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The incidence and relative risk of PD-1/PD-L1 inhibitors-related colitis in non-small cell lung cancer: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: The programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) inhibitors have shown encouraging merits in non-small cell lung cancer (NSCLC) patients, however, they are often related to potentially fatal immune-related adverse events (irAEs) including colitis. Considering the incidence and characteristics of immune-related colitis may have significant implications for the appropriate utilization of PD-1/PD-L1 inhibitors in clinical practice, we conduct this meta to systematically analyze the correlation between PD-1/PD-L1 inhibitors for the treatment of NSCLC and the incidence of immune-associated colitis.

Methods: Electronic databases including PubMed, Embase, Cochrane Library and ClinicalTrials.gov (http://clinicaltrials.gov/) were searched up to May 2019, clinical trials reporting all grade (1–5), higher grade (3–5) colitis and grade 3–5 diarrhea were included, data were expressed as relative risk (RR), incidence, corresponding p value and 95% confidence intervals (CIs).

Results: 9 randomized controlled trials (RCTs) were identified (7 with PD-1 inhibitors [n = 4526]) and 2 with PD-L1 inhibitors [n = 1464]). The overall incidence of PD-1/PD-L1 target agents was 1.40% for all grade colitis, 0.89% for severe colitis, 11.62% for all grade diarrhea and 1.36% for severe diarrhea. Compared with chemotherapy group, the PD-1/PD-L1 inhibitors had a significantly higher risk of all grade (RR: 3.68, $p < 0.001$) and high-grade (RR: 2.97, $p = 0.01$) colitis. Additional analysis of relative risk of diarrhea revealed that PD-1/PD-L1 treatment moderately reduce the risk of all grade diarrhea (RR: 0.64, $p = 0.03$), while the difference was not statistically significant in the risk of grade 3–5 diarrhea (RR: 0.83, $p = 0.64$). Subgroup analyses showed that the RR of all grade and higher grade colitis in PD-1 inhibitors was more significant (RR: 3.56, $p = 0.001$ vs RR: 2.98, $p = 0.02$ respectively). However, there was no appreciable difference in PD-L1 inhibitors (RR: 4.75, $p = 0.15$ vs RR: 2.85, $p = 0.52$ respectively). When compared with first-line therapy, second-line therapy associated with a higher risk of all grade colitis than first-line therapy (RR: 3.29, $p = 0.006$; RR: 4.69, $p = 0.026$).

Conclusion: Our meta-analysis indicates when compared with control group, the PD-1/PD-L1 inhibitors may lead to a higher risk of all grade and high grade immune-mediated colitis, but may result in a reduction in all grade diarrhea. PD-1 inhibitors in NSCLC patients, but not PD-L1 inhibitors, increase the risk of all- and high grade colitis. These results suggest that clinicians shall pay more attention to this rare but life-threatening toxic effect.

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality throughout the world [1]. Non-small cell lung cancer (NSCLC), the most common histologic subtype of tumors, represents nearly 85% of all diagnoses [2]. Because of inadequate screening tools and late onset of clinical symptoms, most patients are often diagnosed with advanced stage, leading to an unfavorable prognosis. Although therapeutic strategies like targeted therapy and chemotherapeutic treatment have improved the outcome of advanced and metastatic NSCLC, their efficacy remains poor [3,4]. As the disease progresses, effective treatment options are limited for patients with NSCLC after conventional therapy.

Owing to the clinical success of cancer immunotherapy, there has been renewed interest in the development of immunomodulatory strategies in oncology treatment. Antimicrobial peptide (AMP), as a structurally important key effector of innate immunity, may exert their

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immunoreactivity on anti-proliferation, pro-apoptosis and anti-metastasis [5]. The other new agents including antigen-specific cancer vaccines can elicit a positive immune response of host defense system, particularly against tumor-related antigens. While there was no clear evidence that the above immunotherapy can significantly prolong survival with NSCLC patients [6]. It seems that immunotherapy remained stagnant until the advent of immune checkpoint inhibitors (ICIs). Recently, research studies investigating ICIs directly against the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway have shown clinical benefit and manifested therapeutic effect in the NSCLC patients. Pembrolizumab, nivolumab (PD-1 inhibitors) and atezolizumab (PD-L1 inhibitor) have been approved by FDA for the NSCLC patients. Moreover, pembrolizumab has been used as first-line therapy for advanced non-squamous NSCLC patients without the presence of driver oncogene alterations [7].

Despite the expanded clinical applications, the immune-related adverse events (irAEs) are inevitable. These irAEs represent immune disorders of normal tissues owing to misdirected activation of the immune system, leading to a great diversity of toxic effects, such as pneumonitis, pruritus, rash, colitis and diarrhea [8,9]. Among which, immune-related colitis is rare, but is often serious or even fatal. Further, several reports show that immune-related colitis can be accompanied by diarrhea, emphasizing the necessity for more systemic analysis across studies. Therefore, considering the incidence and characteristics of immune-related colitis may have implications for the appropriate applications of PD-1/PD-L1 inhibitors in clinical practice, we collected available randomized clinical trials (RCTs) to systematically assess the incidence and relative risk of colitis and diarrhea associated with PD-1/PD-L1 inhibitors in NSCLC patients.

2. Methods

2.1. Search strategy

We searched electronic databases including PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov (http://clinicaltrials.gov/) for the comprehensive literature. Abstracts and meeting presentations were also reviewed from all major conference proceedings, including American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) from 2014 to 2019. The dates searched were from the inception of all searched databases to May 28, 2019. The following keywords or corresponding Medical Subject Heading terms were used: PD-1, PD-L1, programmed death receptor 1, programmed death receptor ligand, immune checkpoint inhibitor, nivolumab, pembrolizumab, atezolizumab, lambrolizumab, durvalumab, NSCLC. To ensure completeness, the references from the included citations were reviewed manually to identify additional studies.

