The efficacy and safety of first-line anti-PD-1/PD-L1 immunotherapy for gastric esophageal cancer: A systematic review and meta-analysis of phase III randomized controlled trials

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Abstract. Immunotherapy-based regiments have potential as first-line treatment for advanced gastric esophageal cancer. The present study aimed to conduct a meta-analysis of the association between the efficacy and safety of first-line immunotherapy combined with chemotherapy in patients with unresectable locally advanced or metastatic gastric esophageal cancer. Subgroup analysis of patients with programmed death ligand 1 (PD-L1) combined positive score (CPS) was conducted to identify the characteristics of patients with immune benefit and to provide a decision-making basis for clinical practice. PubMed, Embase, Cochrane Library and other databases were searched to collect randomized controlled trials of immunotreatment-based regimens (experimental group) versus conventional first-line chemotherapy regimens (control group) for unresectable locally advanced or metastatic gastric esophageal cancer. The main outcome measures included progression-free survival (PFS), overall survival (OS), objective response rate, disease control rate and safety, and the secondary outcomes were the differences in OS and PFS between patients with PD-L1 CPS ≥10 and those with PD-L1 CPS <10. In addition, Asian and non-Asian populations were analysed. Nine studies with a total of 6,820 patients were included. The OS of patients treated with immunotherapy-based regimens was significantly longer than that of those treated with chemotherapy alone [HR=0.74; 95% CI (0.69, 0.80); P<0.00001]. The OS of patients with PD-L1 CPS ≥10 and PD-L1 CPS <10 in the experimental group was significantly longer than that of patients in the control group [HR=0.68; 95% CI (0.59, 0.77); P<0.00001 and HR=0.73; 95% CI (0.62, 0.87); P=0.0005]. The PFS of patients being treated with immunotherapy-based regimens was significantly longer than that of those treated with chemotherapy alone [HR=0.71; 95% CI (0.59, 0.86); P=0.0003]. In addition, the PFS of patients with PD-L1 CPS ≥10 and PD-L1 CPS <10 in the experimental group was significantly longer than that of patients in the control group [HR=0.67; 95% CI (0.49, 0.92); P=0.01 and HR=0.63; 95% CI (0.48, 0.83); P=0.001]. There was no significant difference in the overall incidence of adverse events and the incidence of grade 3 or above adverse events between the experimental and control groups [RR=1; 95% CI (0.99, 1.02); P=0.65 and RR=0.97; 95% CI (0.84, 1.12); P=0.69, respectively]. In conclusion, treatment with immunotherapy-based regimens may prolong the OS of patients with unresectable locally advanced or metastatic gastric esophageal cancer and this treatment regimen is safe compared with chemotherapy alone.

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Introduction

Gastric esophageal cancer can be categorized into gastric cancer, esophageal cancer and esophagogastric junction cancer. Gastric esophageal cancer is a common tumour with high morbidity and mortality worldwide. The 2020 Global Cancer Statistics show that the incidence and mortality rates of esophageal cancer were 3.1 and 5.5%, respectively. The incidence (5.6%) and mortality (7.7%) rates of gastric cancer ranked fifth and fourth, respectively, among all cancers (1). Gastric esophageal cancer is insidious and aggressive. Most patients have advanced to the local stage at the time of diagnosis and have thus lost the best opportunity for surgery (2). For locally advanced or metastatic cancers of the esophagus, stomach, or esophagogastric junction that are unresectable, it is generally accepted that comprehensive treatment including chemotherapy, targeted therapy and other systemic antitumour drugs should be adopted. Despite comprehensive treatment regimens, patients still have a high rate of metastasis and

recurrence, which is one of the leading causes of death, and the current five-year survival rate for gastric esophageal cancer is between 15 and 25% (3,4).

In recent years, immune checkpoint inhibitors have become a new therapeutic method for improving the survival of patients with malignant tumours after molecular targeted therapy. Immune checkpoint inhibitors mainly include PD-1 (programmed death receptor 1), PD-L1 (programmed death receptor ligand 1) and CTLA-4 (cytotoxic T lymphocyte-associated protein 4). T lymphocytes play an important role in cancer immune monitoring, but cancer cells can evade tumour reactive T lymphocyte hyperplasia, leading to the occurrence and development of tumours. Immune checkpoint inhibitors mainly block the chain of action of tumour cells by acting on the immune checkpoint on the body's lymphocytes or tumour surface to achieve antitumour effects. CTLA-4 is an immunosuppressive molecule expressed on the surface of regulatory T cells (TreGs), activated CD4+ T cells and depletion-like T cells. CD80/CD86 in antigen-presenting cells (APCs) activates the immune response by binding to the costimulatory receptor CD28, whereas CTLA-4 competes with CD28 to bind CD80/CD86 with greater affinity, resulting in CD28 shedding from APCs. Thus, its ability to further mediate immune activation, induce immune tolerance and produce depletion-like T cells is limited (5). The use of anti-CTLA-4 mab can block the above inhibition, restore the immunoactivation signal mediated by the binding of CD28 to CD80/CD86, and stimulate the activation and proliferation of tumour-specific T cells in lymph nodes. Since CTLA-4-expressing Tregs and depletion-like T cells are also present in the tumour microenvironment, anti-CTLA-4 monoclonal antibodies can also play a role locally in the tumour (5-6). In addition, whole-human immunoglobulin G1 and the toxicity of IgG1-mediated cytotoxicity (ADCC) can be influenced by the combination of ipilimumab and CTLA-4 on Treg cells. Macrophages in the tumour microenvironment are induced to clear Tregs with high expression of CTLA-4, and CD8+ effector T cells with low expression of CTLA-4 are retained to improve the efficiency of the antitumour immune response (7). Anti-ctla-4 mab also stimulates Th1-like CD4+ T-cell expansion during adaptive immune response initiation and the early stage and promotes memory T-cell formation and migration to tumour tissue (8).

On the lymphocyte surface of the body, the combination of programmed cell death protein-1 (PD-1) with programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2) on the surface of tumour cells can inhibit lymphocyte function, decrease the antitumour immune response, increase the incidence of tumour immune escape, and then lead to a decrease in the ability of the immune system to clear the tumour. The use of anti-PD-1 or PD-L1 monoantibodies can block this inhibitory signal and enhance CD8+ effector T-cell proliferation and the local tumour immune response. Other types of immune cells (eg. dendritic cells and B cells) can also be inhibited by the PD-1/PD-L1 pathway, so anti-PD-1 or PD-L1 monoantibodies can simultaneously produce non-T-cell-dependent antitumour effects (9-11).

