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Association between immune-related adverse events and immunotherapy efficacy in non-small-cell lung cancer: a meta-analysis

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Objective: Our study aimed to identify potential correlations between anti-tumor efficacy and immune-related adverse events (irAEs) in non-small-cell lung cancer (NSCLC).

Methods: We conducted a comprehensive search of online electronic databases up to March 2023 to identify any correlations between irAEs and immune checkpoint inhibitor (ICI) efficacy in NSCLC. We used meta-analysis RevMan 5.3 software to calculate pooled results.

Results: Our meta-analysis of 54 studies revealed that patients who experienced irAEs achieved a significantly higher objective response rate (p < 0.00001) and longer progression-free survival (PFS) (p < 0.00001) and overall survival (OS) (p < 0.00001) than those who did not experience irAEs. Additionally, patients with ≥ 2 irAEs had better PFS, whereas no significant difference was observed between patients with or without squamous cell carcinoma. Subgroup analysis of irAE types indicated that irAEs (thyroid dysfunction and gastrointestinal, skin, or endocrine irAEs) were associated with better PFS and OS. However, no significant differences were observed between patients with pneumonitis or hepatobiliary irAEs.

Conclusion: Our study showed that the occurrence of irAEs was a strong predictor of survival efficacy in patients with NSCLC treated with ICIs. Specifically, patients with ≥ 2 irAEs and those with thyroid dysfunction and gastrointestinal, skin, or endocrine irAEs achieved a better survival benefit.

Systematic Review Registration: Website: https://www.crd.york.ac.uk/prospero/, Identifier: CRD42023421690

KEYWORDS

immune-related adverse events, clinical efficacy, immune checkpoint inhibitors, metaanalysis, non-small-cell lung cancer

Introduction

Immunotherapy, which targets the programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) pathway, has emerged as a revolutionary and highly efficient treatment alternative for advanced-stage non-small-cell lung cancer (NSCLC) (Assi et al., 2018). Specifically, immune checkpoint inhibitors (ICIs), including those that



target the PD-1/PD-L1 axis, enhance T-cell-mediated attack and exert anti-tumor effects (Wei et al., 2018).

In contrast to conventional chemotherapy, the use of ICIs can sometimes lead to a unique toxicity effect resembling autoimmune disorders. This "self-response" of the immune system is known as immune-related adverse events (irAEs) (Young et al., 2018).

Several retrospective studies have highlighted that the occurrence of irAEs in patients with melanoma is associated with improved survival outcomes (Freeman-Keller et al., 2016; Hua et al., 2016; Nakamura et al., 2017), suggesting that irAEs may be a predictive marker for the clinical benefit of ICIs.

However, achieving the maximum therapeutic efficacy with ICIs requires a careful balance between anti-tumor immunity and autoimmunity. Conversely, studies on patients with advanced NSCLC have identified a correlation between adverse events and clinical outcomes of ICIs. Whether the occurrence of irAEs is associated with the clinical efficacy in NSCLC remains a subject of ongoing research. However, the results of current studies investigating the correlation between anti-tumor efficacy and the development of irAEs have been inconsistent (Kothari et al., 2017; Haratani et al., 2018; Cortellini et al., 2019).

Study year Immune checkpoint Follow-up period inhibitor design Haratani et al. (2018) Retrospective Nivolumab 134 (90/44) 68 Japan December 2015 and 7 study August 2016 Sato et al. (2018) Retrospective Nivolumab 38 (28/10) 68.5 Japan December 2015 and 8 February 2017 study January and December Teraoka et al. (2017) Nivolumab 43 (27/16) 70 7 Retrospective Japan 2016 study Lesueur et al. (2018) Nivolumab 104 (67/37) 7 Retrospective 60.3 France During 2014 study September 2014 to June Owen et al. (2018) Nivolumab 91 (39/52) 67 America 7 Retrospective study 2016 Toi et al. (2018) January 2016 and January 7 Retrospective Nivolumab 137 (61/76) 68 Japan study 2018 7 Baldini et al. (2020) 1 Retrospective Nivolumab 1,959 (1327/632) 1 Italy study Ricciuti et al. (2019) Retrospective Nivolumab 195 (128/67) 63 Italy October 2013 and 8 September 2017 study 7 Naqash et al. (2020) Retrospective Nivolumab 531 (NA) / America 1 study Lisberg et al. (2018) Pembrolizumab 97 (50/47) August 2012 and 8 Retrospective 67 America December 2016 study Pembrolizumab Osorio et al. (2017) Retrospective 51 (NA) / America 4 March 2011 and 7 11 December 2018 study Tambo et al. (2020) Pembrolizumab 95 (NA) February 2017 to 7 Retrospective / Iapan study December 2018 Kim et al. (2017) 89.0 days 8 Nivolumab/pembrolizumab 58 (43/15) 63.1 Retrospective Korea study Ksienski et al. (2019) June 2015 to November Retrospective Nivolumab/pembrolizumab 271 (116/114) 66 Canada 8 study 2017 Cortellini et al. (2019) Retrospective Nivolumab/pembrolizumab 559 (379/180) / Italy 1 7 study Retrospective Suh et al. (2018) Nivolumab/pembrolizumab 54 (42/12) 70 Korea 1 7 study Yamaguchi et al. (2020) Nivolumab/pembrolizumab 131 (98/33) 77 January 2016 and 7 Retrospective Japan study February 2018 Grangeon et al. (2019) Retrospective Anti-PD-L1 or anti-PD-1 270 (NA) 1 France April 2013 to February 8 2017 study Aso et al. (2020) 155 (117/38) January 2016 to April 7 Retrospective Nivolumab/pembrolizumab 68 Japan study 2018 Sonehara et al. (2021) Retrospective Nivolumab/pembrolizumab/ 80 (65/15) / February 2016 and 7 Japan study atezolizumab February 2020. Morimoto et al. (2021) Pembrolizumab/atezolizumab January 2019 and 7 Retrospective 70 (51/19) 69 5 Japan study September 2019 Pembrolizumab Shukla et al. (2021) Retrospective 92 (59/33) 64 Japan March 2015 to November 8 2016 study Chmielewska et al. Retrospective Nivolumab 35 (20/15) 65.8 Poland November 2016 to 8 (2021)study January 2020 Daniello et al. (2021) Retrospective Nivolumab/pembrolizumab/ 894 (536/358) 65 Germany. October 2012 and June 8 study atezolizumab 2020

TABLE 1 Characteristics of the include studies.

