Efficacy and safety of ICIs/ICIs combined with chemotherapy vs chemotherapy in advanced gastrointestinal tract cancer: a systematic review and meta-analysis

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Research Article

Keywords: ICIs/ICIs combined with chemotherapy, advanced gastrointestinal tract cancer, Efficacy and safety, meta-analysis

Posted Date: April 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-376445/v1

Abstract

Objective: To systematically access the efficacy and safety of ICIs monotherapy or ICIs combined with chemotherapy versus chemotherapy in advanced gastrointestinal cancers.

Methods: Retrieved the randomized controlled trials (RCTs) of ICIs or ICIs combined with chemotherapy and chemotherapy in advanced gastrointestinal tumors included in PubMed, Cochrane Library, Embase, and Web of sciences. Meta-analysis was performed using Review Manager 5.3 software. The primary outcomes are overall survival (OS) and progression-free survival (PFS), and secondary outcomes include objective response rate (ORR) and adverse events (AEs).

Results: A total of 13 RCTs including 5166 patients with advanced gastrointestinal tumors were included in this meta-analyses. ICIs or ICIs combined with chemotherapy exhibited superior OS (HR: 0.84, 95% CI: 0.76-0.94, *P*=0.001) compared with chemotherapy. Subgroup analysis shows that the use of anti-PD-1 antibodies significantly benefits OS (HR:0.80, 95%CI:0.70-0.91, *P*=0.0009). The second-line application of ICIs or ICIs combined with chemotherapy will have more significant OS benefits than chemotherapy (HR: 0.85, 95%CI: 0.79-0.97, P=0.01). No significant difference was observed in PFS and ORR. The PFS of squamous cell carcinoma seemed to be better (HR:0.72, 95%CI:0.60-0.87, *P*=0.0005). No significant difference in AEs and grade≥3 AEs. But the incidence of AEs decreased when ICIs monotherapy (RR:0.81, 95%CI:0.66-0.99, *P*=0.04).

Conclusion: For gastrointestinal malignant tumors, patients who received ICIs or ICIs combined with chemotherapy had a superior OS compared with chemotherapy, not at the cost of increased AEs, the proportion of AEs is reduced than chemotherapy while ICIs monotherapy. PFS and ORR are not significantly improved.

Introduction

Gastrointestinal malignancies mainly include colorectal cancer, gastric cancer, and esophageal cancer. Globally, the morbidity rank 3rd, 5th, and 7th, and the mortality rank 2nd, 4rd, and 6th of the three cancer types in 2020 [1]. In recent years, the overall prognosis of advanced gastrointestinal tumors is still poor despite the application of multidisciplinary integrated therapies, including targeted and immunotherapy. Using immune checkpoint inhibitors (ICIs), such as targeted programmed death receptor 1 (PD-1) and its ligand (programmed death ligand 1, PD-L1), cytotoxic T lymphocyte antigen 4 (CTLA-4) has transformed the treatment mode of advanced malignant tumors from chemotherapy and targeted therapy to immunotherapy.

Immune checkpoints play an important role in maintaining immune homeostasis and preventing autoimmune diseases by inhibiting T cells over-activation. However, in the process of cancer progression, immune checkpoints are usually activated to suppress the anti-tumor immune response [2]. PD-1 is an immune protein expressed on tumor cells and tumor-infiltrating immune cells, CTLA-4 is mainly expressed in regulatory T cells [3]. They can inhibit T cell activation and encourages tumor cells to evade

immune surveillance [4]. CTLA-4 inhibits the activation of naïve T cells in lymph nodes, while PD-1 later inhibits T cell immune responses in peripheral tissues. Their mechanism two is not consistent [5].

Studies have reported that the positive expression rate of PD-L1 is closed to 50% in advanced gastrointestinal malignant tumors, which is an important risk factor affecting the prognosis of gastrointestinal tumors, especially esophageal cancer [6]. Many studies also reported the positive effects of anti-PD-1/PD-L1 in the treatment of advanced gastrointestinal tumors. But not all ICIs achieve satisfactory treatment expectations. There is no unified understanding of its clinical efficacy and safety in gastrointestinal malignancies [7].

Whether ICIs have a prognostic advantage in advanced gastrointestinal tumors is a key debate. Therefore, this study conducted a meta-analysis to analyze the effects of ICIs on the efficacy and safety of advanced gastrointestinal tumors.

Methods

Search Strategy

We searched PubMed, Embase, Web of Science, and Cochrane Library from inception to August 2020, for randomized clinical trials of immune checkpoint inhibitors (ICIs) that compared with chemotherapy in gastrointestinal tract cancers. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting statement by the Cochrane Collaboration. Keywords for the literature search included tumor names such as Gastrointestinal Neoplasm, Gastrointestinal Tract Cancer, Esophageal Neoplasm, Esophageal Tumor, Esophageal Cancer, Stomach Neoplasm, Gastric Neoplasm, Gastric Cancer, Stomach Cancer, Gastroesophageal junction cancer, Colorectal Neoplasm, Colorectal Cancer, Rectal Neoplasm; and ICIs names such as PD-1, PD-L1, Programmed Cell Death 1 Receptor, Programmed Cell Death 1 Protein, CD279 Antigen, B7-H1 Antigen, Programmed Cell Death 1 Ligand 1, B7-H1 Immune Costimulatory Protein, Nivolumab, pembrolizumab, tezolizumab, durvalumab, cemiplimab-rwlc, avelumab, Tislelizumab; and Randomized Controlled Trial, Randomized, placebo. Search items were limited to the title, abstract, and keywords.

Selection Criteria

Studies meeting the following criteria were included: (1) Randomized controlled trials that investigated ICIs or ICIs combined with chemotherapy compared with chemotherapy in gastrointestinal tract tumors, whether open or blind. (2) Patients who were diagnosed with esophageal cancer or gastric cancer or gastroesophageal junction cancer or colon cancer or rectal cancer or anal cancer, and was confirmed by clinical-pathological examination. (3) No restriction on the age, gender, race, and nationality of patients. (4) Excluding non-randomized controlled trials, retrospective studies, case reports, repeated published studies, studies without complete outcome data, and non-Chinese and English literature.