2.2. Study selection

The selection of studies was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10]. Clinical trials met the following predetermined criteria were eligible for inclusion: (a) Phase II or III RCTs published in English; (b) Participants who received PD-1/PD-L1 targeting agents in NSCLC; (c) Reporting of colitis and diarrhea for all grade (grade 1–5) or high grade (grade 3–5); (d) Studies that administered PD-1/PD-L1 inhibitors in conjunction with other agents only the groups with chemotherapeutic agents were eligible.

2.3. Data extraction

Two investigators independently searched the databases, any controversies between reviewers were discussed and resolved with consensus. The following data were extracted for each article: first author's name, year of publication, study type, study phase, agents, line of therapy, median overall survival, median follow-up durations, number of treated patients, and number of all grade (grade 1–5) and high grade (grade 3–5) colitis and diarrhea events.

2.4. Risk of bias assessment

Each study was assessed by the Cochrane risk of bias assessment to identify the quality of included randomized trials. Evaluation criteria include the following components: random sequence generation, allocation concealment, blinding, incomplete outcome data, and other sources of bias.

2.5. Data analysis

The main purpose of this study was to investigate the incidence and relative risk of colitis and diarrhea in NSCLC patients with PD-1/PD-L1 treatment. Therefore, we estimated the incidence rate of immune-related colitis and diarrhea in forest plots with 95% confidence intervals (CIs) using exact binomial methods. The RR, 95% CIs were also used to analyze the prospective risk of colitis and diarrhea in patients treated with PD-1/ PD-L1 inhibitors compared with chemotherapeutic drugs. Moreover, we have performed subgroup analyses to examine potential differences between PD-1 or PD-L1 inhibitors. All comparisons of incidence between groups were performed using chi-square test. The statistical heterogeneity was assessed by the Cochrane's Q statistic and I^2 statistic. P value < 0.05 and $I^2 > 50\%$ was defined as the presence of heterogeneity. The statistical analyses were performed using the Review Manager (version 5.3, The Cochrane Collaboration, Oxford, United Kingdom), Stata version 12.0 (Stata Corp, College Station, TX) and R packages of R 3.6.0 (www.r-project.org).

3. Results

3.1. Literature search

Based on the search terminology and evaluation of other references, a total of 2412 records were retrieved. After screening and eligibility assessment, 20 eligible studies were selected on the basis of relevance to the study topic. After reviewing the remaining articles for abstracts and full texts, 9 trials involving 5990 patients were included in the final analysis. All studies were published in the last 5 years. The selection flow diagram is shown in Fig. 1.

3.2. Study characteristics

The main characteristics of nine included studies and detailed information for all grade or grade 3–5 colitis and diarrhea in NSCLC patients were summarized in Table 1. All the included trials estimated the therapeutic efficacy and adverse events of PD-1/PD-L1 inhibitors therapies with chemotherapy. Among the nine studies, seven trials enrolled patients with PD-1 inhibitors, and the other two with PD-L1 inhibitors. Additionally, there were 8 phase III trials, 1 phase II trials. All included articles were randomized controlled trials.

3.3. Incidence and relative risk of colitis

All trials encompassing a total of 5990 patients were included for incidence and relative risk of colitis. In the overall cohort, the incidence of all grade colitis in NSCLC patients treated with PD-1/PD-L1 inhibitors was significantly higher than chemotherapy groups (1.40%, 95% CI: 1.03–1.91 vs 0.53%, 95% CI: 0.28–1.00; $p < 0.001$) (Fig. 2). Also, we found higher incidence of grade 3–5 colitis with PD-1/PD-L1 inhibitors in comparison with control arms (0.89%, 95% CI: 0.59–1.35 vs 0.41%, 95% CI: 0.20–0.83; $p = 0.003$) (Fig. 3).

Furthermore, to evaluate if PD-1/PD-L1 inhibitors as predictive risk factors of colitis, relative risk of all grade or higher grade colitis was

