



# Immune-Related Adverse Events Associated With Outcomes in Patients With NSCLC Treated With Anti-PD-1 Inhibitors: A Systematic Review and Meta-Analysis

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**Background and Objective:** Although anti-programmed cell death protein 1 (PD-1) antibodies have exerted remarkable anticancer activity in non-small cell lung cancer (NSCLC), it remains a challenge to identify patients who can benefit from these treatments. Immune-related adverse events (irAEs) may be associated with improved clinical outcomes after immune checkpoint inhibition. However, no conclusive evidence of this correlation has been summarized in patients with NSCLC receiving PD-1 inhibitors. We performed a systematic review and meta-analysis to evaluate the association between irAEs induced by anti-PD-1 antibodies and clinical outcomes in patients with NSCLC.

**Methods:** Various databases were searched from their inception to January 9, 2021, followed by screening of eligible studies. Hazard ratios were used for the pooled analysis of overall survival (OS) and progression-free survival (PFS), while odds ratios (ORs) were utilized to pool objective response rates (ORRs) and disease control rates (DCRs). A random-effects model was applied to all analyses.

**Results:** A total of 26 cohorts, including 8,452 patients with NSCLC receiving anti-PD-1 antibodies, were enrolled in the study. Significantly improved OS (HR: 0.51; 95% CI: 0.44-0.60;  $P < 0.01$ ) and PFS (HR: 0.50; 95% CI: 0.43-0.58;  $P < 0.01$ ) were found to be correlated with irAEs. In addition, patients with NSCLC who developed irAEs after PD-1 inhibition demonstrated better responses to therapies, confirmed by pooled ORs of ORRs (OR: 3.41; 95% CI: 2.66-4.35;  $P < 0.01$ ) and DCRs (OR: 4.08; 95% CI: 2.30-7.24;  $P < 0.01$ ). Furthermore, subgroup analysis suggested that both skin and endocrine irAEs are closely correlated with a reduced risk of death, whereas pulmonary irAEs showed no association with longer OS.

**Conclusions:** In patients with NSCLC treated with anti-PD-1 therapies, the presence of irAEs was strongly correlated with better survival and response, suggesting its potential role as a predictive biomarker for outcomes after PD-1 inhibition.

**Keywords:** immune-related adverse event, non-small cell lung cancer, PD-1 inhibitor, outcome, prognosis

## INTRODUCTION

In recent decades, immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) have revolutionized the treatment landscape for patients with advanced cancer (1). Anti-PD-1 antibodies (nivolumab and pembrolizumab), which have significant anticancer activity, have garnered approvals from the U.S. Food and Drug Administration for various malignancies, including advanced non-small cell lung cancer (NSCLC), melanoma, head and neck squamous cell carcinoma, renal cell carcinoma, and urothelial carcinoma (2).

Nevertheless, the efficacy of anti-PD-1 drugs varies among individuals, only a fraction of whom benefit from immune checkpoint inhibition. Among all cancer types, previously treated NSCLC exhibited a relatively low response rate to PD-1 inhibitors (<20%) (3–6). Therefore, there is an urgent need to establish predictive biomarkers to identify patients with NSCLC who may benefit from PD-1 inhibition. Several predictive approaches have recently been developed for NSCLC treatment, including biomarkers of PD-L1 expression (6, 7), tumor-infiltrating lymphocytes (8), and tumor mutation burden (9). While these biomarkers were developed primarily to focus on the histological or molecular features of the tumor, evidence for predictive capacity of other clinical characteristics is unclear.

Recent studies have demonstrated some correlations between immune-related adverse events (irAEs) and outcomes after ICI treatments. IrAEs are inflammatory side effects related to the activation of the immune system that are triggered by an immune checkpoint blockade, with most involving the skin, endocrine glands, gastrointestinal tract, liver, and lungs (10). In a recent pooled analysis of 30 studies and 4,324 patients, irAEs were shown to predict favorable responses and survival in patients with solid tumors receiving various ICI treatments (11). In addition, another review of 48 clinical trials of nivolumab, used to treat multiple solid tumors, revealed that the objective response rates (ORRs) of nivolumab were positively associated with incidence rates of gastrointestinal, skin, and endocrine irAEs (12). In a retrospective analysis of 1,010 patients with NSCLC treated with pembrolizumab, irAEs were shown to be significantly related to higher ORRs and better progression-free survival (PFS) and overall survival (OS) (13). However, no existing articles have comprehensively summarized a conclusive association between irAEs and the outcomes of anti-PD-1 regimens in patients with NSCLC. Hence, our current study involved a systematic review and pooled analyses of the literature to reveal possible correlations between the irAEs induced by PD-1 blockade and favorable clinical outcomes in patients with NSCLC.

## MATERIALS AND METHODS

### Search Strategy

We performed a literature search of the PubMed, EMBASE, and the Cochrane Library databases from their inception to January 9, 2021 for published studies assessing prognostic effects of irAEs in patients with NSCLC receiving anti-PD-1 regimens. The search strategy was developed by combining different descriptions of irAEs, various prognostic outcomes, keywords specific to NSCLC, and currently available anti-PD-1 antibodies. Detailed keywords used for the search are listed in **Supplementary Table S1**. Additionally, we screened studies included in two recent systematic reviews (11, 14) and identified 13 related published articles.

### Study Selection

All the research was independently screened by two investigators to select eligible studies for further analysis. We only included studies that met the following criteria: (1) full text original research including patients diagnosed with NSCLC receiving anti-PD-1 treatment; (2) published articles in the English language; and (3) reported correlations between irAEs and clinical outcomes (OS, PFS, or ORR). We excluded case reports, reviews, meta-analyses, systematic reviews, conference abstracts, and correspondence letters. In addition, studies that included patients with another type of cancer or who were treated with other ICIs were also excluded.