Data extraction

The primary outcome were the overall survival (OS) and progression-free survival (PFS). The secondary outcome was the objective response rate (ORR) and adverse events (AEs). The main items of the studies were extracted, including the National Clinical Trials identification number, first author, publication time, study phase, trial designs, treatment lines, blinding status, cancer types, pathologic types, intervention measures, patients' number, age, and sex distributions, OS, PFS and their hazard ratios (HRs) with 95% CIs and *P*-value, the incidence of ORR and AEs.

Quality assessment

The quality for every trial was appraised using the Review Manager 5.3 software which was recommended Cochrane Handbook version 6.10. The following aspects were tested, such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selectivity reporting, and other biases. We accessed each aspect and classified the risk of bias as high, low, or unknown.

All the above work was carried out independently by two investigators, included search and filter literature, extracte data, evaluated literature bias, and cross-checked. We discussed together to achieve consensus when the opinions were inconsistent.

Statistical Analysis

Hazard ratio (HR) was used as the effect size of time-event data such as OS and PFS, and risk ratio (RR) was used as the effect size of binary variables such as ORR and AEs. Using Review Manager 5.3 software to analyze. Perform subgroup analysis based on treatment types, antibody types, tumor types, histopathological classification, and third-line treatment modes. Hazard ratios were pooled using the inverse variance method. Heterogeneity was assessed with the Cochrane *Q* test and the inconsistency statistic (I^2). (P<0.10 or I^2 > 50% indicates high statistical heterogeneity) [8]. The random-effects model was used to analyze when heterogeneity is high.

Using STATA 12.0 software to carry out the sensitivity analysis to evaluate the stability of results. Begg's tests were used to appraise the publication bias, and the significance was set to P<0.1. A P-value <0.05 demonstrates a statistically significant difference in all statistical tests.

Results

Eligible studies and Characteristics

A total of 1443 related literatures were identified through the initial search strategy. 248 publications were excluded because of duplications. After the titles and abstracts review, 1021 studies were eliminated by the condition of the topics were irrelevant references, reviews, conference abstracts, and meta-analyses. With the detailed review of URL links, 128 articles were removed owing to uncompleted clinical studies and non-randomized controlled clinical studies. The remaining 46 studies were screened in strict

accordance with the inclusion criteria: 20 studies excluding repeated reports; 13 studies without available data. 13 eligible RCT studies were included finally. An illustration of the literature screening process is shown in *Figure 1.*

Overall, we enrolled 13 studies of advanced gastrointestinal cancer, 4 of 13 studies were esophageal cancer [9-12], 5 of 13 trials were gastric cancer [13-17], and 4 of 13 reports were colorectal cancer [18-21]. 11 of 13 studies were dual-arm studies, of which 8 studies reported the effects of ICIs versus chemotherapy, 1 study accounted for the effects of ICIs versus ICIs combined with chemotherapy. 2 of 13 studies were three-arm studies, and described the effects of ICIs vs. chemotherapy vs. ICIs combined with chemotherapy (*Table 1*). Besides, there was a multi-arm study (NCT02291289) [21], which illustrated the effects of ICIs combined with chemotherapy versus chemotherapy in two groups, the chemotherapy drugs in the combination group were different. Following this process, 5166 patients with gastrointestinal tumors in the 13 studies were incorporated into this analysis, including 2028 patients treated with ICIs, 1003 patients were given ICIs combined with chemotherapy, and 2143 patients received chemotherapy. The analysis included 3824 male patients and 1342 female patients. The assessment risk of bias was illustrated in *Figure 2*.

OS Comparison

12 studies reported OS data, including two three-arm studies. The pooled results suggested that patients had longer OS from treatments containing ICIs or ICIs combined with chemotherapy compared with chemotherapy in advanced gastrointestinal tract cancer (Hazard Ratio, 0.84, 95%CI, 0.76-0.94, *P*=0.001) *(Figure 3*). This result meaning that the risk of death from ICIs drugs was reduced by approximately 16% compared with chemotherapy.

Moreover, we performed five subgroup analyses of OS based on different therapeutic methods, antibody types, cancer types, histological types, and therapy lines (*Table 2*). When stratified by therapeutic methods, ICIs monotherapy (HR: 0.84 (95%CI: 0.73-0.96, *P*=0.009) or combined with chemotherapy (HR: 0.86, 95%CI: 0.75-1.00, *P*=0.04) obtained better OS than chemotherapy (*Supplementary Figure 1*). For different antibodies, OS was obviously advantaged for patients who used anti-PD-1 (HR: 0.80, 95% CI: 0.70-0.91, *P*=0.0009) than chemotherapy, but not who used anti-PD-L1 or anti-CTLA-4 (*Supplementary Figure 2*). Among different cancer types, the OS values were significantly prolonged for patients treated with ICIs or ICIs combined with chemotherapy compared with chemotherapy in esophageal cancer (HR: 0.76, 95%CI: 0.65- 0.89, P=0.0009), but not in gastric cancer or colorectal cancer (*Supplementary Figure 3*). In different histological types, OS got dramatically benefits in adenosquamous carcinoma (HR: 0.73, 95%CI: 0.58-0.94, *P*=0.01) while ICIs or ICIs combined with chemotherapy compared with chemotherapy (*Supplementary Figure 4*). When applied in the second-line treatment of the subgroup, patients had more significant OS benefits (HR: 0.85, 95%CI: 0.79-0.97, *P*=0.01) while ICIs or ICIs combined with chemotherapy compared with chemotherapy (*Supplementary Figure 5*).

PFS Comparison

All the 13 studies reported PFS data, including two three-arm studies and one multi-arm study. The results revealed that, in advanced gastrointestinal cancer, patients couldn't get longer PFS from treatments containing ICIs or ICIs combined with chemotherapy compared with chemotherapy (HR: 1.09, 95%CI: 0.92-1.29, *P*=0.33) (*Figure 4*).

For subgroup analysis about different therapeutic methods or antibody types or cancer types or therapy lines, there were no significant superior PFS between ICIs or ICIs combined with chemotherapy and chemotherapy (*Supplementary Figure 6-9*). Among different histological types, patients receiving ICIs or ICIs combined with chemotherapy to exhibit better PFS than those receiving chemotherapy in squamous cell carcinoma (HR: 0.72, 95% CI: 0.60-0.87, *P*=0.0005) (*Supplementary Figure 10*) (*Table 3*).

