The Efficacy and Safety of Anti-bodies Targeting PD-1 for Treatment in Advanced Esophageal Cancer: A Systematic Review and Meta-analysis

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Research Article

Keywords: immunotherapy, meta-analysis, esophageal cancer, PD-1, chemotherapy

Posted Date: January 25th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-137104/v1

Abstract

Background: A novel therapy based on programed death 1 (PD-1) inhibitors has been proved to be effective in advanced esophageal cancer. This article is a meta-analysis aiming to compare the efficacy and safety of anti-PD-1 therapy with chemotherapy in esophageal cancer.

Patients and methods: Data were collected from eligible studies searched from PubMed, Web of Science, Cochrane Library and Embase. Pooled hazard ratio (HR) for overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) was estimated to assess the efficacy of PD-1 inhibitors versus chemotherapy. The subgroup analysis were also performed to evaluate the OS benefits. The OR for occurrence of treatment-related adverse effect was calculated to assess the safety of anti-PD-1 therapy.

Results: A total of 4 studies were analyzed. Compared with patients with chemotherapy, patients with anti-PD-1 therapy had a significant improvement in OS (HR=0.79, 95% CI: 0.71-0.88, P<0.001), but no significant relationship was observed in PFS (HR=0.96, 95% CI: 0.76-1.20, P=0.69) and ORR (OR=1.92, 95% CI: 0.98-3.72, P=0.06). A similar result was observed in esophageal squamous cell carcinoma (ESCC). The significant predictor for treatment benefit with combination therapy versus chemotherapy alone were histology (P=0.009). The incidence of grade 3 to 5 treatment-related adverse effect in anti-PD-1 therapy was distinctly lower than that in chemotherapy, but there is no statistical difference in all treatment-related adverse effect.

Conclusion: Anti-PD-1 therapy significantly prolonged the OS, simultaneously lowered grade 3 to 5 treatment-related adverse effect versus chemotherapy.

Background

Esophageal cancer is one of the most common malignancies in the world, ranking the 8th in morbidity and the 6th in mortality among all malignancies[1, 2]. There were 572,034 cases of new diagnosed esophageal cancer worldwide and 508,585 deaths were reported in 2018, which is a real global health challenge[3]. Generally, esophageal cancer can be divided into 2 categories: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) [4, 5]. Because the clinical symptoms of early esophageal cancer are obscure, more than half of the patients are in the advanced stage when they are detected[6]. For patients with unresectable or metastatic esophageal cancer, systemic chemotherapy is the first choice. The National Comprehensive Cancer Network (NCCN) guidelines recommended cisplatin or oxaliplatin together with fluorouracil or capecitabine as first-line chemotherapy regimen for esophageal cancer[7]. However, due to the resistance and dose-limiting toxicity of chemotherapy, there are still a large number of patients who have not been satisfied with treatment[8, 9]. Therefore, it is urgent to improve the existing treatment measures, especially to find a new treatment model, to increase the survival of esophageal cancer patients.

In recent years, immunotherapy has provided new treatment options for patients with a variety of tumors[10, 11]. Programmed death-1 (PD-1), a member of the CD28 superfamily, is an important immunosuppressive molecule[12, 13]. Normally, the interaction between PD-1 and programed death ligand 1 (PD-L1) can suppress T-cell migration, proliferation, and secretion of cytotoxic mediators, and restrict cancer cell death[14]. Blocking the interaction between PD-1 and PD-L1 can restore the activity of T cells, enhance the immune response, reduce the metastasis of tumor cells and reduce the tumor volume[15]. A number of experiments have confirmed that the high expression of PD-1 and PD-L1 in esophageal cancer is closely related to the depth of tumor infiltration and poor prognosis[16–18]. Therefore, blocking the PD-1 pathway by PD-1 or PD-L1 inhibitors will provide an effective approach for the therapy of esophageal cancer.

As the monoclonal antibody of (PD-1) and its ligand (PD-L1) has made breakthroughs in the treatment of malignant melanoma, non-small cell lung cancer, kidney cancer and other tumors, clinical trials focusing on the mechanism and efficacy of anti-PD-1 therapy in esophageal cancer have been gradually carried out with initial achievements[19–21]. Up to now, several monoclonal antibodies targeting PD-1 or PD-L1 have already been developed. Pembrolizumab is the first PD-1 inhibitor to enter clinical trials and also is the most widely approved[22–24]. In 2018, the FDA of US approved pembrolizumab for the treatment of recurrent locally unresectable or metastatic gastric and esophagogastric junction adenocarcinoma. Nivolumab is another representative PD-1 monoclonal antibody. Some studies suggest that nivolumab alone was effective and safe in patients with esophageal cancer[25, 26]. In addition, there are still many PD-1 inhibitors, such as SHR-1210, Sintilimab and so on, that made initial achievements in esophageal cancer[27–30]. Based on these study results, the anti-PD-1 therapy exerts a highly promising treatment paradigm in patients with advanced esophageal cancer. However, the adverse effects of PD-1 inhibitor cannot be ignored, which has been reported previously in several studies[18].

Meta-analysis is generally considered a powerful statistical tool to overcome the limitations of different sample sizes from individual studies to generate the best overall estimation. Thus, it is necessary to perform a meta-analysis to explore the efficacy and safety of immunotherapy for esophageal cancer patients. This article is a meta-analysis of currently available trials comparing PD-1 inhibitor with chemotherapy will provide important and clinically useful information.