In recent years, a number of clinical studies on ICIs have shown that they have a good antitumour effect in the treatment of melanoma, NSCLC, pancreatic cancer and other systemic tumours (12-14). At present, according to domestic and foreign guidelines, immune checkpoint inhibitors combined with chemotherapy have become the new standard of first-line therapy for advanced metastatic gastric esophageal cancer. Surgery combined with neoadjuvant chemotherapy-radiotherapy or concurrent chemoradiotherapy is the standard of care for patients with locally advanced esophageal squamous cell carcinoma. However, some locally advanced patients cannot be treated because of complications and other reasons. Several studies, such as KEYNOTE-590, ORIENT-15, and CHECKMATE-648, included patients with inoperable locally advanced esophageal squamous cell carcinoma who were not candidates for radical surgery or radical concurrent chemotherapy. However, the spatial and temporal heterogeneity of gastric esophageal cancer is strong, and the tumour microenvironment is complex. There are differences in epidemiological characteristics, clinicopathological characteristics, biological behaviour, treatment mode and drug selection between Eastern and Western populations of gastric esophageal cancer (15). Therefore, some patients do not benefit from immunotherapy. The selection of markers for predicting tumour immunotherapy can predict the efficacy of immunotherapy. A common immunotherapy sensitivity biomarker is programmed death ligand 1 (PD-L1). Patients with PD-L1 CPS ≥10 have a predictive role for clinical guidance (16). Additionally, the mechanism of immune resistance should be further explored to provide guidance for the follow-up treatment of patients to prolong the overall survival of patients.

Based on the above background, this meta-analysis systematically evaluated the efficacy and safety of first-line immunotherapy combined with chemotherapy compared with conventional chemotherapy for unresectable locally advanced or metastatic gastric esophageal cancer. The study aimed to provide an evidence-based reference for clinical medication.

Subjects and methods

Literature search strategy. The PubMed, Embase and Cochrane Library electronic databases were searched. The search terms included 'esophagogastric junction carcinoma', 'esophageal cancer', 'gastric cancer', 'PD-1', 'immunotherapy', 'RCT', etc. The databases were searched from inception to June 2022. Subject words and free words were used for retrieval. In addition, the reference lists of the included studies were manually searched to identify eligible articles. Detailed search strategies are presented in Table SI. Our study has registered in Prospero and the ID is CRD42022351575.

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Randomized controlled trials (RCTs) published in English; ii) inoperable locally advanced stage or metastatic gastric esophageal cancer patients of any race, nationality, gender and age; iii) patients in the experimental group were treated with immunotherapy-based regimens (including nivolumab + ipilimumab, nivolumab + FP/SOX, toripalimab + TP, etc.), while patients in the control group were treated with chemotherapy alone (including SOX, FP, CAPOX, TP or DP); and iv) outcome indicators included

overall survival (OS) and progression-free survival (PFS) in the total population, PD-L1 CPS ≥10 and PD-L1 <10, objective response rate (ORR), disease control rate (DCR), adverse event (AEs) and adverse event grade ≥3.

The exclusion criteria were as follows: i) Duplicate literature, case reports, editorials or review literature, etc.; ii) non-first-line therapy literature for patients with inoperable locally advanced stage or metastatic gastric esophageal cancer; iii) literature with missing primary data; and iv) non-English articles.

Study outcome. The primary outcomes of interest of this study were a meta-analysis of the efficacy and safety of first-line immunotherapy combined with chemotherapy in patients with unresectable locally advanced or metastatic gastroesophageal cancer. The secondary outcomes of interest of this study were the OS and PFS of patients with PD-L1 expression level (CPS ≥10, CPS <10). In addition, Asian and non-Asian populations were analysed.

Data extraction. Two investigators independently screened the literature according to the inclusion and exclusion criteria. In case of disagreement, the third investigator was consulted and settled. The following data were extracted: experiment name, first author and publication year, country, number of patients, PD-L1 expression level (CPS ≥10, CPS <10), efficacy (OS, PFS, ORR, DCR) and safety (AEs, grade ≥3 AEs).

Outcome index. According to the curative effect evaluation criteria of solid tumours RECIST1.1 (Response Evaluation Criteria In Solid Tumours version 1.1) (17), the curative effect was divided into complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD). Objective response rate (ORR)=(CR cases + PR cases)/total cases x100%, disease control rate (DCR)=(CR cases + PR cases + SD cases)/total cases x100%.

Quality assessment. The quality of the included RCTs was evaluated using the risk of bias assessment tools recommended in the Cochrane Manual for Systematic Reviewers 5.1.0, including random sequence generation, allocation hiding, blinding of subjects and investigators, blinded evaluation of study outcomes, integrity of outcome data, selective reporting of study results, and other sources of bias. Each item was categorized as low risk of bias, high risk of bias, or unclear risk of bias (18).

Statistical analysis. RevMan 5.3 software was used for meta-analysis. Enumeration data were expressed as the risk ratio (RR), hazard ratio (HR) and 95% confidence interval (CI). The chi-square test and I^2 value were used to analyse the heterogeneity among studies. If there was no statistical heterogeneity among studies (P>0.1, I^2<50%), the fixed effects model was used. In contrast, if there was statistical heterogeneity among the studies, a leave-one-out sensitivity analysis was performed to explore the possible sources of heterogeneity. After analysing the sources of heterogeneity and excluding heterogeneity, a random effects model was used for analysis. OS and PFS were subgroup analysed according to the expression of PD-L1. P<0.05 was considered to indicate a statistically significant difference. Funnel plots were used to analyse publication bias.

Results

Search results and characteristics. The literature selection process of this study is detailed in the flow chart (Fig. 1). Through data retrieval and manual retrieval, a total of 2487 articles were identified. After reading the title, abstract and full text, letters or reviews, meta-analyses, cases, animal trials, conference abstracts, bioinformatics and other related articles were deleted. A total of nine phase III randomized controlled trials (RCTs) were included (19-27), although KEYNOTE-062 and CHECKMATE- 648 had two evaluable experimental treatment groups. All included papers were published between 2020 and 2022. A total of 6,820 patients with gastric esophageal cancer were involved in the included studies: 3,798 patients in the experimental group and 3,152 patients in the control group. Asian populations and non-Asian populations were included in the study. Four of the studies focused only on EC, while the others focused on GC/GEJC or EC/GEJC. Detailed basic characteristics are shown in Table I.

Efficacy outcomes of the immunotherapy-based regimens. OS was reported in all 7 studies, and there was no significant statistical heterogeneity (P=0.22, I^2=26%). Therefore, we used the fixed effects model for meta-analysis, and the results showed that the OS of the experimental group (immunotherapy-based regimens) was significantly longer than that of the control group (chemotherapy alone) [HR=0.74; 95% CI (0.69-0.80); P<0.00001] (Fig. 2A).

With respect to PFS, all 7 studies reported PFS, with significant statistical heterogeneity among studies (P<0.00001, I^2=87%). Therefore, we used the random effects model for meta-analysis, and the results showed that the PFS of the experimental group (immunotherapy as the main regimen) was significantly longer than that of the control group (chemotherapy alone) [HR=0.71; 95% CI (0.59, 0.86); P=0.0003] (Fig. 2B). A leave-one-out sensitivity analysis revealed that the source of heterogeneity in the examination of PFS was the CHECKMATE-648 2022 NIVO + IPI group. The forest plot was redrawn without this study, and the heterogeneity was significantly reduced (Fig. S1).

