PD-1/PD-L1 based immunochemotherapy vs chemotherapy alone for advanced esophageal squamous cell carcinoma: a meta-analysis focus on PD-L1 expression level

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Abstract

Objective: Immunochemotherapy has become a new treatment for advanced esophageal squamous cell carcinoma (ESCC). We aimed to study the clinical efficacy and toxicity of immunochemotherapy based on PD-1/PD-L1 compared with chemotherapy alone in the treatment of advanced ESCC, focusing on analyzing the influence of PD-L1 expression level. Methods: Randomized controlled trials comparing PD-1/PD-L1 based immunochemotherapy wirh chemotherapy alone for advanced ESCC were included. We extracted efficacy data [objective response rate (ORR), disease control rate (DCR), overall survival (OS) rate, progression-free survival (PFS) rate] and safety data (treatment-related adverse events, treatment-related mortality) and performed meta-analyses. Results: 5 articles were included. Compared with chemotherapy alone, the ORR and DCR of immunochemotherapy increased by 2.05 times and 1.54 times, respectively. Overall, patients receiving immunochemotherapy had a significant long-term survival advantage [OS: hazard ratio (HR)=0.68, 95% hazard ratio (CI) 0.61-0.75; PFS: HR=0.62, 95%CI 0.55, 0.70, respectively]. Even with PD-L1 tumor proportion score <1%, immunochemotherapy also showed a significant survival advantage [OS: HR=0.65, 95%CI 0.46-0.93; PFS: HR=0.56, 95%CI 0.46-0.69, respectively]. However, for PD-L1 combined positive score (CPS)<1, the survival advantage of immunochemotherapy was not significant [OS: HR=0.89, 95%CI 0.42-1.90; PFS: HR=0.71, 95%CI 0.47-1.08, respectively]. The toxicity of immunochemotherapy was higher than that of chemotherapy alone, but there was no statistical difference in treatment-related mortality (odds ratio=1.11, 95%CI 0.67-1.83). Conclusions: In this study, PD-1/PD-L1 based immunochemotherapy significantly could improve survival outcomes in patients with advanced ESCC. For patients with CPS<1, the survival advantage of immunochemotherapy was not significant. The toxicity of immunochemotherapy was acceptable.

1 Introduction:

Squamous cell carcinoma is one of the main subtypes of esophageal cancer, and the prognosis is still unsatisfactory.[1,2]The early stage of esophageal cancer is often overlooked due to the lack of distinctive clinical features. By the time patients present with typical symptoms (e.g., progressive dysphagia, retrosternal pain), the disease is often locally advanced or even terminal. When the disease progresses to an advanced stage, surgery is no longer able to cure it, and the survival of the patient is greatly threatened.

In the past, the treatment of advanced esophageal squamous cell carcinoma (ESCC) depends on the entire body of chemotherapy, radiation therapy and targeted therapy, but the effect is not ideal.[3-5] Immunotherapy is a new treatment option that has shown encouraging efficacy in many cancers [6,7]. With the advent of Immunotherapy era, the treatment of advanced esophageal cancer is gradually changing. Clinically, there are two main immunotherapy options for patients with esophageal cancer, namely, anti-programmed cell death 1 (anti-PD-1)/anti-programmed cell death 1 ligand 1 (anti-PD-L1) and anti-cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) therapy.[8] Phase I/II studies in pilot trials have demonstrated antitumor activity and safety of PD-1/L1 based immunotherapy in patients with unresectable advanced or recurrent esophageal

cancer or gastroesophageal junction cancer.[9-15] With the deepening of the cognition of immunotherapy, immunotherapy combined with chemotherapy, radiotherapy and even double immunotherapy are gradually derived, and their effects are exciting.[16-18] However, the clinical application of immune checkpoint inhibitors is still in its early stages. Compared with other treatments, the survival benefit of immunotherapy has also been widely concerned.

Since the release of KEYNOTE-590 trial results, immunotherapy combined with chemotherapy has officially entered the first-line treatment of advanced esophageal cancer [19]. Currently, the results of a number of clinical trials comparing immunotherapy combined with chemotherapy versus chemotherapy alone have been published.[19-23] In this meta-analysis, we attempted to comprehensively analyze the efficacy and safety of PD-1/PD-L1 based immunotherapy combined with chemotherapy for advanced ESCC, and to evaluate the effect of PD-L1 expression level on the treatment outcome.

