Systematic Review and Meta-Analysis

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The overall safety evaluation of programmed cell death/programmed cell death ligand 1 (PD-1/PD-L1) treatment for lung cancer patients

An updated systematic review and meta-analysis

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Abstract

Background: We performed the meta-analysis to evaluate the overall safety of programmed cell death-1 (PD-1) or ligand 1 (PD-L1) inhibitor treatment for lung cancer patients.

Method: Randomized controlled trials were collected according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Risk ratio (RR) of PD-1/PD-L1 inhibitor treatment-related death, treatment-related adverse events, any serious events, and any events leading to discontinuation were all taken into account for the final evaluation.

Results: Fourteen studies were collected for the meta-analysis. The RR of treatment-related death for PD-1/PD-L1 was significantly lower than that of the control group (RR = 0.37, 95% confidence interval, CI: [0.21, 0.66]). Similar analysis results could also be seen for the RR of treatment-related adverse events and adverse events leading to discontinuation. When PD-1/PD-L1 was combined with chemotherapy, it increased the RR of adverse events leading to discontinuation (RR = 1.68, 95% CI: [1.22, 3.32]). The RR of overall treatment-related adverse events was lower in nivolumab (PD-1) than that of the control group (nivolumab + ipilimumab) (RR = 0.77, 95% CI: [0.65, 0.90]). Similar analysis results could also be seen in the RR of treatment-related adverse events for grade 3 to 5 and adverse events leading to discontinuation.

Conclusion: Compared with chemotherapy, RR of the treatment-related deaths associated with PD-1/PD-L1 inhibitor was significantly lower than that of the chemotherapy group, while it did not increase the RR when they were combined with chemotherapy or other drugs. When PD-1/PD-L1 was combined with chemotherapy, it increased the RR of adverse events leading to discontinuation.

Abbreviations: CI = confidence interval, NSCLC = non-small cell lung cancer, PD-1 = programmed cell death-1, PD-L1 = programmed cell death ligand 1, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RR = risk ratio, SCLC = small cell cancer.

Keywords: lung cancer, meta-analysis, programmed cell death-1/programmed cell death ligand 1, safety

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HS, ZZ, AF and XY contributed equally to this work.

This study belongs to the type of data analysis and rearrangement, and does not involve human or animal related ethical issues.

The authors have no conflicts of interest to disclose.

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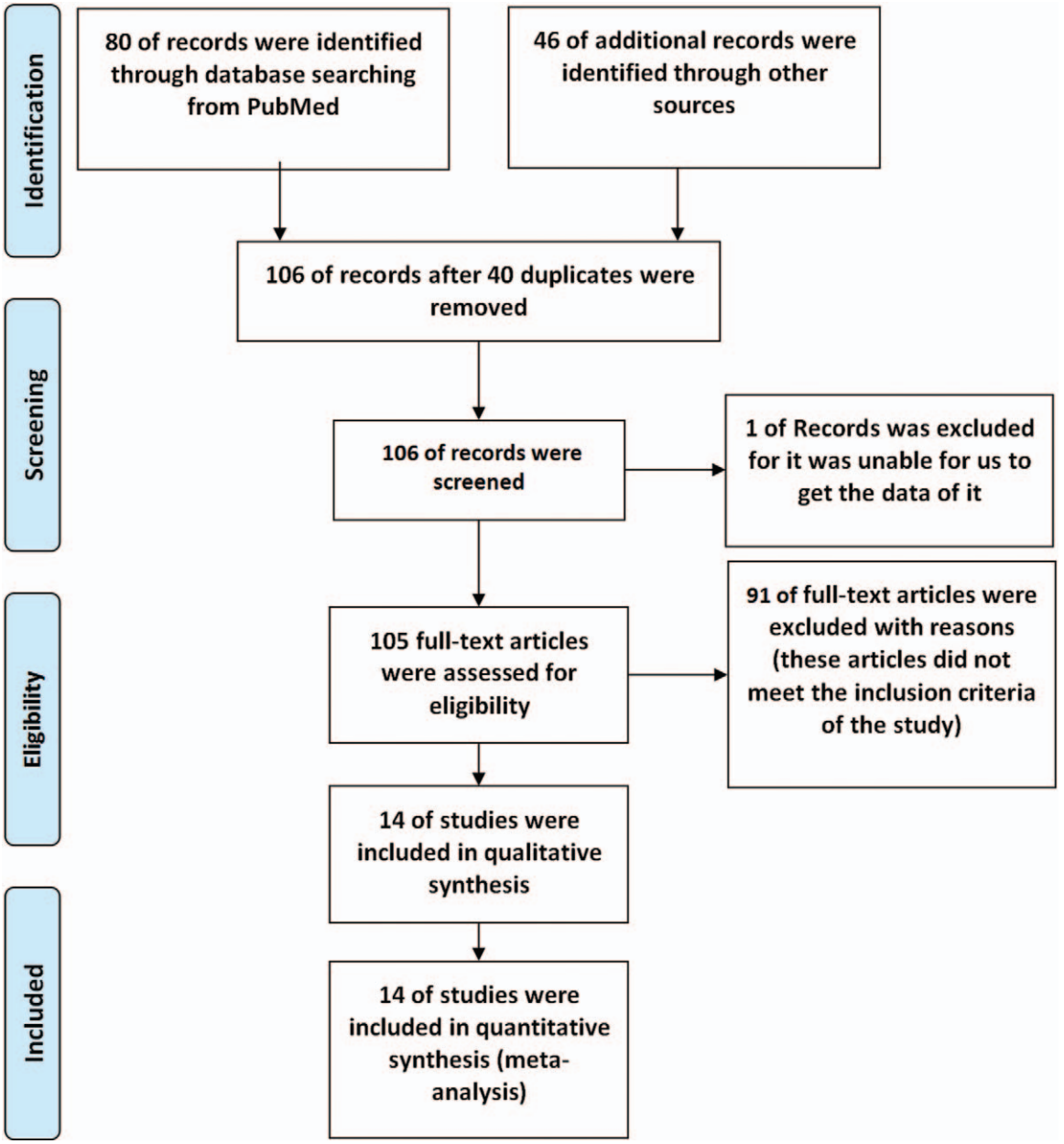

Figure 1. Study flow diagram of inclusion.

