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ORIGINAL ARTICLE

Severe immune-related adverse events of immune checkpoint inhibitors for advanced non-small cell lung cancer: a network meta-analysis of randomized clinical trials

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Abstract

Objective A complete toxicity profile, toxicity profile, and safety ranking of immune checkpoint inhibitors (ICIs) for treatment of advanced non-small cell lung cancer (NSCLC) will be provided in this network meta-analysis.

Methods We searched 14 randomized clinical trials (RCTs) including 9572 NSCLC patients by PubMed, EMBASE, Cochrane, and ClinicalTrials.gov. Randomized pairwise and network meta-analyses were used to compare the incidence of severe immune-related adverse events (irAEs) across different ICIs-based treatments using risk ratios (RRs) and 95% confidence intervals (CI).

Results For severe dermatologic irAEs, the corresponding ranking of incidences of the nine groups from high to low was: nivolumab + ipilimumab + platinum (79.1%), pembrolizumab (75.2%), nivolumab + ipilimumab (72.9%), camrelizumab + platinum (64.9%), atezolizumab + platinum (47.4%), nivolumab (44.2%), durvalumab (40.5%), pembrolizumab + platinum (15.5%), platinum-based chemotherapy (10.3%). For severe colitis, the corresponding ranking of incidences of the seven groups from high to low was: nivolumab + ipilimumab + platinum (72.4%), nivolumab (63.1%), atezolizumab + platinum (56.9%), durvalumab (56.6%), pembrolizumab (54.9%), pembrolizumab + platinum (38.6%), platinum-based chemotherapy (7.4%). For severe endocrine irAEs, the corresponding ranking of incidences of the nine groups from high to low was: durvalumab (74.3%), atezolizumab + platinum (54.5%), nivolumab + ipilimumab (54.0%), camrelizumab + platinum (51.7%), nivolumab + ipilimumab + platinum (51.6%), pembrolizumab + platinum (49.8%), pembrolizumab (49.2%), nivolumab (46.3%), platinum-based chemotherapy (18.6%). For severe pneumonitis, the corresponding ranking of incidences of the nine groups from high to low was: nivolumab (84.3%), pembrolizumab (84.1%), durvalumab (66.1%), camrelizumab + platinum (61.4%), atezolizumab + platinum (50%), pembrolizumab + platinum (43.4%), platinum-based chemotherapy (16.2%), atezolizumab (6.2%). For severe hepatitis, the corresponding ranking of incidences of the eight groups from high to low was: pembrolizumab (68.8%), nivolumab + ipilimumab + platinum (65%), pembrolizumab + platinum (64.6%), durvalumab (57.9%), nivolumab (47.1%), atezolizumab + platinum (43.4%), camrelizumab + platinum (42%), platinum-based chemotherapy (11.2%).

Conclusions In addition to platinum-based chemotherapy, pembrolizumab + platinum for severe dermatologic irAEs and colitis, nivolumab for severe endocrine irAEs, atezolizumab for severe pneumonitis, camrelizumab + platinum for severe hepatitis may be associated with lower rates of irAEs than other immune-based regimens.

Keywords Severe immune-related adverse events · Non-small cell lung cancer · Network meta-analysis · Immune checkpoint inhibitor · Randomized clinical trial

Abbreviations

95% CI	95% Confidence interval
CTLA4	Cytotoxic T lymphocyte-associated antigen-4
ICI	Immune checkpoint inhibitor
ICIs	Immune checkpoint inhibitors
irAEs	Immune-related adverse events
MCMC	Markov chain Monte Carlo
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
PD-1	Programmed cell death receptor 1
PD-L1	Programmed cell death ligand-1

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PD-L2	Programmed cell death ligand-2
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
RCTs	Randomized clinical trials
RRs	Risk ratios
SUCRA	Surface under the cumulative ranking curve

Introduction

According to World Health Organization, it is estimated that more than 1.8 million people will die of lung cancer worldwide in 2021 [1, 2]. Over the past decade, the treatment paradigm for NSCLC, which accounts for 80–85% of all lung cancers, has changed slightly as biomarkers can be used for targeted therapy [3, 4]. Analysis of data from the US Surveillance, Epidemiology, and End Results (SEER) database shows that mortality based on NSCLC incidence has gone down since 2013, nearly doubling each year [5] which is tentatively consistent with FDA approval of erlotinib as a first-line treatment for patients with epidermal growth factor receptor(EGFR)-mutated NSCLC [6, 7]. However, patients with NSCLC who benefit from targeted therapies are fewer than 25%, and resistance is almost universal during treatment [8]. And for NSCLC patients without target gene mutations, platinum-based chemotherapy with a response rate of only 15.5% remains the standard first-line therapy; however, the high toxicity and poor tolerance of platinum-based chemotherapy limit its wide application in clinical practice [9, 10].

However, in recent years, negative regulators of immune response, namely immune checkpoints, have been detected in a variety of tumors, and ICIs have changed the treatment status of many cancers, especially in NSCLC [11, 12]. ICIs that include anti-programmed cell death receptor 1(PD-1), ligands programmed cell death ligand-1(PD-L1), and T lymphocyte-associated antigen-4(CTLA4) are known to be widely studied in NSCLC. Currently, anti-CTLA-4 antibodies (ipilimumab, tremelimumab), PD-1 (pembrolizumab, nivolumab), and its ligand, PD-L1 (atezolizumab and durvalumab) have been focused on Clinical use. And a series of randomized clinical trials suggest that ICIs alone or in combination with conventional platinum-based chemotherapy as first-line treatment for patients with advanced NSCLC show better clinical benefits and fewer side effects than conventional platinum-based chemotherapy [13–26]. However, CTLA4, PD1, and PD-L1 are key regulators of immune tolerance and they prevent autoimmune responses from occurring in physiological states. Persistent inflammation (specifically interferon-γ) upregulated cell surface expression of these immune checkpoint proteins and can alleviate inflammation (such as autoimmune, tumor inflammation, or tissue damage) in a variety of situations. Thus, ICI-related drugs can lead to antitumor immunity while leading to autoinflammation in other sites, clinically presenting as irAEs [27]. The development of irAEs caused by PD-1 or PD-L1 inhibitors was dose independent, with a prevalence of 27% for all grades and 6% for grade 3 or higher [28]. The overall incidence of irAEs caused by CTLA-4 inhibitors fluctuates according to the dose and is higher at 72% for all grades and 24% for grade 3 or higher [29]. And statistics shows that 8% to 10% among patients with advanced NSCLC receiving ICIs develop severe (grade 3–5) irAEs [30], among which dermatologic irAEs (pruritus and rash), endocrine irAEs (hypothyroidism and hyperthyroidism), colitis, pneumonitis, and hepatitis are common target organs [31]. Grade 3 irAEs indicate that it is severe but not immediately threatening life, grade 4 irAEs indicates that it will threaten life, and grade 5 indicates death-related events [32]. According to the reports [33], death from moderate, severe, or life-threatening irAEs has been reported in 1–2% of patients, such as colitis and pneumonia. Chen et al. [34] showed that seventeen percent of studies over stated the safety of the experimental regimen, and although glucocorticoids and steroids [35] can be used for irAES, some patients still die because of late diagnosis, which emphasize the importance of determining the predictors of irAEs and early management and prevention. If not properly treated, any of these severe IRAE will result in treatment termination, failure, and may even be life threatening. Therefore, it was very important to better grasp the severe irAEs most likely to be caused by each treatment regime, and to prevent, detect, and treat them in time. However, it was controversial for which treatment regime was more likely to induce severe irAEs.

