Original Article

Impact of treatment line on risks and benefits of immune checkpoint inhibitor in patients with advanced non-small cell lung cancer and interstitial lung disease: a systematic review and meta-analysis of cohort studies

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Background: There is no clear consensus regarding the safety and efficacy of immune checkpoint inhibitors (ICIs) in patients with advanced non-small cell lung cancer (NSCLC) and pre-existing interstitial lung disease (ILD). We aimed to elucidate the impact of ICIs on pre-existing ILD.

Methods: We systematically queried PubMed-MEDLINE, Embase-Scopus, and ISI Web of Science databases up to January 10, 2022. The pooled any-grade and grade 3–5 ICI-associated pneumonitis (ICIP) rate and objective response rate (ORR) in patients with pre-existing ILD were mainly evaluated. The relative risk (RR) was also evaluated for pre-existing ILD and usual interstitial pneumonia (UIP) patterns. Sensitivity and subgroup analyses were performed to assess the heterogeneity.

Results: In total, 17 studies involving 5,529 patients were included in the meta-analysis. The pooled ICIP rate was 30% [95% confidence interval (CI): 24–36%]; it was found to be significantly higher in patients with pre-existing ILD relative to those without (RR =3.05, 95% CI: 2.53–3.69; I2=0.0%). The pooled grade 3–5 ICIP rate was 12% (95% CI: 9–15%); this was also significantly higher in patients with pre-existing ILD (RR =3.19, 95% CI: 2.32–4.38; I^2=0.0%). According to subgroup analysis, these ICIP rates were not significantly different among the treatment lines (first, ≥ second, and mixed) (P=0.33) whereas the pooled ORR was 36% (95% CI: 24–48%; I^2=53.7%) with a significant difference among the treatment lines (P=0.027). The pooled ICIP rate was independent of the UIP pattern (RR =1.06, 95% CI: 0.86–1.32; I^2=0.0%).

Conclusions: Overall, ICIs should be administered cautiously in patients with pre-existing ILD, regardless of the treatment line. Moreover, the risks of ICIP may outweigh ICI benefits, especially in second-or later-line treatment. These results need to be further confirmed by meta-analyses including more observational cohort studies in clinical setting.

Keywords: Immune checkpoint inhibitors (ICIs); non-small cell lung cancer (NSCLC); pre-existing interstitial lung disease; pneumonitis

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Introduction

Globally, non-small cell lung cancer (NSCLC) is a common cause of cancer-related mortality (1). Most patients with NSCLC are at an advanced stage on first diagnosis (2).

In recent years, the continued development of immune checkpoint inhibitors (ICIs), a breakthrough treatment strategy for advanced NSCLC, have enabled durable survival for several years (3,4). A favorable response to ICIs results in longer survival for patients. However, a small number of patients achieve such benefits; some patients show immune-related adverse events (irAEs), including cutaneous lesions, nephritis, hepatitis, colitis, endocrinopathies, neuropathies, and pneumonitis (5). These irAEs can potentially become serious and fatal; in NSCLC particularly, pneumonitis is reported to be the most serious and fatal AE (6).

Interstitial lung disease (ILD) is one of the most common complications at the diagnosis of lung cancer (7). A previous study reports that approximately 10–20% of patients with ILD have combined LC conditions in the real-world setting (8). Despite such a staggering number, patients with pre-existing ILD are almost always excluded from clinical trials of NSCLC owing to the concerns regarding treatment-associated pneumonitis due to chemotherapies and radiotherapy. Therefore, there are relatively fewer studies in this group of patients (9,10). ICIs are drugs that also cause treatment-associated pneumonitis, and pre-existing ILD is a risk factor associated with ICI-associated pneumonitis (ICIP) in patients with different cancer types (11).

Although the safety and efficacy have been evaluated in a few prospective observational studies with a small number of cases and multiple retrospective observational studies (12-28), there is no consensus regarding the use of ICIs in NSCLC patients with pre-existing ILD. Thus, we performed a meta-analysis using the available reports to elucidate the risks and benefits of ICIs for advanced NSCLC patients with pre-existing ILD. Our systematic review and meta-analysis were conducted following the PRISMA reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-162/rc).

Methods

Search strategy

Our systematic review and meta-analysis were conducted following the PRISMA guidelines. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD 42022302783). We systematically queried the PubMed-MEDLINE, Embase-Scopus, and Web of Science databases to screen eligible studies published before January 10, 2022. The following search terms were used for the literature screen: "Non-Small Cell Lung Cancer" OR "NSCLC" AND "immune checkpoint inhibitor" OR "ICI" OR "immunotherapy" OR "nivolumab" OR "pembrolizumab" OR "atezolizumab" OR "durvalumab" OR "programmed death-1" OR "PD-1" OR "programmed death ligand-1" OR "PD-L1" AND "interstitial pneumonia" OR "interstitial pneumonitis" OR "interstitial lung".

Selection criteria

The inclusion criteria were as follows: (I) cohort studies that evaluated advanced NSCLC patients who had undergone ICI-based treatment; (II) non-comparative or comparative studies including patients with pre-existing ILD; (III) studies with safety data on any-grade and grade 3–5 ICIP rate, and (IV) articles written in English. Reviews, case reports, animal studies, and duplicated publications were excluded.

