Efficacy and safety of PD-1/PD-L1 inhibitors combined with chemotherapy in patients with advanced gastric or gastro-esophageal junction cancer: A systematic review and meta-analysis

SHIQING SU

Emergency Department, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian 362000, P.R. China

Abstract. Although the efficacy and safety of programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitor combined with chemotherapy vs. chemotherapy alone has been analyzed, there have been no in-depth studies on the outcomes of patients with PD-L1 positive advanced gastric or gastro-esophageal junction cancer patients (GC/GEJC). This systematic review and meta-analysis focused on comparing the efficacy and safety of PD-1/PD-L1 inhibitors vs. PD-1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy in PD-L1 positive advanced GC/GEJC patients, aiming to provide more precise guidance for the clinical treatment of GC/GEJC. In this meta-analysis, PubMed, Embase, and Cochrane Library were searched from the establishment of the database till June 2022. Randomized controlled trials (RCTs) in which control patients underwent chemotherapy and experimental group patients underwent PD-1/PD-L1 inhibitors or PD-1/PD-L1 inhibitors combined with chemotherapy were included in this investigation. Investigations without complete information, studies from which information could not be extracted, duplicate articles, animal studies, review articles, and systematic reviews were excluded. The pooled results suggested that chemotherapy combined with immunotherapy prolonged overall survival (OS) in patients with advanced GC/GEJC, while progression free-survival (PFS) with PD-1/PD-L1 inhibitors alone or in combination with chemotherapy were all improved compared with chemotherapy alone. However, PD-1/PD-L1 inhibitors did not significantly increase objective response rates (ORR) in PD-L1-positive patients compared with chemotherapy, but in combination with chemotherapy, they did improve ORR. The pooled results also showed that patients treated with PD-1/PD-L1 inhibitors had higher stable disease (SD) and progressive disease (PD) rates compared to chemotherapy in PD-L1-positive patients. Additionally, in PD-L1-positive patients, PD-1/PD-L1 inhibitors alone or combined with chemotherapy increased OS compared with chemotherapy alone. However, PD-1/PD-L1 inhibitors only prolonged PFS compared with chemotherapy alone in patients with a combined positive score (CPS; 100% of cells were required to be positively stained) for PD-L1, but when combined with chemotherapy, OS and PFS were prolonged in all PD-L1-positive patients compared with chemotherapy alone. Finally, the pooled results showed that the incidence of adverse events of PD-1/PD-L1 inhibitors in PD-L1-zpositive patients was significantly lower than that in patients treated with chemotherapy alone. In conclusion, single agent of PD-1/PD-L1 inhibitor alone or combined with chemotherapy significantly prolongs the survival of patients compared with chemotherapy alone, with fewer adverse effects. However, the degree of CPS may affect efficacy, thus further investigation is required.

Correspondence to: Dr Shiqing Su, Emergency Department, The Second Affiliated Hospital of Fujian Medical University, 34 Zhongshan North Road, Quanzhou, Fujian 362000, P.R. China
E-mail: 93868725@qq.com

Introduction

Gastric cancer, including gastro-esophageal junction cancer (GC/GEJC), is the fourth leading cause of cancer-related death worldwide (1). Patients with newly diagnosed advanced GC/GEJC often have a poor prognosis, with a life expectancy of ~1 year (2). For advanced GC/GEJC, chemotherapy with platinum and fluoro-pyrimidine is currently the standard first-line therapy (3,4). However, initial chemotherapy is frequently unsuccessful, and the majority of patients will experience a relapse with a tendency of systemic metastasis, necessitating second-line treatments (2). Second-line treatment options for advanced or metastatic GC/GEJC patients include docetaxel, paclitaxel, or irinotecan, and the anti-vascular

endothelial growth factor receptor 2 antibody ramucirumab as either monotherapy or in combination with paclitaxel (5-7). Although chemotherapy regimens for these patients have recently developed, the prognosis of advanced GC/GEJC is still disappointing. Thus, novel treatment options for patients with advanced gastric or gastroesophageal junction cancer are urgently required.

Immune checkpoint inhibitors (ICIs) such as programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors have been recommended as treatments for GC/GEJC, which overexpress immune checkpoint ligands (8-10). A previous meta-analysis investigated the efficacy and safety of anti-PD-1/PD-L1 agents vs. chemotherapy in patients with GC/GEJC (11). Additionally, Zheng et al (12) also pooled data on the efficacy and safety of PD-1/PD-L1 inhibitor combined with chemotherapy in patients with advanced GC/GEJC. However, the patients examined in these two previous meta-analyses included both PD-L1-positive and negative patients. Notably, PD-1/PD-L1 inhibitors inhibit T cell activation by blocking the binding of the PD-1 receptor, an immune checkpoint protein expressed on tumor cells, to PD-1 on the surface of T cells, leading to tumor immune escape (13). Therefore, the present systematic review and meta-analysis focused on comparing the efficacy and safety of PD-1/PD-L1 inhibitors or PD-1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy alone in PD-L1 positive GC/GEJC patients, defined as patients whose tumors had a PD-L1 combined positive score (CPS) of ≥1, aiming to provide more precise guidance for the clinical treatment of GC/GEJC patients.

Materials and methods

Literature search. The inclusion criteria were: Study object, patients with advanced GC/GEJC; intervention measures, PD-1/PD-L1 inhibitors, PD-1/PD-L1 inhibitors combined with chemotherapy, or chemotherapy alone. All included studies were randomized controlled trials (RCTs) limited to English. Outcome indicators included were: Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), stable disease (SD) rate, progressive disease (PD) rate, and incidence of adverse events.

The exclusion criteria were: Studies where full text could not be obtained, lacking information, studies on which data could not be extracted, studies using animal experiments, reviews, and systematic reviews.

Search strategy. PubMed, Embase, and Cochrane Library databases were searched from the establishment of the database till June 2022, with the following search terms: 'Stomach Neoplasm', 'gastric cancer', 'stomach cancer', 'gastroesophageal cancer' AND 'Nivolumab', 'Pembrolizumab', 'Durvalumab', 'Tremelimumab', 'Avelumab', 'Atezolizumab', 'PD-1', 'PD-L1' AND 'Chemotherapy', 'Chemotherapeutics'.

Literature screening and data extraction. Relevant studies were independently identified by two researchers, with disagreements being resolved through discussion with a third investigator. Information extracted from relevant studies included the experiment name, study design, sample size of

all patients, sex, age, Eastern Cooperative Oncology Group ECOG performance status, the sample size of patients that were PD-L1 positive, interventions, and outcome indicators including OS, PFS, ORR, SD rate, PD rate, and incidence of adverse events.

Literature quality assessment. RevMan 5.3 (The Cochrane Collaboration) risk assessment tool was used by two investigators to independently assess study quality based upon the Cochrane risk assessment scale (14), which assesses study quality based on random sequence generation, allocation concealment, blinding method, whether research results were evaluated in a blinded manner, and the completeness of reported data. Studies were also examined for potential selective reporting, sex bias, and other biases. This meta-analysis was executed in compliance with the PRISMA statement (15).

Data synthesis and statistical analysis. All data were analyzed using STATA (version 15.1, Stata Corporation) (16). OS and PFS were evaluated based on the hazard ratio (HR) with 95% confidence intervals (CIs), while ORR, SD rate, PD rate, and incidence of adverse events were assessed based on risk ratio (RR) and 95% CI. Heterogeneity was evaluated based on the I^2 statistic, with fixed effects models being used to analyze normally distributed data ($P \geq 0.1$ and $I^2 \leq 50\%$), whereas a random-effects model or descriptive statistics, were used in cases where the data were not normally distributed ($P < 0.1$, $I^2 > 50\%$) and the sources of such heterogeneity could not be determined through sensitivity analyses. Since the literature included in the indicators evaluated in this study were all <3, the publication bias of the literature was not evaluated.

Results

Results of the literature search. In this meta-analysis, a total of 797 studies from PubMed, Embase, and Cochrane Library were obtained. After eliminating duplicate studies, 536 studies remained. After reading the titles and abstracts, 434 studies were retained. After browsing the full text, 6 studies were obtained and excluded any that did not report the outcomes of interest and other ablation methods. Finally, 6 studies were included in the final meta-analysis (Fig. 1).

Baseline characteristics and quality assessment of the included studies
Baseline characteristics of the included studies. In total, 6 RCTs (16-21) were included in this meta-analysis. The patient sample size totaled 5,030, including 2,518 in the experimental group and 2,512 in the control group. The median age of the patients ranged from 59-64. The sample size of patients with PD-L1 positive cancer totaled 3,286, including 1,640 in the experimental group and 1,646 in the control group. Interventions include PD-1/PD-L1 inhibitors or PD-1/PD-L1 inhibitors combined with chemotherapy (Table I).