Here, this network meta-analysis aims to compare the incidences of severe irAEs and rank the safety of ICI + chemotherapy, ICI alone, and dual ICIs combination, which will help clinicians improve early prediction, early detection, and early treatment of sever irAEs.

Methods

Data sources and searches

This network meta-analysis (NMA) was completed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) [36, 37] and PRISMA extended guidelines for an NMA. Web of science and Cochrane were used to search RCTs on ICIs versus platinum-based chemotherapy as the first-line treatment of advanced NSCLC from 2015 to 2020. The National Institutes of Health ongoing Trial Registry (Clinicaltrials.gov) was also used to search data which were not explicitly given in the RCTs. And a combination of MeSH and free-text words was completely consistent with the PICOS principle.

Search terms and their combinations used in the search strategy included: (PD-L1 OR PD-1 OR CTLA-4 inhibitor OR pembrolizumab OR nivolumab OR ipilimumab OR atezolizumab OR durvalumab) AND (non-small cell lung cancer OR non-small-cell lung carcinoma) AND chemotherapy AND (randomized controlled trial). A preliminary screening of the searched topics and abstracts was conducted by two independent reviewers (Jingjing Gu and Weidong Zhang), and if the topics and abstracts of one article did not meet the criteria, we will further read the full text, and all references might be evaluated as potentially relevant articles.

Inclusion and exclusion criteria

Inclusion criteria for RCTs of this NMA were as follows: (1) study type: advanced NSCLC with only phase II or III double-blind RCTs; (2) participants: patients that were pathologically diagnosed as advanced NSCLC; (3) experimental group: patients who received immunotherapy alone or an immune-based combination as first-line treatment, control group: patients who received only platinum-based chemotherapy as first-line treatment; (4) outcome indicators: at least one severe irAE in the RCTs or Clinicaltrials.gov.

Exclusion criteria: non-English articles, reviews, studies with invalid data, editorials, meta-analyses, repeat studies, commentary letters.

Data extraction

Two authors screened out the articles that met the predetermined inclusion criteria by reading the titles, abstracts, and full texts, and relative data were collected: (1) trial information, first author, study year, and trial id; (2) study endpoint, stage information, and sample size of treatment; (3) patient characteristics at baseline included median age, sex, and the numbers of patients with severe dermatologic irAEs, colitis, endocrine irAEs, pneumonitis, and hepatitis (grade 3–5). And the extracted data were checked by the two authors before data analysis.

Risk of bias assessment

Two reviewers (Jingjing Gu and Weidong Zhang) evaluated the quality of the literature by using the Cochrane risk bias assessment tool [38] (Fig. 1). Three grades including 'yellow represents unclear risk,' 'green represents low risk', and 'red represents high risk' were assessed by the Cochrane risk bias assessment tool classified seven major sources of biases (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias).

Outcome measures

The study endpoints were grade 3–5 of dermatologic irAEs (pruritus and rash), colitis, endocrine irAEs (hypothyroidism and hyperthyroidism), pneumonitis, and hepatitis. Review criteria fitted the National Cancer Institute Common Terminology Criteria for Adverse Events [39]. The combined RRs and 95% CI were used to assess the probability of associated adverse events for each treatment regimen.

Data synthesis and statistical analysis

The loops to illustrate the network geometry were generated by Stata13.0. In this NMA, summary RRs and 95% confidence intervals were used to assess the effect size of ICI-based drugs on the risk of severe irAEs in NSCLC patients. If RR was greater than 1, which showed a low probability of irAEs in the control group. Random effects and consistency models were established by Markov chain Monte Carlo (MCMC) to calculate the RR and 95% confidence intervals within the Bayesian framework using R (version 4.0.1) (CoreTeam 2019, Vienna, Austria) and JAGS (version 4.3.0) with the package 'getmtc' (version 0.8.2) [40, 41]. I^2 statistics was used to assess heterogeneity of the included studies. I^2 values below 25%, between 25 and 50%, and above 50% respectively represented low, medium, and high heterogeneity [42]. If the study was low heterogeneity, the fixed effects model would be selected, otherwise the random effects model would be selected. For exploring the inter-study heterogeneity of each outcome comparison, the values of different parameters of a log-normal distribution were fitted as a prior distribution [43]. 10,000 burn-ins and 50,000 iterations of 4 each chain and a thinning interval of 10 were generated for each outcome by using MCMC methods for obtaining the posterior distribution. Whether each MCMC chain reached a stable and good iteration during the calculation process was judged through the Brooks–Gelman–Rubin diagnostic plot with a cutoff value of 1. The surface under the cumulative ranking curve (SUCRA) metric was a tool which could rank the probabilities of irAEs of each treatment and identify the best treatment. And the SUCRA value ranged from 0 to 1, the closer to 1 this value approached, the higher its incidence of severe immune-related adverse event was in this network meta-analysis [44]. The publication bias was assessed by funnel plot and symmetrical distribution in funnel plot indicated no publication bias [45]. The stability of the results was considered stable if there was significant consistency between direct and indirect results by sensitivity analysis [46]. The nodal analysis was used to conduct an inconsistency test (that is, the comparison of the differences between direct and indirect comparisons) and $P > 0.05$ indicated that there is no inconsistency [47, 48].