ORR Comparison

ORR data were reported in 12 studies, including two three-arm studies and one multi-arm study. The results showed that in advanced gastrointestinal malignancies, patients couldn't obtain higher ORR from treatments containing ICIs or ICIs combined with chemotherapy compared with chemotherapy (Risk Ratio, RR: 1.29, 95%CI:0.88-1.89, *P*=0.20) (*Figure 5*).

For subgroup analysis about different therapeutic methods or antibody types or cancer types, there were no significant higher ORR between ICIs or ICIs combined with chemotherapy and chemotherapy (*Supplementary Figure 6-9*). Among different histological types and therapy lines, patients receiving ICIs or ICIs combined with chemotherapy to exhibit better ORR than those receiving chemotherapy in squamous cell carcinoma (RR: 3.36, 95%CI:1.97-5.71，*P*＜0.0001) (*Supplementary Figure 14*) and in the second-line application (RR: 1.88, 95%CI:1.18-3.02，*P*=0.008) (*Supplementary Figure 15*) (*Table 4*).

Safety Analysis

Nine of the 13 studies reported AE data, including two three-arm studies. The overall safety profiles of ICIs or ICIs combined with chemotherapy and chemotherapy were comparable for both AEs (RR: 0.88, 95%CI: 0.76-1.01, *P*=0.08)) (*Figure 6*) and grade≥3 AEs (RR:0.80, 95%CI: 0.55-1.17, *P*=0.25) (*Figure 7*).

Subgroup analysis results showed that the incidence of AEs was significantly lower when ICIs monotherapy than chemotherapy (RR: 0.81, 95%CI: 0.66-0.99, *P*=0.04). For subgroup analysis about different cancer types or therapy lines, there were no significant superior AEs between ICIs or ICIs combined with chemotherapy and chemotherapy, but the incidence of grade≥3 AEs was significantly lower than chemotherapy in esophageal cancer (RR: 0.52, 95%CI: 0.42-0.65, *P*＜0.00001).According to the subgroup analysis of antibody types, the incidence of AEs and grade≥3 AEs significantly higher when used CTLA-4 than chemotherapy (AEs, RR: 1.18, 95%CI:1.06-1.31, *P*=0.003; grade≥3 AEs, RR: 3.23, 95% CI: 1.93-5.46, *P*<0.0001). In different histological types, the incidence of AEs and grade≥3 AEs was significantly lower in ICIs than chemotherapy of adenocarcinoma or squamous cell carcinoma (AEs, RR: 0.72, 95% CI: 0.66-0.78, *P* <0.00001; grade≥3 AEs, RR: 0.55, 95% CI: 0.37-0.82, *P*<0.0001). (*Table 5*).

Furthermore, we found that the most common AEs were diarrhea, decreased appetite, nausea, anemia, fatigue. ICIs or ICIs combined with chemotherapy compared with chemotherapy, the adverse reactions such as loss of appetite, anemia, fatigue, weakness, asthenia, alopecia, neutrophil count decreased, WBC decreased, peripheral sensory neuropathy, stomatitis, were significantly reduced, and pruritus and hypothyroidism were definitely increased (Table 6) (*Supplementary Figure 16-17*).

Sensitivity analysis

We examined the stability and reliability of the combined HR by omitting individual studies and conducted sensitivity analyses for OS and PFS. The results showed that the OS and FPS results were statistically stable (*Figure 8*).

Publication bias

The Begg's test and Egger's test were used to evaluating the publication bias of OS and PFS. The results showed that there was no significant publication bias, OS (Begg, P =1.00) and PFS (Begg, P =0.822) (*Figure 9*).

Discussion

Immune checkpoint inhibitor therapy has been developed rapidly in the past decade.ICIs have been used in multiple cancer types. Compared with traditional chemotherapy, ICIs revealed better survival benefits. But it is undeniable that not all patients can achieve good expectations with ICIs. Our results suggest that patients who received ICIs or ICIs combined with chemotherapy had noticeably longer OS compared with chemotherapy, not at the cost of increased PFS and ORR have not been statistically significant improvement.

One study reported that blockade of PD-1/PD-L1 in advanced GC/GEJC can significantly prolong the OS, but PFS has no obvious benefit [22]. Another study came to the inconsistent conclusion, OS and PFS are no noticeable changes in advanced GC/GEJC between PD-1/PD-L1 inhibitors with chemotherapy [23]. Numerous studies have confirmed that the expression of PD-L1 is dramatically associated with the prognosis, and PD-L1 overexpression is a high-risk factor for poor prognosis of colorectal cancer [24-26]. It has been confirmed that the positive expression of PD-L1 in tumor cells is a risk factor for the prognosis of advanced gastrointestinal tumors, especially esophageal cancer [27]. However, the analysis of the efficacy and safety of ICIs inhibitors for colorectal cancer and esophageal cancer has not been reported.

To our knowledge, this is the first meta-analysis to evaluate the efficacy and safety between ICIs or ICIs combined with chemotherapy and chemotherapy in advanced gastrointestinal tumors. Our study included 13 clinical studies on advanced gastrointestinal malignancies and analyzed a total of 5166 patients from different countries and races. The trial design was rigorous and the clinical data were reliable. Furthermore, we conduct multiple subgroup analyses from various aspects such as treatment methods, tumor types, tumor histological classification, therapy lines. We evaluate the effects of different

factors on OS, PFS, ORR, AEs, and grade≥3 AEs in patients with advanced gastrointestinal tumors comprehensively.

For different tumor types, we found that ICIs or ICIs combined with chemotherapy compared with chemotherapy, OS of esophageal cancer was dramatically prolonged, but no significant differences of PFS and ORR, the incidence of AEs with grade≥3 decreased notably (RR: 0.52, P < 0.00001). The OS, PFS, ORR, and the incidence of AEs, grade ≥ 3 AEs were no markedly different in Gastric cancer and colorectal cancer. Although the pooled PFS was not greatly prolonged compared with chemotherapy, there were superior PFS outcomes.in NCT03099382[12] and ONO-4538-12 studies, and patients with PD-L1 CPS>10 (HR, 0.73, 95%CI: 0.54-0.97) in the KEYNOTE-181 study [9].

