Original Article

Prognostic relevance of immune-related adverse events in lung cancer patients undergoing immune checkpoint inhibitor therapy: a systematic review and meta-analysis

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Background: Immune checkpoint inhibitors (ICIs) work by activating the immune system, a mechanism that may also cause immune-related adverse events (irAEs). This study seeks to investigate on how different irAEs impact prognosis of advanced lung cancer (LC) patients and identify useful approaches to manage irAEs.

Methods: A thorough literature search of PubMed, Embase, the Cochrane Library and manual searches up to January 2024 were undertaken. Treatment outcomes including progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR) were obtained. Meta-analysis was conducted using R software (version 4.3.1).

Results: There were 106 studies with 41,050 advanced or recurrent LC patients included. The occurrence of irAEs was correlated with better PFS [hazard ratio (HR) =0.54; 95% confidence interval (CI): 0.49–0.59], OS (HR =0.57; 0.51–0.63), ORR [risk ratio (RR) =2.03; 95% CI: 1.81–2.28] and DCR (RR =1.55; 95% CI: 1.40–1.72) and remained significant after adjusting programmed death-ligand 1 (PD-L1) level. IrAEs affecting skin (OS: HR =0.45; 95% CI: 0.38–0.53) and endocrine system (OS: HR =0.51; 95% CI: 0.41–0.62), of mild severity (OS: HR =0.52; 95% CI: 0.35–0.79), arising in multiple sites (OS: HR =0.47; 95% CI: 0.38–0.59), induced by monotherapy (OS: HR =0.58; 95% CI: 0.52–0.65), with a delayed onset (cutoff: 3 months; OS: HR =0.37; 95% CI: 0.19–0.71) were identified as positive prognostic markers. In contrast, though pulmonary irAEs were found to be corelated with enhanced treatment response (ORR: RR =1.75; 95% CI: 1.37–2.25), they may harm survival, especially those with grade ≥3 (OS: HR =2.40; 95% CI: 1.39–4.14). Treatment resumption tended to improve PFS but might not reduce the risk of death compared to permanent discontinuation.

Conclusions: IrAEs suggest better treatment outcomes generally, yet severe pneumonia could increase mortality risk. Close supervision and appropriate handling protocols are warranted to weigh treatment benefit against risk.

Keywords: Immune-related adverse event (irAE); immune checkpoint inhibitors (ICIs); lung cancer (LC); prognosis; meta-analysis

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Introduction

Background

In recent times, immune checkpoint inhibitors (ICIs) have surfaced as an innovative therapeutic approach for individuals with advanced lung cancer (LC) (1), which have been acknowledged as an effective approach to improve prognosis (2-5). Different from traditional treatments like radiotherapy and chemotherapy, the therapeutic effect of ICIs is carried out by reversing the abnormal immune tolerance towards malignancy and eliminating tumors. Nonetheless, this unique mechanism can occasionally result in an overactivated immune environment, characterized by elevated autoantibodies and inflammatory cytokines, heightened T-cell activity against antigens common to both tumor and healthy tissue, and intensified complement-mediated inflammation, ultimately leading to autoimmunity in specific tissues, which we called immune-related adverse events (irAEs) (6-8). Pooled analyses have indicated that more than half of the patients receiving ICIs treatment tend to suffer from any-type of irAEs (2,9).

Highlight box

Key findings

- Immune-related adverse events (irAEs) generally indicate improved treatment outcomes, but severe pneumonia may elevate the risk of mortality.

What is known and what is new?

- IrAEs induced by immune checkpoint inhibitors can lead to organ damage and dysfunction. Conversely, their presence is associated with immune function activation. Therefore, the prognostic impact of irAEs on advanced lung cancer patients varies and needs further investigation.
- The emergence of irAEs was strongly associated with enhanced survival and treatment response, independent of programmed death-ligand 1 expression levels. This connection was especially pronounced for skin and endocrine-related irAEs, which typically presented with mild severity, occurred at multiple sites, were induced by monotherapy, and had a delayed onset. Nonetheless, patients with severe irAEs, particularly those involving the lungs, may face an increased risk of mortality despite improved treatment response.

What is the implication, and what should change now?

- The development of irAEs indicates better treatment response and improved survival generally, yet vigilant monitoring, particularly for respiratory symptoms, and prompt intervention are crucial to prevent severe toxicity levels.

Rationale and knowledge gap

Compared to typical drug treatment-related adverse events, the relationship between irAEs and survival is more complex and involves two considerations. On one hand, irAEs can cause organ damage and dysfunction, potentially worsening survival (10). Conversely, the presence of irAEs is linked to the activation of immune function (11), which may lead to a better treatment response, thereby alleviating the disease and improving survival benefits. Therefore, the relationship between irAEs and clinical outcomes requires validation in large populations.

Currently, numerous studies have examined the correlation between irAEs and treatment outcomes, which turns out to be of great heterogeneity. The most extensively studied organ-specific irAEs, those related to the skin and the endocrine system (mainly thyroid), have been shown to correlate with improved survival and treatment response (12,13). In contrast, the impact of checkpoint inhibitor pneumonitis (CIP) and gastrointestinal toxicity on clinical outcomes remains controversial (14-20). In addition, issues involving whether irAEs with different onsets impact dissimilarly, and could irAEs be indicator for ICIs treatment outcomes independent of programmed death-ligand 1 (PD-L1) expression still lack integrated analysis to fully understand (21,22). Moreover, the prognostic impact of irAEs-related treatment discontinuation and whether ICIs resumption is necessary remain disputable (23).

Objective

Herein, our objective was to clarify the association between irAEs and clinical outcomes in advanced LC patients treated with ICIs with the latest evidence. We present this article in accordance with the PRISMA reporting checklist (24) (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-299/rc).

Methods

The systematic review and meta-analysis adhered to the protocols outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. Furthermore, the study underwent pre-registration on PROSPERO with the registration number CRD42023484376.

Inclusion criteria

The targeted population comprised patients with advanced or recurrent LC, irrespective of demographic factors. Intervention was immunotherapy, specifically ICIs directed at programmed cell death protein-1 (PD-1), PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Plus, the use of ICIs within the perioperative (neoadjuvant/adjuvant) scope for operable LC patients was excluded. The main outcomes of interest encompassed progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR) in patients with or without irAEs, which were defined as potential immunologically mediated adverse events requiring monitoring or immunosuppression.

Literature search

We performed an exhaustive exploration of electronic databases including PubMed, Embase, and Cochrane Library to identify pertinent studies published until January 20, 2024, and retrieved the reference lists of articles as supplement. Our search utilized terms such as "lung cancer", "immune checkpoint inhibitors", and "immune-related adverse events". The complete search strategy is accessible in the supplementary material (Appendix 1).

Study selection and data collection

Two independent evaluators screened the titles and abstracts to identify potentially eligible studies. Subsequently, full-text articles were reviewed to ascertain suitability for inclusion. Data extraction from qualified studies was performed by two independent reviewers utilizing a standardized data extraction form. The following information was collected from each article: study characteristics (study design, case included), patient characteristics (age, sex, histology), treatment details (agent of ICI, line of therapy), percentage of patients developing irAEs, type of irAE, outcomes [hazard ratio (HR) of OS, PFS, ORR and DCR in patients with or without irAEs]. If the article reports reverse HR, we handle the calculation by taking the reciprocal. Preference was given to multivariate HRs if both multivariate and univariate ones were provided.

The meta-analysis consisted of two parts: an overall analysis and subgroup analyses. The overall analysis incorporated irAEs of any nature to derive a widely applicable conclusion. Specifically, when studies reported HRs for both global and organ-specific irAEs, preference was given to the former. In instances where studies presented HRs for both grade-specific and all-grade irAEs, the latter was chosen. Additionally, priority was given to results from time-dependent Cox regression model or Mantel-Byar test to reduce immortal-time bias (ITB) (25). Subgroup analyses delved into the prognostic impact of irAEs occurring in specific organs, of different characteristics, induced by varied treatment regimens, and managed with different approaches to offer a more comprehensive understanding.

Quality assessment

The included studies underwent a methodological quality assessment based on the Cochrane Collaboration's revised risk of bias tool for randomized trials (RoB2) (26) and non-randomized trials (ROBINS-I) (27). We also assessed the certainty of irAEs diagnosis in each study according to the criteria developed by Barron *et al.* (28), which comprised four levels: certain (reported pathology biopsy), probable (reported laboratory and radiological examinations), possible (only physical examination conducted), and unclear (no relevant description). The reviewers independently evaluated each included study and resolved any disagreements through reciprocal consultation.