(Continued on following page)

Study year Immune checkpoint Follow-up period inhibitor design Chen et al. (2021) Retrospective Anti-PD-L1 or anti-PD-1 191 (139/52) 1 China August 2016 to 7 November 2019 study Fujimoto et al. (2018) Retrospective Nivolumab 613 (NA) / Japan January and December 6 2016 study Ahn et al. (2019) Nivolumab or pembrolizumab 155 (113/42) March 2014 and January 7 Retrospective 64 Korea 2019 study Berner et al. (2019) Anti-PD-1 73 (44/29) Switzerland 1 July 2016 to 7 Retrospective 68.1 study 31 December 2018 September 2015 to April Bjørnhart et al. (2019) Retrospective Anti-PD-L1 or anti PD-1 118 (44/74) Denmark 7 66 study 2018 Imai et al. (2020) Pembrolizumab 87 (40/47) February 2017 and 7 Retrospective 79 Japan study February 2018 Nivolumab, pembrolizumab, or December 2015 and 7 Sugano et al. (2020) Retrospective 130 (98/32) 1 Japan study atezolizumab November 2018 February 2017 to August Noguchi et al. (2020) Retrospective Pembrolizumab 94 (82/12) / Japan 7 2019 study 7 Kubo et al. (2020) Retrospective Nivolumab or pembrolizumab 95 (77/18) 79 Japan December 2015 to December 2017 study Akamatsu et al. (2020) Nivolumab, pembrolizumab, or 23 (18/5) December 2015 and 7 Retrospective 69 Japan atezolizumab September 2018 study Campredon et al. Retrospective Nivolumab 183 (72/111) 61 France May 2015 and December 7 (2019) 2016 study Cui et al. (2020) Anti-PD-L1 or anti-PD-1 276 (205/71) 61 China September 2015 and 7 Retrospective 31 August 2019 study Nivolumab 191 (121/70) 7 Dupont et al. (2019) 63 19 September 2014 and Retrospective France 31 December 2016 study Fukihara et al. (2019) / January 2016 and March Retrospective Nivolumab or pembrolizumab 170 (125/45) Japan 8 study 2018 Isono et al. (2021) Retrospective Nivolumab, pembrolizumab, or 180 (140/40) 68.5 Japan 1 January 2016 to 7 atezolizumab 31 March 2019 study Retrospective Kobayashi et al. (2020) Ipilimumab, nivolumab, 108 (79/29) 67 Japan 2 November 2015 and 7 pembrolizumab, or study 30 August 2019 atezolizumab Bouhlel et al. (2020) Retrospective Nivolumab 69 (NA) / France March 2015 to March 7 2017 study Peiró et al. (2019) Nivolumab 55 (NA) / During 2016 7 Retrospective Spain study During 2019 7 Park et al. (2021) Retrospective Pembrolizumab or nivolumab 1.181 (932/249) 67 Korea study Rose et al. (2020) Ipilimumab, nivolumab, 233 (NA) July 2011 and October 7 Retrospective 70 America study pembrolizumab, or 2019 atezolizumab Rubino et al. (2021) Retrospective Pembrolizumab or nivolumab 251 (109/64) 70.6 Italy 1 October 2017 to 31 July 8 2020 study Thuillier et al. (2021) Nivolumab 134 (94/40) 20 July 2015 and 30 June 7 Retrospective 62.5 France 2018 study Zhang et al. (2021) Pembrolizumab 65.5 January 2014 and 7 Retrospective 63 (32/31) America study February 2019 7 Schweizer et al. (2020) Anti-PD-L1 104 (76/28) / Germany Retrospective study

TABLE 1 (Continued) Characteristics of the include studies.

(Continued on following page)

Study year	Study design	Immune checkpoint inhibitor	No. of patients (male/female)	Median age	Region	Follow-up period	NOS
Zhou et al. (2021)	Retrospective study	Anti-PD-1	191 (138/53)	/	China	10 October 2016 and 1 April 2020	7
Sayer et al. (2023)	Retrospective study	Anti-PD-L1 or anti-PD-1	354 (190/164)	/	America	2014 and 2018	8
Socinski et al. (2023)	Retrospective study	Atezolizumab	2,503 (1519/984)	63.1	America	During February 2022	8
Guezour et al. (2022)	Retrospective study	Ipilimumab, nivolumab, or pembrolizumab	201 (132/69)	63	France	1 January 2016 and 31 December 2019	7
Cortijo-Cascajares et al. (2023)	Retrospective study	Nivolumab	75 (51/24)	/	Spain	February 2015 to May 2020	7
Wang et al. (2022)	Retrospective study	Anti-PD-L1 or anti-PD-1	222 (179/43)	/	China	1	7

TABLE 1 (Continued) Characteristics of the include studies.

irAEs, immune-related adverse events; NOS, Newcastle-Ottawa Quality Assessment Scale; NA, not available.