1. Introduction

In recent years, more and more clinical trial results showed that programmed cell death-1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors had satisfactory clinical efficacy for lung cancer patients, especially for non-small cell lung cancer (NSCLC), whether it was monotherapy or combined with chemotherapy.[1–14] The expression of PD-L1 is common in NSCLC patients, and the interaction of PD-1 with PD-L1 and PD-L2 ligands inhibits T-cell activation and promotes tumor immune escape.[15,16] The toxic effects associated with PD-1/PD-L1 inhibitors may affect any organ and result from the activation of autoreactive T cells, thereby damage the host tissue and even jeopardize the patient's life.[1–14] So, it was necessary for more and more clinicians to pay their attentions to the drug toxicities caused by PD-1/PD-L1, especially for life-threatening side effects.

In recent years, a large number of meta-analysis on PD-1/PD-L1 safety and toxic side effects have been published.[17–22] Due to the fact that there were too few incorporation data or insufficient subgroup analysis in the previous meta, the conclusions obtained were not accurate enough. As the completion of 6 large clinical trials of PD-1/PD-L1 related to lung cancer in 2018,[1–6] we believed that we could get a new and more accurate conclusion of the PD-1/PD-L1 safety assessment. So, we designed the meta-analysis to evaluate the overall safety of PD-1 or PD-L1 inhibitor treatment for lung cancer patients.

2. Methods

This systematic review and meta-analysis was put into practice according to the Preferred Reporting Items

for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[23]

2.1. Types of enrolled studies

In order to meet the preliminary inclusion criteria, the study must report randomized clinical trials or observational studies to investigate the efficacy and side effects of PD-1/PD-L1 monotherapy or combination therapy for lung cancer patients. The reported results of the included studies must include at least 1 of the following information: treatment-related death, treatment-related adverse events, any serious events, or any events leading to discontinuation. Review articles, commentaries, editorials, protocols, case series, or case reports would be firstly excluded from the inclusion criteria. If the enrolled study met the above requirements, but the control group was a placebo rather than an antitumor drug, the study would also be excluded from the final comprehensive analysis.

2.2. Search strategy

Original articles, related to results of prospective clinical trials of PD1/PD-L1 inhibitor regimens for lung cancer patients, were verified by a PubMed search. The date was defined from January 22, 2013 to February 28, 2019. Key words were displayed just as the followings: "lung cancer," "NSCLC," "SCLC," "non-small cell lung cancer," "small cell lung cancer," "PD1/PD-L1," "nivolumab," "BMS-963558," "pembrolizumab," "MK-3475," "atezolizumab," "MPDL3280A," "Avelumab," "Durvalumab," "safety," and "toxicity". Studies were limited in human beings, shown in full text, abstract, or poster form. Four members of our team (Z.Z., S.Z., Y.Z., and Q.Z.) were appointed to identify their eligibility independently. References from review articles, editorials, and included studies were reviewed and cross-referenced to check completeness. If no useful information was collected, we would try to get in touch with the corresponding author for more information, or the study would be precluded from the final meta-analysis. The characteristics of enrolled studies, including first author, year of publication, journal of article publication, drug name, treatment regimen, study design, phase, number of patients, number of PD-1/PD-L1-related death, and baseline demographic characteristics were collected and would be displayed in a table.

2.3. Assessment of study quality and publication bias

Risk of bias was evaluated by the Cochrane Collaboration tool for assessing risk of bias in randomized trials.[24] The publication bias was evaluated by Funnel plot and Egger's test.[25,26] Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting would be assessed by 4 members of our team independently and shown in a figure together. Finally, the corresponding author of the article would combine all the results to make the final decision.

2.4. Outcome and exposure of interest

The primary data was incidence rate of PD-1/PD-L1 treatment-related death. Incidence of PD-1/PD-L1 inhibitor treatment-related adverse events, any serious events, any events leading to discontinuation were also taken into account for comprehensive evaluation.