### Data Extraction

The following data were extracted from each study: name of the first author, year of publication, patient number, study type, median time of follow-up, country or area of study, irAE type and grade, irAE evaluation criteria, drugs administered, and any correlations between irAEs and ICI treatment outcomes (survival data or ORRs). The Newcastle-Ottawa Scale (NOS), ranging from 0 to 9, was applied as a quality assessment of all included studies.

### Statistical Analysis

To evaluate the association between irAEs and clinical outcomes, hazard ratios (HRs) with 95% confidence intervals (CIs) were used for survival data (OS or PFS), while odds ratios (ORs) were calculated for ORRs and disease control rates (DCRs). The heterogeneity among the different studies was assessed by the Cochrane's  $\chi^2$  and Higgins and Thompson's  $I^2$  statistic (15). For heterogeneity analysis, P value < 0.05 studies were considered as significant heterogeneity.  $I^2$  values < 50%, 50–75%, and > 75% were respectively defined as low, moderate, and high heterogeneity.

For pooled analysis, a random-effects model was utilized. Funnel plots were used to assess any publication bias. In this study, *P* values less than 0.05 were considered statistically significant. All analyses were performed using the “meta” package of the R software (V3.6.2).

## RESULTS

### Characteristics of Eligible Studies

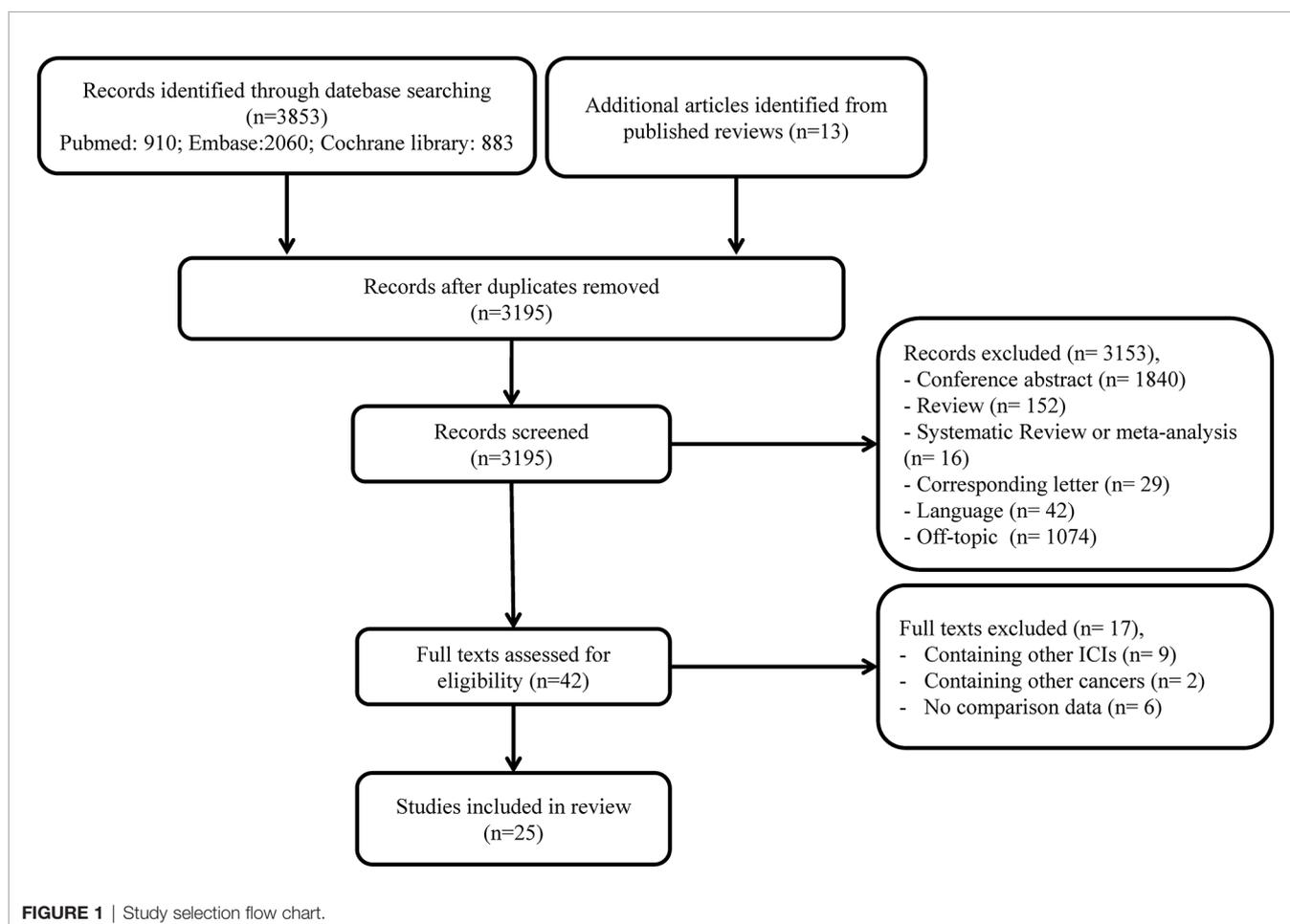
A total of 3,866 studies were identified in our initial search. After the removal of duplicate records, 3,195 were left for screening. Thereafter, 3,153 articles were excluded due to irrelevant titles or abstracts. The full text of the remaining 42 studies was further assessed for eligibility, and 17 additional publications were excluded. Eventually, 25 articles, including 8,452 patients with confirmed NSCLC receiving anti-PD-1 treatment, were enrolled in our meta-analysis (13, 16–39). The process of study selection is illustrated in **Figure 1**.