Statistical analysis

The meta-analysis was conducted using R software version 4.3.1 under a systematic methodological guidance (29). Statistical significance for outcomes was set at $P<0.05$, with all P values reported as two-tailed. The results were presented in forest plots. Heterogeneity was assessed using I^2 statistics, with significant heterogeneity defined as $I^2>50\%$ or $P<0.1$. A random-effects model was applied if significant heterogeneity existed or a fixed-effects model in the lack of significant heterogeneity. Sensitivity analyses assessed robustness of the synthesized results with leave-one-out

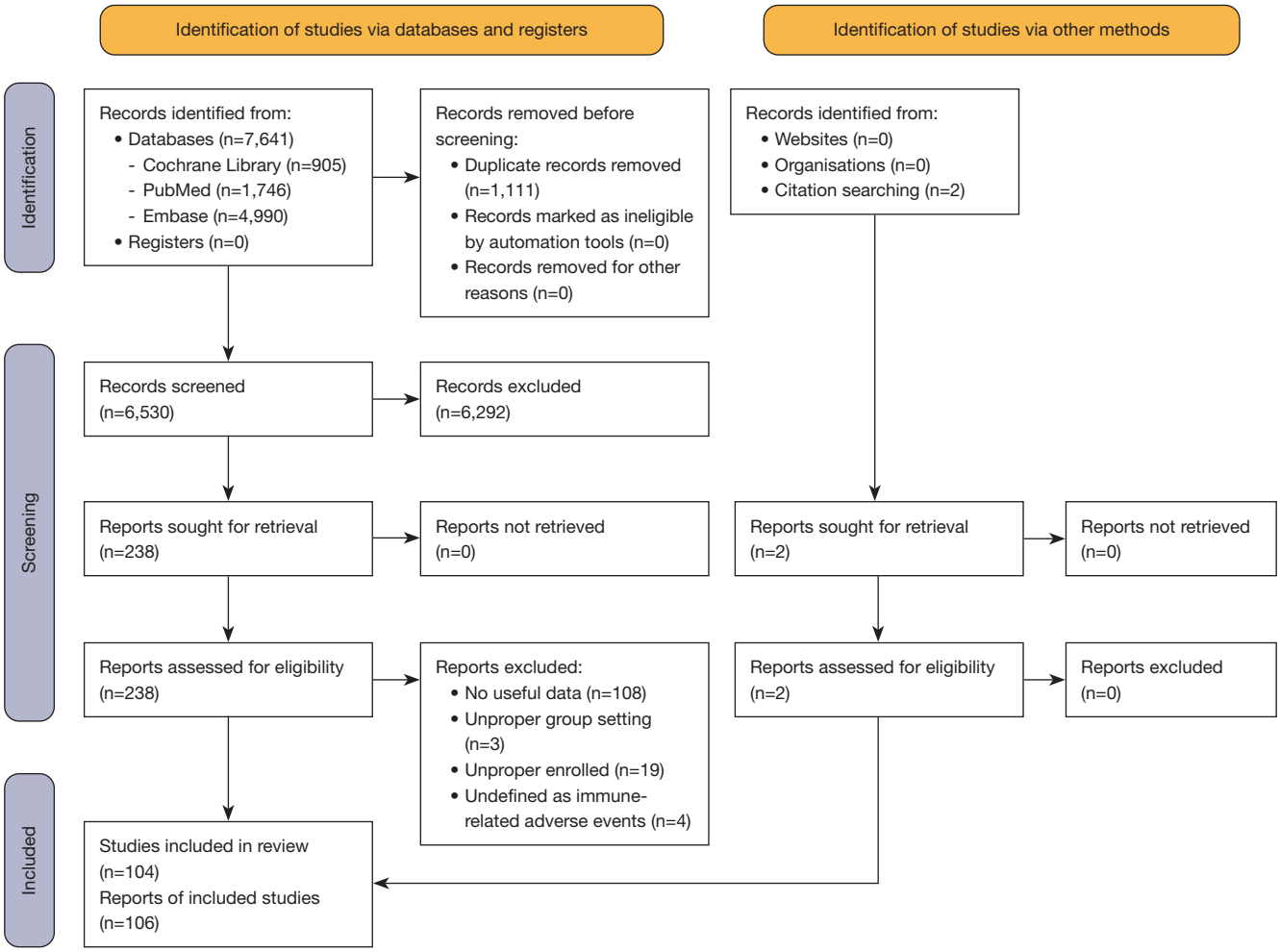

Figure 1 Literature search and study selection process guided by PRISMA 2020 flow chart for systematic reviews.

method. Multiple meta-regression through a procedure called multi-model inference (30) were performed to investigate heterogeneity factors. Publication bias was evaluated using the funnel plot and symmetric tests: Egger's test for continuous outcomes, Peters test for dichotomous outcomes or AS-Thompson test if large between-study heterogeneity was observed (31). Trim-and-fill method plus moderators were adopted to adjust asymmetric funnel plot.

Results

Eligible studies

After removing duplicate studies, a total of 6,532 records were obtained from PubMed, Embase, the Cochrane Library database and manual retrieval. Screening identified 240 potentially relevant reports. Upon thorough examination of the full text, 134 reports were excluded. One hundred and six reports for 104 studies involving a total of 41,050 patients were ultimately included in the review. The flow chart, as per PRISMA guidelines, offers an overview of the selection process (*Figure 1*).

Studies characteristics

The included reports were published from 2017–2024, with 25 meeting abstracts and 81 articles. Detailed quality assessment for each included cohort could been checked in https://cdn.amegroups.cn/static/public/tlcr-24-299-1.xlsx; Figure S1. Most cohorts had focused on

non-small cell lung cancer (NSCLC), other 3 (32-34) and 7 cohorts (35-41) each for small cell lung cancer (SCLC) and LC. Thirty-two cohorts had explored irAEs induced by specific antigen, including nivolumab (n=15), pembrolizumab (n=13), durvalumab (n=1) and atezolizumab (n=3). Details about the enrolled cohorts are presented in *Table 1*.

Overall analysis

Regarding patient prognostic outcomes, 71 cohorts provided HR for PFS, and 75 cohorts provided HR for OS. Pooled analysis revealed that the occurrence of any kind of irAE favors both PFS [HR =0.54; 95% confidence interval (CI): 0.49–0.59; P<0.001; *Figure 2A*] and overall survival (HR =0.57; 95% CI: 0.51–0.63; P<0.001; *Figure 2B*). When it comes to treatment efficacy, 42 and 21 studies were respectively included to calculate ORR and DCR. Statistically significant better ORR (RR =2.03; 95% CI: 1.81–2.28; P<0.001; *Figure 2C*) and DCR (RR =1.55; 95% CI: 1.40–1.72; P<0.001; *Figure 2D*) was observed in patients having irAEs.

Subgroup analysis

Subgroup analysis based on stratified irAE traits, treatment strategies and long-term survival effects were conducted (*Figure 3*) and https://cdn.amegroups.cn/static/public/tlcr-24-299-1.xlsx displays the studies included for each analysis.

IrAEs in specific organs

Our pooled analysis showed that skin and endocrine irAEs predicted better clinical outcomes, with significantly longer PFS (skin: HR =0.50; 95% CI: 0.44–0.58; P<0.001; endocrine: HR =0.56; 95% CI: 0.47–0.66; P<0.001), OS (skin: HR =0.45; 95% CI: 0.38–0.53; P<0.001; endocrine: HR =0.51; 95% CI: 0.41–0.62; P<0.001) and higher ORR (skin: RR =2.01; 95% CI: 1.58–2.55; P<0.001; endocrine: RR =1.53; 95% CI: 1.34–1.75; P<0.001), DCR (skin: RR =1.62; 95% CI: 1.43–1.83; P<0.001). However, patients experiencing pulmonary irAEs had shortened OS (HR =1.31; 95% CI: 1.06–1.61; P=0.01), not significantly better PFS (HR =0.94; 95% CI: 0.75–1.17; P=0.58), but still better response to treatment (ORR: RR =1.75; 95% CI: 1.37–2.25; P<0.001; DCR: RR =1.50; 95% CI: 1.27–1.77; P<0.001). The occurrence of gastrointestinal or musculoskeletal irAEs was associated with longer survival. Liver-specific irAEs seemed to foretell neither survival nor response in ICIs treated patients.

IrAEs of different characteristics

Severity

Patients developing mild irAEs were found to have better prognosis (PFS: HR =0.40; 95% CI: 0.25–0.62; P<0.001; OS: HR =0.52; 95% CI: 0.35–0.79; P=0.002). There was no significant difference found in PFS and OS between patients with severe irAEs and those without (PFS: HR =0.96; 95% CI: 0.87–1.07; P=0.47; OS: HR =0.93; 95% CI: 0.67–1.29; P=0.67). However, the occurrence of severe irAEs could still foretell better ORR (RR =1.37; 95% CI: 1.17–1.59; P<0.001).

Number

Single or multiple occurrence of irAEs could both predict better clinical outcomes for patients underwent ICIs treatment, with longer PFS (single: HR =0.63; 95% CI: 0.49–0.81; P<0.001; multiple: HR =0.44; 95% CI: 0.25–0.75; P=0.003) and OS (single: HR =0.57; 95% CI: 0.44–0.74; P<0.001; multiple: HR =0.47; 95% CI: 0.38–0.59; P<0.001), as well as higher treatment response rate (single: RR =1.65; 95% CI: 1.48–1.85; P<0.001; multiple: RR =2.18; 95% CI: 1.36–3.48; P=0.001). Furthermore, it appeared that patients who had multiple irAEs had a more favorable prognosis when compared to those who had experienced one or none.

Onset

A total of four studies (73,79,97,111) have investigated the predictive value of irAEs onset time for prognosis. Among them, three studies (73,79,97) adopted 3 months as a cutoff point distinguishing early- and late-onset irAEs. The remaining one (111) used median onset time (69 days) as the cutoff. Our pooled analysis showed that the development of early-onset irAEs after initiation of treatment was associated with higher risk of death (any cutoff: HR =2.63; 95% CI: 1.93–3.59; P<0.001; 3-month cutoff: HR =2.72; 95% CI: 1.41–5.25; P=0.003) or disease progression (any cutoff: HR =2.16; 95% CI: 1.62–2.89; P<0.001; 3-month cutoff: HR =2.38; 95% CI: 1.56–3.62; P<0.001), but with no significant impact on treatment response (ORR: RR =0.76; 95% CI: 0.47–1.25; P=0.28).