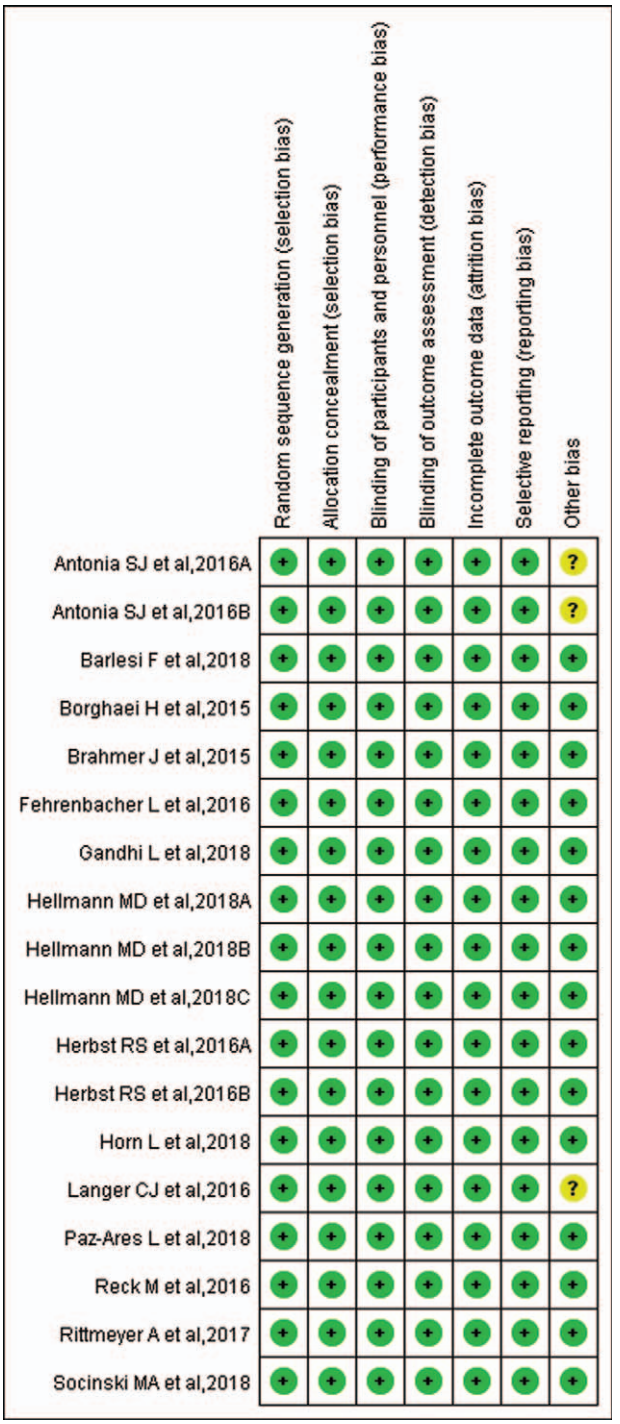

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

2.5. Assessment of heterogeneity and statistical analysis

Newcastle–Ottawa[27] scale, proposed by the Cochrane Collaboration, was used to evaluate the quality of study. Cochrane's Q statistic and the I^2 statistic were used for accessing the heterogeneity among studies just as proposed by Higgins et al,[28] while Harbord test was taken to check publication bias for all enrolled studies. Heterogeneity was considered low, moderate or high for I^2 values $<25\%$, 25% to 50%, and

Table 1

Basic characteristics of the included studies.

No.	References	Drug name	PD-1 or PD-L1	Treatment regimen	Number of evaluable patients	Treatment-related death	Previous therapy	Phase	Randomized controlled trial	Tumor stage	Tumor Type
1	[1]	Atezolizumab	PD-L1	Atezolizumab + carboplatin + etoposide vs. placebo + carboplatin + etoposide	394	6	No	III	Yes	Extensive	SCLC
2	[2]	Avelumab	PD-L1	Avelumab vs. docetaxel	758	18	Yes	III	Yes	IIIB/IV or recurrent	NSCLC
3	[3]	Atezolizumab	PD-L1	Atezolizumab + bevacizumab + carboplatin + paclitaxel vs. bevacizumab + carboplatin + paclitaxel	787	20	No	III	Yes	Metastatic	Non-squamous NSCLC
4	[4]	Nivolumab	PD-1	Nivolumab vs. nivolumab + ipilimumab	299	15	No	III	Yes	IV or recurrent	NSCLC
	[4]	Nivolumab	PD-1	Nivolumab vs. chemotherapy							
	[4]	Ipilimumab	CTLA-4	Nivolumab + ipilimumab vs. chemotherapy							
5	[5]	Pembrolizumab	PD-1	Pembrolizumab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel	558	41	No	III	Yes	Metastatic	Squamous NSCLC
6	[6]	Pembrolizumab	PD-1	Pembrolizumab + pemetrexed + a platinum based drug vs. placebo + pemetrexed + a platinum based drug	607	39	NO	III	Yes	Metastatic	Non-squamous NSCLC
7	[7]	Atezolizumab	PD-L1	Atezolizumab vs. docetaxel	1187	1	Yes	III	Yes	IIIB/IV	Squamous or non-squamous NSCLC
8	[8]	Atezolizumab	PD-L1	Atezolizumab vs. docetaxel	277	4	Yes	II	Yes	Advanced or metastatic	NSCLC
9	[9]	Pembrolizumab	PD-1	Pembrolizumab vs. chemotherapy*	304	4	No	III	Yes	Advanced	NSCLC
10	[10]	Pembrolizumab	PD-1	Pembrolizumab + pemetrexed + a platinum based drug vs. placebo + pemetrexed + a platinum based drug	123	3	No	II	Yes	IIIB/IV	Non-squamous NSCLC
11	[11]	Pembrolizumab	PD-1	Pembrolizumab (2 mg/kg) vs. docetaxel	991	11	Yes	II/III	Yes	Advanced	NSCLC
	[11]	Pembrolizumab	PD-1	Pembrolizumab (10 mg/kg) vs. docetaxel							
12	[12]	Nivolumab	PD-1	Nivolumab vs. nivolumab (1 mg/kg) + ipilimumab (3 mg/kg)	213	2	Yes	I/II	N/A	Limited or extensive	SCLC
	[12]			Nivolumab vs. nivolumab (3 mg/kg) + ipilimumab (1 mg/kg)							
13	[13]	Nivolumab	PD-1	Nivolumab vs. docetaxel	272	3	Yes	III	Yes	Advanced	Squamous NSCLC
14	[14]	Nivolumab	PD-1	Nivolumab vs. docetaxel	582	5	Yes	III	Yes	Advanced	Non-squamous NSCLC

CP = carboplatin plus paclitaxel, NA = No Available, NSCLC = non-small cell lung cancer, PC = pemetrexed and a platinum-based drug, PD-1 = programmed cell death 1, PD-L1 = programmed cell death ligand 1, SCLC = small cell lung cancer.

* Chemotherapy = carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel.