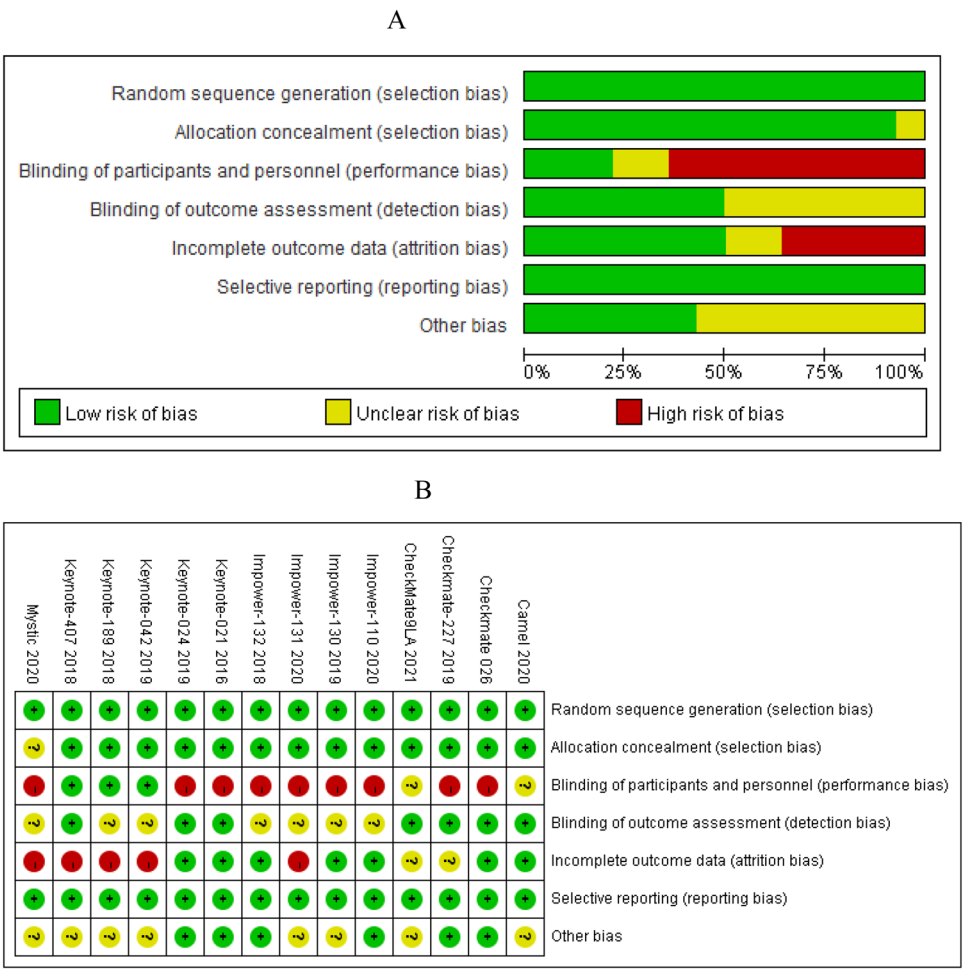

Fig. 1 The Cochrane risk bias assessment tool was used to evaluate bias from seven key sources: 1. random sequence generation; 2. allocation concealment; 3. blindness of subjects and researchers; 4. blindness of outcome evaluation; 5. incomplete data; 6. selective reporting of results; 7. other biases. Green represents low risk, yellow represents unclear risk, and red represents high risk. **A** Risk of bias graph; **B** risk of bias summary

Results

Literature search results and study characteristics

Through the literature search, 551 studies were initially retrieved. After removing 186 duplicate articles, 319 articles that did not meet the requirements were excluded by reading the titles and abstracts, and then, 32 studies were excluded by screening full text. Finally, we included 14 RCTs [13–26] including 9,572 patients with advanced NSCLC were considered eligible for inclusion in this network meta-analysis. Figure 2 shows the literature retrieval strategy. The included RCTs involved 1 phase I/II trial and 13 phase III trials and described ten treatment regimes (pembrolizumab, nivolumab, durvalumab, atezolizumab, pembrolizumab+platinum, atezolizumab+platinum, nivolumab+ipilimumab, camrelizumab+platinum, nivolumab+ipilimumab+platinum, platinum-based chemotherapy). Figure 3 shows the network diagrams of comparisons on all outcomes in this network meta-analysis. The severe dermatologic irAEs (pruritus and rash) involved nine different treatment regimens (pembrolizumab, nivolumab, durvalumab, pembrolizumab+platinum, atezolizumab+platinum, nivolumab+ipilimumab and camrelizumab+platinum, nivolumab+ipilimumab+platinum, platinum-based chemotherapy) in 13 studies [13–22, 24–26] (Figure 3A). The severe colitis involved seven different treatment regimens (pembrolizumab, nivolumab, durvalumab, pembrolizumab+platinum, atezolizumab+platinum, nivolumab+ipilimumab+platinum, and platinum-based chemotherapy) in 11 studies [13–22, 26] (Figure 3B). The severe endocrine irAEs (hypothyroidism and hyperthyroidism) involved nine different treatment regimens (pembrolizumab, nivolumab, durvalumab, pembrolizumab+platinum, atezolizumab+platinum, nivolumab+ipilimumab and camrelizumab+platinum, nivolumab+ipilimumab+platinum, platinum-based chemotherapy) in 13 studies [13–22, 24–26] (Figure 3C). The severe pneumonitis involved nine different treatment regimens (pembrolizumab, nivolumab, durvalumab, atezolizumab, pembrolizumab+platinum, atezolizumab+platinum, camrelizumab+platinum, nivolumab+ipilimumab+platinum, and platinum-based

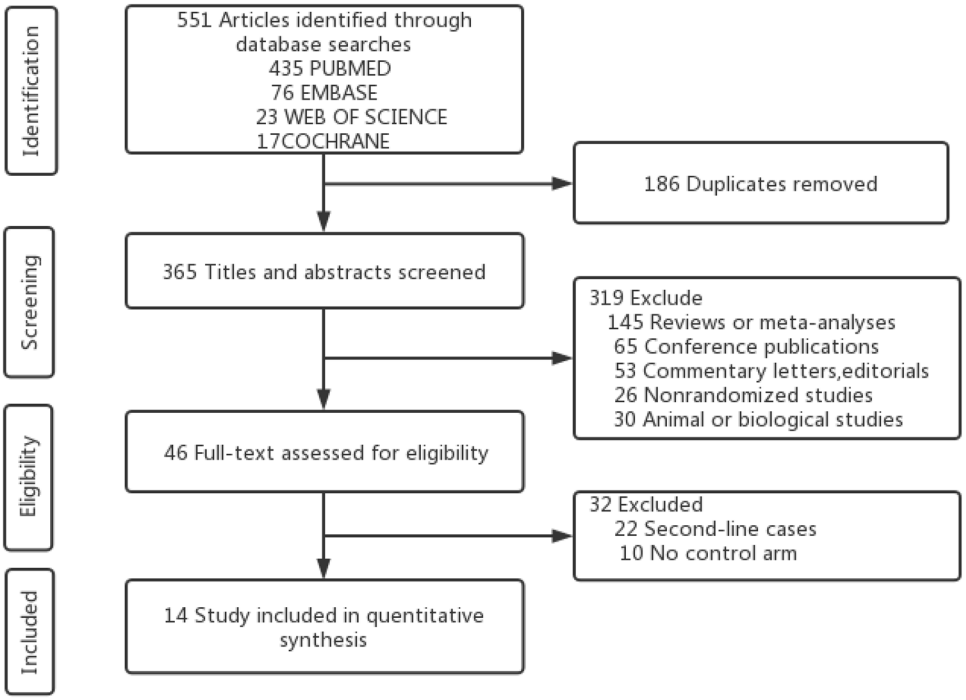

Fig. 2 Flowchart of the systematic search PRISMA flow diagram

chemotherapy) in 13 studies [13–23, 25, 26] (Figure 3D). The severe hepatitis involved eight different treatment regimens (pembrolizumab, nivolumab, durvalumab, atezolizumab, pembrolizumab+platinum, atezolizumab+platinum, camrelizumab+platinum, nivolumab+ipilimumab+platinum, and platinum-based chemotherapy) in 12 studies [13–22, 25, 26] (Figure3E). Key features of all the studies are shown in Tables 1 and 2.

