European Journal of Clinical Pharmacology (2021) 77:1079–1088
https://doi.org/10.1007/s00228-020-03083-9

REVIEW

Incidence risk of PD-1/PD-L1–related pneumonia and diarrhea in non-small cell lung cancer (NSCLC) patients: a systematic review and meta-analysis of randomized controlled trials

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Received: 10 October 2020 / Accepted: 28 December 2020 / Published online: 10 February 2021

Abstract

Background Programmed cell death-1 (PD-1) and programmed cell death ligand-1(PD-L1) inhibitor therapy have been approved for the treatment of many cancers, although their incidence of some side effects was high. We aim to fully investigate the incidence risk of PD-1/PD-L1 inhibitors–related pneumonia and diarrhea in NSCLC patients, as well as treatment-related deaths.

Methods PubMed, Medline, Cochrane Library, and Clinical trials.gov databases were searched up to Sep 17, 2020, for clinical trials of PD-1 inhibitors and PD-L1 inhibitors in the treatment of NSCLC. Randomized controlled trials and their references were screened.

Results Seventeen trials were included in our meta-analysis, including 11,363 patients. PD-1/PD-L1 inhibitors significantly increased the risk of developing all-grade and high-grade (grade ≥ 3) pneumonia (risk ratio [RR] = 2.28; 95% CI: 1.39–3.76; $P < 0.01$; RR = 2.38; 95% CI: 1.72–3.29; $P < 0.01$, respectively). The use of PD-1/PD-L1 inhibitor did not increase the risk of developing all-grade and high-grade diarrhea (RR = 0.79; 95% CI: 0.62–1.01; $P = 0.06$; RR = 0.96; 95% CI: 0.70–1.31; $P = 0.78$, respectively). There was no significant difference between the rate of death in PD-1 and PD-L1 inhibitors ($P = 0.079$).

Conclusion These data suggest that PD-1/PD-L1 inhibitors significantly increase the risk of all-grade and high-grade pneumonia in NSCLC patients and PD-1/PD-L1 monotherapy increases the risk of all-grade pneumonia in NSCLC patients compared to PD-1/PD-L1 inhibitor combination regimens. Physicians should pay more attention to NSCLC patients who treated with PD-1/PD-L1 inhibitors.

Keywords PD-1/PD-L1 inhibitors, · NSCLC, · Pneumonia, · Diarrhea, · Meta-analysis

Introduction

In recent years, immunotherapy has made a significant breakthrough in anticancer treatment, especially the research of immune checkpoint inhibitors (ICIs). Programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) inhibitors have shown strong clinical benefits for a variety of solid tumors. PD-1 was expressed by activated T lymphocytes and combined with PD-L1 (on the surface of tumor cells) to restrict the activation of T lymphocytes. ICIs can reactivate T cell-mediated antitumor immunity by blocking the PD-1 and PD-L1 pathway [1, 2]. Until now, there are five PD-1/PD-L1 inhibitors approved by the FDA for treatment of different advanced solid tumors, including two PD-1 inhibitors (nivolumab and pembrolizumab) and three PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab).

However, for its characteristic of increasing the activity of the immune system, it may also affect various organ systems, which consequently lead to immune-related adverse effects (irAEs), such as pruritus, rash, diarrhea, colitis, hypophysitis, thyroiditis, pancreatitis, nephritis, and pneumonitis [3–6]. Among patients treated with these monoclonal antibodies, diarrhea occurs in more than one-quarter of patients regardless of the type of cancer, and the mortality rate is high although the incidence of pneumonia is not high [7–9]. Since pneumonia and diarrhea can seriously affect the quality of life (QOL) of patients, close concern should be paid to the immune-related adverse effects of PD-1/PD-L1 inhibitors. However, among different clinical trials, NSCLC patients treated with PD-1/PD-L1 inhibitors have substantial differences in the risk of developing pneumonia and diarrhea, and the risk factors

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behind these differences have not been identified. Therefore, we performed a meta-analysis of 17 randomized controlled trials (RCTs) to research irAEs of PD-1/PD-L1 inhibitors in NSCLC patients.

Materials and methods

Search strategy and study selection

Two researchers (ZQ.T. and DY.W.) independently searched the PubMed, Medline, Cochrane Library, and Clinical trial.gov databases until Sep 17, 2020, with the following keywords: "NSCLC," "non-small cell lung cancer," "nivolumab/Opdivo/MDX 1106," "pembrolizumab/Keytruda/MK-3475," "atezolizumab/Tecentriq/MPDL3280A," "avelumab/MSB0010718C/Bavencio," and "durvalumab/MEDI-4736/Imfinzi." Studies were considered suitable for inclusion if (1) they are published in peer-reviewed journals and were phase II or III randomized controlled trials; (2) they studied individuals diagnosed with squamous or non-squamous NSCLC; (3) the intervention arms were patients with PD-1/PD-L1 inhibitors monotherapy or PD-1/PD-L1 inhibitors combination therapy (plus chemotherapy and/or targeted therapy); (4) the comparative arms were patients with chemotherapy or placebo; and (5) the outcomes should include the incidence of pneumonia and diarrhea as well as treatment-related death. We excluded studies if they were performed in animals, or the full text could not be retrieved, or if they were published as reviews (including meta-analysis), commentaries, interim analyses, or case reports. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline.