The ORR was reported in all 8 studies, and there was significant statistical heterogeneity among the studies (P<0.00001, I^2=64%). Therefore, we used the random effects model for meta-analysis, and the results showed that the ORR of the two groups of patients was compared. The ORR of the experimental group (immunotherapy as the main regimen) was significantly higher than that of the control group (chemotherapy alone) [RR=1.34; 95% CI (1.22, 1.46); P=0.004] (Fig. 3A).

Five studies presented data on DCR, and there was significant statistical heterogeneity among the studies (P=0.0002, I^2=79%). Therefore, we used the random effects model for meta-analysis, and the results showed that there was no significant difference in DCR between the two groups [RR=1.03; 95% CI (0.97, 1.10); P=0.32] (Fig. 3B). A leave-one-out sensitivity analysis showed that the source of heterogeneity was CHECKMATE-648 NIVO + IPI arm (Fig. S2).

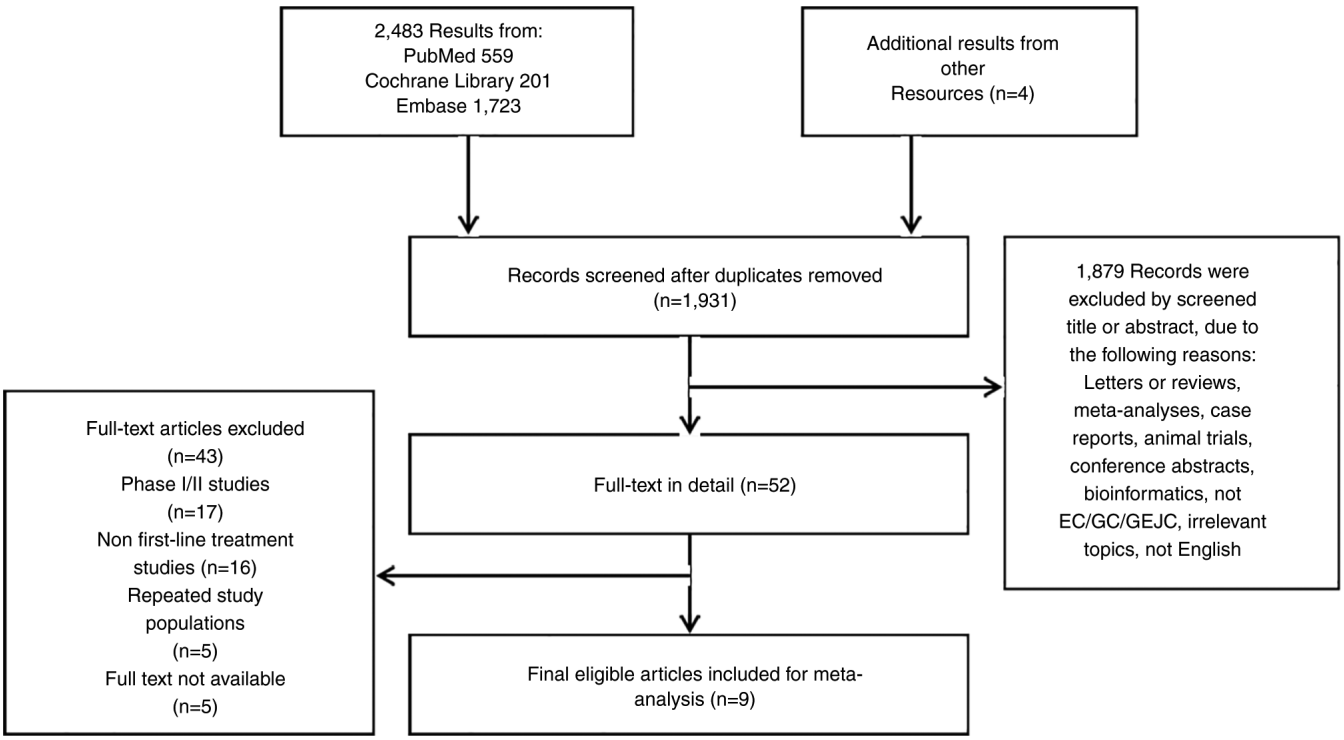

Figure 1. Flow diagram depicting the strategies of systematic review and meta-analyses. EC, esophageal cancer; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer.

Subgroup analysis of PD-L1 expression state with PFS and OS. Subgroup analysis was performed based on PD-L1 CPS ≥10 and PD-L1 CPS <10. JUPITER-06, KEYNOTE-590, KEYNOTE-062 and ORIENT-15 reported the OS data of the outcome subgroups. With respect to the OS of patients with PD-L1 CPS ≥10, there was no significant statistical heterogeneity (P=0.61, I^2=0%). Therefore, we used the fixed effects model for meta-analysis. Meta-analysis showed that the OS of patients with PD-L1 CPS ≥10 in the experimental group was significantly longer than that in the control group [HR=0.68; 95% CI (0.59, 0.77); P<0.00001] (Fig. 4A). For the OS of patients with PD-L1 CPS <10, there was no significant statistical heterogeneity (P=0.18, I^2=43%). Therefore, we used the fixed effects model for meta-analysis, The OS of patients with PD-L1 CPS <10 in the experimental group was also longer than that in the control group [HR=0.73; 95% CI (0.62, 0.87); P=0.0005] (Fig. 4B). We also showed OS no statistical difference between CPS ≥10 and CPS <10 groups (P=0.46) (Fig. S3). The HR for OS in patients with PD-L1 CPS ≥10 and CPS <10 groups were respectively 0.68 (95% CI 0.59-0.77; P<0.01) and 0.73 (95% CI 0.62-0.87; P<0.01) .

With respect to PFS of patients with PD-L1 CPS ≥10, all 4 studies reported, with significant statistical heterogeneity among studies (P=0.002, I^2=80%). Therefore, we used the random effects model for meta-analysis. The results of subgroup analysis showed that the PFS of patients with PD-L1 CPS ≥10 in the experimental group was significantly longer than that in the control group [HR=0.67; 95% CI (0.49, 0.92); P=0.01] (Fig. 4C). A leave-one-out sensitivity analysis showed that the source of heterogeneity was KEYNOTE-062 PEMBRO arm (Fig. S4). The PFS of patients with PD-L1 CPS <10 was reported in all 3 studies, with significant statistical heterogeneity among studies (P=0.05, I^2=67%). Therefore, we used the random effects model for meta-analysis. The PFS of patients with PD-L1 CPS <10 in the two groups was also prolonged in the experimental group compared with the control group [HR=0.63; 95% CI (0.48, 0.83); P=0.001] (Fig. 4D). PD-L1 CPS <10 had heterogeneity, which was found by a leave-one-out sensitivity analysis, and the source of heterogeneity was KEYNOTE-590 (Fig. S5). We also showed PFS no statistical difference between CPS ≥10 and CPS <10 groups (P=0.002) (Fig. S6). The HR for OS in patients with PD-L1 CPS ≥10 and CPS <10 groups were respectively 0.67 (95% CI 0.49-0.92; P=0.01) and 0.63 (95% CI 0.48-0.83; P<0.01).