Data extraction and quality assessment

Two investigators (KM and TS) independently extracted the following data from the included studies: the first name of the authors, year of publication, type of study, sample size, age, treatment lines, treatment regimen, any-grade ICIP rate, grade 3–5 ICIP rate, objective response rate (ORR), disease control rate (DCR), and median progression-free survival (PFS). The main outcomes were pooled any-grade ICIP rate, grade 3–5 ICIP rate, and ORR. Additionally, we evaluated the pooled DCR, and the relative risk (RR) for

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pre-existing ILD (yes *vs.* no) and radiological patterns (UIP *vs.* non-UIP). The Newcastle-Ottawa scale (NOS) standard was used for research quality assessment of observational studies (29), wherein low quality referred to studies with scores ≤4. The two authors evaluated the quality of the extracted studies. Any differences in opinions regarding the studies between the two authors were resolved with the help of a third investigator (TK).

Statistical analysis

The Stata (version 17.0; Stata Corporation, College Station, TX) tool was used to calculate the pooled any-grade ICIP rate, grade 3–5 ICIP rate, ORR, DCR, and the RR for pre-existing ILD and radiological patterns.

Heterogeneity between studies was assessed using the I^2 statistics (30). According to the heterogeneity test using I^2 statistics, the fixed-effects model was preferred over the random-effects model in the absence of statistically moderate or high heterogeneity (I^2>50%) between the studies. An integrated analysis was performed to calculate the 95% confidence interval (CI); subsequently, the forest plots were plotted for the pooled effect sizes and RR.

The potential effects in presence of a significant heterogeneity (I^2>50%) in the pooled effect size (31) were assessed. Subgroup analyses were performed for the treatment lines (first, ≥ second, and mixed). Differences between subgroups were evaluated using the I^2 statistics. Additionally, sensitivity analyses were performed using leave-one-out method and the heterogeneity was re-evaluated after excluding the study that most affected the pooled outcomes and had the lowest sample size.

Potential publication biases were further validated using Funnel plots, Begg's and Egger's tests and trim and fill analysis (32). All statistical analyses were two-sided. Statistical significance was set at P<0.05.

Results

Search results

The PRISMA flowchart for this meta-analysis is shown in *Figure 1*. Duplicate and irrelevant studies were removed after construing a total of 487 titles. In total, 319 records were screened and 300 articles were excluded based on their titles and abstracts. All investigators fully assessed the remaining 19 articles and agreed to include 17 eligible studies comprising 5,529 patients in the subsequent meta-analysis (12-28).

Study characteristics

The extracted data are listed in *Table 1*. Three prospective and 14 retrospective cohort studies were included. The eligible studies were published between 2017 and 2021 and the sample sizes ranged between 5 and 221; a total of 543 patients with pre-existing ILD and 4,986 patients without ILD were analyzed. In most studies, the median age was around 70 years (range, 63–78 years) and the treatment lines and regimen were described. Two studies described the first-line treatment of patients with pembrolizumab alone (18,25), while six studies described only the second-line treatment (12-14,19,23,26). Of the six studies, only nivolumab was administered in five studies (12-14,23,26), and atezolizumab in one study (19). In the remaining nine studies, ICIs such as nivolumab, pembrolizumab, atezolizumab, and durvalumab were administered in various treatment lines (15-17,20-22,24,27,28).

Most observational studies (14 of 17) were scored 6 to 8 points for the NOS assessment without inclusion of the low-quality studies. The results of the quality assessment of the included studies are presented in Table S1.

The pooled ICIP rate in NSCLC patients with pre-existing ILD

The pooled any-grade and grade 3–5 ICIP rates were obtained from 17 and 16 eligible studies, respectively (12-28). The pooled any-grade ICIP rate was 30% [95% confidence interval (CI): 24–36%] (12-28) and statistically significant heterogeneity was obtained through analysis (I^2=53.7%, P=0.01) (*Figure 2A*). Therefore, a subgroup analysis was performed based on the treatment line to examine the cause of heterogeneity. The treatment lines could not explain the heterogeneity between the studies because the subgroup interactions did not show any statistical significance (P=0.33) (Figure S1A). Moreover, we performed a sensitivity analysis using leave-one-out method and excluding the study by Fujita *et al.* (18) (Figure S1B). The pooled any-grade ICIP rate was almost unchanged (28%; 95% CI: 22–33%), which suggested the robustness of the outcome whereas significant heterogeneity disappeared (I^2=38.8%, P=0.07) (Figure S1C).

