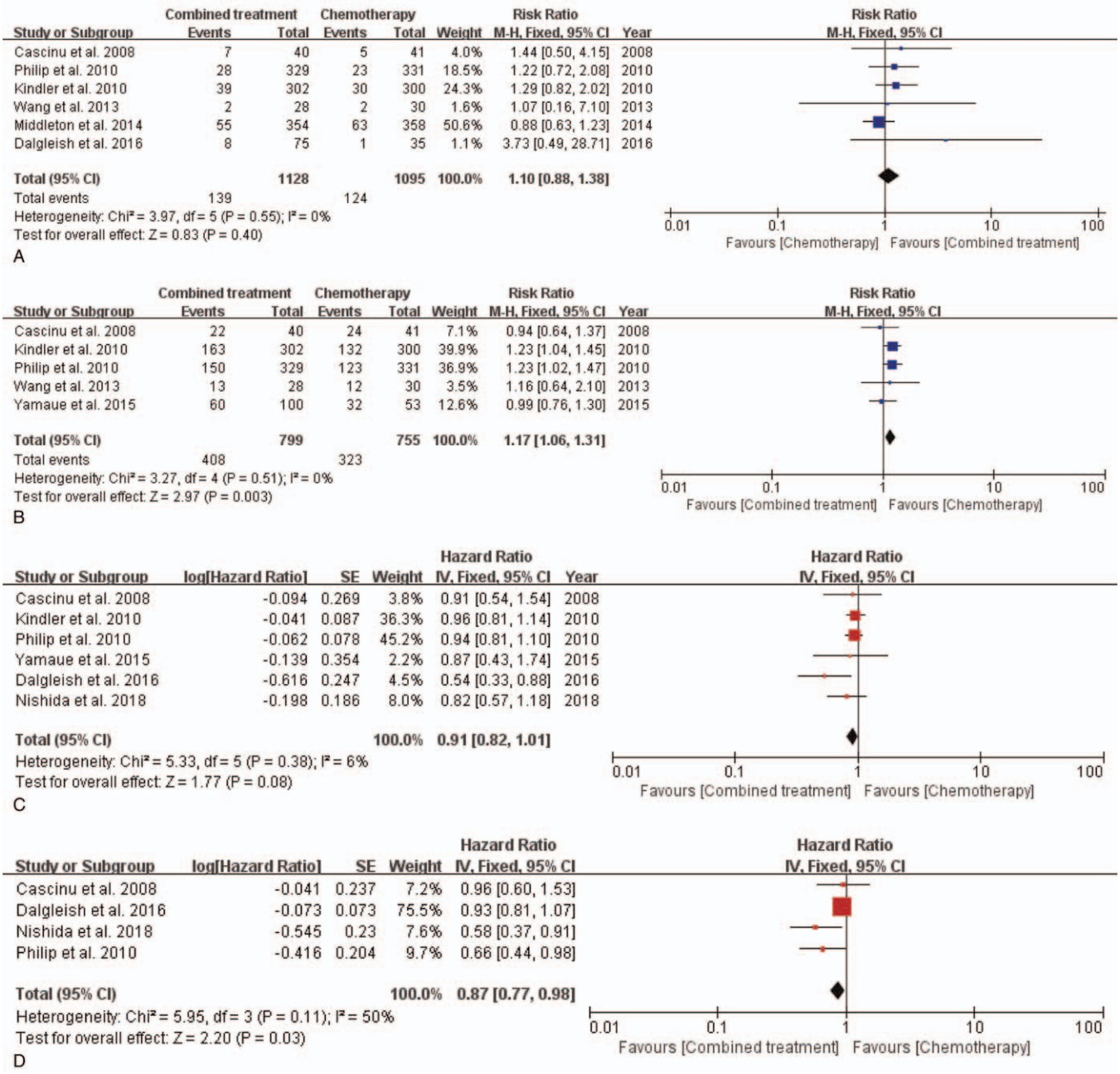

Figure 4. RR of (A) ORR, (B) DCR, (C) OS, and (D) PFS for combined treatment and chemotherapy alone in pancreatic cancer. ORR = objective response rate, OS = overall survival, PFS = progression-free survival.

