PD-1/PD-L1 Inhibitors vs. Chemotherapy For Previously Treated Advanced Gastroesophageal Cancer: A Meta-Analysis of Randomized Controlled Trials

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Research Article

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Abstract

Background: Patients with advanced gastroesophageal cancer refractory to previous regimen of chemotherapy suffered from poor prognosis without many effective treatment options. Immune checkpoint inhibitors (ICIs) provide promising efficacy, but the relevant clinical trials have offered controversial data. Therefore, we performed this meta-analysis to compare the efficacy and safety of inhibitors against programmed cell death receptor 1 (PD-1) and its ligand PD-L1 versus chemotherapy as second or third-line therapy in patients with advanced gastroesophageal cancer.

Materials and methods: We systematically searched PubMed, Cochrane Library, Web of Science, Embase, and China National Knowledge Web. All studies regarding ICIs compared chemotherapy for advanced gastroesophageal cancer were included. Outcomes included the overall survival (OS) progression-free survival (PFS), objective response rate (ORR) and treatment-related adverse events (TRAEs). The hazard ratio (HR) and odds ratio (OR) were the principal measure of effect.

Results: Finally we selected 7 randomized controlled trials (RCTs) including 3,141 patients. One study compared ICIs with placebo therapy only as reference. The meta-analysis was performed by combining 6 RCTs about the comparing ICIs with chemotherapy. Results indicated that both ORR (RR = 1.39, 95%CI 0.85-2.25, P = 0.188) and PFS (HR = 1.14, 95%CI 0.88-1.46, P = 0.316) were not significantly improved by ICIs compared with chemotherapy. However, the OS was significantly prolonged (HR = 0.85, 95%CI 0.75-0.97, P = 0.018) in ICIs group compared with chemotherapy. Subgroup analysis showed that ICIs provide statistically significant OS benefits over chemotherapy in patients of PD-L1 positive, squamous cell carcinoma, Asia origin, esophageal cancer, second-line treatment, male and patients aged 65 or older. Compared with chemotherapy, the TRAEs risk of ICIs was reduced by 33% (RR = 0.67, 95%CI 0.62-0.73, P = 0.000). And the risk of grade 3-5 TRAEs was reduced by 60% (RR = 0.40, 95%CI 0.33-0.49, P = 0.000).

Conclusions: Compared to chemotherapy, ICIs appears to improve OS and are better tolerated in previously treated patients with advanced esophageal cancer. We recommend PD-1/PD-L1 inhibitors as an optimal treatment option for patients with positive PD-L1 expression, squamous cell carcinoma, Asia origin, esophageal cancer, second-line treatment, male and ≥65 years of age.

Background

Upper gastrointestinal cancer is one of the leading cause of cancer-related death in the world, with about 1.6 million new cases and 1.3 million deaths in 2018 [1]. Because of concealed incidence and rapid development, the prognosis of gastroesophageal cancer is really poor. Most of the patients tend to be diagnosed at advanced stages and lost the opportunity for operation. For these patients with advanced gastroesophageal cancer, combined chemotherapy based on 5-fluorouracil and platinum is the standard first-line treatment [2]. However, it is easy to develop drug resistance and result in disease progression after first-line treatment, while the efficacy of the following chemotherapy regime is not desirable with severe side effects. The patients who have failed in previous regimens are often in poor physical condition and are difficult to bear subsequent treatment. The medicines targeting epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER-2) and vascular endothelial growth factor (VEGF) showed effect on some patients, but the benefits are limited [3]. Therefore, how to improve the efficacy of patients with advanced gastroesophageal cancer refractory or intolerant to previous chemotherapy is an urgent problem.

Recently, a number of clinical trials have shown that immune checkpoint inhibitors, represented by PD-1/PD-L1 inhibitors, exerted their potential in the posterior line treatment of advanced gastroesophageal cancer. However, there were still some trials without favorable outcomes. In addition, the correlation among pathological types, PD-L1 expression level, and curative effect, as well as the anti-tumor efficacy between ICIs and chemotherapy are still worthy of further exploration. At present, there is still lack of meta-analysis of related randomized controlled trials. Thus, we performed this meta-analysis to integrate the efficacy, prognostic marker, and side effect of ICIs in published clinical trials of advanced esophageal cancer (EC), gastric cancer (GC), and gastroesophageal junction cancer (GEJC).

Materials And Methods

2.1 Search strategy

Two investigators searched PubMed, Cochrane Library, Web of Science, EMBASE, the CNKI database and abstracts of ASCO meetings respectively, and screened all related literatures up to October, 2020. The following MeSH terms and free key words, including “esophageal or gastric or gastroesophageal junction”, and “cancer or carcinoma or neoplasm or tumor or adenocarcinoma”, and “PD-1 or PD-L1 or immune checkpoint inhibitor or pembrolizumab or nivolumab or avelumab or atezolizumab or durvalumab or camrelizumab or SHR-1210 or toripalimab or sintilimab or tislelizumab”, and “study or trial or clinical trial or randomized clinical trial or randomized controlled trial or randomized controlled clinical trial” were used for search.

2.2 Inclusion and exclusion criteria

Studies eligible for inclusion met all of the following criteria: (1) prospective RCTs; (2) patients were clinically diagnosed as advanced EC/GC/GEJC and progressed after failure of one or more chemotherapy regimens; (3) the trial group was treated with a single PD-1/PD-L1 inhibitor, and the control group was treated with chemotherapy; (4) the outcome index included clinical efficacy and survival analysis were judged by RECIST criteria, and TRAEs were classified and graded.

The exclusion criteria were as follows: (1) non-RCTs; 2) repeated publication of data; (3) the outcome index was ambiguous or could not be merged.

2.3 Data extraction and quality assessment

Two investigators reviewed the full text, and evaluated the quality of the included literature respectively. The literature authors, publication time, study design, number of patients, expression level of PD-L1, intervention measures, and outcome indicators were extracted and summarized. The HR of OS and PFS, ORR, TRAEs, and supplementary information were obtained from each eligible trial. According to Cochrane system Evaluation Manual [4], the included RCTs were evaluated in seven aspects by Review Manager 5.3 software: (1) Random sequence generation; (2) Allocation concealment; (3) Blinding of participants and personnel; (4) Blinding of outcome assessment; (5) Incomplete outcome data; (6) Selective reporting; (7) Other bias. Each item was divided into low risk, high risk or risk unknown. Any discrepancies were resolved by discussion.