Second, the pooled grade 3–5 ICIP rate was 12% (95% CI: 9–15%) (12-26, 28). No statistically significant

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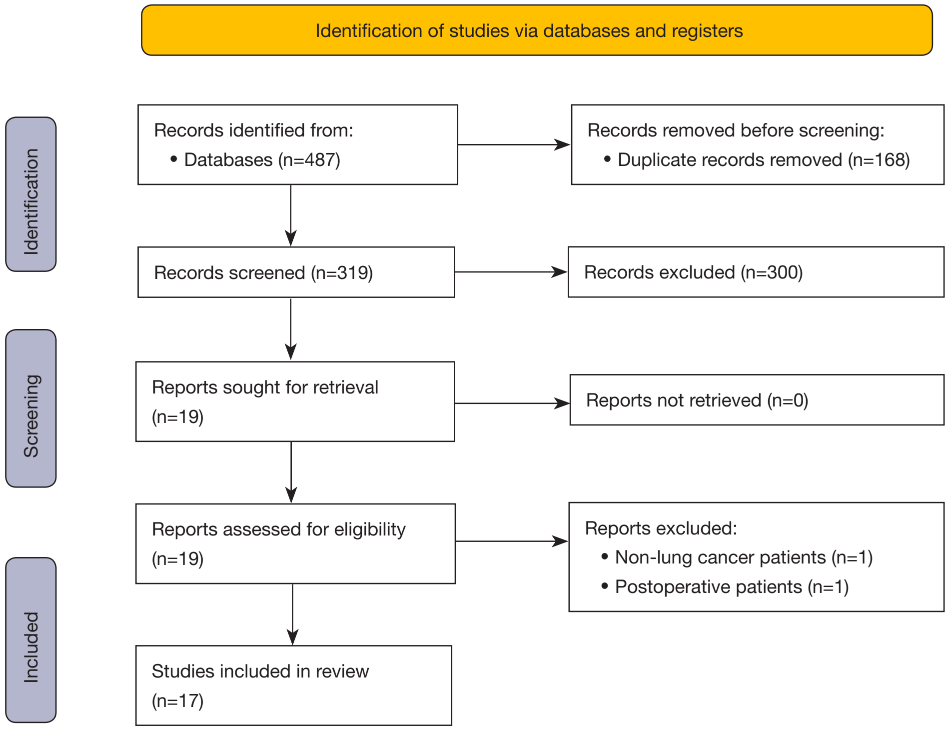

Figure 1 Flow diagram for search and selection of studies for meta-analysis.

heterogeneity was obtained (I^2=0.0%, P=0.64) and there was little variation among the studies (*Figure 2B*).

The funnel plots for the pooled any-grade and grade 3–5 ICIP rates, shown in Figure S2, suggest the presence of publication biases (Begg's and Egger's tests, P=0.07 and 0.034, and P=0.009 and 0.022, respectively). The symmetry in the funnel plots may have been shown if the studies by Fujimoto *et al.* and Byeon *et al.* were not excluded in these meta-analyses (12,14,17). Additionally, a trim and fill method revealed that the re-evaluated pooled any-grade and grade 3–5 ICIP rates with imputed studies were similar to the observed outcomes (28%; 95% CI: 20–35% and 10%; 95% CI: 8–13%, respectively), indicating the stability against publication biases.

The pooled ORR and DCR of ICIs in NSCLC patients with pre-existing ILD

The ORR data were obtained from a total of 11 eligible studies (12-15,17-20,24,25,27). The pooled ORR was 36% (95% CI: 24–48%), indicating high heterogeneity (I^2=74.7%, P<0.001) (*Figure 3A*). A subgroup analysis based on the treatment line was performed, and the results suggested that the treatment line could explain the heterogeneity among the studies since the subgroup interactions were statistically significant (P=0.027) (*Figure 3B*). When the ICIs were used in the first line and ≥second line, the pooled ORR were 67% (95% CI: 43–91%) and 26% (95% CI: 7–45%), respectively.

The DCR data were obtained from ten eligible studies (12-15, 17-20, 24, 25). The pooled DCR was 69% (95% CI: 62–76%), suggesting little heterogeneity (I^2=8.0%, P=0.37) (*Figure 3C*).

Funnel plots for the pooled ORR and DCR were largely symmetrical (Figure S3), which indicated no publication biases (Begg's and Egger's tests, P=0.64 and 0.26, and P=0.47 and 0.62, respectively).

The association between the ICIP and pre-existing ILD

The any-grade and grade 3–5 ICIP rates were compared between patients with and without pre-existing ILD. The data were obtained from ten (13,15-17,21,23-27) and nine (13,15-17,21,23-26) eligible studies, respectively. The any-grade ICIP rate was significantly higher in patients with pre-existing ILD relative to those without (RR =3.05, 95%

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Table 1 Characteristics of cohort studies

