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Review Article

Comparison of Efficacy and Safety of First-Line Chemoimmunotherapy in Advanced Esophageal Squamous Cell Carcinoma: A Systematic Review and Network Meta-Analysis

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Background. Chemoimmunotherapy has become the first-line treatment for advanced esophageal squamous cell carcinoma (ESCC). We aimed to compare the efficacy and toxicity of different chemoimmunotherapy combinations to determine the optimal treatment option. *Methods*. PubMed, Web of Science, Cochrane Library, Embase, and abstracts of recent relevant meetings were searched to identify phase III randomized controlled trials (RCTs) of first-line programmed cell death-1 (PD-1)/its receptor (PD-L1) inhibitors plus chemotherapy for ESCC up to July 2022. A network meta-analysis (NMA) following Bayesian approaches was conducted in R software. *Result*. Our study included six RCTs and 3,611 patients. According to the NMA, toripalimab plus chemotherapy ranked first to prolong overall survival (OS). Sintilimab plus chemotherapy and camrelizumab plus chemotherapy consistently yielded the greatest benefits regarding progression-free survival (PFS). The maximal complete response rate (CRR) and objective response rate (ORR) were achieved with nivolumab plus chemotherapy. Tislelizumab plus chemotherapy attained the highest likelihood of achieving a disease control rate (DCR). The addition of immunotherapy to chemotherapy was associated with improved survival and increased adverse events. Subgroup analysis revealed that patients with PD-L1 tumor positive score (TPS) ≥10% showed a better OS than those with lower values when undergoing first-line chemoimmunotherapy. Anti-PD-1 inhibitor with platinum plus paclitaxel (TP) regimen showed a superior PFS benefit over anti-PD-1 inhibitor with platinum plus fluorouracil (FP) regimen. *Conclusion*. The NMA analysis suggested that sintilimab plus chemotherapy was the preferred regimen for treatment-naive advanced ESCC patients with the best balance between efficacy and safety. Anti-PD-1 inhibitors with the TP regimen were associated with more favorable PFS than those with the FP regimen.

1. Introduction

Esophageal carcinoma is the seventh most common type of malignancy and the sixth leading cause of cancer death worldwide [1]. Due to the nonspecificity of symptoms during the early stage, patients with esophageal cancer are mostly diagnosed at an advanced stage. Despite the application of systemic chemotherapy, the prognosis of advanced patients remains dismal, with a five-year overall survival (OS) rate of approximately 5% [2].

Pathologically, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the predominant subtypes of esophageal cancer. Increasing evidence suggests that ESCC and EAC are different disease entities with distinct epidemiology, pathogenesis, and genomic alterations [3–5]. Chronic smoking and excessive alcohol consumption are the major risk factors for ESCC, while EAC is heavily correlated with obesity and gastroesophageal reflux disease [6]. Differences in tumorigenic factors cause different changes at the molecular level [7]. Scholars found that ESCC was more similar to squamous carcinomas of other organs than to EAC with respect to the genomic landscape [3, 8]. Additionally, ESCC usually exhibits more aggressive behavior and a worse prognosis than EAC [9]. Hence, it is urgent to find novel and effective approaches for advanced ESCC.

Recently, immune checkpoint inhibitors (ICIs), especially antiprogrammed cell death-1 (PD-1)/its receptor (PD-L1) inhibitors, have revolutionized the treatment paradigm of ESCC. For instance, KEYNOTE-181 and ATTRACTION-3 reported that anti-PD-1 inhibitor monotherapy as a second-line or later-line treatment showed significant survival benefits over standard chemotherapy in patients with advanced ESCC [10, 11]. Its intrinsic mechanism is mainly attributed to breaking tumor immune tolerance. Anti-PD-1/PD-L1 agents can block the PD-1/PD-L1 pathway and antagonize the cosuppression effect on the immune response, leading to immune activation [12]. Currently, several phase III randomized controlled trials (RCTs) have investigated the combinations of immunotherapy (IO) plus chemotherapy compared with chemotherapy alone as the first-line treatment for ESCC patients, and most of them have reached the primary endpoints and reported positive results [13–18]. Furthermore, the National Comprehensive Cancer Network (NCCN) guidelines have recommended anti-PD-1 inhibitor plus chemotherapy as a first-line treatment option for patients with ESCC. Since no head-to-head trials have compared these diverse combinations, the selection of an optimal protocol for individual cancer patients remains an important challenge.

Previous studies compared IO-based treatments in patients with ESCC by pairwise meta-analysis, without offering evidence of the best available intervention [19, 20]. Several attempts have been made to provide indirect evidence, but these do not contain the latest trials and are with limited subgroup analysis [21]. Indeed, there is still a lack of sufficient and up-to-date analysis for the comparison and selection of first-line chemoimmunotherapy scenarios for treatment-naive ESCC patients. Network meta-analysis (NMA) by indirect comparisons could estimate the relative effectiveness of several interventions simultaneously and provide synthetic conclusions by visualization [22]. Meanwhile, compared with conventional pairwise meta-analysis, NMA was found to increase the precision of the assessments [22, 23]. Herein, we performed an updated NMA to systematically compare and rank different combinations of PD-1 pathway inhibitors plus chemotherapy for previously untreated advanced ESCC patients. Survival benefits and risk of adverse events (AEs) were fully evaluated among these combined regimens. The purpose of this study was to determine the optimal chemoimmunotherapy combination to serve specific subpopulations.