Subgroup analysis of Asian and non-Asian with OS. Subgroup analysis was performed based on Asian and non-Asian ethnicity. CHECKMATE-648, CHECKMATE-649, KEYNOTE-590 and ORIENT-15 reported the OS data of the outcome subgroups. there was no significant statistical heterogeneity (P=0.57, I^2=0%). Therefore, we used the fixed effects model for meta-analysis, and the results showed that in the Asian population, the OS of the experimental group (immunotherapy-based regimens) was significantly longer than that of the control group (chemotherapy alone) [HR=0.71; 95% CI (0.64-0.78); P<0.00001]. In the non-Asian population, the OS of the experimental group (immunotherapy-based regimens) was also significantly longer than that of the control group (chemotherapy alone) [HR=0.78; 95% CI (0.70-0.87); P<0.00001] (Fig. S7).

Safety evaluation of anti-PD-1/PD-L1 immunotherapy. The overall incidence of adverse events was reported in all 9 studies, and there was moderate statistical heterogeneity

Table I. The characteristics of included studies.

First author, year	Clinical trial	Study design	Ethnicity	N, P/C	Line of therapy	Histology	Arms, P vs. C	ORR %, P/C	DCR %, P/C	PFS, HR (95% CI)	OS, HR (95%CI)	≥Grade 3 AEs %, P/C	Any grade AEs %, P/C	(Refs.)
Luo, 2021	ESCORT-1st	RCT/III	Asian	298/298	1st	EC	Camrelizumab+ CT vs. CT alone	72.1/62.1	91.3/88.9	0.56 (0.46-0.68)	0.70 (0.56-0.88)	63.4/67.7	99.3/97	(21)
Sun, 2021	KEYNOTE-590	RCT/III	Asian and non-Asian	373/376	1st	EC/GEJC	Pembrolizumab +CT vs. CT alone	45/29.3	NA	0.56 (0.46-0.68)	0.73 (0.62-0.86)	86/83	100/99	(23)
Janjigian, 2021	KEYNOTE-811	RCT/III	Asian and non-Asian	133/131	1st	EC	Pembrolizumab +trastuzumab+ CT vs. placebo+ trastuzumab+CT	74.4/51.9	96.2/89.3	NA	NA	57.1/57.4	97.2/98.1	(24)
Shitara, 2020	KEYNOTE-062	RCT/III	Asian and non-Asian	256 (P1)/ 257 (P2)/ 250 (C)	1st	GC/GEJC	Pembrolizumab (P1) vs. Pembrolizumab +CT (P2) vs. CT (C)	NA	NA	NA	NA	16.9 (P1)/ 73.2 (P2)/ 69.3 (C)	95.3(P1)/ 97.6 (P2)/ 98.4 (C)	(20)
Janjigian, 2021	CHECKMATE-649	RCT/III	Asian and non-Asian	789/792	1st	GC/GEJC/ EC	Nivolumab+CT vs. CT	60/45	NA	0.77 (0.68-0.87)	0.8 (0.68-0.94)	59.6/44	94.4/88.5	(22)
Doki, 2022	CHECKMATE-648	RCT/III	Asian and non-Asian	321 (P1)/ 325 (P2)/ 324 (C)	1st	EC	Nivolumab+ ipilimumab (P1) vs. Nivolumab+ CT (P2) vs. CT (C)	28 (P1)/ 47 (P2)/ 27 (C)	59.4 (P1)/ 79.4 (P2)/ 72.5 (C)	P1 vs..C:1.26 (1.04-1.52) P2 vs.C:0.81 (0.64-1.04)	P1 vs. C:0.78 (0.62-0.98) P2 vs. C:0.74 (0.58-0.96)	32 (P1)/ 47 (P2)/ 36 (C)	80 (P1)/ 96 (P2)/ 90 (C)	(19)
Kang, 2022	ATTRACTION-4	RCT/III	Asian	362/362	1st	GC/GEJC	Nivolumab+ CT vs. CT	57/48	NA	0.68 (0.51-0.90)	0.90 (0.71-1.08)	20/16	98/97	(25)
Lu, 2022	ORIENT-15	RCT/III	Asian and non-Asian	327/332	1st	EC	Sintilimab+CT vs. CT	66/45	90/84	0.56 (0.46- 0.68)	0.63 (0.51-0.78)	60/55	98.2/98.2	(26)
Wang, 2022	JUPITER-06	RCT/III	Asian	257/257	1st	EC	Toripalimab+ CT vs. CT	69.3/52.1	89.1/82.1	0.58 (0.46-0.74)	0.58 (0.43-0.78)	73.2/70	99.2/99.2	(27)

N, number of patients; CT, chemotherapy; RCT, randomized controlled trial; ORR, objective response rate; DCR, disease control rate; AEs, adverse effects; PFS, progression-free survival; OS, overall survival; NA, not available; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; EC, esophageal cancer; P, experimental group; C, control group.