Author, year	Type of study	Pre-existing ILD group													Non-ILD group					
		n	Age, years	Treatment line	Regimen	ORR (%)	DCR (%)	mPFS (months)	Any grade ICIP rate (%)	Grade≥3 ICIP rate (%)	UIP pattern, n	ICIP rate (%) (UIP pattern)	Non-UIP pattern, n	ICIP rate (%) (non-UIP pattern)	n	Age, years	Treatment line	Regimen	Any grade ICIP rate (%)	Grade ≥3 ICIP rate (%)
Fujimoto, 2017 (12)	Prospective	6	72 [64–81]	≥2nd line: 6	Nivolumab: 6	50.0 (3/6)	100 (6/6)	5.2 (NA)	0 (0/6)	0 (0/6)	0	0	6	0 (0/6)	NA	NA	NA	NA	NA	NA
Kanai, 2018 (13)	Retrospective	26	71 [55–85]	≥2nd line: 26	Nivolumab: 26	26.9 (7/26)	57.7 (15/26)	2.7 [1.7–5.3]	30.8 (8/26)	19.2 (5/26)	12	25.0 (3/12)	14	35.7 (5/14)	190	69 [30–89]	≥2nd line: 190	Nivolumab: 190	11.6 (22/190)	5.3 (10/190)
Fujimoto, 2019 (14)	Prospective	18	71.5 [68.5–76.3]	≥2nd line: 18	Nivolumab: 18	38.9 (7/18)	72.2 (13/18)	7.4 [1.8–16.8]	11.1 (2/18)	0 (0/18)	0	0	18	11.1 (2/18)	NA	NA	NA	NA	NA	NA
Shibaki, 2019 (15)	Retrospective	14	63 [33–83]	1st line: 4; ≥2nd line: 10	Nivolumab: 9; Pembrolizumab: 5	21.4 (3/14)	57.1 (8/14)	4.3 [1.1–19]	28.6 (4/14)	7.1 (1/14)	NA	NA	NA	NA	196	61 [30–83]	1st line: 35; ≥2nd line: 161	Nivolumab: 118; Pembrolizumab: 78	11.2 (22/196)	4.1 (8/196)
Byeon, 2020 (17)	Retrospective	6	63 [59–72]	1st line: NA; ≥2nd line: NA	Nivolumab: NA; Pembrolizumab: NA	16.7 (1/6)	50.0 (3/6)	1.4 (NA)	0 (0/6)	0 (0/6)	5	0 (0/5)	1	0 (0/1)	231	NA	1st line: NA; ≥2nd line: NA	Nivolumab: NA; Pembrolizumab: NA	3.9 (9/231)	1.7 (4/231)
Nakanishi, 2019 (16)	Retrospective	13	NA	1st line: NA; ≥2nd line: NA	Nivolumab: NA; Pembrolizumab: NA	NA	NA	NA	46.2 (6/13)	15.4 (2/13)	3	66.7 (2/3)	10	40.0 (4/10)	70	NA	1st line: NA; ≥2nd line: NA	Nivolumab: NA; Pembrolizumab: NA	11.4 (8/70)	8.6 (6/70)
Fujita, 2020 (18)	Retrospective	5	78 [75–81]	1st line: 5	Pembrolizumab: 5	60.0 (3/5)	80 (4/5)	NA	80.0 (4/5)	40.0 (2/5)	1	100 (1/1)	4	75.0 (3/4)	NA	NA	NA	NA	NA	NA
Ikeda, 2020 (19)	Prospective	17	70 [66–73]	≥2nd line: 17	Atezolizumab: 17	6.3 (1/16)	62.5 (10/16)	3.4 [0.8–5.9]	29.4 (5/17)	23.5 (4/17)	7	57.1 (4/7)	11	9.1 (1/11)	NA	NA	NA	NA	NA	NA
Nishiyama, 2020 (20)	Retrospective	48	70 [52–83]	1st line: 13; ≥2nd line: 35	Nivolumab: 21; Pembrolizumab: 25; Atezolizumab: 2	45.8 (22/48)	68.8 (33/48)	4.7 (NA)	14.6 (7/48)	10.4 (5/48)	9	11.1 (1/9)	39	15.4 (6/39)	NA	NA	NA	NA	NA	NA
Shibaki, 2020 (21)	Retrospective	17	66 [33–83]	1st line: 5; ≥2nd line: 12	Nivolumab: 12; Pembrolizumab: 5	NA	NA	NA	29.4 (5/17)	11.8 (2/17)	NA	NA	NA	NA	314	62 [30–84]	1st line: 36; ≥2nd line: 278	Nivolumab: 236; Pembrolizumab: 78	9.9 (31/314)	3.8 (12/314)
Ichimura, 2022 (28)	Retrospective	33	NA	1st line: 8; ≥2nd line: 25	Nivolumab: 18; Pembrolizumab: 12; Atezolizumab: 3	NA	NA	NA	33.3 (11/33)	21.2 (7/33)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Takahara, 2021 (22)	Retrospective	14	NA	1st line: NA; ≥2nd line: NA	Nivolumab: NA; Pembrolizumab: NA; Durvalumab: NA	NA	NA	NA	57.1 (8/14)	28.6 (4/14)	3	66.7 (2/3)	11	54.5 (6/11)	NA	NA	NA	NA	NA	NA
Yamamoto, 2021 (23)	Retrospective	221	NA	≥2nd line: 221	Nivolumab: 221	NA	NA	NA	25.3 (56/221)	10.9 (24/221)	NA	NA	NA	NA	3380	NA	≥2nd line: 3,380	Nivolumab: 3,380	8.5 (288/3,380)	3.5 (117/3,380)
Tasaka, 2021 (24)	Retrospective	49	71 [57–83]	1st line: 14; ≥2nd line: 35	Nivolumab: 22; Pembrolizumab: 27	49.0 (24/49)	69.4 (34/49)	5.9 (NA)	30.6 (15/49)	16.3 (8/49)	8	NA	41	NA	412	69 [34–88]	1st line: 97; ≥2nd line: 315	Nivolumab: 247; Pembrolizumab: 165	9.5 (39/412)	3.6 (15/412)
Yamaguchi, 2021 (25)	Retrospective	10	NA	1st line: 10	Pembrolizumab: 10	70.0 (7/10)	90.0 (9/10)	8.6 (NA)	20.0 (2/10)	10.0 (1/10)	1	0 (0/1)	9	22.2 (2/9)	62	NA	1st line: 62	Pembrolizumab: 62	22.6 (14/62)	11.3 (7/62)
Yamaguchi, 2021 (26)	Retrospective	26	NA	≥2nd line: 26	Nivolumab: 26	NA	NA	NA	38.5 (10/26)	7.7 (2/26)	9	44.4 (4/9)	17	35.3 (6/17)	70	NA	≥2nd line: 70	Nivolumab: 70	5.7 (4/70)	0 (0/70)
Isono, 2021 (27)	Retrospective	20	NA	1st line: NA; ≥2nd line: NA	Nivolumab: 12; Pembrolizumab: 8	35.0 (7/20)	NA	NA	35.0 (7/20)	NA	3	NA	17	NA	61	NA	NA	NA	6.6 (4/61)	NA