2. Methods

2.1. Search Strategy. This systematic review and network meta-analysis compared first-line combinations of immunotherapy plus chemotherapy in patients with ESCC. It was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) reporting guidelines (Supplementary Table 1) [24]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022353376). We searched the PubMed, Web of Science, Cochrane Library, and Embase databases to identify eligible trials that were conducted until July 1, 2022. In addition, the up-to-date conference abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) congress were also screened up to July 4, 2022. The main search strategy was as follows: (esophageal neoplasms OR esophageal cancer OR esophagus tumor) AND (immune checkpoint inhibitor OR immunotherapy OR PD-1 inhibitor OR PD-L1 inhibitor OR nivolumab OR pembrolizumab OR camrelizumab OR sintilimab OR toripalimab OR tislelizumab OR avelumab OR durvalumab OR atezolizumab) AND (randomized controlled trial OR controlled clinical trial OR trial). We restricted our search strategy to phase III RCTs and to patients in first-line treatment. Figure 1 presents the detailed process of the literature search and selection, and the results from Embase as an example are shown in Supplementary Table 2.

2.2. Inclusion and Exclusion Criteria. We included phase III RCTs that compared first-line systemic therapies in patients with ESCC (with chemotherapy as the control arm and a combination of anti-PD-1/PD-L1 inhibitor plus chemotherapy as the treatment arm).

Other inclusion criteria were as follows:

(1) The study population was required to be adults with histologically or cytologically confirmed advanced ESCC.

(2) Patients were randomly assigned to receive anti-PD-1/PD-L1 inhibitors plus chemotherapy or chemotherapy in the first-line setting.

(3) Overall survival (OS) was defined as the time from randomization until death from any cause. Progression-free survival (PFS) was defined as the time from randomization to disease progression or death from any cause.

(4) The complete response rate (CRR) was defined as the proportion of patients who achieved a complete response (CR). The objective response rate (ORR) was defined as the proportion of patients who achieved a CR or partial response (PR). The disease control rate (DCR) was defined as the proportion of patients who achieved either a CR or PR or stable disease (SD).

(5) The grade of treatment-related adverse events (TRAEs) and immune-related adverse events (irAEs) was assessed by the National Cancer Institute Common Terminology Criteria for adverse events (AEs).

(6) Trials reported on one or all of the following clinical outcomes: OS, PFS, CRR, ORR, DCR, any grade TRAEs, ≥3-grade TRAEs, any grade irAEs, and ≥3-grade irAEs.

We excluded observational studies, study protocols, case reports, editorials, reviews, and letters. Trials with ambiguous clinical outcomes or overlapping data were also excluded.

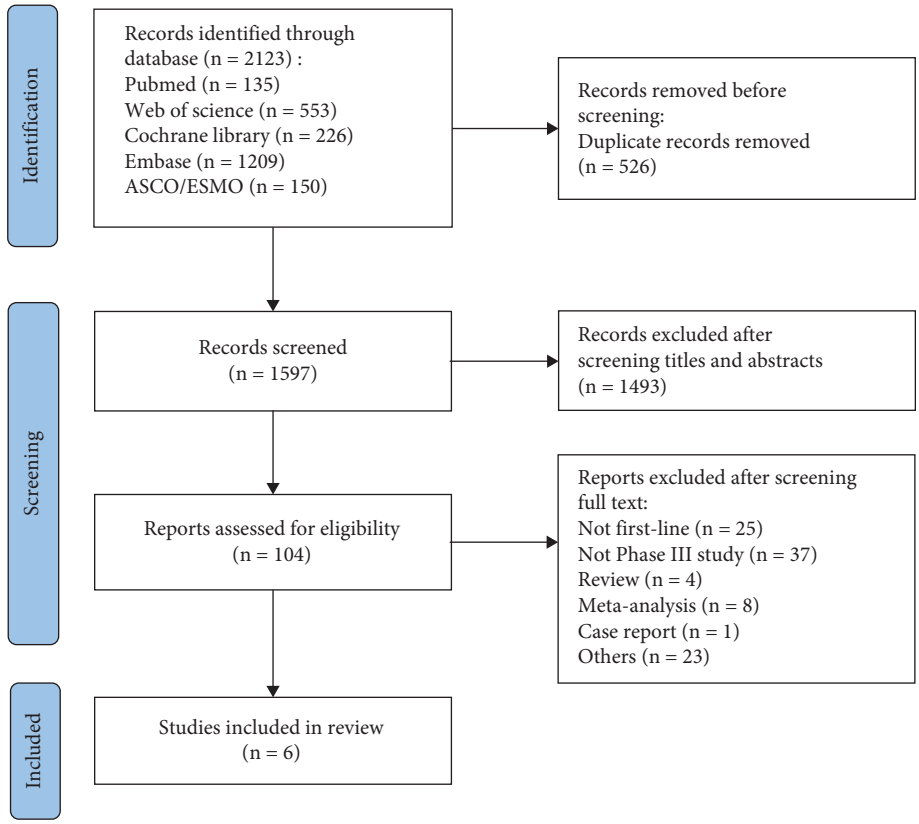


Figure 1: The search flow chart.

2.3. Study Selection and Data Extraction. Two investigators (X. M. and M. W.) independently screened the titles and abstracts according to the inclusion and exclusion criteria. Then, they reviewed the full texts to choose potentially relevant studies for further selection. Any disagreements were resolved by consultation with a third reviewer (Y. D.). Data extraction from the included studies was performed by two investigators (J. Q. and X. C.). The following items were collected: study identification, trial design, treatment strategy, sample size, patient characteristics, and the outcomes of interest. All the discrepancies were resolved by a consensus of the senior author (N. X.).