Material And Methods

Search strategy

A comprehensive search for studies published in English was performed in the PubMed, Web of Science, Cochrane Library and Embase in order to collect all relevant citations. The date of the latest search was Oct 1, 2020. Meeting abstracts were also searched from the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO). Keywords were used for the search: “Esophageal Neoplasms”, “Esophageal Neoplasm”, “Neoplasm, Esophageal”, “Esophagus Neoplasm”, “Esophagus Neoplasms”, “Neoplasm, Esophagus”, “Neoplasms, Esophagus”, “Neoplasms, Esophageal”,

“Cancer of Esophagus”, “Cancer of the Esophagus”, “Esophagus Cancer”, “Cancer, Esophagus”, “Cancers, Esophagus”, “Esophagus Cancers”, “Esophageal Cancer”, “Cancer, Esophageal”, “Cancers, Esophageal”, “Esophageal Cancers”, “Nivolumab”, “Opdivo”, “Pembrolizumab”, “Lambrolizumab”, “Atezolizumab”, “Camrelizumab”, “SHR-1210”, “Tislelizumab”, “Toripalimab”, “JS001”, “Sintilimab”, “PD-1”.

We evaluated all searched results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The publication language was limited to English.

Selection criteria

Inclusion criteria are the followings: randomized clinical Phase II or III trials in patients with advanced esophageal cancer; random assignment of single anti-PD-1 therapy or chemotherapy alone; studies including one or all of the following information: objective response rate (ORR), overall survival (OS), progression-free survival (PFS) and the frequency of adverse effect events (AEs). Observational studies, editorials, commentaries, reviews, case reports, and duplicate publications were excluded. If data sets were duplicated or overlapped, only the most recent information was included. Two authors (Guan LL and Lu Y) independently selected studies for inclusion in the systematic review by searching the databases. The full texts of relevant articles were retrieved for eligibility.

Data extraction

Data were extracted independently by two authors (Lu Y and Wang F) from eligible studies and all disagreements were resolved by consensus of all investigators. Study characteristics, including authors, treatment strategy, ORR, PFS, OS, duration of response (DOR), 12-month survival rate, the frequency of AEs, number of patients, age, sex, region, Eastern Cooperative Oncology Group performance status (ECOG PS), histological type, lymph node metastasis, and PD-L1 status were extracted from each eligible study. When we needed additional information that were not provided, we contacted the corresponding authors to request it. Two authors (Xu ML and Wang F) assessed the quality of included trials independently according to the five-point Jadad scoring system[31].

Statistical analyses

We derived the HRs and 95% confidence intervals (CI) for OS and PFS from each individual study of advanced esophageal cancer. For ORR, odds ratio (OR) and corresponding 95% CI are the principal summary measures. Relevant data were extracted from each study, and the pooled ORs and HRs were estimated through a meta-analysis. We performed a number of subgroup analyses to explore the variables on immunotherapy efficacy for esophageal cancer. Statistical heterogeneity between studies was evaluated using Cochran’s Q test and Higgins I^2 statistic. The random-effect model was chosen if obvious heterogeneity was present ($I^2 > 50\%$), otherwise the fixed-effect model was selected. All analyses were performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and Stata 12.0 (Stata Corporation). All reported P-values were two sided and $P < 0.05$ was considered as statistically significant. We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISM) guidelines for this meta-analysis.

Results

Literature selection process and Characteristics of the selection studies

The PRISMA diagram for the study selection is summarized in Fig. 1. In total, our search strategy identified 464 potentially relevant records from databases and conferences. A total of 168 studies were excluded for duplication and 278 for not meeting the eligibility criteria in the selection. A total of 4 studies were considered eligible for the current meta-analysis. The characteristics of these 4 studies were summarized in Table 1. 4 studies involving 1685 patients with advanced esophageal cancer were included in the following analysis[24, 25, 28, 30]. All trials were Phase III randomized controlled clinical trials and compared the efficacy and safety of PD-1 inhibitor with chemotherapy.

Efficacy outcomes of PD-1 inhibitor versus chemotherapy in all patients

At final analysis, a significant improvement in OS was found among advanced esophageal cancer patients treated with PD-1 inhibitors compared with those treated with chemotherapy (HR: 0.79; 95% CI: 0.71–0.88; P < 0.001; heterogeneity: P = 0.34) (Fig. 2A). However, there were limited benefit in terms of PFS (HR: 0.96; 95% CI: 0.76–1.20; P = 0.69; heterogeneity: P = 0.003) (Fig. 2B). In addition, analyses of ORR also showed no significant difference (OR = 1.92; 95% CI: 0.98–3.72; P = 0.06; heterogeneity: P = 0.006) (Fig. 2C).

Efficacy outcomes of PD-1 inhibitor versus chemotherapy in ESCC

Meanwhile, we also reported the analysis among ESCC patients was performed to figure out the benefit of anti-PD-1 therapy in ESCC. Same as before, esophageal squamous cell carcinoma patients treated with PD-1/PD-L1 inhibitors received superior OS to chemotherapy (HR: 0.75; 95% CI: 0.66–0.84; P < 0.001; heterogeneity: P = 0.90)(Fig. 3A), and there are no significant improvement in PFS (HR: 0.91; 95% CI: 0.74–1.10; P = 0.33; heterogeneity: 0.02)(Fig. 3B) and ORR (OR: 2.01; 95% CI: 0.98–4.10; P = 0.06; heterogeneity: P = 0.004)(Fig. 3C).