Quality assessment

Two researchers independently reviewed the quality and potential bias of the included studies. Select the Cochrane Collaboration's RCT bias risk assessment tool, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. The risk of bias graph and risk of bias summary of these studies were shown in Supplemental Figs. S1 and S2. Select the GRADE approach to describe the overall quality of the evidence. GRADE evidence profile (EP) and Summary of Findings table (SOF) were shown in Supplemental Figs. S3 and S4.

Data extraction

Data were independently extracted by two researchers. Disagreements were resolved by consensus. Data including clinical trial information of the study, first author, year of publication, trial phases, study drugs, the dosage of PD-1/PD-L1 inhibitors, total number of patients evaluated for safety, number of patients with pneumonia and diarrhea, as well as treatment-related deaths were extracted. The most of the included studies used Common Terminology Criteria for Adverse Events (CACTE) 4.0 to evaluate the grade of pneumonia and diarrhea.

Statistical analysis

Data were analyzed using Review Manager version 5.3. Calculate 95% CI for all types of data and risk ratio (RR) for the dichotomous data and select Mantel-Haenszel method as statistical method. The heterogeneity test was performed by Cochrane's Q test and the I^2 statistic was selected to estimate. According to the heterogeneity of the included studies, different effect models were chosen to calculate the RR value. If $I^2 > 50\%$, the random effect model was selected; otherwise, the fixed effect model was selected. Subgroup analysis was performed to evaluate whether the RR of pneumonia and diarrhea varied with drug type (PD-1 vs PD-L1), histology (squamous vs non-squamous), control group (placebo vs chemotherapy vs monoclonal antibody), and treatment regimen (PD-1/PD-L1 monotherapy vs combination). The significance of the subgroup analysis was evaluated using the Mantel-Haenszel method.

Results

Literature search

The literature search produced 2371 potential-related experiments. Based on inclusion and exclusion criteria, the preliminary screening excluded 2310 articles for one of the following reasons: review, letter, non-randomized controlled trial, case report, cohort studies, meta-analyses, and animal studies. The remaining 61 RCTs were carefully read and screened, 44 of which were excluded because date did not adequate for evaluation of pneumonia and diarrhea or other reasons. The remaining 17 RCTs met the inclusion criteria for systematic evaluation and meta-analysis (3 phase II and 14 phase III trials, Fig. 1) [10–26].

Characteristics of included studies

Totally, 11,363 patients were included in 17 studies for meta-analysis. Of these, eleven investigated PD-1 inhibitors (five focused on nivolumab and six were about pembrolizumab) and six researched PD-L1 inhibitors, including atezolizumab ($n = 4$), avelumab ($n = 1$), and durvalumab ($n = 1$). Histologic types of NSCLC included 3074 (27.05%) squamous cell carcinoma and 8289 (72.95%) non-squamous carcinoma. All studies used a randomized approach, 14 of which were

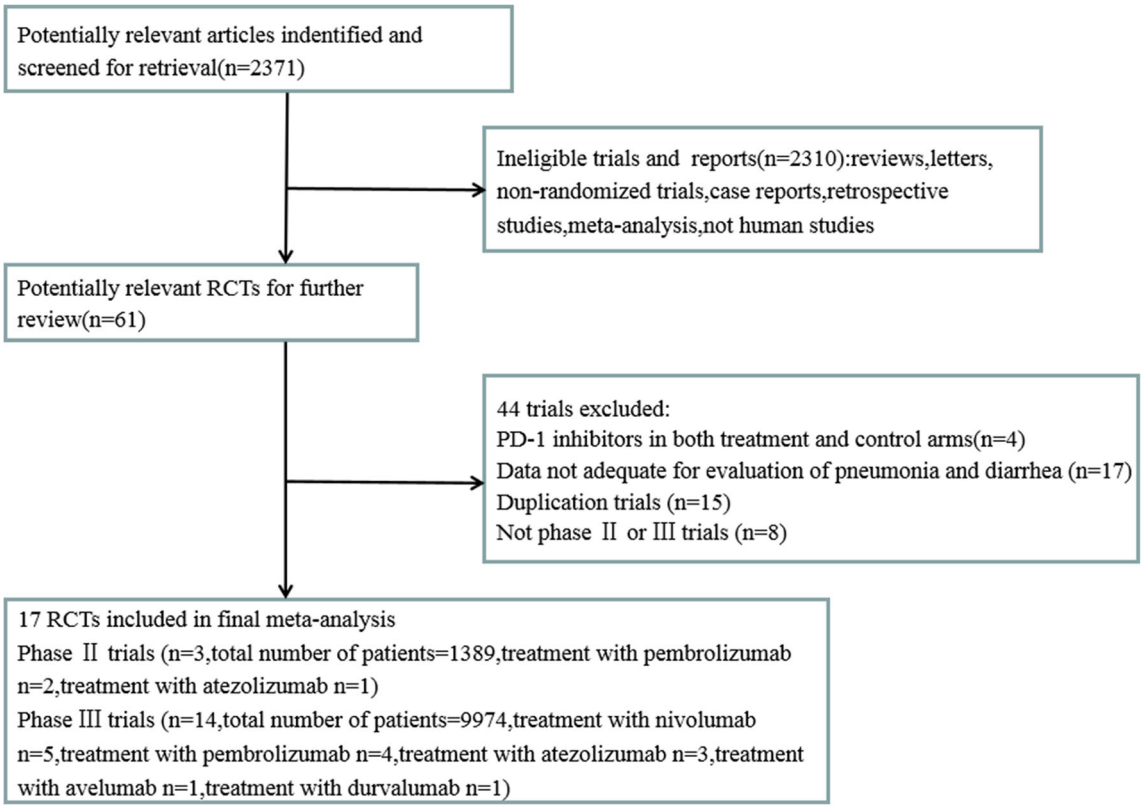

Fig. 1 Flow chart showing the selection of studies included in the present article

open-label studies and 3 were three-blind studies. Table 1 summarizes the characteristics of included trials.