2.4. Risk of Bias Assessment. The quality of the included studies was assessed by using the Cochrane Collaboration Tool (Supplementary Figure 1). Using this tool, studies were evaluated according to the following aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. The overall bias was rated as low if the risk of bias was low in all domains, unclear if the risk of bias was unclear in at least one domain and with no judgment of a high risk of bias, or high if the risk of bias was high in at least one domain. The risk of bias assessment was independently performed by two authors (X. M. and Y. D.). Disagreements were resolved by discussion and consensus.

2.5. Statistical Analysis. The primary outcomes were OS and PFS, and the secondary outcomes were CRR, ORR, DCR, any grade TRAEs, ≥3-grade TRAEs, any grade irAEs, and ≥3-grade irAEs. Hazard ratios (HRs) along with their 95% confidence intervals (CIs) were used for the analysis of PFS and OS. For tumor response and adverse event incidence, odds ratios (ORs) with 95% CIs were calculated for subsequent analysis. Prior to the conduction of NMA, conventional pairwise meta-analysis was conducted by using the "meta" package of *R* (version 4.1.1). For each pairwise meta-analysis, both the Cochrane *Q* test and I^2 statistics were used to evaluate heterogeneity across studies. If a p value of <0.05 or an I^2 value of >50% indicated statistically significant heterogeneity, the random effect model was employed; otherwise, the fixed-effect model was applied [25]. The Bayesian approach using a Markov chain Monte Carlo simulation method was adopted in conducting NMA with the "gemtc" *R* package and JAGS software, which could compare the relative effectiveness of different interventions simultaneously. Each NMA was fitted using four chains, each with 20,000 samples and 5,000 samples as burn-in. To assess treatment optimality with respect to various outcomes, the ranking probabilities for all interventions were estimated using the surface under the cumulative ranking area (SUCRA). The treatment hierarchies were visualized by rankogram and the SUCRA values for all outcomes were summarized in a heat plot. Subgroup results were presented by forest plot with the "forest plot" package of *R*. Publication bias of the primary outcomes was evaluated by funnel plots.

Sensitivity analysis was conducted by omitting each study by turn to test the stabilities of the results.

3. Results

3.1. Search Results and Patient Characteristics. The literature search yielded 1,973 publications, with an additional 150 records identified through ASCO and ESMO conferences. Following the removal of duplicate publications, a total of 1,597 records were screened assessing titles and abstracts. After that, 104 articles remained for full-text review. Based on the inclusion and exclusion criteria, we finally identified six articles (Figure 1).

The network construction of the included treatment comparisons is represented in Supplementary Figure 2. Moreover, Table 1 shows the main characteristics of the six enrolled trials. All of them were phase 3 RCTs comparing first-line IO plus chemotherapy combinations versus chemotherapy alone. A total of 3,611 patients were enrolled in the study to receive the following treatments: pembrolizumab plus chemotherapy (pembro-chemo), nivolumab plus chemotherapy (nivo-chemo), sintilimab plus chemotherapy (sinti-chemo), camrelizumab plus chemotherapy (camre-chemo), toripalimab plus chemotherapy (tori-chemo), tislelizumab plus chemotherapy (tisle-chemo), and chemotherapy. KEYNOTE-590 reported the results for pembrolizumab plus chemotherapy versus chemotherapy alone in advanced esophageal cancer, and we only extracted the patient's data from its ESCC subgroup.

3.2. Comparison of OS and PFS. The analysis of OS and PFS included six trials, and there was no significant heterogeneity in the pairwise comparison of different combination regimens (OS $I^2 = 0\%$; PFS $I^2 = 31\%$). Regarding OS, all the combinations of IO plus chemotherapy had a statistically significantly better OS than chemotherapy (Figure 2(a)). Specifically, tori-chemo, sinti-chemo, and tisle-chemo yielded HRs of 0.58 (95% CI 0.43–0.78), 0.63 (95% CI 0.51–0.78), and 0.66 (95% CI 0.54–0.80), respectively. According to the rankogram and SUCRA estimates (Figures 2(c) and 3), toripalimab plus chemotherapy (SUCRA 84%) appeared to be the preferred treatment option compared to other combined regimens.

Regarding PFS, head-to-head comparisons revealed that compared with chemotherapy, PFS was improved significantly in patients treated with sinti-chemo (HR 0.56 95% CI: 0.46–0.68), camre-chemo (HR 0.56 95% CI: 0.46–0.68), tori-chemo (HR 0.58 95% CI: 0.46–0.74), tisle-chemo (HR 0.62 95% CI: 0.52–0.75), and pembro-chemo (HR 0.65 95% CI: 0.54–0.78). From the league table of PFS (Figure 2(b)), sinti-chemo and camre-chemo were found to provide marked PFS benefits over nivo-chemo. Based on the results of the rankogram and SUCRA (Figures 2(d) and 3), sinti-chemo (SUCRA 79%) and camre-chemo (SUCRA 78%) could be proposed as the preferred treatments.

3.3. Comparison of CRR, ORR, and DCR. For antitumor activity, five trials were included for the subsequent analysis. No significant heterogeneity was detected in the CRR, ORR, or DCR groups (CRR $I^2 = 0\%$; ORR $I^2 = 7\%$; DCR $I^2 = 0\%$). Analysis of treatment ranking (Figures 3, 4(a)–4(c)) revealed that nivo-chemo (SUCRA 78%), tisle-chemo (SUCRA 62%), and camre-chemo (SUCRA 61%) had the highest likelihood of being the preferred treatment option for achieving CR. Nivo-chemo (SUCRA 78%), tisle-chemo (SUCRA 73%), and sinti-chemo (SUCRA 70%) were the most likely related to the best objective tumor response. The higher disease control rates (DCR) occurred in the tisle-chemo (SUCRA 81%), tori-chemo (SUCRA 69%), and sinti-chemo (SUCRA 65%).