The characteristics of these selected articles are listed in **Table 1** and **Supplementary Table S2**. As one article included two independent cohorts, we are presenting them as two separate studies (26). The 26 included studies consisted of 21 retrospective

cohorts and 5 prospective cohorts. In 18 studies, clinical outcomes for patients with and without any irAEs were compared. The other eight cohorts included specific adverse events (AEs), including skin reactions (two studies), pneumonitis (three studies), and thyroid dysfunction (three studies). The average incidence of irAEs triggered by PD-1 blockade was 34.9%, which varied from 10% to 67%. In 12 cohorts, patients were treated with nivolumab, while pembrolizumab was administered in six studies. Additionally, eight studies included patients receiving either nivolumab or pembrolizumab monotherapy. Some other detailed clinical features of the enrolled NSCLC patients in each study were illustrated in **Supplementary Table S2**, including clinical stage, histological type, PD-L1 expression status and driver gene mutation information.

### Correlation Between irAEs and Survival Results

The occurrence of irAEs in patients with NSCLC treated with anti-PD-1 antibodies was associated with better survival. The pooled OS data from the 18 studies enrolled in our analysis revealed a significantly lower risk of death in patients with irAEs (HR: 0.51; 95% CI: 0.44–0.60; *P* < 0.01; **Figure 2A**). Meanwhile, moderate but significant heterogeneity was observed in the pooled OS data ( $I^2 =$



**TABLE 1 |** Characteristics of included studies.

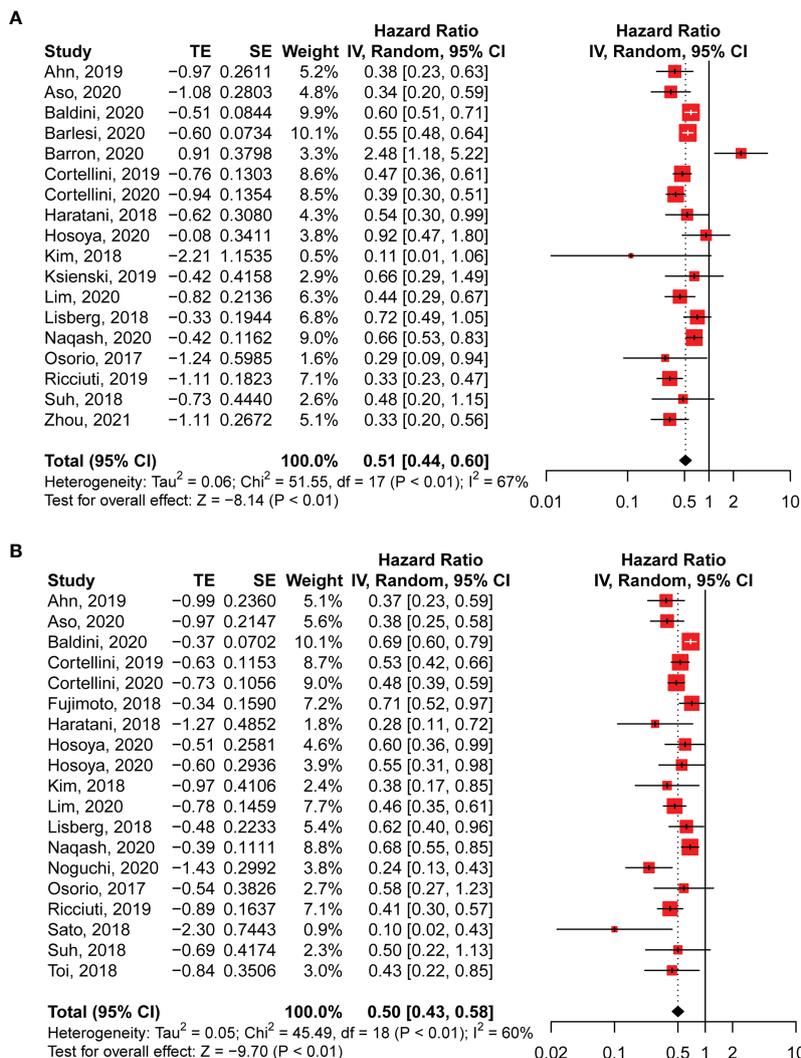
Author/year	N	Country	Study type	Follow up (months)	Type of toxicity/criteria	% irAEs	Drug	OS (HR, 95%CI)	PFS (HR, 95%CI)	ORR	Analysis	NOS
Ahn/2019	155	Korea	retrospective	NR	any G1-4/CTCAE v4.0	61.9	P N	0.38 (0.23-0.64)	0.37 (0.23-0.58)	41.2 vs. 26.7	UVA	6
Aso/2020	155	Japan	retrospective	NR	skin reaction all grades/CTCAE v4.0	58.1	P N	0.34 (0.20-0.60)	0.38 (0.25-0.58)	57 vs. 19	UVA	6
Baldini/2020	1959	Italy	retrospective	NR	any G1-4/CTCAE v4.0	17.8	N	0.60 (0.51-0.71)	0.69 (0.60-0.79)	27.2 vs. 16.5	UVA	7
Barlesi/2020	1420	France	prospective cohort	18	any G1-4/-	34.9	N	0.55 (0.48-0.64)	–	–	UVA	8
Barron/2020	101	Mexico	retrospective	9.22	pneumonitis G <sub>≥</sub> 2/CTCAE v4.0	21.8	P N	2.48 (1.18-5.23)	–	–	UVA	8
Cortellini/2019	559	Italy	retrospective	11.2	any G1-4/CTCAE v4.0	41.3	P N	0.47 (0.36-0.60)	0.53 (0.42-0.66)	46.5 vs. 25.7	UVA	7
Cortellini/2020	1010	Italy	retrospective	14.8	any G1-4/CTCAE v4.0	32.9	P	0.39 (0.30-0.51)	0.48 (0.39-0.59)	61.5 vs. 41.3	UVA	9
Fujimoto/2018	613	Japan	retrospective	NR	pneumonitis G3-5/CTCAE v4.0	10	N	–	0.71 (0.52-0.97)	37 vs. 18	MVA	4
Fukihara/2019	170	Japan	retrospective	9.9	pneumonitis G1-5/CTCAE v4.0	16	P N	–	–	30 vs. 24		8
Haratani/2018	134	Japan	retrospective	NR	any all grades/-	51	N	0.54 (0.29-0.97)	0.28 (0.10-0.67)	–	MVA	6
Hasan/2016	41	Switzerland	retrospective	NR	skin reaction Grade 1-2/CTCAE v4.0	17	N	–	–	71.4 vs. 21.9		4
Hosoya/2020	148	Japan	retrospective	NR	any G1-4/CTCAE v4.0	27	P	–	0.55 (0.31-0.98)	77 vs. 44	UVA	6
Hosoya/2020	76	Japan	prospective cohort	NR	any G1-4/CTCAE v4.0	49	N	0.92 (0.47-1.79)	0.60 (0.36-0.99)	39 vs. 13	UVA	6
Kim/2018	58	Korea	prospective cohort	3	thyroid dysfunction all grades/-	32.7	P N	0.11 (0.01-0.92)	0.38 (0.17-0.85)	31.6 vs. 10.3	MVA	7
Ksienski/2019	190	Canada	retrospective	6.1	any G1-2/-	34.7	P	0.66 (0.29-1.48)	–	–	MVA	6
Lim/2020	299	Korea	retrospective	30.1	any G1-4/CTCAE v4.0	32	N	0.44 (0.29-0.67)	0.46 (0.35-0.62)	32 vs. 11	UVA	7
Lisberg/2018	97	US	retrospective	NR	any G1-4/CTCAE v4.0	40	P	0.72 (0.49-1.05)	0.62 (0.4-0.96)	38.5 vs. 8.9	MVA	6
Naqash/2020	531	US	retrospective	NR	any G1-4/CTCAE v4.0	33	N	0.66 (0.52-0.82)	0.68 (0.55-0.85)	40.1 vs. 14.1	UVA	5
Noguchi/2020	94	Japan	retrospective	9.4	any G1-4/CTCAE v4.0	67	P	–	0.24 (0.13-0.42)	–	UVA	6
Osorio/2017	51	US	retrospective	NR	thyroid dysfunction all grades/CTCAE v4.0	21	P	0.29 (0.09-0.94)	0.58 (0.27-1.21)	–	UVA	5
Ricciuti/2019	195	Italy	retrospective	26	any G1-4/CTCAE v4.0	43.6	N	0.33 (0.23-0.47)	0.41 (0.30-0.57)	43.5 vs. 10	UVA	8
Sato/2018	38	Japan	prospective cohort	5.6	any G1-4/CTCAE v4.0	36.8	N	–	0.10 (0.02-0.37)	63.6 vs. 7.4	UVA	6
Suh/2018	54	Korea	retrospective	26.2	any all grades/CTCAE v4.0	22.2	P N	0.48 (0.20-1.14)	0.5 (0.22-1.13)	66.6 vs. 23.8	UVA	8
Teraoka/2017	43	Japan	prospective cohort	NR	any G1-4/CTCAE v4.0	44.2	N	–	–	37 vs. 17	UVA	5
Toi/2018	70	Japan	retrospective	NR	any G1-4/CTCAE v4.0	40	N	–	0.43 (0.21-0.83)	57 vs. 12	UVA	5
Zhou/2021	191	China	retrospective	NR	thyroid dysfunction all grades/CTCAE v5.0	20.9	P N	0.33 (0.20-0.57)	–	–	MVA	6

CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; HR, hazard ratio; irAEs, immune-related adverse events; MVA, multivariate analysis; N, nivolumab; NR, not reported; NOS, Newcastle-Ottawa Scale; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PFS, progression-free survival; UVA, univariate analysis.

67%,  $P < 0.01$ ; **Figure 2A**). Correspondingly, significantly improved PFS correlated with the existence of irAEs (HR: 0.50; 95% CI: 0.43–0.58;  $P < 0.01$ ; **Figure 2B**). For the PFS analysis, pooled HRs also showed moderate heterogeneity ( $I^2 = 60%$ ,  $P < 0.01$ ; **Figure 2B**).

## Correlation Between irAEs and Responses to PD-1 Blockade

Further pooled analyses of ORRs and DCRs revealed remarkably higher responses to anti-PD-1 inhibition in patients who exhibited irAEs. Among all the included studies, 19 studies compared ORRs



**FIGURE 2 |** Pooled hazard ratios of overall survival (A) and progression-free survival (B) in patients with NSCLC with and without irAEs treated with anti-PD-1 antibodies. CI, confidence interval.

between patients with and without irAEs, whereas only nine cohorts investigated DCRs. For ORR analyses, we found that irAEs were significantly related to higher rates of objective responses to PD-1 blockade (OR: 3.41; 95% CI: 2.66–4.35;  $P < 0.01$ ; **Figure 3A**) with moderate heterogeneity ( $I^2 = 56%$ ,  $P < 0.01$ ; **Figure 3A**). Likewise, pooled ORs of DCRs demonstrated that patients exhibiting irAEs had better responses to anti-PD-1 regimens than patients without irAEs (OR: 4.08; 95% CI: 2.30–7.24;  $P < 0.01$ ; **Figure 3B**). The analyses of DCRs showed high heterogeneity ( $I^2 = 79%$ ,  $P < 0.01$ ; **Figure 3B**).