months, especially in patients with metastatic cancer, with a median survival time of 2.8 to 5.7 months.[22] Our pooled results showed that the DCR of the combined treatment was higher than that of chemotherapy alone (RR = 1.17, 95% CI: 1.06–1.31) and the PFS of the combined treatment was longer than that of chemotherapy alone (HR = 0.87, 95% CI: 0.77–0.98). Cancer immunotherapy is a promising strategy for treating pancreatic cancer. Unfortunately, immunotherapy in large or late clinical trials failed to show satisfactory clinical results, which can be expected in some early studies.[23,24] So far, immune checkpoint inhibitors, including anti-PD1/PDL1 and CTLA-4, have also failed to achieve the desired goal.[25] The relative absence of immunotherapy efficacy in pancreatic cancer might also partly be related to specific carcinoma-associated fibroblasts, which secrete CXCL12 and thus stop T cells from accessing cancer cell regions in the stroma.[26,27] Considering the difficulty of developing cancer immunotherapies for pancreatic cancer, our pooled results provide a way to increase the anti-tumor response of patients.

We also explored the safety of the combination therapy. Findings show that in addition to the combination treatment, the incidence of pancreatic cancer vomiting was higher than that of

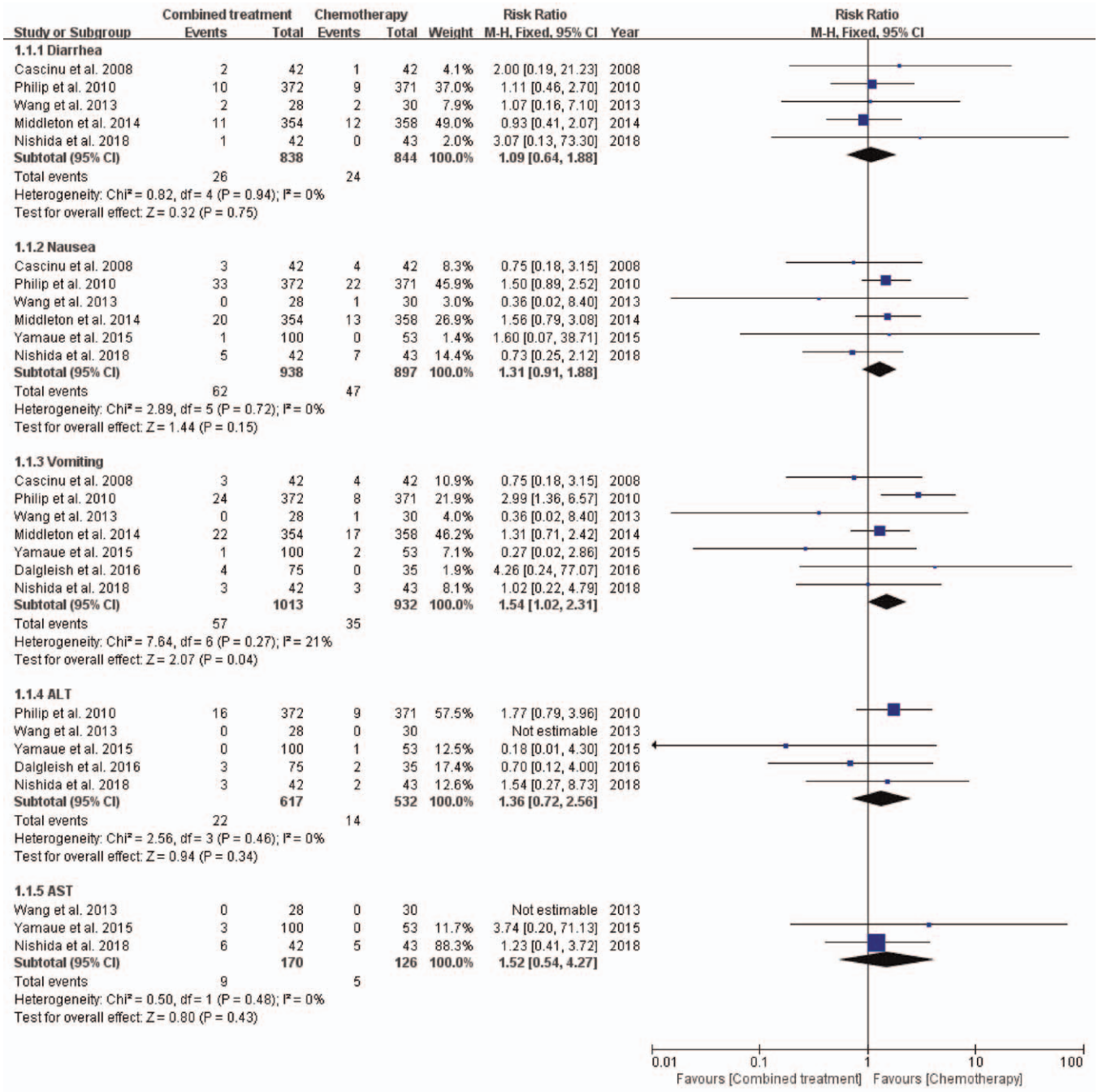