3.4. Safety of Treatment. In terms of treatment-related AEs, five trials were available for the analysis of any grade TRAEs and ≥3-grade TRAEs. No significant heterogeneity was observed in the group of any grade TRAEs ($I^2 = 27\%$). Of note, there was significant heterogeneity in the group of ≥3-grade TRAEs ($I^2 = 55\%$). Despite a higher rate of any grade TRAEs (SUCRA 94%), camre-chemo was associated with the lowest rate of ≥3-grade TRAEs (SUCRA 16%) (Figures 3, 4(d), and 4(e)). Tisle-chemo followed by sinti-chemo was associated with a low rate of any grade TRAEs and ≥3-grade TRAEs.

For irAEs, a total of four trials were available for the analysis of any grade irAEs and ≥3-grade irAEs. The group of ≥3-grade irAEs had a low heterogeneity of $I^2 = 40\%$. Otherwise, the group of any grade irAEs had a high heterogeneity of $I^2 = 94\%$. Despite having the highest rate of any grade irAEs (SUCRA 85%), camre-chemo had the lowest rate of ≥3-grade irAEs (SUCRA 28%) (Figures 3, 4(f), and 4(g)). Tisle-chemo had the highest likelihood of ≥3-grade irAEs (SUCRA 82%), and it also had a relatively high rate of any grade irAEs (SUCRA 64%).

3.5. Subgroup Analysis. Since both the combined positive score (CPS) and tumor positive score (TPS) are scoring methods of PD-L1 expression, we evaluated their predictive efficacy for OS and PFS by pooling the available HR from the experimental subgroups (Supplementary Figure 3). The results of the comparisons were further visualized by forest plots (Figure 5). From Figure 5(a), patients with PD-L1 TPS ≥10% had a superior OS benefit compared to those with PD-L1 TPS <10% ($P = 0.03$), whereas CPS, at the cut-off of 10, showed an insignificant stratification effect for OS ($P = 0.05$). Figure 5(b) shows that neither CPS nor TPS as the method of PD-L1 expression could have a clear PFS discrimination.

Subgroup analysis stratified by chemotherapeutic regimen showed that the OS benefit was consistent between the anti-PD-1 inhibitor plus FP (fluorouracil + platinum) group and the anti-PD-1 inhibitor plus TP (paclitaxel + platinum) group (Figure 5(a)). Of note, the combination of anti-PD-1 inhibitor plus TP group had a longer PFS than the combination of anti-PD-1 inhibitor plus FP group ($P = 0.02$) (Figure 5(b)).

3.6. Study Quality and Publication Bias. The Cochrane risk of bias assessment tool was used to assess the quality of the enrolled studies (Supplementary Figure 1). The funnel plot

Table 1: The main characteristics of six eligible RCTs.

Trials	Treatments	Chemotherapy	No. of patients experiment	control	OS (m)	HR for OS	PFS (m)	HR for PFS	ORR	≥3 TRAEs	PD-L1 detection
KEYNOTE-590 (ESCC) NCT03189719	Pembrolizumab	Cisplatin + fluorouracil	274	274	12.6 vs. 9.8	HR 0.72 (95% CI 0.60–0.88)	6.3 vs. 5.8	HR 0.65 (95% CI 0.54–0.78)	—	—	22C3
CheckMate 648 NCT03143153	Nivolumab	Cisplatin + fluorouracil	321	324	13.2 vs. 10.7	HR 0.74 (95% CI 0.61–0.89)	5.8 vs. 5.6	HR 0.81 (98.5% CI 0.64–1.04)	47.3% vs. 26.9%	49.0% vs. 37.5%	28–8
ORIENT-15 NCT03748134	Sintilimab	(1) Cisplatin + fluorouracil (2) Cisplatin + paclitaxel	327	332	16.7 vs. 12.5	HR 0.63 (95% CI 0.51–0.78)	7.2 vs. 5.7	HR 0.56 (95% CI 0.46–0.68)	66.1% vs. 45.5%	59.9% vs. 54.5%	22C3
ESCORT-1st NCT03691090	Camrelizumab	Cisplatin + paclitaxel	298	298	15.3 vs. 12.0	HR 0.70 (95% CI 0.56–0.88)	6.9 vs. 5.6	HR 0.56 (95% CI 0.46–0.68)	72.1% vs. 62.1%	63.4% vs. 67.7%	6E8
JUPITER-06 NCT03829969	Toripalimab	Cisplatin + paclitaxel	257	257	17.0 vs. 11.0	HR 0.58 (95% CI 0.43–0.78)	5.7 vs. 5.5	HR 0.58 (95% CI 0.46–0.74)	69.3% vs. 52.1%	64.6% vs. 56.0%	JS311
RATIONALE-306 NCT03783442	Tislelizumab	(1) Platinum + fluoropyrimidine (2) Platinum + paclitaxel	326	323	17.2 vs. 10.6	HR 0.66 (95% CI 0.54–0.80)	7.3 vs. 5.6	HR 0.62 (95% CI 0.52–0.75)	63.5% vs. 42.4%	66.7% vs. 64.5%	SP263

RCTs: randomized controlled trials; ESCC: esophageal squamous cell carcinoma; OS: overall survival; HR: hazard ratio; PFS: progression-free survival; ORR: objective response rate; TRAEs: treatment-related adverse events; PD-L1: programmed cell death ligand 1.