Quality assessment of the included studies. All the studies included in this meta-analysis described their random sequence generation strategies; three studies were double-blinded, whereas the other three did not use any blinding methods (Figs. 2 and 3). Additionally, allocation concealment was
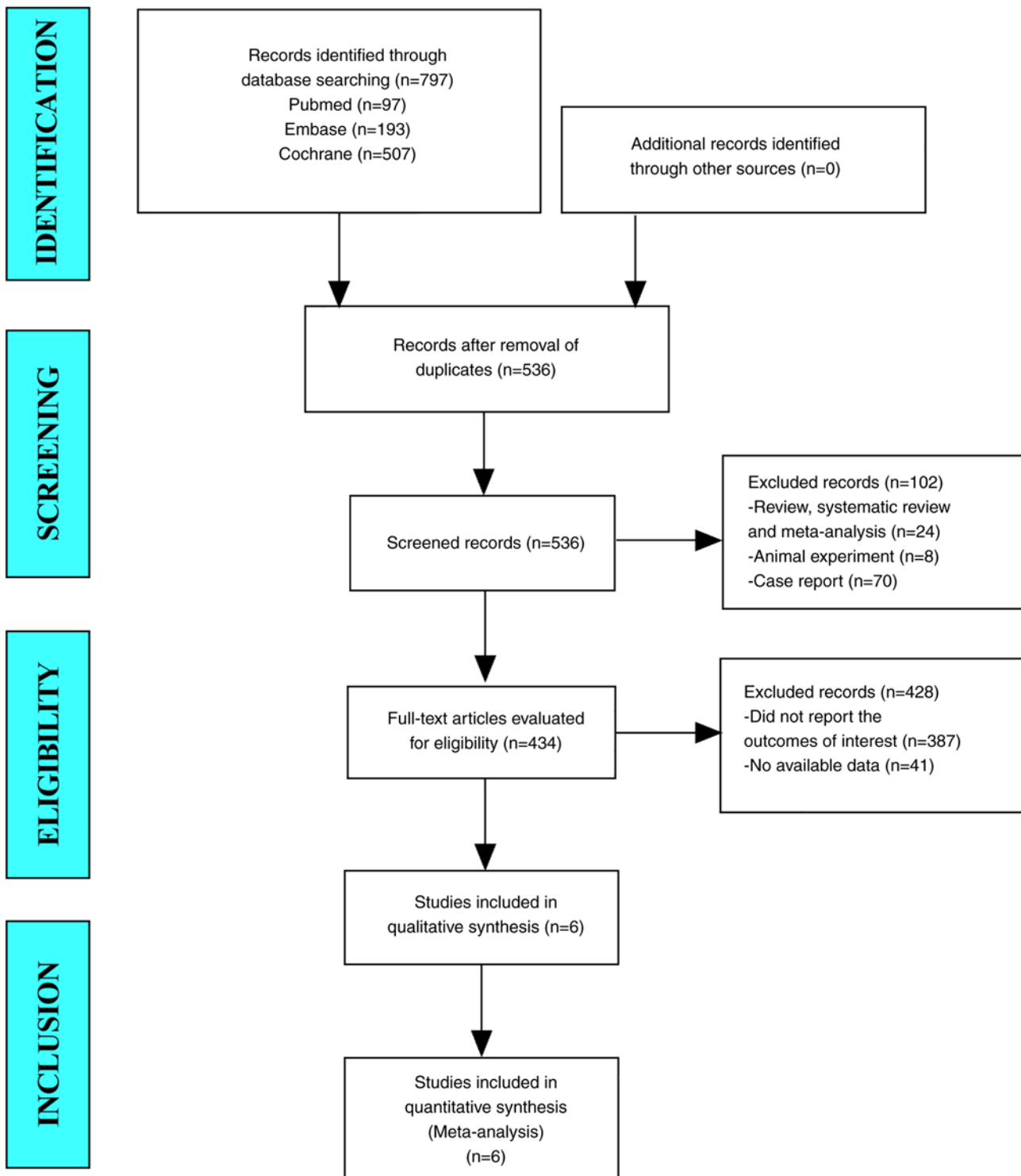
Figure 1. Flow diagram for the selection of studies.

performed in 5 studies. Overall, the quality of the included studies was relatively high.

Efficacy for all patients

OS. Only 2 studies reported on the OS of all patients that underwent PD-1/PD-L1 inhibitors vs. chemotherapy. Since there was no significant heterogeneity ($I^2=36.1\%$, P=0.211), a fixed effects model was used. The pooled results indicated that the PD-1/PD-L1 inhibitors did not improve the OS compared with patients that underwent chemotherapy alone (HR=0.98; 95% CI, 0.86-1.13; P=0.817; Fig. 4). In addition, 3 studies reported on the OS of all patients that underwent chemo-therapeutic treatment alone or combined with PD-1/PD-L1 inhibitors. Since there was no significant heterogeneity ($I^2=28.7\%$, P=0.246), the fixed effects model was used. The OS of PD-1/PD-L1 inhibitors combined with chemotherapy for patients with advanced GC/GEJC was significantly longer than that of chemotherapy alone (HR=0.80; 95% CI, 0.73-0.88;

Table I. Baseline features of the included randomized controlled trials.

| First author, year	Study name	Sample sizes		Sex, n, male/female		Age, year		Eastern Cooperative Oncology Group performance status		Sample size of patients with PD-L1 positive cancer		Interventions		(Refs.)
		Experimental group	Control group	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group	
Fuchs et al, 2022	KEYNOTE-061	296	296	202/94	208/88	62.5 (27-87)	60.0 (20-86)	0/1/2:127/169/0	0/1/2:137/158/1	196	199	Pembrolizumab	Paclitaxel	(16)
Shitara et al, 2020	KEYNOTE-062	256	250	180/76	179/71	61.0 (20-83)	62.5 (23-87)	125 (1)	135 (1)	256	250	Pembrolizumab	Cisplatin and fluorouracil	(17)
Shitara et al, 2020	KEYNOTE-062	257	250	195/62	179/71	62.0 (22-83)	62.5 (23-87)	138 (1)	138 (1)	257	250	Pembrolizumab plus cisplatin and fluorouracil	Cisplatin and fluorouracil	(17)
Bang et al, 2018	JAVELIN Gastric 300	185	186	140/45	127/59	59.0 (29-86)	61.0 (18-82)	0/1:66/169	0/1:62/124	46	39	Avelumab	Paclitaxel	(18)
Janjigian et al, 2021	CheckMate 649	789	792	331/142	349/133	62.0 (54-69)	61.0 (53-68)	0/1/2:194/279/0	0/1/2:203/278/0	641	655	Nivolumab plus XELOX or FOLFOX	XELOX or FOLFOX	(19)
Kang et al, 2022	ATTRACTION-4	362	362	253/109	270/92	64.0 (25-86)	65.0 (27-89)	0/1:195/167	0/1:194/168	58	56	Nivolumab plus SOX or CAPOX	SOX or CAPOX	(20)
Sun et al, 2021	KEYNOTE590	373	376	306/67	319/57	64.0 (28-94)	62.0 (27-89)	0/1/2:149/223/1	0/1/2:150/225/1	186	197	Pembrolizumab plus 5-fluorouracil and cisplatin	Fluorouracil and cisplatin	(21)
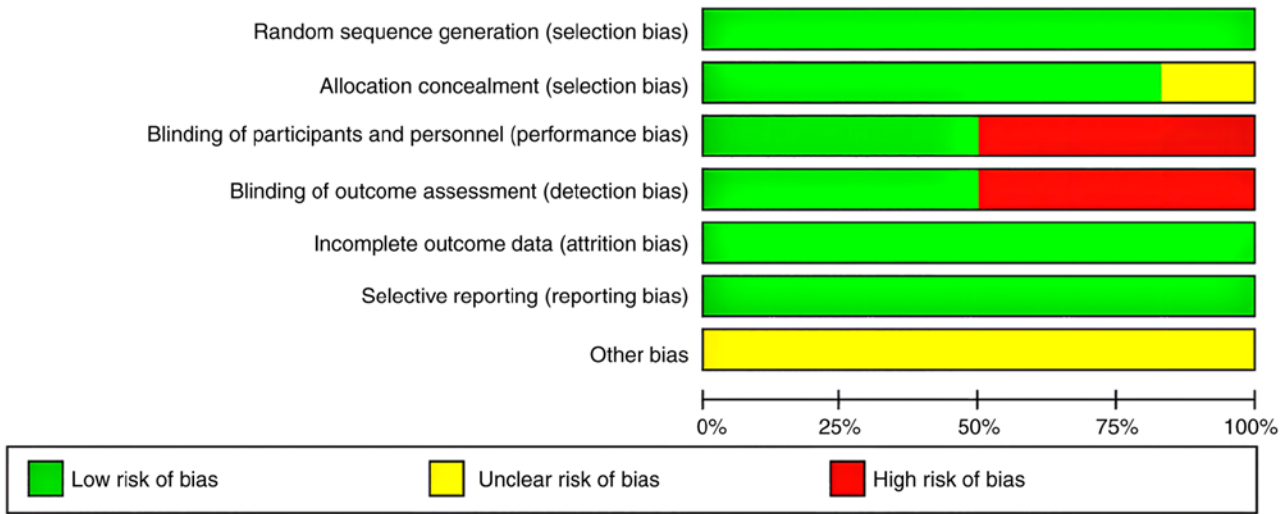
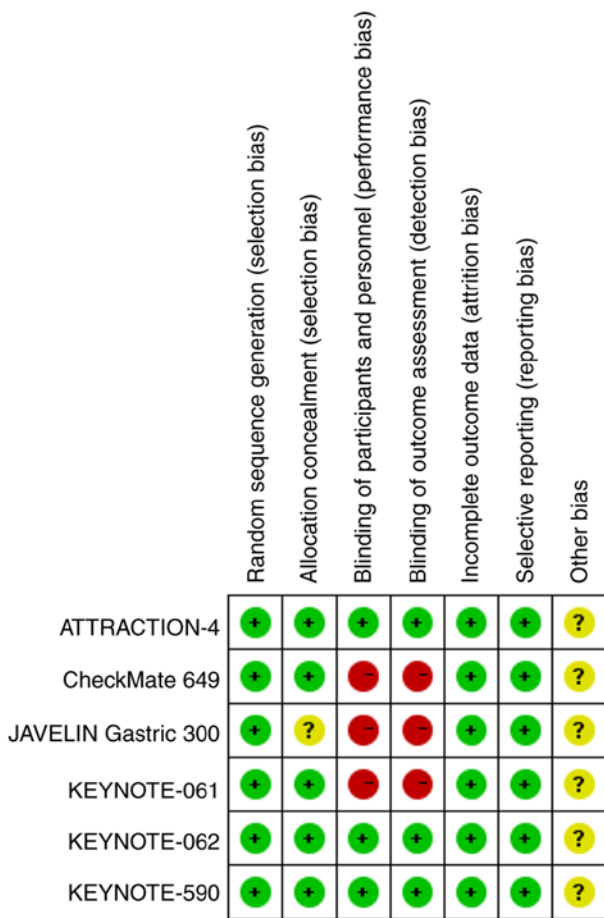Figure 2. Risk of bias graph to show the proportional distribution of risk.

Figure 3. Risk of bias summary for assessing the overall quality of the literature.

$P \le 0.001$; Fig. 4). These results suggest that chemotherapy combined with immunotherapy prolongs OS in patients with advanced GC/GEJC.

PFS. The JAVELIN Gastric 300 study (19) reported that the PFS of patients with advanced GC/GEJC treated with PD-1/PD-L1 inhibitors was significantly lower than that of patients treated with chemotherapy alone (HR=1.73, 95% CI,

1.38-2.17; $P \le 0.001$; Fig. 5). In addition, 3 studies reported on the PFS of all patients that underwent chemotherapeutic treatment alone or combined with PD-1/PD-L1 inhibitors. Since there was no significant heterogeneity (I^2=0.0%, P=0.246), a fixed effects model was used. The PFS of PD-1/PD-L1 inhibitors combined with chemotherapy for advanced GC/GEJC was significantly longer than that of chemotherapy alone (HR=0.80, 95% CI, 0.73-0.88; $P \le 0.001$; Fig. 5). The above results showed that for advanced GC/GEJC, the PFS with PD-1/PD-L1 inhibitors alone or in combination with chemotherapy was improved compared with chemotherapy.