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ahn BC 2019	-0.7257	0.327	3.0%	0.48 [0.25, 0.92]	
Akamatsu H 2020	-0.7985	0.7188	1.4%	0.45 [0.11, 1.84]	· · · · · · · · · · · · · · · · · · ·
Baldini E 2020	0.5128	0.0863	4.1%	1.67 [1.41, 1.98]	
Bjørnhart B 2019	-0.755	0.411	2.6%	0.47 [0.21, 1.05]	
Chen X 2021	-0.2744	0.2789	3.2%	0.76 [0.44, 1.31]	
Cortellini A 2019	-0.5978	0.1499	3.8%	0.55 [0.41, 0.74]	
Cortijo-Cascajares S 2023	-1.0217	0.275	3.3%	0.36 [0.21, 0.62]	
Daniello L 2021	-0.9676	0.1744	3.7%	0.38 [0.27, 0.53]	
Dupont R 2019	-1.0217	0.2999	3.1%	0.36 [0.20, 0.65]	
Grangeon M 2019	-1.2379	0.2433	3.4%	0.29 [0.18, 0.47]	
Haratani K 2018	-1.2758	0.5239	2.1%	0.28 [0.10, 0.78]	·
mai H 2020	-0.2485	0.5227	2.1%	0.78 [0.28, 2.17]	
sono T 2021	-0.4943	0.2282	3.5%	0.61 [0.39, 0.95]	
Kim HI 2017	-2.2074	1.2234	0.6%	0.11 [0.01, 1.21]	•
Kobayashi T 2020	-0.2231	0.3666	2.8%	0.80 [0.39, 1.64]	
Ksienski D 2019	0.2927	0.4929	2.2%	1.34 [0.51, 3.52]	
Kubo T 2020	0.4637	0.2736	3.3%	1.59 [0.93, 2.72]	
esueur P 2018	-0.4462	0.266	3.3%	0.64 [0.38, 1.08]	
isberg A 2018	-0.3284	0.1964	3.6%	0.72 [0.49, 1.06]	
Morimoto K 2021	-0.4155	0.4023	2.6%	0.66 [0.30, 1.45]	
Naqash AR 2020	-0.4155	0.1216	3.9%	0.66 [0.52, 0.84]	
Osorio JC 2017	-1.2378	0.597	1.8%	0.29 [0.09, 0.93]	· · · · · · · · · · · · · · · · · · ·
Du Yamaguchi 2020	-0.1863	0.2485	3.4%	0.83 [0.51, 1.35]	
Owen DH 2018	1.0116	0.2958	3.1%	2.75 [1.54, 4.91]	
Park JH 2021	-0.6349	0.2417	3.4%	0.53 [0.33, 0.85]	
Ricciuti B 2019	-0.9676	0.1936	3.7%	0.38 [0.26, 0.56]	
Rose LM 2020	-0.844	0.3657	2.8%	0.43 [0.21, 0.88]	
Rubino R 2021	-1.3471	0.3537	2.8%	0.26 [0.13, 0.52]	
Sayer MR 2023	-0.6733	0.1369	3.9%	0.51 [0.39, 0.67]	
Schweizer C 2020	-0.2357	0.8147	1.2%	0.79 [0.16, 3.90]	
Socinski MA 2023	-0.3711	0.0713	4.1%	0.69 [0.60, 0.79]	-
Sonehara K 2021	-1.204	0.3889	2.7%	0.30 [0.14, 0.64]	
Suh KJ 2018	-0.734	0.4467	2.4%	0.48 [0.20, 1.15]	
Wang W 2022	0.5423	0.6304	1.7%	1.72 [0.50, 5.92]	
Zhang M 2021	-2.5257	0.7073	1.5%	0.08 [0.02, 0.32]	·
Fotal (95% CI)			100.0%	0.58 [0.47, 0.71]	•
Heterogeneity: $Tau^2 = 0.27$; Chi ² = 227.15, df =	34 (P <	0.00001)	$1^2 = 85\%$	
Test for overall effect: $Z = S$	5.15 (P < 0.00001)				Favours [irAEs] Favours [no irAEs]
GURE 2					

Analysis of OS between IrAEs and ICI efficacy.

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Naqash AR 2020	-0.3285	0.2176	17.0%	0.72 [0.47, 1.10]	
Lisberg A 2018	-0.2877	0.1311	18.4%	0.75 [0.58, 0.97]	
Kubo T 2020	0.1655	0.2664	16.1%	1.18 [0.70, 1.99]	
Guezour N 2022	0.9163	0.2277	16.8%	2.50 [1.60, 3.91]	
Cortijo-Cascajares S 2023	-1.273	0.3915	13.5%	0.28 [0.13, 0.60]	
Cortellini A 2019	-0.7985	0.143	18.2%	0.45 [0.34, 0.60]	
Total (95% CI)			100.0%	0.78 [0.47, 1.31]	
Heterogeneity: Tau ² = 0.35; Test for overall effect: Z = 0	Chi ² = 49.94, df = 5 .94 (P = 0.35)	(P < 0.0	0001); I ²	= 90%	0.1 0.2 0.5 1 2 5 10 Favours [≥2] Favours [<2]
FIGURE 3 Sub-group analysis of OS betw	een IrAEs and ICI effic	acy with	the numb	per of irAEs.	

With the aim to provide a systematical, up-to-date assessment of the potential predictive value of irAEs in NSCLC and gain a better understanding of the relationship between irAEs and clinical outcomes, we performed an update meta-analysis of the association between the occurrence of irAEs and anti-tumor efficacy.

Materials and methods

Search strategy

The meta-analysis was based on the Cochrane Manual of Intervention System Assessments and Guidelines for Systematic Reviews and Meta-Analyses. PubMed, Embase, and the Cochrane Library were searched for articles published up to March 2023. The process was conducted to find all relevant studies using the following keywords: "non-small cell lung cancer" AND "immune checkpoint inhibitors" OR "immunotherapy" AND "immune-related adverse events" AND "prognosis" terms, and the relevant Medical Subject Heading terms were used during the literature search process. The reference lists were also checked for retrieving additional relevant articles.

Eligibility criteria

Articles that met the following criteria were included: (1) patients had clinical diagnosis of NSCLC treated with an ICI; (2) trials focused on assessing the effectiveness of ICI in relation to the advent of irAEs; (3) outcomes of interest were effectiveness (overall survival [OS], progression-free survival [PFS], and tumor response) and selection of AE designation related to treatment; and (4) only full texts were included.