ILD, interstitial lung disease; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; ICIP, immune checkpoint inhibitor-associated pneumonitis; UIP, usual interstitial pneumonia; NA, not applicable.

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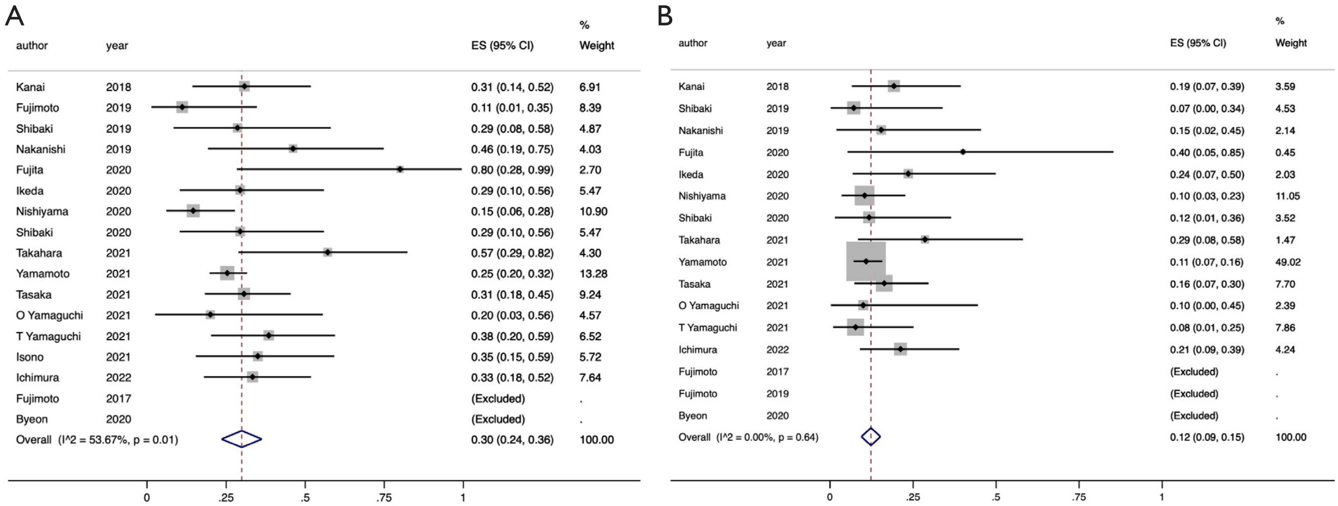

Figure 2 Forest plot of ICIP rates in advanced NSCLC patients with pre-existing ILD. The point estimate of ICIP rate for each study is represented by the filled diamond, and the horizontal line crossing the diamond represents the 95% CI. The open diamond represents the pooled ES. (A) Any grade ICIP rates; (B) grade 3–5 ICIP rates. ICIP, immune checkpoint inhibitor-associated pneumonitis; NSCLC, non-small cell lung cancer; ILD, interstitial lung disease; CI confidence interval; ES, effect size.

CI: 2.53–3.69). Moreover, no heterogeneity was observed in this analysis (I^2=0.0%, P=0.61) (*Figure 4A*).

The grade 3–5 ICIP rate was also significantly higher in patients with pre-existing ILD relative to those without (RR =3.19, 95% CI: 2.32–4.38); no heterogeneity was observed in this analysis (I^2=0.0%, P=0.86) (*Figure 4B*).

Funnel plots showed the absence of publication biases (Begg's and Egger's tests, P=0.59 and 0.49, and P=0.92 and 0.69, respectively) (Figure S4).

The association between the ICIP and radiological patterns

Finally, the any-grade ICIP rate was compared between the patients with UIP and non-UIP patterns, and the data were obtained from eight eligible studies (13,16,18-20,22,25,26). The any-grade ICIP rate was almost equivalent between the two groups of patients (RR =1.06, 95% CI: 0.86–1.32). Moreover, no heterogeneity was observed in this analysis (I^2=0.0%, P=0.99) (*Figure 5*).

Funnel plots showed the absence of any publication biases (Begg's and Egger's tests, P=0.90 and 0.97) (Figure S5).