Subgroup analysis

In the term of OS, we performed subgroup analyses according to some basic information, histological type, lymph node metastasis and PD-L1 status (Fig. 4). PD-L1 tumor proportion score (TPS) was assessed by a central laboratory using immunohistochemistry. In all subgroup analysis, only histology could predict OS benefit from anti-PD-1 therapy over chemotherapy (squamous HR = 0.75 vs adenocarcinoma HR = 1.12; P = 0.009). None of the other factors predicted OS benefit with the anti-PD-1 therapy versus chemotherapy, including age (P = 0.532), sex (P = 0.572), region (P = 0.298), ECOG PS (P =

0.298), lymph node metastasis (P = 0.350), PD-L1 expression (< 1% vs ≥ 5% P = 0.093; <5% vs ≥ 5% P = 0.387; <10% vs ≥ 10% P = 0.510).

The analysis on safety of anti-PD-1 therapy

Treatment-related adverse effect is an important evaluation index for any antitumor therapies. Many treatments have to be discounted for the severe adverse effects caused by the treatment agents. To evaluate the safety of PD-1 inhibitors in advanced esophageal cancer patients, data of the total treatment-related adverse effect events and grade 3 to 5 treatment-related adverse effect events were collected and analyzed. The OR of the total adverse effect events for patients receiving anti-PD-1 therapy versus chemotherapy was 0.37 (95% CI: 0.09–1.55; P = 0.17; heterogeneity: P < 0.001) (Fig. 5A), and the OR of grade 3 to 5 adverse effect events was 0.25 (95%: CI 0.13–0.46; P < 0.001; heterogeneity: P = 0.001) (Fig. 5B). On the basis of the observed results, no significant difference was found in the incidence of all treatment-related adverse effect events, however, it was indicated that the incidence of grade 3 to 5 treatment-related adverse effect events caused by PD-1 inhibitors was significantly lower than that caused by chemotherapy.

Study quality and Sensitivity analysis

All trials included in this study were multicenter and open label. The Jadad score were all 4, indicating that the quality was high (Table 1). To evaluate the robustness of the combined outcomes, we carried out sensitivity analyses by omitting specific studies or altering statistical models. The results showed that the pooled HRs for OS were stable in our analysis and no significant deviation from the overall results was detected (Fig. 6).

Discussion

Rapid progression during or after the standard chemotherapy in patients with advanced esophageal cancer indicates that a new effective treatment diagram is in urgent need[32]. Recently, it is worth noting that the successive discovery and further study of immune checkpoints, such as PD-1, make immunotherapy served as the fourth antitumor strategies following surgery, radiotherapy and chemotherapy[33]. Single agent PD-1 inhibitors have been explored as treatment strategies for advanced esophageal cancer patients. We conducted this meta-analysis to investigate the efficacy and safety of anti-PD-1 therapy for advanced esophageal cancer patients.

In this study, we first compared the efficacy of PD-1 inhibitors with chemotherapy in advanced esophageal cancer patients. OS, PFS and ORR were selected as the primary endpoints. We observed that PD-1 inhibitors significantly improved OS in advanced esophageal cancer when compared with chemotherapy, however, no significant improvement in PFS and ORR was found. Similar results were found in patients with ESCC. In the subgroup analysis, squamous cell carcinoma was more effective than adenocarcinoma for anti-PD-1 therapy. Hence, it was concluded that the anti-PD-1 therapy significantly improved the OS rather than the PFS and ORR when compared with chemotherapy, especially in ESCC. In addition to histology, overall survival assessed consistently favoured PD-1 inhibitors versus

chemotherapy in all subgroups. Although significant interactions were observed for age ≥ 65, female and ECOG PS = 0, the HRs were less than 1, suggesting there was no change in the direction of the treatment effect. Then, we compared the safety of PD-1 inhibitors with chemotherapy in esophageal cancer patients. On the basis of the observed results, no significant difference was found in the incidence of all treatment-related adverse effect events. However, our results show that PD-1 inhibitors had a lower incidence of grade 3 to 5 treatment-related adverse events than the chemotherapy, which demonstrated patients receiving PD-1 inhibitors had a significant overall improvement in quality of life.

Several recent trials demonstrated that PD-L1 expression had a significant correlation with OS, PFS, and ORR, however, the significance of PD-L1 expression level for anti-PD-1 therapy is still controversial[34]. Here, we conducted a subgroup analysis to clarify the OS benefit of PD-1 inhibitors in esophageal cancer patients with different PD-L1 expression. The OS benefit with PD-1 inhibitors occurred for patients in whom the PD-L1 TPS was at least 1% (OR = 0.83; 95% CI: 0.67–1.02; P = 0.07), and when the PD-L1 TPS was less than 1%, the OS benefit with PD-1 inhibitors was not statistical difference(OR = 0.64; 95% CI: 0.51–0.79; P < 0.001). However, the magnitude of OS benefit was not significantly different among subgroups of PD-L1 TPS which indicated the survival benefit with PD-1 inhibitors occurred regardless of patients' level of tumor PD-L1 expression. Therefore, exploratory clinical trials and extended follow-up are needed to fully evaluate the role of PD-L1 expression in immunotherapy.

The results of our study are consistent with previous studies. KEYNOTE 180 showed that pembrolizumab had long-term clinical benefits with controlled adverse events, which provided treatment options for patients with esophageal cancer who had previously failed treatment[23]. KEYNOTE 181 achieved the main-OS endpoint, which has demonstrated a survival benefit in esophageal cancer immunotherapy[24]. In ATTRACTION-03 trial, nivolumab group showed a statistically significant improvement in OS compared with chemotherapy group, and the survival benefit of nivolumab was observed regardless of the expression level of PD-L1 in tumors. In terms of PFS and ORR, there was no significant improvement between the nivolumab group and the chemotherapy group[25]. The subgroup analyses in Huang *et al*. showed that PD-L1 was not significantly associated with ORR in the clinical trial of SHR-1210 for esophageal cancer[27].