Quality assessment

Two authors (Li Lin and Yu Liu) separately justified the quality of the retrieved articles. Study quality was assessed using the Newcastle–Ottawa Quality Assessment Scale (Cook and Reed, 2015). The process was conducted by two researchers independently, and differences were resolved through discussion. The Newcastle–Ottawa Scale method uses three domains to assess the quality of cohort studies: the selection of patients with cancer, comparability between two groups, and assessment of outcomes. According to the NOS method, four, two, and three points were awarded to the three domains, respectively. Studies with \geq 7 points were identified as having high quality, but those with \leq 6 points were identified as having low quality. Publication bias was evaluated using funnel plots.

Data extraction

A data extraction form was used independently to retrieve the content containing the first author, publication year, ICI treatment regimen, region, number of patients, mean age, study design, followup period, and outcomes of interest. Two researchers (Li Lin and Yu Liu) independently evaluated the data. If there was a disagreement, a third researcher (Wei Li) resolved the disagreement through discussion.

Statistical analysis

Heterogeneity between studies was analyzed using the I² statistic (Higgins and Thompson, 2002). A value of I² > 50% implied a high degree of heterogeneity (Higgins et al., 2003). The random-effects model was used when there was high heterogeneity among the articles; otherwise, a fixed-effects model was used. Statistically significant differences were identified using a *p*-value of <0.05. Statistical analyses were conducted using the ReviewManager software package version 5.3 (RevMan; Cochrane Collaboration, Oxford, United Kingdom). Odds ratios (ORs) and 95% confidence intervals (CIs) were used for binary data and effect sizes in the meta-analysis. Forest plots were used to present the results of the study.

Results

Overview of the literature search

A total of 658 articles were identified as potentially eligible for inclusion. Using the criteria outlined in the Methods section,

Study or Subaroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV. Random. 95% CI	Hazard Ratio IV. Random, 95% Cl
4.1.1 Thyroid dysfun	ction		neight	,	
Grangeon M 2019	-0.7765	0.3111	3.8%	0.46 [0.25, 0.85]	
Kim HI 2017	-2.2073	1.2234	0.6%	0.11 [0.01, 1.21]	*
Morimoto K 2021	-0.6349	0.717	1.4%	0.53 [0.13, 2.16]	
Nagash AR 2020	-0.2357	0.2037	4.9%	0.79 [0.53, 1.18]	
Osorio JC 2017	-1.2379	0.597	1.9%	0.29 [0.09, 0.93]	·
Thuillier P 2021	-1.1394	0.3537	3.4%	0.32 [0.16, 0.64]	
Zhou Y 2021	-1.0966	0.272	4.2%	0.33 [0.20, 0.57]	
Subtotal (95% CI)			20.2%	0.44 [0.29, 0.64]	◆
Heterogeneity: Tau ² = Test for overall effect:	0.11; Chi ² = 11.25, Z = 4.16 (P < 0.000)	df = 6 (P 1)	= 0.08);	$I^2 = 47\%$	
4.1.2 Pneumonitis					
Ahn BC 2019	1.4296	0.5505	2.1%	4.18 [1.42, 12.29]	— — →
Cortellini A 2019	0.2776	0.2619	4.3%	1.32 [0.79, 2.21]	
Grangeon M 2019	0.3507	0.5863	1.9%	1.42 [0.45, 4.48]	
Morimoto K 2021	0.1398	0.5388	2.1%	1.15 [0.40, 3.31]	
Naqash AR 2020	0.3001	0.2126	4.8%	1.35 [0.89, 2.05]	
Ricciuti B 2019	-0.7765	0.3319	3.6%	0.46 [0.24, 0.88]	
Subtotal (95% CI)			18.8%	1.24 [0.76, 2.02]	
Heterogeneity: Tau ² = Test for overall effect:	0.22; Chi ² = 14.01, Z = 0.84 (P = 0.40)	df = 5 (P	= 0.02);	$l^2 = 64\%$	
4.1.3 Hepatitis					
Cortellini A 2019	0.0862	0.4184	2.9%	1.09 [0.48, 2.48]	
Grangeon M 2019	-0.0305	0.5987	1.8%	0.97 [0.30, 3.14]	
Naqash AR 2020	0.1655	0.3202	3.7%	1.18 [0.63, 2.21]	
Ricciuti B 2019	-0.0619	0.2924	4.0%	0.94 [0.53, 1.67]	
Subtotal (95% CI)	a an aday - same a		12.4%	1.04 [0.73, 1.49]	•
Heterogeneity: Tau ² = Test for overall effect:	0.00; $Chi^2 = 0.30$, di Z = 0.24 (P = 0.81)	f = 3 (P =	= 0.96); l'	⁴ = 0%	
4.1.4 GI					
Cortellini A 2019	-0.4943	0.2415	4.5%	0.61 [0.38, 0.98]	
Grangeon M 2019	-1.4271	1.061	0.7%	0.24 [0.03, 1.92]	
Naqash AR 2020	-0.4308	0.3158	3.8%	0.65 [0.35, 1.21]	100 100
Subtotal (95% CI)	-0.6931	0.3336	3.0%	0.50 [0.26, 0.96]	
Heterogeneity: Tau ² -	0.00; Chi ² - 1.06 d	f - 2 (D -	- 0 70) 12	- 0%	•
Test for overall effect:	Z = 3.33 (P = 0.0009)	9)	- 0.79), 1	- 070	
4.1.5 Skin					
Ahn BC 2019	-0.8675	0.4861	2.4%	0.42 [0.16, 1.09]	
Berner F 2019	-1.2379	0.4502	2.7%	0.29 [0.12, 0.70]	
Cortellini A 2019	-0.844	0.2374	4.6%	0.43 [0.27, 0.68]	
Marimoto K 2018	-1.5606	0.7322	1.4%	0.21 [0.05, 0.88]	
Nagach AP 2021	-0.9165	0.5550	2.1%	0.40 [0.14, 1.14]	
Ricciuti B 2019	-0.2231	0.2300	4.4%	0.80 [0.46, 1.39]	
Subtotal (95% CI)	-0.2231	5.2025	21.7%	0.50 [0.37. 0.68]	•
Heterogeneity: Tau ² = Test for overall effect:	0.03; $Chi^2 = 7.64$, d Z = 4.49 (P < 0.000	f = 6 (P = 01)	= 0.27); l ²	2 = 21%	•
4.1.6 Endocrine					
Chmielewska I 2021	-0.6539	0.3945	3.1%	0.52 [0.24, 1.13]	
Cortellini A 2019	-0.5978	0.2023	4.9%	0.55 [0.37. 0.82]	
Haratani K 2018	-0.6931	1.4354	0.4%	0.50 [0.03, 8.33]	· · · ·
Morimoto K 2021	-0.7765	0.73	1.4%	0.46 [0.11, 1.92]	
Ricciuti B 2019	-0.7985	0.2421	4.5%	0.45 [0.28, 0.72]	
Subtotal (95% CI)			14.3%	0.51 [0.38, 0.67]	•
Heterogeneity: Tau ² = Test for overall effect:	0.00; $Chi^2 = 0.43$, d Z = 4.83 (P < 0.000)	f = 4 (P = 01)	= 0.98); I ²	2 = 0%	
Total (95% CI)			100.0%	0.63 [0.52, 0.76]	
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff	0.15; $Chi^2 = 73.69$, Z = 4.76 (P < 0.000) erences: $Chi^2 = 22.84$	df = 32 (01) 4, df = 5	P < 0.000 ($P = 0.00$	(01); $I^2 = 57\%$ (004), $I^2 = 78.1\%$	0.1 0.2 0.5 1 2 5 10 Favours [irAEs] Favours [no-irAEs]