Incidence and risk ratio of pneumonia

Of the 6112 patients in the PD-1/PD-L1 inhibitor group, 296 patients (4.84%) occurred all-grade pneumonia, while 112 patients (2.13%) occurred all-grade pneumonia among the 5251 patients in the control group. The RR of all-grade pneumonia was 2.28 (95% CI 1.39–3.76; $P < 0.01$) (Fig. 2). High-grade pneumonia occurred in 145 patients (2.37%) in the PD-1/PD-L1 inhibitor group and in 43 patients (0.82%) in the control group. The RR of high-grade pneumonia was 2.38 (95% CI 1.72–3.29; $P < 0.01$) (Fig. 3). The incidence of all-grade pneumonia in PD-1/PD-L1 inhibitors therapy was significantly higher than that in platinum-based chemotherapy (RR = 4.41, 95% CI 1.36–14.27, $P = 0.01$) (Supplemental Fig. S5). In the case of high-grade pneumonia, it was also higher in PD-1/PD-L1 inhibitors therapy (RR = 4.48, 95% CI 2.48–8.08, $P < 0.01$) (Supplemental Fig. S6).

The results of all-grade pneumonia in different drug types, histological types, control groups, and treatment regimens were significantly heterogeneous ($P < 0.01$, $I^2 = 69\%$). Therefore, a subgroup analysis was performed based on these differences. Table 2 summarized RR of all-grade pneumonia in the subgroup analysis. "Treatment" was identified as the patients treated with immunotherapy, and "Control" was treated with non-immunotherapy. There were no significant differences in RR for two drug types (PD-1 vs PD-L1) ($P = 0.21$). RR for all-grade pneumonia was significantly different for histological types (squamous:RR = 4.00 vs non-squamous:RR = 1.76; $P < 0.001$).

According to a further stratification study of the control treatment, the RR of all-grade pneumonia was found to be significantly different between the three groups (placebo, chemotherapy, and other monoclonal antibodies, $P < 0.001$). We found that there was no difference in the risk of all-grade pneumonia between PD-1/PD-L1 inhibitors and other monoclonal antibodies ($P = 0.20$). However, patients treated with PD-1/PD-L1 inhibitors had a significantly increased risk of all-grade pneumonia when compared with non-immunotherapy (chemotherapy or placebo). Further stratification studies were performed according to the treatment regimen (PD-1/PD-L1 inhibitor monotherapy vs combination therapy). The treatment regimen (monotherapy:RR = 2.44 vs combination:RR = 1.82; $P < 0.001$) was significantly different for RR of all-grade pneumonia. Hence, patients treated with PD-1 inhibitors, patients with squamous histological type, and patients treated with PD-1/PD-L1 inhibitor monotherapy had higher risk of all-grade pneumonia.

Table 1 Characteristics of studies included in the meta-analysis (PD-1/PD-L1 inhibitors vs chemotherapy/placebo)