2 Materials and Methods

2.1 Literature retrieval

We performed keyword searches in electronic databases of PubMed, Cochrane Library, Web of Science and EMBASE to identify all relevant records. In addition, conference abstracts published by the International Society for Diseases of the Esophagus (ISDE), the European Society of Medical Oncology (ESMO), and the American Society of Clinical Oncology (ASCO) are also included in our search. Search terms included "esophageal, esophageal carcinoma, esophageal cancer, esophageal squamous cell carcinoma, esophageal malignancy", "PD-1, PD-L1, immunotherapy, immunochemotherapy", and "pembrolizumab, nivolumab, avelumab, atezolizumab, durvalumab, camrelizumab, toripalimab, sintilimab", language limited to English. In addition, we searched references of relevant published studies and review articles to supplement the insufficient of keyword retrieval. The literature search was conducted by two independent authors following systematic review and meta-analysis guidelines.[24]

2.2 Inclusion and exclusion criteria

Study inclusion criteria: (1) Randomized controlled trial (RCT); (2) Patients received chemotherapy combined with immunotherapy based on PD-1/PD-L1 or chemotherapy alone; (3) Advanced esophageal squamous cell carcinoma was diagnosed; (4) The outcome of interest is efficacy and toxicity; (5) Studies published in English. Study exclusion criteria: (1) Retrospective studies and non-randomized controlled clinical trials; (2) Patients with a history of any other malignancy were included in the study. If the results of a clinical trial were published in different journals or in different years, the article with the most complete data was selected.

2.3 Data extraction

Two independent authors recorded basic information about each study, including study name, intervention, year of publication, sample size, trial phase, and pathology. Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), hazard ratios (HR), 95% confidence intervals (CI) and safety data [treatment-related adverse event (TRAE), treatment-related mortality (TRM)] were extracted. A more in-depth subgroup analysis of PFS and OS was also performed according to the expression of PD-L1, namely tumor proportion score (TPS), combined positive score (CPS).

2.4 Assessment of risk of bias

The overall risk of bias of the literature was assessed according to the Cochrane Handbook of systematic reviews [25]. The Cochrane Handbook of systematic reviews consists of 7 parts: random sequence generation, allocation hiding, blindness of participants and personnel, blindness of result evaluations, incomplete result data, selective result reporting, and other sources of bias. Two independent authors evaluated the included articles, and the other author made the final decision on controversial sections.

2.5 Statistical methods

For time-survival variables, HR and 95%CI were extracted to calculate logHR and SE. For categorical variables, such as ORR, DCR and safety events, the number of events and sample size were extracted. Meta-analyses were performed using random-effects model in Revman software. The I^2 test was used to calculate inter-study heterogeneity and p value of heterogeneity. If inter-study heterogeneity was too high (I^2>50%, p<0.05), sensitivity analysis was further performed to assess the robustness of the meta-analysis and determine the source of heterogeneity.

3 Resluts

3.1 Literature results

Supplementary figure 1 shows the literature retrieval and screening process. 5 RCTs were included, all of which were multi-center phase III clinical trials with a total of 2962 patients (Table 1).[19-23] 1 RCT included ESCC and esophageal adenocarcinoma (EAC), from which we can extract relevant data of ESCC. The overall risk of bias was assessed according to the Cochrane Handbook for systematic reviews of interventions, and all the studies were of high quality (Supplementary Table 1).

3.2 ORR and DCR

4 studies provided comparisons of ORR for immunochemotherapy and chemotherapy alone. Overall, the ORR was significantly higher in patients who received immunochemotherapy than in patients who received chemotherapy alone. Meta-analysis showed that the ORR was approximately 2.05 times higher in the combination group than in the chemotherapy alone group (odds ratio (OR)=2.05, 95%CI 1.68-2.50) (Figure 1A). Heterogeneity test I^2=28%, p=0.24, indicating no significant heterogeneity between studies.

4 studies provided comparisons of DCR for immunochemotherapy and chemotherapy alone. Disease control rates were significantly higher in the immunochemotherapy group than in the chemotherapy group alone, approximately 1.54 times higher (OR=1.54, 95%CI 1.22-1.95) (Figure 1B). Similarly, according to the results of heterogeneity test, there was no significant heterogeneity between studies (I^2 =0, p=0.80).

3.3 OS and PFS

5 studies provided comparisons of OS and PFS for immunochemotherapy and chemotherapy alone. The meta-analysis showed that, without distinguishing the level of PD-L1 expression, compared with chemotherapy alone, the immunochemotherapy significantly improved the overall survival and disease-free survival of patients [OS: HR=0.68, 95%CI 0.61-0.75; PFS: HR=0.62, 95%CI 0.55-0.70, respectively] (Figure 2A,B). There was no significant heterogeneity was found between studies comparing OS (I^2=0, p=0.67; I^2=43%, p=0.14, respectively).

