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ORIGINAL ARTICLE

Immune-related adverse events: promising predictors for efficacy of immune checkpoint inhibitors

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Abstract

Purpose This study was designed to investigate the correlation between immune-related adverse events (irAEs) of immune checkpoint inhibitors (ICIs) and corresponding efficacy, and to explore the potential of predicting the efficacy of ICIs via irAEs.

Methods Electronic databases including PubMed, Embase, Cochrane Library, CNKI and Wanfang were applied to search for relevant studies. The primary endpoint was overall survival (OS) or progression-free survival (PFS), and the secondary endpoint was objective response rate (ORR). Stratification analyses were conducted according to the type of irAEs and ICIs, region of studies and primary tumors. Furthermore, statistical analyses were realized by means of RevMan 5.3 software.

Results Altogether, 40 studies with 8,641 participants were enrolled, among which the incidence of irAEs ranged from 15.34 to 85.23% and the major sites reached out to skin, endocrine organ, gastrointestinal tract, liver and lung. The ORR, OS and PFS in irAE group were significantly higher than those in non-irAE group as per pooled analyses and stratification analyses. Importantly, patients with irAEs in skin, endocrine organ or gastrointestinal tract rather than in liver and lung were found to obtain survival benefits ($p < 0.05$).

Conclusion IrAEs, especially in skin, endocrine organ or gastrointestinal tract, triggered by ICIs indicate significant survival benefits.

Keywords Immune-related adverse events (irAEs) · Immune checkpoint inhibitors (ICIs) · Efficacy

Introduction

Immune checkpoint inhibitors (ICIs) have initiated a major revolution with epoch-making significance in the history of tumor therapy. Currently, ICIs have played a key role in treating advanced malignancies, such as melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), urothelial cancer (UC), Hodgkin lymphoma (HL) and so on [1–10]. However, the efficacy of ICIs remains to be fully exerted, bearing overall effective rate of 10%–30% only [11]. Consequently, it is critical to identify dominant population and prognostic indicators of ICIs.

At present, some recommended predictive indexes for efficacy include PD-L1 expression, tumor mutation burden (TMB), and microsatellite instability-high (MSI-H) [12, 13]. However, these indexes are incompetent to fully identify all candidate population for ICIs.

Notably, mounting evidence demonstrated that irAEs triggered by ICIs were compelling enough to predict the efficacy. ICIs activate the immune system, up-regulate the immune response, and trigger a storm of inflammatory cytokines that attack normal organs, thus resulting in a variety of toxic and side effects, which are generally termed as immune-related adverse events (irAEs) [14]. Some studies on melanoma revealed a positive correlation between irAEs and efficacy of ICIs [15–17], but others on NSCLC indicated that pneumonia mediated by ICIs predicted a poor prognosis [18]. Up to date, the correlation between irAEs and efficacy

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of ICIs remains to be fully elucidated. Accordingly, a comprehensive analysis on 40 studies incorporating 8,641 cases was carried out to explore whether irAEs could served as a predictor of ICI efficacy and to determine candidate population for ICIs.

Materials and methods

Literature search

This study was conducted conforming to *Preferred Reporting Items for Systematic Reviews* and *Meta-Analysis (PRISMA) Guidelines* [19] and *Meta-Analysis of Observational Studies in Epidemiology (MOOSE)* [20]. As of 31 March 2020, electronic databases such as PubMed, Embase, Cochrane Library, CNKI and Wanfang were applied in search of relevant trials without language restriction by entering the following keywords: immune-related adverse events, immune checkpoint inhibitors, immune efficacy, efficacy of cancer immunotherapy, efficacy of immune checkpoint inhibitors, nivolumab, pembrolizumab, atezolizumab and ipilimumab. General reviews on this topic were scrutinized and excluded. In addition, references of the included studies were manually reviewed to screen additional articles. Meanwhile, letters, comments, expert opinions, reviews without original data, and case reports were excluded.

Selection of studies

Initially, two researchers independently performed a rapid screening of titles and abstracts, and then proceeded with the full-text searches to hunt for relevant studies.

Inclusion criteria

The following criteria are essential for eligible trials: (1) malignant tumor had been administrated with ICIs; (2) the analyses included overall survival (OS) or progression-free survival (PFS) of irAE group and non-irAE group; (3) response rate was determined by the *Response Evaluation Criteria in Solid Tumors (RECIST 1.1 Standards)*; (4) adverse events were assessed in accordance with the *National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0/4.0/5.0)* and the diagnosis and severity of irAEs were determined based on clinical examinations, biological and imaging data; (5) the included study was prospective or retrospective; (6) hazard ratio (HR) with 95% confidence interval (CI) of survival data was available.