66 publications were evaluated by browsing the full set of studies; however, some did not provide sufficient outcome data from the two approaches. Finally, 54 articles (Ahn et al., 2019; Akamatsu et al., 2020;

Aso et al., 2020; Baldini et al., 2020; Berner et al., 2019; Bjørnhart et al., 2019; Bouhlel et al., 2020; Campredon et al., 2019; Cortellini et al., 2019; Chen et al., 2021; Chmielewska et al., 2021; Cui et al., 2020; Cortijo-

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Baldini E 2020	0.1989	0.0766	68.5%	1.22 [1.05, 1.42]	
Ksienski D 2019	-0.1985	0.2732	5.4%	0.82 [0.48, 1.40]	
Lesueur P 2018	-0.2485	0.2477	6.6%	0.78 [0.48, 1.27]	
Lisberg A 2018	-0.0202	0.3537	3.2%	0.98 [0.49, 1.96]	
Sonehara K 2021	-0.2877	0.3081	4.2%	0.75 [0.41, 1.37]	
Suh KJ 2018	-0.2485	0.3407	3.5%	0.78 [0.40, 1.52]	
Thuillier P 2021	-0.1054	0.2154	8.7%	0.90 [0.59, 1.37]	
Total (95% CI)			100.0%	1.08 [0.96, 1.23]	•
Heterogeneity: Chi ² =	8.38, $df = 6 (P = 0.2)$	21); $I^2 = 1$	28%		
Test for overall effect	Z = 1.24 (P = 0.21)				Favours [squamous] Favours [non-squamous]

FIGURE 5

Sub-group analysis of OS between IrAEs and ICI efficacy with pathological subtypes of irAEs.

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ahn BC 2019	-0.8347	0.2693	3.5%	0.43 [0.26, 0.74]	
Akamatsu H 2020	-1.204	0.5605	2.0%	0.30 [0.10, 0.90]	
Baldini E 2020	0.3716	0.0717	4.6%	1.45 [1.26, 1.67]	
Bjørnhart B 2019	-0.3425	0.3057	3.3%	0.71 [0.39, 1.29]	
Chen X 2021	-0.478	0.1867	4.1%	0.62 [0.43, 0.89]	
Cortellini A 2019	-0.5276	0.116	4.4%	0.59 [0.47, 0.74]	
Cortijo-Cascajares S 2023	-1.4697	0.2911	3.4%	0.23 [0.13, 0.41]	
Daniello L 2021	-2.9957	1.4632	0.4%	0.05 [0.00, 0.88]	←────
Fujimoto D 2018	-0.2744	0.165	4.2%	0.76 [0.55, 1.05]	
Grangeon M 2019	-0.8675	0.1387	4.3%	0.42 [0.32, 0.55]	
Haratani K 2018	-0.634	0.3081	3.3%	0.53 [0.29, 0.97]	
Imai H 2020	-0.3567	0.3537	3.0%	0.70 [0.35, 1.40]	
Kim HI 2017	-0.9676	0.4104	2.7%	0.38 [0.17, 0.85]	
Lesueur P 2018	-0.4155	0.2186	3.9%	0.66 [0.43, 1.01]	
Lisberg A 2018	-0.478	0.2236	3.8%	0.62 [0.40, 0.96]	
Morimoto K 2021	-0.6349	0.2904	3.4%	0.53 [0.30, 0.94]	
Nagash AR 2020	-0.3857	0.1083	4.4%	0.68 [0.55, 0.84]	
Noguchi S 2020	-1.1087	0.3384	3.1%	0.33 [0.17, 0.64]	
Osorio JC 2017	-0.5447	0.3901	2.8%	0.58 [0.27, 1.25]	· · · · · · · · · · · · · · · · · · ·
Ou Yamaguchi 2020	-0.3147	0.2139	3.9%	0.73 [0.48, 1.11]	
Park JH 2021	-0.6539	0.2477	3.7%	0.52 [0.32, 0.85]	
Ricciuti B 2019	-0.734	0.1759	4.1%	0.48 [0.34, 0.68]	
Rubino R 2021	-1.273	0.3185	3.2%	0.28 [0.15, 0.52]	
Sato K 2018	-2.3026	0.8212	1.2%	0.10 [0.02, 0.50]	<u>ــــــــــــــــــــــــــــــــــــ</u>
Sayer MR 2023	-0.6539	0.1213	4.4%	0.52 [0.41, 0.66]	
Schweizer C 2020	-0.4155	0.6921	1.5%	0.66 [0.17, 2.56]	
Sonehara K 2021	-1.4697	0.2911	3.4%	0.23 [0.13, 0.41]	
Teraoka S 2017	-0.462	0.3785	2.9%	0.63 [0.30, 1.32]	
Toi Y 2018	-0.844	0.3657	2.9%	0.43 [0.21, 0.88]	
Wang W 2022	-0.6349	0.1698	4.1%	0.53 [0.38, 0.74]	
Total (95% CI)			100.0%	0.51 [0.42, 0.63]	•
Heterogeneity: Tau ² = 0.23;	; Chi ² = 197.05, df =	29 (P < 0	0.00001);	$I^2 = 85\%$	
Test for overall effect: $Z = 6$	5.47 (P < 0.00001)				Favours [irAEs] Favours [no irAEs]
IGURE 6					
nalvsis of PES between IrAEs	and ICI efficacy.				