Discussion

This systematic review and meta-analysis demonstrated that pre-existing ILD was associated with the incidence of pneumonitis caused by ICIs in patients with advanced NSCLC. The ORR and DCR were slightly higher in patients with pre-existing ILD than reported previously such as Checkmate 017 and 057 (3,4); however, these may be dependent on the treatment line. Any-grade and grade 3–5 ICIP rates were markedly higher in patients with pre-existing ILD (3,4,33). Additionally, the findings elucidated that the UIP pattern did not significantly increase the ICIP rate.

Thus, our findings provide the greatest evidence of the clinical safety and efficacy of immunotherapies for NSCLC patients with pre-existing ILD and may also have a large impact on combination therapy with ICIs (34).

Previously, several chemotherapies have been reported to increase the risk of pneumonitis in NSCLC patients with pre-existing ILD. Some retrospective cohort studies demonstrate that 14% and 12% of patients with ILD who received docetaxel and pemetrexed monotherapy, respectively, developed drug-associated pneumonitis (35,36). Many mechanisms, including cytotoxic and immune disorders, are involved in drug-associated pneumonitis. These mechanisms, sometimes independently or in combination, may be implicated in different forms of lung injury (37).

The mechanisms underlying ICIP remain poorly understood in patients with pre-existing ILD. However, a study showed that Th2 inflammation caused by the

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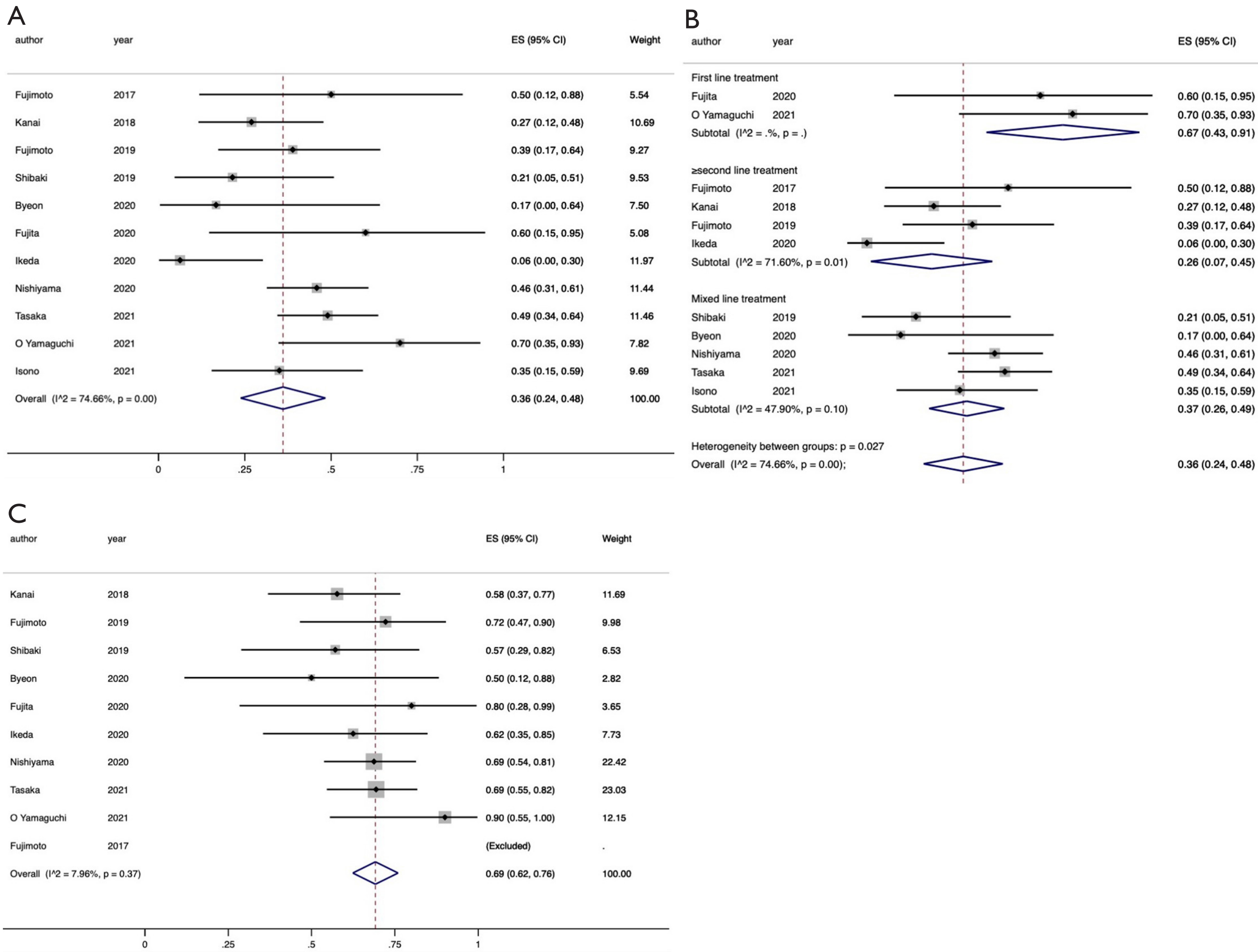