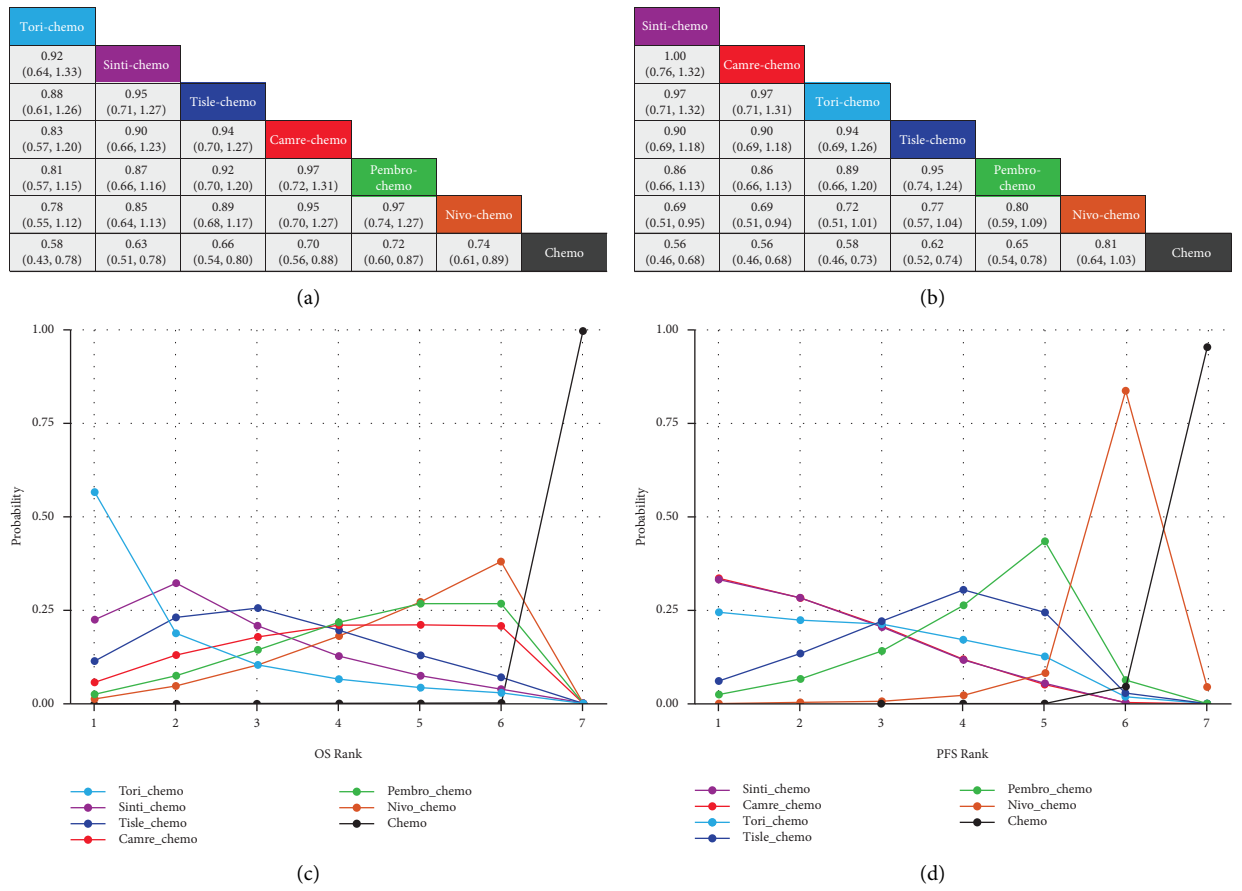


Figure 2: (a) The league table for OS. (b) The league table for PFS. (c) The rankogram for OS. (d) The rankogram for PFS. OS: overall survival; PFS: progression-free survival; tori: toripalimab; sinti: sintilimab; tisle: tislelizumab; camre: camrelizumab; pembro: pembrolizumab; nivo: nivolumab; chemo: chemotherapy.

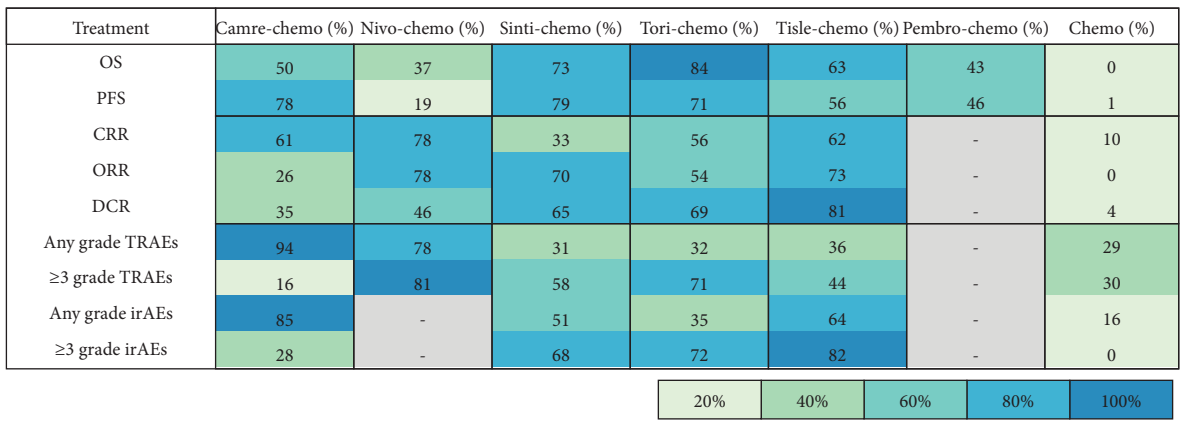


Figure 3: Heat plot for the analysis of different IO combinations. IO: immunotherapy; OS: overall survival; PFS: progression-free survival; CRR: complete response rate; ORR: objective response rate; DCR: disease control rate; TRAEs: treatment-related adverse events; irAEs: immune-related adverse events. camre: camrelizumab; nivo: nivolumab; sinti: sintilimab; tori: toripalimab; tisle: tislelizumab; pembro: pembrolizumab; chemo: chemotherapy.

of OS (Supplementary Figure 4) appeared symmetrical, indicating no potential publication bias. The funnel plot of PFS showed slight asymmetry, and further sensitivity analysis (Supplementary Figure 5) with heterogeneity results considered that there was no significant publication bias.