3.4 Stratified according to TPS

Subgroup analysis with TPS=10% as cutoff value, whether TPS[?]10% or TPS<10%, showed that the OS [TPS[?]10%: HR=0.54, 95%CI 0.41-0.70; TPS<10%: HR=0.72, 95%CI 0.60-0.88, respectively] (Figure 3A,B) and PFS [TPS[?]10%: HR=0.53, 95%CI 0.42-0.66; TPS<10%: HR=0.57, 95%CI 0.49-0.68, respectively] (Figure 3C,D) of patients in the immunochemotherapy group were better than those in the chemotherapy group.

Subgroup analysis with TPS=5% as cutoff value, whether TPS[?]5% or TPS<5%, showed that the OS [TPS[?]5%: HR=0.64, 95%CI 0.51-0.80; TPS<5%: HR=0.68, 95%CI 0.54-0.86, respectively] (Figure 4A,B) and PFS [TPS[?]5%: HR=0.53, 95%CI 0.43-0.65; TPS<5%: HR=0.58, 95%CI 0.49-0.70, respectively] (Figure 4C,D) of patients in the immunochemotherapy group were better than those in the chemotherapy group.

Subgroup analysis with TPS=1% as cutoff value, whether TPS[?]1% or TPS<1%, showed that the OS [TPS[?]1%: HR=0.62, 95%CI 0.52-0.75; TPS<1%: HR=0.65, 95%CI 0.46-0.93, respectively] (Figure 5a,b) and PFS [TPS[?]1%: HR=0.57, 95%CI 0.48-0.68; TPS<1%: HR=0.56, 95%CI 0.46-0.69, respectively] (Figure 5C,D) of patients in the immunochemotherapy group were better than those in the chemotherapy group.

3.5 Stratified according to CPS

Subgroup analysis with CPS=10 as cutoff value, whether CPS[?]10 or CPS<10, showed that the OS [CPS[?]10: HR=0.61, 95%CI 0.51-0.73; CPS<10: HR=0.62, 95%CI 0.48-0.80, respectively] (Figure 6A,B) and PFS [CPS[?]10: HR=0.60, 95%CI 0.49-0.74; CPS<10: HR=0.54, 95%CI 0.44-0.68, respectively] (Figure 6C,D) of patients in the immunochemotherapy group were better than those in the chemotherapy group.

Subgroup analysis with CPS=1 as cutoff value, for patients with CPS[?]1, the OS [HR=0.60, 95%CI 0.49, 0.72] and PFS [HR=0.55, 95%CI 0.47-0.65] in the immunochemotherapy group were significantly better than those in the chemotherapy group (Figure 7A,C). However, for patients with CPS<1, the significant benefit of OS [HR=0.89, 95%CI 0.42-1.90] and PFS [HR=0.71, 95%CI 0.47-1.08] in the immunochemotherapy group did not exist (Figure 7B,D).

3.6 Safety

5 studies showed the incidence of the TRAEs and TRM. In addition, one study (KEYNOTE-590) presented the incidence of the TRAEs and TRM for EAC and ESCC, which was included in the meta-analysis considering that adverse events were mostly multiorgan systemic. Compared with the chemotherapy group, the incidence of any grade or [?] grade 3 TRAEs in the immunochemotherapy group was higher [OR=1.74, 95%CI 1.32-2.29; OR=1.32, 95%CI 1.00-1.75, respectively] (Supplementary Figure 2A,B). In addition, the incidence of serious TRAEs, any grade immune-related adverse events (irAEs), and [?] grade 3 irAEs was reported in four studies respectively, and the incidence of immunochemotherapy group was significantly higher than that of chemotherapy group [OR=1.65, 1.29-2.09; OR=3.39, 95%CI 1.56-7.36; OR=3.16, 95%CI 2.05-4.89, respectively] (Supplementary Figure 2C,D,E). Although patients in the immunochemotherapy group were more likely to develop TRAEs, there was no significant difference in TRM between the two groups [OR=1.11, 95%CI 0.67-1.83] (Supplementary Figure 2F).