2.4 Statistical analysis

Statistical software stata14.2 was used for meta-analysis, and publication bias test. For survival indicators (PFS and OS), HR was used to aggregate the statistics, and 95% confidence interval (CI) for estimating each point was calculated. Relative RR and its corresponding 95% CI were used as effect indicators for ORR and TRAEs data. Heterogeneity test was carried out for each analysis, and chi-square test was used to evaluate it, which was expressed by I^2 index and P value. When $I^2 \leq 50\%$ or $P \geq 0.10$, it was considered that there was no heterogeneity among studies, and we used fixed effect model. On the contrary, it represented that there was heterogeneity among the studies, we used random effect model, and looked for the possible sources of heterogeneity. If a reasonable cause was found, a subgroup analysis was carried out. The difference was statistically significant when $P < 0.05$. Finally, we verified the credibility of the study through sensitivity analysis, and published bias evaluation.

Results

3.1 Search results and quality evaluation

In this study, we identified a total of 3337 related literature. After screening the titles and abstracts of these articles, we excluded 3216 studies because they were repetitive or irrelevant. After perusing 121 potentially eligible articles, we eventually included 7 studies [5-11]. A flow chart of the above screening process is shown in **Fig.1**. Almost all the quality evaluations in the included literature were of low risk except ORIENT-2 [11]. ORIENT-2 had a slightly higher risk of bias, because this study was only presented by a meeting report, and the specific study process was unknown, and the expression of PD-L1 in patients was not reported. The relevant quality evaluation is shown in **Fig.2**.

3.2 Characteristics of the included studies

The seven included studies were prospective RCTs. However, the ATTRACTION-2 [5] was only viewed as a reference, and didn't be included in the pooled analysis, because this study was designed as an PD-1 inhibitor versus placebo treatment. Of the other six trails, ORIENT-2 [11] was a phase 2 clinical trial, and the rest were phase 3 clinical trials. In terms of research region, three of the seven studies were from east Asia, and the other five studies were from many countries around the world. The characteristics of the included studies are shown in **Table 1**.

3.3 Objective response rate (ORR)

The significant ORR benefit advantage of PD-1 inhibitor versus placebo was shown in the ATTRACTION-2 study, with an ORR of 11.2% in the treatment of advanced GC/GEJC after second line [5]. Then we combined and analyzed six included studies comparing PD-1/PD-L1 inhibitors with chemotherapy for advanced gastroesophageal cancer. The results showed that the short-term efficacy of anti-PD-1/PD-L1 in advanced gastroesophageal cancer was similar to that of chemotherapy, and there was no significant difference in ORR (RR = 1.39, 95%CI 0.85-2.25, P = 0.188) (**Fig.3**). In addition, we conducted a subgroup analysis according to tumor types, and found that patients with the squamous subtype receiving PD-1/PD-L1 inhibitors showed significant ORR improvement compared with chemotherapy (RR = 1.89, 95% CI 1.03-3.44, P = 0.039), and the difference was statistically significant. However, as for the ORR of adenocarcinoma, there was no significant difference (RR = 0.88, 95% CI 0.60-1.29, P = 0.524) (**supplementary Fig.1**).

3.3 Progression-free survival (PFS)

The relatively high heterogeneity was observed among the six RCTs in the PSF ($P < 0.001$, $I^2 = 88.7\%$), so the random effect model was used for meta-analysis. The results showed that ICIs had no benefit in prolonging the PFS of advanced gastroesophageal cancer compared with that of chemotherapy (HR = 1.14, 95% CI 0.88-1.46, P = 0.316) (**Fig.4**). Subgroup analysis was performed across 6 RCTs. Survival benefit was not obtained in squamous group for the PFS compared between two kinds of treatment (HR = 0.91, 95% CI 0.74-1.11, P = 0.329). On the other hand, for patients with adenocarcinoma, ICIs was less beneficial to PFS than that of chemotherapy (HR = 1.58, 95% CI 1.37-1.82, P = 0.000) (**supplementary Fig.2**).

3.4 Overall survival (OS)

As shown in the forest plot, the OS among the six RCTs including 2,648 patients was compared between ICIs and chemotherapy (**Fig.5**). ICIs did prolong the OS of the patients compared that of chemotherapy (HR = 0.85, 95% CI 0.75-0.97, P = 0.018). Subgroup analysis showed that the ICIs significantly increased the OS of squamous cell carcinoma (HR = 0.75, 95% CI 0.66-0.84, P = 0.000). However, there was no difference of the OS for adenocarcinoma treated by two treatment regimens (HR = 1.00, 95% CI 0.86-1.16, P = 0.984) (**supplementary Fig.3**). In addition, the analysis of the pooled data indicated that ICIs significantly improved the OS of the EC compared with that of chemotherapy (HR = 0.79, 95% CI 0.70-0.88). As for GEJC, ICIs also showed some clinical benefit, although there was no statistically difference (HR = 0.71, 95% CI 0.51-1.00). On the other hand, these RCTs didn't provide enough data to support the same conclusion for GC. According to the PD-L1 expression status, ICIs remarkably reduced the risk of death of PD-L1-positive patients compared that of chemotherapy (HR = 0.73, 95% CI 0.63-0.84, P = 0.000), while there was no survival advantage for PD-L1-negative patients (HR = 1.00, 95% CI 0.81-1.24, P = 0.998). Furthermore, the pooled results showed that PD-1/PD-L1 inhibitors significant benefits in the subgroups of second-line application, Asian region, male, and aged 65 or older (**Table 2**).

3.5 Treatment-related adverse events (TRAEs)

We compared all the TRAEs between the research group and the control group. After exclusion of ESCORT study which brought heterogeneity, we found that the incidence of TRAEs on immunotherapy was significantly lower than that on chemotherapy (RR = 0.67, 95% CI 0.62-0.73, P = 0.000) (**Fig.6 (a)**). For severe (grade 3-5) TRAEs, the risk of immunotherapy was 60% lower than that of chemotherapy (RR = 0.40, 95% CI 0.33-0.49, P = 0.000) (**Fig.6 (b)**). The most common TRASs in both groups were fatigue, nausea, diarrhea, anemia, neutrophil count decreased, white blood cell (WBC) count decreased and bone marrow toxicity, which were significantly lower in the immunotherapy group (**supplementaryTable 1** and **supplementary Table 2**). The incidence of hypothyroidism increased significantly for ICIs, but without grade 3-5 hypothyroidism. The risk of pulmonary infection in the immunotherapy group was also higher than that in the chemotherapy group, but the difference was not statistically significant. The incidence of death caused by TRAEs was similar between the two groups.