4. Discussion

The combination of anti-PD-1 inhibitor plus chemotherapy has become the standard of care first-line treatment for advanced ESCC. Individuals undergoing antitumor

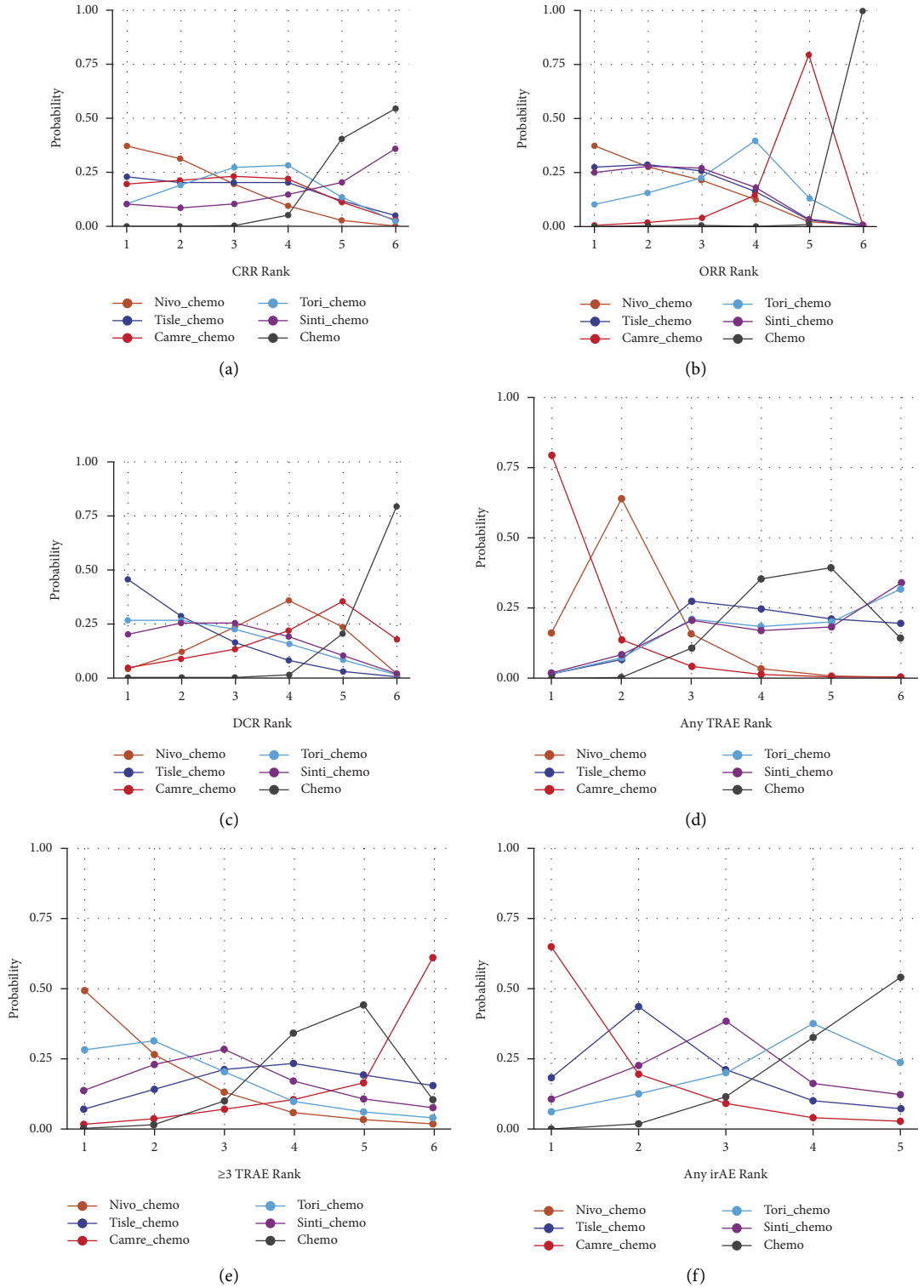
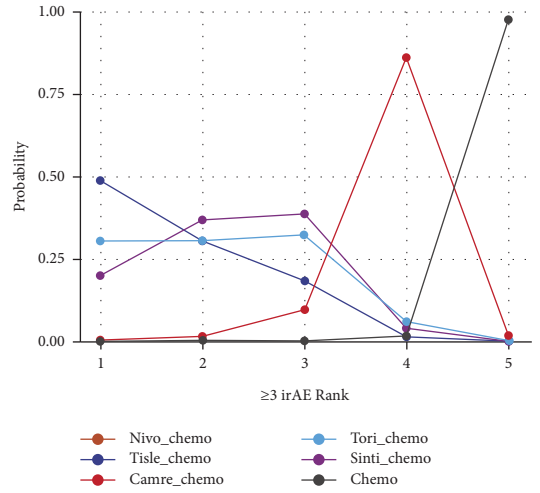
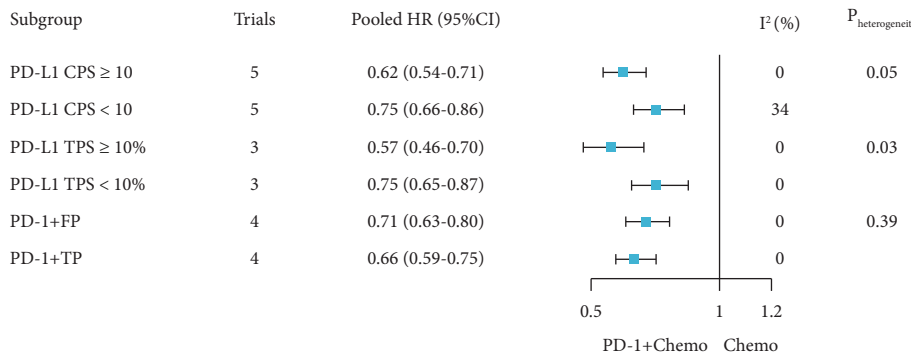