There were some exploratory biomarker analyses to evaluate the role of PD-1 inhibitors in patients with esophageal cancer, in whom treatment options have been very limited for decades and the prognosis remains poor. Some esophageal cancer patients were reported to carry frequent amplification of chromosome 11q13 and those patients without 11q13 amplification, had significantly better ORR and PFS when compared with 11q13 amplified individuals[35]. Several studies have shown that both PFS and OS are prolonged with the increase of tumor mutation burden (TMB) with immunotherapy, and TMB has the potential to be a biomarker to evaluate the efficacy of immunotherapy[36–38]. Greally *et al* analyzed the relationship between TMB and survival in 62 patients of immunotherapeutic esophageal cancer and this clinical study found that patients in the high TMB group obtained significant survival benefits.[39] Microsatellite instability (MSI) is usually caused by deficiencies mismatch repair (dMMR) [40]. The microenvironment of dMMR made it more likely to express PD-L1, which influenced the efficacy of PD-1

inhibitors, and dMMR tumors were associated with prolonged PFS compared with mismatch repair-proficient tumors, regardless of the origin tissue of cancer[41]. Although the incidence of MSI-H in ESCC is rare and only about 8%, this biomarker is very important and may affect the efficacy of immune checkpoint inhibitors.[42] This may explain why patients with advanced esophageal cancer might benefit from improved on OS when treated with PD-1 inhibitors and the difference of PFS and ORR in these studies.

To the best of our knowledge, this is the first meta-analysis to explore the efficacy and safety of PD-1 inhibitors for advanced esophageal cancer patients. The topic of this paper is novel and the high quality of the data included in the meta-analysis. We observed several limitations in this research. The number of included studies is limited. At the same time, one study were limited from the abstract of ASCO meeting abstract.

Anti-PD-1 therapy has showed initial efficacy in the treatment of advanced esophageal cancer and become one of the main research directions in the treatment of advanced esophageal cancer. With the increase of biomarker analysis and clinical experience, anti-PD-1 therapy will have a broader application prospect in esophageal cancer. It is imperative to comprehensively carry out more randomized controlled studies to further explore the immune mechanism of esophageal cancer and screen out reasonable biomarkers to identify the beneficial population.

Conclusion

In conclusion, our analysis revealed that PD-1 inhibitors significantly prolonged the OS when compared with chemotherapy, while no significantly difference in PFS and ORR for the population of esophageal cancer. Patients with esophageal squamous cell carcinoma might receive more OS benefit from the anti-PD-L1 therapy than esophageal adenocarcinoma. Based on the analysis of grade 3 to 5 treatment-related adverse effect events, a lower risk was associated with the anti-PD-1 therapy versus chemotherapy. As a result, anti-PD-1 therapy may be an optional treatment for esophageal cancer patients.

Abbreviations

ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; OR: Odds ratio; HR: Hazard ratio; PD-1: Programmed cell death 1; PD-L1: Programmed cell death 1 ligand 1; AEs: Adverse events; CI: Confidence interval.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors have contributed to read and approved this manuscript and declare that there are no conflicts of interest to be disclosed.

Funding

This research was supported by the National Natural Science Funds of China (No. 81672442) and the Scientific and technological projects in Henan Province (No.182102310379).

Author Contribution

Conceived and designed the protocol/experiments: Lu Y, Wang F; Searching the databases: Lu Y and Guan LL; Data extraction: Lu Y and Wang F; Assessing the quality of included trials: Xu ML and Wang F.