3.7 Sensitivity analysis

Significant inter-study heterogeneity was found in the comparison of grade [?]3 TRAEs and any grade irAEs [I^2=70%, p=0.01; I^2=94%, p<0.01, respectively] (Supplementary Figure 2B,D). Sensitivity analyses showed that the greatest heterogeneity came from ESCORT-1st trial (Supplementary Figure S1a,b). After omitting the escort-1st test, OR=1.47 (95%CI 1.18-1.83) for grade [?]3 TRAEs and OR=2.30 (95%CI 1.65-3.21) for any grade irAEs (Supplementary Figure 3A,B).

Moderate heterogeneity was also found in subgroup analyses of OS with TPS <1% and CPS <1 [I^2=58, p=0.12; I^2=54, p=0.14, respectively] (Figure 5B, Figure 7B). As only two studies were included, the source of heterogeneity could not be judged. Since the heterogeneity is moderate and the random effect model has been used to avoid the influence of heterogeneity as much as possible, the results have certain reliability.

3.8 Publish bias assessment

The egger's funnel plot showed no significant publication bias in OS meta-analysis, p=0.50 (Supplementary Figure 4).

4 Discussion

Our study demonstrated that compared with the chemotherapy alone, PD-1/PD-L1-based immunochemotherapy significantly improved survival outcomes in patients with advanced ESCC. More importantly, immunochemotherapy had excellent long-term efficacy regardless of TPS value. This could help to provide useful guidance for future research and treatment programs. However, in patients with CPS<1, there was no significant survival advantage in patients receiving immunochemotherapy. In addition, TAREs were significantly increased in the immunochemotherapy group compared with the chemotherapy group, but TRM was not significantly different between the two groups.

The treatment of early stage ESCC depends on surgical resection or endoscopic treatment.[26-28] When the disease progresses to a locally advanced stage, the efficacy of surgery alone is very limited. After the publication of the results of the CROSS and NEOCRTEC5010 trials, preoperative neoadjuvant chemoradiotherapy combined with surgery became the standard treatment for locally advanced resectable ESCC, and patients'

postoperative survival was significantly improved.[29,30] However, for patients with advanced esophageal cancer, surgery has been unable to achieve a radical cure. In terms of survival, surgery has lost its meaning. In addition, traditional treatment methods such as chemotherapy and radiotherapy have limited effect on patients with advanced esophageal cancer, so the treatment of these patients has always been a difficult problem.

In recent 10 years, immune checkpoint inhibitors have become a new entry point for cancer treatment.[6,7] Currently, three commonly used immune checkpoint inhibitors are anti-PD-1, anti-PD-L1 and anti-CTLA4 derivatives. Inhibition of activated CTLA-4, PD-1 and PD-L1 pathways can reverse T helper cell-mediated immunosuppression. As an epoch-making groundbreaking treatment, immunotherapy has demonstrated efficacy in many advanced cancers.[6,7] Immunotherapy based on PD-1/PD-L1 has long been applied in the field of esophageal cancer. Many phase I/II trials have proved that immunotherapy is effective as a second-line or multi line treatment for advanced esophageal cancer.[9-15] There was also a study comparing the efficacy of immune checkpoint inhibitors and chemotherapy, further confirming that immunotherapy could improve the long-term survival rate of patients.[31] This increased great confidence for immunotherapy to advance into the field of first-line treatment of advanced esophageal cancer.

A number of clinical trials are underway around first-line treatments. KEYNOTE-590 trial (pembrolizumab and chemotherapy (cisplatin/5-fluorouracil) vs. placebo and chemotherapy) is the first clinical trial to report results of immunochemotherapy as first-line treatment for locally advanced/unresectable or metastatic adenocarcinoma, ESCC, or Siewert Type 1 gastroesophageal junction adenocarcinoma.[19] The study showed that the OS of pembrolizumab plus chemotherapy group was significantly longer than that of placebo plus chemotherapy group (12.4 months vs. 9.8 months, HR=0.73, p<0.0001,), and the benefit of OS was superior in patients with ESCC and CPS[?]10 (median survival time: 13.9 vs. 8.8 months; HR=0.57; P<0.0001). This study paved the way for pembrolizumab to enter the first-line treatment of advanced esophageal cancer. On March 22, 2021, the USFDA approved pembrolizumab in combination with platinum and fluorouracil for the first-line treatment of advanced esophageal cancer and gastroesophageal junction cancers. Since then, the results of various clinical trials have been published. The results of ESCORT-1st (Camrelizumab), CheckMate-648 (Nivolumab), ORIENT-15 (sintilimab), and JUPITER-06 (toripalimab) trials all showed that for advanced ESCC, the long-term efficacy of immunochemotherapy as a first-line treatment regimen was significant than chemotherapy alone.[20,22-24] Our meta-analysis showed that immunochemotherapy reduced the overall risk of death by 32% (HR=0.68, 95%CI 0.61-0.75) and the risk of disease progression by 38% (HR=0.62, 95%CI 0.55, 0.70) in patients with advanced ESCC compared with chemotherapy alone. To date, no clinical trials have been conducted for EAC alone, so we did not analyze this group of patients. Before the KEYNOTE-590 trial, the CheckMate-649 trial conducted a comparative study of nivolumab combined chemotherapy and chemotherapy alone in the treatment of gastric cancer, gastroesophageal junction cancer and EAC.[19,32] Encouragingly, both KEYNOTE-590 and CheckMate-649 trials showed that immunochemotherapy improved overall survival of EAC [HR=0.74, 95%CI 0.54-1.02; HR=0.82, 95%CI 0.60-1.13, respectively].