Figure 4: Continued.

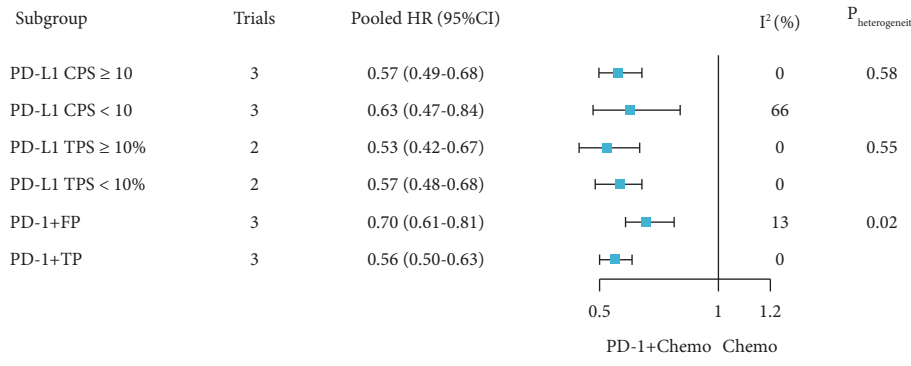


(g)

Figure 4: Rankograms for CRR (a), ORR (b), DCR (c), any TRAEs (d), ≥3 TRAEs (e), any irAEs (f), and ≥3 irAEs (g). CRR: complete response rate; ORR: objective response rate; DCR: disease control rate; TRAEs: treatment-related adverse events; irAEs: immune-related adverse events; camre: camrelizumab; nivo: nivolumab; sinti: sintilimab; tori: toripalimab; tisle: tislelizumab; pembro: pembrolizumab; chemo: chemotherapy.



(a)



(b)

Figure 5: (a) Forest plot showing subgroup analysis of OS. (b) Forest plot showing subgroup analysis of PFS. PD-L1: programmed cell death ligand 1. CPS: combined positive score; TPS: tumor positive score; FP: fluorouracil + platinum; TP: paclitaxel + platinum; OS: overall survival; PFS: progression-free survival; HR: hazard ratio.

treatment have a variety of treatment options and face a confusing decision-making process. The network meta-analysis included six head-to-head combinations (pembro-chemo, sinti-chemo, tori-chemo, camre-chemo, tisle-chemo, and nivo-chemo), providing a comprehensive and up-to-date overview of the efficacy and safety data available

for the first-line treatment of ESCC. According to the NMA analysis, the addition of immunotherapy to chemotherapy manifested an improved survival benefit compared with chemotherapy alone, although it resulted in an increase in toxicity. For the primary outcomes of OS, tori-chemo could be the preferred therapeutic strategy, followed by sinti-chemo. Camre-chemo and sinti-chemo showed superior PFS over other chemoimmunotherapy. However, camre-chemo was also associated with a higher incidence of any grade TRAEs and any grade irAEs. Nivo-chemo yielded a higher CRR and ORR than the others, and it was more likely to cause ≥3-grade TRAEs simultaneously. Tisle-chemo had the best likelihood of achieving DCR and had a higher probability of occurring ≥3-grade irAEs. Overall, based on available evidence, sinti-chemo was found to have the optimal balance between efficacy and safety.

The addition of immunotherapy to chemotherapy showed significant clinical benefits in terms of OS and PFS. This phenomenon could be explained by the fact that during the antitumor process, chemotherapy-induced cytotoxicity increases tumor immunogenicity which contributes to the immunological conversion of "cold" tumors to "hot" lesions [26, 27]. Thus, chemotherapy has a synergistic effect with immunotherapy based on the abovementioned mechanism. We also found that the TP regimen with immunotherapy could exhibit a more improved PFS than the FP regimen according to the subgroup analysis. Before the advent of immunotherapy, the first-line systemic therapy regimens for advanced ESCC included platinum plus paclitaxel (TP) and platinum plus fluorouracil (FP), which are commonly used in China and Western countries, respectively [28]. A few retrospective studies supported that the TP regimen was a more robust therapeutic strategy than the FP regimen for ESCC [29, 30]. Furthermore, concerning immunostimulatory capacity, paclitaxel might realize its potential for promoting immunogenic death and inducing the inflammatory immune microenvironment [26, 31]. Therefore, future efforts should focus on continuously optimizing the combinations of chemoimmunotherapy from the perspective of how to maximize the synergistic effect.