Author, year	Phase	Masking	Histology	Treatment arms	Number of patients	Age in years (median)	Follow-up duration (months)	CTCAE version
Borghaei 2015 [10]	III	Open label	Non-squamous NSCLC	Nivolumab 3 mg/kg Q2w Docetaxel	287 268	61 64	Minimum 13.2	4.0
Brahmer 2015 [11]	III	Open label	Squamous NSCLC	Nivolumab 3 mg/kg Q2w Docetaxel	131 129	62 64	Minimum 11	4.0
Carbone 2017 [12]	III	Open label	NSCLC	Nivolumab 3 mg/kg Q2w Platinum-based chemotherapy	267 263	63 65	Median 13.5	4.0
Gandhi 2018 [13]	III	Quadruple	Non-squamous NSCLC	Pembrolizumab combination 200 mg Placebo combination	410 206	65.0 63.5	Median 10.5	4.0
Hellmann 2018 [14]	III	Open label	NSCLC	Nivolumab 3 mg/kg Q2w Platinum-based chemotherapy	391 570	64 64	Minimum 11.2	4.0
Herbst 2016(1)[15]	II/III	Open label	NSCLC	Pembrolizumab 2 mg/kg Q3w Docetaxel	339 309	63 62	Median 13.1	4.0
Herbst 2016(2)[15]	II/III	Open label	NSCLC	Pembrolizumab 10 mg/kg Q3w Docetaxel	343 309	63 62	Median 13.1	4.0
L. Paz-Ares 2018 [16]	III	Triple	Squamous NSCLC	Pembrolizumab combination 200 mg Placebo combination	278 281	65 65	Median 7.8	4.0
Langer 2016 [17]	I/II	Open label	NSCLC	Pembrolizumab combination 200 mg Chemotherapy	59 62	62.5 63.2	Median 10.6	4.0
Reck 2016 [18]	III	Open label	NSCLC	Pembrolizumab 200 mg Q3w Platinum-based chemotherapy	154 150	64.5 66	Median 11.2	4.0
Wu 2019 [19]	III	Open label	NSCLC	Nivolumab 3 mg/kg Q2w Docetaxel	338 166	60 60	Minimum 8.8	4.0
Mok 2019 [20]	III	Open label	NSCLC	Pembrolizumab 200 mg Q3w Platinum-based chemotherapy	636 615	63 63	Median 12.8	4.0
West 2019 [21]	III	Open label	Non-squamous NSCLC	Atezolizumab-chemotherapy 1200 mg/Q3w Chemotherapy	473 232	64 65	Median 18.5	4.0
Fehrenbacher 2016 [22]	II	Open label	NSCLC	Atezolizumab 1200 mg/Q3w Docetaxel	144 143	62 62	Median 14.8	4.0
Rittmeyer 2016 [23]	III	Open label	NSCLC	Atezolizumab 1200 mg/Q3w Docetaxel	425 425	63 64	Median 21.0	4.0
Socinski 2018 [24]	III	Open label	Non-squamous NSCLC	Atezolizumab-bevacizumab-Chemotherapy 1200 mg Bevacizumab-chemotherapy	400 400	63 63 Median 15.5	Minimum 9.5	4.0
Barlesi 2018 [25]	III	Open label	NSCLC	Avelumab 10 mg/kg Q2w Docetaxel	393 365	64 63	Median 18.3	4.03
Antonia 2017 [26]	III	Quadruple	NSCLC	Durvalumab 10 mg/kg Q2w Docetaxel	476 237	64 64	Median 14.5	4.03

NSCLC: non-small cell lung cancer, PD-1: programmed cell death-1, PD-L1: programmed cell death ligand-1; Q2w/Q3w: every 2/3 weeks
Quadruple: Participant, Care Provider, Investigator, Outcome assessor; Triple: Participant, Investigator, Outcome assessor

Incidence and risk ratio of diarrhea

Of the 6112 patients in the PD-1/PD-L1 inhibitor group, 840 patients (13.74%) occurred all-grade diarrhea, while of the 5251 patients in the control group, 760 (14.47%) occurred all-grade diarrhea. The RR of all-grade diarrhea was 0.79 (95% CI 0.62–1.01; $P = 0.06$) (Fig. 4). High-grade of diarrhea occurred in 90 patients (1.47%) in the PD-1/PD-L1 inhibitor group and in 69 patients (1.31%) in the control group. The RR of high-grade diarrhea was 0.96 (95% CI 0.70–1.31; $P = 0.78$) (Fig. 5). The incidence of all-grade and high-grade diarrhea in PD-1/PD-L1 inhibitors therapy was higher than that in platinum-based chemotherapy, but they were not statistically significant ($P = 0.06$, $P = 0.10$, respectively) (Supplemental Figs. S7–S8).

Similarly, the results of all-grade diarrhea in different drug types, histological types, control groups, and treatment regimens were significantly heterogeneous ($P < 0.01$, $I^2 = 83\%$). Table 3 summarized RR of all-grade diarrhea in the subgroup analysis. There were no significant differences in RR between