Head-to-head comparisons for the endpoints

In terms of severe dermatologic irAEs, platinum-based chemotherapy had the lowest rate compared to pembrolizumab + platinum (RR, 1.15, 95% CI, 0.44 to 3.01), durvalumab (RR, 2.88, 95% CI, 0.30 to 27.79), nivolumab (RR, 3.80, 95% CI, 0.59 to 24.65), atezolizumab + platinum (RR, 3.82, 95% CI, 0.65 to 22.45), camrelizumab + platinum (RR, 9.27, 95% CI, 0.50 to 173.25), nivolumab + ipilimumab (RR, 10.60, 95% CI, 1.45 to 77.34), pembrolizumab (RR, 12.71, 95% CI, 2.40 to 67.30), and nivolumab + ipilimumab + platinum (RR, 19.00, 95% CI, 1.10 to 327.71) (Fig. 4A). In terms of severe colitis, platinum-based chemotherapy had the lowest rate compared to pembrolizumab + platinum (RR, 2.56, 95% CI, 0.80 to 8.22), pembrolizumab (RR, 4.77, 95% CI, 0.82 to 27.87), durvalumab (RR, 4.80, 95% CI, 0.23 to 100.25), atezolizumab + platinum (RR, 4.82, 95% CI, 0.85 to 27.26), nivolumab (RR, 6.97, 95% CI, 0.36 to 135.67), and nivolumab + ipilimumab + platinum (RR, 10.88, 95% CI, 0.60 to 197.42) (Fig. 4B). For severe endocrine irAEs, platinum-based chemotherapy had the lowest rate compared to nivolumab (RR, 2.41, 95% CI, 0.20 to 28.85), pembrolizumab (RR, 2.66, 95% CI, 0.24 to 29.38), pembrolizumab + platinum (RR, 2.69, 95% CI, 0.41 to 17.78), nivolumab + ipilimumab + platinum (RR, 2.93, 95% CI, 0.12 to 72.24), camrelizumab + platinum (RR, 3.04, 95% CI, 0.12 to 75.16), atezolizumab + platinum (RR, 3.11, 95% CI, 0.51 to18.82), nivolumab + ipilimumab (RR, 3.17, 95% CI, 0.23 to 44.13), and durvalumab (RR, 8.68, 95% CI, 0.47 to 161.81) (Fig. 4C). For severe pneumonitis, atezolizumab had the lowest rate compared to platinum-based chemotherapy (RR, 1.58, 95% CI, 0.59 to 4.20), nivolumab + ipilimumab + platinum (RR, 2.71, 95% CI, 0.56 to 13.14), pembrolizumab + platinum (RR, 3.16, 95% CI, 0.84 to 11.93), atezolizumab + platinum (RR, 3.72, 95% CI, 1.07 to 12.88), camrelizumab + platinum (RR, 6.46, 95% CI, 0.58 to 71.8), durvalumab (RR, 7.60 95% CI, 0.71 to 80.85), pembrolizumab (RR, 15.94, 95% CI, 2.69 to 94.41), and nivolumab (RR, 23.90, 95% CI, 1.15 to 495.17 Fig. 4D). For severe hepatitis, platinum-based chemotherapy had the lowest rate compared to camrelizumab + platinum (RR, 2.56, 95% CI, 0.49 to 13.36), atezolizumab + platinum (RR, 2.63, 95% CI, 0.62 to 11.12), nivolumab (RR, 2.97, 95% CI, 0.12 to 73.14), durvalumab (RR, 4.80, 95% CI, 0.23 to 100.25), pembrolizumab + platinum (RR, 5.68, 95% CI, 1.00 to 32.23), nivolumab + ipilimumab + platinum (RR, 6.88, 95% CI, 0.35 to 133.72), and pembrolizumab (RR, 7.19, 95% CI, 0.85 to 60.91) (Fig. 4E).

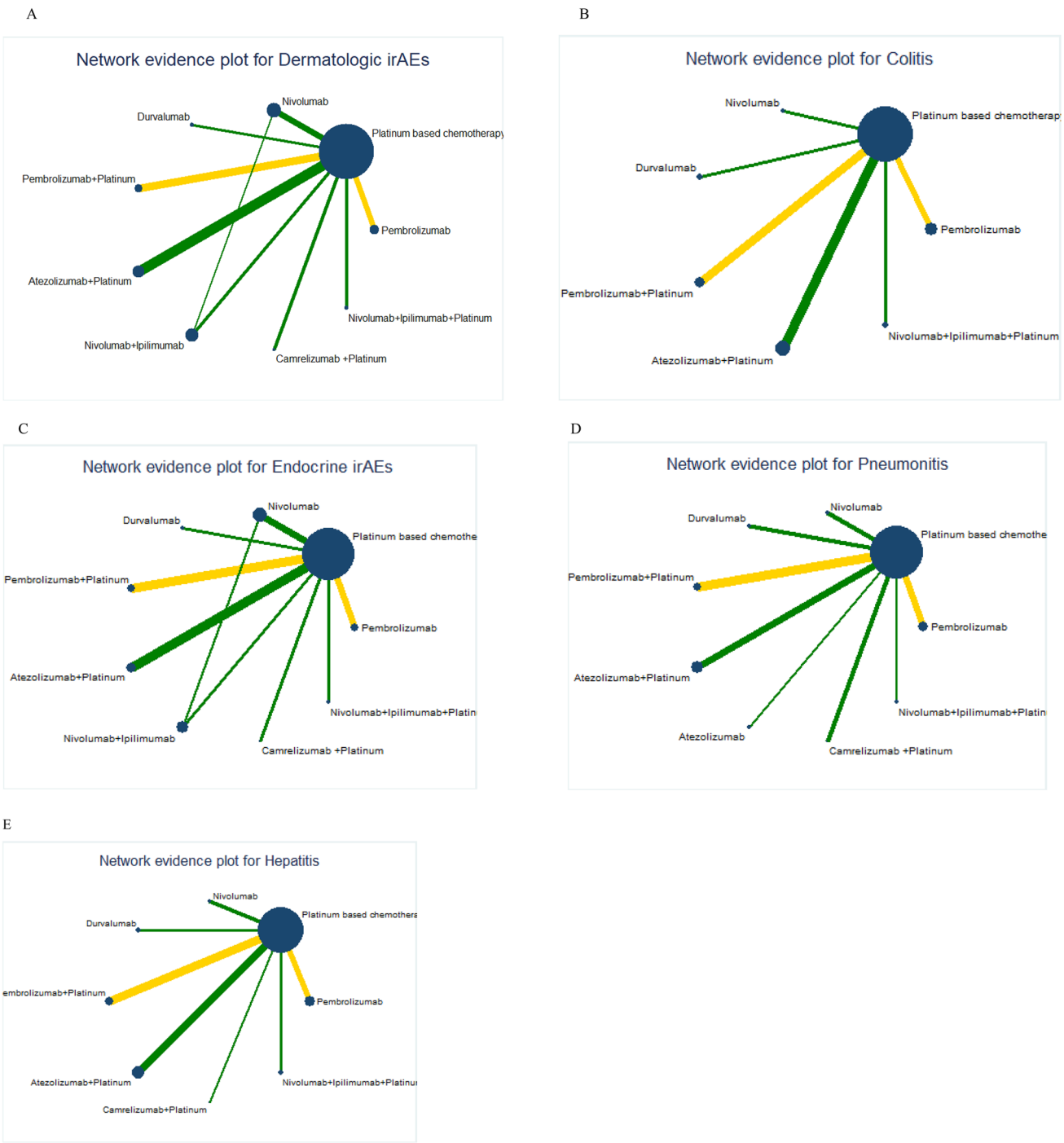

Fig. 3 Network diagrams of comparisons on all outcomes in this network meta-analysis. **A** Comparisons on severe dermatologic irAEs in patients with advanced NSCLC. **B** Comparisons on severe colitis in patients with advanced NSCLC. **C** Comparisons on severe endocrine irAEs in patients with advanced NSCLC. **D** Comparisons on severe pneumonitis in patients with advanced NSCLC. **E** Comparisons on severe hepatitis in patients with advanced NSCLC. (The circles represent treatment regimens and the size of each circle represents the number of participants, while the yellow line represents double-blind RCTs and the green is not blind)

Determining the ranking

The probabilities of immune-related adverse events were ranked for all treatments by estimating the SUCRA value. A higher SUCRA value indicated a higher probability of irAEs and a poorer treatment regimen. For severe dermatologic irAEs, the corresponding ranking of incidences of the nine groups from high to low was:

Table 1 General characteristics of the included randomized control trials for this network meta-analyses