3.6 Publication bias assessment and sensitivity analyses

Due to the limited number of included clinical studies (n<10), we didn't detect publication bias. Sensitivity analysis was performed by excluding the literature one by one (**Table 3**). The results showed that there was no significant difference in the ORR, and indicated the robustness and reliability of the conclusion. The PFS was significantly changed after the exclusion of ESCORT study, while the heterogeneity of the remaining five studies was still large (I^2 = 77.3%, P = 0.001). However, after the subgroup analysis based on the pathological type, the heterogeneity was significantly reduced (SCC group, I^2 = 0.0%, P = 0.572; ACC group: I^2 = 5.1%, P = 0.305), suggesting that histology was the main source of heterogeneity of PFS. The sensitivity analysis suggested that histology was also the main factor affecting the effect of OS.

Discussion

In this paper, we compared the efficacy and safety of ICIs against chemotherapy beyond the first-line of advanced gastroesophageal cancer. First, for the short-term efficacy, ORR and PFS of the immunotherapy group was not significantly improved compared with that of chemotherapy group. Regarding ORR, there was a tendency that ICIs was superior to chemotherapy in the squamous cell carcinoma subgroup, however, there was no statistic difference. And, there was no difference in the PFS. On the other hand, for the adenocarcinoma, there was no difference between ICIs and chemotherapy in ORR, and the PFS of ICIs was even inferior to chemotherapy. However, the ICIs was superior to chemotherapy in long-term efficacy, especially for squamous cell carcinoma. In addition, our data suggested that patients with positive PD-L1 expression, Asian regions, esophageal tumors, scheduled for second-line treatment, males and ≥65 years of age could benefit from ICIs, instead of chemotherapy.

Gastroesophageal cancer is a disease with extensive heterogeneity among different histologic types and tumor sites. Studies have shown that esophageal squamous cell carcinoma has unique molecular characteristics, while esophageal adenocarcinoma and gastric adenocarcinoma have more similarities [12]. Our meta-analysis showed that there were significant differences in the effect-size of the primary outcomes between the squamous cell carcinoma group and the adenocarcinoma group, and the sensitivity analysis showed that the histology was the main factor affecting PFS and OS. Therefore, it might be better to investigate adenocarcinoma and squamous cell carcinoma separately in clinical trials of gastroesophageal cancer. The results of subgroup analysis confirmed that PD-L1 was a good predictor of ICIs for gastroesophageal cancer. PD-L1 overexpression is more common in esophageal squamous cell carcinoma (ESCC) (41%), compared with gastric adenocarcinoma (GAC) (10%), esophageal adenocarcinoma (EAC) (9%) and gastroesophageal junction adenocarcinoma (GEJAC) (8%), while high microsatellite instability (MSI-H) and high tumor mutational burden (TMB-H) are rare in gastroesophageal cancer [12]. This may be one of the reasons for the better benefits of immunotherapy in squamous cell carcinoma. Due to the different detection methods of PD-L1 expression in different studies, such as Combined Positivity Score (CPS) and Tumor Proportion Score (TPS), we were unable to further analyze the relationship between PD-L1 expression level and efficacy.

Only the JAVELIN Gastric 300 study involved third-line and subsequent treatments. Due to insufficient data, we were unable to conduct a combined analysis. Four single-arm studies on the third-line and subsequent treatment of EC, including JapicCTI-No.142422 , Keynote-028 , Keynote-180 and NCT02742935 , showed that patients treated with PD-1 inhibitors achieved an ORR of 14.3% - 33.3%, and grade 3 - 5 TRAEs were 10% - 17%. Among which two studies reported the mOS of 7.0 months and 10.8 months, respectively. The related studies of GC and GEJC, including JAVELIN Gastric 300 , ATTRACTION-2 and KEYNOTE-059 cohort 1 , showed that the patient's ORR was 3.2% - 16.4%, mOS was 4.2 - 5.6 months, grade 3-5 TRAEs were 9.2% - 23.3%. Therefore, ICIs were effective in the third line and later in EC, but not satisfactory in GC and GEJC.

As for the third-line and the subsequent treatment, due to insufficient data, we were unable to conduct a combined analysis. Only the JAVELIN Gastric 300 study was involved in this paper. Four single-arm studies on the third-line and subsequent treatment of EC, including JapicCTI-No.142422 [13], Keynote-028 [14], Keynote-180 [15] and NCT02742935 [16], showed that patients treated with PD-1 inhibitors achieved an ORR of 14.3% - 33.3%, and grade 3-5 TRAEs were 10% - 17%. Among which two studies reported the mOS of 7.0 months and 10.8 months, respectively. The related studies of GC and GEJC, including JAVELIN Gastric 300 [6], ATTRACTION-2 [5] and KEYNOTE-059 cohort 1 [17], showed that the patient's ORR was 3.2% - 16.4%, mOS was 4.2 - 5.6 months, grade 3-5 TRAEs were 9.2% - 23.3%. Therefore, in general, PD-1/PD-L1 inhibitors were effective in the third line and later application of EC, but not satisfactory in GC and GEJC.

In this meta-analysis, we observed that the ORR of immunotherapy was consistent with that of OS for both squamous cell and adenocarcinoma. However, in the immunotherapy group, tendency of PFS and OS was not the same. We suggest that the reason for this contradiction may be related to the antitumor response of ICIs as opposed to chemotherapy. First of all, one of the major differences between immunotherapy and cytotoxic therapy is that the lag of response [18]. For example, ATTRACTION-3 [9] showed that the median time of onset of ICIs was later than chemotherapy (2.6 months vs. 1.5 months). Secondly, immunotherapy shows a long duration of response (DOR). KEYNOTE-061 [7], ATTRACTION-3 [9], ESCORT [10] and ORIENT-2 [11] showed that the median DOR of immunotherapy was longer than that of chemotherapy (18.0 months vs 5.5 months, 6.9 months vs 3.9 months, 7.4 months vs 3.4 months, 8.3

months vs 6.2 months, respectively). There was an intersection point of the Kaplan-Meier curve of PFS in all the second-line trails in this paper, except the JAVELIN Gastric 300 study for the third-line application. The PFS curve of the immunotherapy group started below the chemotherapy group, crossed at about 4 months to 10 months, and then appeared above the chemotherapy group. This means that patients who were effective in immunotherapy got a long durable response and progress more slowly than those treated by chemotherapy. The five studies [7-11] of second-line trails showed that the 6-month OS rate of the immune group was similar to that of the chemotherapy group, while the 1-year OS rate and 18-month OS rate were significantly higher than that of the chemotherapy group, which were 1.3 to 1.8 times and 1.4 to 1.8 times, respectively. Therefore, we propose that the rates of OS at 6 months, 1-year and 18 months are reliable indicator for immunotherapy.