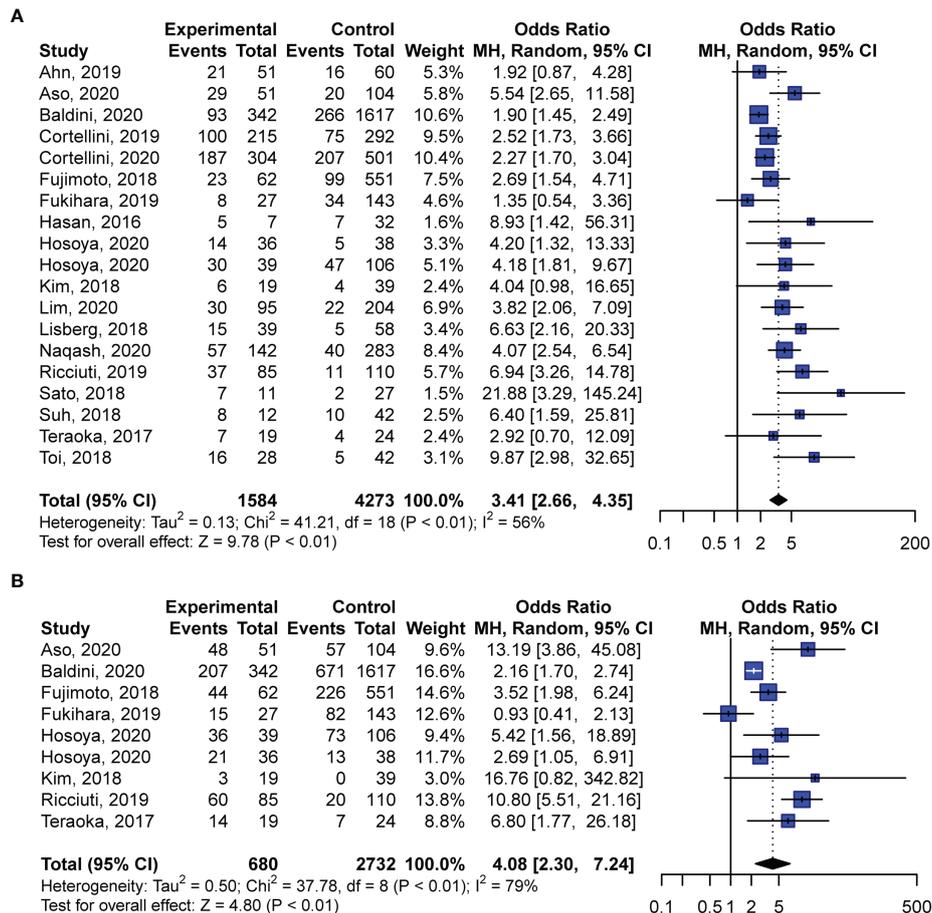
### Publication Bias and Study Quality Assessment

Begg’s funnel plots along with Egger’s tests ( $P = 0.5479$ ) illustrated that the pooled analysis of OS in this study did not have any obvious publication bias (**Supplementary Figure S1**). However,

possible publication bias existed in the analyses of PFS ( $P = 0.0041$ ; **Supplementary Figure S2**) and ORR results ( $P = 0.0010$ ; **Supplementary Figure S3**). The number of studies with DCR results did not meet the level of publication bias. In the enrolled 26 studies, the median NOS score was 6 (range: 4–9). Over one-half of the studies (14/26) did not report the follow-up time for the cohorts, lowering their NOS scores. In addition, we performed sensitivity analysis by omitting one study at a time for the pooled analyses to evaluate the potential influence of each study on our conclusions. The results showed that not a single study affected the association between better outcome and irAEs (**Supplementary Figure S4**).

### Subgroup Analysis

To further investigate the influence of different AEs, we performed subgroup analyses for pulmonary, skin, and



**FIGURE 3** | Pooled odds ratios of objective response rates (A) and disease control rates (B) in patients with NSCLC with and without irAEs treated with anti-PD-1 antibodies. CI, confidence interval.

endocrine irAEs. In addition to the aforementioned eight studies of specific irAEs (17, 20, 22, 23, 25, 27, 33, 39), we also extracted survival data from the other five articles that reported HRs for these three AEs (13, 16, 21, 24, 34). The analysis revealed that skin (HR: 0.41; 95% CI: 0.32–0.52;  $P < 0.01$ ) and endocrine (HR: 0.41; 95% CI: 0.33–0.51;  $P < 0.01$ ) irAEs were significantly associated with longer OS, whereas pulmonary irAEs showed no correlation (HR: 0.98; 95% CI: 0.53–1.83;  $P = 0.96$ ) (Figure 4A). In addition, the subgroup analysis of PFS found that all three irAEs had significant associations with better disease control (Figure 4B).