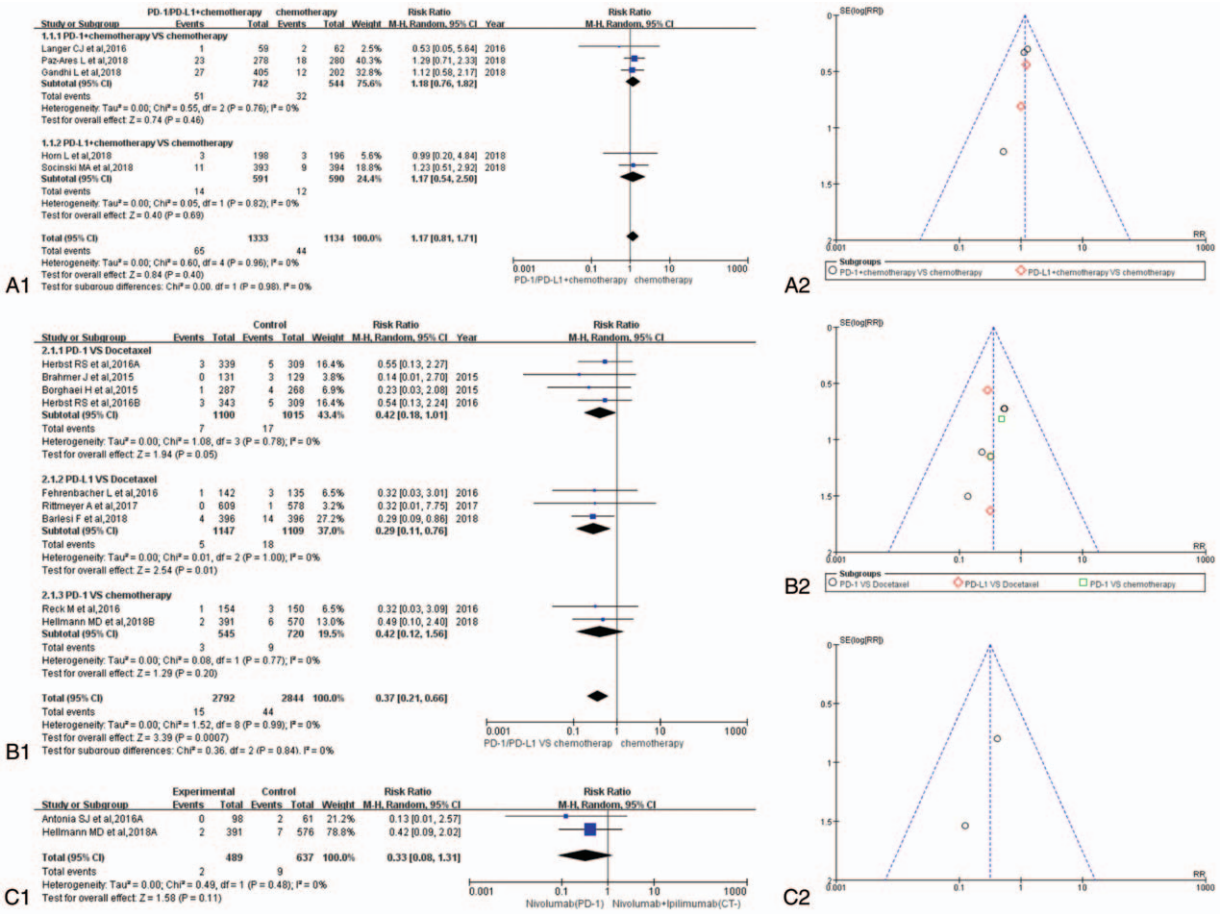

Figure 3. Forest plots and funnel plots for the risk ratio of overall treatment-related adverse events. (A1) Forest plots for the risk ratio of overall treatment-related adverse events (PD-1/PD-L1 + chemotherapy vs. chemotherapy). (A2) Funnel plots for the risk ratio of overall treatment-related adverse events (PD-1/PD-L1 + chemotherapy vs. chemotherapy). (B1) Forest plots for the risk ratio of overall treatment-related adverse events (PD-1/PD-L1 vs. chemotherapy). (B2) Funnel plots for the risk ratio of overall treatment-related adverse events (PD-1/PD-L1 vs. chemotherapy). (C1) Forest plots for the risk ratio of overall treatment-related adverse events (nivolumab vs. nivolumab + ipilimumab). (C2) Funnel plots for the risk ratio of overall treatment-related adverse events (nivolumab vs. nivolumab + ipilimumab). PD-1 = programmed cell death 1, PD-L1 = programmed cell death ligand 1.

>50%, respectively. Risk ratio (RR), and 95% confidence interval (CI) would be calculated by random effect for the heterogeneity inherent in the data.[29] $P < .05$ was considered to be statistically significant for all the results of meta-analysis. Statistical tests were all two-sided. Meta-analysis was performed by Review Manager (version 5.3, Nordic Cochrane Center: Copenhagen, Denmark). We divided all the data into subgroup by drug type (PD-1 or PD-L1 inhibitor) and treatment regimens. We performed a number of subgroup analysis to assess the potential association between PD-1/PD-L1 inhibitor and chemotherapy in overall safety evaluation.

3. Results

3.1. Literature search results

After preliminary literature reading and screening, a total of 126 articles were deemed to meet our preliminary screening criteria. We read and reviewed the abstracts of the documents and found that 14 of them met our final inclusion criteria and were taken to be in the meta-analysis.[1–14] The flow diagram of the meta-analysis is displayed in Figure 1, while the risk of bias summary is shown in Figure 2. All the included studies had a control group.

3.2. Characteristics of identified trials

The basic characteristics of 14 enrolled studies are shown in Table 1. They were divided into 3 groups according to the treatment regimens. The specific grouping schemes were listed as follows: group A (PD-1/PD-L1 + chemotherapy vs. chemotherapy),[1,3,5,6,10] group B (PD-1/PD-L1 vs. chemotherapy),[2,4,7–9,11,13,14] and group C (PD-1/PD-L1 vs. PD-1/PD-L1 + CTLA-4).[4,12] Among all the clinical trials, 10 were phase III clinical trials,[1–7,9,13,14] 2 were phase II clinical trials,[8,10] 1 was phase I/II clinical trial,[12] and 1 was phase II/III clinical trial.[11] A total of 7352 participants were included in the clinical trials, of which 172 were reported to be related to treatment-related deaths. Among all the enrolled clinical trials, 12 were related to NSCLC,[2–11,13,14] and 2 were just related to small cell lung cancer (SCLC).[1,12] Seven trials (1 SCLC and