In addition, we also conducted an in-depth study according to the expression level of PD-L1 in ESCC. When the expression level of PD-L1 was evaluated by TPS value, we found that the immune checkpoint inhibitors had excellent long-term efficacy regardless of TPS value, and the long-term efficacy of immunochemotherapy was significantly better than that of chemotherapy alone. When the expression level of PD-L1 was evaluated by CPS value, it was found that in patients with CPS<1, although immunochemotherapy reduced the risk of long-term death and disease progression compared with chemotherapy alone, there was no significant difference [OS: HR=0.89, 95%CI 0.42-1.90; PFS: HR=0.71, 95%CI 0.47-1.08, respectively]. Although we only included two studies, it still reminds us that PD-1/PD-L1 pathway inhibitors may not be suitable for all patients, and the cutoff value of PD-L1 expression level and other characteristic biomarkers still needs to be further studied.

While immunotherapy brings hope for survival, TRAEs, especially irAEs, should not be ignored. These have been reported in all cancers, and in severe cases leads to drug withdrawal and even death.[33-35] In the

clinical trials we included, almost all of the studies reported higher toxicity of immunochemotherapy than chemotherapy alone. The meta-analysis after summary confirmed this point: compared with chemotherapy alone, the incidence of any grade TRAEs, grade [?]3 TRAEs, serious TRAEs, any grade irAEs, grade [?]3 irAEs in patients with immunochemotherapy were significantly higher. However, there was no significant difference in TRM between the two treatments. This is not difficult to understand, as the use of immune checkpoint inhibitors becomes more widespread and physicians become better equipped to manage their related adverse reactions.

Although the included studies were prospective RCT_S and all were of high quality as assessed by the Cochrane Handbook, limitations remained in this meta-analysis. First, we did not have access to data on every patient, so we could't do a more detailed analysis. Second, although all the drugs we studied were derived from PD-1/PD-L1, the use of chemotherapy drugs was not completely consistent. Third, not all trials reported the study endpoints we wanted to analyze, and some endpoints only included 2 studies, which would have an impact on the results of the meta-analysis. Finally, heterogeneity was found in subgroup analysis of OS with TPS<1% and CPS<1 (I^2=58%, p=0.12; I^2=54%, p=0.14, respectively) (Figure 5B, Figure 7B). Although we used the random effect model to avoid the effect of heterogeneity as much as possible, the source of heterogeneity could not be analyzed because only two studies were included, so the interpretation of the results should be cautious. Because the heterogeneity of these two subgroup analyses was moderate, the results were somewhat convincing.

5 Conclusions

Overall, PD-1/PD-L1 based immunotherapy combined with chemotherapy significantly improve survival outcomes in patients with advanced ESCC. The toxicity of immunochemotherapy is acceptable. In ESCC with CPS<1, the survival advantage of immunochemotherapy is not significant compared with chemotherapy alone. Larger clinical trials are needed to further analyze the effect of PD-L1 expression levels on the efficacy of immune checkpoint inhibitors.

6 Abbreviations

Programmed cell death 1	PD-1
Programmed cell death 1 ligand 1	PD-L1
Cytotoxic T-lymphocyte-associated antigen-4	CTLA-4
Randomized controlled trial	RCT
Objective response rate	ORR
Disease control rate	DCR
Progression-free survival	PFS
Overall survival	OS
Hazard ratios	HR
Confidence intervals	CI
Treatment-related adverse event	TRAE
Treatment-related mortality	TRM
Tumor proportion score	TPS
Combined positive score	CPS
Esophageal squamous cell carcinoma	ESCC
Esophageal adenocarcinoma	EAC
Odds ratio	OR
Immune-related adverse event	irAE

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Table 1. Specific data of 5 randomized controlled trials.