Efficacy for patients with PD-L1 positive cancer

ORR. First, the ORR of PD1/PD-L1 inhibitors vs. chemotherapy was compared for patients with PD-L1 CPS≥1, and three studies reported on the ORR of patients with PD-L1 CPS≥1 that underwent PD-1/PD-L1 inhibitors vs. chemotherapy. Since there was significant heterogeneity (I^2=85.8%, P=0.001) (Fig. S1), sensitivity analysis was performed, and it was found that the KEYNOTE-62 had a notable impact on the results of this study. Heterogeneity was significantly reduced after excluding this study (I^2=0.0%, P=0.728). The pooled results indicated that the PD-1/PD-L1 inhibitors did not improve the ORR in patients with PD-L1 CPS≥1 that underwent chemotherapy (RR=1.18, 95% CI: 0.74-1.86, P=0.481; Fig. 6A). Additionally, the KEYNOTE-61 study (17) reported that there was no significant difference in the ORR between PD1/PD-L1 inhibitors and chemotherapy for patients with PD-L1 CPS≥5 (RR=1.40, 95% CI: 0.74-2.67, P=0.306; Fig. 6A). There were also two studies that reported on the ORR of patients with PD-L1 CPS≥10 that underwent PD-1/PD-L1 inhibitors vs. chemotherapy. Since there was significant heterogeneity (I^2=85.6%, P=0.008), the analysis was performed using the random effects model. The pooled results showed that there was no significant difference in ORR between PD1/PD-L1 inhibitors and chemotherapy for patients with PD-L1 CPS≥10 (RR=0.92, 95% CI: 0.62-1.35, P=0.751; Fig. 6A). These results suggest that PD1/PD-L1 inhibitors do not significantly increase ORR in PD-L1-positive patients compared with chemotherapy.
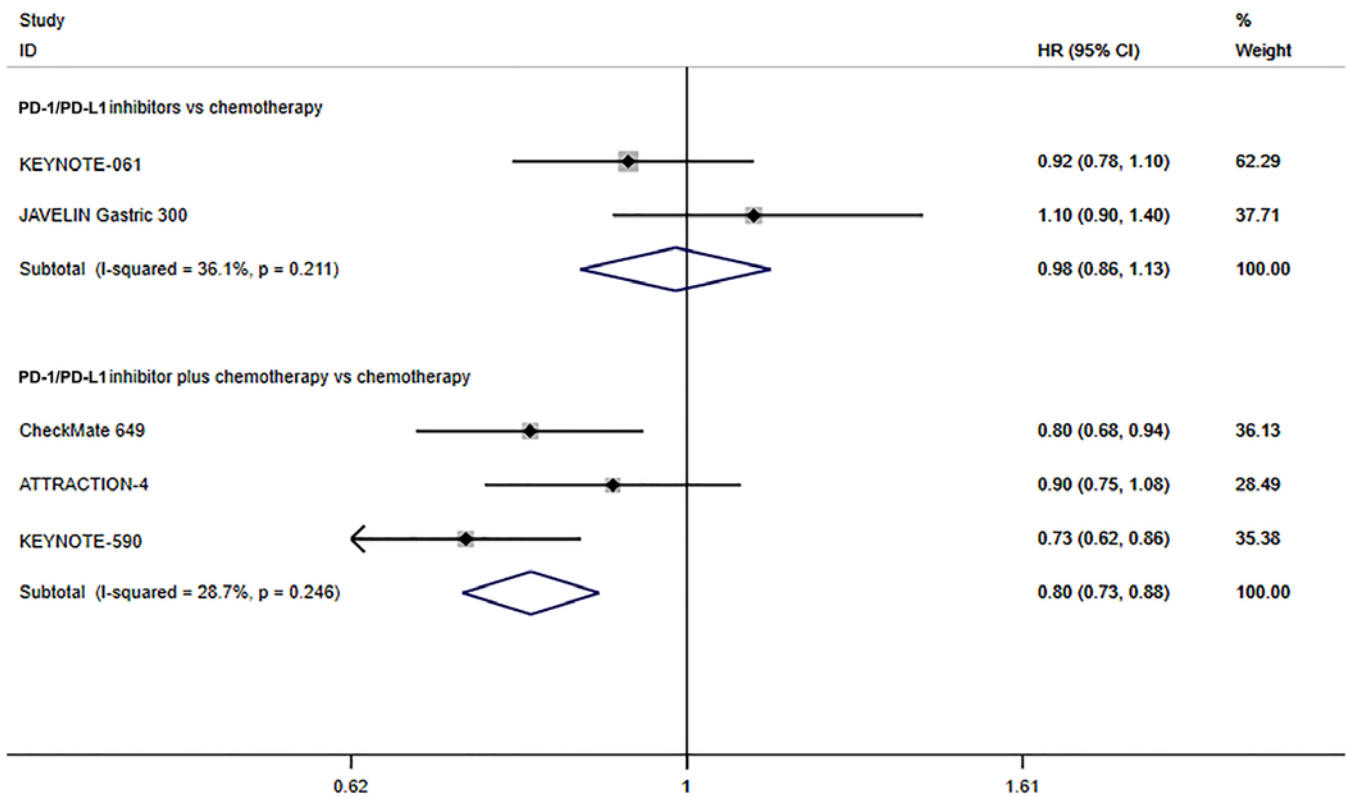
Figure 4. OS of treatment with PD1/PD-L1 inhibitors or PD1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy for all patients with advanced GC/GEJC. GC/GEJC, gastric or gastro-esophageal junction cancer patients; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; HR, hazard ratio; CI, confidence interval.

Two studies reported on the ORR of patients with PD-L1 CPS≥1 that underwent PD-1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy. Since there was no significant heterogeneity (I^2=0.0%, P=0.998), the analysis was performed using a fixed effects model. The pooled results showed that the ORR of PD-1/PD-L1 inhibitors combined with chemotherapy in patients with PD-L1 CPS≥1 was significantly higher than that of chemotherapy alone (RR=1.31, 95% CI: 1.19-1.43, P≤0.001; Fig. 6B). In addition, the results of CheckMate 649 (20) and KEYNOTE-062 (18) showed that PD-1/PD-L1 inhibitor combined with chemotherapy significantly increased ORR compared with chemotherapy alone in patients with PD-L1 CPS≥5 (RR=1.32, 95% CI: 1.15-1.51, P≤0.001; Fig. 6B) and PD-L1 CPS≥10 (RR=1.50, 95% CI: 1.09-2.06, P=0.014; Fig. 6B), respectively. The above results suggest that for PD-L1-positive patients, the ORR of PD1/PD-L1 inhibitors combined with chemotherapy was significantly higher than that of chemotherapy.

SD rate. Two studies reported on the SD rate of patients with PD-L1 CPS≥1 that underwent PD-1/PD-L1 inhibitors vs. chemotherapy. Since there was no significant heterogeneity (I^2=43.9%, P=0.182), the analysis was performed using a fixed effects model. The pooled results showed that the SD rate of PD-1/PD-L1 inhibitors in patients with PD-L1 CPS≥1 was significantly lower than that of chemotherapy (RR=0.58, 95% CI: 0.48-0.70, P≤0.001; Fig. 7A). Notably, the results of KEYNOTE-061 (17) showed that PD-1/PD-L1 inhibitor had a significantly lower SD rate than chemotherapy in patients with PD-L1 CPS≥5 (RR=0.52, 95% CI: 0.37-0.73, P=0.003;

Fig. 7A). Furthermore, the pooled results also showed that the SD rate of PD-1/PD-L1 inhibitors in patients with PD-L1 CPS≥10 was significantly lower than that of chemotherapy (RR=0.52, 95% CI: 0.37-0.73, P≤0.001; Fig. 7A). In summary, PD-1/PD-L1 inhibitors have higher SD rates compared to chemotherapy in PD-L1-positive patients.

As for the SD rate of patients with PD-L1 positive cancer who underwent PD1/PD-L1 inhibitor combined with chemotherapy vs. chemotherapy, the results of CheckMate 649 (20) showed that there was no significant difference in the SD rate of patients with PD-L1 CPS≥5 between PD-1/PD-L1 inhibitor combined with chemotherapy and chemotherapy alone (RR=0.81, 95% CI: 0.66-1.01, P=0.062; Fig. 7B).

PD rate. Two studies reported on the PD rate of patients with PD-L1 CPS≥1 that underwent treatment with PD-1/PD-L1 inhibitors vs. chemotherapy. Since there was significant heterogeneity (I^2=90.5%, P=0.001), the analysis was performed using a random effects model. The pooled results showed that the PD rate of PD-1/PD-L1 inhibitors in patients with PD-L1 CPS≥1 was significantly higher than that of chemotherapy (RR=3.15, 95% CI: 1.35-7.37, P=0.008; Fig. 8A). In addition, the results of KEYNOTE-061 (17) showed that PD-1/PD-L1 inhibitors significantly increased the PD rate compared with chemotherapy in patients with PD-L1 CPS≥5 (RR=2.16, 95% CI: 1.39-3.35, P=0.001; Fig. 8A). Furthermore, the pooled results also showed that the PD rate of PD-1/PD-L1 inhibitors in patients with PD-L1 CPS≥10 was significantly higher than that of chemotherapy (RR=2.78, 95% CI: 1.73-4.41, P≤0.001; Fig. 8A). In summary,
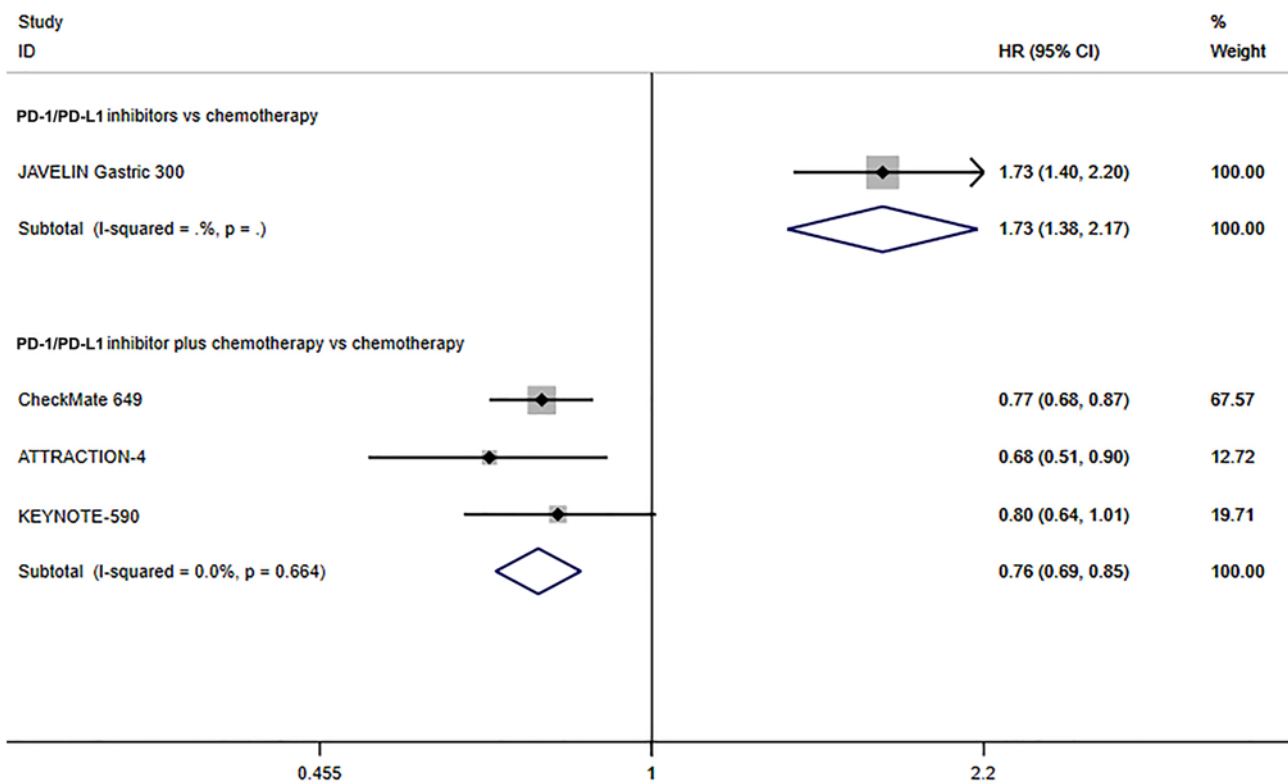
Figure 5. PFS of treatment with PD1/PD-L1 inhibitors or PD1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy alone for all patients with advanced GC/GEJC. GC/GEJC, gastric or gastro-esophageal junction cancer patients; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PFS, progression free survival. HR, hazard ratio; CI, confidence interval; HR, hazard ratio; CI, confidence interval.