In the subgroup analysis among histological classification, OS, PFS, and ORR were remarkably increased in squamous cell carcinoma (*P* =0.01, *P* =0.0005, and *P* <0.00001) The incidence of AEs and grade≥3 AEs decreased in adenocarcinoma or squamous cell carcinoma, (*P*＜0.00001 and *P*=0.03). This may be related to the high level of positive expression of PD-L1 in esophageal cancer [27], and squamous cell carcinoma is more common in esophageal cancer. Another study supports our results. Compared with esophageal adenocarcinoma EAC and gastric adenocarcinoma GAC (10%), the expression of PD-L1 in esophageal squamous cell carcinoma ESCC is higher [28]. However, our sample size is relatively small and we lack relevant data on the expression levels of PD-L1 in other types of tumors. The relationship between them needs to be further studied.

Also, for advanced gastrointestinal tumors, whether ICIs are used alone or in combination with chemotherapy, patients have superior OS outcomes (*P* =0.009 and *P* =0.04). When ICIs were used alone, the incidence of AEs decreased significantly (*P*=0.04). In the second-line application of ICIs or ICIs combined with chemotherapy, the patient's OS (*P* =0.01) and ORR (*P* =0.008) were remarkably increased. Studies have found that platinum-based chemotherapy may up-regulate the expression of PD-L1 in tumor tissues [29] and increase the sensitivity of tumor cells to PD-1/PD-L1 inhibitors [30]. This may be the reason for the second-line application of ICIs or ICIs combined with chemotherapy obtain better efficacy. In addition, a study of lung cancer found that compared with first-line or second-line treatment, patients treated with ICIs in ≥ the third-line treatment had worse PFS and OS, which may be somehow relevant to the ECOG score of patients [31].

When comes to different antibodies, we found that OS was obviously advantaged for patients who used anti-PD-1 (*P*=0.0009) than chemotherapy, but not those who used anti-PD-L1 or anti-CTLA-4. The incidence of AEs increases only with the CTLA-4 antibody. Another meta-analysis got a similar conclusion that patients who used anti-PD-1 obtained longer OS and PFS than anti-PD-L1 in solid tumors, and there is no appreciable difference in the incidence of AEs [32]. The possible cause might be the different mechanisms between anti-PD-1 and anti-PD-L1. At the same time as PD-1 antibodies bind to PD-1, it can further block the binding of PD-1 to its ligands PD-L1 and PD-L2 [33]. However, the PD-L1 antibody can only prevent the binding of PD-1 to PD-L1, but not PD-1 to PD-L2. The activation of T cells is still inhibited, and cancer cells may escape from the anti-immune response through the PD-1-PD-L2 pathway [34].

Moreover, PD-L2 can be induced by a variety of immune cells and non-immune cells, and PD-1 has a higher binding affinity for PD-L2 than PD-L1 [35, 36]. The complex differences in the treatment of these antibody cancers are related to their inherent mechanisms.

CTLA-4 and PD-1/PD-L1 have different mechanisms of action. In the immune response, CTLA-4 mainly regulates T cell proliferation in the early stage of lymph nodes, while PD-1 mainly suppresses T cells in a late stage of peripheral tissues [5]. A significant manifestation of CTLA-4 blockade is the persistence of objective responses [37]. In the CO.26 study, chemotherapy showed a better ORR than CTLA-4 antibody combined with chemotherapy, but the longest response time was 21 months in one patient who received CTLA-4 antibody [20]. Blocking CTLA-4 not only causes immune attacks on tumor cells but also on other normal parts of the body. Therefore, the apparent increase in the incidence of AES using anti-CTLA-4 antibodies may be related to the persistence of the objective response.

Limitations

Our research also has several limitations. Because of a few studies and small samples of the subgroups, the evaluation results may be biased. Some different subgroups show similar results, one of the reasons is the similarity of the included literature, and the results may be unfair. Besides, the efficacy evaluation was not carried out based on different PD-L1 expression levels due to the lack of sufficient data. Furthermore, we did not consider the risk of drug dosage and drug type. Different drug dosages may produce different curative effects, and the combination or comparison with different chemotherapeutics and targeted drugs also affects the outcome.

We revealed the efficacy of ICIs or ICIs combined chemotherapy compared with chemotherapy in the treatment of advanced gastrointestinal tumors, and no additional AEs were increased. In the future, there will be more studies to detect the expression level of PD-L1, the subgroup analysis may be more complete. Multiple other therapies such as the combination of CTLA-4 and PD-L1/PD-1 antibodies or ICIs combined with molecularly targeted drugs, maybe a more effective treatment that not only prolongs OS but also improves ORR can be found.

Conclusion

This meta-analysis demonstrates that ICIs or ICIs combined with chemotherapy have a better OS than chemotherapy in patients with gastrointestinal malignant tumors, not at the cost of increased AEs. When ICIs were used alone, the incidence of AEs decreases. PFS and ORR have not been statistically significant improvements.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the National Natural Science Foundation of China (U1904152).

Data Availability Statements

The authors declare that the data supporting the findings of this study are available within the article and its supplementary information files.

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Author Contributions

Dr Qilong Gao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Lanwei Guo and Yulong Chen devised study concept and design. Xiuqi Fan, Yicun Han, and Wei Meng carried out literature retrieval and screening, and data extraction. Xiuqi Fan made a systematic analysis of the data, and was the major contributor in writing the manuscript.

Acknowledgements

Not applicable.

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Tables

Due to technical limitations the Table file is available as download in the Supplementary Files.