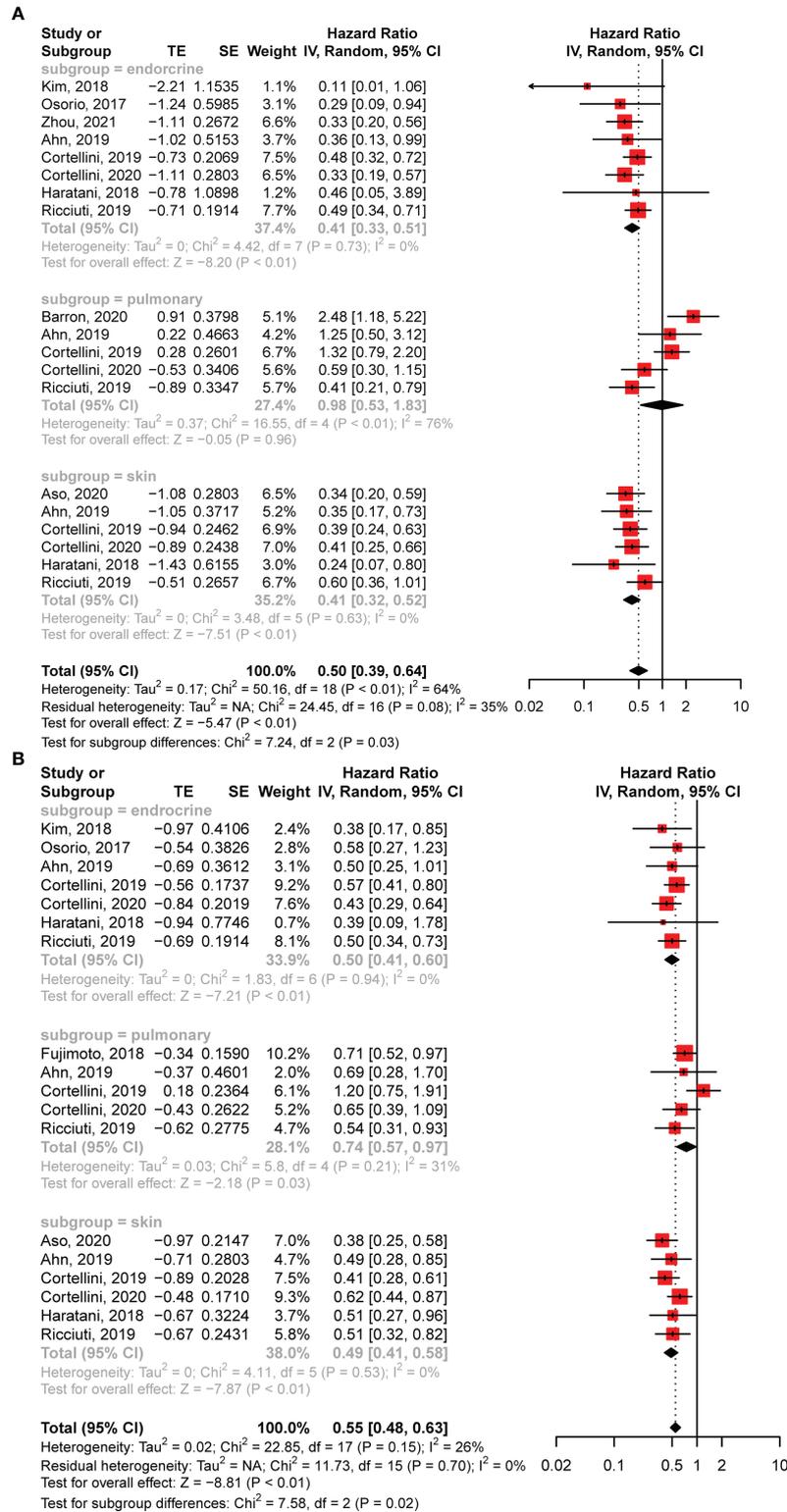
More subgroup analyses based on the features of the included studies were also performed. The pooled analyses for prospective studies suggested that irAEs were associated with better PFS (HR: 0.36; 95% CI: 0.16–0.81;  $P = 0.01$ ) but not OS (HR: 0.60; 95% CI: 0.35–1.03;  $P = 0.07$ ) (Supplementary Figure S5). For retrospective studies, the occurrence of irAEs was found to have correlations with better OS (HR: 0.50; 95% CI: 0.42–0.61;  $P < 0.01$ ) and PFS (HR: 0.51; 95% CI: 0.44–0.59;  $P < 0.01$ ) (Supplementary Figure S5). Also, the subgroup analyses for Asian and non-Asian studies both showed that the presence of

irAEs was correlated with longer OS and PFS (Supplementary Figure S6). Additionally, the subgroup analyses separated by the anti-PD-1 drugs used in the studies revealed that the association between irAEs and better outcomes existed no matter nivolumab or pembrolizumab was used for treatment (Supplementary Figure S7).

## DISCUSSION

This is the first and most comprehensive review of studies investigating the association between irAEs and clinical outcomes of patients with NSCLC receiving anti-PD-1 antibodies. In our pooled analysis of the 26 cohorts, we report a strong correlation between the presence of irAEs and improved patient response and prognosis, suggesting the significance of irAEs as a predictor of anti-PD-1 therapeutic efficacy in patients with NSCLC.

In addition to the recognition of antigens combined with major histocompatibility complexes by T-cell receptors, the stimulation of B7-CD28, known as the costimulatory signal, is



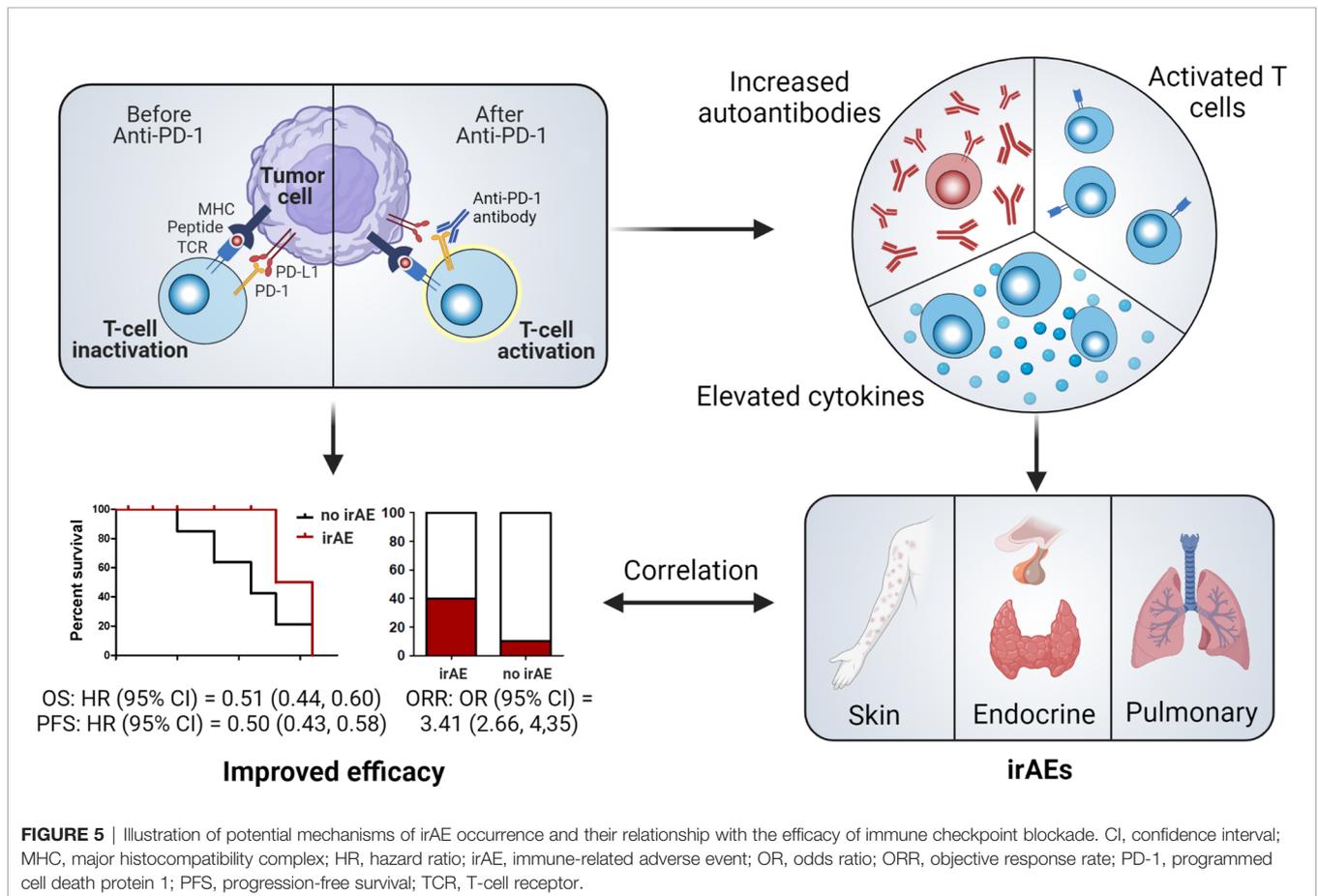
**FIGURE 4 |** Forest plots of subgroup analysis. **(A)** The association between overall survival and different toxicity types in patients with NSCLC treated with anti-PD-1 antibodies. **(B)** The association between progression-free survival and various irAEs in patients with NSCLC receiving anti-PD-1 antibodies. CI, confidence interval.