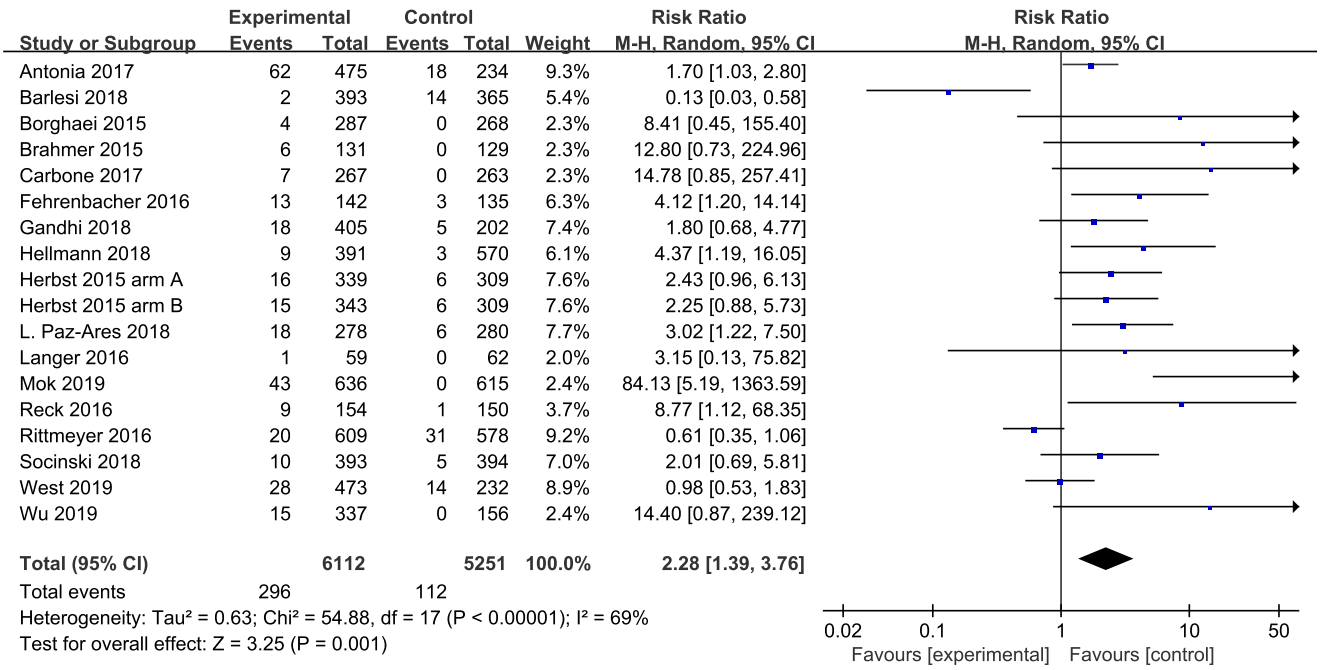

Fig. 2 Forest plots for the risk ratio of all-grade pneumonia (PD-1/PD-L1 inhibitors vs chemotherapy/placebo)

two drug types (PD-1 vs PD-L1) ($P = 0.10$). The RR for all-grade diarrhea was significantly different for histological types ($P < 0.001$). According to a further stratified study of control treatment, there was no significant difference in RR of all-grade diarrhea between the three groups (placebo, chemotherapy, and other monoclonal antibodies, $P = 0.32$). However, patients treated with PD-1/PD-L1 inhibitors had a significantly increased risk of all-grade diarrhea when compared with non-immunotherapy. Further stratification studies were performed according to the treatment regimen (PD-1/PD-L1 inhibitor monotherapy vs combination therapy). Treatment regimens ($P = 0.94$) showed no significant difference in RR for all-grade diarrhea.

Treatment-related deaths

Totally, 67 treatment-related deaths were reported ($n = 5944$). There were 34 deaths related to PD-1 inhibitors and 33 related

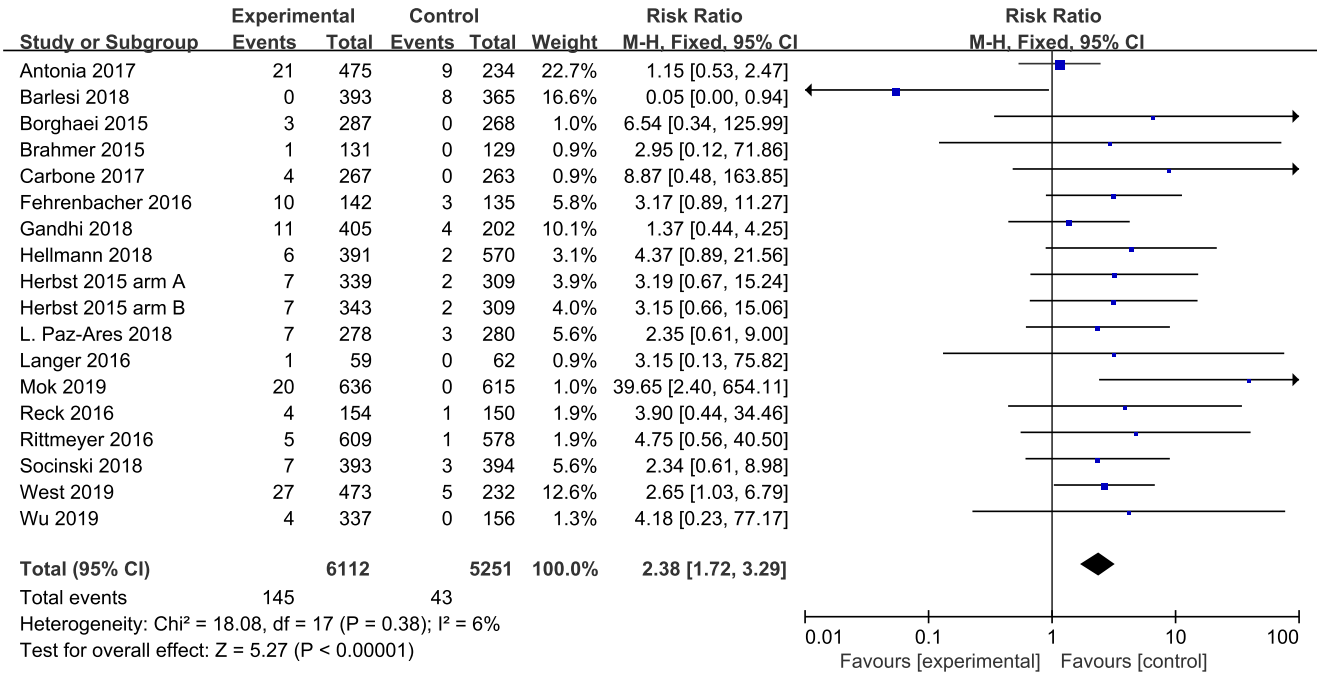

Fig. 3 Forest plots for the risk ratio of high-grade pneumonia (PD-1/PD-L1 inhibitors vs chemotherapy/placebo)

Table 2 Summary risk ratios of all-grade pneumonia associated with PD-1/PD-L1 inhibitors in the subgroup analysis