Figures

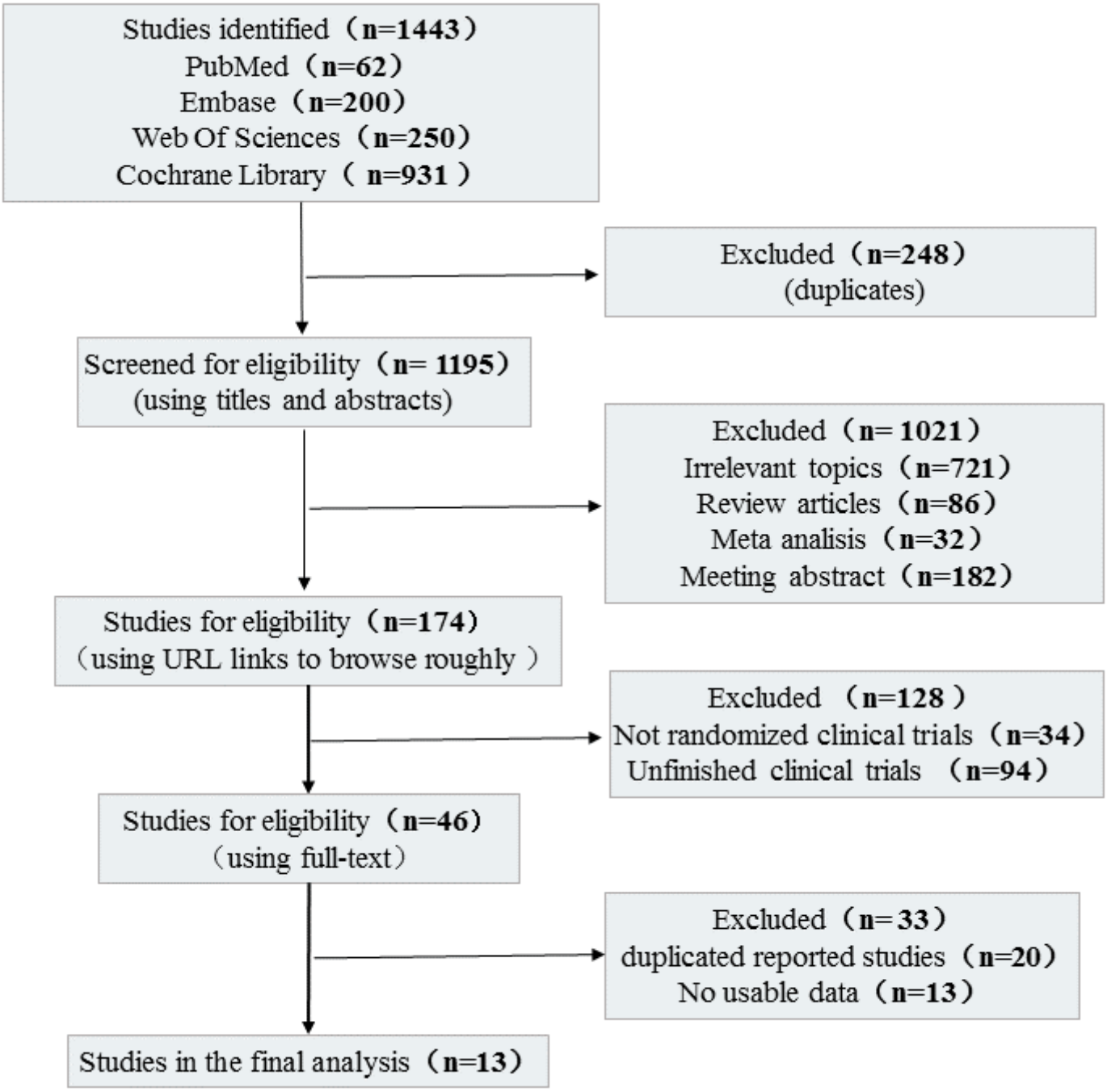

Figure 1

Flowchart of Study selected

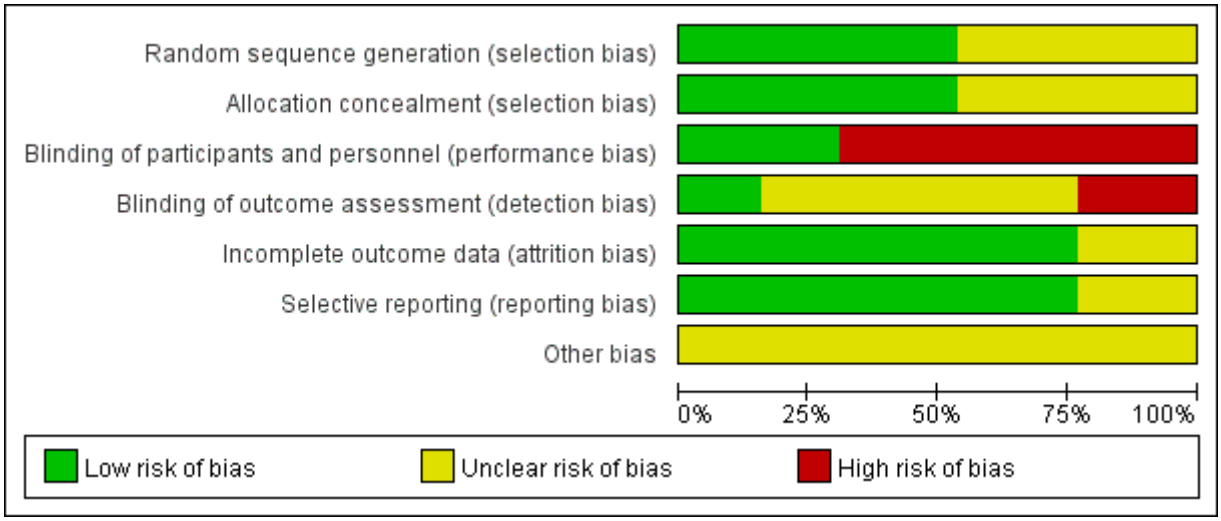

Figure 2

Risk of bias graph and summary of the included RCTs

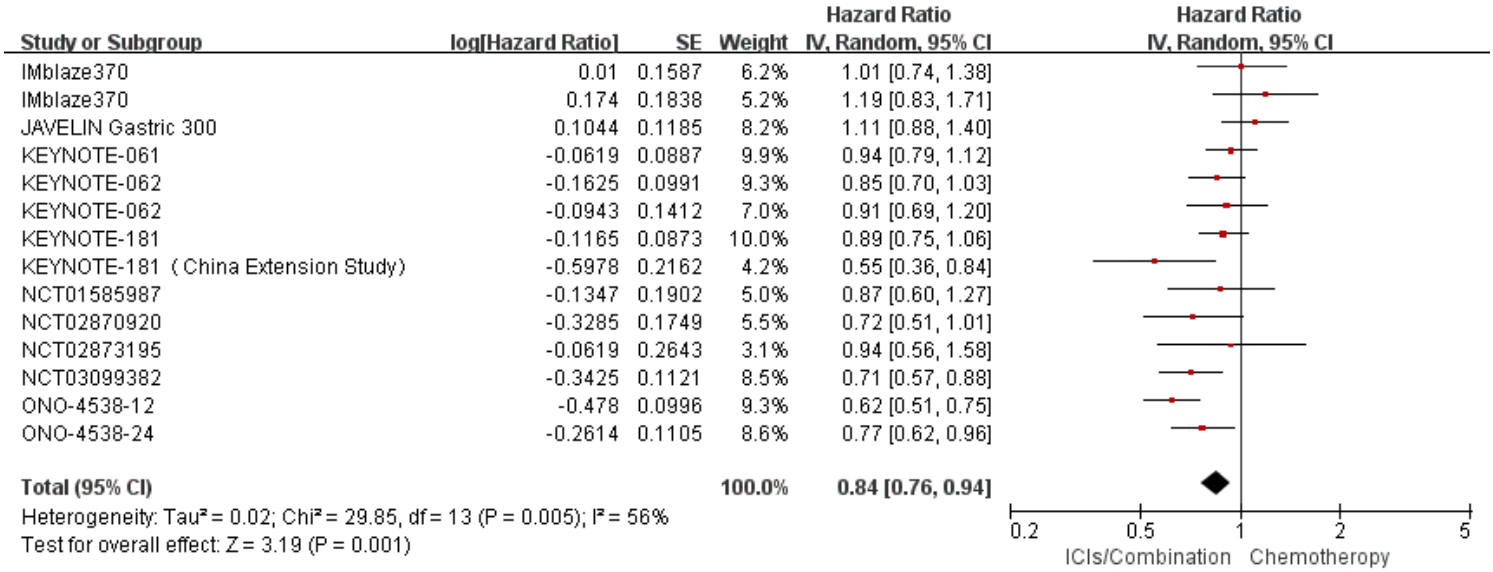

Figure 3

Forest plot of hazard ratios for OS in patients with