Cascajares et al., 2023; Daniello et al., 2021; Dupont et al., 2019; Fujimoto et al., 2018; Fukihara et al., 2019; Grangeon et al., 2019; Guezour et al., 2022; Haratani et al., 2018; Imai et al., 2020; Isono et al., 2021; Kim et al., 2017; Kobayashi et al., 2020; Ksienski et al., 2019; Kubo et al., 2020; Lesueur et al., 2018; Lisberg et al., 2018; Morimoto et al., 2021; Naqash et al., 2020; Noguchi et al., 2020; Osorio et al., 2017; Owen et al., 2018; Park et al., 2021; Peiró et al., 2019; Ricciuti et al., 2019; Rose et al., 2021; Rubino et al., 2021; Sato et al., 2018; Sayer et al., 2023; Schweizer et al., 2020; Shukla et al., 2021; Sonehara et al., 2021; Socinski et al., 2023; Sugano et al., 2020; Suh et al., 2018; Tambo et al., 2020; Teraoka et al., 2017; Thuillier et al., 2021; Toi et al., 2018; Wang et al., 2022; Yamaguchi et al., 2020; Zhang et al., 2021; Zhou et al., 2021) were assessed for eligibility in the meta-analysis. Figure 1 illustrates the search process. A brief description of the 54 studies is provided in Table 1.



A total of 54 studies had high methodological quality. Table 1 summarizes the quality appraisal process.

Outcomes and synthesis of results

Pooled analysis of the OS between IrAEs and ICI efficacy

A high statistical between-study heterogeneity was found in the ORs of the studies (I² = 85%), and a random-effects model was used for merging. As shown in Figure 2, the pooled effect size estimates showed that there was a statistically significant difference in OS when comparing the irAEs with the no-irAE group (HR = 0.58, 95% CI = 0.47–0.71, p < 0.00001).

With regard to the number of irAEs developed, no significant difference was found in patients with ≥ 2 irAEs than those with <2 irAEs (HR = 0.78, 95% CI = 0.47–1.31, p = 0.35) (Figure 3).

When survival outcomes were analyzed according to the types of irAEs, patients who developed any irAEs (p < 0.00001), thyroid dysfunction (p < 0.00001), and gastrointestinal (p = 0.0009), skin (p < 0.00001), or endocrine (p < 0.00001) irAEs experienced a significantly longer OS, whereas there was no significant change observed in patients with pneumonitis (p = 0.40) and hepatobiliary (p = 0.81) irAEs (Figure 4).

In terms of the pathological subtype, no differences were observed between the presence and absence of squamous cell carcinoma (HR = 1.08, 95% CI = 0.96-1.23, p = 0.21) (Figure 5).

Pooled analysis of the PFS between the IrAEs and ICI efficacy

A statistical between-study heterogeneity was found in the OR of studies (I² = 85%); therefore, a random-effects model was used for merging. When the PFS was pooled, it was found that patients with irAEs were associated with a better PFS than those without irAEs (HR = 0.51, 95% CI = 0.42–0.63, p < 0.00001) (Figure 6).

As shown in Figure 7, the pooled effect size estimates showed a significant statistical difference in PFS for patients with an increasing number of irAEs compared with those with <2 irAEs (HR = 0.49, 95% CI = 0.30–0.79, p = 0.004).

Subgroup analyses of treatment-related AEs revealed that PFS was significantly better in patients with any irAEs (p < 0.00001), thyroid dysfunction (p = 0.001), and gastrointestinal (p = 0.0007),

skin (p < 0.00001), or endocrine (p < 0.0001) irAEs (Figure 8). However, no statistically significant differences were detected in the PFS of patients with irAEs associated with pneumonitis (p = 0.51) or hepatobiliary disease (p = 0.39).

As shown in Figure 9, a pooled estimates of effect size showed no significant statistical difference in patients with or without squamous cell carcinoma (HR = 0.68, 95% CI = 0.41-1.14, p = 0.14).

Pooled analysis of the objective response rate between IrAEs and ICI efficacy

A statistical between-study heterogeneity was found in the OR of the studies (I² = 58%), and a random-effects model was used for merging. As shown in Figure 10, ORR (OR 3.44, 95% CI = 2.71–4.37), p < 0.00001) was longer for patients with irAEs than those without irAEs.

Publication Bias

Forest plots were used to present the publication bias. The Figure 11 has shown the funnel plots of the OS, PFS, and ORR.

Discussion

ICIs are believed to initiate irAEs as a consequence of the body's anti-tumor response (Naidoo et al., 2015; Champiat et al., 2016). Evidence suggests that patients who experienced irAEs are more likely to derive survival benefits from ICIs (Downey et al., 2007; Weber et al., 2012). However, a growing body of evidence has supported this hypothesis. The relationship between irAEs and their impact on clinical efficacy in NSCLC remains poorly defined owing to conflicting data.