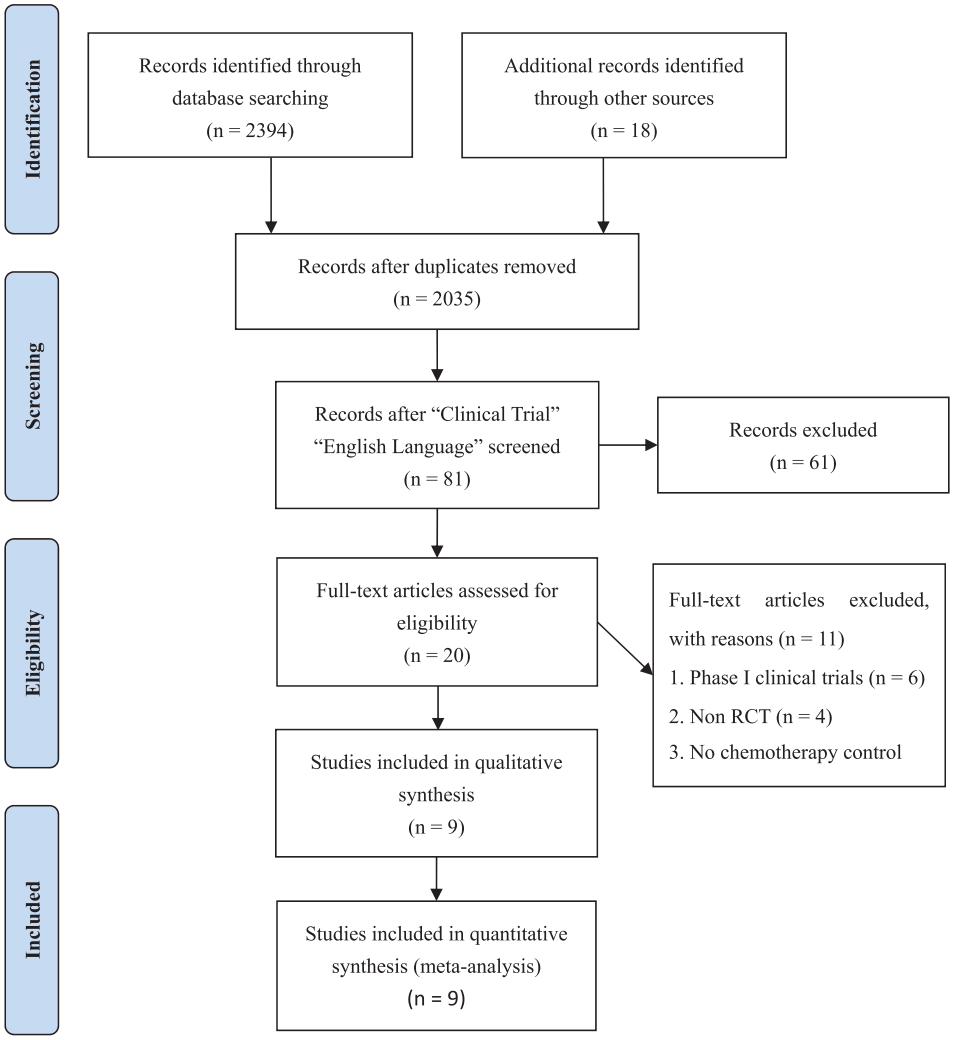

Fig. 1. PRISMA flow diagram of included studies.

performed. As is shown in Fig. 4, the PD-1/PD-L1 inhibitors had a significantly higher risk of all grade colitis (RR: 3.68, $p < 0.001$), there was no heterogeneity ($I^2 = 0\%$, $p = 0.97$). Similarly, treatment with PD-1/PD-L1 inhibitors did also significantly increase the risk of high-grade colitis (RR: 2.97, $p = 0.012$). No heterogeneity was observed ($I^2 = 0\%$, $p = 1.00$). All above results suggest that PD-1/PD-L1

Table 1
Characteristic of randomized controlled trials included in the meta-analysis.

Source	Author, Year	Study type	Study phase	Agents	Line of therapy	Median OS (Mos)	Median follow-up (Mos)	No. of patients	No. of colitis events		No. of diarrhea events	
									All grade	Grade 3–5	All grade	Grade 3–5
NCT02775435 [30]	Paz-Ares et al. (2018)	RCT	III	Pembrolizumab	First line	15.9	7.8	278	7	6	83	11
				Chemotherapy		11.3		280	4	3	65	6
NCT02008227 [31]	Rittmeyer et al. (2017)	RCT	III	Atezolizumab	Second line	13.8	21	609	2	0	98	4
				Docetaxel		9.6		578	0	0	141	11
NCT01642004 [32]	Brahmer et al. (2015)	RCT	III	Nivolumab	Second line	9.2	Minimum 11	131	1	1	10	0
				Docetaxel		6.0		129	0	0	26	3
NCT01673867 [33]	Borghaei et al. (2015)	RCT	III	Nivolumab	Second line	12.2	Minimum 13.2	287	2	1	22	2
				Docetaxel		9.4		268	0	0	62	3
NCT01905657 [34]	Herbst et al. (2016)	RCT	III	Pembrolizumab	Second line	10.4	13.1	682	6	4	46	2
				Docetaxel		8.5		309	0	0	56	7
NCT02142738 [35]	Reck et al. (2016)	RCT	III	Pembrolizumab	First line	NA	11.2	154	3	2	22	6
				Chemotherapy				150	0	0	20	2
NCT02578680 [36]	Gandhi et al. (2018)	RCT	III	Pembrolizumab	First line	NA	10.5	405	9	3	125	21
				Chemotherapy				202	0	0	43	6
NCT01903993 [37]	Fehrenbacher et al. (2016)	RCT	II	Atezolizumab	Second line	12.6	14.8	142	2	1	10	1
				Docetaxel		9.7		135	0	0	30	3
NCT02220894 [38]	Mok et al. (2019)	RCT	III	Pembrolizumab	First line	20.2	12.8	636	7	4	34	5
				Chemotherapy		12.2		615	2	1	46	1

Abbreviations: *RCT* Randomized controlled trial, *OS* Overall survival, *Mos* Months, *NA* Not applicable.