Figure 3 Forest plot of ORR and DCR in advanced NSCLC patients with pre-existing ILD. The point estimates of ORR and DCR for each study are represented by the filled diamond, and the horizontal line crossing the diamond represents the 95% CI. The open diamond represents the pooled ES. (A) ORR; (B) subgroup analysis of ORR based on treatment line (first line, ≥ second line, and mixed line); (C) DCR. ORR, objective response rate; DCR, disease control rate; NSCLC, non-small cell lung cancer; ILD, interstitial lung disease; CI, confidence interval; ES, effect size.

blockade of PD-1/PD-L2 interaction is a possible underlying mechanism (38). Moreover, others demonstrate that interleukin-6 (IL-6) plays an important role in ICIP, and anti-IL-6 antibodies are effective against ICIP (39,40). Increased IL-6 levels are detected in patients with acute exacerbation of idiopathic pulmonary fibrosis (IPF); moreover, IL-6 is a poor prognostic prediction factor in patients with ILD (41,42). Thus, ICIs may induce Th2 inflammation, thereby enhancing levels of IL-6 in pre-existing ILD, which may induce pneumonitis and allergy-like immune responses.

Recently, Zhang *et al.* first reported a meta-analysis regarding the clinical outcomes of ICIs in patients with advanced NSCLC and pre-existing ILD (43). They interpreted that the ICIs had favorable efficacy in patients with pre-existing ILD and ICIP was often mild and easily manageable. According to a report by Fujita *et al.* in the meta-analysis, three out of four patients with ICIP used steroid pulse therapy and managed to recover; however, two of them finally needed home oxygen therapy (18). Hence, the interpretation that ICIP is often mild and easily manageable may be risky. Moreover, we added seven more

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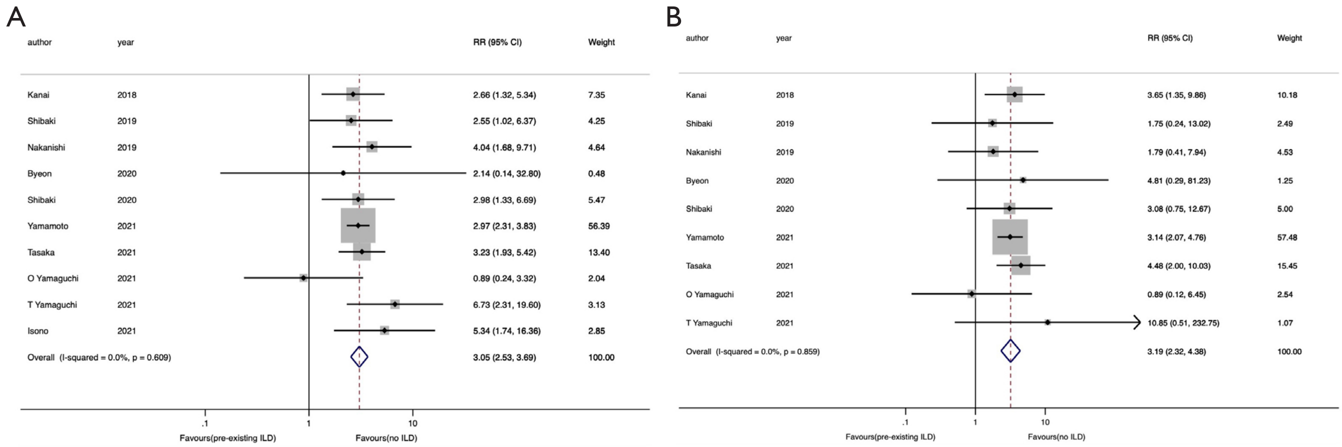

Figure 4 Forest plots of RR of ICIP rates in advanced NSCLC patients with pre-existing ILD compared to patients without ILD. The point estimate of RR for each study is represented by the filled diamond, and the horizontal line crossing the diamond represents the 95% CI. The open diamond represents the pooled RR. (A) Any grade ICIP rates; (B) grade 3–5 ICIP rates. RR, relative risk; ICIP, immune checkpoint inhibitor-associated pneumonitis; NSCLC, non-small cell lung cancer; ILD, interstitial lung disease; CI, confidence interval.