First author, year	Study ID	Region	Trial phase	Trail number	Experimental group	Control group
Carbone 2017	Checkmate 026	MN	III	423	Nivolumab 3 mg/kg	Platinum-based chemotherapy
Naiyer 2020	Mystic	MN	III	721	Durvalumab 20 mg/kg	Platinum-based chemotherapy
Paz-Ares 2018	Keynote-407	USA	III	559	Pembrolizumab 200 mg + platinum-based chemotherapy	Platinum-based chemotherapy
Gandhi 2018	Keynote-189	MN	III	616	Pembrolizumab 200 mg + platinum-based chemotherapy	Platinum-based chemotherapy
Mok 2019	Keynote-042	MN	III	1274	Pembrolizumab 200 mg	Platinum-based chemotherapy
Reck 2019	Keynote-024	MN	III	305	Pembrolizumab 200 mg	Platinum-based chemotherapy
Borghaei 2016	Keynote-021	USA, Taiwan	I/II	123	Pembrolizumab 200 mg + platinum-based chemotherapy	Platinum-based chemotherapy
Rivero 2018	Impower 132	MN	III	578	Atezolizumab 1200 mg + platinum-based chemotherapy	Platinum-based chemotherapy
Robert 2018	Impower 131	MN	III	1021	Atezolizumab 1200 mg + platinum-based chemotherapy	Platinum-based chemotherapy
West 2019	Impower 130	MN	III	724	Atezolizumab 1200 mg + platinum-based chemotherapy	Platinum-based chemotherapy
Spigel 2019	Impower 110	MN	III	572	Atezolizumab 1200 mg	Platinum-based chemotherapy
Hellmann 2018	Checkmate 227	MN	III	1537	Nivolumab 3 mg/kg, Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg	Platinum-based chemotherapy
Caicun Zhou 2020	CameL	China	III	412	Camrelizumab + platinum-based chemotherapy	Platinum-based chemotherapy
Luis Paz-Ares 2021	CheckMate 9LA	MN	III	707	Nivolumab + ipilimumab + platinum-based chemotherapy	Platinum-based chemotherapy

MN multinational, *NA* not applicable

nivolumab + ipilimumab + platinum (79.1%), pembrolizumab (75.2%), nivolumab + ipilimumab (72.9%), camrelizumab + platinum (64.9%), atezolizumab + platinum (47.4%), nivolumab (44.2%), durvalumab (40.5%), pembrolizumab + platinum (15.5%), platinum-based chemotherapy (10.3%) (Fig. 5A, supplementary figure S1A). For severe colitis, the corresponding ranking of incidences of the seven groups from high to low was: nivolumab + ipilimumab + platinum (72.4%), nivolumab (63.1%), atezolizumab + platinum (56.9%), durvalumab (56.6%), pembrolizumab (54.9%), pembrolizumab + platinum (38.6%), platinum-based chemotherapy (7.4%) (Fig. 5B, supplementary figure S1B). For severe endocrine irAEs, the corresponding ranking of incidences of the nine groups from high to low was: durvalumab (74.3%), atezolizumab + platinum (54.5%), nivolumab + ipilimumab (54.0%), camrelizumab + platinum (51.7%), nivolumab + ipilimumab + platinum (51.6%), pembrolizumab + platinum (49.8%), pembrolizumab (49.2%), nivolumab (46.3%), platinum-based chemotherapy (18.6%) (Fig. 5C, supplementary figure S1C). For severe pneumonitis, the corresponding ranking of incidences of the nine groups from high to low was: nivolumab (84.3%), pembrolizumab (84.1%), durvalumab (66.1%), camrelizumab + platinum (61.4%), atezolizumab + platinum (50%), pembrolizumab + platinum (43.4%), platinum-based chemotherapy (16.2%), atezolizumab (6.2%) (Fig. 5D, supplementary figure S1D). For severe hepatitis, the corresponding ranking of incidences of the eight groups from high to low was: pembrolizumab (68.8%), nivolumab + ipilimumab + platinum (65%), pembrolizumab + platinum 64.6%), durvalumab (57.9%), nivolumab (47.1%), atezolizumab + platinum (43.4%), camrelizumab + platinum (42%), platinum-based chemotherapy (11.2%) (Fig. 5E, supplementary Figure S1E).

Table 2 Patient characteristics and extracted data for study endpoints in the included randomized controlled trials

Study ID	Treatment	Trail number	Dermatologic irAEs (pruritus and rash)	Colitis	Endocrine irAEs (hypothyroidism and hyperthyroidism)	Pneumonitis	Hepatitis
Checkmate 026	Nivolumab 3 mg/kg	267	2	3	0	7	1
	Platinum-based chemotherapy	263	1	0	0	0	0
Mystic	Durvalumab 20 mg/kg	369	3	2	4	5	2
	Platinum-based chemotherapy	352	1	0	0	1	0
Keynote-407	Pembrolizumab 200 mg + platinum-based chemotherapy	278	3	6	2	7	5
	Platinum-based chemotherapy	280	1	3	0	2	0
Keynote-189	Pembrolizumab 200 mg + platinum-based chemotherapy	405	8	3	2	11	4
	Platinum-based chemotherapy	202	4	0	0	4	0
Keynote-042	Pembrolizumab 200 mg	636	11	4	2	22	7
	Platinum-based chemotherapy	615	1	1	0	1	0
Keynote-024	Pembrolizumab 200 mg	154	8	3	0	4	1
	Platinum-based chemotherapy	150	0	0	0	1	0
Keynote-021	Pembrolizumab 200 mg + platinum-based chemotherapy	59	1	2	0	1	1
	Platinum-based chemotherapy	62	0	0	0	0	0
Impower 132	Atezolizumab 1200 mg + platinum-based chemotherapy	291	3	2	1	9	3
	Platinum-based chemotherapy	274	0	0	0	4	1
Impower 131	Atezolizumab 1200 mg + platinum-based chemotherapy	334	2	4	1	10	2
	Platinum-based chemotherapy	334	0	0	0	2	1
Impower 130	Atezolizumab 1200 mg + platinum-based chemotherapy	473	1	2	3	9	3
	Platinum-based chemotherapy	232	0	0	0	3	0
Impower 110	Atezolizumab 1200 mg	286	NA	NA	NA	7	NA
	Platinum-based chemotherapy	263	NA	NA	NA	10	NA
Checkmate 227	Nivolumab 3 mg/kg	576	73	NA	NA	NA	NA
	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg	391	117	NA	NA	NA	NA
	Platinum-based chemotherapy	570	34	NA	NA	NA	NA
Camel	Camrelizumab + platinum-based chemotherapy	205	4	NA	1	4	5

Table 2 (continued)

Study ID	Treatment	Trail number	Dermatologic irAEs (pruritus and rash)	Colitis	Endocrine irAEs (hypothyroidism and hyperthyroidism)	Pneumonitis	Hepatitis
	Platinum-based chemotherapy	207	0	NA	0	1	2
CheckMate9LA	Nivolumab + Ipilimumab + platinum-based chemotherapy	358	9	5	1	7	3
	Platinum-based chemotherapy	349	0	0	0	4	0

irAE immune-related adverse event, *MN* multinational, *NA* not applicable

Model convergence, heterogeneity, and publication bias

All comparisons of different severe irAEs in supplementary figure S2 all suggested that the contraction factor in Brooks–Gelman–Rubin diagnostic plots was equal to the predefined cutoff value 1, which indicated that the study model had good convergence. Low, medium, or high heterogeneity of the comparisons was showed in this network meta-analysis (supplementary Figure S3), and then, the random effects model was selected. The funnel plots in Fig. 6 indicated no publication bias.