PD-1/PD-L1 inhibitors had higher PD rates compared to chemotherapy in PD-L1-positive patients.

As for the PD rates of patients with PD-L1 positive cancer undergoing PD1/PD-L1 inhibitor combined with chemotherapy vs. chemotherapy alone, the results of CheckMate 649 (20) showed that there was no significant difference in the PD rate of patients with PD-L1 CPS≥5 when treated with PD-1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy alone (RR=0.64, 95% CI: 0.40-1.02, P=0.062; Fig. 8B).
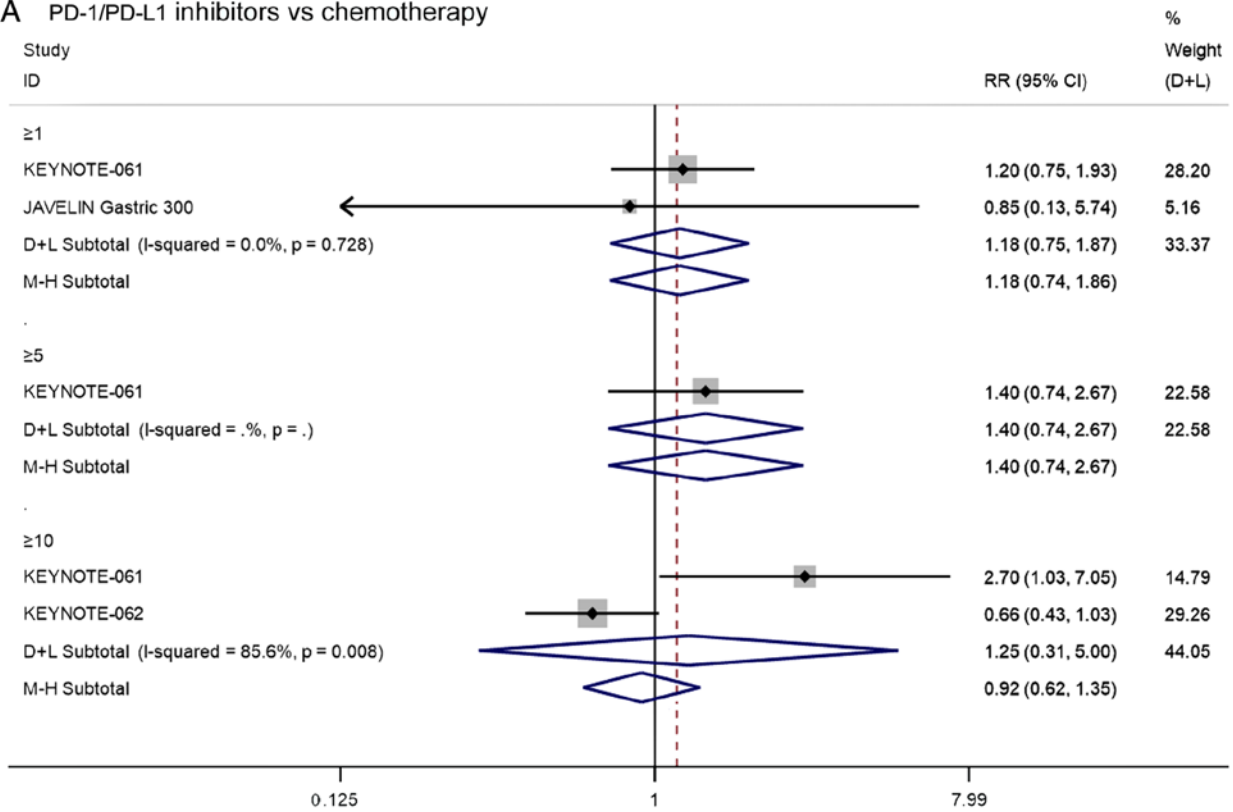
OS. Three studies reported on the OS of patients with PD-L1 CPS≥1 that underwent treatment with PD-1/PD-L1 inhibitors vs. chemotherapy. Since there was no significant heterogeneity (I^2=0.0%, P=0.739), the analysis was performed using a fixed effects model. The pooled results showed that the OS of PD-1/PD-L1 inhibitors in patients with PD-L1 CPS≥1 was significantly longer than that of chemotherapy (HR=0.85, 95% CI: 0.73-1.00, P=0.049; Fig. 9A). In addition, the results of KEYNOTE-061 (17) showed that PD-1/PD-L1 inhibitor-treated group had a significantly longer OS than chemotherapy in patients with PD-L1 CPS≥5 (HR=0.72, 95% CI: 0.53-0.98, P=0.039; Fig. 9A). As for the OS of patients with PD-L1 CPS≥10, the pooled results also showed that the OS of PD-1/PD-L1 inhibitors in patients with PD-L1 CPS≥10 was significantly longer than that of chemotherapy (HR=0.69, 95% CI: 0.53-0.90, P=0.006; I^2=0.0%, P=1.000; Fig. 9A). Altogether, in PD-L1-positive patients, PD-1/PD-L1 inhibitors increased OS compared with chemotherapy.

Three studies reported on the OS of patients with PD-L1 CPS≥1 that underwent treatment with PD-1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy alone. Since there was no significant heterogeneity (I^2=0.0%, P=0.513), the analysis was performed using a fixed effects model. The pooled results showed that the OS of PD-1/PD-L1 inhibitors combined with chemotherapy in patients with PD-L1 CPS≥1 was significantly longer than that of chemotherapy alone (HR=0.83, 95% CI: 0.74-0.94, P=0.003; Fig. 9B). In addition, the results of CheckMate 649 (20) showed that PD-1/PD-L1 inhibitor-treated group combined with chemotherapy had a significantly longer OS than chemotherapy alone in patients with PD-L1 CPS≥5 (HR=0.71, 95% CI: 0.59-0.86, P≤0.001; Fig. 9B). As for the OS of patients with PD-L1 CPS≥10, the pooled results also showed that the OS of the PD-1/PD-L1 inhibitors combined with chemotherapy in patients with PD-L1 CPS≥10 was significantly longer than that of chemotherapy alone (HR=0.71, 95% CI: 0.52-0.97, P=0.030; I^2=59.5%, P=0.116; Fig. 9B). In conclusion, in PD-L1-positive patients, PD-1/PD-L1 inhibitors combined with chemotherapy also prolonged OS compared with chemotherapy alone.