Treatment strategies

Antigen

Nivolumab and pembrolizumab are the most widely used drugs in research. Both nivolumab and pembrolizumab induced irAEs were positively associated with longer PFS (nivolumab: HR =0.55; 95% CI: 0.45–0.69; P<0.001; pembrolizumab: HR =0.60; 95% CI: 0.47–0.77; P<0.001) and OS (nivolumab: HR =0.62; 95% CI: 0.55–0.70; P<0.001; pembrolizumab: HR =0.47; 95% CI: 0.30–0.73;

Table 1 Study characteristics

Cohort	Study type	Case	Population	Treatment	IrAEs certainty	IrAEs grade	IrAEs/all (%)	IrAEs analyzed in meta-analysis	Objectives
Abed *et al.*, 2022, (42)	Cohort study (prospective and retrospective)	156	Locally advanced/ mNSCLC	N/P/A	Unclear	Any	49.4	Any	OS, PFS
Ahmed *et al.*, 2019, (43)	Cohort study (retrospective)	185	aNSCLC (IIIB or IV)	N/P	Probable	Any	20.5	Thyroid	PFS
Ahn *et al.*, 2019, (44)	Real-world (retrospective)	155	aNSCLC	N/P	Probable	Any	38.1	Any, skin, lung, endocrine	OS, PFS, ORR
Akamatsu *et al.*, 2020, (45)	Cohort study (prospective)	106	aNSCLC	N/P/A	Possible	Any	29.3	Any	ORR
Aso *et al.*, 2020, (13)	Cohort study (retrospective)	155	aNSCLC	N/P	Possible	Any	58.1	Skin, lung, endocrine, gastrointestinal, liver	OS, PFS, ORR, DCR
Atchley *et al.*, 2021, (35)	Real-world (retrospective)	315	LC	N/P/I+N	Probable	Any	NA	Lung	OS
Baldini *et al.*, 2020, (46)	Cohort study (retrospective)	1,959	aNSCLC	N	Unclear	Any	17.5	Any	OS, PFS, ORR, DCR
Barrón *et al.*, 2020, (47)	Real-world (retrospective)	101	NSCLC (III or IV)	N/P	Certain	Any	21.8	Lung	OS
Becerra *et al.*, 2021, (40)	Cohort study (retrospective)	76	aLC	ICIs	Unclear	Any	55.3	Any	OS, PFS
Berner *et al.*, 2019, (48)	Cohort study (prospective)	73	NSCLC	N/P	Certain	Any	34.2	Skin	OS, PFS, ORR, DCR
Bjørnhart *et al.*, 2019, (49)	Real-world (retrospective)	118	aNSCLC (III or IV) or rNSCLC	N/P	Possible	3–4	NA	Any	OS, PFS
Blasi *et al.*, 2023, (50)	Real-world (retrospective)	156	aNSCLC	P	Unclear	Any	35.0	Any	OS, PFS
Blazek *et al.*, 2023, cohort A, (51)[a]	Cohort study (retrospective)	662	aNSCLC (III or IV)	N	Unclear	Any	14.1	Any	OS
Blazek *et al.*, 2023, cohort B, (51)[a]	Cohort study (retrospective)	84	aNSCLC (III or IV)	N	Unclear	Any	29.8	Any	OS, PFS, ORR
Bouhlel *et al.*, 2020, (52)	Cohort study (retrospective)	69	aNSCLC	N	Probable	Any	44.9	Any, endocrine	OS, PFS, ORR
Boussageon *et al.*, 2019, (53)	Cohort study (retrospective)	80	mNSCLC	N/P/A	Unclear	Any	28.8	Any	PFS
Chen *et al.*, 2020, (54)	Real-world (retrospective)	97	aNSCLC (IIIB or IV)	N/P	Possible	Any	46.4	Any	PFS
Chen *et al.*, 2021, (55)	Real-world (retrospective)	191	NSCLC, III–IV (88.0%)	ICIs	Probable	Any	36.6	Any	OS, PFS, ORR, DCR
Conde-Estévez *et al.*, 2021, (56)	Cohort study (retrospective)	70	a/rNSCLC	N/P/A	Possible	Any	44.3	Any	OS, PFS, ORR
Cook et al., 2023, 2024, (57,58)[b]	Real-world (retrospective)	803	mNSCLC	N/P/A	Unclear	Any	37.0	Any	OS
Cortellini *et al.*, 2019, (59)	Real-world (retrospective)	559	aNSCLC	N/P	Unclear	Any	41.3	Any, skin, lung, endocrine, gastrointestinal, liver	OS, PFS, ORR

Table 1 (*continued*)

Table 1 (*continued*)

Cohort	Study type	Case	Population	Treatment	IrAEs certainty	IrAEs grade	IrAEs/all (%)	IrAEs analyzed in meta-analysis	Objectives
Cortellini *et al.*, 2020, (60)	Real-world (retrospective)	877	mNSCLC	P	Possible	Any	37.2	Any, skin, lung, endocrine, gastrointestinal	OS, PFS, ORR
Cortijo-Cascajares *et al.*, 2023, (61)	Real-world (retrospective)	75	aNSCLC (III or IV)	N	Unclear	Any	42.7	Any	OS, PFS
Cui *et al.*, 2020, (62)	Cohort study (retrospective)	276	aNSCLC (IIIB or IV) or rNSCLC	N/P/A/D	Certain	Any	NA	Lung	PFS, ORR
Dabana *et al.*, 2023, (63)	Cohort study (prospective)	79	aNSCLC	N/P/A	Probable	2–5	NA	Any	OS, PFS
Daniello *et al.*, 2020, 2021, (64,65)[c]	Real-world (retrospective)	894	mNSCLC	N/P/A	Probable	Any	22.2	Any	OS, PFS
Dey *et al.* 2022, (66)	RCT	617	mNSCLC	ICIs	Certain	Any	35.0	Any	OS, PFS, ORR
Fountzilas *et al.*, 2022, (67)	Real-world (retrospective)	73	aNSCLC	ICIs	Probable	Any	67.1	Any	OS, PFS
Frost *et al.*, 2023, (36)	Cohort study (retrospective)	1,376	m/rLC or unoperable stage III NSCLC	ICIs	Unclear	Any	NA	Any, lung	OS
Fujimoto *et al.*, 2018, (68)	Real-world (retrospective)	613	aNSCLC (IIIB or IV)	N	Unclear	Any	NA	Any, lung	PFS, ORR, DCR
Fujimoto *et al.*, 2021, (69)	Real-world (retrospective)	299	aNSCLC (III or IV) or rNSCLC	P + chemotherapy	Probable	Any	NA	Lung	OS, PFS
Fujisaki *et al.*, 2021, (70)	Cohort study (retrospective)	231	aNSCLC (III or IV) or rNSCLC	N/P	Unclear	Any	40.3	Any	OS, PFS, ORR, DCR
Fukihara *et al.*, 2019, (20)	Real-world (retrospective)	170	a/rNSCLC	N/P	Probable	Any	NA	Lung	ORR, DCR
López Gallego *et al.*, 2020, (71)	Cohort study (retrospective)	104	aNSCLC	ICIs	Unclear	Any	65.0	Any	PFS
Jurado García *et al.*, 2023, (72)	Real-world (retrospective)	510	aNSCLC	Anti-PD1/anti-PD-L1	Unclear	Any	60.0	Any	OS, ORR
Ghisoni *et al.*, 2021, (37)	Real-world (retrospective)	178	a/rLC	ICIs	Unclear	2–5	NA	Any	OS
Grangeon *et al.*, 2019, (73)	Real-world (retrospective)	270	mNSCLC	Anti-PD1/Anti-PD-L1	Probable	Any	44.0	Any, lung, endocrine, gastrointestinal, liver	OS, PFS, ORR, DCR
Guezour *et al.*, 2022, (74)	Real-world (retrospective)	201	aNSCLC (IIIB or IV)	N/P/I+N	Unclear	3–4	NA	Any	OS
Guo *et al.*, 2022, (75)	Cohort study (retrospective)	99	mNSCLC	ICIs	Unclear	2–5	NA	Any	OS, PFS, ORR, DCR
Haratani *et al.*, 2018, (76)	Cohort study (retrospective)	134	aNSCLC (IIIB or IV) or rNSCLC	N	Unclear	Any	51.0	Any, skin, endocrine	OS, PFS
Hazama *et al.*, 2024, Cohort A, (77)[d]	Real-world (retrospective)	124	a/rNSCLC (pulmonary sarcomatoid carcinoma)	ICIs	Unclear	Any	56.64	Any	OS, PFS
Hazama *et al.*, 2024, Cohort B, (77)[d]	Real-world (retrospective)	40	a/rNSCLC (pulmonary sarcomatoid carcinoma)	N/P/A + chemotherapy	Unclear	Any	NA	Any	OS, PFS

Table 1 (*continued*)

Table 1 (*continued*)