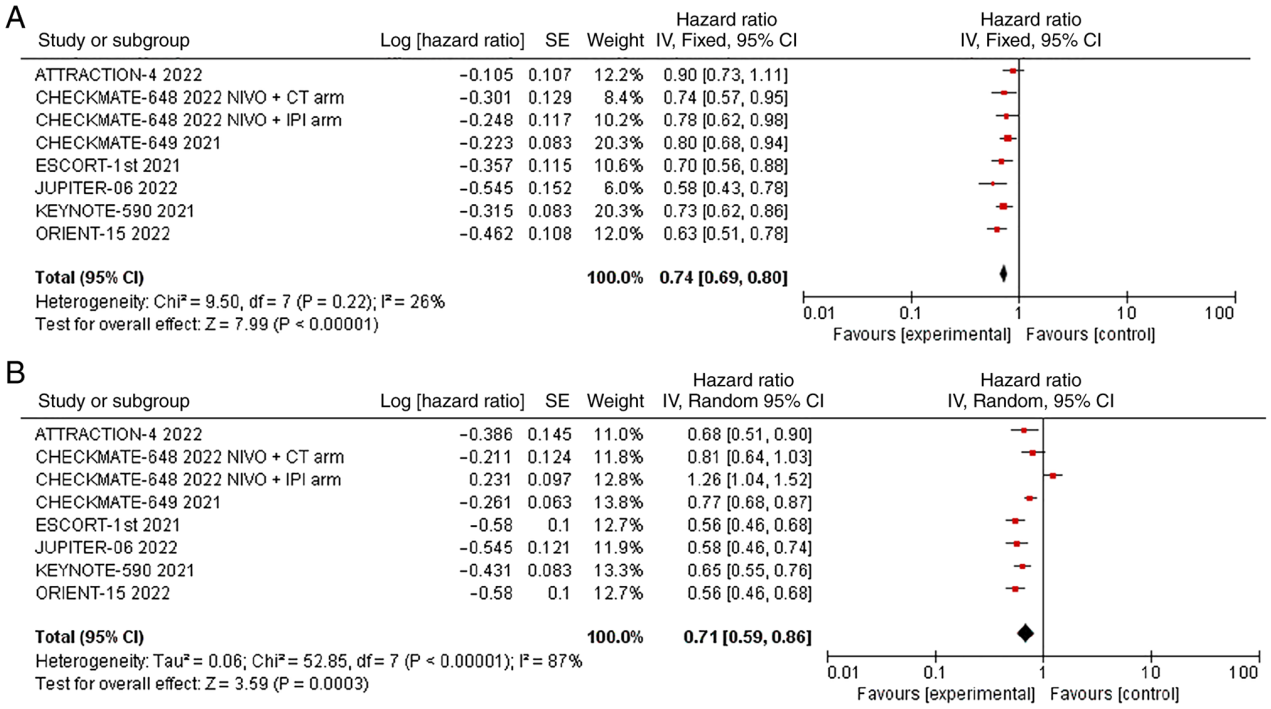

Figure 2. Forest plot of the efficacy of immunotherapy-based regimens compared with chemotherapy in EC/GC/GEJC. (A) Overall survival. (B) Progression-free survival. IPI, ipilimumab; NIVO, nivolumab; CT, chemotherapy; SE, standard error.

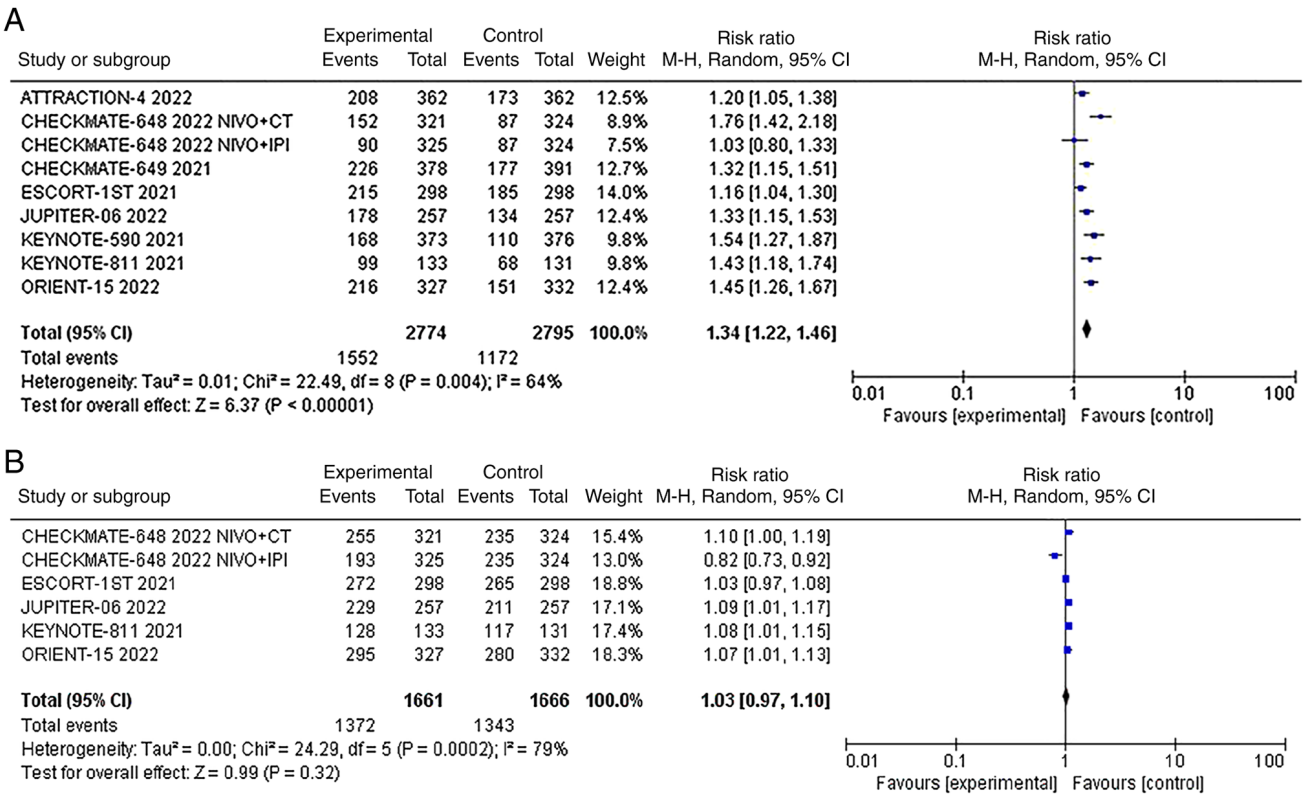

Figure 3. Forest plot of the efficacy of immunotherapy-based regimens compared with chemotherapy in EC/GC/GEJC. (A) Overall response rate. (B) Disease control rate. IPI, ipilimumab; NIVO, nivolumab; CT, chemotherapy; SE, standard error.

(P<0.01, I^2=79%). Therefore, we used the random effects model for meta-analysis, and the results showed that there was no difference in the overall incidence of adverse events between the experimental group and the control group [RR=1; 95% CI (0.99, 1.02); P=0.65] (Fig. 5A). The incidence of grade 3 or higher adverse events was reported in 9 studies,