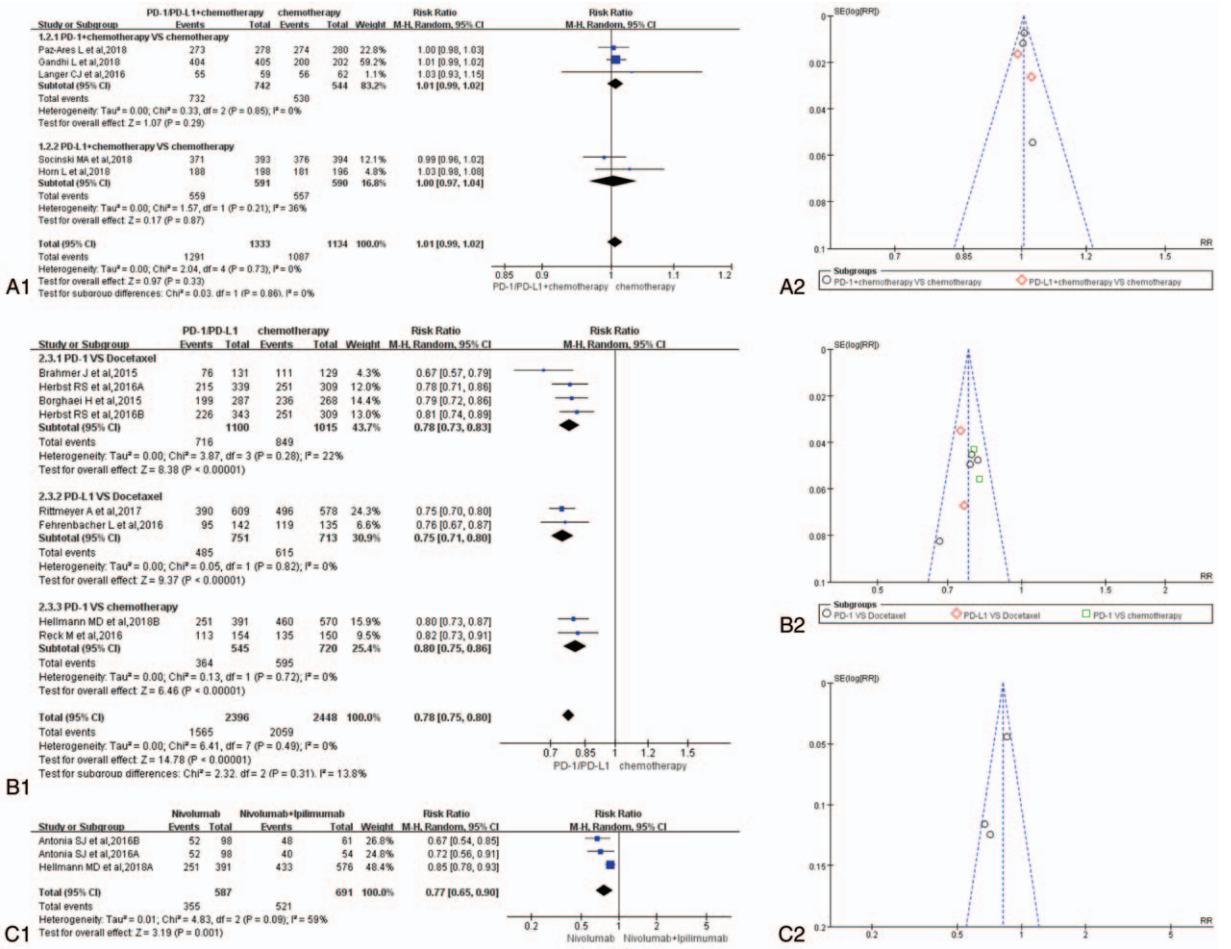

Figure 4. Forest plots and funnel plots for the risk ratio of treatment-related adverse events for grade 3 to 5. (A1) Forest plots for the risk ratio of treatment-related adverse events for grade 3 to 5 (PD-1/PD-L1 + chemotherapy vs. chemotherapy). (A2) Funnel plots for the risk ratio of treatment-related adverse events for grade 3 to 5 (PD-1/PD-L1 + chemotherapy vs. chemotherapy). (B1) Forest plots for the risk ratio of treatment-related adverse events for grade 3 to 5 (PD-1/PD-L1 vs. chemotherapy). (B2) Funnel plots for the risk ratio of treatment related-adverse events for grade 3 to 5 (PD-1/PD-L1 vs. chemotherapy). (C1) Forest plots for the risk ratio of treatment-related adverse events for grade 3 to 5 (nivolumab vs. nivolumab + ipilimumab). (C2) Funnel plots for the risk ratio of overall treatment-related adverse events (nivolumab vs. nivolumab + ipilimumab). PD-1 = programmed cell death 1, PD-L1 = programmed cell death ligand 1.

6 NSCLC) had received other antitumor treatments before receiving PD1/PD-L1 medication,[2,7,8,11–14] while PD-1/PD-L1 treatment regimen was prescribed as the first-line therapy for the other 7 trials.[1,3–6,9,10] The drugs used in 9 clinical trials were PD-1 inhibitors,[4–6,9–14] while they were PD-L1 inhibitors in the other 5 clinical trials.[1–3,7,9]

3.3. Risk of bias

Newcastle–Ottawa scale was used to evaluate study quality and risk of bias in enrolled studies. Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias) would be assessed by 4 members of our team independently and shown in Figure 2. Publication bias, evaluated by Harbord-Egger test, could be seen in funnel plot (Figs. 3–5).

3.4. RR of treatment-related death

The RR of treatment-related death for group A is shown in Figure 6A (RR = 1.17, 95% CI: [0.81, 1.71], $I^2 = 0\%$, Z = 0.84 [$P = .40$]),[1,3,5,6,10] while the result of group C is shown in Figure 6C (RR = 0.33, 95% CI: [0.08, 1.31], $I^2 = 0\%$, Z = 1.58 [$P = .11$]).[4,12] The results of group A and group C were of no statistical significance. Unlike group A and group C, the results of group B showed that the incidence risk of drug-related deaths for PD-1/PD-L1 inhibitors was significantly lower than that of the control group (RR = 0.37, 95% CI: [0.21, 0.66], $I^2 = 0\%$, Z = 3.39 [$P = .0007$]; Fig. 6B).[2,4,7–9,11,13,14] Subgroup analysis of group B showed the same trend (Fig. 6B1). Funnel plots of them are provided in Figure 6A2, B2, and C2. No heterogeneity was found among them ($I^2 = 0\%$).