All-grade pneumonia	No. of trials	No. of events/total		RR [95% CI]	*P*	*P* value for group difference
		Treatment	Control			
Type of drug						
PD-1	11	161/3627	27/3313	5.45 [3.63, 8.17]	< 0.001	0.21
PD-L1	6	135/2485	85/1938	1.24 [0.95, 1.61]	0.11	
Histology						
Squamous	2	24/409	6/409	4.00 [1.65, 9.68]	0.002	< 0.001
Non-squamous	4	60/1558	24/1096	1.76 [1.10, 2.81]	0.02	
Control therapy						
Placebo	2	36/688	11/487	2.32 [1.19, 4.51]	0.01	< 0.001
Chemotherapy	14	250/5031	96/4370	2.26 [1.79, 2.85]	< 0.001	
Monoclonal antibody	1	10/393	5/394	2.01 [0.69, 5.81]	0.20	
Treatment regimen						
PD-1/PD-L1 monotherapy	12	221/4499	82/4076	2.44 [1.90, 3.13]	< 0.001	< 0.001
Combination	5	75/1613	30/1175	1.82 [1.20, 2.76]	0.005	

to PD-L1 inhibitors. There was no significant difference between the rate of death in PD-1 and PD-L1 inhibitors (P = 0.079). The most treatment-related deaths were attributed to pneumonitis or pneumonia (n = 23). Trials reporting treatment-related deaths and causes of deaths were summarized in Supplemental Table S1.

Publication bias

Funnel plots for the risk ratio of pneumonia and diarrhea were shown in Supplemental Fig. S9. The funnel plots of all-grade and high-grade pneumonia had significant publication bias, while no significant publication bias was found for all-grade and high-grade diarrhea.

Discussion

In recent years, ICIs have become one of the most popular therapeutic regimens for various types of cancer. Compared with traditional antitumor therapies, PD-1/PD-L1 inhibitors can kill tumor cells by activating their immune system. PD-1

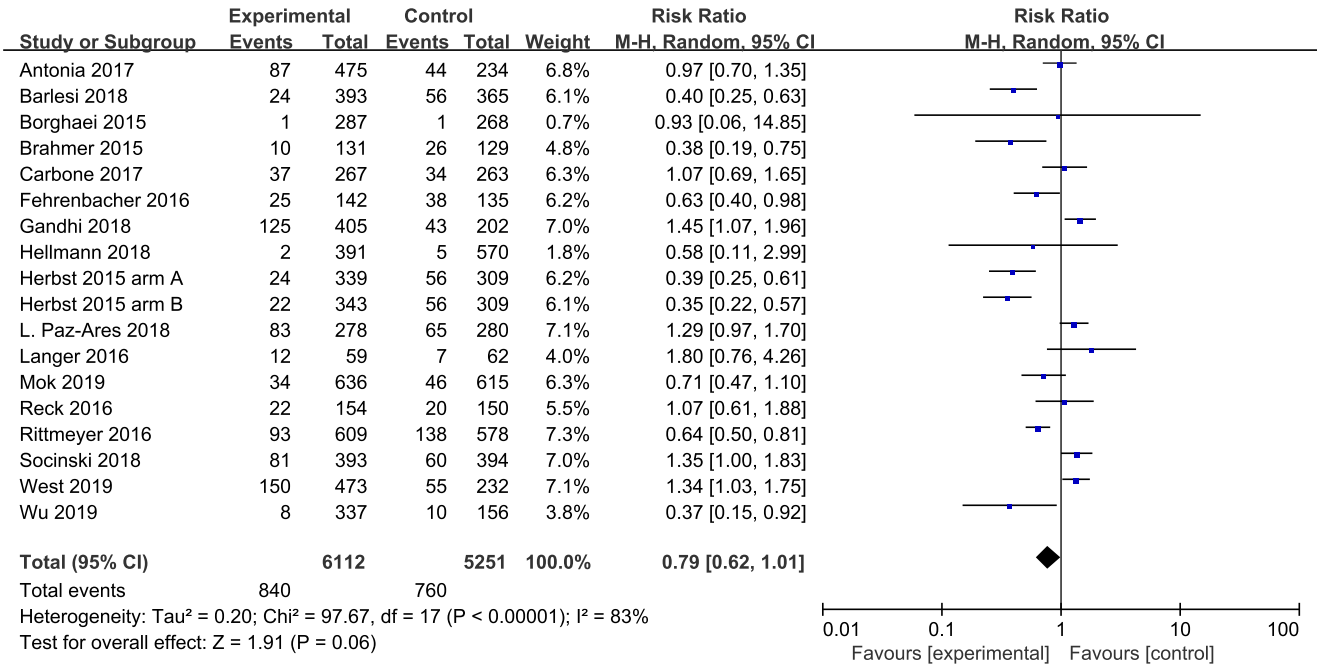

Fig. 4 Forest plots for the risk ratio of all-grade diarrhea (PD-1/PD-L1 inhibitors vs chemotherapy/placebo)