Cohort	Study type	Case	Population	Treatment	IrAEs certainty	IrAEs grade	IrAEs/all (%)	IrAEs analyzed in meta-analysis	Objectives
Hazama *et al.*, 2024, Cohort C, (77)[d]	Real-world (retrospective)	56	a/rNSCLC (pulmonary sarcomatoid carcinoma)	P/A/I+N	Unclear	Any	NA	Any	OS, PFS
Hazama *et al.*, 2024, Cohort D, (77)[d]	Real-world (retrospective)	28	a/rNSCLC (pulmonary sarcomatoid carcinoma)	N/P	Unclear	Any	NA	Any	OS, PFS
Hosoya *et al.*, 2020, Cohort A, (78)	Cohort study (prospective)	76	aNSCLC (IIIB or IV) or rNSCLC	N	Possible	Any	57.9	Any, skin, gastrointestinal	OS, PFS, ORR, DCR
Hosoya *et al.*, 2020, Cohort B, (78)	Cohort study (retrospective)	148	aNSCLC (IIIB or IV) or rNSCLC	P	Possible	Any	27.0	Any, skin, gastrointestinal	PFS, ORR, DCR
Hsiehchen *et al.*, 2022, (79)	Cohort study (retrospective)	154	aNSCLC	ICIs	Probable	Any	64.3	Any	OS, PFS, ORR
Hu *et al.*, 2023, (80)	Real-world (retrospective)	149	aNSCLC	ICIs	Probable	Any	55.7	Any	PFS
Huang *et al.*, 2020, (81)	Cohort study (retrospective)	61	aNSCLC (IIIB or IV)	N/P/A/I+N	Unclear	Any	39.3	Any	OS, PFS, ORR
Isono *et al.*, 2021, (82)	Cohort study (retrospective)	180	a/rNSCLC (III or IV)	N/P/A	Unclear	Any	47.2	Any	OS, ORR
Jun *et al.*, 2023, (83)	Real-world (retrospective)	324	aNSCLC	ICIs	Unclear	Any	NA	Any	PFS
Kichenadasse *et al.*, 2020, (84)	RCT	1,548	aNSCLC	A	Unclear	Any	65.0	Any	OS, PFS, ORR
Kim *et al.*, 2017, (85)	Cohort study (retrospective)	58	mNSCLC	N/P	Probable	Any	NA	Endocrine	OS, PFS, ORR
Knox *et al.*, 2023, (86)	Real-world (retrospective)	449	NSCLC, mNSCLC (68.0%)	ICIs	Unclear	Any	24.0	Any	OS
Kothari *et al.*, 2017, (87)	Cohort study (retrospective)	175	aNSCLC	N	Unclear	Any	16.0	Any	OS, PFS
Koyama *et al.*, 2019, (88)	Cohort study (retrospective)	132	a/rNSCLC	N/P	Probable	Any	NA	Endocrine	ORR, DCR
Ksienski *et al.*, 2019, Cohort A, (89)[e]	Cohort study (retrospective)	271	m/rNSCLC	N/P	Possible	Any	42.8	Any	OS
Ksienski, 2019 *et al.*, Cohort B, (89)[e]	Cohort study (retrospective)	230	m/rNSCLC	N	Possible	Any	NA	Any	OS
Kubo *et al.*, 2020, (90)	Cohort study (retrospective)	110	a/rNSCLC	N/P/A	Unclear	Any	NA	Any	PFS
Kurokawa *et al.*, 2022, Cohort A, (91)	Real-world (retrospective)	74	a/rNSCLC	P + chemotherapy	Probable	Any	62.2	Any	PFS
Kurokawa *et al.*, 2022, Cohort B, (91)	Real-world (retrospective)	74	a/rNSCLC	P	Probable	Any	54.1	Any	PFS
Lin *et al.*, 2022, (41)	Real-world (retrospective)	107	aLC	ICIs	Probable	Any	NA	Lung	OS, PFS, ORR
Luo *et al.*, 2021, Cohort A, (92)[f]	Cohort study (retrospective)	744	aNSCLC	ICIs	Probable	Any	NA	Endocrine	PFS
Luo *et al.*, 2021, Cohort B, (92)[f]	Cohort study (retrospective)	551	aNSCLC	ICIs	Probable	Any	NA	Endocrine	OS, ORR

Table 1 (*continued*)

Table 1 (*continued*)

Cohort	Study type	Case	Population	Treatment	IrAEs certainty	IrAEs grade	IrAEs/all (%)	IrAEs analyzed in meta-analysis	Objectives
Medri *et al.*, 2023, (93)	Cohort study (retrospective)	99	mNSCLC	N/P ± I	Certain	Any	24.2	Skin	ORR, DCR
de Miguel *et al.*, 2019, (94)	Cohort study (retrospective)	66	aNSCLC	ICIs	Unclear	Any	55.0	Any	PFS
Morimoto *et al.*, 2021, (95)	Real-world (retrospective)	70	aNSCLC (III or IV) or rNSCLC	P/A + chemotherapy	Unclear	Any	60.0	Any, skin, lung, endocrine	OS, PFS, ORR, DCR
Murata *et al.*, 2023, (96)	Cohort study (retrospective)	141	a/rNSCLC	Anti-PD1/anti-PD-L1	Probable	Any	17.7	Lung	OS, PFS
Naqash *et al.*, 2020, (97)	Cohort study (retrospective)	531	mNSCLC	N	Possible	Any	33.0	Any, skin, lung, endocrine, gastrointestinal, liver, musculoskeletal	OS, PFS
Ni *et al.*, 2023, (34)	Cohort study (prospective and retrospective)	53	ES-SCLC (IIIC–IV)	C/A/D + chemotherapy	Unclear	Any	35.9	Any	PFS
Noguchi *et al.*, 2020, (98)	Cohort study (retrospective)	94	aNSCLC	P	Unclear	Any	67.0	Any	PFS
Osorio *et al.*, 2017, (99)	RCT	48	mNSCLC	P	Probable	Any	NA	Endocrine	OS, PFS
Park *et al.*, 2021, (100)	Real-world (retrospective)	1,181	m/rNSCLC (III–IV)	N/P	Unclear	Any	48.5	Any	OS, PFS
von Pawel *et al.*, 2017, (101)	RCT	419	aNSCLC (IIIB or IV)	A	Probable	Any	31.0	Any	OS
Pîrlog *et al.*, 2023, (102)	Cohort study (retrospective)	79	NSCLC, mNSCLC (81.0%)	N/P	Unclear	Any	43.0	Any	OS
Ramos *et al.*, 2023, (103)	Cohort study (retrospective)	131	mNSCLC	ICIs	Unclear	Any	NA	Any	OS, PFS
Raynes *et al.*, 2023, (104)	Cohort study (retrospective)	262	aNSCLC	P	Probable	Any	31.68	Any, skin, endocrine, lung, liver, gastrointestinal, musculoskeletal	OS, PFS
Riudavets *et al.*, 2019, (105)	Cohort study (retrospective)	267	aNSCLC	ICIs	Unclear	Any	57.0	Any	DCR
Rizwan *et al.*, 2021, (106)	Real-world (retrospective)	161	mNSCLC	P	Unclear	Any	39.5	Any	OS, PFS
Rogado *et al.*, 2018, (107)	Cohort study (retrospective)	40	aNSCLC	N	Unclear	Any	25.0	Any	OS, PFS, ORR
Romano *et al.*, 2019, (108)	Real-world (prospective)	147	Locally advanced/ mNSCLC	Anti-PD1/anti-PD-L1	Unclear	Any	49.0	Any, endocrine	OS, PFS
Rose *et al.*, 2020, (109)	Real-world (retrospective)	89	NSCLC, mNSCLC (94.0%)	N/P/A	Probable	Any	NA	Any	OS
Sato *et al.*, 2018, (110)	Cohort study (prospective)	38	aNSCLC (IIIB or IV) or rNSCLC	Anti-PD1/anti-PD-L1	Unclear	Any	28.9	Any	PFS, ORR
Sayer *et al.*, 2023, (111)	Real-world (retrospective)	354	NSCLC, III–IV (91.0%)	N/P/A	Unclear	Any	43.0	Any	OS, PFS

Table 1 (*continued*)

Table 1 (*continued*)

Cohort	Study type	Case	Population	Treatment	IrAEs certainty	IrAEs grade	IrAEs/all (%)	IrAEs analyzed in meta-analysis	Objectives
Serino *et al.*, 2022, (112)	Cohort study (retrospective)	184	NSCLC, mNSCLC (98.4%)	Anti-PD1/anti-PD-L1	Probable	Any	26.6	Any	OS, PFS, DCR
Serrano *et al.*, 2019, (113)	Cohort study (retrospective)	98	aNSCLC	Anti-PD1/anti-PD-L1	Unclear	Any	30.6	Any	OS, PFS
Shah *et al.*, 2017, (114)	Cohort study (retrospective)	122	aNSCLC	ICIs	Unclear	Any	24.6	Any	ORR
Shankar *et al.*, 2020, Cohort A, (115)[g]	Cohort study (retrospective)	623	aNSCLC (III or IV)	Anti-PD1/anti-PD-L1	Certain	Any	33.1	Any, skin, lung, endocrine, gastrointestinal	OS, PFS
Shankar *et al.*, 2020, Cohort B, (115)[g]	Cohort study (retrospective)	527	aNSCLC (III or IV)	N/P	Certain	Any	NA	Any	OS, PFS
Shantzer *et al.*, 2021, (116)	Cohort study (retrospective)	94	aNSCLC	ICIs + chemotherapy	Unclear	Any	43.6	Any	OS
Shimomura *et al.*, 2022, (117)	Cohort study (retrospective)	172	aNSCLC	N/P	Unclear	Any	84.0	Any	OS
Socinski *et al.*, 2023, (118)	RCT	1,577	aNSCLC	A + chemotherapy	Unclear	Any	48.4	Any	OS, ORR
Melià Sosa *et al.*, 2018, (119)	Cohort study (retrospective)	64	mNSCLC	Anti-PD1/anti-PD-L1	Unclear	Any	25.0	Any	OS
Valencia Soto *et al.*, 2023, (120)	Real-world (retrospective)	94	aNSCLC (IIIB or IV)	P	Possible	Any	63.8	Any	OS, PFS, ORR
Sugano *et al.*, 2020, (121)	Cohort study (retrospective)	130	aNSCLC	N/P/A	Probable	Any	30.0	Any, lung	PFS, ORR, DCR
Sung *et al.*, 2018, (122)	Cohort study (retrospective)	97	mNSCLC	ICIs	Unclear	Any	51.0	Any	ORR
Teraoka *et al.*, 2017, (123)	Cohort study (prospective)	43	aNSCLC (IIIB or IV)	N	Probable	1–3	62.8	Any	ORR, DCR
Tiu *et al.*, 2022, (38)	Real-world (retrospective)	13,113	aLC	Anti-PD1/anti-PD-L1	Possible	Any	22.0	Lung	OS
Toi *et al.*, 2018, (124)[h]	Cohort study (retrospective)	70	aNSCLC	N	Probable	Any	40.0	Any	PFS, ORR, DCR
Toi *et al.*, 2019, (125)[h]	Cohort study (retrospective)	154	aNSCLC	N/P	Unclear	Any	NA	Skin, lung, endocrine, liver	ORR
Toi *et al.*, 2023, (126)	Cohort study (prospective)	139	Unresectable stage III NSCLC	D	Unclear	Any	58.0	Any	OS
Tone *et al.*, 2019, (127)	Cohort study (retrospective)	71	aNSCLC (III or IV) or rNSCLC	ICIs	Probable	Any	40.9	Any, lung	OS, PFS, ORR, DCR
Usui *et al.*, 2017, (128)	Cohort study (retrospective)	93	aNSCLC	N	Unclear	Any	22.6	Skin	PFS, ORR, DCR
Virik *et al.*, 2018, (129)	Cohort study (retrospective)	47	aNSCLC	N/P/D	Unclear	Any	61.7	Any	ORR, DCR
Wood *et al.*, 2021, (130)	Real-world (retrospective)	153	mNSCLC	P	Unclear	Any	42.4	Any	OS
Wu *et al.*, 2022, (131)	Cohort study (retrospective)	101	mNSCLC	Anti-PD1/anti-PD-L1	Probable	Any	44.6	Any	OS, PFS