3.5. RR of overall treatment-related adverse events

Fourteen studies were taken into account for the meta-analysis of overall treatment-related adverse events.[1–14] There was no

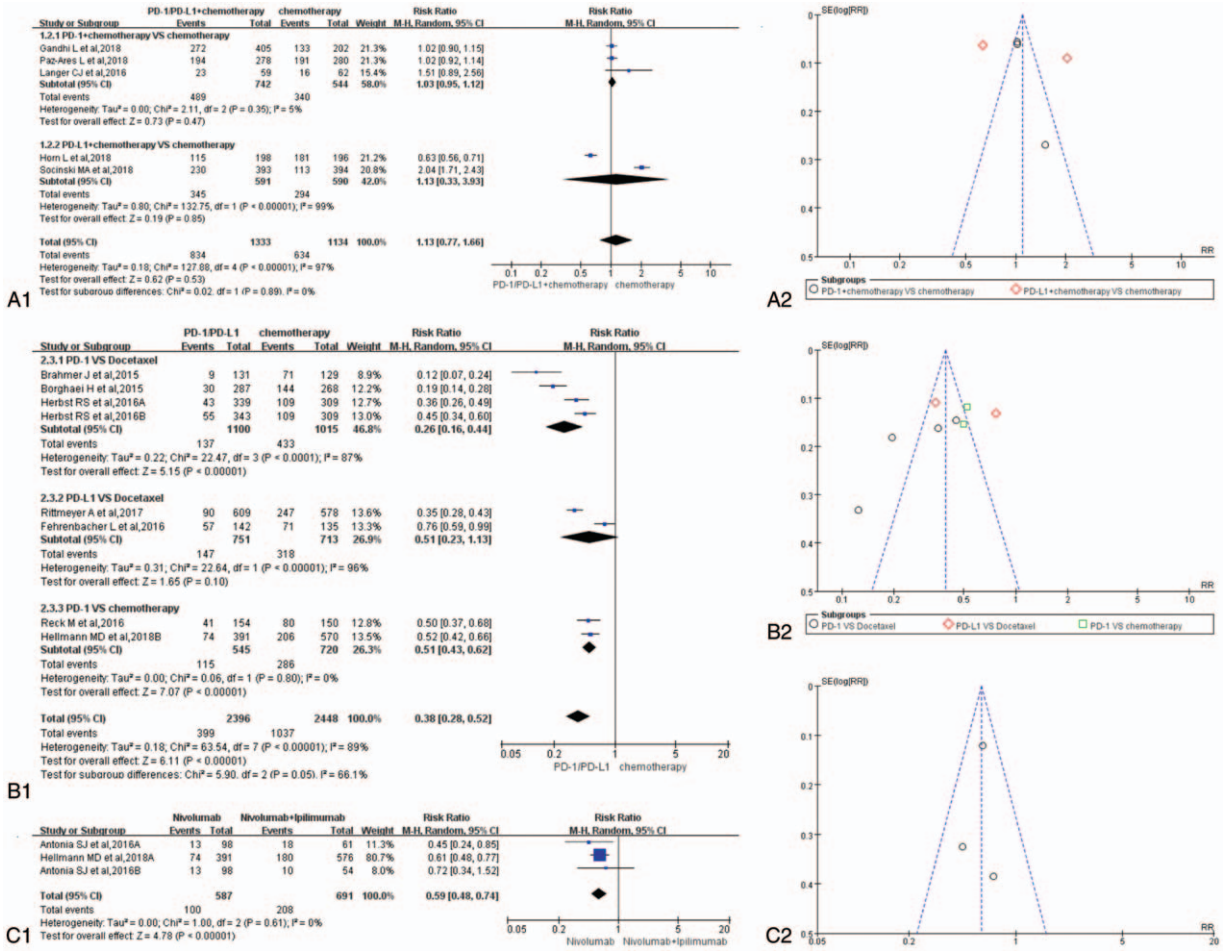

Figure 5. Forest plots and funnel plots for the risk ratio of adverse events leading to discontinuation. (A1) Forest plots for the risk ratio of adverse events leading to discontinuation (PD-1/PD-L1 + chemotherapy vs. chemotherapy). (A2) Funnel plots for the risk ratio of adverse events leading to discontinuation (PD-1/PD-L1 + chemotherapy vs. chemotherapy). (B1) Forest plots for the risk ratio of adverse events leading to discontinuation (PD-1/PD-L1 vs. chemotherapy). (B2) Funnel plots for the risk ratio of adverse events leading to discontinuation (PD-1/PD-L1 vs. chemotherapy). (C1) Forest plots for the risk ratio of adverse events leading to discontinuation (nivolumab vs. nivolumab + ipilimumab). (C2) Funnel plots for the risk ratio of adverse events leading to discontinuation (nivolumab vs. nivolumab + ipilimumab). PD-1 = programmed cell death 1, PD-L1 = programmed cell death ligand 1.

statistically significant difference in the analysis results of group A for overall treatment-related adverse events between the experimental group and the control group (RR = 1.01, 95% CI: [0.99, 1.02], $I^2 = 0\%$, Z = 0.97 [$P = .33$]; Fig. 3A1).[1,3,5,6,10] The results of the meta-analysis for group B were gathered at the bottom of Figure 3B1. Different from the above results of group A, the RR of PD-1/PD-L1 inhibitor group was significantly lower than that of the control group, furthermore the difference was statistically significant (RR = 0.78, 95% CI: [0.75, 0.80], $I^2 = 0\%$, Z = 14.78 [$P < .00001$]; Fig. 3B1).[2,4,7–9,11,13,14] Similar to the results of group B, the meta-analysis of group C was displayed in (RR = 0.77, 95% CI: [0.65, 0.90], $I^2 = 59\%$, Z = 3.19 [$P = .001$]) Figure 3C1. The funnel plots of all the enrolled 14 studies were shown in Figure 3A2, B2, and C2 independently according to the group type. Heterogeneity could be seen in ($I^2 = 39\%$) Figure 3C1.[4,12]