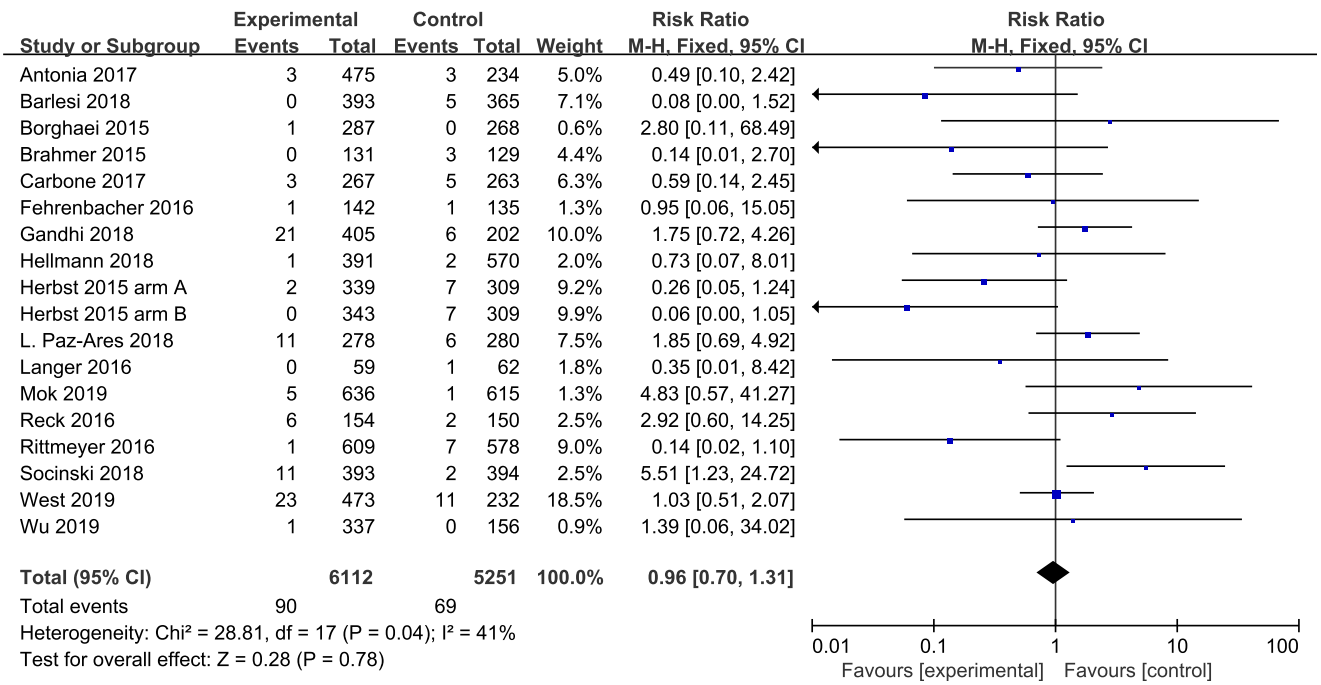

Fig. 5 Forest plots for the risk ratio of high-grade diarrhea (PD-1/PD-L1 inhibitors vs chemotherapy/placebo)

is an essential immunological checkpoint receptor that is expressed on activated T cells and activates the autoimmune system and recognizes tumor cells by triggering cytotoxic CD4+/CD8+ T cell activation. PD-1/PD-L1 has proven to be a valuable clinical target for the treatment of cancer [27, 28]. Although some clinical trials have shown that ICIs have the potential to prolong PFS and OS, irAEs are completely different from traditional chemotherapy and targeted therapy-related adverse effects. They are usually characterized by organ specificity, nonlinear dose dependence, and delayed onset [29]. Among those immune-related adverse reactions, pneumonia is usually clinically severe and can be life-threatening. Although diarrhea rarely causes death, it seriously affects patients' quality of life. Therefore, it is vital for us to understand the incidence risk of pneumonia and diarrhea.

This meta-analysis revealed that PD-1/PD-L1 inhibitors significantly increased the risk of developing all-grade and high-grade pneumonia and incidence of pneumonia was 4.84% for all-grade and 2.37% for high-grade. Compared to chemotherapy, patients received PD-1/PD-L1 inhibitors were

Table 3 Summary risk ratios of all-grade diarrhea associated with PD-1/PD-L1 inhibitors in the subgroup analysis

All-grade diarrhea	No. of trials	No. of events/total		RR [95% CI]	*P*	*P* value for group difference
		Treatment	Control			
Type of drug						
PD-1	11	380/3627	369/3313	0.94 [0.82, 1.08]	0.375	0.10
PD-L1	6	460/2485	391/1938	0.92 [0.81, 1.04]	0.163	
Histology						
Squamous	2	93/409	91/409	1.02 [0.79, 1.32]	0.867	< 0.001
Non-squamous	4	357/1558	159/1096	1.58 [1.33, 1.87]	< 0.001	
Control therapy						
Placebo	2	208/688	108/487	1.36 [1.11, 1.66]	0.003	0.32
Chemotherapy	14	723/5031	689/4370	0.91 [0.83, 1.01]	0.059	
Monoclonal antibody	1	81/393	60/394	1.35 [1.00, 1.83]	0.051	
Treatment regimen						
PD-1/PD-L1 monotherapy	12	389/4499	530/4076	0.67 [0.59, 0.75]	< 0.001	0.94
Combination	5	451/1613	230/1175	1.43 [1.24, 1.64]	< 0.001	