Acknowledgments

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

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Table

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

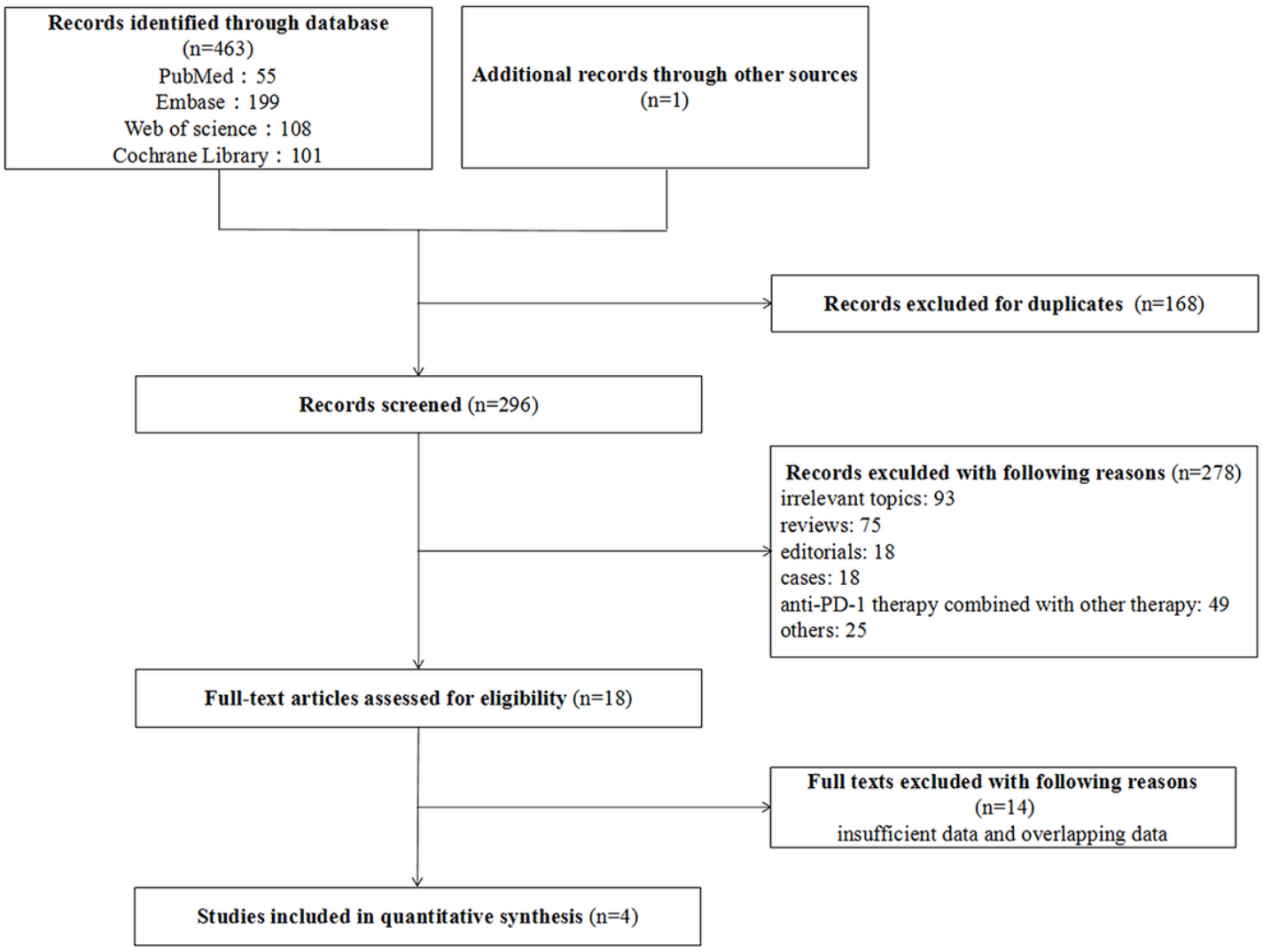

Figure 1

The flowchart of the study selection process for the meta-analysis.

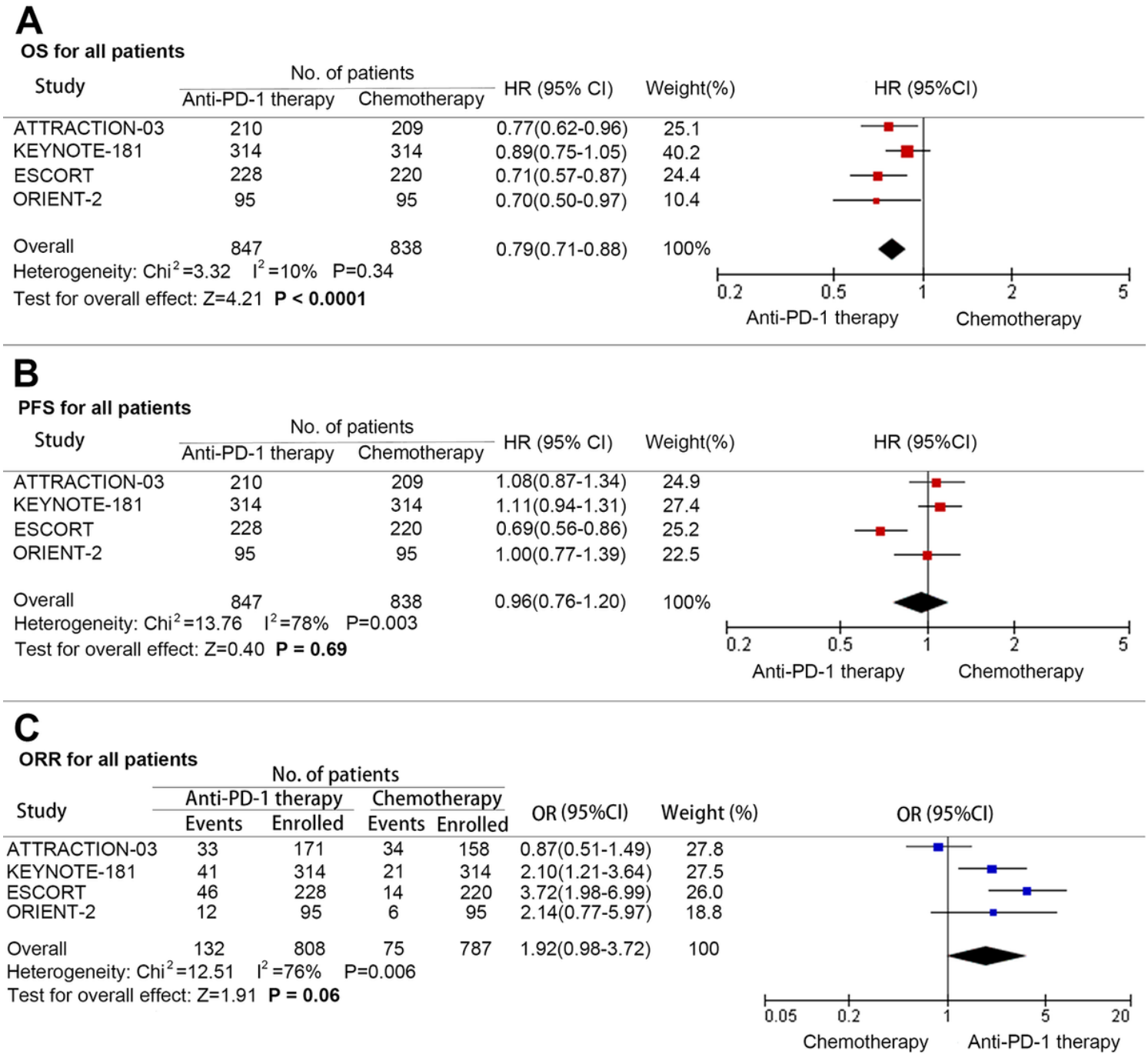

Figure 2

Pooled hazard ratio for overall survival (A), progression-free survival (B), and pooled odds ratio for objective response rate (C) in advanced esophageal cancer treated with anti-PD-1 versus chemotherapy. (HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval; PD-1: Programmed cell death 1)