PFS. Three studies reported on the PFS of patients with PD-L1 CPS≥1 that underwent treatment with PD-1/PD-L1 inhibitors vs. chemotherapy alone. Since there was significant heterogeneity (I^2=53.7%, P=0.116), the analysis was performed using a random effects model. The pooled results showed that the PFS of PD-1/PD-L1 inhibitors in patients with PD-L1 CPS≥1 was significantly shorter than that of chemotherapy (HR=1.48, 95% CI: 1.19-1.86, P=0.001; Fig. 10A). However, the results of KEYNOTE-061 (17) showed that there was no significant difference between PD-1/PD-L1 inhibitors and chemotherapy in patients with PD-L1 CPS≥5
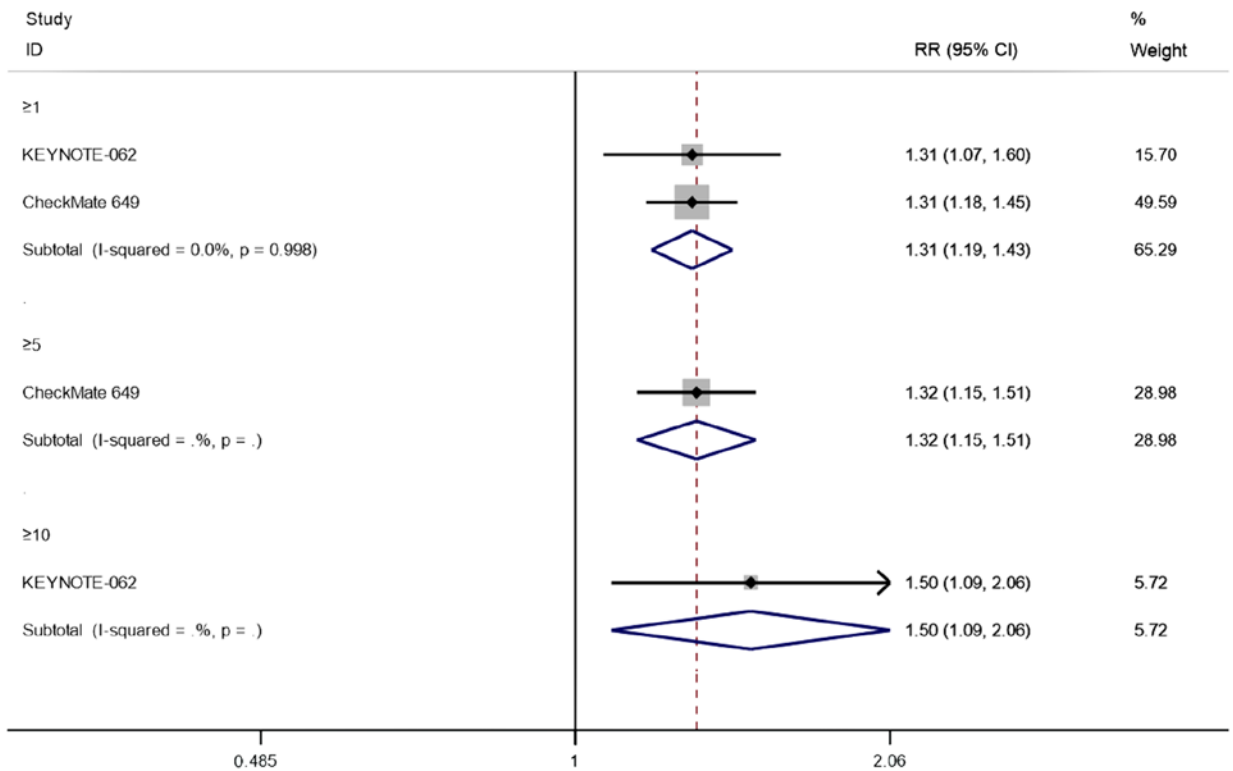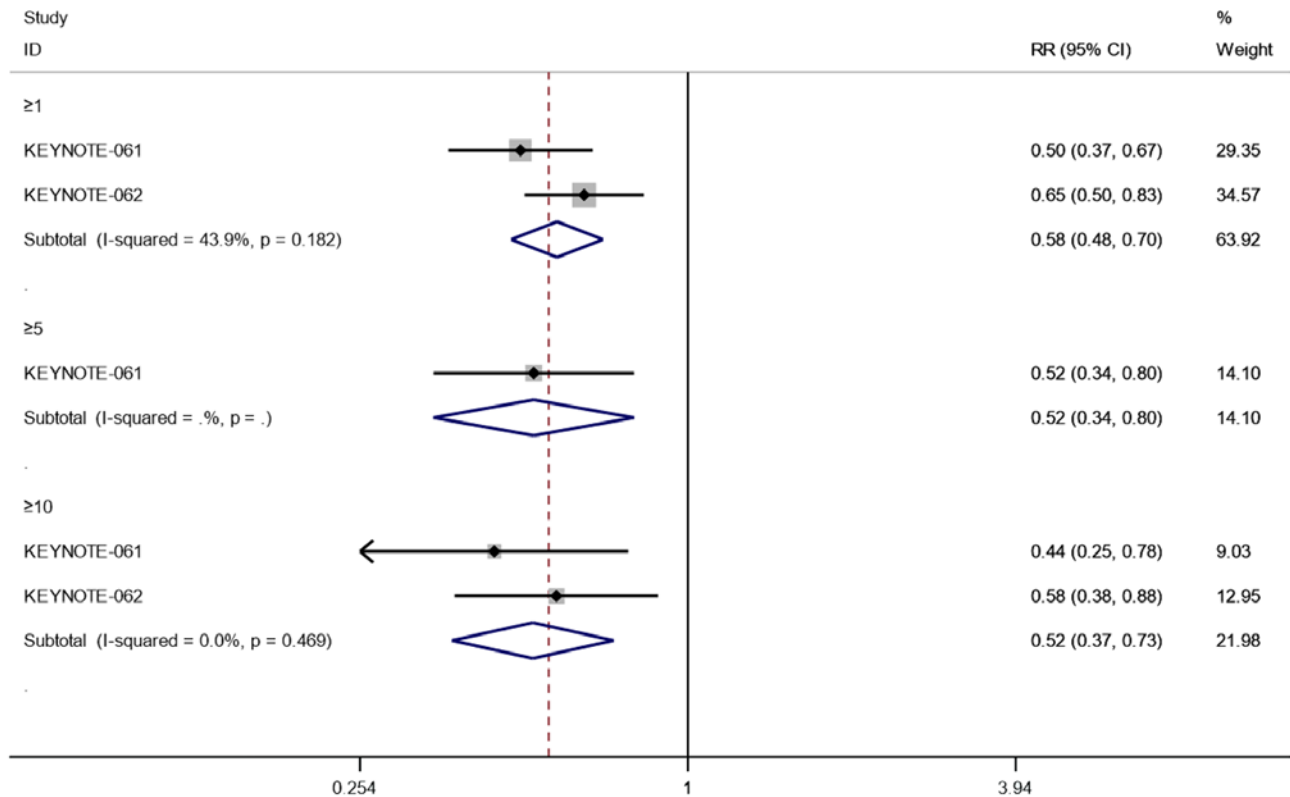
Figure 6. ORR of treatment with (A) PD1/PD-L1 inhibitors or (B) PD1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy alone for all patients with advanced GC/GEJC. GC/GEJC, gastric or gastro-esophageal junction cancer patients; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; ORR, objective response rate; RR, ratio rate; CI, confidence interval.

(HR=0.98, 95% CI: 0.71-1.35, P=0.901; Fig. 10A). As for the PFS of patients with PD-L1 CPS≥10, the pooled results also showed that there was no significant difference between treatment with PD-1/PD-L1 inhibitors and chemotherapy in patients with PD-L1 CPS≥10 (HR=0.98, 95% CI: 0.75-1.27, P=0.857; I^2=30.7%, P=0.230; Fig. 10A). The results suggest

A PD-1/PD-L1 inhibitors vs chemotherapy

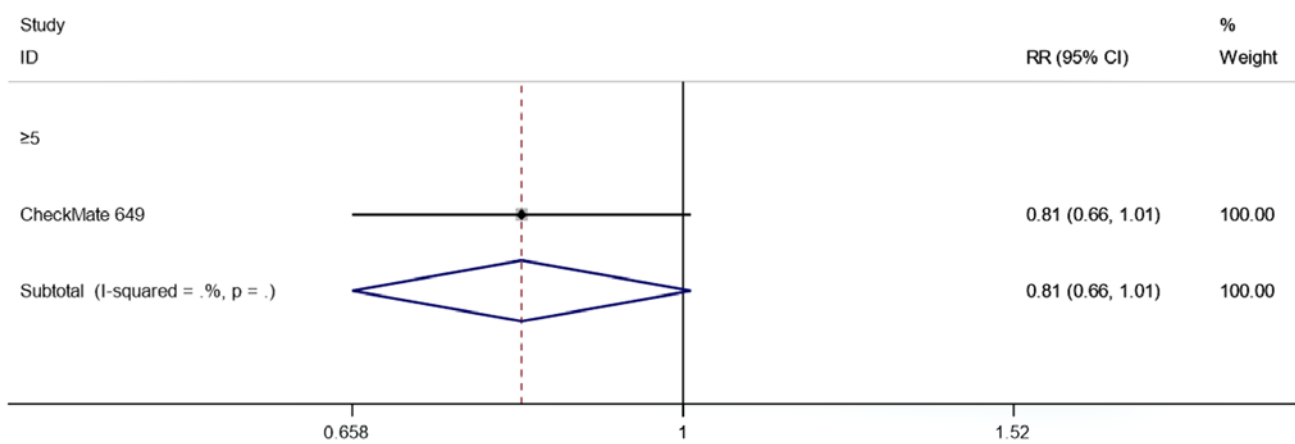B PD-1/PD-L1 inhibitors plus chemotherapy vs chemotherapy

Figure 7. SD rate of patients treated with (A) PD1/PD-L1 inhibitors or (B) PD1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy for patients with PD-L1 positive advanced GC/GEJC. GC/GEJC, gastric or gastro-esophageal junction cancer patients; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; SD, stable disease; RR, ratio rate; CI, confidence interval.
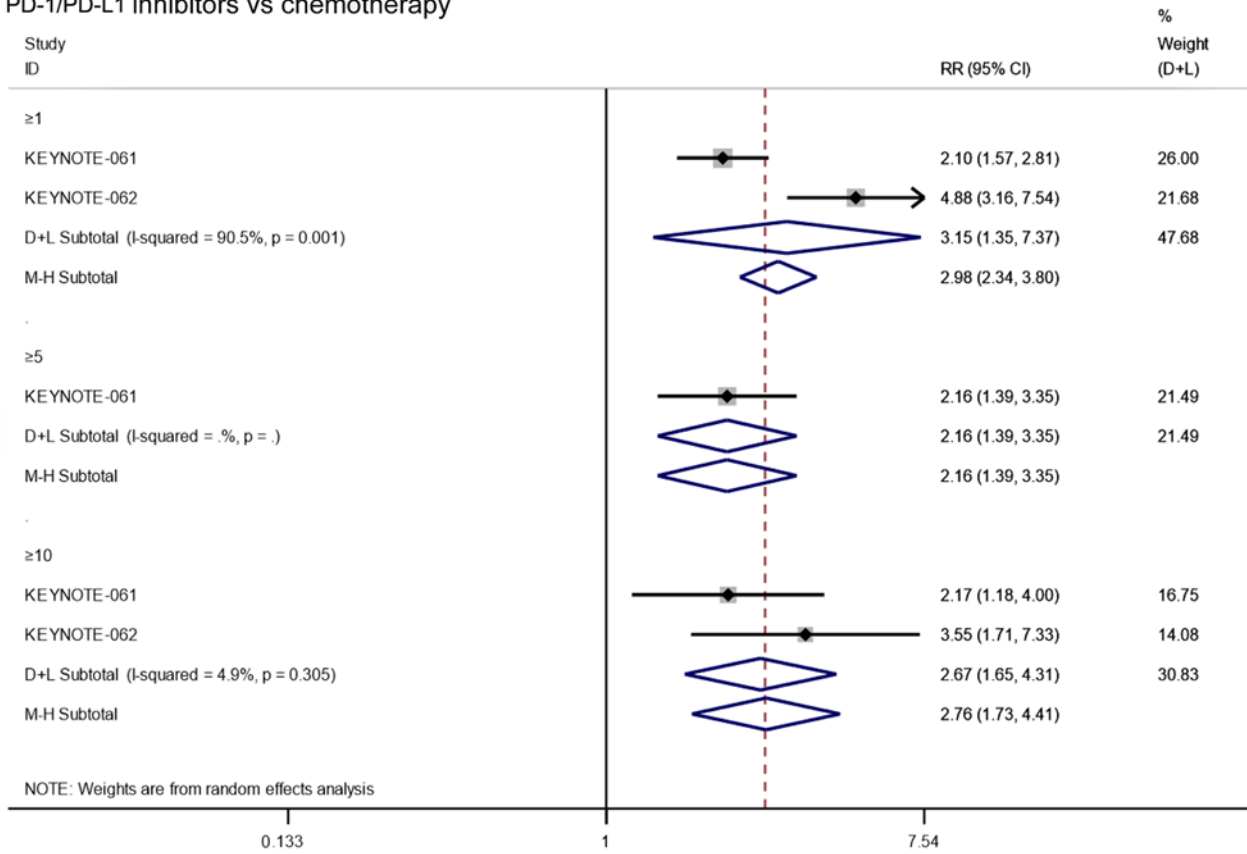
that PD-1/PD-L1 inhibitors can prolong PFS in patients with PD-L1 CPS≥1 compared with chemotherapy, but this conclusion does not hold in patients with PD-L1 CPS≥5 or 10, indicating that there was a potential correlation between the CPS and drug efficacy.