Table 1 (*continued*)

Table 1 (*continued*)

Cohort	Study type	Case	Population	Treatment	IrAEs certainty	IrAEs grade	IrAEs/all (%)	IrAEs analyzed in meta-analysis	Objectives
Yamauchi *et al.*, 2019, (39)	Cohort study (retrospective)	118	aLC	N	Probable	Any	NA	Endocrine	OS, PFS
Yokoo *et al.*, 2023, (32)	Cohort study (retrospective)	40	ES-SCLC or rSCLC	ICIs	Unclear	Any	37.5	Any	OS, ORR, DCR
Yoneda *et al.*, 2022, (132)	Real-world (retrospective)	435	m/rNSCLC	N/P/A	Unclear	Any	51.0	Any, skin, lung, endocrine	OS, PFS
Yu *et al.*, 2024, (25)	Cohort study (retrospective)	425	a/rNSCLC (III or IV)	Anti-PD1/anti-PD-L1	Probable	Any	29.88	Any, skin, endocrine, lung, liver	OS, PFS, ORR, DCR
Zhang *et al.*, 2021, (133)	Cohort study (retrospective)	63	mNSCLC	P	Unclear	Any	38.0	Any	OS
Zhang *et al.*, 2023, (33)	Cohort study (retrospective)	219	SCLC	Anti-PD1/anti-PD-L1	Unclear	Any	51.0	Any, endocrine	OS, PFS
Zhou *et al.*, 2021, (134)	Cohort study (retrospective)	191	aNSCLC (IIIB or IV) or rNSCLC	N/P	Probable	0–3	20.9	Endocrine	OS, PFS

[a,d-h], Blazek, 2023, Cohort B, Hazama, 2024, Cohort B–D, Ksienski, 2019, Cohort B, Luo, 2021, Cohort B, Shankar, 2020, Cohort B, and Toi, 2018 were subgroups from Blazek, 2023, Cohort A, Hazama, 2024, Cohort A, Ksienski, 2019, Cohort A, Luo, 2021, Cohort A, Shankar, 2020, Cohort A and Toi, 2019 respectively. Rigorous examination was performed to avoid cohort duplication in meta-analysis. [b,c], the cohort of Cook, 2024 and Daniello, 2021 were reported in a meeting abstract and an updated article respectively, we adopted data from the article. irAE, immune-related adverse event; RCT, randomized controlled trial; mNSCLC, metastatic non-small cell lung cancer (stage IV); aNSCLC, advanced non-small cell lung cancer; LC, lung cancer; aLC, advanced lung cancer; rNSCLC, recurrent non-small cell lung cancer; rSCLC, recurrent small cell lung cancer; m/rLC, metastatic/recurrent lung cancer; a/rLC, advanced/recurrent lung cancer; ES-SCLC, extensive stage small cell lung cancer; N, nivolumab; P, pembrolizumab; A, atezolizumab; I, ipilimumab; ICIs, immune checkpoint inhibitors; D, durvalumab; PD1, programmed cell death 1; PD-L1, programmed death-ligand 1; NA, not applicable; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate.

P=0.001). Similar results were also observed in treatment response (ORR for nivolumab: RR =2.80; 95% CI: 1.80–4.36; P<0.001; ORR for pembrolizumab: RR =2.00; 95% CI: 1.48–2.71; P<0.001). In addition, patients suffering atezolizumab-induced irAEs were also likely to have longer OS (HR =0.70; 95% CI: 0.63–0.78; P<0.001). Yet, the existing limited evidence did not support a correlation between atezolizumab-induced irAEs and PFS (HR =0.95; 95% CI: 0.81–1.11; P=0.74).

Treatment line

Irrespective of treatment lines, chances are that patients with irAEs may experience prolonged PFS (first: HR =0.64; 95% CI: 0.52–0.80; P<0.001; second/later: HR =0.61; 95% CI: 0.48–0.76; P<0.001), OS (first: HR =0.59; 95% CI: 0.45–0.77; P<0.001; second/later: HR =0.65; 95% CI: 0.57–0.75; P<0.001) and improved ORR (first: RR =1.48; 95% CI: 1.24–1.76; P<0.001; second/later: HR =1.79; 95% CI: 1.48–2.17; P<0.001). However, for disease control, similar results were only found to be significant for second/later treatment line, but ambiguous for first line treatment.

Treatment regimen

We firstly looked at the impact of irAEs within population receiving ICIs monotherapy and found favorable outcomes in both survival (PFS: HR =0.52; 95% CI: 0.45–0.59; P<0.001; OS: HR =0.58; 95% CI: 0.52–0.65; P<0.001) and treatment response (ORR: RR =2.41; 95% CI: 1.87–3.09; P<0.001; DCR: RR =1.56; 95% CI: 1.30–1.86; P<0.001). However, irAEs induced from combination therapy appeared to only have significant association with patients' treatment response (ORR: RR =1.64; 95% CI: 1.48–1.82; P<0.001), but nothing to do with survival (PFS: HR =0.65; 95% CI: 0.33–1.30; P=0.22; OS: HR =0.76; 95% CI: 0.50–1.15; P=0.19).

Predictive role of irAEs in patients with different PD-L1 expression levels

Four studies (13,60,104,130) had specifically probed into the predictive value of irAEs occurrence among patients with high PD-L1 expression. The results indicated that development of irAEs could foretell longer survival (PFS:

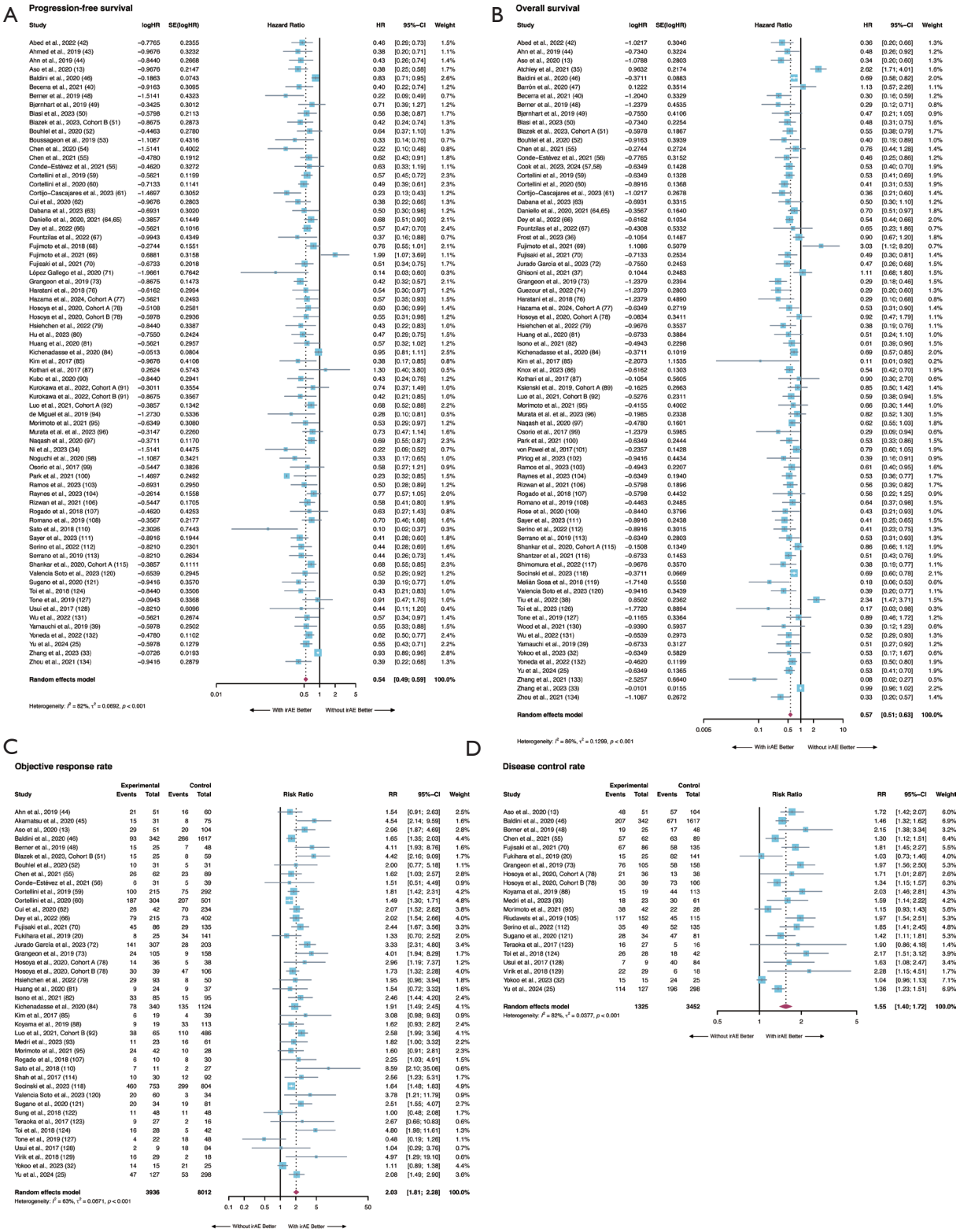

Figure 2 Forest plots presenting the association between irAEs occurrence and treatment outcomes from overall meta-analysis. (A) Progression-free survival; (B) overall survival; (C) objective response rate; (D) disease control rate. HR, hazard ratio; SE, standard error; CI, confidence interval; irAE, immune-related adverse event; RR, risk ratio.