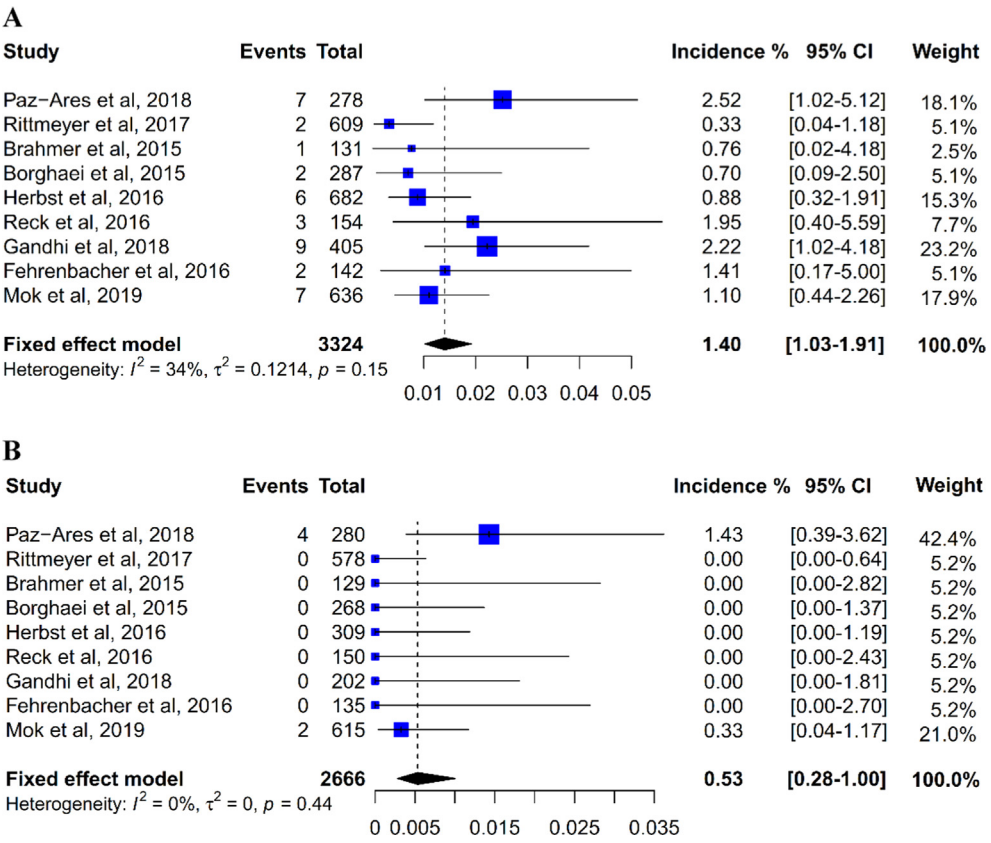

Fig. 2. Incidence of all grade colitis treated with PD-1/PD-L1 inhibitors (A) versus chemotherapy (B).

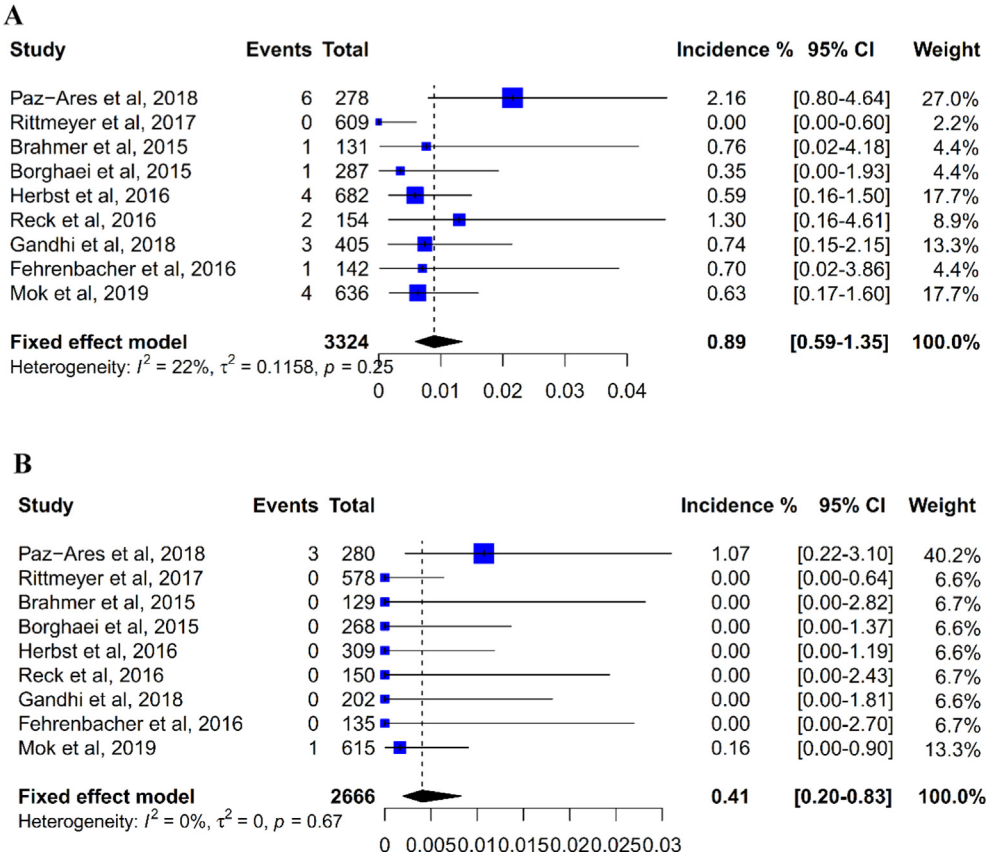

Fig. 3. Incidence of high grade colitis treated with PD-1/PD-L1 inhibitors (A) versus chemotherapy (B).