3.6. RR of treatment-related adverse events for grade 3 to 5

Thirteen studies were taken into account for evaluation of treatment-related adverse events for grade 3 to 5.[1,3–14] There was no statistically significant difference in the analysis results of group A for overall treatment-related adverse events between the experimental group and the control group (RR = 1.13, 95% CI: [0.77, 1.66], $I^2 = 97\%$, Z = 0.62 [$P < .00001$]; Fig. 4A1).[1,3,5,6,10] The results of the meta-analysis for group B were gathered at the bottom of Figure 4B1. Different from the above results of group A, the RR of PD-1/PD-L1 inhibitor group was significantly lower than that of the control group, furthermore the difference was statistically significant (RR = 0.38, 95% CI: [0.28, 0.52], $I^2 = 89\%$, Z = 6.11 [$P < .00001$]; Fig. 4B1).[4,7–9,11,13,14] Similar to the results of group B, the meta-analysis of group C was displayed in (RR = 0.59, 95% CI: [0.48, 0.74], $I^2 = 0\%$, Z = 4.78 [$P < .00001$]) Figure 4C1. The funnel plots of all the enrolled 14 studies were shown in Figure 4A2, B2, and C2 independently according to the group type. Publication bias could be seen in Figure 4A2 and B2. Obvious heterogeneity could be seen in Figure 4A1 and B1.

3.7. RR of adverse events leading to discontinuation

Thirteen studies, reported with the data of adverse events leading to discontinuation, were taken into account for the meta-

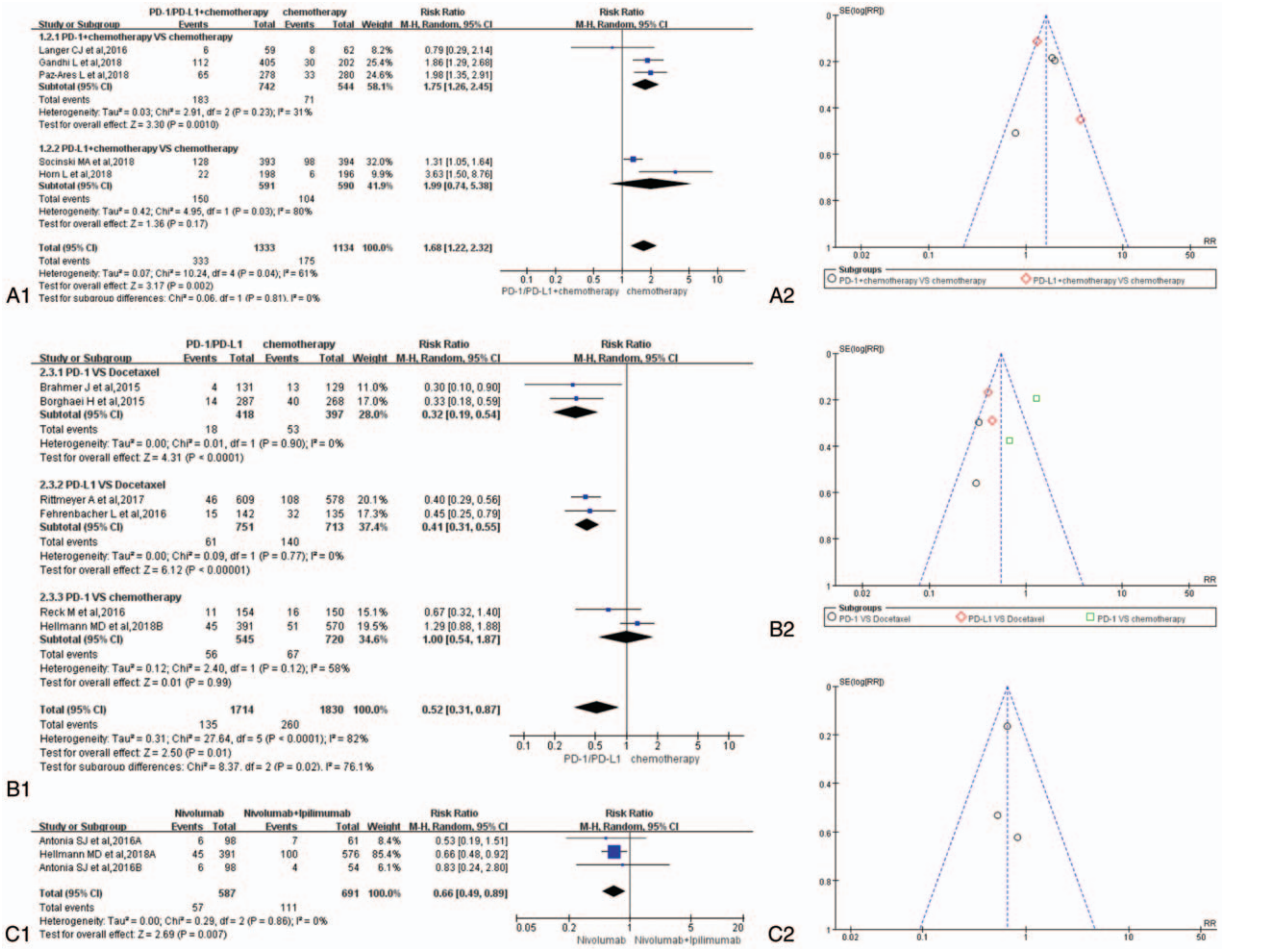

Figure 6. Forest plots and funnel plots for the risk ratio of treatment-related death. (A1) Forest plots for the risk ratio of treatment-related death (PD-1/PD-L1 + chemotherapy vs. chemotherapy). (A2) Funnel plots for the risk ratio of treatment-related death (PD-1/PD-L1 + chemotherapy vs. chemotherapy). (B1) Forest plots for the risk ratio of treatment-related death (PD-1/PD-L1 vs. chemotherapy). (B2) Funnel plots for the risk ratio of treatment-related death (PD-1/PD-L1 vs. chemotherapy). (C1) Forest plots for the risk ratio of treatment-related death (nivolumab vs. nivolumab + ipilimumab). (C2) Funnel plots for the risk ratio of treatment-related death (nivolumab vs. nivolumab + ipilimumab). PD-1 = programmed cell death 1, PD-L1 = programmed cell death ligand 1.