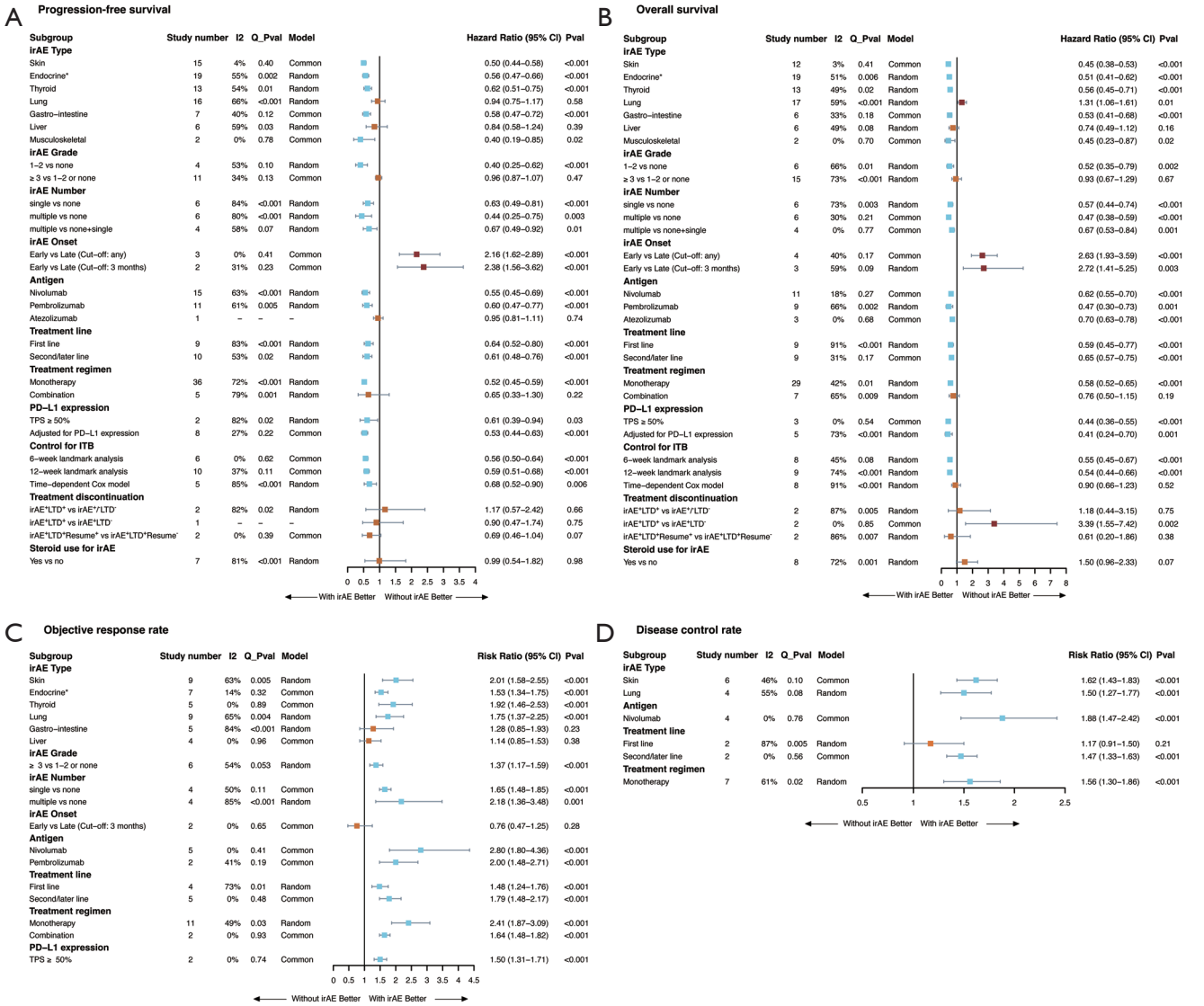

Figure 3 Forest plots demonstrating the association between specific category irAEs and treatment outcomes and the prognostic impact of irAEs management approaches from subgroup meta-analysis. (A) Progression-free survival; (B) overall survival; (C) objective response rate; (D) disease control rate. *, irAEs involving thyroid were also included in the subgroup analysis for endocrine irAEs. CI, confidence interval; irAE, immune-related adverse event; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score; ITB, immortal time bias; LTD, leading to discontinuation.

HR =0.61; 95% CI: 0.39–0.94; P=0.03; OS: HR =0.44; 95% CI: 0.36–0.55; P<0.001) and better treatment response (ORR: RR =1.50; 95% CI: 1.31–1.71; P<0.001) amongst patients with tumor proportion score (TPS) ≥50%. The positive correlation between irAEs and survival remained robust after adjusting for PD-L1 expression level (PFS: HR =0.53; 95% CI: 0.44–0.63; P<0.001; OS: HR =0.41; 95% CI: 0.24–0.70; P=0.001). Furthermore, cumulative meta-analyses were conducted by adding the studies one by one based on proportion of patients with negative PD-L1 expression (*Figure 4*). In this method, effect size without adjustment for PD-L1 were adopted. As studies were added, no discernible one-way change pattern of effect sizes was observed. Plus, the results from Pearson or Spearman analysis also disapproved significant correlation between effect size and proportion of patient with negative PD-L1

expression. For individuals with low PD-L1 expression, the occurrence of irAEs may serve as a favorable predictor for treatment outcomes as well.

Control for immortal time bias

The 6- and 12-week landmark analyses were amongst the most adopted methods to diminish ITB. The effect of irAEs on PFS (6-week: HR =0.56; 95% CI: 0.50–0.64; P<0.001; 12-week: HR =0.59; 95% CI: 0.51–0.68; P<0.001) and OS (6-week: HR =0.55; 95% CI: 0.45–0.67; P<0.001; 12-week: HR =0.54; 95% CI: 0.44–0.66; P<0.001) were both significant after 6 and 12 weeks from treatment initiation. When adopting time-dependent Cox model, the prognostic effect of irAEs only remains significant in terms of PFS (HR =0.68; 95% CI: 0.52–0.90; P=0.006), not OS (HR =0.90; 95% CI: 0.66–1.23; P=0.52).

Actions implemented following irAEs

Leading-to-discontinuation (LTD) irAEs and ICIs treatment resumption

IrAEs with grade ≥2 may need treatment discontinuation (135). However, the impact of irAEs-related treatment interruption and the value of ICIs resumption remain debatable. Several included studies have explored this question. No significant difference in survival was found between those who had LTD irAEs and who did not (PFS: HR =1.17; 95% CI: 0.57–2.42; P=0.66; OS: HR =1.18; 95% CI: 0.44–3.15; P=0.75). Among patients experiencing irAEs, treatment interruption had inconspicuous effect on PFS (HR =0.90; 95% CI: 0.47–1.74; P=0.75), but failed to bring expected better OS (HR =3.39; 95% CI: 1.55–7.42; P=0.002). Compared to irAEs related permanent treatment discontinuation, immunotherapy resumption had the tendency to improve PFS but may not lower the risk of death (PFS: HR =0.69; 95% CI: 0.46–1.04; P=0.07; OS: HR =0.61; 95% CI: 0.20–1.86; P=0.38).

Steroid use for irAEs

Eight studies (55,66,74,79,104,113,117,126) in total have examined the prognostic influence of steroid treatment for irAEs. After meta-analysis, we were unable to identify a unidirectional impact of steroid use on patient survival (PFS: HR =0.99; 95% CI: 0.54–1.82; P=0.98; OS: HR =1.50; 95% CI: 0.96–2.33; P=0.07). This inconclusive result may be attributed to varying administration doses and timing, which we will address in detail later.

Controversial prognostic impacts of pulmonary irAEs

Considering the controversial impact of pulmonary irAEs on patient survival, subgroup analyses were conducted to further identify major prognostic factors (*Figure 5*). Results indicated that pneumonitis of different severity could lead to distinct outcomes. Mild pneumonitis and those did not lead to permanent treatment discontinuation might be positive predictor for better survival, while severe ones would significantly harm prognosis, with increased risk for both disease progression and death (PFS: HR =1.93; 95% CI: 1.22–3.05; P=0.005; OS: HR =2.40; 95% CI: 1.39–4.14; P=0.002).

Between-study heterogeneity exploration

Significant heterogeneity was observed among studies included in global analysis, with I^2 being 82%, 86%, 63% and 82% for PFS, OS, ORR and DCR respectively. We performed sensitivity analysis by leave-one-out method firstly, which proved the robustness of our meta-analysis (Figure S2). Considering this, multiple meta-regression was performed to explore major contributors to between-study heterogeneity. Differences in irAEs type, sample size, study type, and study area, etc. were found to be main possible accounts (Figure S3).

Publication bias evaluation

Asymmetry of funnel plots plus test results showed probable existence of publication bias (Figure S4). However, large sample size or huge heterogeneity may also lead to asymmetry or test failure (31). Therefore, trim-and-fill method was adopted to adjust each contour-enhanced funnel plot. The results showed that only few studies (n=0/3/1/1, for PFS/OS/ORR/DCR respectively) appeared to be missing in statistically non-significant area (0.1>P>0.05), indicating publication bias could only account for a small part of asymmetry (136). The heterogeneity factors derived from the preceding evaluation were subsequently leveraged to calibrate the funnel plots, consequently achieving enhanced symmetry. Thus, there may exist little publication bias, with between-study heterogeneity being major cause of asymmetry.