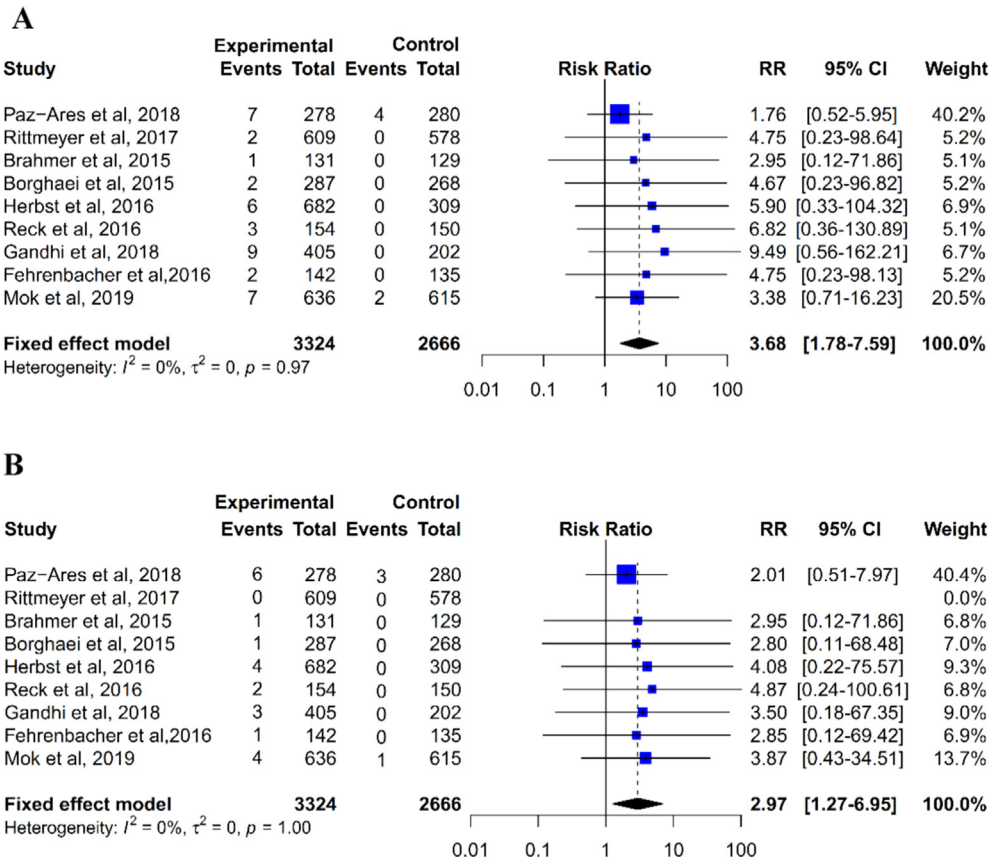

Fig. 4. Relative risks of all grade colitis (A) and high grade colitis (B) in the patients treated with PD-1/PD-L1 inhibitors compared with chemotherapy.

targeting agent is a significant risk factor for colitis.

3.4. Incidence and relative risk of diarrhea

The incidence of all grade diarrhea was notably lower when compared with chemotherapy groups (11.62%, 95% CI: 7.32–18.45 vs 18.47%, 95% CI: 14.63–23.32; p < 0.001) (Fig. 5), while there was no significant difference in grade 3–5 diarrhea (1.36%, 95% CI: 0.65–2.83 vs 1.95%, 95% CI: 1.45–2.63; p = 0.97) (Fig. 6).

Additional analysis of relative risk revealed that PD-1/PD-L1 treatment may moderately reduce the risk of all grade diarrhea (RR: 0.64, p = 0.03), whereas grade 3–5 diarrhea seemed to be no significant decrease in the experimental arms (RR: 0.83, p = 0.64) (Fig. 7). There was significant statistical heterogeneity assessed by the I^2 and p value in both analyses (I^2 = 89%, p < 0.01; I^2 = 59%, p = 0.01, respectively), thus we used random-effects models and performed sensitivity analyses to explore potential sources of heterogeneity between studies.

3.5. Subgroup analysis

To further investigate the type of PD-1 or PD-L1 inhibitors could affect the incidence and relative risk of colitis, we performed subgroup analyses based on these two different ICIs. The incidence of any grade colitis did not differ significantly between PD-1 and PD-L1 inhibitors, although not statistically significant, a slightly higher likelihood of all grade colitis was noted in patients (1.52%, 95% CI: 1.10–2.11 vs 0.68%, 95% CI: 0.26–1.81; p = 0.06) (Supplementary Fig. 1). We also found the incidence of grade 3–5 colitis was statistically different in both groups (0.95%, 95% CI: 0.62–1.46 vs 0.35%, 95% CI: 0.07–1.70; p = 0.04) (Supplementary Fig. 2).

Treatment with PD-1 inhibitors may significantly result in the increase of RR of any grade and high grade colitis compared with the control arms (RR: 3.56, p = 0.001; RR: 2.98, p = 0.02), while no significant differences were found between PD-L1 inhibitors for all grade (RR: 4.75, p = 0.15) and high grade colitis (RR: 2.85, p = 0.52) (Supplementary Fig. 3).

Moreover, we evaluated the potential role of ICIs for patients receiving first-line therapy or second-line therapy. In patients receiving PD-1/PD-L1 inhibitors, the incidence of all grade colitis was significantly higher in patients receiving first-line therapy than second-line therapy (1.88%, 95% CI: 1.28–2.75 vs 0.78%, 95% CI: 0.45–1.33; p = 0.01) (Supplementary Fig. 4). Similarly, there were significant differences in the incidence of grade 3–5 colitis between first-line therapy and second-line therapy (1.18%, 95% CI: 0.71–1.95 vs 0.51%, 95% CI: 0.25–1.04; p = 0.02) (Supplementary Fig. 5).