The pooled results showed that the PFS of PD-1/PD-L1 inhibitors combined with chemotherapy in patients with PD-L1 CPS≥1 was significantly longer than that of chemotherapy alone (HR=0.76, 95% CI: 0.67-0.86, P≤0.001; I^2=20.5%, P=0.284; based on three studies; Fig. 10B). Additionally, the results of CheckMate 649 (20) showed that the PFS of PD-1/PD-L1 inhibitors combined with

chemotherapy in patients with PD-L1 CPS≥5 was significantly longer than that of chemotherapy alone (HR=0.77, 95% CI: 0.68-0.87, P≤0.001; Fig. 10B). As for the PFS of patients with PD-L1 CPS≥10, the pooled results also showed that the PFS of PD-1/PD-L1 inhibitors combined with chemotherapy was significantly longer than that of chemotherapy alone (HR=0.60, 95% CI: 0.42-0.85, P=0.004; I^2=68.9%, P=0.073; Fig. 10B). These results suggest that PD1/PD-L1 inhibitors combined with chemotherapy can prolong PFS regardless of the CPS.

Adverse events for patients with PD-L1 positive cancer. The incidence of adverse events of PD-1/PD-L1 inhibitors vs.
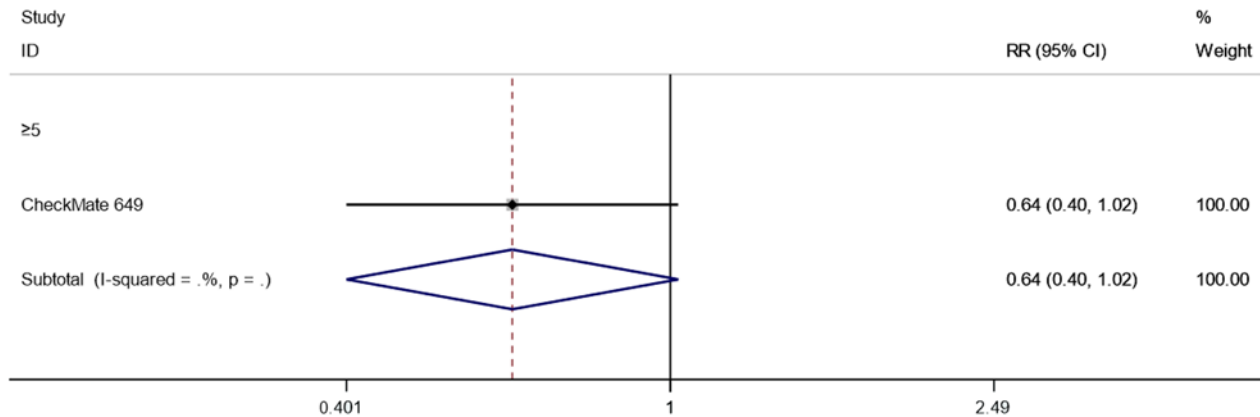
Figure 8. PD of patients treated with (A) PD1/PD-L1 inhibitors or (B) PD1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy for patients with PD-L1 positive advanced GC/GEJC. GC/GEJC, gastric or gastro-esophageal junction cancer patients; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PD, progressive disease; RR, ratio rate; CI, confidence interval.

chemotherapy in patients with PD-L1 positive cancer was also analyzed. Since there was significant heterogeneity (I^2=53.7%, P=0.116), the analysis was performed using a random effects model. The pooled results showed that the incidence of adverse events of PD-1/PD-L1 inhibitors in patients with PD-L1 positive cancer was significantly lower than that of chemotherapy (RR=0.34, 95% CI: 0.18-0.62, P≤0.001; Fig. 11).

Sensitivity analysis. To assess whether any individual study included in this meta-analysis had an undue impact on the overall results, sensitivity analysis was performed wherein individual studies were sequentially excluded from the summary analysis. This approach indicated that none of the included studies biased the overall results of the meta-analysis, as evidenced by the stability of the results, further emphasizing the reliability of these findings (Figs. S2-S6).

Discussion

Patients diagnosed with advanced GC/GEJC often have poor outcomes despite the use of standard treatments, such as chemotherapy and biologic agents. Previous studies have focused on evaluating combinations of ICIs, standard chemotherapy, and biologic agents as well as novel biomarkers to
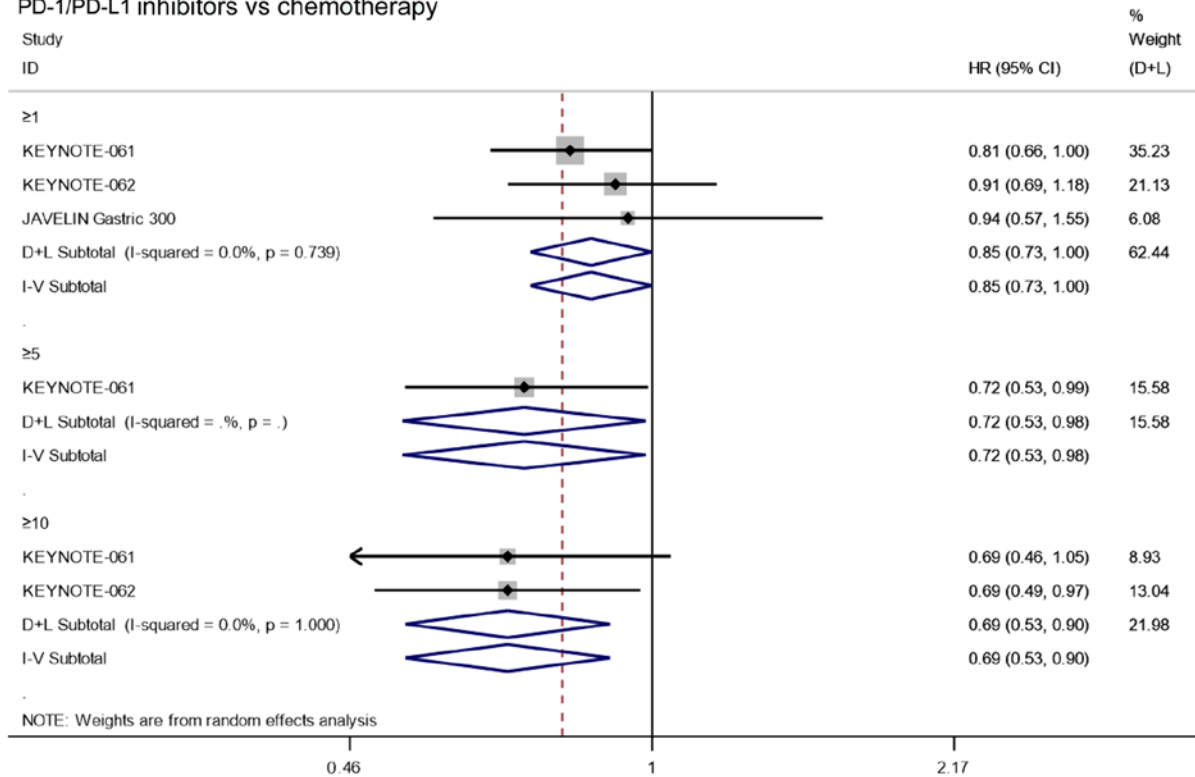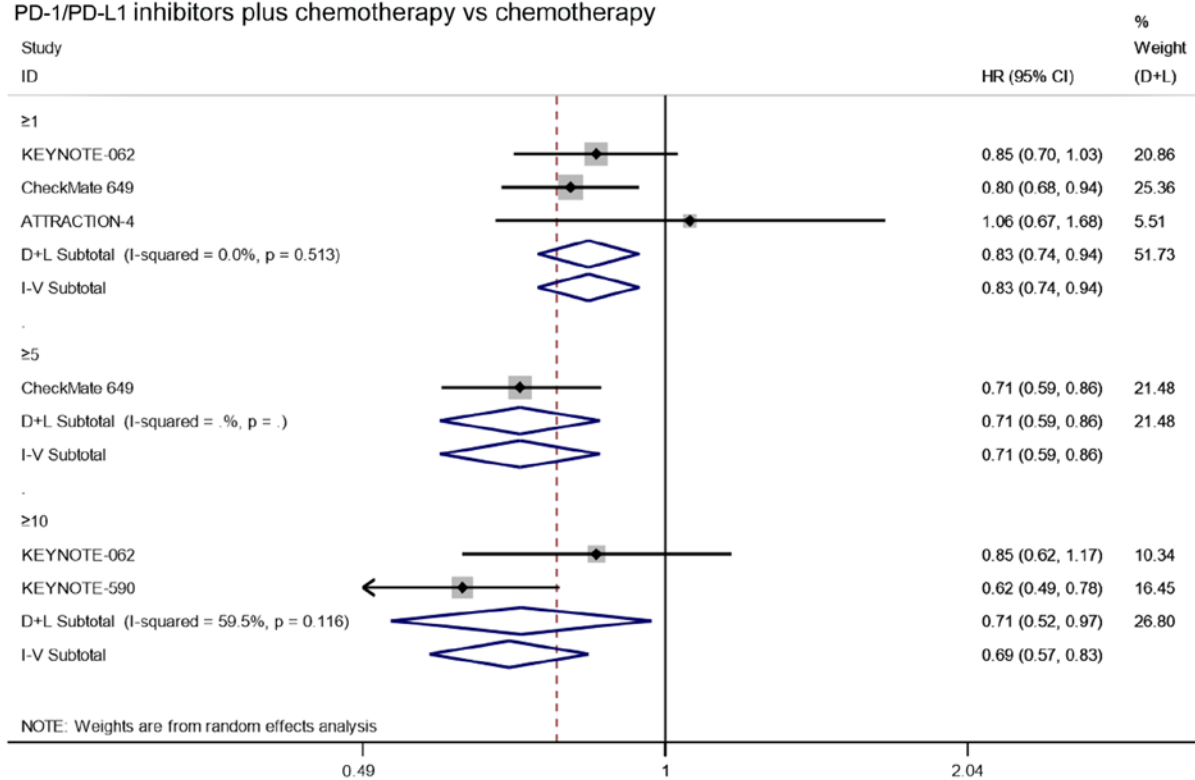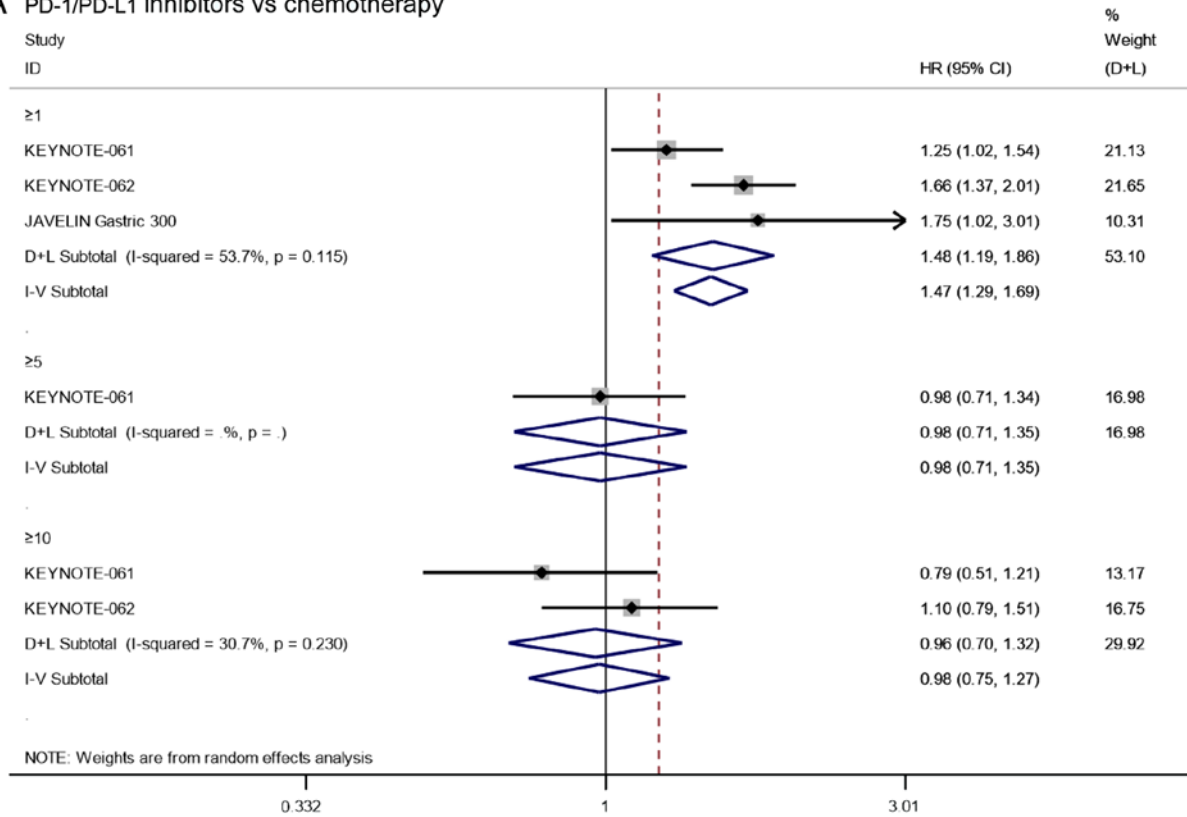
Figure 9. OS of PD1/PD-L1 inhibitors (A) or PD1/PD-L1 inhibitors combined with chemotherapy (B) vs. chemotherapy alone for PD-L1 positive advanced GC/GEJC patients. GC/GEJC, gastric or gastro-esophageal junction cancer patients; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; OS, overall survival; HR, hazard ratio; CI, confidence interval.