Regarding safety profiles, chemoimmunotherapy as first-line therapy for patients with ESCC increased the incidence of any grade TRAEs and any grade irAEs. Previous research work suggested that there is an intimate association between the response to and toxicity from ICIs [32, 33]. One major supposition for the increase in AEs, especially irAEs, is the similarities between antigens presented on tumor tissues and normal cells [34]. Although patients with low-grade AEs show mild symptoms, most of those with grade 3 or 4 AEs have to discontinue the treatment. Hence, as combination patterns are pursued, the risk of AEs should be fully evaluated frequently. It is critical to identify the occurrence of AEs early and prevent progression to serious AEs. Efforts should be made to develop biomarkers for the earlier prediction of AEs [35, 36].

It had been reported that patients with a high level of PD-L1 expression indicated a better response to PD-1 pathway inhibitors [37, 38], and the PD-L1 expression level was considered the most correlated with the prediction of the clinical benefits from immunotherapy [39]. An increasing number of studies have supported the clinical interchangeability of different antibodies for PD-L1 detection; thus, we conducted a subgroup analysis based on PD-L1 expression [40, 41]. First, survival benefits in terms of OS and PFS could be observed in ESCC patients treated with chemoimmunotherapy regardless of the level of PD-L1 expression. Second, compared to patients with PD-L1 TPS <10%, there was a trend for better OS in patients with PD-L1 TPS ≥10%. Third, we did not observe a statistically significant effect of the PFS correlation on PD-L1 TPS or CPS stratification. Currently, there is a lack of consensus on the use of TPS or CPS for PD-L1 expression scoring, although our results suggested that the assessment of PD-L1 via TPS might be more beneficial. Considering that TPS could serve as a predictive indicator but not a trigger marker, there is still a need for standardizing the definition and assessment of PD-L1 expression [42].

Existing evidence has suggested that ESCC should be viewed as a specific disease that is extremely different from EAC clinically and biologically [2, 4]. Recent studies even found that with a high burden of tumor mutation, massive infiltration of inflammatory cells, and increased expression of immunosuppression, ESCC seems to be associated with a favorable tumor microenvironment that could have a good response to ICIs [43]. Therefore, it was necessary to investigate the efficiency and toxicity of first-line chemo-immunotherapy in ESCC which also aligned with the principles of precision medicine. In addition, given the absence of head-to-head comparisons between chemo-immunotherapy, the approach of NMA incorporated both direct and indirect comparisons, providing valuable guidance to clinicians. It is worth mentioning that Bayesian analysis could directly interpret the probability that an intervention produces a survival benefit. Thus, this approach provided more convenience than classical statistical methods, contributing to decision-making in clinical practice [44].

We acknowledge some potential limitations of this NMA. First, the ethnicity of the included studies was predominantly Asian, which might limit the generalizability of our findings to populations with diverse racial distributions. Second, the study (RATIONALE-306) was searched from the ESMO meetings with preliminary results, which presented a source of risk of bias. Third, the relatively low number of included RCTs and participants might limit the power of the subgroup analysis. Additionally, comparisons among the combinations of IO plus chemotherapy followed by obtaining the SUCRA value were indirect. More randomized controlled trials comparing the effectiveness and safety profiles of different combinations of head-to-head are needed.

5. Conclusion

In summary, the NMA analysis favored chemo-immunotherapy combinations over standard chemotherapy for survival benefits. Sinti-chemo seemed to be the most favorable treatment by offering the best balance between

efficacy and safety for previously untreated ESCC patients. Patients with high TPS expression had better OS than patients with low TPS expression. The immunotherapy plus TP regimen was associated with a longer PFS than the immunotherapy plus FP regimen. Our findings fully assessed the efficacy and safety of current phase 3 RCTs for ESCC with the aim of selecting the most appropriate chemo-immunotherapy combination, providing up-to-date results for guiding decisions across various clinical scenarios.

Data Availability

The data supporting the findings of the study could be acquired from the corresponding author.

Ethical Approval

This is a systematic review and meta-analysis. The institutional ethics committee has confirmed that no ethics approval is required.

Consent

Consent was not applicable to this study.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. N. X. and J. Q. conceptualized the study; X. M. and N. X. performed methodology; X. M., M. W., J. Q., and X. C. extracted the data; X. M., J. Q., and N. X. performed data analysis; X. M. and Y. D. wrote the original draft and reviewed and edited the article; N. X. administered the project. All authors have read and agreed to the published version of the manuscript. Xiaolu Ma and Yongfeng Ding contributed equally to the article.

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Supplementary Materials

Supplementary Table 1. PRISMA Checklist. *Supplementary Table 2*. Embase search strategy. *Supplementary Figure 1*. Risk of bias assessment by using the Cochrane Collaboration Tool. *Supplementary Figure 2*. Network construction of eligible treatment comparisons. Abbreviations: camre: camrelizumab; nivo: nivolumab; sinti: sintilimab; tori: toripalimab; tisle: tislelizumab; pembro: pembrolizumab; chemo: chemotherapy. *Supplementary Figure 3(A)*. Subgroup analysis of OS. *(B)* Subgroup analysis of PFS. Abbreviations: PD-L1: programmed cell death ligand 1. CPS: combined positive score; TPS: tumor positive score; FP: fluorouracil + platinum; TP: paclitaxel + platinum; OS: overall survival; PFS: progression-free survival; camre: camrelizumab; nivo: nivolumab; sinti: sintilimab; tori: toripalimab; tisle: tislelizumab; pembro: pembrolizumab; chemo: chemotherapy. *Supplementary Figure 4(A)*. Funnel plot assessing publication bias for OS. *(B)* Funnel plot assessing publication bias for PFS. Abbreviations: OS: overall survival; PFS: progression-free survival. *Supplementary Figure 5*. Sensitivity analysis of PFS. Abbreviations: PFS: progression-free survival; HR: hazard ratio; CI: confidence interval. (*Supplementary Materials*)

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