We also assessed whether RR may vary with treatment regimens. The result implicated that when compared with first-line therapy, second-line therapy associated with an augment risk of all grade colitis (RR: 3.29, p = 0.006; RR: 4.69, p = 0.026). Whereas for grade 3 and higher colitis, patients receiving primary PD-1/PD-L1 inhibitors may have more propensity in lead to enhanced RR of all grade colitis (RR: 2.85, p = 0.043) than previously chemotherapy treatment (RR: 3.25, p = 0.141) (Supplementary Fig. 6).

3.6. Quality assessment and sensitivity analysis

The Cochrane risk of bias tool was used to measure the quality of the included studies. As presented in Supplementary Fig. 7, no clinical trial was verified to be high risk, evidence of overall risk of bias was limited, indicating that the quality of all included studies was qualified. Funnel plot analysis for publication bias was not performed owing to the small size.

Sensitivity analysis showed that omitting any one of the studies at a time did not influence the overall result of the pooled analysis. The data

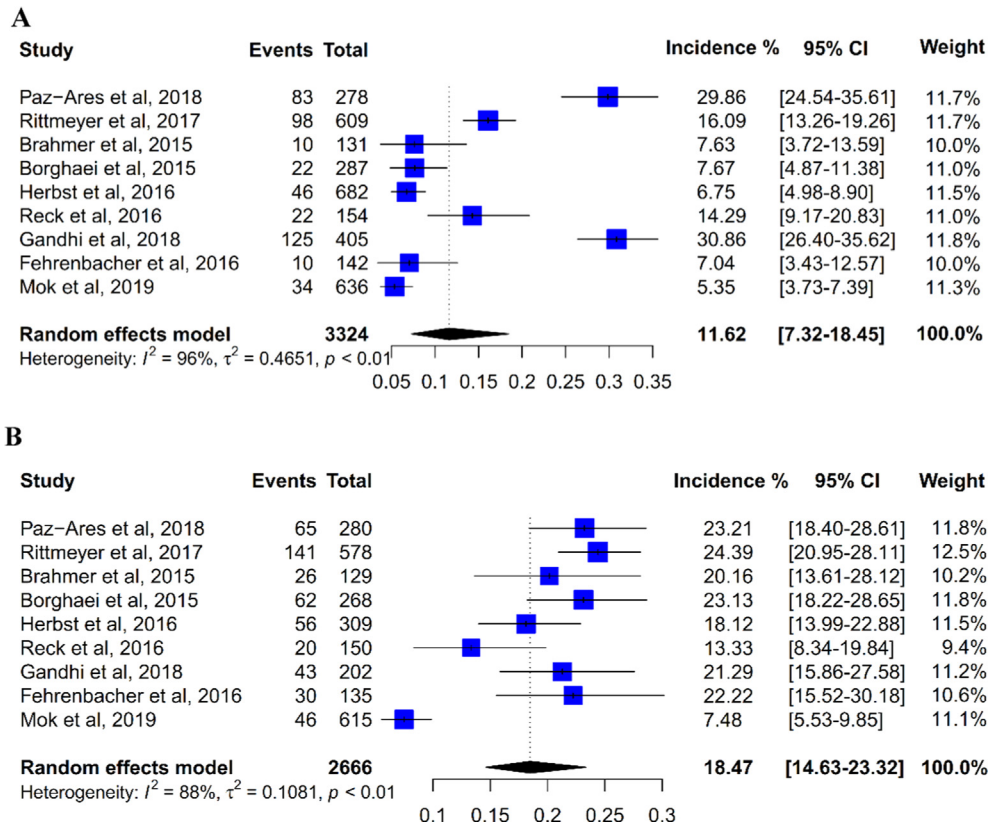

Fig. 5. Incidence of all grade diarrhea treated with PD-1/PD-L1 inhibitors (A) versus chemotherapy (B).