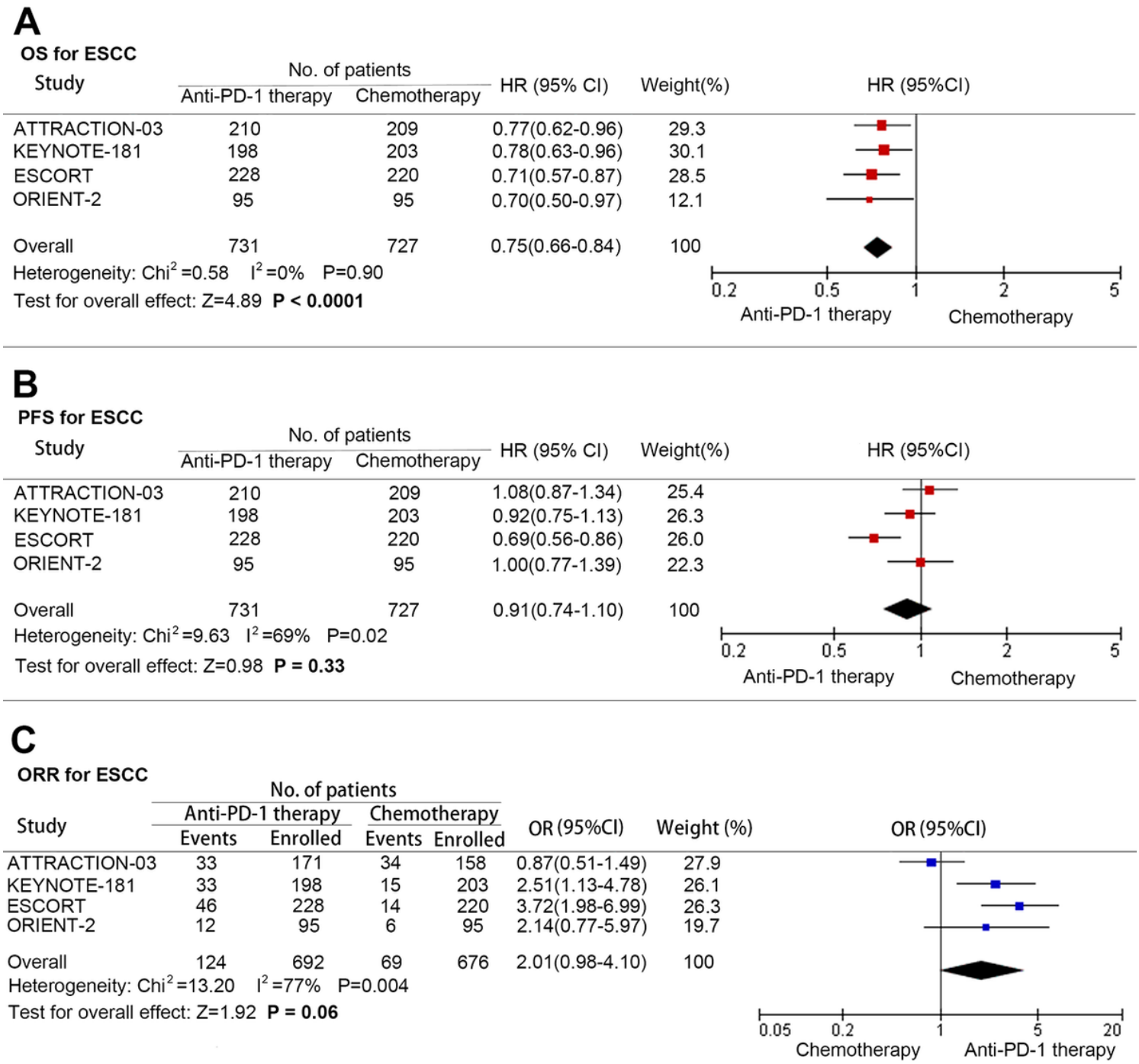

Figure 3

Pooled hazard ratio for overall survival (A), progression-free survival (B), and pooled odds ratio for objective response rate (C) in advanced esophageal squamous cell carcinoma treated with anti-PD-1 versus chemotherapy. (HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval; PD-1: Programmed cell death 1)