Study	Year	Histology	ICI	N1	N2	OS HR	OS 95%CI	PFS HR	PFS 95%CI	TRAE	irAE
KEYNOTE-590	2021	ESCC	PEMBRO	274	274	0.72	0.60-0.88	0.65	0.54-0.78	364 vs 360	95 vs 43
KEYNOTE-590	2021	EAC	PEMBRO	99	102	0.74	0.54-1.02	0.63	0.46-0.87		
ESCORT-1st	2021	ESCC	CAMRE	298	298	0.70	0.56-0.88	0.56	0.46-0.68	296 vs 288	252 vs 98
CheckMate-648	2022	ESCC	NIVO	321	324	0.74	0.58-0.96	0.81	0.64-1.04	297 vs 275	-
ORIENT-15	2022	ESCC	SINTI	327	332	0.63	0.51-0.78	0.56	0.46-0.68	321 vs 326	155 vs 81
JUPITER-06	2022	ESCC	TORIPA	257	257	0.58	0.43-0.78	0.58	0.46-0.74	183 vs 158	95 vs 68

Abbreviations: ICI, immune checkpoint inhibitor; OS, overall survival; PFS: progression-free survival; HR, hazard ratio; 95%CI, 95% confidence interval; TRAE, treatment-related adverse event; irAE, immune-related adverse event; TRD, treatment-related death; ESCC, esophageal squamous cell carcinomas; EAC, esophageal adenocarcinoma; PEMBRO, pembrolizumab; CAMRE, camrelizumab; NIVO, nivolumab; SINTI, sintilimab; TORIPA, toripalimab.

Figure Legends

Figure 1. Forest plot of ORR (A) and DCR (B) comparison between immunochemotherapy and chemotherapy.

Figure 2. Forest plot of OS (A) and PFS (B) comparison between immunochemotherapy and chemotherapy.

Figure 3. TPS=10% was used as cutoff value to classify patients and compare the efficacy of immunochemotherapy and chemotherapy. (A) OS of TPS[?]10%; (B) OS of TPS<10%; (C) PFS of TPS[?]10%; (D) PFS of TPS<10%.

Figure 4. TPS=5% was used as cutoff value to classify patients and compare the efficacy of immunochemotherapy and chemotherapy. (A) OS of TPS[?]5%; (B) OS of TPS<5%; (C) PFS of TPS[?]5%; (D) PFS of TPS<5%.

Figure 5. TPS=1% was used as cutoff value to classify patients and compare the efficacy of immunochemotherapy and chemotherapy. (A) OS of TPS[?]1%; (B) OS of TPS<1%; (C) PFS of TPS[?]1%; (D) PFS of TPS<1%.

Figure 6. CPS=10 was used as cutoff value to classify patients and compare the efficacy of immunochemotherapy and chemotherapy. (A) OS of CPS[?]10; (B) OS of CPS<10; (C) PFS of CPS[?]10; (D) PFS of CPS<10.

Figure 7. CPS=1 was used as cutoff value to classify patients and compare the efficacy of immunochemotherapy and chemotherapy. (A) OS of CPS[?]1; (B) OS of CPS<1; (C) PFS of CPS[?]1; (D) PFS of CPS<1.

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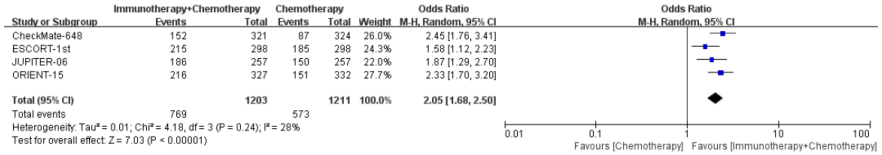

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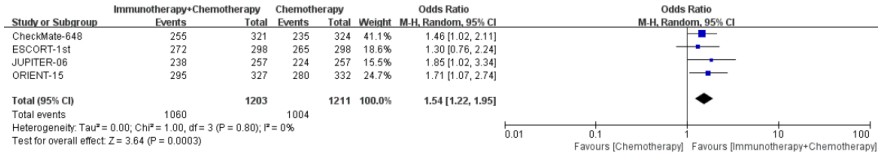