In terms of safety, immunotherapy had better tolerance, with a 33% and 60% reduction in the risk of grade 1-5 TRAEs, and grade 3-5 TRAEs compared with chemotherapy, respectively. The inevitable autoimmune attack also occurs when the immune system is activated to fight cancer [19, 20]. Nonetheless, most immune-related adverse events are controllable by withdrawal of ICIs and steroids [18]. A new and special adverse reaction, reactive cutaneous capillary endothelial proliferation (RCCEP), was reported only in the ESCORT study, with an incidence of 79%, mainly grade 1-2. RCCEP was also observed in other studies of camrelizumab [21]. Interestingly, the analysis showed that RCCEP was associated with higher ORR and longer OS [10, 21]. Moreover, in the ORIENT-2 [11] study, a lower neutrophil to lymphocyte ratio (NLR < 3) at baseline and week 6 was found to be associated with a longer OS. Different types of ICIs have slightly different molecular mechanisms, which may relate differences in TRAEs. Attention should be paid to the observation and analysis of the relationship between TRAEs and tumor response.

There are still some shortcomings of this study as follows: 1) There is insufficient data to support the benefits of ICIs compared with chemotherapy in third-line and subsequent applications; 2) Due to different detection methods for PD-L1 expression, it is difficult to conduct in-depth analysis of the relationship between the expression level of PD-L1 and efficacy; 3) The number of studies included is limited, so we could not perform a subgroup analysis of PD-1 inhibitors and PD-L1 inhibitors respectively.

Conclusions

In summary, PD-1/PD-L1 inhibitors appear to improve OS and have better tolerance compared to chemotherapy in the recurrence of advanced gastroesophageal carcinoma. Especially for patients with positive PD-L1 expression, squamous cell carcinoma, Asian region, esophageal cancer, second-line application, male and 65 years of age or older. Due to the different antitumor response patterns of PD-1/PD-L1 inhibitors and cytotoxic drugs, more reasonable indicators such as survival at some time point, are necessary for efficacy evaluation. More clinical trials are needs to concern about the different histology, PD-L1 expression level, and multiple lines treatment.

Abbreviations

ICIs Immune checkpoint inhibitors

PD-1 Programmed cell death receptor 1

PD-L1 Programmed cell death ligand 1

OS Overall survival

PFS Progression-free survival

ORR Objective response rate

TRAEs Treatment-related adverse events

HR Hazard ratio

OR Odds ratio

RCTs Randomized controlled trials

EGFR Epidermal growth factor receptor

HER-2 Human epidermal growth factor receptor 2

VEGF Vascular endothelial growth factor

EC Advanced esophageal cancer

GC Gastric cancer

GEJC Gastroesophageal junction cancer

CI Confidence interval

WBC White blood cell

ESCC Esophageal squamous cell carcinoma

GAC Gastric adenocarcinoma

EAC Esophageal adenocarcinoma

GEJAC Gastroesophageal junction adenocarcinoma

MSI-H High microsatellite instability

TMB-H High tumor mutational burden

CPS Combined positivity score

TPS Tumor proportion score

DOR Duration of response

RCCEP Reactive cutaneous capillary endothelial proliferation

NLR Neutrophil to lymphocyte ratio

Declarations

Ethics approval and consent to participate

Since this meta-analysis was conducted based on previously published studies, ethical approval and patient consent are not required.

Consent for publication

Not applicable for this study.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

None.

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Authors' contributions

Conception and design: ZMX, ZYX. Data collection: ZMX, ZXZ, XJM, YYB. Quality assessment: ZMX, ZXZ. Final approval of studies: ZYX. Statistical analysis: ZMX, XJM. Article writing: ZMX, ZYX. All authors have read and approved the manuscript.

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Tables

Table 1 Characteristics of eligible studies included in meta-analysis

Trial	Geographic area	Tumor type	Year	Design	Medication	No. of patients	Clinical stage	Gender (M/F)	Median age(y)	PD pa
ATTRACTION-2	East Asia	GEJC/GC	2017	Phase 3	Nivolumab (3mg/kg q2w) vs. placebo	NIV: 330 PLA: 163	NA	NIV: 229/101 PLA: 119/44	NIV: 62 PLA: 61	NI (12 PL
JAVELIN Gastric 300	Europe, Asia, North America and the rest of the world	GEJC/GC	2018	Phase 3	Avelumab (10 mg/kg q2w) vs. chemotherapy (paclitaxel/irinotecan)	AVE: 185 CHE:186	NA	AVE: 140/45 CHE:127/59	AVE: 59 CHE:61	AV 46 CH
KEYNOTE-061	Europe, Asia, North America, and the rest of the world	GEJC/GC	2018	Phase 3	Pembrolizumab (200mg q3w) vs. chemotherapy (paclitaxel)	PEM:296 CHE:296	NA	PEM:202/94 CHE:208/88	PEM:62.5 CHE:60.0	PE CH
KEYNOTE-181	Asia and the rest of world	EC/GEJC	2019	Phase 3	Pembrolizumab (200 mg q3w) vs. chemotherapy (paclitaxel/docetaxel/irinotecan)	PEM:314 CHE:314	NA	PEM:273/41 CHE:271/43	PEM:63 CHE:62	PE 8 CH 8
ATTRACTION-3	Europe,, east Asia, and the USA	ESCC	2019	Phase 3	Nivolumab (240mg q2w) vs. chemotherapy (paclitaxel/docetaxel)	NIV: 210 CHE 209	II-III:21;IV 194;UN 12	NIV: 179/31 CHE 185/24	NIV: 64 CHE: 67	NI 10 CH 10
ESCORT	East Asia	ESCC	2020	Phase 3	Camrelizumab (200mg q2w) vs. chemotherapy (docetaxel/irinotecan)	CAM: 228 CHE: 220	NA	CAM: 208/20 CHE: 192/28	CAM: 60 CHE: 60	CA CH
ORIENT-2	East Asia	ESCC	2020	Phase 2	Sintilimab (200mg q3w) vs. chemotherapy (paclitaxel/irinotecan	SIN: 95 CHE 95	SIN: III 13; IV 175; NA 2	SIN: 88/7 CHE:84/11	SIN: 58.8 CHE: 59.4	NA

Abbreviations: No. = number; M = male; F = female; EC = esophageal cancer; ESCC = esophageal squamous cell carcinoma; GC = gastric cancer; GEJC = gastroesophageal junction cancer; NIV = nivolumab; AVE = avelumab; PEM = pembrolizumab; SIN= Sintilimab; CHE = chemotherapy; NA = not available.