Risk of bias assessment and sensitivity analysis

As shown in Fig. 1, 9 included RCTs [13, 14, 18–24] had high risk on blinding of participants and personnel and 5 included RCTs [14–17, 21] had high risk on incomplete outcome data. Other domains indicated unclear risk or low risk. The inconsistency test conducted that P values > 0.05 indicated that all comparisons showed significant consistency between direct and indirect results, and then, the sensitivity analysis indicated stable results (supplementary Figure S4A-E).

Discussion

ICIs included PD-1/PD-L1 inhibitors and anti-CTLA-4. PD-1 is a type I transmembrane glycoprotein expressed in T cells, B cells, and natural killer cells, and plays a role in regulating central and peripheral immune tolerance [49]. Both specific PD-L1 and programmed cell death ligand-2 (PD-L2) on the surface of antigen presenting cells can bind to and interact with it. PD-1 can be activated by tumor cells, therefore promoted the binding of PD-1 with PD-L1 and PD-L2 thus inhibiting the proliferation of effector T cells and preventing T cells from recognizing tumor cells, which resulting in the failure of tumor cells to be killed in time, thus enabling tumor cells to evade the pursuit of immune cells and establishing a microenvironment that permitted tumor growth. CTLA-4 is a leukocyte differentiation antigen and a transmembrane receptor on T cells. It shares the B7 molecular ligand with CD28, while CTLA-4 induces T cells to be in reactive after binding to B7 molecule, and participates in the negative regulation of immune response. Tumor cells complete immune escape by immune checkpoint; however, PD-1/PD-L1 inhibitors, by inhibiting the expression of PD-1/PD-L1, promote the activation and proliferation of T cells, thus killing tumor cells and CTLA-4 inhibitors can allow T cells to proliferate and attack tumor cells by inhibiting the molecule CTLA-4 [12]. Therefore, ICIs increased clinical benefit for NSCLC patients. However, with the extensive clinical application of ICIs, irAEs represented an entirely new toxicity spectrum which could affect any tissue or organ and the severe irAEs showed a tendency to be more prevalent in ICIs than in chemotherapy. Studies had shown that drug type, tumor type, irAE history, and other immune-related history all had a certain influence on the incidence and severity of irAE [50], and different ICIs had different immune mechanisms, and even belonging to the same mechanism had different tolerability to different irAEs. Thus, immune-combined chemotherapy or dual immune-combined therapy has become the focus of various clinical trials to improve the survival time or reduce irAEs. And these RCTs suggested that ICI + chemotherapy, ICI alone, or dual ICIs obviously improved the survival time and living quality of patients with NSCLC, because of which, ICIs including nivolumab [51], pembrolizumab [52], and atezolizumab [53] were approved for NSCLC by FDA and had become an important part of treatment options in advanced NSCLC [54]. However which treatment regime could be better tolerated was worth studying for us to help clinicians better prevent and manage severe irAE.

Here, we ranked the probability of severe irAEs caused by ICI + platinum, ICI alone, and dual ICIs combination in advanced NSCLC through NMA. The irAEs data were extracted from published studies and Clinicaltrials.

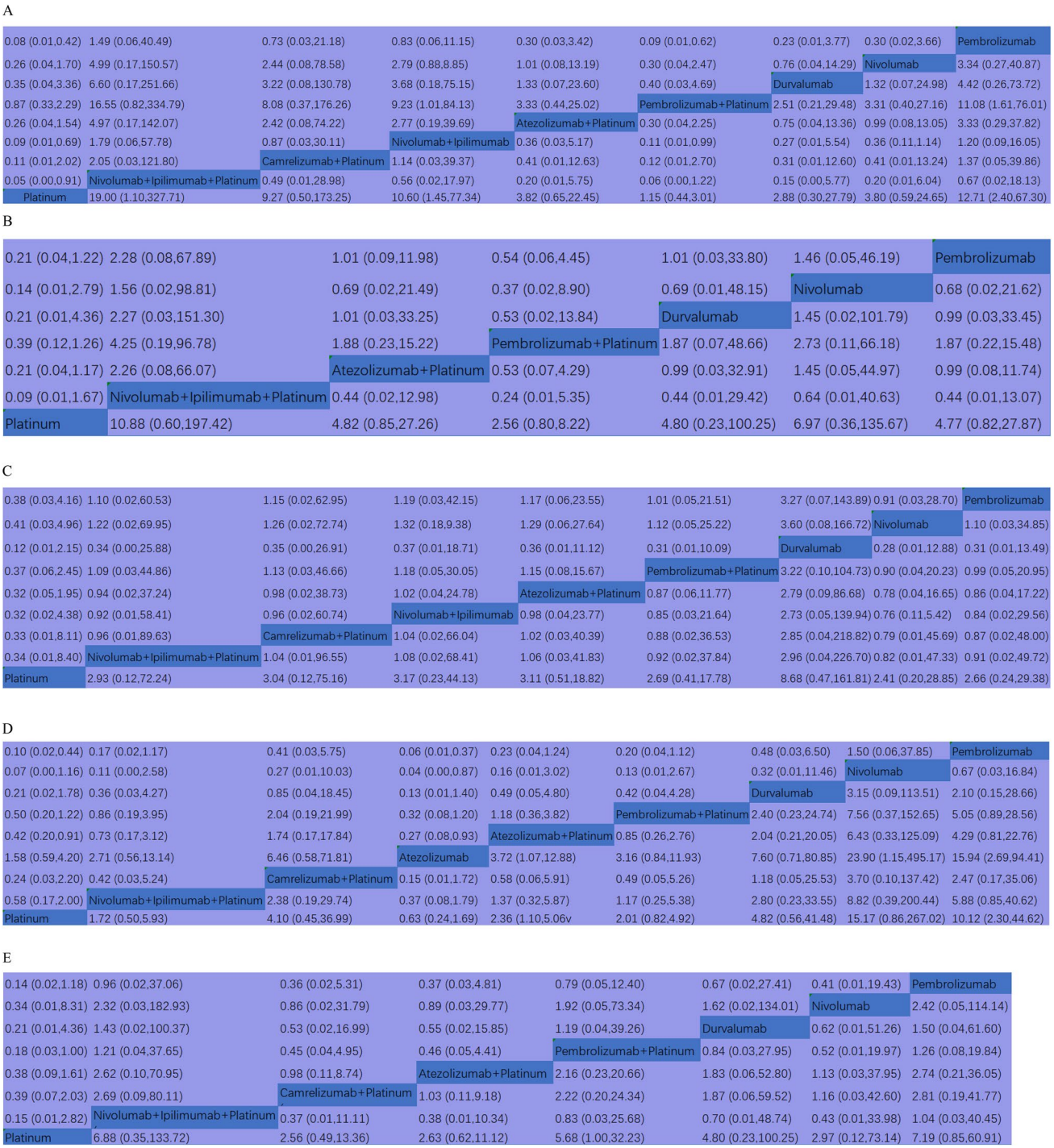

Fig. 4 Pooled estimates of the network meta-analysis. **A** Multiple treatment comparison for severe dermatologic irAEs based on network consistency. **B** Multiple treatment comparison for severe colitis based on network consistency model. **C** Multiple treatment comparison for severe endocrine irAEs based on network consistency model. **D** Multiple treatment comparison for severe pneumonitis based on network consistency model. **E** Multiple treatment comparison for severe hepatitis based on network consistency model. (OR > 1 means the treatment in top left is worse; Platinum = platinum-based chemotherapy)

gov in five years. Finally, we included 14 phase II or III randomized clinical trials (RCTs) including 9572 patients with NSCLC in this network meta-analysis. And this NMA concluded that ICI-based therapy showed a higher incidence of irAEs than platinum-based chemotherapy for severe dermatologic irAEs, colitis, endocrine irAEs, and hepatitis,