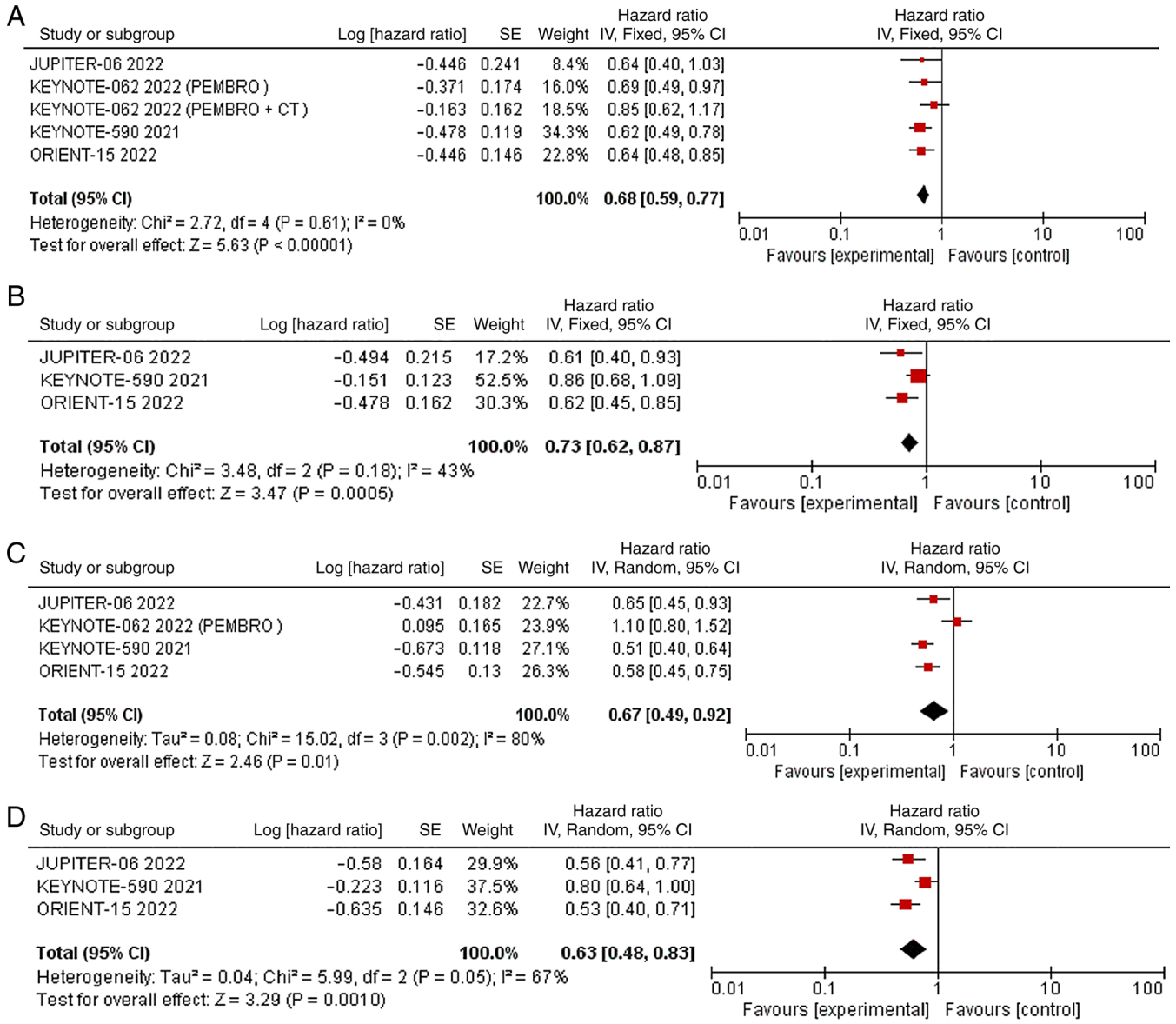

Figure 4. Subgroup analysis of OS and PFS in patients with PD-L1 CPS ≥10 and <10. (A) Overall survival of patients with PD-L1 CPS ≥10. (B) Overall survival of patients with PD-L1 CPS <10. (C) Progression-free survival of patients with PD-L1 CPS ≥10. (D) Progression-free survival of patients with PD-L1 CPS <10. IPI, ipilimumab; NIVO, nivolumab; CT, chemotherapy; SE, standard error.

with high statistical heterogeneity among studies (P<0.01, I^2=93%). Therefore, we used the random effects model for meta-analysis, and the results showed that there was no difference in the incidence of grade 3 or higher adverse events between trial patients and the control group [RR=0.97; 95% CI (0.84, 1.12); P=0.69] (Fig. 5B). Grade ≥3 adverse events had a high heterogeneity of 93%. Sensitivity analysis showed that the source of heterogeneity was KEYNOTE-062 PEMBRO arm, and the degree of heterogeneity was reduced to 77% after deletion of this study (Fig. S8).

Publication bias. To detect publication bias, PFS and OS were used to draw an inverted funnel plot, as shown in Fig. 6. The scattered points of each study were basically symmetric and evenly distributed in the inverted funnel plot, suggesting that there was little possibility of publication bias in our meta-analysis.

Assessment of study quality. The quality of the 9 RCTs included was evaluated by the risk of bias assessment tool recommended by the Cochrane Systematic Reviewers Manual 5.1.0. The results showed that the quality of the articles was high, and the overall risk of bias was low (Fig. 7).

Discussion

Gastric esophageal cancer is an aggressive tumour that significantly affects cancer-related mortality worldwide. For patients with locally advanced esophageal squamous cell carcinoma who are not eligible for surgery combined with neoadjuvant chemotherapy-radiotherapy or concurrent chemoradiotherapy, immuno/chemotherapy as the first line of the gold standard treatment options. In addition, most gastric esophageal cancers are advanced at the time of diagnosis and cannot be surgically resected, resulting in poor