advanced gastrointestinal tract cancer between ICIs/Combinations group and Chemotherapy group.

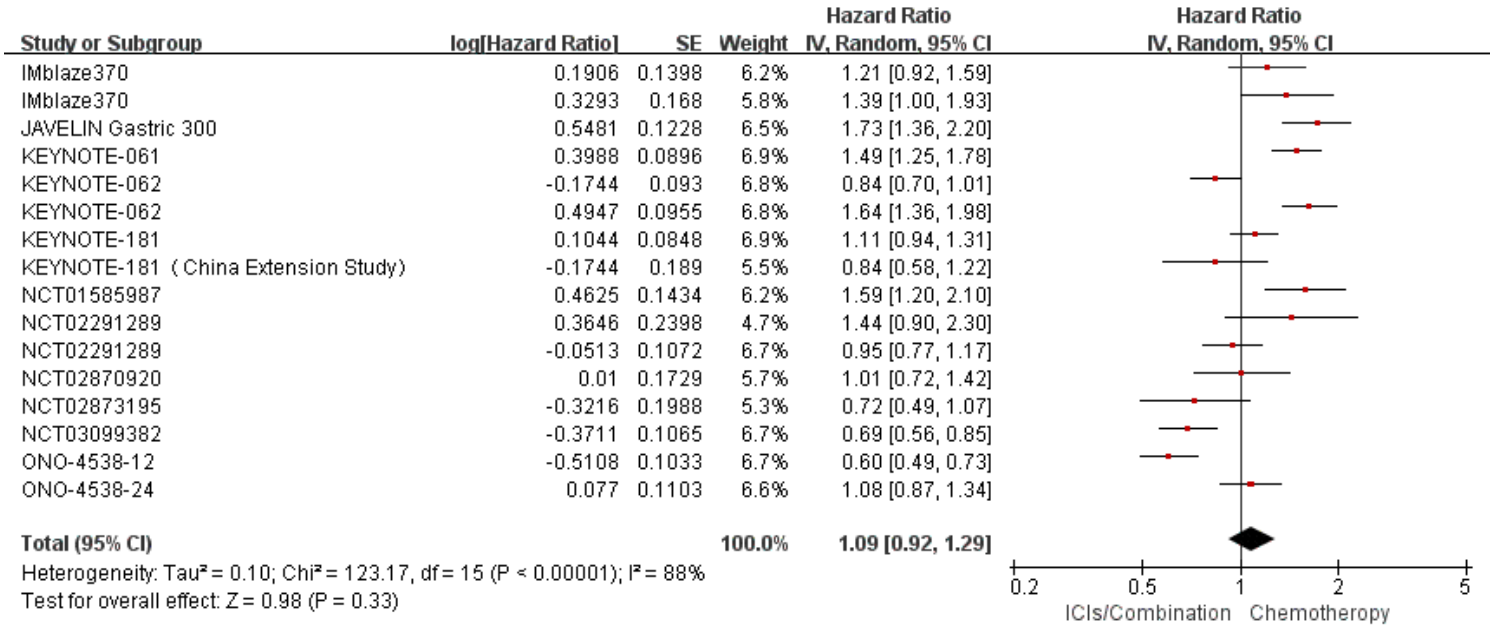

Figure 4

Forest plot of hazard ratios for PFS in patients with advanced gastrointestinal tract cancer between ICIs/Combinations group and Chemotherapy group