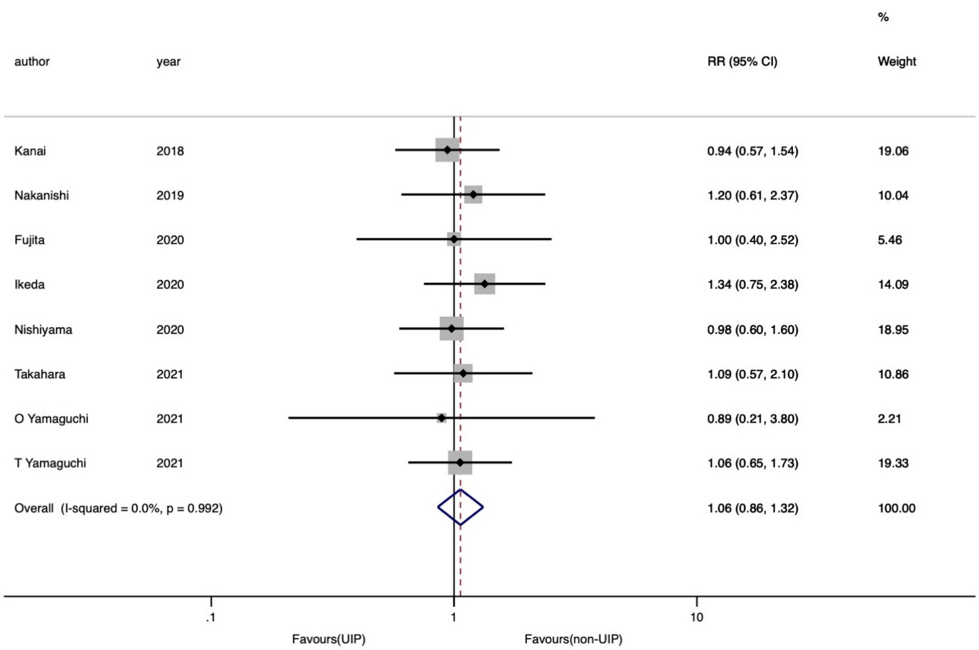

Figure 5 Forest plots of RR of any grade ICIP rates in advanced NSCLC patients with UIP pattern compared to patients with non-UIP patterns. The point estimates of RR for each study are represented by the filled diamond, and the horizontal line crossing the diamond represents the 95% CI. The open diamond represents the pooled RR. RR, relative risk; ICIP, immune checkpoint inhibitor-associated pneumonitis; NSCLC, non-small cell lung cancer; UIP, usual interstitial pneumonia; CI, confidence interval.

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studies in addition to the studies reported by Zhang *et al.*, including approximately three times as many patients with pre-existing ILD (543 patients *vs.* 179 patients). We further performed a subgroup analysis by treatment lines thorough the study protocol, and newly revealed that the pooled ORR may be dependent on the treatment lines and was 26% (95% CI: 7–45%) in the second-or later-line treatment, which was equivalent to the real-world data with ICI monotherapies in pretreated patients with NSCLC (44). Another real-world study reported the incidence of any-grade and grade 3–5 ICIP rates, which were approximately 10% and 4%, in the NSCLC patients treated with nivolumab (45). Therefore, considering the present ICIP rates, which were 30% in any-grade and 12% in grade 3–5, the risks of ICI monotherapy may outweigh its benefits, especially in second-or later-line treatment.

In this study, the ICIP rate was not significantly different between the UIP and non-UIP groups. IPF generally indicates a poorer prognosis relative to other idiopathic interstitial pneumonias and the incidence of acute exacerbation increases according to the UIP pattern (46,47). The reason for such difference remains unclear, and therefore, this warrants further investigation.

Finally, ICIs currently are used as key drugs for the treatment of patients with advanced NSCLC, along with various agents such as anti-angiogenic, cytotoxic, and molecularly targeted compounds (34,48). Such combination therapies are more effective than previous treatments; however, they also exert greater toxic effects. A previous meta-analysis of ICIs plus chemotherapy demonstrated that the RR was 2.92 (95% CI: 1.95–4.37) for the pooled ICIP compared to chemotherapy alone (49). The present meta-analysis included few patients with ICIs plus chemotherapy; therefore, ICIP may develop at a higher rate when ICIs plus chemotherapy are administered to patients with pre-existing ILD. Thus, treatments including ICIs should be cautiously administered for patients with pre-existing ILD.

This study had certain limitations. First, our meta-analysis included a small number of studies and sample sizes, which may have led to statistical insignificance of the results. Second, most of our sample included retrospective observational studies; therefore, there may have been several causes of inherent bias owing to the study design and unaccounted confounding factors. Third, due to the lack of detailed data, such as age, tumor proportion score, and respiratory function values, we could not perform appropriate subgroup and sensitivity analyses. Forth, most of the selected studies were of relatively poor-to-mild quality because the follow-up period as well as the final follow-up results were not stated. Therefore, all studies were selected to avoid systematic selection bias, which may have led to overestimation. Fifth, all the studies included only Asians, who may be more likely to develop ICIP compared to non-Asians, thereby, limiting the external validity of our findings (50). Sixth, we evaluated single arm of ICI monotherapies, and it is desirable to compare with a control arm in patients with pre-existing ILD. Finally, we mainly aimed to evaluate the safety and we did not assess the efficacy using indicators, such as PFS and OS. In clinical practice, a treatment should be decided on the basis of both efficacy and safety. Our findings are beneficial for generating hypotheses for future studies.

In summary, based on the findings of this meta-analysis, pre-existing ILD may be a risk factor for the incidence of ICIP in patients with NSCLC. Both any and severe grade ICIP rates were much higher in patients with pre-existing ILD than those of the previous reports whereas the ORR was comparable to that of previous reports on second-or later-line treatment. Therefore, ICIs should be administered cautiously in patients with pre-existing ILD, regardless of the treatment line. Moreover, the risk of ICIP may outweigh ICI benefits, especially in second-or later-line treatment. These results need to be further confirmed by meta-analyses, including more observational cohort studies in clinical setting.

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Footnote

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