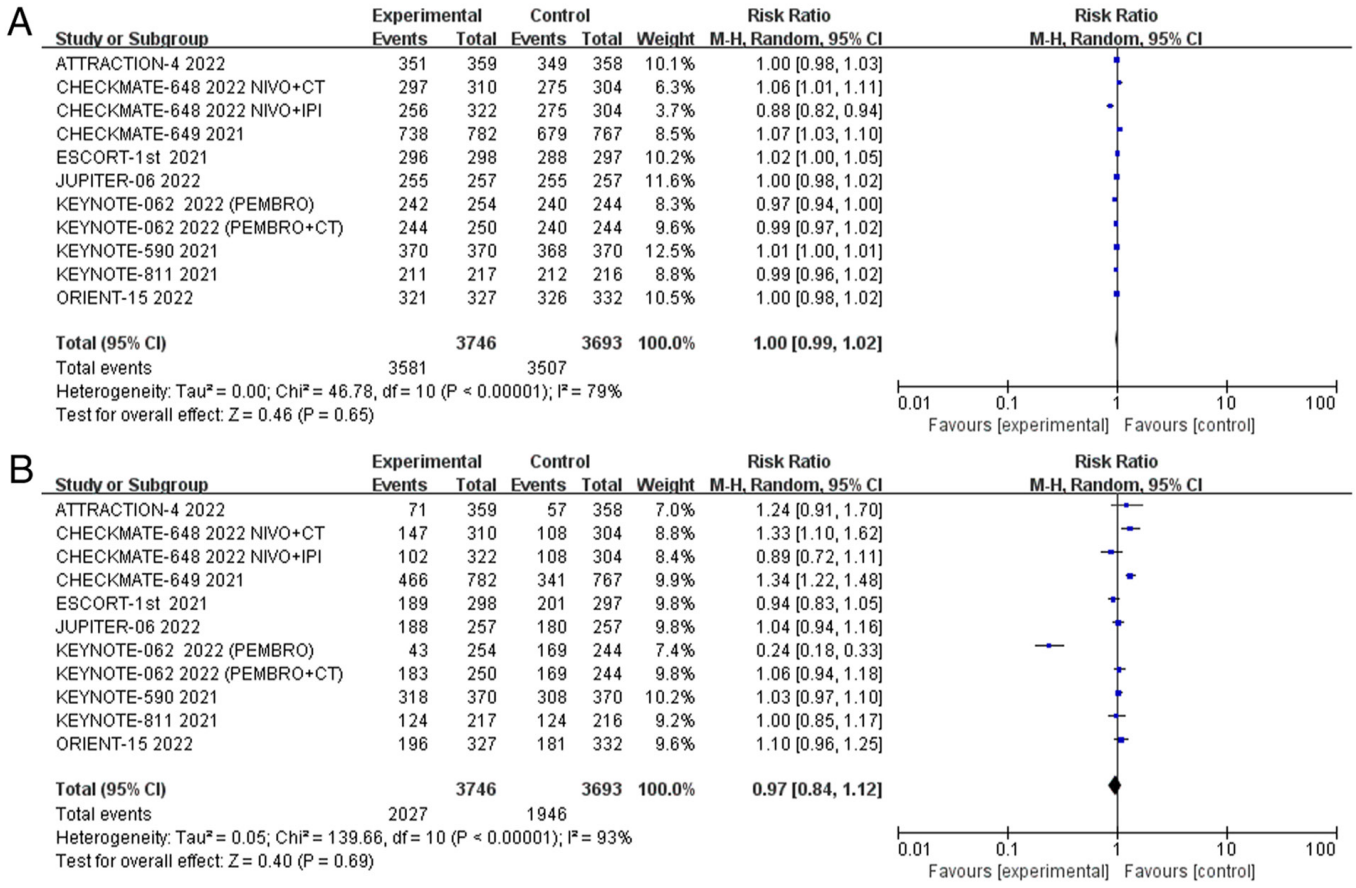

Figure 5. Meta-analysis forest plot of the overall incidence of adverse events and the incidence of grade 3 and above adverse events in the two groups. (A) Overall incidence of adverse events. (B) Incidence of grade 3 adverse events. IPI, ipilimumab; NIVO, nivolumab; CT, chemotherapy; SE, standard error.

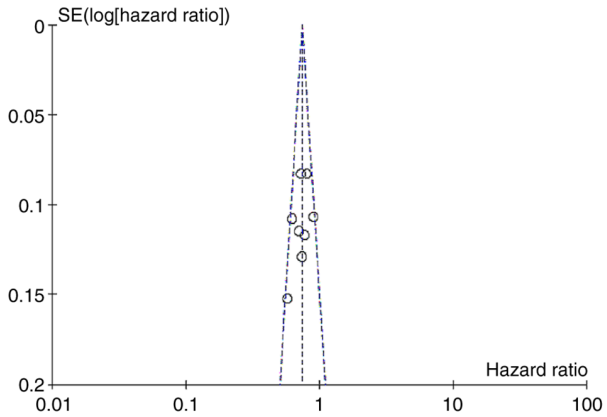

Figure 6. Funnel plot for publication bias.

prognosis and short survival. Recently, in the treatment of gastric esophageal cancers, immunotherapy, as a new treatment regimen, has the advantages of prolonging the survival time of patients and reducing the incidence of adverse reactions compared with conventional chemotherapy (4). However, due to the short time of approval of immunocombination therapy for the first-line treatment of advanced gastric esophageal cancer, its unique immune-related adverse events and high price, its clinical application is limited.

This meta-analysis of 9 articles that examined anti-PD-1/PD-L1 immunotherapy as a first-line treatment for advanced gastric esophageal cancer and systematically evaluated the efficacy and safety of this treatment. Additionally, the programmed death ligand 1 binding positive score (CPS) subgroup was also analysed to identify the characteristics of patients with immune benefit and provide a decision-making basis for clinical practice.

The results of this study show that combined immunotherapy can prolong PFS and OS and reduce the risk of disease recurrence and death in patients with gastric oesophageal cancer compared with conventional first-line chemotherapy. Moreover, combined immunotherapy does not increase toxicity compared with chemotherapy alone.

Therefore, biomarkers such as PD-L1 expression may have a potential predictive role. In previous studies of gastroesophageal adenocarcinoma, increasing the CPS threshold from 1 to 5 or 10 maximizes the therapeutic index of immunotherapy (28).

Therefore, PD-L1 detection as a biomarker needs to be further considered to determine whether it is related to tumour heterogeneity, the interval between biopsy and treatment, antibodies and staining methods, cut-off value definition, inconsistent immunohistochemical evaluation criteria and other factors. However, some studies have found that patients with microsatellite instability (MSI) and EBV positivity have a better response to immunotherapy. Second, gastric cancer is also correlated with tumour mutation burden (TMB), ctDNA