analysis.[1,3–14] The data analysis of group A showed that the RR of the experimental group was significantly higher than that of the control group (RR = 1.68, 95% CI: [1.22, 3.32], $I^2 = 61\%$, Z = 3.17 [$P = .002$]; Fig. 5A1),[1,3,5,6,10] while the opposite meta-analysis results of group B and group C were shown in (RR = 0.52, 95% CI: [0.31, 0.87], $I^2 = 82\%$, Z = 2.50 [$P = .01$]) Figures 5B1 and (RR = 0.66, 95% CI: [0.49, 0.89], $I^2 = 0\%$, Z = 2.69 [$P = .007$]) C1.[4,7–9,12–14] The funnel plots of all the enrolled 13 studies were shown in Figure 5A2, B2, and C2 independently according to the group type. Publication bias could be seen in Figure 5B2.[4,7–9,13,14] Heterogeneity could be seen in Figure 5A1 ($I^2 = 61\%$) and B1 ($I^2 = 58\%$).[1,3–10,13,14]

4. Discussion

Treatment regimens, including targeted therapies for those with oncogenic alterations, anti-programmed death 1 (PD-1) monotherapy for those with programmed death ligand 1 (PD-L1) expression on at least 50% of tumor cells,[9] anti-PD-1 plus platinum-doublet chemotherapy for those with non-squamous cancer,[6] and anti-PD-L1 antibody regardless of PD-L1 expression were recommended for metastatic NSCLC. PD-1 and PD-L1 inhibitors have shown promising efficacy and acceptable safety profiles for lung cancer patients, especially for NSCLC.[2–11,13,14,30,31] While PD-1/PD-L1 inhibitors had achieved satisfactory clinical efficacy, new toxic side effects had been reported and some of them were fatal.[1–6] As the completion of 6 large clinical trials of PD-1/PD-L1 related to lung cancer patients in 2018,[1–6] we had the opportunity to collect their data and conducted a comprehensive analysis for evaluating the safety of PD-1/PD-L1 inhibitors. We believed that we could get a new and more accurate conclusion of the PD-1/PD-L1 safety assessment.

All enrolled studies were deemed to be of high quality. The quality evaluation results were summarized in Figure 2. It meant that the results of our analysis originated from these high-quality data were much more credible.[1–14] Compared with chemotherapy, the mortality associated with PD-1/PD-L1 treatment was significantly lower than that of the chemotherapy group, and the difference was statistically significant (Fig. 6B1).[2,4,7–9,11,13,14] Whether combined with chemotherapy (Fig. 6A1) or other types

of immune inhibitors (Fig. 6C1), it did not increase the patient's treatment-related mortality.[1,3–6,10,12] Similar analysis results could also be seen for the RR of overall treatment-related adverse events (Fig. 3A1, B1, and C1). Heterogeneity could be seen in Figure 3C1 ($I^2=39\%$).[4,12] The study data of group C could not be taken into further subgroup analysis to clarify the source of heterogeneity, so the heterogeneity was considered to be derived from included data themselves.[4,12]

The RR of PD-1/PD-L1-related adverse events for grade 3 to 5 was significantly lower than that of the control group, furthermore the difference was statistically significant (RR = 0.38, 95% CI: [0.28, 0.52], $I^2=89\%$, $Z=6.11$ [$P<.00001$]; Fig. 4B1).[4,7–9,11,13,14] Similar to the results of group B, the meta-analysis of group C was displayed in (RR = 0.59, 95% CI: [0.48, 0.74], $I^2=0\%$, $Z=4.78$ [$P<.00001$]) Figure 4C1. Different from the former ones (Figs. 3 and 6), publication bias could be seen in Figure 4A2 and B2. Obvious heterogeneity could be seen in Figure 4A1 and B1. Subgroup analysis revealed that the heterogeneity in group A was mainly derived from 2 studies in the PD-L1 inhibitor group.[1,3] A subgroup analysis of group B showed that the heterogeneity was mainly derived from 2 subgroups (PD-1 vs. docetaxel) and (PD-L1 vs. docetaxel) (Fig. 4B1).[4,7–9,11,13,14]

For adverse events leading to discontinuation,[1,3–14] the data analysis of group A showed that the RR of the experimental group was significantly higher than that of the control group (RR = 1.68, 95% CI: [1.22, 3.32], $I^2=61\%$, $Z=3.17$ [$P=.002$]; Fig. 5A1),[1,3,5,6,10] while the opposite meta-analysis results of group B and group C were shown in (RR = 0.52, 95% CI: [0.31, 0.87], $I^2=82\%$, $Z=2.50$ [$P=.01$]) Figure 5B1 and (RR = 0.66, 95% CI: [0.49, 0.89], $I^2=0\%$, $Z=2.69$ [$P=.007$]) C1.[4,7–9,12–14] It meat that PD-1/PD-L1 plus chemotherapy would increase the RR of adverse events leading to discontinuation, which were different from the former analysis results (Figs. 3, 4, 6). Publication bias could be seen in Figure 5B2.[4,7–9,13,14] Heterogeneity could be seen in ($I^2=61\%$) Figure 5A1 and ($I^2=58\%$) B1.[1,3–10,13,14] We performed a subgroup analysis of group A and the results showed that the heterogeneity was mainly from the PD-L1 subgroup (PD-L1 + chemotherapy vs. chemotherapy).[1,3] The similar subgroup analysis showed that the heterogeneity of group B was mainly from the PD-1 subgroup (PD-1 vs. chemotherapy).[4,9]

After a comprehensive evaluation of all enrolled studies, we found that PD-1/PD-L1 inhibitors were excellent antitumor drugs with good safety and low incidence of adverse events in patients with lung cancer.

5. Conclusions

Compared with chemotherapy, RR of the treatment-related deaths associated with PD-1/PD-L1 inhibitor was significantly lower than that of the chemotherapy group, while it did not increase the RR when they were combined with chemotherapy or other drugs. When PD-1/PD-L1 was combined with chemotherapy, it only increased the RR of adverse events leading to discontinuation.

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