Figure 5. The incidence of AEs of combined treatment and chemotherapy alone in pancreatic cancer. AEs = adverse events.

chemotherapy alone, and the incidence of other complications was not significantly different from that of treatment alone. This also strengthens our confidence in the use of combination therapies for pancreatic cancer.

This meta-analysis had some limitations. Since the number of included articles was less than 10, we did not carry out Egger bias test, which may have led to some potential publication bias. Future studies need to include more RCTs to further verify our pooled results.

3.7. Conclusion

Chemotherapy combined with immunotherapy for pancreatic cancer can not only improve treatment efficiency but also will not

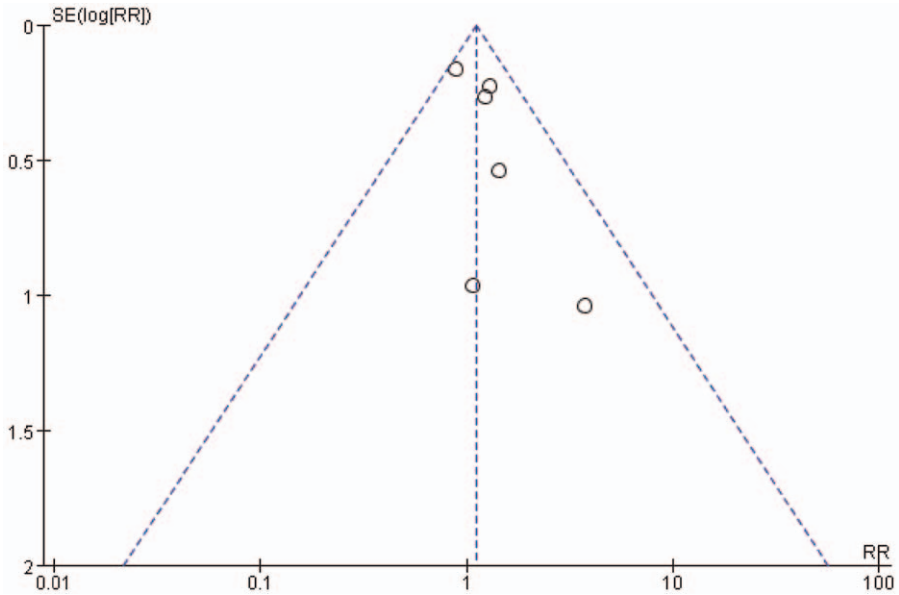

Figure 6. Funnel plot for evaluating the publication bias of this meta-analysis.

cause serious adverse reactions. This treatment strategy should be widely used clinically.

Author contributions

Yang Huang conceived the study and wrote the manuscript. Xu Yan and Tian Ren provided the direction. Fan Yi and Qi Li participated in data collection. Chunyang Zhang conceived the final approval of the version to be submitted and obtaining of funding.

Conceptualization: Yang Huang.
Data curation: Xu Yan, Tian Ren, Fan Yi, Qi Li.
Writing – original draft: Yang Huang.
Writing – review & editing: Chunyang Zhang.

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