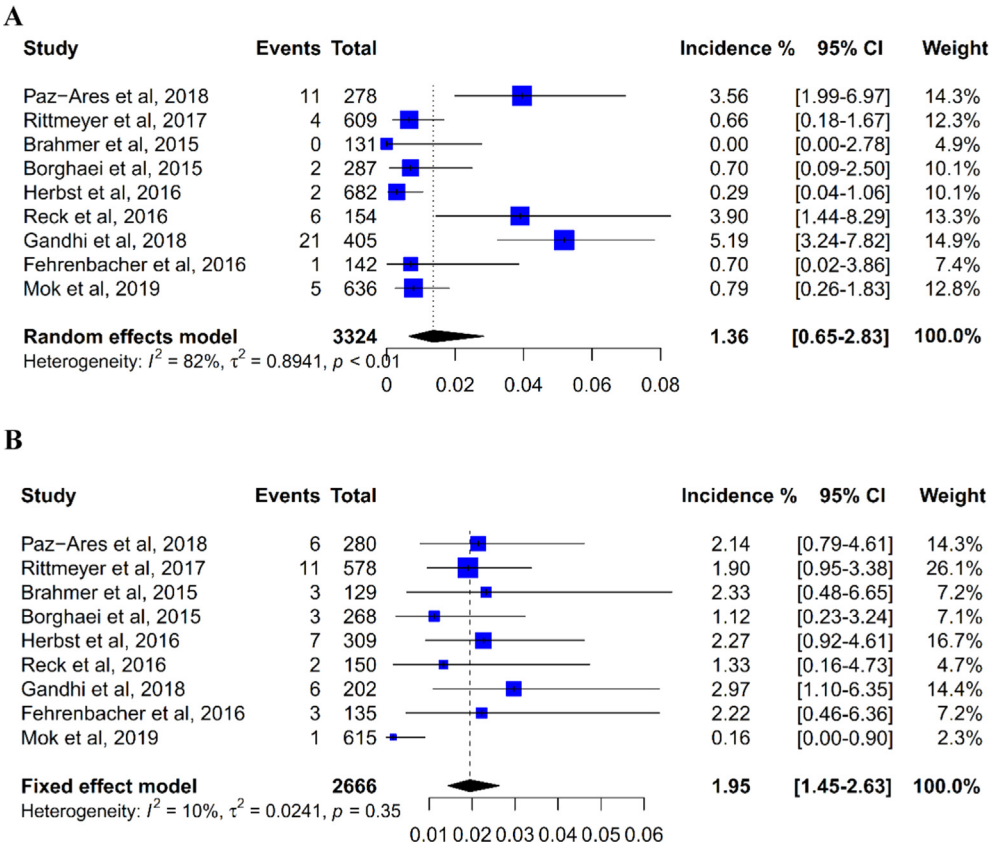

Fig. 6. Incidence of high grade diarrhea treated with PD-1/PD-L1 inhibitors (A) versus chemotherapy (B).

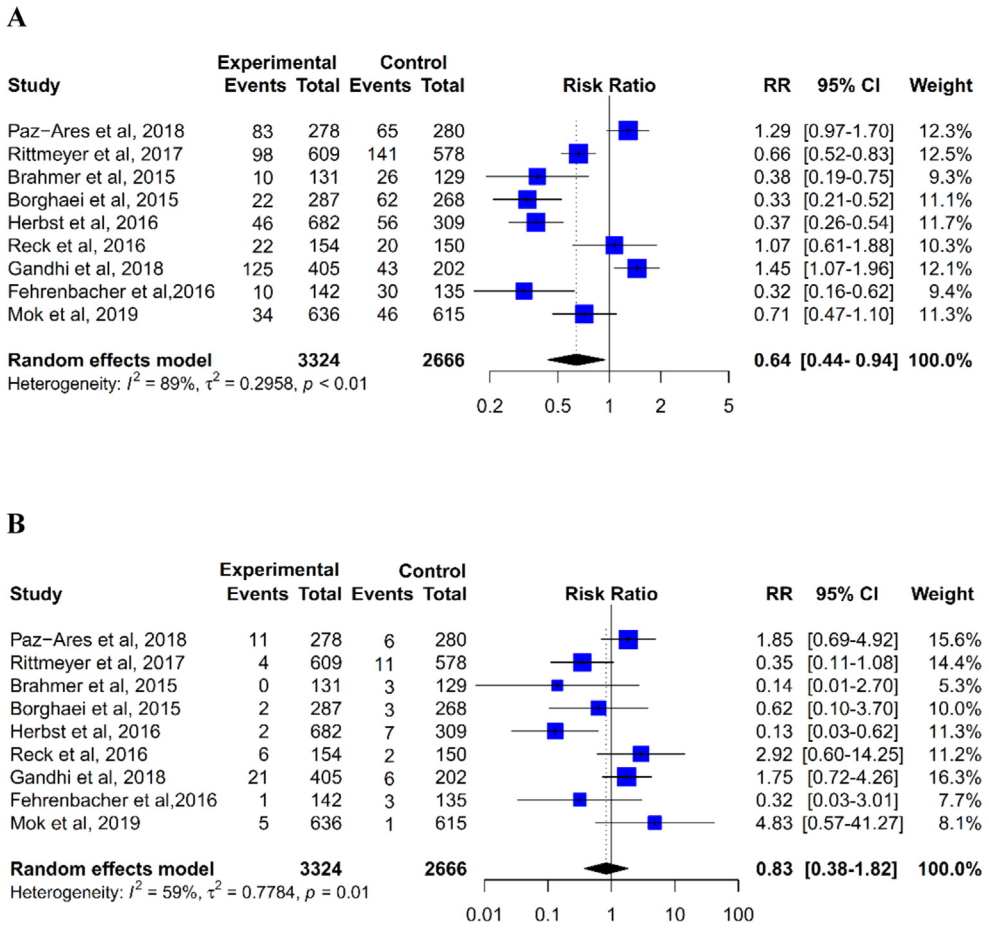

Fig. 7. Relative risks of all grade diarrhea (A) and high grade diarrhea (B) in the patients treated with PD-1/PD-L1 inhibitors compared with chemotherapy.

is shown in Supplementary Fig 8.

4. Discussion

The therapeutic modalities have dramatically altered in recent years owing to the advent of PD-1/PD-L1 inhibitors in NSCLC patients. As the great improvements of prolonged overall survival (OS) and progression-free survival (PFS), nivolumab and pembrolizumab was first approved for clinical applications in advanced NSCLC after progressing to first-line platinum-based chemotherapy [11]. Many additional checkpoint blocking agents are currently undergoing clinical evaluation. While despite the significant efficacy, the risk of irAEs cannot be ignored. IrAEs clinically manifest as symptoms including pulmonary, gastrointestinal, hepatic, endocrine and dermatologic events [12], which also affect the blood, heart and nervous system [13]. Among these IrAEs, the risk of gastrointestinal disorders such as colitis and diarrhea have recently raised more concerns. Although a small number of patients with colitis and diarrhea had been reported in RCTs of PD-1/L1 inhibitors, none of these trials were collected to systematically assess these rare events. To our knowledge, this is the first meta-analysis assessing the incidence and relative risk of colitis and diarrhea targeting PD-1/PD-L1 inhibitors in NSCLC patients.