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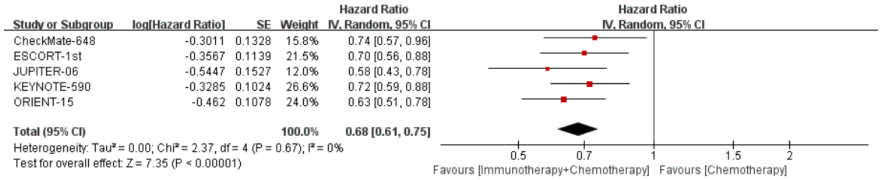

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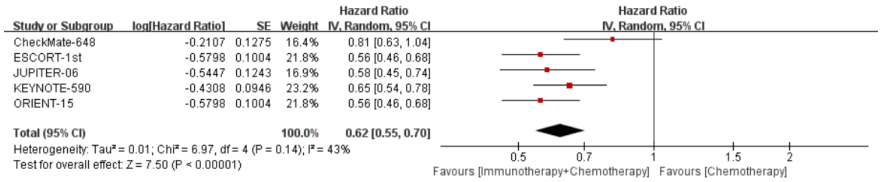

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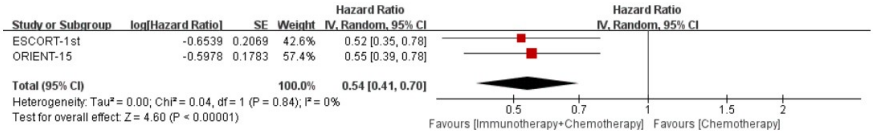

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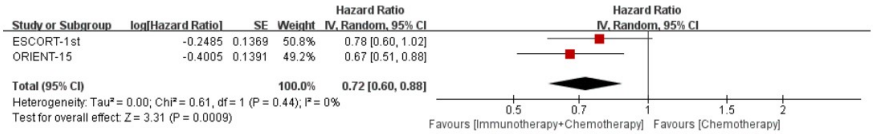

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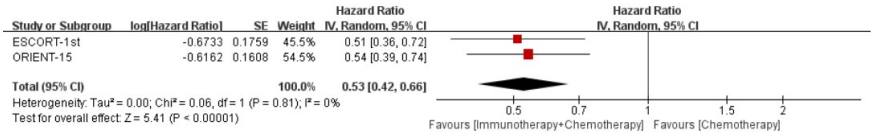

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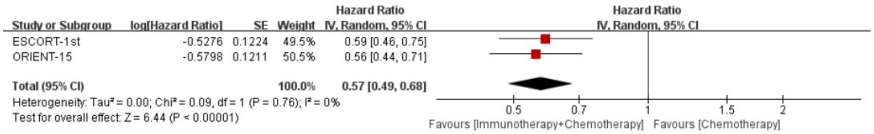

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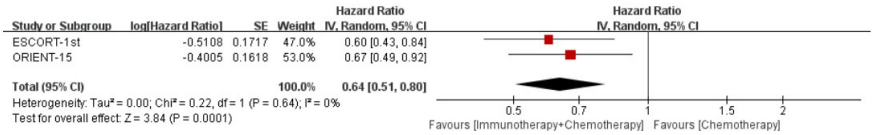

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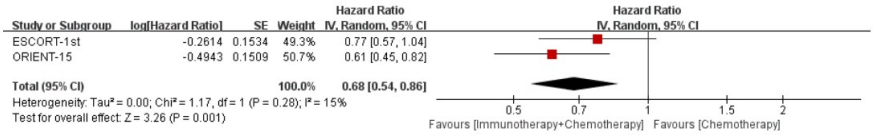

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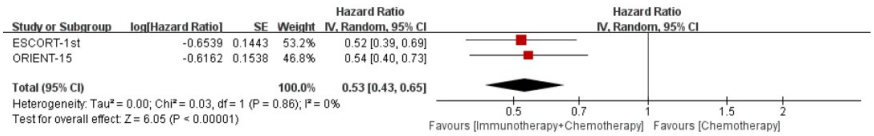

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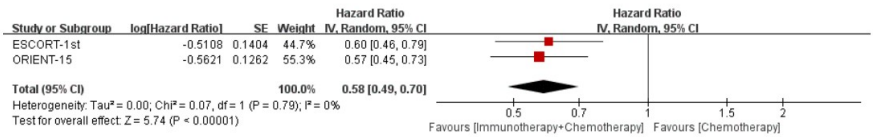

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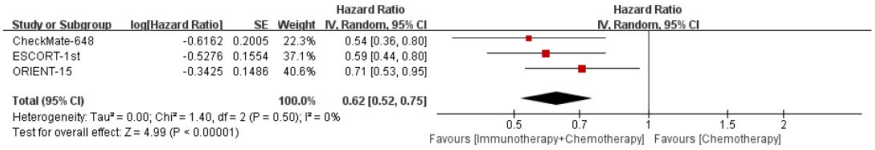