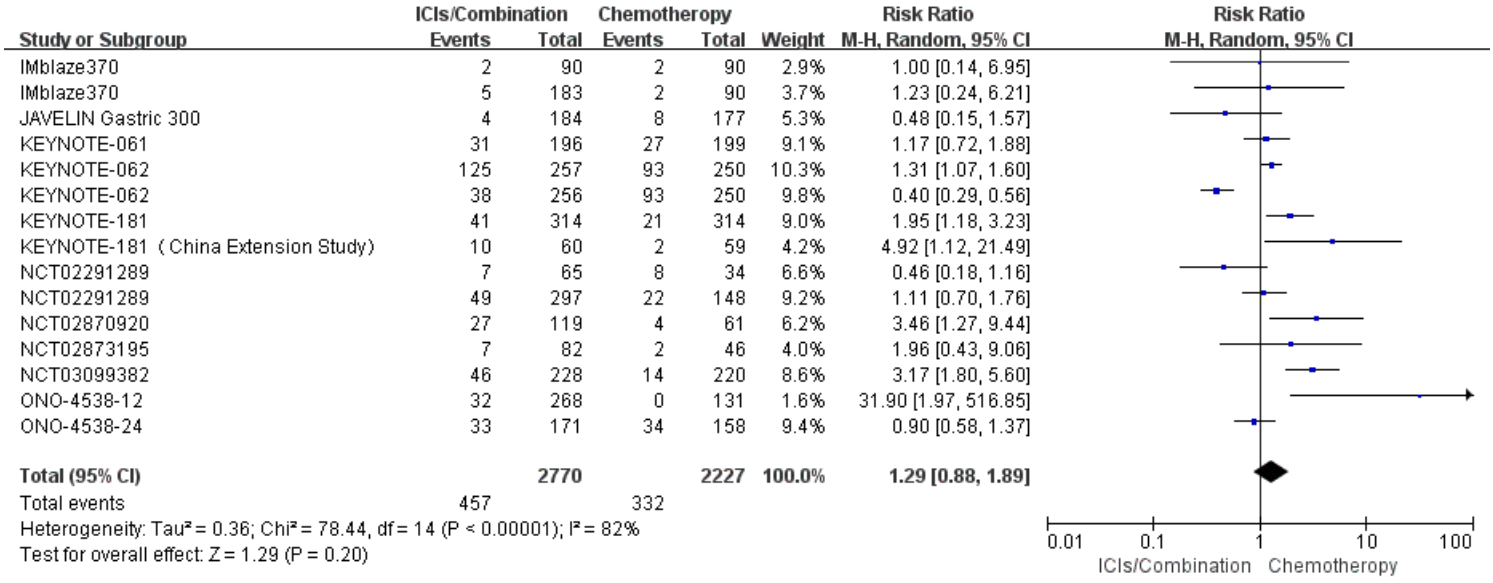

Figure 5

Forest plot of Risk ratios for ORR in patients with advanced gastrointestinal tract cancer between ICIs/Combinations group and Chemotherapy group.

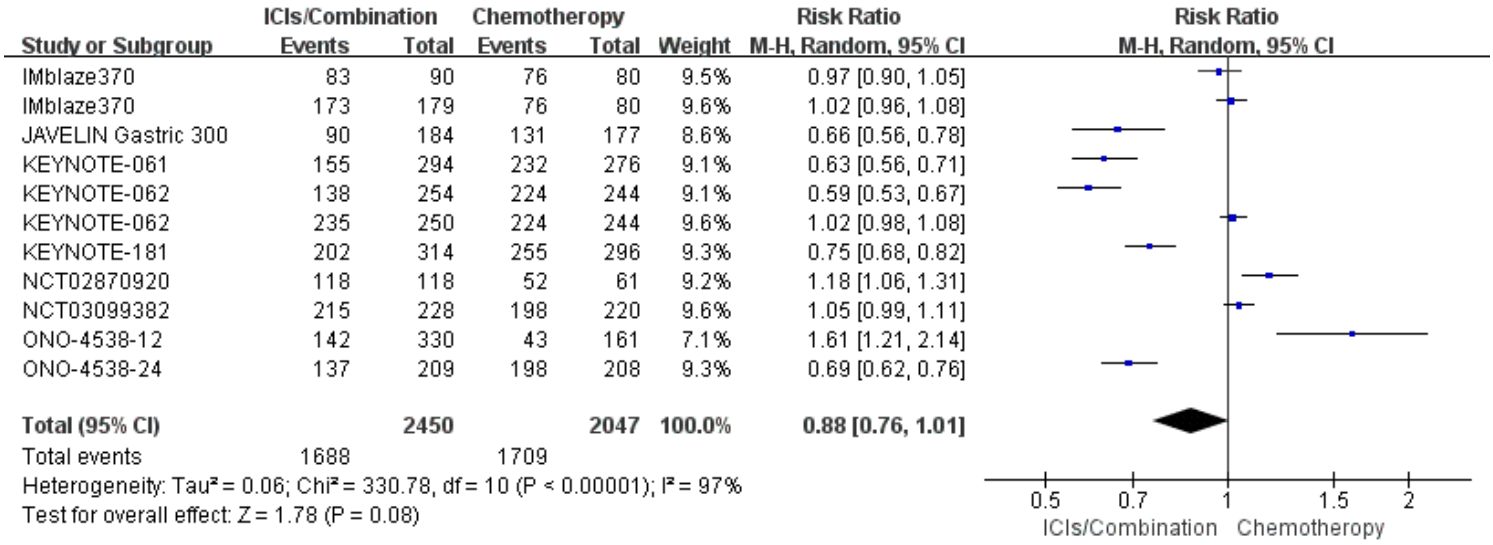

Figure 6

Forest plot of Risk ratios for AEs in patients with advanced gastrointestinal tract cancer between ICIs/Combinations group and Chemotherapy group.