indispensable for T-cell activation (40). To avoid the overactivation of T-cells and restrict their autoimmune responses, CTLA-4 (on T-cells) (41, 42) and PD-1 (on T-cells, B-cells, monocytes, natural killer cells, and dendritic cells) exert inhibitory effects by binding to their ligands (PD-L1 or PD-L2) (43). However, in tumor tissues, these immune checkpoint pathways help cancer cells escape the immune system (44). Therefore, ICIs are used to block the overactivation of these pathways to enhance the antitumor immune responses mediated by T-cells (Figure 5). Two anti-PD-1 inhibitors (nivolumab and pembrolizumab), which exhibit outstanding efficacy to prolong cancer patient survival, have been approved for the treatment of NSCLC.

Apart from their anticancer efficacy, ICIs also trigger autoimmunity, which results in irAEs (45). Although the precise pathophysiology of irAE onset is still unclear, the possible mechanisms may involve the overactivation of T-cells, stimulation of autoantibodies, and elevation of cytokine levels (Figure 5) (10). Therefore, the occurrence of irAEs demonstrates that a patient's immune responses have been activated and that irAE development might be an effective biomarker of ICI efficacy. However, whether this clinical event can help predict responses to ICIs requires additional evidence. Certain irAEs specific to some cancer types have been found to be more strongly associated with improved clinical outcomes.

For example, vitiligo, an irAE that mainly occurs in melanoma patients treated with ICIs but rarely in patients with other cancers, has been shown to be closely correlated with favorable outcomes (46, 47). Except for this well-established correlation, other real-world studies have failed to provide definitive associations (37, 48–50). Recent systematic reviews and meta-analyses have suggested the presence of significant associations between irAEs and beneficial clinical outcomes in a pan-cancer setting (11, 51). However, these studies involve patients with different cancers receiving various ICIs, which contradicts the principles of personalized medicine. Further comprehensive research of patients with specific cancer types receiving specific ICIs is thus urgently needed for clinical application.

To avoid such heterogeneity and improve study comparability, we focused our analysis on patients with NSCLC treated with anti-PD-1 antibodies. Consistent with the subgroup analysis results of NSCLC from other systematic reviews (11, 51, 52), our research revealed that the occurrences of irAEs in patients with NSCLC treated with anti-PD-1 antibodies were closely associated with improved clinical outcomes, including OS, PFS, ORRs, and DCRs. Our results demonstrated that patients with NSCLC who developed any irAE after anti-PD-1 treatment showed a 50% reduction in the risks of death and disease progression compared to those without any AEs related to ICIs. Additionally, patients with irAEs



**FIGURE 5** | Illustration of potential mechanisms of irAE occurrence and their relationship with the efficacy of immune checkpoint blockade. CI, confidence interval; MHC, major histocompatibility complex; HR, hazard ratio; irAE, immune-related adverse event; OR, odds ratio; ORR, objective response rate; PD-1, programmed cell death protein 1; PFS, progression-free survival; TCR, T-cell receptor.

exhibited better responses to immune checkpoint blockade. These data indicate that irAEs play a critical role in predicting the efficacy of PD-1 therapies in patients with NSCLC. Since these findings are concluded in a specific cancer, our current investigation is closer to clinical usage than existing studies.

We also analyzed the correlations of pulmonary, skin, and endocrine irAEs with survival data. Strikingly, skin and endocrine AEs predicted better survival, whereas pulmonary irAEs were only associated with prolonged PFS but not with OS. Another meta-analysis enrolling patients with various types of cancers showed that various AEs (except pneumonitis) were correlated with improved clinical outcomes (11). In addition, a recent systematic review calculated the correlations between ORRs after nivolumab treatment and incidences of different nivolumab-related irAEs in patients with different solid tumors, revealing that the ORRs were positively associated with skin ( $r = 0.79$ ,  $P < 0.001$ ) and endocrine ( $r = 0.44$ ,  $P = 0.05$ ) irAEs but not with pulmonary irAEs (12). These results confirm our findings from the subgroup analysis. Although antitumor immune responses in patients with lung cancer and pulmonary irAEs are similar, suggesting that pneumonitis may be a favorable biomarker for the efficacy of ICIs in NSCLC, the predictive effects of these AEs may be compromised by several reasons. First, the incidence rates of pulmonary irAEs are low in patients receiving PD-1 antibodies (53, 54) or other ICIs (55), which would cause a disparity between patients with and without immune-related pneumonitis, making it difficult to compare the two groups. Second, pulmonary irAEs are always associated with severe disease and mortality during treatment with ICIs (56), which might also be associated with poor outcomes after immune checkpoint blockade. Taken together, our analysis indicates that endocrine and skin irAEs might be effective predictors of improved outcomes after anti-PD-1 therapies in patients with NSCLC. However, more investigations are needed to determine the specific role of pulmonary irAEs in patients with NSCLC receiving ICIs.