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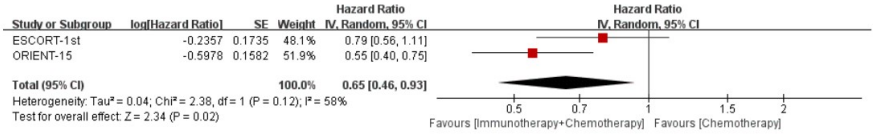

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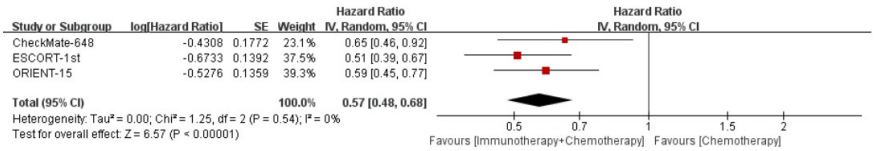

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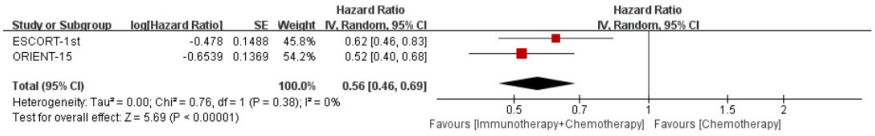

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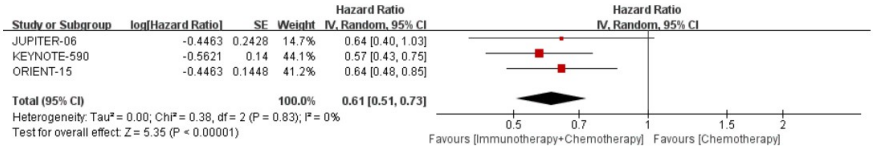

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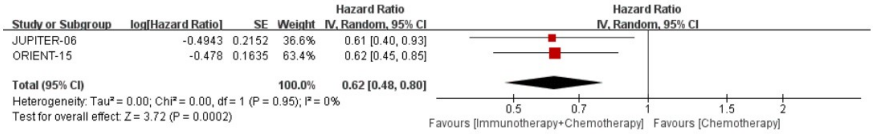

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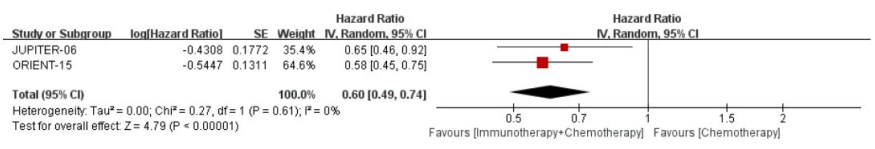

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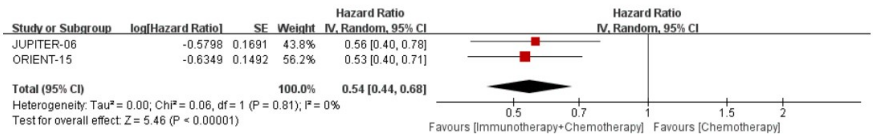

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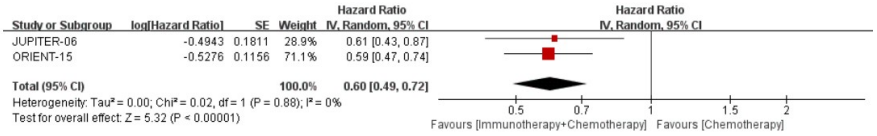

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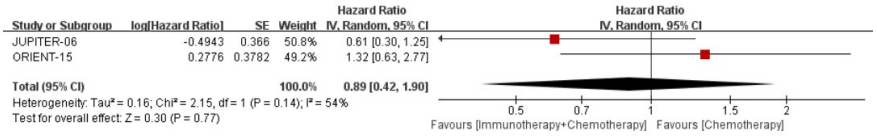

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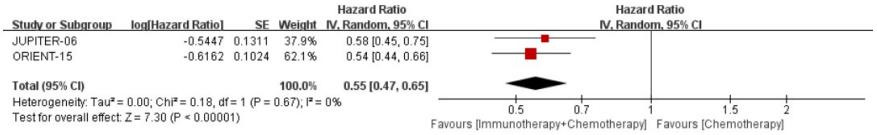

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