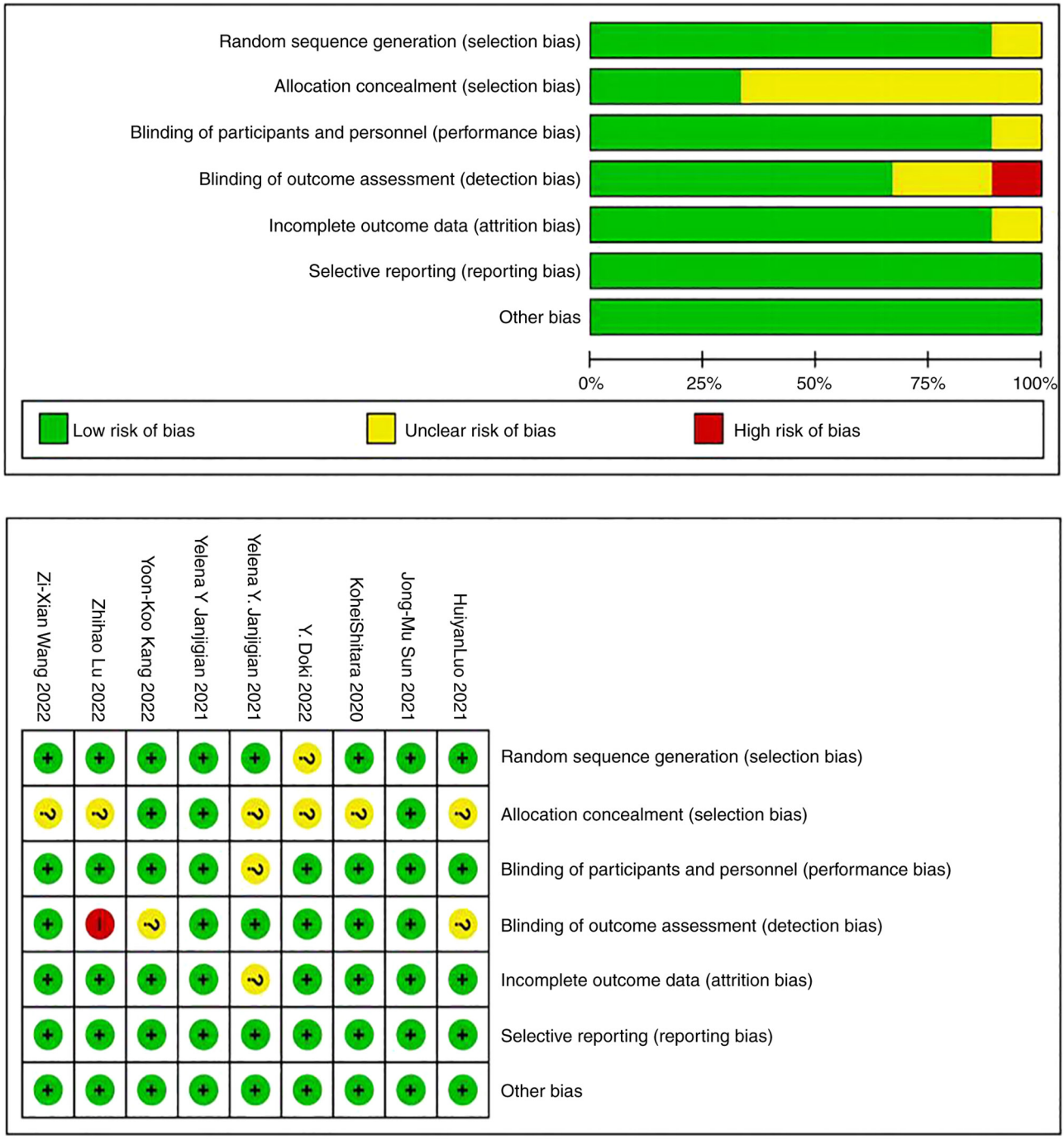

Figure 7. The risk of bias graph and the risk of bias summary.

mutation burden and other factors, which may become potential biomarkers for immunotherapy (16). The results of this meta-analysis also showed that immune checkpoint inhibitors in the treatment of advanced gastric oesophageal cancer prolonged the overall survival of patients in the PD-l1 (+) subgroup.

Asian and non-Asian populations were divided into two groups for meta-analysis. Based on the above subgroup analysis, there was no heterogeneity between the two groups (I^2=0%, P>0.1), meaning that the efficacy of gastric oesophageal cancer was not affected in Asian and non-Asian populations, and the risk of death was reduced in both Asian and non-Asian populations. Among them, there was no intra-group heterogeneity in the Asian population, and the results of 5 studies were combined. The fixed-effect model was selected to combine the effect size HR, which was 71% and significant (z=6.63, P=0.00001<0.05), meaning that immunotreatment-based regimens significantly reduced the risk of death in the Asian population, only 71 percent of that of chemotherapy alone. Secondly, there was no intra-group heterogeneity in the non-Asian population, and the results of four studies were combined. The fixed-effect model combined the effect size HR, which was 78% and significant (z=4.58, P=0.00001<0.05), meaning that immunotreatment-based regimens significantly reduced the risk of death in the non-Asian population, to only 78% of that of

chemotherapy alone. Zhang *et al* (29) showed that Asian and Western patients have similar responses to systemic therapy in unresectable gastric or gastroesophageal adenocarcinoma. However, first-line immunotherapy in Asian populations showed better OS in unresectable gastric or gastroesophageal adenocarcinoma than in Western populations. This was considered to be related to inconsistencies in enrolment studies and treatment lines.

While immune checkpoint inhibitors are widely used, they can also cause autoimmune or inflammatory responses called immune-related adverse events (irAEs) (30), which occur in more than 80% of patients receiving immune checkpoint inhibitors, and the incidence of grade ≥3 TRAEs is low. Therefore, the safety of immune checkpoint inhibitor therapy is good. Noori *et al* (31) showed that first-line ICIs plus chemotherapy prolonged OS and PFS in patients with advanced esophageal gastric cancer compared with chemotherapy alone. And the incidence of AE was higher in the combined treatment group. Regarding the incidence of adverse reactions, firstly, the inclusion of this study was inconsistent with that of literature studies, so this study was included in Phase III randomized controlled study. Second, when the incidence of grade 3 or higher adverse events was analysed, the heterogeneity of grade ≥3 adverse events was high (93%). A leave-one-out sensitivity analysis showed that the source of heterogeneity was KEYNOTE-062 pembrolizumab combined with chemotherapy, and the degree of heterogeneity was reduced to 77% after deletion of this study.

One limitation of this study is that PD-L1 is an imperfect biomarker of choice for upper gastrointestinal tumours. There is a lack of standardization of platforms and antibodies for evaluation (16). Different studies used different scoring systems, antibodies, and positive thresholds, making it difficult to combine all available data. The PD-L1 CPS treatment threshold was dependent on tumour histology and treatment cycle, and the PD-L1 positive threshold was not consistent across trials. Although different antibodies were used, the study with pembrolizumab applied CPS ≥1 and 10, whereas the study with nivolumab used a cut-off value of 5. The spatial and temporal heterogeneity of tumours makes the detection of PD-L1 status more difficult. The most reliable biomarkers may require multiple biopsies and repeated testing during disease progression. However, it is not clear how to interpret the inconsistent results (determining treatment based on the lowest or highest CPS). In addition to PD-L1, upper gastrointestinal tumours should also be detected for microsatellite high instability (MSI-H) and tumour mutational burden (TMB). The Food and Drug Administration (FDA) has approved pembrolizumab for patients with mismatch repair defects and/or a high tumour mutation burden. Similar to other diseases, MSI-H status is a strong predictive biomarker of IO response in upper gastrointestinal tumours (32). Therefore, all patients should be tested for MSI status or MMR protein expression. Therefore, we urgently need to continue to optimize the detection of the biomarker PD-L1 and find new biomarkers for biological prediction. It is hoped that more in-depth stratified analyses will be conducted in the future to identify the beneficiary population of immunotherapy.

There are also the methodological limitations of their systematic review and meta-analysis. Although statistical heterogeneity existed between studies, a leave-one-out sensitivity analysis was used to explore possible sources of heterogeneity. However, almost all the included studies have the risk of bias in quality assessment, mainly due to the lack of important outcome data, which needs to be further discussed and analysed in future studies, such as the analysis of different cancer types.

In conclusion, immunotherapy-based regimens are superior to standard chemotherapy in the first-line treatment of advanced gastric oesophageal cancer, with significantly improved OS, PFS, DCR, and ORR. Furthermore, patients in the PDL1 CPS ≥10 subgroup appeared to benefit more significantly than the total population. The incidence of adverse reactions in the immunotherapy-based group was not higher than that in the chemotherapy-based group. Our results suggest that immunotherapy-based regimens may be a new choice for first-line chemotherapy in patients with advanced gastric esophageal cancer. Our results highlight the need to conduct additional randomized controlled trials, to further examine PD-L1 CPS treatment thresholds, and to detect additional biomarkers to identify immune therapy beneficiary populations.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JS, HD, XD, RQ and MY designed the study. HD, XD, RQ and MY reviewed the literature, designed the article structure and extracted the data. JS, HD, XD and RQ analysed and interpreted the data results. HD and XD wrote the manuscript. JS and HD revised and edited key points in the manuscript. XD and RQ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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