Here, we demonstrate that when compared with chemotherapy arms, PD-1/PD-L1 inhibitors may increase the incidence and relative risk of all-grade and high-grade colitis. This is presumably due to the fact that PD-1/PD-L1 inhibitors may alter intestinal mucosal immune response. Recent studies have found newly subpopulation of T cell, named tissue-resident memory T (T_{RM}) cells, which are mainly present in peripheral tissues like skin, intestinal tract and joint [14,15]. It has been reported that T_{RM} cells appear to represent important components in immune surveillance [16]. Blockade of PD-1 receptor on T_{RM} cells may strongly promote the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) and Interleukin 17 (IL-17) [17,18]. Persistent stimulation of these pro-inflammatory signal leads to epithelial destruction predisposing for perpetuation of intestinal inflammation. Similar hypothesis was confirmed in animal experiments. Zundler et al demonstrated that accumulation of T_{RM} cells in the colon may trigger the initiation of colitis, suggesting the secretion of inflammatory factors may be a latent mechanism of colitis [19].

Furthermore, PD-1 inhibitors are also consistently related to higher incidence and RR of colitis than PD-L1 inhibitors. Similar results had been reported in the meta-analysis about PD-1/PD-L1 inhibitors-related pneumonitis [20]. In addition, Tartarone et al also demonstrated that PD-L1 inhibitors showed a more favorable trend than PD-1 inhibitors in the incidence of pneumonia [21]. The potential mechanism remains to be elucidated. It has been documented that PD-1/PD-L1 mediating immune pathways play a pivotal role in anti-tumor immune responses. Blockage of PD-1 inhibitory checkpoint may rescue T cells from exhausted state. At the same time, ligands of PD-1 receptor including PD-L1 and PD-L2 were also blocked. By contrast, PD-L1 inhibitors only depress the affinity between PD-1 and PD-L1, maintaining possible immunomodulatory function of PD-L2 [22]. Mechanistic studies in mice further substantiate the indispensable effect of PD-L2 on resistance to infection [23,24].

In addition, treatment naïve patients tend to suffer from higher occurrence of all grade and grade 3–5 colitis, debunking the false belief that lung cancer patients who receive prior chemotherapy were more likely to develop higher incidence of adverse events. Moreover, it is highly possible that PD-1/PD-L1 inhibitors may reduce the occurrence

and RR of all grade diarrhea, indicating that we cannot equate the incidence of diarrhea with the occurrence of colitis.

Timely and appropriate management of Immune mediated colitis and diarrhea is crucial for favorable prognosis. Early diagnosis would be likely to prevent complications of persistent or progressive symptoms and also to reduce the duration of ICI treatment intervention [25]. Knowledge of the timing of suspected symptom onset is helpful for diagnosis, the majority severe colitis and diarrhea tend to occur within the first 6 months of commencing treatment [26]. Clinical, endoscopic and histological characteristics can also be available to assist the diagnosis [27]. The following management of ICI-related colitis and diarrhea should be depended on the severity of symptoms. For mild symptoms, supportive measures and anti-motility agents like loperamide may be used for the relief of symptoms. For moderate symptoms, ICIs therapy could be temporarily held and oral or Intravenous glucocorticoids could be administered with an initial dose corresponding to 0.5–1 mg/kg/day of methylprednisolone until improvement of symptoms. If diarrhea and colitis persist despite treatment, hospitalization must be considered. Methylprednisolone dosage may be increased to 2 mg/kg/day, if no improvement within 2–3 days, commence infliximab or vedolizumab. Sigmoidoscopy and biopsy may assist in determining the duration of treatment [25,28].

The current limitations of our meta-analysis are listed below: (a) The major challenge was the overlap in Common Terminology Criteria for Adverse Events (CTCAE) definitions which may limit understanding of the true incidence of adverse events of special interest. Immune-modulated colitis can be characterized by diarrhea and abdominal pain, this could result in a potential uncertainty regarding the data quality, which will require to be elucidated for further studies of immunotherapy. (b) Our meta-analysis lack of individual patient data providing adequate information about immunotherapy, which may help assess therapeutic efficacy according to disease and patient variables. Therefore, we are unable to investigate whether the occurrence and risk of immune-related colitis in different race/ethnic or different locales are similar. (c) Although our meta-analysis searched comprehensive databases, the overall sample size was relatively small. Consequently, the statistical performance of certain outcome indicators may be limited, more RCTs with much larger samples are needed to validate these clinical outcomes. (d) Our study provides critical insights into the adverse events from treatment with PD-1/PD-L1 inhibitors, while anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) agents were not included for the following assessment. A report involving ICI-related fatal toxic effects indicated immune-related colitis are more frequent with anti-CTLA-4 monotherapy or combination treatment than PD-1/PD-L1 inhibitors [29]. Therefore, it is plausible to surmise that immune-related colitis in our meta-analysis was underestimated.

5. Conclusion

In this meta-analysis of RCTs, we demonstrated PD-1/PD-L1 inhibitors may lead to a higher incidence and RR of all grade and high grade immune-induced colitis but lower incidence and RR of all grade diarrhea as compared with chemotherapy groups, which may provide a basis to increase clinician awareness. Timely diagnosis and prompt effective management are also required for clinicians to avoid potentially life-threatening evolution. Future studies with more complete understanding of immune-mediated colitis, clinicians may overcome the present concerns about this life-threatening adverse event.

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Compliance with ethical standards

Ethical approval. The article does not contain any studies with human participants performed by any of the authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105975.

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