Table 2 Subgroup analysis of OS (PD-1/PD-L1 inhibitors vs. chemotherapy)

Subgroup	Total no. of studies	Total no. of patients	HR	95%CI
Histological type				
SCC	4	1458	0.75	0.66~0.84
ACC	2	872	1.00	0.86~1.16
Tumor site				
EC	4	1685	0.79	0.70~0.88
GEJC	2	246	0.71	0.51~1.00
GC	2	520	1.07	0.82~1.40
Line				
2	5	2186	0.82	0.73~0.92
3*	1	371	1.10	0.90~1.40
PD-L1 expression status#				
positive	5	1096	0.73	0.63~0.84
negative	4	890	1.000	0.81~1.24
ECOG performance status				
0	4	606	0.94	0.69~1.28
1	4	1026	0.79	0.62~1.02
Sex				
Male	4	1217	0.83	0.73~0.93
Female	4	316	0.84	0.51~1.38
Age at baseline, years				
<65	4	989	0.82	0.64~1.05
≥65	4	644	0.83	0.70~0.99
Region				
Asia	6	1592	0.76	0.65~0.88
Non-Asia	3	524	0.90	0.71~1.16

Abbreviations: No. = number; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; PD-L1 = programmed death ligand-1; SCC = squamous cell carcinoma; ACC = adenocarcinoma; EC = esophageal cancer; ESCC = esophageal squamous cell carcinoma; GC = gastric cancer; GEJC = gastroesophageal junction cancer. * The data of third-line applications came from all the participants in the JAVELIN Gastric 300 study. The study focused on second-line and third-line applications, of which 86% were third-line applications. # With regard to the determination of the expression state of PD-L1, three studies, including JAVELIN Gastric 300 and ESCORT, were conducted with Tumor Proportion Score (TPS), KEYNOTE-061 and KEYNOTE-181 with Combined Positivity Score (CPS).

Table 3 The sensitivity analyses of the study

Sensitivity analyses	No. of studies	RR(95%CI)		HR(95%CI)			
		No. of patients	ORR	No. of patients	PFS	No. of patients	OS
Total studies	6	2648	1.39 0.85~2.25	2648	1.14 0.88~1.46	2648	0.85 0.75~0.97
JAVELIN Gastric 300 excluded	5	2277	1.55 0.94~2.55	2277	1.05 0.81~1.35	2277	0.82 0.73~0.92
KEYNOTE-061 excluded	5	2056	1.54 0.88~2.71	2056	1.07 0.81~1.43	2056	0.83 0.71~0.98
KEYNOTE-181 excluded	5	2020	1.28 0.71~2.28	2020	1.14 0.83~1.58	2020	0.84 0.71~1.00
ATTRACTION-3 excluded	5	2229	1.51 0.83~2.72	2229	1.15 0.85~1.56	2229	0.87 0.75~1.10
ESCORT excluded	5	2200	1.16 0.77~1.76	2200	1.26 1.04~1.53	2200	0.89 0.78~1.01
ORIENT-2 excluded	5	2458	1.31 0.76~2.25	2458	1.16 0.87~1.55	2458	0.87 0.76~1.00

Abbreviations: No. = number; RR = relative risk ratio; HR = hazard ratio; ORR = objective response rate; PFS = progression free survival; OS = overall survival.