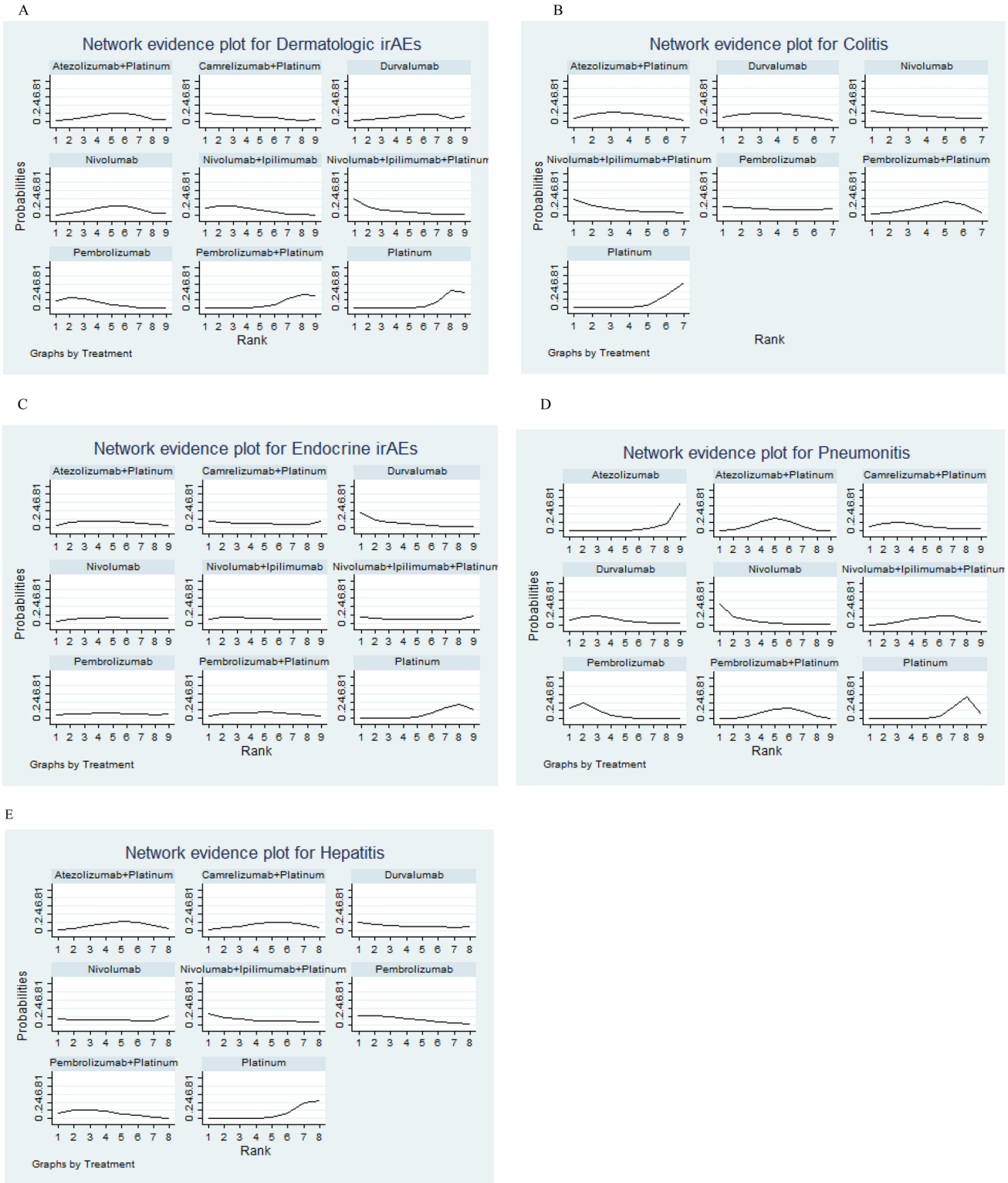

Fig. 5 Sequence diagram of the network meta-analysis. **A** Multiple treatment comparison for severe dermatologic irAEs based on SUCRA. **B** Multiple treatment comparison for severe colitis based on SUCRA. **C** Multiple treatment comparison for severe endocrine irAEs based on SUCRA. **D** Multiple treatment comparison for severe pneumonitis based on SUCRA. **E** Multiple treatment comparison for severe hepatitis based on SUCRA. (Platinum = platinum-based chemotherapy)