In our meta-analysis, we demonstrated significant differences in both PFS/OS and ORR between patients who did and did not experience irAEs, indicating a strong correlation between treatment-related irAEs and their clinical benefits. However, the underlying mechanisms remain unclear. This may be explained by the fact that there may be an abnormal presentation of the molecular mimicry of antigens shared between tumor and normal tissues, which leads to simultaneous T-cell- and B-cell-mediated crossreactions (Rose and Bona, 1993). This increases the possibility that latent "tissue-specific" autoimmunity may be associated with

study or Subgroup log[H	azard Ratio] SE	Weight I	V, Random, 95% CI	IV, Random, 95% CI
3.1.1 Thyroid dysfunction				
Grangeon M 2019	-0.5447 0.2025	4.1%	0.58 [0.39, 0.86]	
(im HI 2017	-0.9676 0.4104	1.9%	0.38 [0.17, 0.85]	
Morimoto K 2021	-0.7765 0.5079	1.4%	0.46 [0.17, 1.24]	
Naqash AR 2020	-0.0202 0.194	4.2%	0.98 [0.67, 1.43]	
Osorio JC 2017	-0.5447 0.3901	2.1%	0.58 [0.27, 1.25]	
Thuillier P 2021	-1.0217 0.275	3.1%	0.36 [0.21, 0.62]	
Subtotal (95% CI)	the set of the second sec	16.9%	0.56 [0.39, 0.80]	•
Heterogeneity: Tau ² = 0.10; C Test for overall effect: Z = 3.1	$hi^2 = 11.37, df = 5 (R = 0.001)$	P = 0.04; 1	2 = 56%	
3.1.2 Pneumonitis				
Ahn BC 2019	0.5224 0.5121	1.4%	1.69 [0.62, 4.60]	
Cortellini A 2019	0.1823 0.233	3.7%	1.20 [0.76, 1.89]	
ujimoto D 2018	-0.3425 0.1589	4.7%	0.71 [0.52, 0.97]	
Grangeon M 2019	0.174 0.4224	1.9%	1.19 [0.52, 2.72]	
Morimoto K 2021	0.0488 0.3889	2.1%	1.05 [0.49, 2.25]	
Nagash AR 2020	0.3075 0.205	4.0%	1.36 [0.91, 2.03]	+ · · ·
Ricciuti B 2019	-0.5798 0.2698	3.2%	0.56 [0.33, 0.95]	
Sugano T 2020	-0.9416 0.3669	2.3%	0.39 [0.19, 0.80]	
Subtotal (95% CI)		23.3%	0.90 [0.65, 1.23]	-
Heterogeneity: $Tau^2 = 0.12$; Contract for overall effect: $Z = 0.6$	$chi^2 = 18.16, df = 7 (Holdson 10, 000) df =$	P = 0.01; I	2 = 61%	
3.1.3 Hepatitis				
Cortellini A 2019	0.3853 0.3642	2.3%	1.47 [0.72, 3.00]	
Grangeon M 2019	-0.0305 0.3919	2.1%	0.97 [0.45, 2.09]	
aqash AR 2020	-0.2877 0.2606	3.3%	0.75 [0.45, 1.25]	
Ricciuti B 2019	-0.3285 0.2873	3.0%	0.72 [0.41, 1.26]	
Subtotal (95% CI)		10.7%	0.87 [0.64, 1.19]	-
Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 0.8	$hi^2 = 2.91, df = 3 (P)$ 36 (P = 0.39)	= 0.41); I ²	= 0%	
3.1.4 GI				19 Cold 1000
Cortellini A 2019	-0.3857 0.1885	4.3%	0.68 [0.47, 0.98]	
Grangeon M 2019	-0.3147 0.3751	2.2%	0.73 [0.35, 1.52]	
Naqash AR 2020	-0.4308 0.3158	2.7%	0.65 [0.35, 1.21]	
Ricciuti B 2019	-0.6539 0.2806	3.1%	0.52 [0.30, 0.90]	
Subtotal (95% CI)	•	12.3%	0.64 [0.50, 0.83]	•
Heterogeneity: Tau ² = 0.00; C	$chi^2 = 0.78, df = 3 (P)$	$= 0.86$; I^2	= 0%	
Test for overall effect: Z = 3.3	8 (P = 0.0007)			
3.1.5 Skin				
Ahn BC 2019	-0.4416 0.3103	2.8%	0.64 [0.35, 1.18]	
Aso M 2020	-0.9676 0.2136	3.9%	0.38 [0.25, 0.58]	
Berner F 2019	-1.5141 0.456	1.7%	0.22 [0.09. 0.54]	←
Cortellini A 2019	-0.7765 0.2014	4.1%	0.46 [0.31, 0.68]	
laratani K 2018	-0.734 0.3754	2.2%	0.48 [0.23, 1.00]	
Morimoto K 2021	-0.3011 0.3268	2.6%	0.74 [0.39 1 40]	
Jagash AR 2020	-0.5978 0.2454	3 5%	0.55 [0.34 0.80]	
Ricciuti B 2019	-0 5621 0 2499	3 5%	0 57 [0 35 0 03]	
Subtotal (95% CI)	-0.3021 0.2488	24.2%	0.49 [0.40 0.60]	•
$deterogeneity: Tau2 = 0.01 \cdot C$	$hi^2 = 7.55 df = 7/0$	- 0 37)- 12	- 7%	· ·
Test for overall effect: $Z = 7.1$.6 (P < 0.00001)	- 0.57), 1	_ //0	
3.1.6 Endocrine				
hmielewska 2021	-0.8916 0.3663	2 204	0.41 [0.20 0.84]	
Cortellini A 2010	-0.6910 0.5003	4 50/	0.41 [0.20, 0.84]	
Jaratani K 2019	-0.462 0.1/1/	4.5%	0.03 [0.45, 0.88]	
larimata K 2021	-1.4271 0.9142	1.30/	0.24 [0.04, 1.44]	
	-0.9676 0.5473	1.3%	0.38 [0.13, 1.11]	
Circluti B 2019	-0.5276 0.1983	4.1%	0.59 [0.40, 0.87]	
Sublotal (95% CI)	1.2 0.00 10 1.5	12.7%	0.57 [0.45, 0.71]	-
Heterogeneity: Tau ² = 0.00; C Fest for overall effect: Z = 4.8	$h_1^* = 2.62, df = 4 (P)$ 32 (P < 0.00001)	= 0.62); I ²	= 0%	
		100.0%	0.64 [0.56 0.74]	
	112 CO 00 16 34	100.0%	0.04 [0.50, 0.74]	
lotal (95% CI)	$n_{1} = 68.89$, $dt = 34$	(P = 0.000)	4); $1^{\circ} = 51\%$	0.1 0.2 0.5 1 2 5 10
lotal (95% Cl) leterogeneity: Tau ² = 0.08; C				
Heterogeneity: Tau ² = 0.08; C Fest for overall effect: Z = 6.4	1 (P < 0.00001)	Solida Statistica		Favours [irAEs] Favours [no-irAEs]
leterogeneity: Tau ² = 0.08; C leterogeneity: Tau ² = 0.08; C lest for overall effect: Z = 6.4 'est for subgroup differences	1 (P < 0.00001) : Chi ² = 16.60, df = 5	5 (P = 0.005)	5), I ² = 69.9%	Favours [irAEs] Favours [no-irAEs]
leterogeneity: Tau ² = 0.08; C est for overall effect: $Z = 6.4$ est for subgroup differences	P = 1 (P < 0.00001) : Chi ² = 16.60, df = 5	5 (P = 0.005	5), I ² = 69.9%	Favours [irAEs] Favours [no-irAEs]
leterogeneity: Tau ² = 0.08; C est for overall effect: Z = 6.4 est for subgroup differences	1 (P < 0.00001) : Chi ² = 16.60, df = 5	5 (P = 0.005	5), I ² = 69.9%	Favours [irAEs] Favours [no-irAEs]