Figures

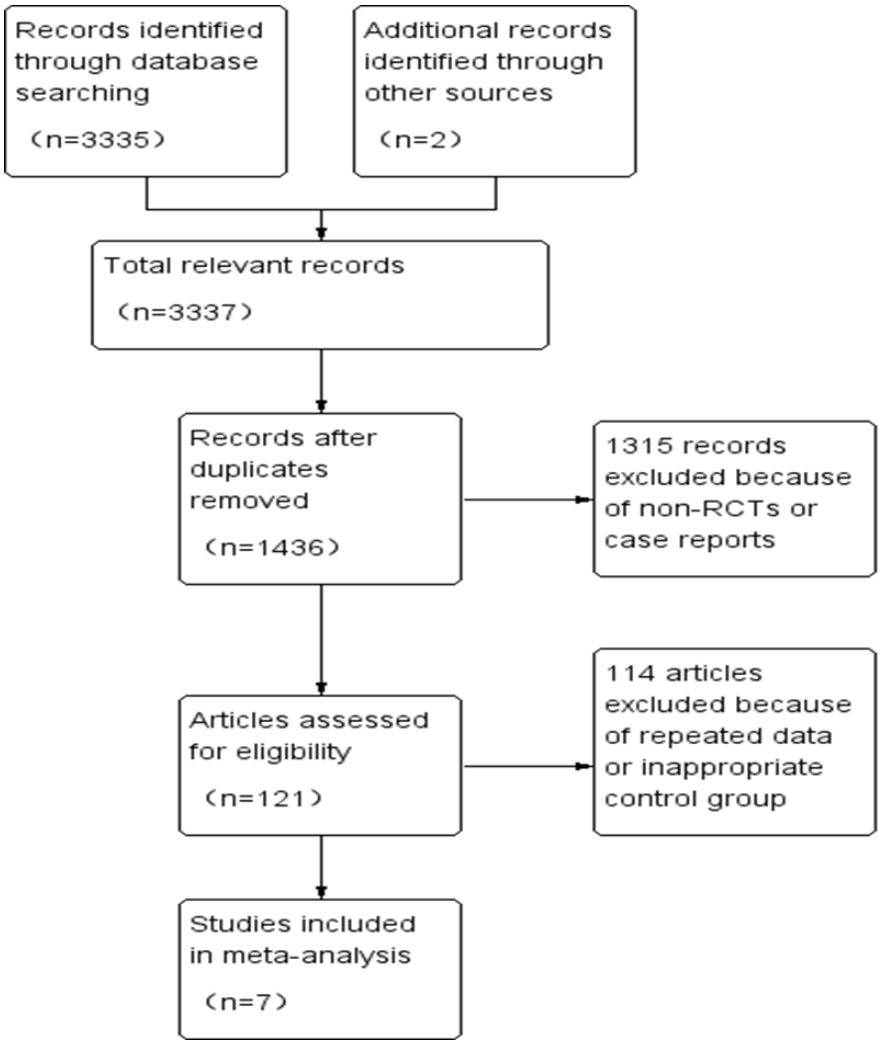

Figure 1

Flow chart of the study selection process

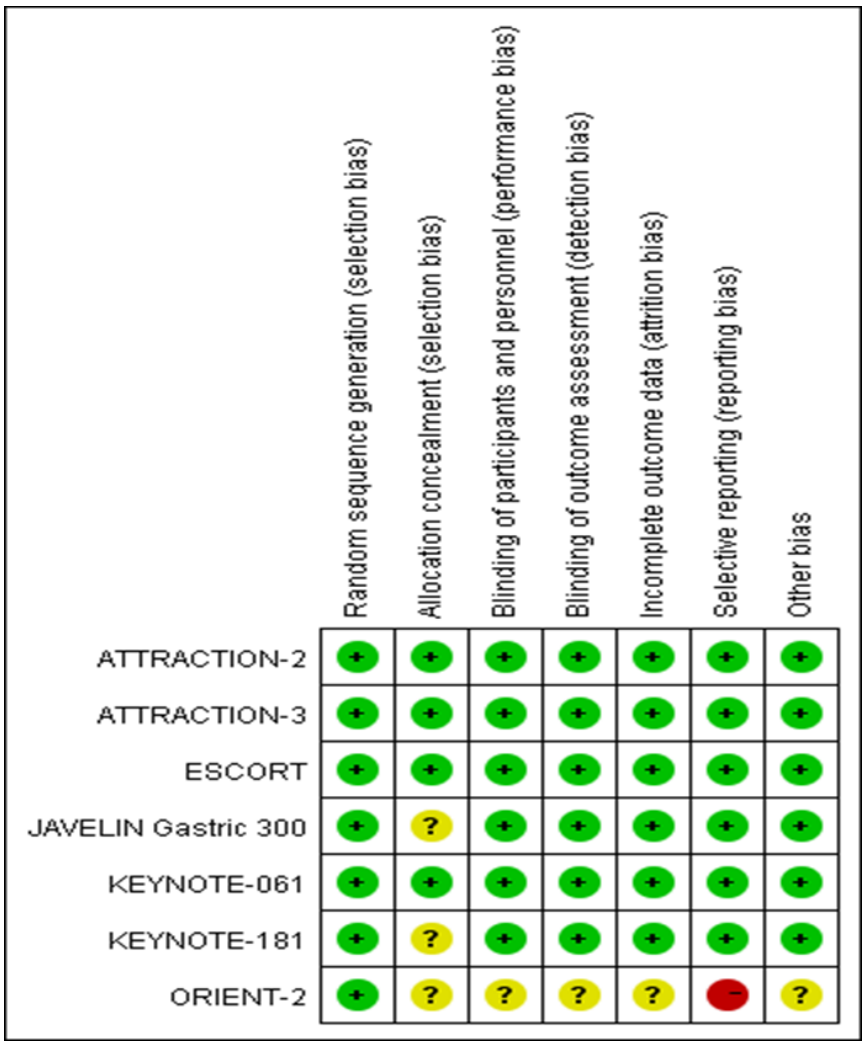

Figure 2

Literature quality evaluation (Notes: Green represents low risk bias, red represents high risk bias, and yellow represents unknown risk bias.)