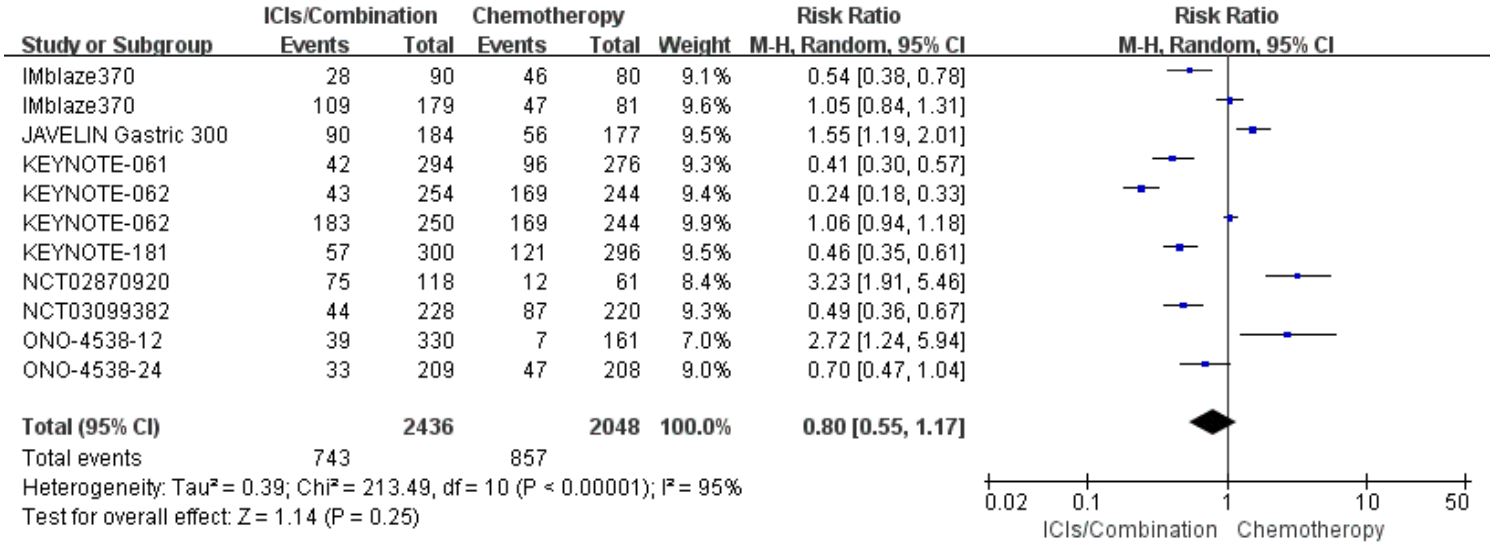

Figure 7

Forest plot of Risk ratios for grade≥3 AEs in patients with advanced gastrointestinal tract cancer between ICIs/Combinations group and Chemotherapy group.

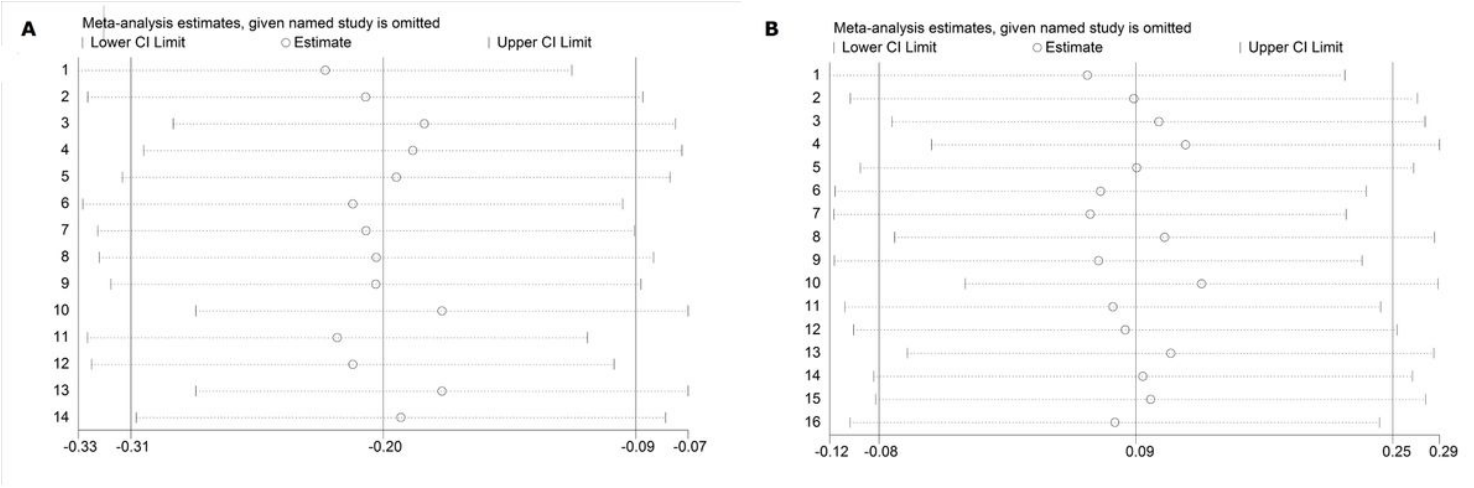

Figure 8

Sensitivity analysis of potential publication bias in studies investigating OS (A)and PFS (B) of patients with advanced gastrointestinal tract cancer between ICIs/Combinations group and Chemotherapy group.

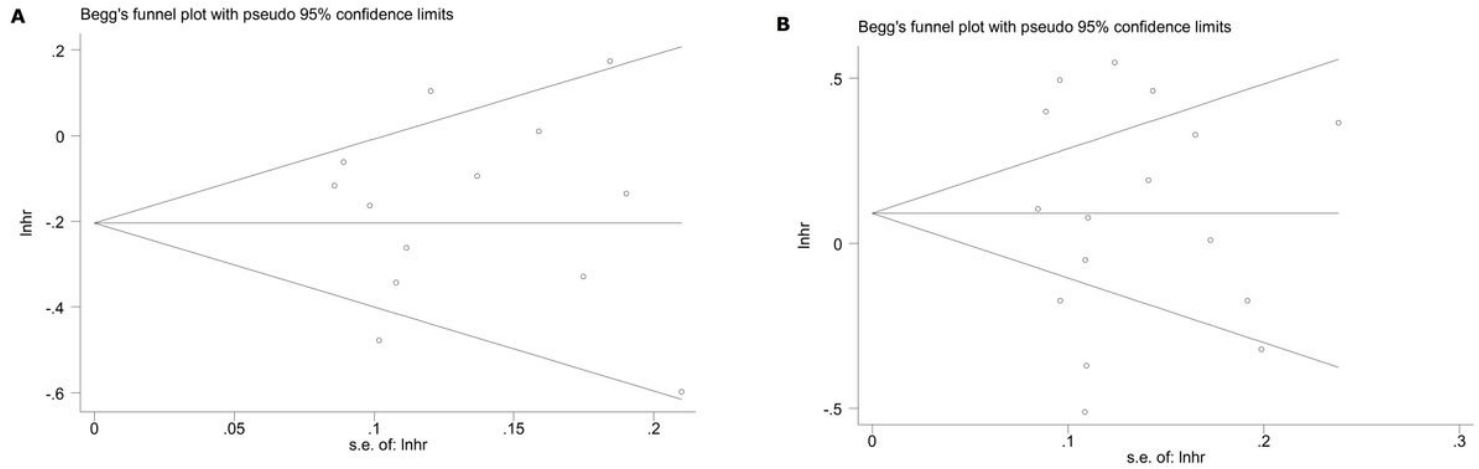

Figure 9

Begg’s funnel plot of potential publication bias in studies investigating OS (A)and PFS (B) of patients with advanced gastrointestinal tract cancer between ICIs/Combinations group and Chemotherapy group.

Supplementary Files

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