Discussion

Based on the latest evidence, the results of our meta-analysis indicated that the development of irAEs was generally correlated with improved survival and treatment response regardless of PD-L1 expression, especially those developed

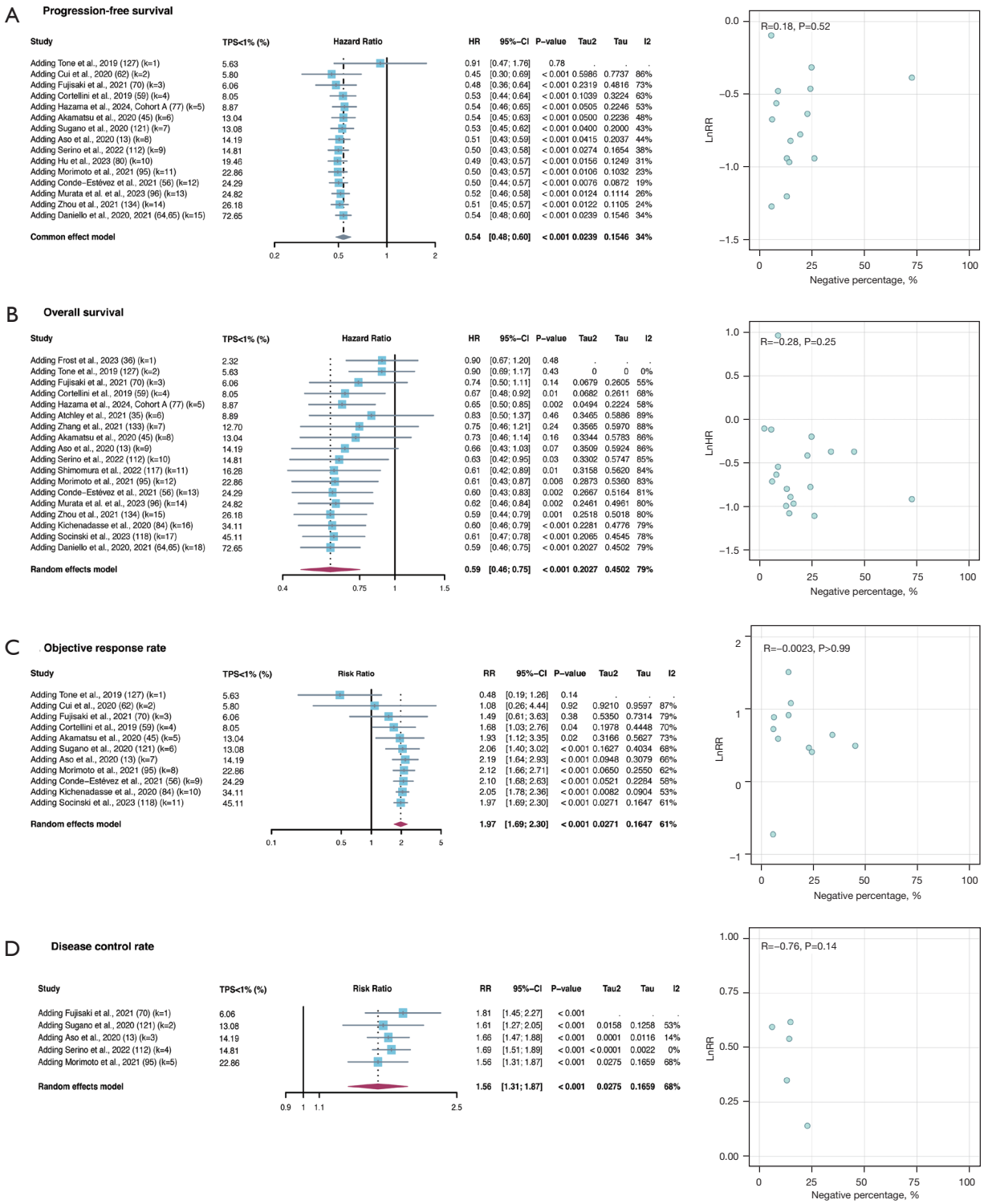

Figure 4 Cumulative meta-analyses performed by sequentially adding studies according to the proportion of patients with negative PD-L1 expression plus dot plots demonstrating the correlation between negative PD-L1 expression portion and effect size (lnHR or lnRR) based on irAEs status. (A) Progression-free survival; (B) overall survival; (C) objective response rate; (D) disease control rate. TPS, tumor proportion score; HR, hazard ratio; CI, confidence interval; PD-L1, programmed cell death-ligand 1; lnHR, natural logarithm of the hazard ratio; lnRR, natural logarithm of the risk ratio; irAE, immune-related adverse event.

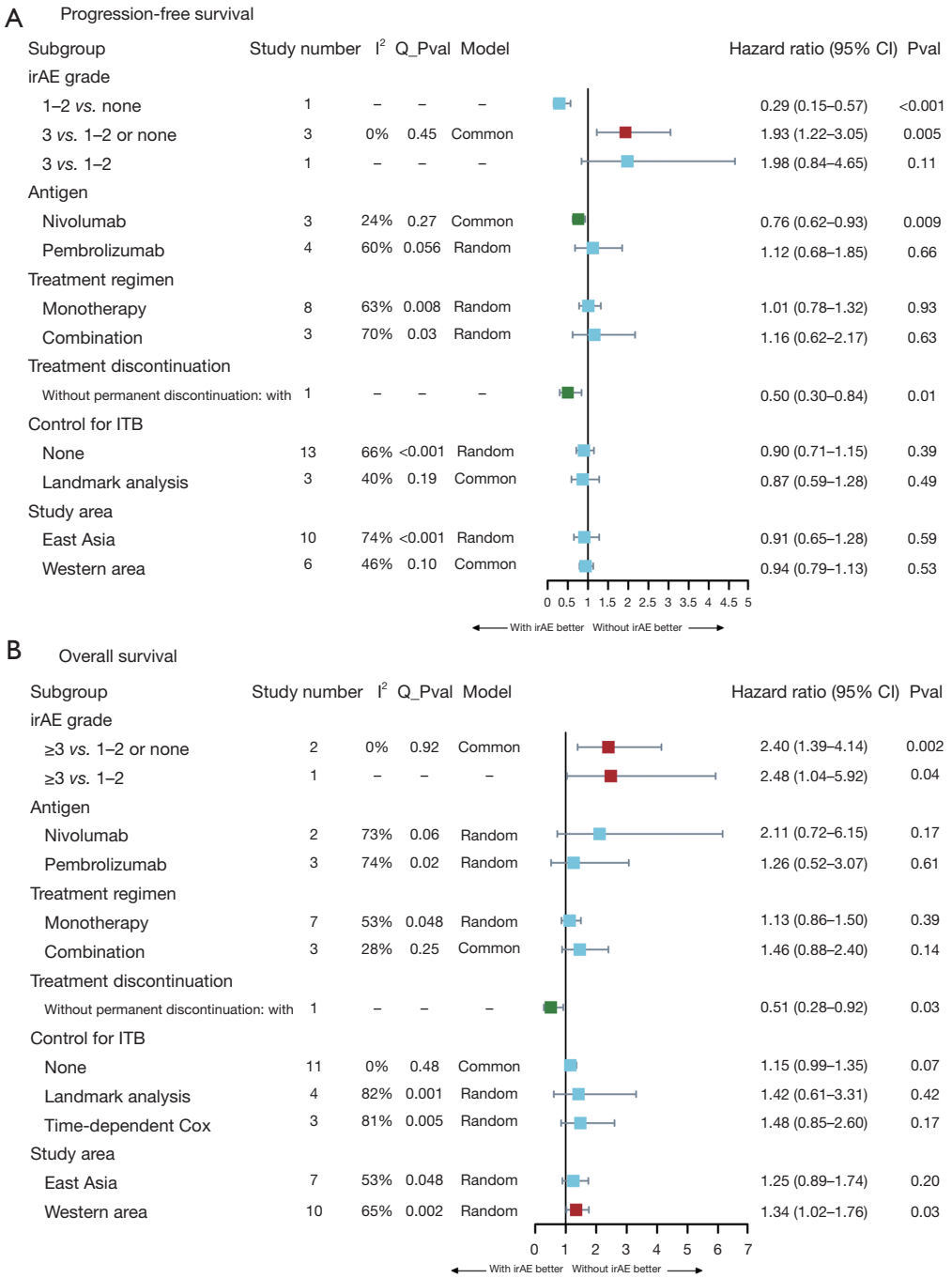

Figure 5 Forest plots revealing the association between pulmonary irAEs of different traits and patient survival. (A) Progression-free survival; (B) overall survival. CI, confidence interval; irAE, immune-related adverse event; ITB, immortal time bias.

within skin and endocrine system, of moderate severity, occurred in multiple sites, with late onset time, induced by monotherapy. However, irAEs leading to severe lung injury may cause undesirable results, especially with a higher risk of death. The prognostic impact of irAE-related treatment interruption remains uncertain, yet it is noteworthy that treatment discontinuation caused by pulmonary irAEs are likely to negatively affect long-term outcomes. However,

the value of immunotherapy resumption and steroid administration still needs validation.