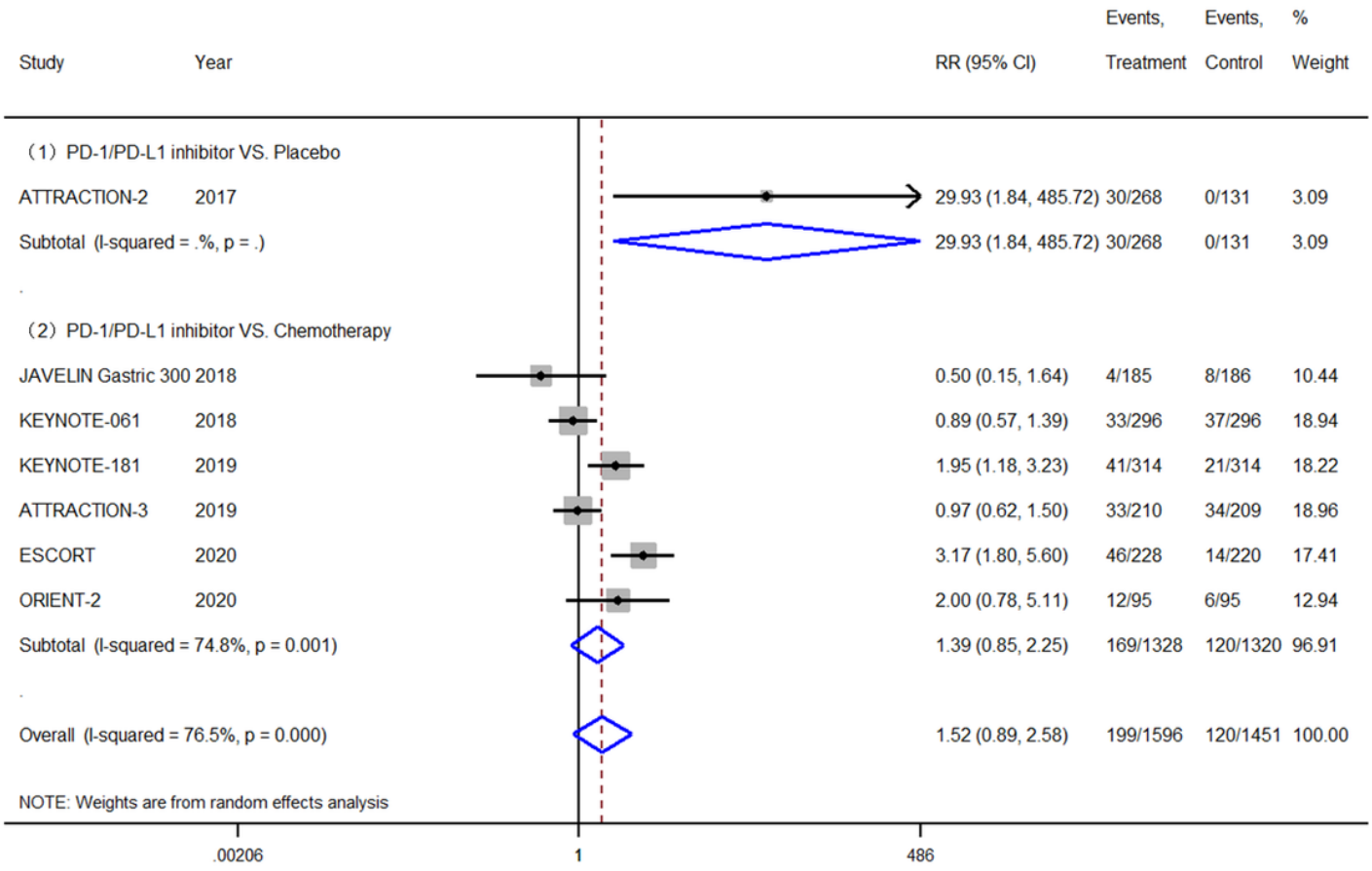

Figure 3

Forest plot of risk ratios for objective response rate (ORR) between PD-1/PD-L1 inhibitors and chemotherapy/placebo

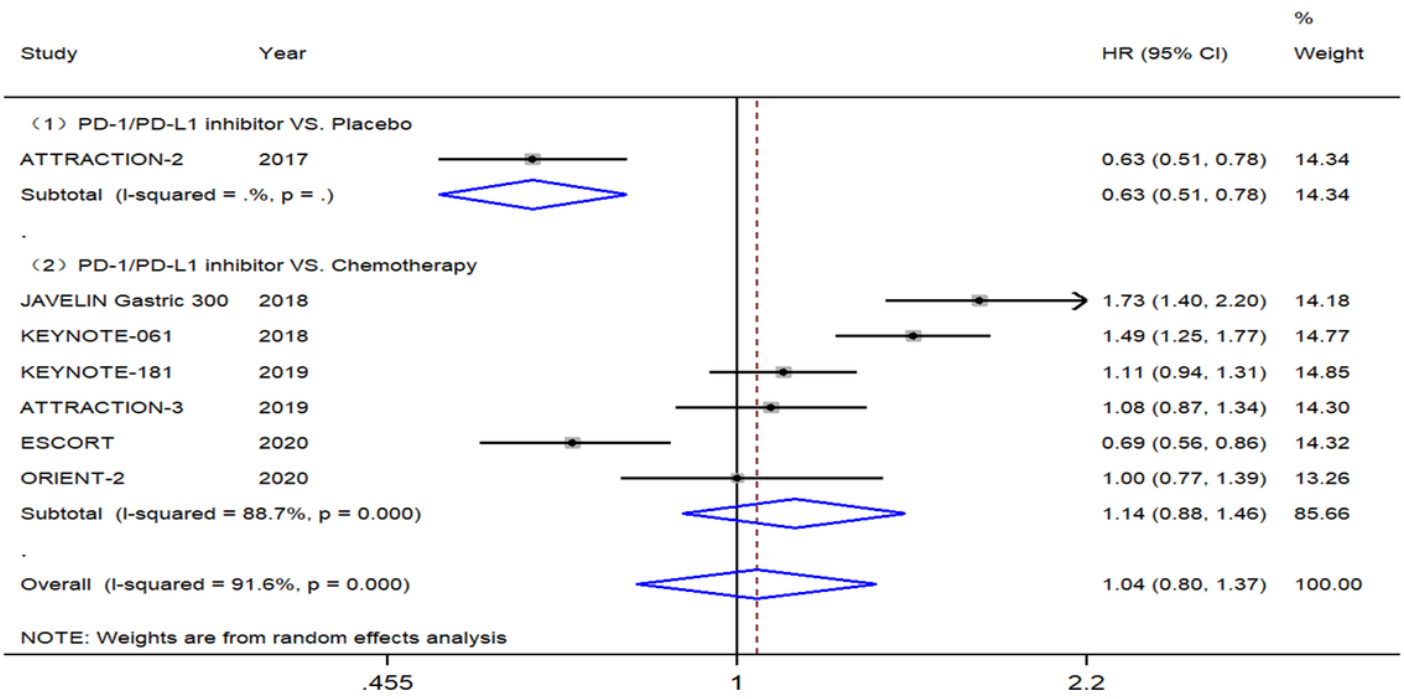

Figure 4

Forest plot of hazard ratios for progression-free survival (PFS) between PD-1/PD-L1 inhibitors and chemotherapy/placebo