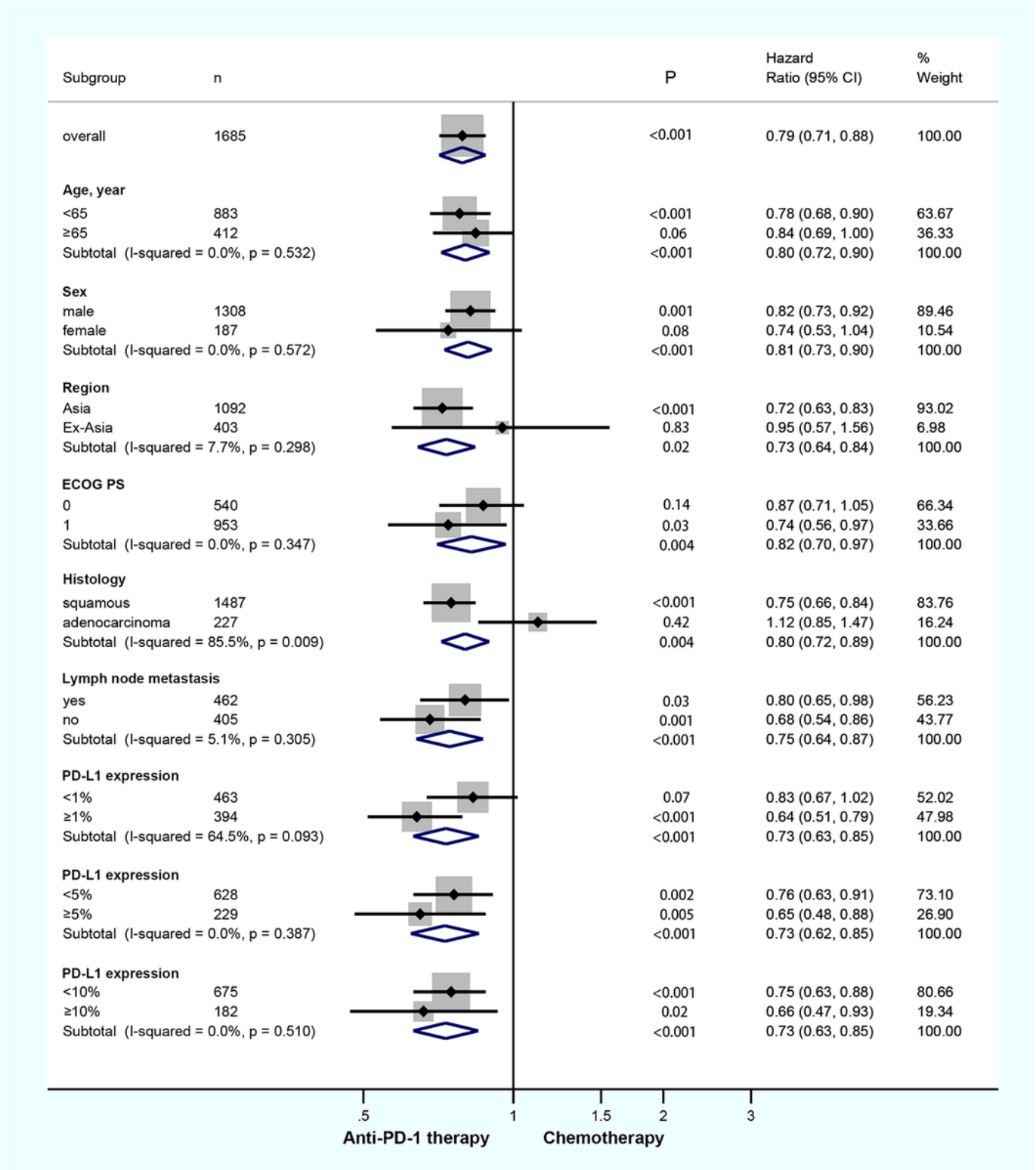

Figure 4

Forest Plot of hazard ratio in subgroup analysis comparing overall survival in patients who received anti-PD-1 therapy versus chemotherapy. (HR: Hazard ratio; CI: Confidence interval; PD-1: Programmed cell death 1)