Data extraction

Two researchers extracted data from each trial independently and disagreements were addressed by consensus. The following information was abstracted from each of the included studies: first author name, year of publication, region of original trial, type of trial, ICI type, number of patients, gender, median age, Eastern Cooperative Oncology Group (ECOG), previous therapy, irAE type, interventions and outcomes. PFS and OS were defined as the primary endpoint to assess the efficacy of irAE group and non-irAE group through HR. Objective response rate (ORR) was defined as the second endpoint. If provided indirectly, HR with 95% CI was calculated from survival curves by means of Tierney's methods [21].

Quality assessment

Two researchers independently assessed quality items and possible difference thereof. Those studies (directly or indirectly) concluded the HR for PFS or OS after the treatment of ICIs were deemed to be qualified studies.

Statistical methods

Statistical analyses were performed via the RevMan 5.3 software. Chi-square and *I*-square tests were adopted to verify the heterogeneity of involved trials. If $P > 0.1$ and $I^2 < 50\%$, the studies were defined as low heterogeneity and fixed effect model was applied, otherwise defined as high heterogeneity and random effect model was adopted accordingly. We also conducted stratification analyses in accordance with the type of irAEs and ICIs, region of studies, and primary tumors.

Subsequently, data analysis generally comprised of pooled risk ratio (RR) for dichotomous endpoints (ORR) resorting to Mantel–Haenszel method [22]. OS and PFS were calculated using effect variables and expressed as the HR. The 95% CIs were calculated and presented in forest plots. Besides, publication bias was evaluated via funnel plots.

Results

Study selection

First, we collected 1,503 relevant studies from the aforementioned databases. Second, 532 duplicates were excluded. Then 891 unrelated ones were further excluded after the title and abstract review. Furthermore, 40 studies failing to meet the inclusion criteria were excluded. Finally, 40 remaining

studies [14, 16, 17, 23–59] were included in this meta-analysis. The retrieval process was portrayed by a flowchart (Fig. 1).

Study characteristics

General characteristics of these enrolled studies are presented in Table 1, among which 9 were prospective and 31 retrospective. Fifteen trials were conducted in Asia, 12 in Europe, and 11 in America. Clinical interventions adopted were as follows: anti-PD-1 therapy was used in 29 studies, anti-CTLA-4 in 3, and anti-PD-L1 in 1. In summary, 8,641 individuals were included, and 3,018 complicated with irAEs.

Data analysis

Incidence of irAEs

The incidence of irAEs in eligible studies ranged from 15.34% to 85.23%, which frequently occurs in the skin (2.56%–56.08%), endocrine organ (0.82%–30.43%), gastrointestinal tract (0%–33.78%), liver (0.64%–16.41%) and lung (0%–4.81%). Furthermore, the correlation between the incidence of irAEs and patients treated with ICIs was as follows: anti-CTLA-4 (46.49%), anti-PD-1 (41.71%), and anti-PD-L1 (31.06%).

Response rate

A total of 22 studies [16, 17, 23, 24, 26, 27, 30–36, 38, 39, 43, 45, 49, 51, 57–59] concluded response rates of irAE group and non-irAE group. Due to the high heterogeneity ($p < 0.0001$, $I^2 = 65\%$), a random effect model was utilized for the meta-analysis. With regard to ORR, a pooled analysis on outcomes displayed a significant difference between irAE group and non-irAE group (RR = 3.00, 95% CI [2.34–3.85], $p < 0.00001$) (Fig. 2a). In stratification analysis, patients with irAEs had higher ORR than those without irAEs in Asia (RR = 2.95, 95% CI [2.16–4.03], $p < 0.00001$), Europe (RR = 2.91, 95% CI [1.69–4.99], $p = 0.0001$) and America (RR = 2.83, 95% CI [2.28–3.51], $p < 0.00001$) (Fig. 2b). Analogously, the irAE group still had higher ORR in NSCLC (RR = 3.03, 95% CI [2.18–4.21], $p < 0.00001$) and melanoma (RR = 2.35, 95% CI [1.41–3.90], $p = 0.0010$) (Fig. 2c). Collectively, individuals with irAEs had higher ORR than those without irAEs.