prolong survival and improve quality of life. However, most chemotherapy therapeutic approaches fail to provide substantial efficacy benefits (22). The present systematic review and meta-analysis included 6 studies consisting of 3,286 PD-L1 positive patients, comparing the OS, PFS, ORR, SD, PD, and incidence of adverse events of PD-1/PD-L1 inhibitor or PD-1/PD-L1 inhibitor combined with chemotherapy vs. chemotherapy in PD-L1-positive GC/GEJC patients, aiming to provide more precise guidance for the clinical treatment of GC/GEJC patients.
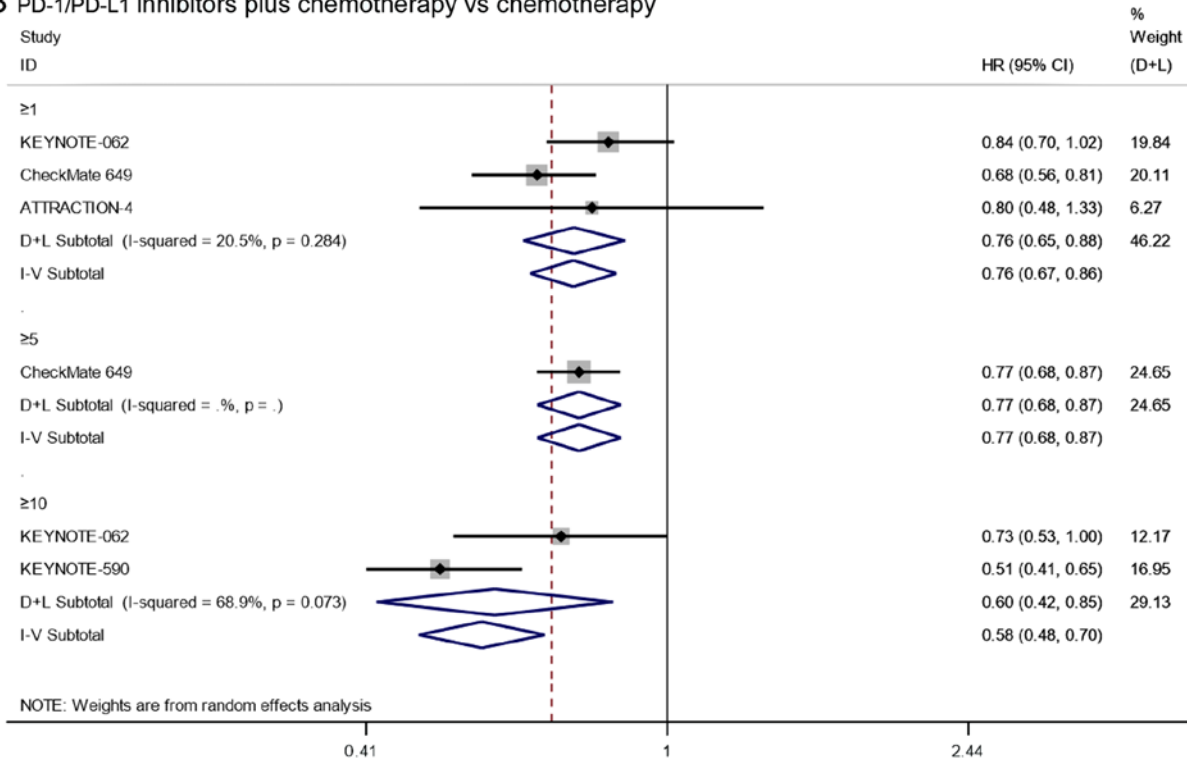
Figure 10. PFS of patients treated with (A) PD1/PD-L1 inhibitors or (B) PD1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy for patients with PD-L1 positive advanced GC/GEJC. GC/GEJC, gastric or gastro-esophageal junction cancer patients; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PFS, progression free survival; HR, hazard ratio; CI, confidence interval.

The present study first analyzed the OS and PFS rates of PD1/PD-L1 inhibitors or PD1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy alone for advanced gastric or gastro-esophageal junction cancer. The pooled results showed that single-agent PD-1/PD-L1 inhibitor did not result in a relative improvement in OS compared with chemotherapy in the treatment of patients with advanced GC/GEJC, which was consistent with the conclusions of Wang et al (11). Conversely, in the analysis of
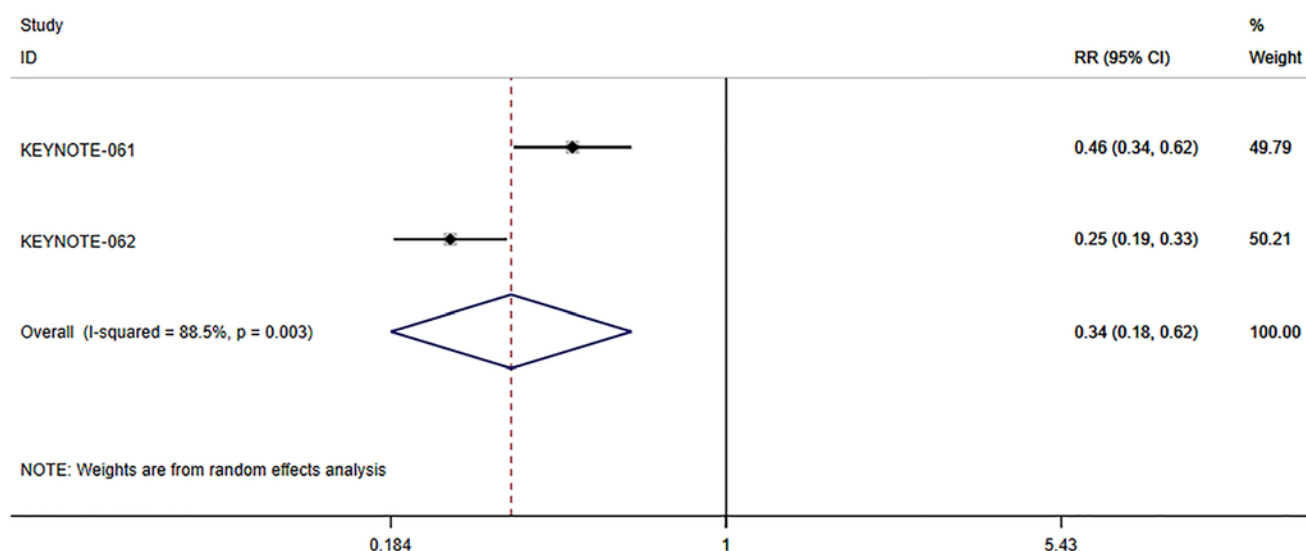
Figure 11. Incidence of adverse events of PD1/PD-L1 inhibitors vs. chemotherapy in PD-L1 positive patients with advanced GC/GEJC. GC/GEJC. GC/GEJC, gastric or gastro-esophageal junction cancer patients; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; RR, ratio rate; CI, confidence interval.