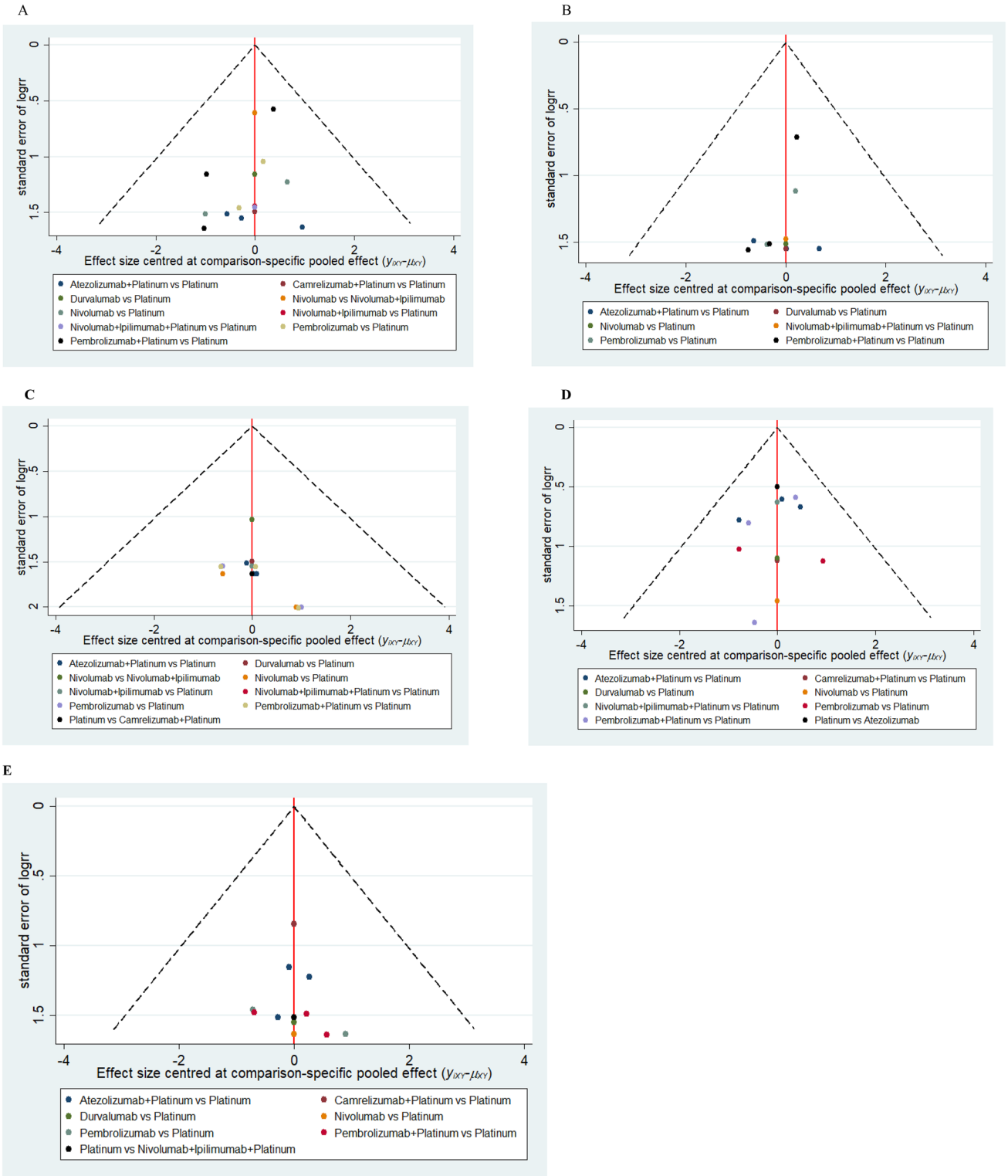

Fig. 6 Funnel plot of **A** severe dermatologic irAEs, **B** severe colitis, **C** severe endocrine irAEs, **D** severe pneumonitis and **E** severe hepatitis in the network meta-analysis (Platinum = platinum-based chemotherapy)

which was consistent with that of Jordi Remon et al. [30]. Pembrolizumab + platinum showed a higher incidence of irAEs than pembrolizumab for dermatologic irAEs, colitis, pneumonitis, and hepatitis, and Slater et al. [55] has the same conclusion; they also concluded that chemotherapy would reduce the probability of severe irAEs might be

related to immunosuppression caused by chemotherapy. We found that only the study of severe dermatologic and endocrine irAEs involved nivolumab + ipilimumab, and interestingly, nivolumab + ipilimumab showed a higher incidence of severe dermatologic and endocrine irAEs than nivolumab; thus, we could see that the combination of the dual ICIs led to more irAEs which could be related to the fact that dual ICIs would increase the imbalance of immune cells, which was consistent with the conclusion of Meichen Li et al. [56] And we found something new that in addition to platinum-based chemotherapy, pembrolizumab + platinum for severe dermatologic irAEs and colitis, nivolumab for severe endocrine irAEs, atezolizumab for severe pneumonitis, and camrelizumab + platinum for severe hepatitis had the least incidence of irAEs, which were different from the conclusion of Cheng Xu et al. [57] and Yafang Huang et al. [58]. Cheng Xu et al. [57] reported all-grade irAEs incidences with ICI monotherapy, ICI monotherapy plus chemotherapy, and chemotherapy for all cancers, and they concluded that atezolizumab had the best overall safety, while the nivolumab showed the best overall safety in the treatment of all types of lung cancer with a combined approach. Yafang Huang et al. [58] investigated PD-1/PD-L1 inhibitors alone and PD-1/PD-L1 inhibitors plus chemotherapy for irAEs, and in the subgroup analyses of NSCLC, they concluded that median ranks on immune-related safety from high to low were: chemotherapy, anti-PD-1 plus chemotherapy, anti-PD-1. However, the reason why our results were different from theirs might be: firstly, compared to their studies, the patients only with advanced NSCLC were included in this NMA, which will reduce some of the confounding factors associated with different tumor types, and all the data of our study were up to date. Secondly, chemotherapy regimen included in the study was platinum-based chemotherapy, and those involving docetaxel or others were excluded. Thirdly, each of the treatment drugs was analyzed individually in our study rather than integrating different drugs with similar mechanisms into the same group.

The current analysis has several strengths. Firstly, to our knowledge, this NMA was the first to analyze the probability of severe irAEs of different treatment regimens for advanced NSCLC and would provide more meaningful data to clinicians. Secondly, some conclusions we concluded were innovative compared to previous studies, which was novel for guiding clinical treatment and subsequent studies. Thirdly, all of the articles included in this NMA were RCTs that were ensured their inherent authenticity by assessing the potential risk of bias in various aspects of RCT design, implementation, and outcome evaluation, and we used Cochrane risk bias assessment tool to examine the quality of included articles. Fourthly, heterogeneity test was used to detect the heterogeneity of the included literature and data in this NMA and funnel plots were used to detect publication bias, and the results indicated that significant publication bias was not found. Fifthly, sensitivity analysis: inconsistency test was used to investigate inconsistencies between direct and indirect comparisons, and the results all suggested that $P > 0.05$, indicating that the results are stable. All of these suggested that our study was quite reliable.

Nonetheless, our article had a few unavoidable limitations. Firstly, due to some delayed irAEs, clinicians were unable to observe the symptoms of patients within the clinical time range, resulting in the loss of clinical data, which may bring some potential heterogeneity to the study. Secondly, although the rating systems and terminology used in the report were consistent and compatible, the diagnosis of each irAE varies depending on the experience of each clinician, which might lead to bias in irAE assessment. Thirdly, different median follow-up times for each randomized controlled trial would likely increase or decrease the frequency of immunotherapy-related IRAE and increase confounders for these events. Fourthly, although we included the latest RCT data that could be retrieved and met the inclusion requirements, the sample size of the study was still limited, which may lead to potential publication bias.

Li Zhong et al. [59] suggested that irAEs are closely related to the survival of cancer patients. Although our study has some limitations, prospects for the prediction and treatment of irAEs are still needed. Currently, some studies have shown that peripheral blood eosinophils are associated with irAEs [60]. And some studies have suggested that the IL-17 cycle [61], the expression of CD177 and CEACAM1 [62], and neutrophils [62] play an important role in the progression of gastrointestinal toxicity. However, there are few studies on the pathogenesis and predictors of other irAEs, and the evaluation system of irAEs needs to be further improved. In the future, more effective irAEs predictors are still needed in clinical management and treatment.

Conclusions

This systematic review and NMA suggests that, in addition to platinum-based chemotherapy, pembrolizumab + platinum for severe dermatologic irAEs and colitis, nivolumab for severe endocrine irAEs, atezolizumab for severe pneumonitis, and camrelizumab + platinum for severe hepatitis may be associated with lower rates of irAEs than other immune-based regimens. Nivolumab + ipilimumab + platinum for severe dermatologic and colitis, durvalumab for severe endocrine irAEs, nivolumab for severe pneumonitis, and pembrolizumab for severe hepatitis may be associated with higher rates of irAEs. These conclusions will be helpful for clinical management, early prediction, early detection, and early treatment. However, more studies are still needed to focus on finding markers of immune-related

adverse events, so as to reduce the incidence of irAEs and increase the therapeutic effect of ICIs, so as to maximize the benefits of patients.

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Availability of data and material The data of this paper came from articles of various large RCTs and Clinical Trails.gov. I'm ready to provide the data if needed.

Code availability Stata13.0, R (version 4.0.1) (CoreTeam 2019, Vienna, Austria) and JAGS (version 4.3.0).

Declarations

Conflict of interest We declare that we have no financial or personal relationships with other people or organizations that could inappropriately influence our work; there is no professional or other personal interest of any nature or kind in any product, service, or company.

Consent for publication All the authors agreed to publish.

Ethical standards This network meta-analysis is a data reintegration based on the original data, which does not involve ethics.

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