FIGURE

Sub-gro

not only therapy but also healthy tissue. Thus, irAEs are more likely to exacerbate host immune function.

To further evaluate the independent prognostic value of the relationship between treatment-related irAEs and improved clinical

outcomes, we performed subgroup analyses to incorporate various clinicopathological covariates. Our results further support the conclusion that this relationship is mediated by confounding factors, such as the number, pathologic subtypes, and various



Sub-group analysis of PFS between IrAEs and ICI efficacy with pathological subtypes.

	irAE	s	no irA	Es		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Baldini E 2020	93	342	266	1617	12.2%	1.90 [1.45, 2.49]	
Chen X 2021	29	70	31	121	7.3%	2.05 [1.10, 3.84]	
Cortellini A 2019	107	231	84	328	10.9%	2.51 [1.75, 3.59]	
Cui P 2020	26	42	70	234	6.6%	3.81 [1.92, 7.54]	
Grangeon M 2019	24	105	9	158	5.4%	4.91 [2.18, 11.05]	· · · · · · · · · · · · · · · · · · ·
Haratani K 2018	23	44	17	61	5.4%	2.83 [1.26, 6.40]	
isberg A 2018	15	39	5	58	3.5%	6.63 [2.16, 20.33]	Community of the second s
Morimoto K 2021	24	42	10	28	4.2%	2.40 [0.90, 6.43]	
Naqash AR 2020	69	173	50	358	9.9%	4.09 [2.67, 6.26]	
Ricciuti B 2019	37	85	11	110	5.9%	6.94 [3.26, 14.78]	
Sato K 2018	7	11	2	27	1.4%	21.88 [3.29, 145.24]	<u></u>
Socinski MA 2023	12	25	9	55	3.8%	4.72 [1.63, 13.63]	· · · · ·
Sonehara K 2021	460	753	299	804	13.0%	2.65 [2.16, 3.25]	
Feraoka S 2017	7	19	4	24	2.4%	2.92 [0.70, 12.09]	
Thuillier P 2021	19	40	12	94	5.0%	6.18 [2.60, 14.72]	
Toi Y 2018	16	28	5	42	3.1%	9.87 [2.98, 32.65]	
Fotal (95% CI)		2049		4119	100.0%	3.44 [2.71, 4.37]	•
Total events	968		884				
Heterogeneity: Tau ² =	0.10; Cl	$hi^2 = 35$	5.90, df =	= 15 (P	= 0.002)	$1^2 = 58\%$	
Test for overall effect	Z = 10.3	11 (P <	0.00001	.)			Favours [irAEs] Favours [no irAEs]

Analysis of ORR between IrAEs and ICI efficacy.



10.3389/fphar.2023.1190001

types of irAEs experienced. In our study, no significant difference in OS was found in patients who developed ≥ 2 irAEs than those who developed <2 irAEs, but PFS showed significant difference. These data suggest that irAEs can serve as a positive predictor of response to therapy, with the balance of its advantages and disadvantages depending on the severity of the irAE itself. In addition, no differences were observed in OS or PFS in terms of pathologic subtypes. This finding indicates that the pathologic subtype had no association with irAEs and survival. IrAEs affecting the skin, gastrointestinal tract, and endocrine system (including thyroid dysfunction) tend to be more manageable than those affecting the lungs and liver. The present study found that patients with these types of irAEs are more likely to experience improved survival benefits. The result may be explained by the toxicities of these irAE subtypes, which could usually be resolved completely with appropriate treatments. Though glucocorticoid is known to be a key element to treat patients with irAEs of pneumonitis and hepatobiliary disease, the effect of steroids still serves as a double-edged sword. The adverse effect of the use of steroids might lead to inferior survival tendency of lung- and liver-related irAEs. In terms of treatment efficacy, further investigation of immune checkpoint therapies based on specific molecular subtypes and genomic alterations may help make informed treatment decisions while maintaining a manageable safety profile.

There are some limitations to our study. First, the retrospective nature and various investigators' irAE-reporting profiles of all the included studies resulted in an imbalance between the two groups. Additional randomized clinical trials are warranted to address these issues. Second, our study did not include potential confounders, such as the duration of response, discontinuation of therapy, different grades of irAEs, and different ICIs, owing to the limited covariate data available for analysis. Therefore, there is a strong need for high-quality research using additional data to clarify this issue.

In summary, our study validated that patients with NSCLC undergoing ICI treatment may experience irAEs, which may have a persistent response to ICI therapy that can be achieved using irAE as

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Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Author contributions

WL and AW designed the study; LL and YL extracted the data; YL and WL analyzed the data; LL drafted the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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