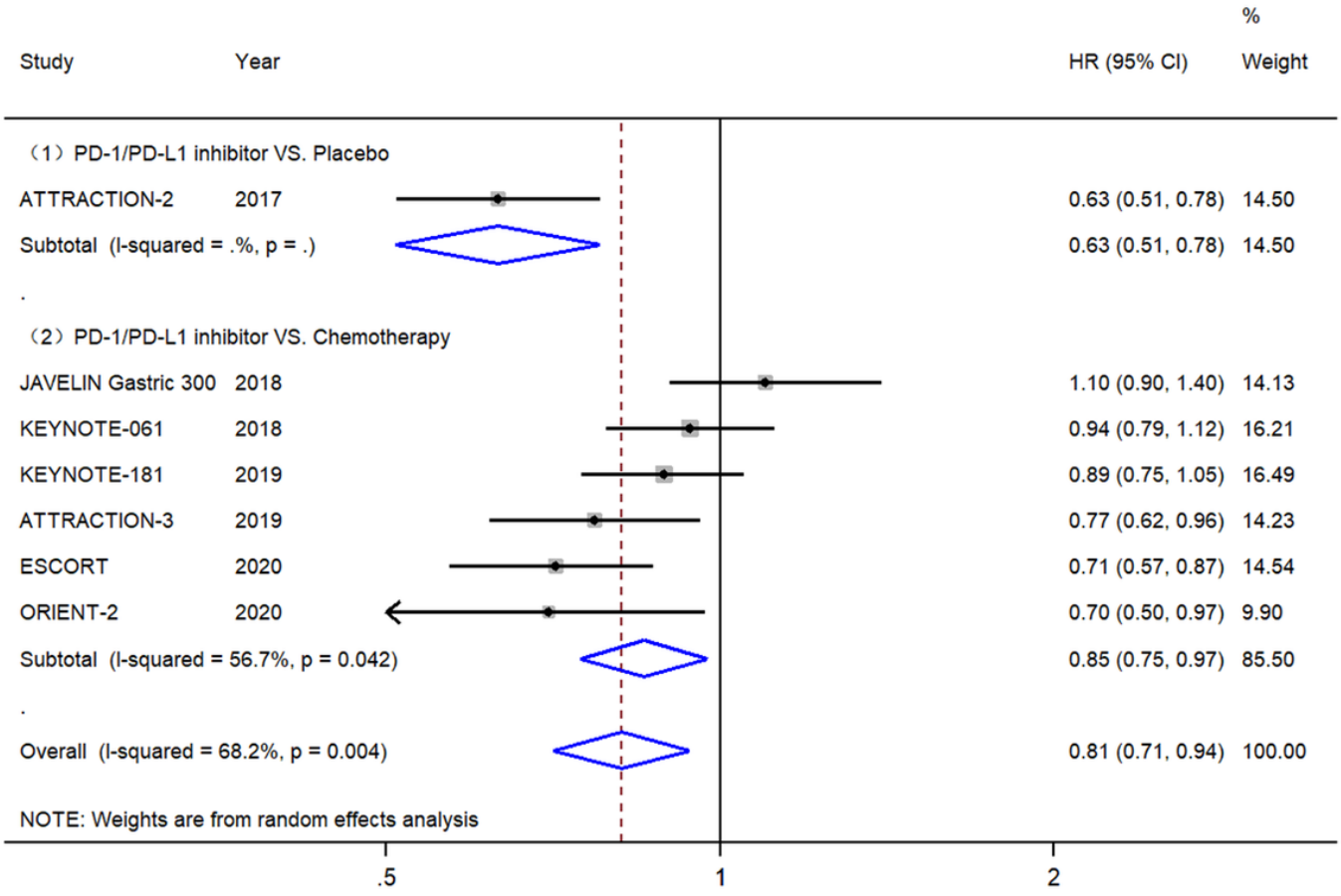

Figure 5

Forest plot of hazard ratios of overall survival (OS) between PD-1/PD-L1 inhibitors and chemotherapy/placebo

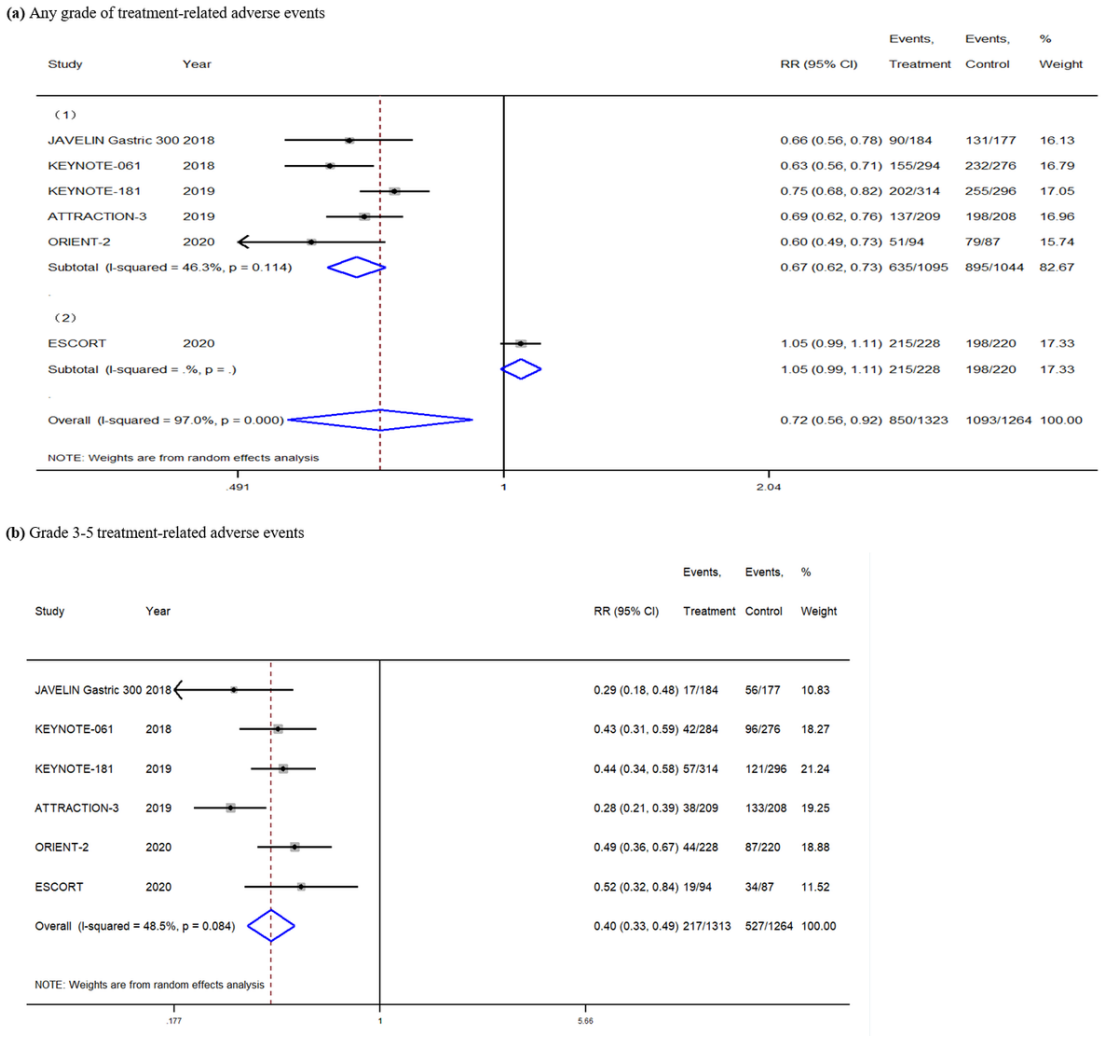

Figure 6

Forest plots of treatment-related adverse events at any grade (a) and grade 3-5 (b)

Supplementary Files

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- 20210202SupplementaryInformation.docx