PFS, the JAVELIN Gastric 300 study (18) reported that the PFS of PD-1/PD-L1 inhibitors for advanced GC/GEJC was significantly lower than that of chemotherapy. Notably, Wang *et al* (11) also reported that GC/GEJC patients treated with PD-1/PD-L1 inhibitors had an improved PFS compared with chemotherapy. These data suggest that PD-1/PD-L1 antagonists may not be superior to chemotherapy in the treatment of patients with advanced GC/GEJC. However, insufficient clinical trials analyzing PFS made it impossible to obtain objective evidence-based medical evidence. In addition, the results showed that the OS and PFS of PD-1/PD-L1 inhibitors combined with chemotherapy were both significantly longer than that of chemotherapy alone.

Next, the analysis of OS, PFS, ORR, SD, and PD, as well as the incidence of adverse events of PD-1/PD-L1 inhibitors or PD-1/PD-L1 inhibitors combined with chemotherapy vs. chemotherapy alone in PD-L1 positive GC/GEJC patients were considered. Pooled results suggested that single-agent PD1/PD-L1 inhibitor did not improve the ORR of patients with PD-L1 positive cancer compared to chemotherapy. However, single-agent PD1/PD-L1 inhibitor did lower the SD rate and increase the PD rate, regardless of CPS level. This showed that the single use of PD1/PD-L1 inhibitors had no advantage in the short-term efficacy of the tumor; that is, in the short term, the disappearance or regression of the tumor, compared with chemotherapy did not notably differ. Encouragingly, in the evaluation of long-term efficacy, the findings found that the OS of PD-1/PD-L1 inhibitors in patients with PD-L1 CPS≥1, 5, and 10 were all significantly longer than that of chemotherapy. Additionally, the HRs of patients with PD-L1 CPS≥1, 5, and 10 were 0.85, 0.72, and 0.69, respectively. Despite the lack of statistical evidence for differential analysis, it is hypothesized that OS may be prolonged with increased PD-L1 expression. Additionally, the pooled results showed that the incidence of adverse events of PD-1/PD-L1 inhibitors in patients with PD-L1 positive was significantly lower than that of chemotherapy. Therefore, it can be suggested that anti-PD1/PD-L1 treatment was safer than chemotherapy.

As for the comparison of PD-1/PD-L1 inhibitor combined with chemotherapy vs. chemotherapy alone in PD-L1 positive GC/GEJC patients, the pooled results first showed that the ORR of PD-1/PD-L1 inhibitors combined with chemotherapy in patients with PD-L1 CPS≥1 was significantly higher than that of chemotherapy alone. In addition, the results of CheckMate 649 (20) and KEYNOTE-062 (18) showed that patients treated with PD-1/PD-L1 inhibitor combined with chemotherapy had a significantly higher ORR than chemotherapy alone in patients with PD-L1 CPS≥5 and PD-L1 CPS≥10. The results of CheckMate 649 (20) showed that there was no significant difference in the SD and PD rates of patients with PD-L1 CPS≥5 between the patients treated with PD-1/PD-L1 inhibitor combined with chemotherapy vs. chemotherapy alone. Although the lack of more clinical trial results challenges the objectivity of the SD and PD rate analysis, the pooled results still suggest that PD-1/PD-L1 inhibitor combined with chemotherapy had better short-term efficacy than chemotherapy alone in patients with PD-L1 positive cancer. Furthermore, the findings suggest that the OS and PFS of PD-1/PD-L1 inhibitors combined with chemotherapy in patients with PD-L1 CPS≥1, 5, and 10 were all significantly longer than that of chemotherapy alone. It can also be speculated that with the increase in PD-L1 expression, the survival advantage of combination therapy over chemotherapy alone may become more apparent.

The present study has some limitations. First, there was heterogeneity in the research in some of the indicators in this study; due to the small number of included studies, it was not possible to identify the source of heterogeneity. Second, due to the lack of relevant clinical trials, some of the results can only be systematically reviewed and not meta-analyzed to obtain more objective evidence-based medical evidence. Third, the lack of clinical trials makes it impossible to assess the publication bias of this study. Future studies need to supplement the assessment of publication bias based on the inclusion of more clinical trials.

In conclusion, single agent of PD-1/PD-L1 inhibitor alone or in combination with chemotherapy significantly prolonged the survival of patients compared with chemotherapy alone with fewer adverse effects. However, the degree of CPS may affect efficacy, but further investigation is needed to verify this.

Availability of data and materials

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

Authors' contributions

SQS wrote the manuscript and analyzed the data. SQS confirms the authenticity of the raw data and has 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.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Digklia A and Wagner AD: Advanced gastric cancer: Current treatment landscape and future perspectives. World J Gastroenterol 22: 2403-2414, 2016.
3. Van Laethem JL, Carneiro F, Ducreux M, Messman H, Lordick F, Ilson DH, Allum WH, Haustermans K, Lepage C, Matysiak-Budnik T, et al: The multidisciplinary management of gastro-oesophageal junction tumours: European Society of Digestive Oncology (ESDO): Expert discussion and report from the 16th ESMO World Congress on Gastrointestinal Cancer, Barcelona. Dig Liver Dis 48: 1283-1289, 2016.
4. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A and Arnold D; ESMO Guidelines Committee: Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 27 (Suppl 5): v38-v49, 2016.
5. Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, Mansoor W, Fyfe D, Madhusudan S, Middleton GW, et al: Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): An open-label, phase 3 randomised controlled trial. Lancet Oncol 15: 78-86, 2014.
6. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, Dogan Y, Gebauer B, Schumacher G and Reichardt P: Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer-a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 47: 2306-2314, 2011.
7. Kang JH, Lee SI, Lim DH, Park KW, Oh SY, Kwon HC, Hwang IG, Lee SC, Nam E, Shin DB, et al: Salvage chemotherapy for pretreated gastric cancer: A randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 30: 1513-1518, 2012.
8. Amatatsu M, Arigami T, Uenosono Y, Yanagita S, Uchikado Y, Kijima Y, Kurahara H, Kita Y, Mori S, Sasaki K, et al: Programmed death-ligand 1 is a promising blood marker for predicting tumor progression and prognosis in patients with gastric cancer. Cancer Sci 109: 814-820, 2018.
9. Kawazoe A, Kuwata T, Kuboki Y, Shitara K, Nagatsuma AK, Aizawa M, Yoshino T, Doi T, Ohtsu A and Ochiai A: Clinicopathological features of programmed death ligand 1 expression with tumor-infiltrating lymphocyte, mismatch repair, and Epstein-Barr virus status in a large cohort of gastric cancer patients. Gastric Cancer 20: 407-415, 2017.
10. Yuan J, Zhang J, Zhu Y, Li N, Tian T, Li Y, Li Y, Li Z, Lai Y, Gao J and Shen L: Programmed death-ligand-1 expression in advanced gastric cancer detected with RNA in situ hybridization and its clinical significance. Oncotarget 7: 39671-39679, 2016.
11. Wang BC, Zhang ZJ, Fu C and Wang C: Efficacy and safety of anti-PD-1/PD-L1 agents vs chemotherapy in patients with gastric or gastroesophageal junction cancer: A systematic review and meta-analysis. Medicine (Baltimore) 98: e18054, 2019.
12. Zheng Z, Guo Y and Zou CP: Oncological outcomes of addition of anti-PD1/PD-L1 to chemotherapy in the therapy of patients with advanced gastric or gastro-oesophageal junction cancer: A meta-analysis. Medicine (Baltimore) 99: e18332, 2020.
13. Sharma P and Allison JP: Immune checkpoint targeting in cancer therapy: Toward combination strategies with curative potential. Cell 161: 205-214, 2015.
14. Moher D, Liberati A, Tetzlaff J, Altman DG and Group P: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 6: e1000097, 2009.
15. Chen Z, Wang J and Lin Y: Comparison of the efficacy and safety of repeated hepatectomy and radiofrequency ablation in the treatment of primary recurrent liver cancer: A meta-analysis. World J Surg Oncol 20: 182, 2022.
16. Fuchs CS, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandala M, Ryu MH, Fornaro L, Olesinski T, Caglevic C, Chung HC, et al: Pembrolizumab versus paclitaxel for previously treated PD-L1-positive advanced gastric or gastroesophageal junction cancer: 2-year update of the randomized phase 3 KEYNOTE-061 trial. Gastric Cancer 25: 197-206, 2022.
17. Shitara K, Van Cutsem E, Bang YJ, Fuchs C, Wyrwicz L, Lee KW, Kudaba I, Garrido M, Chung HC, Lee J, et al: Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: The KEYNOTE-062 phase 3 randomized clinical trial. JAMA Oncol 6: 1571-1580, 2020.
18. Bang YJ, Ruiz EY, Van Cutsem E, Lee KW, Wyrwicz L, Schenker M, Alsina M, Ryu MH, Chung HC, Evesque L, et al: Taieb, Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: Primary analysis of JAVELIN Gastric 300. Ann Oncol 29: 2052-2060, 2018.
19. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, Wyrwicz L, Yamaguchi K, Skoczylas T, Campos Bragagnoli A, et al: First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): A randomised, open-label, phase 3 trial. Lancet 398: 27-40, 2021.
20. Kang YK, Chen LT, Ryu MH, Oh DY, Oh SC, Chung HC, Lee KW, Omori T, Shitara K, Sakuramoto S, et al: Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): A randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 23: 234-247, 2022.
21. Sun JM, Shen L, Shah MA, Enzinger P, Adenis A, Doi T, Kojima T, Metges JP, Li Z, Kim SB, et al: Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): A randomised, placebo-controlled, phase 3 study. Lancet 398: 759-771, 2021.
22. Miceli R, Tomasello G, Bregni G, Di Bartolomeo M and Pietrantonio F: Adjuvant chemotherapy for gastric cancer: Current evidence and future challenges. World J Gastroenterol 20: 4516-4525, 2014.