Mechanisms underlying the occurrence of irAEs and its predictive role

Firstly, the reactivation of T cells is a pivotal factor in the efficacy of immunotherapy. Berner *et al.* found that prognostic value of skin irAEs could be attributed to shared T-cell targeted antigens in skin and lung (48). Of note, Abed *et al.* discovered that patients with homozygosity at one or more human leukocyte antigen (HLA)-I loci, but not at HLA-II, were less likely to develop irAEs (RR =0.61; 95% CI: 0.33–0.95; P=0.04), specifically with respect to the risk of lung toxicity or disease severity, which explained the question on genetic level (42). Secondly, growing evidence have shown the crucial role of humoral immune responses, which involve B cells and autoantibodies (137). For example, pre-existing rheumatoid factor (RF) could foretell autoimmune skin reaction (13). Likewise, the emergence of anti-thyroid antibodies was observed to be synchronous with thyroid dysfunction following ICIs (99). Finally, the positive-going effects of irAEs occurrence could be seen as a representation of enhanced immunomodulatory function by inflammatory cytokines. Akamatsu *et al.* (45) found that the level of fibroblast growth factor-2 (FGF-2) and monocyte chemoattractant protein (MCP) behaved differently between responders with and without irAEs, providing an explanation for their distinct PFS (HR =0.30; 95% CI: 0.10–0.85; P=0.02).

Biomarkers for irAEs

The above evidence has proved the clinical translational value of the relationship between irAEs and prognosis. Therefore, it is of vital importance to further explore biomarkers for irAEs occurrence, identifying patient who has the potential to benefit from ICIs. Based on the mechanism behind irAEs occurrence, predictive biomarkers could be categorized into blood cell counts, circulating cytokines and autoantibodies, serum proteins, and genomic characteristics (HLA genotypes, gene variation and gene expression level, etc.). Till now, many a study have confirmed blood cell counts as a low-cost, convenient, and efficient way to predict irAEs. It is suggested that elevated baseline level of absolute lymphocyte count (ALC) and absolute eosinophil count (AEC) (138), as well as high neutrophil-to-lymphocyte ratio (NLR) (139) were worthy risk factor for irAEs. Other biomarkers, such as thyroid-stimulating hormone (TSH) (140) and autoantibodies (141) were also found to be sensitive to certain type irAEs. Moreover, at genomic level, a recent genome-wide association study (GWAS) has identified interleukin (IL)-7 germline variation as a major risk factor for irAEs (142). Thus, integrating these biomarkers into a predictive model may contribute to personalized treatment, enabling improved disease management.

Different impact of irAEs of specific traits

Organ-specific irAEs

Our subgroup analysis investigated the impact of irAEs in skin, endocrine system, lung, gastro-intestinal tract, and liver, with the impact of ICI-related pneumonitis (ICI-P) being most disputable among different studies. ICI-P is one of the most encountered irAEs of ICIs treatment for NSCLC patients, with a relatively high possibility to be severe (all grade: 2.8–8.3%; ≥3 grade: 1.5–6.5%) (143,144). Despite enhanced treatment response to ICIs, our study revealed that developing ICI-P, especially severe one dramatically decreased survival outcomes for patients, which is consistent with the previous study (21). This may be because LC patients themselves are complicated with lung injury, and the effect of organ damage on survival is greater than the benefit of treatment. We also observed heterogenic effect of ICI-P among studies, especially in the research of Cui *et al.*, of which the result indicated longer PFS with ICI-P development (HR =0.38; 95% CI: 0.22–0.66; P=0.001) (62). Further investigation found that this cohort had the smallest proportion of patients with severe CIP (7/42, 16.67%). However, the cumulative meta-analysis failed to conclude a strong correlation between severe ICI-P proportion and effect size from each study (Figure S5). This implies that elements beyond the severity of ICI-P alone, such as the reliability of ICI-P diagnosis (which may not be fully attributable to immune causes but rather interstitial lung disease or radiotherapy), difference in ICI-P management, study area and racial characteristics, could have impacted the disparities in effect observed across different studies.

In addition to those common organ-specific irAEs analyzed in our study, evidence had suggested the incidence of immune-related acute kidney injury (irAKI) might be raised under combined therapy (145). Knox *et al.* conducted a real-world study investigating the impact of irAKI on NSCLC patient survival outcomes (146), with the result

showing that the occurrence of irAKI was associated with longer OS (HR =0.35; 95% CI: 0.20–0.60; P=0.01). Other types of irAEs, such as neurological irAEs which need timely intensive care are worth attention as well (147).

Onset

Our pooled analysis suggested that irAEs developing three months after treatment initiation were related to better outcomes compared to earlier ones. However, it is necessary to exclude possible confounding factors before investigating essential differences between early- and late-onset irAEs. Discrepancy in irAEs severity, duration of ICIs exposure, rate of treatment discontinuation, use of steroid or immunosuppressive agents, and survival time (longer survival time is a must to observe the development of late onset irAEs) should be considered. In the research conducted by Naqash *et al.* (97), 82.8% of treatment interruptions were due to early irAEs, but with no observed correlation between either the timing of onset and discontinuation of ICIs or the grade of irAEs. In another study of Hsiehchen *et al.* (79), the results stayed the same after controlling clinical confounders including sex, age, treatment strategies and survival time by multivariable Cox regression and 6-week landmark analysis. The above analyses indicated that inherent difference may exist biologically. For example, delayed humoral immune response may account for occurrence of late onset irAEs as hypothesized by Khan *et al.* in their case report of a late-onset (>20 months) Raynaud's phenomenon after ICIs treatment (148). However, doubt remained as the difference in steroid administration was hard to examine and the best cut-off defining early- or late-onset is worth further investigation.

PD-L1 expression

Our analysis implied that irAEs could be an independent indicator for prognosis irrespective of PD-L1 expression level. In line with our findings, Boussageon *et al.* observed favored PFS in patients with irAEs after matching the PD-L1 levels as well (53). Further rigorously designed prospective trial should be conducted to validate this finding.

Proper managements for irAEs are of vital importance

LDT irAEs and ICIs resumption

The prognostic impact of irAEs-related ICIs treatment discontinuation presented great heterogeneity among different populations according to our analysis. To further explore this issue, we encountered a previous case-control matched study (149) indicating that patients with early LTD-irAEs exhibited better treatment response compared to those without such events. However, the risk of disease progression was significantly elevated. Particularly, treatment interruptions resulting from pulmonary irAEs posed a higher risk to survival according to several study outcomes (21,149). Thus, we came up with the potential rationale for the conflicting prognostic impact of LDT-irAEs as follows: severe/early irAEs may signify activation of anti-tumor immune response, though the risk of organ damage as well as a shortened exposure to treatment could outweigh the therapeutic benefit in some cases. In addition, immunotherapy resumption showed similar efficacy as permanent discontinuation. A meta-analysis examining the value of ICIs rechallenge arrived at a conclusion resembling ours (150). The study further observed ICI rechallenge correlated with a substantially increased prevalence of all-grade irAEs versus frontline management (OR =3.81; 95% CI: 2.15–6.74; P<0.001). ICIs resumption did not seem to offer notable gains.

Use of steroid

The benefit brought by steroid remained ambiguous according to our meta result. This may be attributed to the discrepancy in administration regimens. Shimomura *et al.* had specifically examined the impact of different steroid dose and timing (117). Their findings showed that compared to patients experiencing irAEs but not treated with steroids, high-dose steroid treatment for irAEs within 60 days had a significantly poorer overall survival outcome while those managed with low-dose steroids had no worse outcomes. Moreover, a study targeted on patients comorbid with autoimmune diseases (AID) was also included (67). The positive relationship between irAEs and PFS maintained significant within this specific group of patients. However, pretreatment of steroid for AID was found to associate with worse PFS.

Limitations

To the best of our awareness, this represents the most extensive meta-analysis to date illuminating the prognostic importance of irAEs for advanced LC patients undergoing ICI treatment. However, it is crucial to approach our conclusions with caution and skepticism (https://cdn.amegroups.cn/static/public/tlcr-24-299-1.xlsx). (I) Most of

the studies we included were retrospective cohorts or real-world data, and the outcomes did not fully align amongst different study designs. (II) Considering that the mechanism of immunotherapy differs from traditional treatments such as chemotherapy, with its effectiveness being more closely tied to the individual's immune response level rather than solely tumor characteristics, we included both NSCLC and SCLC patients in our meta-analysis to comprehensively investigate the prognostic effect of irAEs on LC patients. However, potential bias may still arise from including SCLC patients, given their worse prognosis compared to NSCLC patients. We then performed subgroup analysis within NSCLC patients and found consistent results with overall analysis (PFS: HR =0.54; 95% CI: 0.49–0.59; P<0.001; OS: HR =0.55; 95% CI: 0.51–0.59; P<0.001; ORR: RR =2.06; 95% CI: 1.86–2.29; P<0.001; DCR: RR =1.58; 95% CI: 1.44–1.74; P<0.001). Due to the small number of studies merely focused on SCLC, it is unsuitable to perform meta-analysis within this subgroup. Nevertheless, we indeed observed less significant impact of irAEs on SCLC. Therefore, our integrated outcome may be more applicable towards NSCLC patients and the prognostic impact of irAEs on other pathological LC types needs further confirmation. (III) The vast majority of the patients we included were advanced/recurrent LC patients, and the prognostic significance of irAEs for early operable stage patients needs to be further clarified. (IV) Many of the included study did not account for immortal time bias, yet results did indicate that predictive role of irAEs on survival might be diminished when adopting time-dependent analysis. Further investigations are necessary to explore this potential effect. (V) Partial data underwent transformation before being incorporated into our meta-analysis, which may potentially result in distortion.

Conclusions

Based on our findings, we could educate patients that there is no need to over-worry about developing irAEs, as their occurrence generally correlates with a better prognosis. However, it remains important to carefully monitor for these side effects, especially respiratory symptoms and intervene promptly as needed to prevent escalation to more severe toxicity levels, since higher grades of toxicity run the risk of counteracting the intended treatment benefits. Close surveillance combined with timely management is key to balancing treatment efficacy and safety.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-299/coif). The authors have no conflicts of interest to declare.

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