The average incidence of an irAE in our analysis (excluding studies only reporting specific AEs) was 39.4% (ranging from 17.8% to 67.0%) for patients with NSCLC treated with PD-1 inhibitors, consistent with findings from other studies (11). Moreover, our study included both prospective and retrospective cohorts, which better approximate real-world data. All studies were carried out in North America, Asia, and Europe. Although more than half of these enrolled studies were conducted in Asia (15/26), the total number of patients in Asia was only 2,298, which is less than the number of patients in the European studies (5,184 patients). These results indicate that our analysis can be applied to patients with NSCLC receiving anti-PD-1 therapies worldwide. Furthermore, we performed some subgroup analyses based on the characteristics of the eligible studies to assess the impact of these features on the analysis. The results of subgroup analyses were consistent with the findings of all-inclusive meta-analyses, proving that the correlation is robust despite of the heterogeneity between the enrolled studies.

By identifying the correlations between irAEs and better immune responses to anti-PD-1 antibodies, our study emphasizes the significance of monitoring, detecting, and

managing irAEs during the course of anti-PD-1 treatments. Patients with NSCLC with few or moderate AEs after treatment with anti-PD-1 antibodies may experience better outcomes than patients without any irAEs. However, the presence of severe irAEs might be unfavorable for patient survival, as these AEs are sometimes life-threatening and affected patients may need to discontinue their ICI therapy. Therefore, close monitoring and early detection of irAEs can help physicians accurately recognize less severe side effects, stratify patients with effective immune responses to PD-1 inhibitors, and prevent irAEs from progressing into more severe AEs. As described in the included studies, patients with common skin irAEs may develop some symptoms like immune-related pruritus, rash, and erythema (24, 34), which can be easy to identify. Some endocrine irAEs following anti-PD-1 therapies include hyper/hypothyroidism with two or more abnormal thyroid function tests (free thyroxine, free triiodothyronine, and thyroid stimulating hormone) (39), and adrenal insufficiency diagnosed by an adrenocorticotrophic hormone stimulation test (57). Once irAEs are identified in a patient, appropriate and prompt management can be carried out in a timely manner to improve patient outcomes. Recently, guidelines for the management of irAEs were published (58, 59). Our study highlights the complex but crucial role of irAEs in the use of anti-PD-1 therapy in patients with NSCLC, which may contribute to the update of guideline for NSCLC.

To the best of our knowledge, this study is the first and most comprehensive systematic review and meta-analysis which summarizes and evaluates the correlation between irAE occurrence and clinical outcomes after receiving anti-PD-1 antibodies in NSCLC. Although some other systematic reviews have suggested the association between irAEs and improved clinical response of ICIs, they did not focus on a specific cancer type or a specific kind of ICIs. Therefore, they only summarized partial reports. Fausto et al. (11) included 10 studies regarding NSCLC patients receiving anti-PD-1 treatments in an overall systematic review of solid tumors. Besides, Park et al. (52) concluded the predictive effects of anti-PD-1/L1-associated irAEs for favorable clinical outcomes in a recent systematic review, which only covered 11 studies of NSCLC treated with anti-PD-1 regimens. Recently, Wang et al. (60) reported that irAEs in lung cancer might predict better ICI efficacy, in which 17 lung cancer cohorts treated with anti-PD-1 regimens were included. Compared to these published reviews, we added approximately 9 more cohorts for meta-analysis, making our review more comprehensive and persuasive. Since the effects of different ICIs in various cancers have totally different mechanisms and manifestations, those results concluded from other cancer categories or drugs can hardly be applicable for the cases discussed in our current study. Hence, our results are more important for personalized treatment for NSCLC patients who undergo anti-PD-1 therapies. However, our study still has some limitations. First, publication bias and heterogeneity existed in our analysis, which may be caused by the differences in the characteristics of the included studies. Nevertheless, our subgroup analyses based on these characteristics and sensitivity

analysis results suggest that heterogeneity between the included studies have little influence on our main conclusions. Second, most of the studies were retrospective cohort studies because of the scarce number of available prospective studies. Even so, the subgroup analyses for prospective studies suggest a significant correlation between irAE occurrence and better survival. Hence, we hope that our study encourages more prospective investigations of the relationship between irAE occurrence and ICI efficacy. Third, based on the available studies, our analysis demonstrates correlations rather than causal results. Other predictive biomarkers developed on the basis of tumor histological or genomic features may not affect our analysis and results. Nevertheless, the underlying mechanisms of how irAEs can predict outcomes after ICIs and whether other biomarkers have relationships with irAE occurrence require more investigation.

## CONCLUSIONS

This study is the first meta-analysis to assess the predictive effects of irAE onset on clinical outcomes for patients with NSCLC receiving anti-PD-1 regimens. We demonstrate a significant correlation between the presence of irAEs and positive prognosis for patients with NSCLC after treatment with anti-PD-1 antibodies, suggesting that irAEs may be a clinical predictive biomarker for efficacy of anti-PD-1 therapy in NSCLC patients.

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## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

## AUTHOR CONTRIBUTIONS

Conceptualization, TY, ZH and CX. Writing—original draft preparation, ZZ and WX. Collection and curation of data, ZW and QJ. Revision of the manuscript, TY, ZW, QJ and CX. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2021.708195/full#supplementary-material>

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