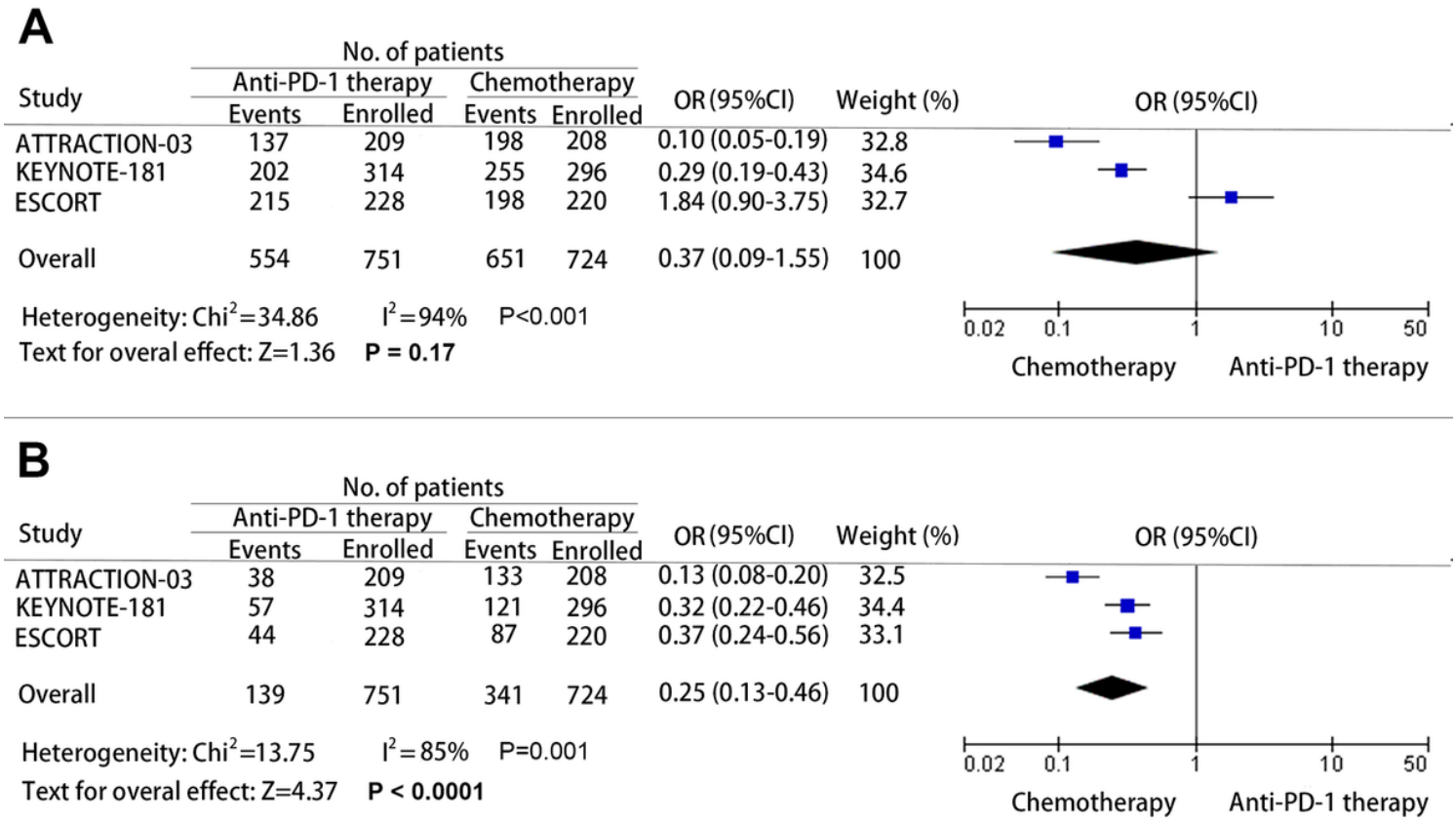

Figure 5

Pooled odds ratio (OR) for incidence of any grade treatment-related adverse effect (A) and grade 3 to 5 treatment-related adverse effect (B). (OR: Odds ratio; CI: Confidence interval; PD-1: Programmed cell death 1)

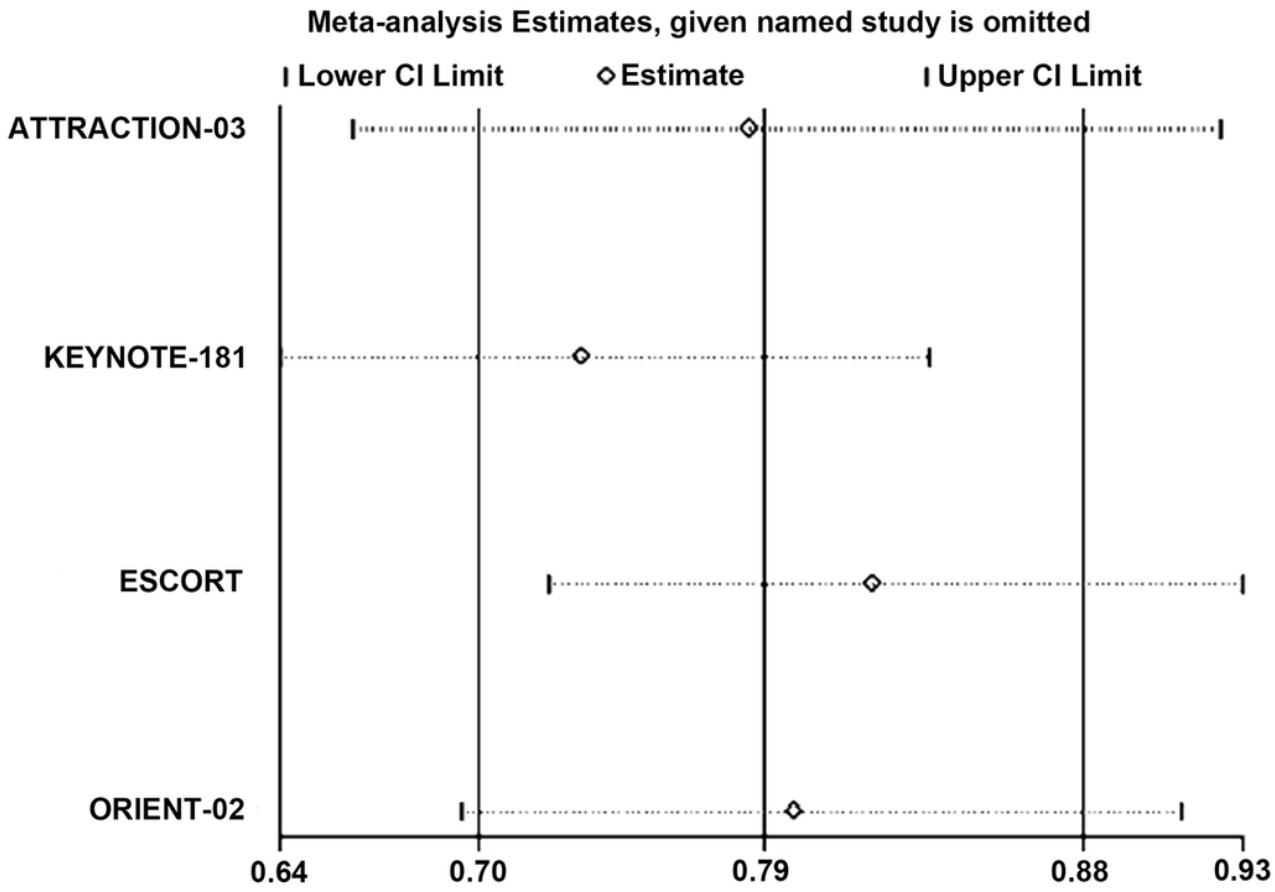

Figure 6

Sensitivity analysis of the hazard ratios of overall survival. (CI: Confidence interval; PD-1: Programmed cell death 1)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.doc