2.28 times more likely to develop all-grade pneumonia and 2.38 times for high-grade. The incidence of diarrhea was 13.74% for all-grade and 1.47% for high-grade in NSCLC patients treated with PD-1 and PD-L1 inhibitors. PD-1/PD-L1 inhibitors did not increase the risk of all-grade and high-grade diarrhea compared to chemotherapy. Ma et al. summarized that in NSCLC treated with ICIs the incidence of pneumonia was 3.1% for all-grade and 1.4% for high-grade, both of which were significantly higher than that in melanoma and head and neck squamous cell carcinoma [30]. Nishino et al. summarized that in NSCLC treated with PD-1 inhibitor monotherapy the incidence of pneumonia was 4.1% for all-grade and 1.8% for high-grade [31]. Besides, Mohamed et al. found that the incidence of all-grade and high-grade pneumonia was higher in PD-1 inhibitor but not in PD-L1 inhibitor when compared to traditional chemotherapy regimens for NSCLC and melanoma [32]. Moreover, Zhang et al. found that the incidence of diarrhea of all grades (grades 1–2 and grades 3–5, respectively) treated with PD-1/PD-L1 inhibitor was lower than that treated with docetaxel alone [33]. The risk of diarrhea with PD-1/PD-L1 inhibitors combined with chemotherapy was higher than with chemotherapy alone. Nishijima et al. and some clinical trials demonstrated that treatment-related adverse events in PD-1 and PD-L1 inhibitors were fewer than that in chemotherapy [10, 11, 34]. However, we proved that patients treated with PD-1 and PD-L1 inhibitors had higher incidence risk of pneumonia than chemotherapy.

Pneumonia and diarrhea were common side effects during treatment with PD-1/PD-L1 inhibitors, and apart from reducing the patient's quality of life, the development of these toxicities may result in changes or termination of the dosing regimen. They were usually mild, but there are also severe case reports (such as death from pneumonia). Thus, as the use of PD-1/PD-L1 inhibitors increases, the identification and management of irAEs will become increasingly important in preventing adverse effects on patients' health-related quality of life. Baseline imaging studies of high-resolution chest CT (with and without comparison) should be performed before starting the use of ICIs. It is important to let patients know the possible signs and symptoms of pneumonia and report to their doctors, including new or increased dyspnea, shortness of breath, cough, chest pain, and fever [35, 36]. Primary pneumonia can be treated with immunosuppressants and careful clinical observation on a dose-withheld basis. It is recommended that the checkpoint inhibitor regimen should not be restarted until chest CT scan shows improvement or complete resolution of pneumonia [37].

Withal, there are several limitations to this study. Firstly, the studies we included were RCTs. In actual work, there were many small trials with nonsignificant results, such as cohort studies and observational studies, and we should include these into meta-analysis showing significant results. Secondly, there was significant heterogeneity between all-grade diarrhea trials, so was all-grade pneumonia trials. Different doses, dosing intervals, and patient's baseline characteristics may increase the heterogeneity of clinical trials. Thirdly, the data were extracted from published clinical trial results, and there was no separate patient information such as medical records. Therefore, it is impossible to analyze other factors that may lead to the development of pneumonia and diarrhea, such as diarrhea induced by food. Fourthly, the funnel plots of all-grade and high-grade pneumonia were shown significant publication bias. This may be due to that the studies were conducted by different investigators in different international agencies who may have a potential bias against the reported incidence of pneumonia and diarrhea. Besides, pneumonia and diarrhea were not the primary end points of the included studies. We described the GRADE results to assess the overall quality of evidence across study end points, including GRADE evidence profile and the Summary of Findings table. GRADE evidence profile indicated that the overall quality of the evidence used to assess pneumonia and diarrhea were high-quality evidence. Specifically, in evaluating the quality of evidence for all-grade and high-grade pneumonia, one point was reduced due to publication bias while one point was increased by the effect size RR > 2, and it was ultimately high-quality evidence. Although GRADE results showed high-quality evidence to support our conclusions, because of publication bias, we still need to be cautious about our conclusions, and more clinical trials are needed to fully investigate PD-1/PD-L1–related pneumonia and diarrhea.

Conclusions

In summary, this study has demonstrated that PD-1/PD-L1 inhibitors significantly increase the risk of all-grade and high-grade pneumonia in NSCLC patients compared to conventional chemotherapy and PD-1/PD-L1 monotherapy increases the risk of all-grade pneumonia in NSCLC patients compared with PD-1/PD-L1 inhibitor combination regimens. Physicians should pay more attention to NSCLC patients who treated with PD-1/PD-L1 inhibitors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-020-03083-9.

Author contribution All authors contributed to the study conception and design. M.D. proposed the study protocol and supervised the progress of the work. ZQ.T. and DY.W. both searched databases, selected studies, extracted data, and analyzed data. ZQ.T. wrote the first draft of the manuscript. D.L. assisted in solving various professional problems encountered during the work and interpreting the results. All authors read and approved the final manuscript.

Funding information This work was supported by the Haiyan Fund Project of the Harbin Medical University Cancer Hospital (JJZD2019-03).

Data Availability All data generated or analyzed during this study are included in this article.

Compliance with ethical standards

Competing interests The authors declare that they have no conflict of interest.

Ethics approval Not applicable.

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