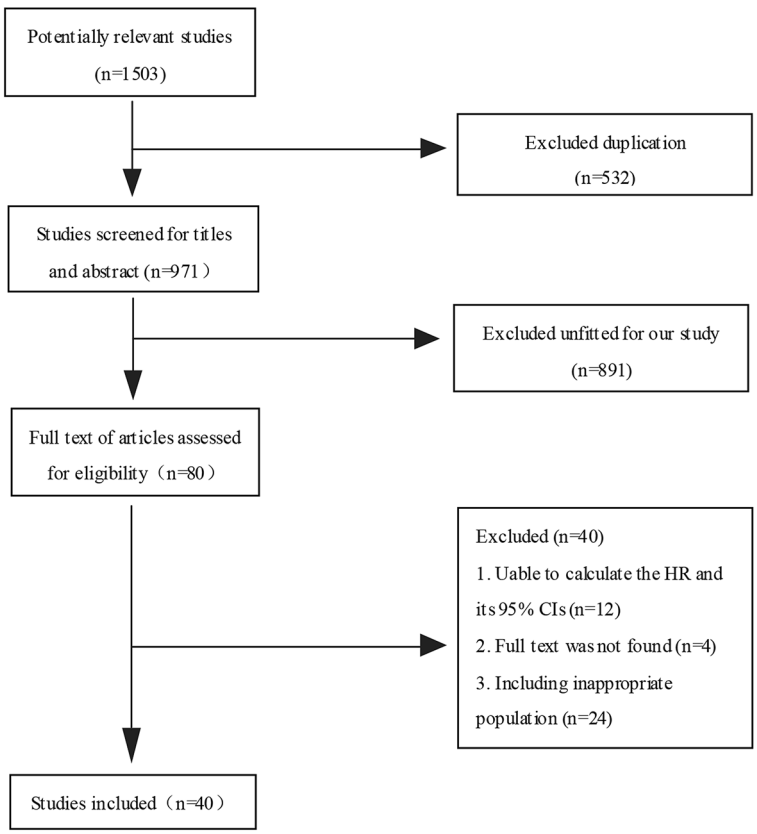

Fig. 1 Flow diagram of included studies

Table 1 Baseline of patients characteristics

Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (years)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (*n*)	irAE (*n*)	Non-irAE (*n*)
Ascierto 2014 [23]	Italy	Melanoma	Ipilimumab	855 (460/395)	61 (16–88)	830/25	0/855	Pruritus (58), rash (64), diarrhea (60), nausea (47), vomiting (15), abdominal pain (11), constipation (7), endocrine (7), liver toxicity (19), fatigue/asthenia (70)	286	569
Cortellini 2019 [24]	Italy	NSCLC	Pembrolizumab or nivolumab	559 (379/180)	69 (24–88)	485/74	116/443	Endocrine (78), gastrointestinal (51), skin (59), pneumological (23), hepatic (10), others (46)	231	328
Elias 2019 [25]	USA	RCC	ICIs	90	NA	NA	NA	Fatigue (25), nausea (9), decreased appetite (8)	38	52
Freeman-Keller 2015 [14]	USA	Melanoma	Nivolumab	148 (87/61)	NA	NA	NA	Rash (67), diarrhea/colitis/enteritis (48), vitiligo (19), hypothyroidism (16), elevated amylase/lipase (7), mucositis (9), pneumonitis (3), hyperthyroidism (2), hypophysitis (1), elevated ALT/AST (1)	101	47
Grangeon 2018 [26]	France	NSCLC	Anti-PD-L1 or anti-PD-1	270 (177/93)	61 (32–84)	233/17	16/254	Thyroiditis (53), rashes (19), colitis (11), hepatitis (8), endocrinopathy (8), pneumonitis (6), nephritis (1), pruritus (9), arthralgia (5), mof (1), myocarditis (1), myocardial ischemia (1), psoriasis (1), irritability (1)	124	146
Horvat 2015 [28]	USA	Melanoma	Ipilimumab	298 (182/116)	65 (21–93)	291/7	193/105	Hepatotoxicity (197), dermatitis (123), diarrhea (87), hypophysitis (17), uveitis (8), other (15)	254	44
Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (years)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (n)	irAE (*n*)	Non-irAE(*n*)
Haratani 2017 [27]	Japan	NSCLC	Nivolumab	134 (90/44)	68 (33–85)	116/12	8/126	Rash (33), pruritus (16), vitiligo (2), pneumonitis (6), thyroiditis/hypothyroidism (10), hypophysitis (1), mucositis (3), diarrhea/colitis (10), hepatitis (5), cholangitis (2), fatigue (7), appetite loss (4), polyarthritis (1), myasthenia gravis (1)	69	65

Table 1 (continued)

Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (years)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (*n*)	irAE (*n*)	Non-irAE (*n*)
Indini 2018 [29]	Germany	Melanoma	Pembrolizumab or nivolumab	173 (107/66)	62 (18–85)	166/6	74/99	Rash (12), pruritus (11), lichen (1), vitiligo (8), fatigue (34), fever (4), infusion-related reaction (2), decreased appetite (6), dysgeusia (2), dry mouth (2), oral mucositis (2), nausea (13), vomiting (1), gastritis (2), colitis (1), diarrhea (10), ast, alt increase (19), γgt increase (1), amylase increased (2), lipase increased (3), hyperglycemia (1), serum creatinine increase (2), acute renal failure (1), cough (5), interstitial pneumonitis (2), arthralgias (12), hypothyroidism (14), hypophysitis (2), anemia (6), thrombocytopenia (4), myasthenia with myositis (1), headache (2), paresthesia (2), peripheric sensory neuropathy (8), peripheric motor neuropathy (1), uveitis (1), conjunctivitis (1), photophobia (2)	102	71
Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (yeaars)	ECOG0–1/≥2	Previous therapy/≥1	IrAE type (n)	irAE (n)	Non-irAE(n)
Kawai 2019 [30]	Japan	UC	Pembrolizumab	30 (25/5)	70 (26–85)	NA	0/30	NA	18	12
Masuda 2019 [31]	Japan	Gastric cancer	Nivolumab	65 (51/14)	66 (35–83)	59/6	NA	Diarrhea/colitis (5), hyperglycemia (2), pruritus (2), rash (2), type 1 dm (2), adrenal insufficiency (1), alt increased (1), ast increased (1), appetite loss (1), appetite loss (1), dry skin (1), edema limbs (1), myalgia (1), peripheral motor neuropathy (1), pneumonitis (1), QTc interval prolonged (1)	14	51
Okada 2018 [32]	Japan	Melanoma	Nivolumab	15 (4/11)	NA	NA	NA	Rash (6), hypothyroidism (4), diarrhea (2), liver dysfunction (1)	8	7

Table 1 (continued)

Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (years)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (*n*)	irAE (*n*)	Non-irAE (*n*)
Okamoto 2019 [33]	Japan	HNC	Nivolumab	100 (79/21)	65(23–81)	95/5	0/100	Dermatitis (3), interstitial lung disease (11), hypothyroidism (8), hyperthyroidism (1), adrenal insufficiency (1), liver dysfunction (4), myositis (1), rheumatoid arthritis (1), eye disorders (1), upper gastrointestinal hemorrhage (1), diarrhea (1), weight loss (1), infusion reaction (1), anemia (1), increased creatinine (1)	30	70
Sato 2018 [36]	Japan	NSCLC	Nivolumab	38 (28/10)	68.5 (49–86)	33/5	NA	TSH elevation (1), hypothyroidism (3), pneumonitis (5), hyperthyroidism (1), rash (1), liver dysfunction (1), hypopituitarism (1)	11	27
Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (years)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (*n*)	irAE (*n*)	Non-irAE(*n*)
Ricciuti 2018 [34]	Italy	NSCLC	Nivolumab	195 (128/67)	63(30–84)	160/35	0/195	Rash (18), psoriasis (3), pruritus (2), dry skin (2), skin desquamation (1), paronychia (1), pneumonitis (16), hyper/hypothyroidism (39), hyperprolactinemia (16), ACTH elevation (4), colitis (21), amylase increase (15), lipase increase (8), nausea/vomiting (8), constipation (1), abdominal pain (2), xerostomia (1), γ-GT (18), ALT (16), AST (16), alkaline phosphatase (16), conjunctivitis (2), uveitis (1), fatigue (38), arthritis (7), polymyalgia rheumatica (1), dermatomyositis (1), anorexia (3), anemia (1), thrombocytopenia (3), Neutropenia (1)	85	110
Rogado 2019 [35]	Spain	Lung cancer melanoma, HL HCC, HNC,UC RC,MCC,GBAC	Nivolumab or pembrolizumab	106 (76/30)	69(32–86)	73/33	21/85	Hypothyroidism (22), hyperthyroidism (3), nephritis (7), rash (3), pneumonitis (5), colitis (1), hepatitis (3), arthritis (3), hypophysitis (1), panhypopituitarism (2), suprarenal insufficiency (2), hyperthyroidism (2), ketoacidotic diabetes (1), encephalitis (1), myositis (1)	40	66

Table 1 (continued)

Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (years)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (*n*)	irAE (*n*)	Non-irAE (*n*)
Shafqat 2018 [37]	USA	NSCLC, RCC, melanoma, UC HNC, Other	Nivolumab or pembrolizumab or atezolizumab	157 (100/57)	65	NA	NA	Colitis (4), pneumonitis (5), hepatitis (1), endocrinopathy (21), skin toxicity (4), other (1), arthralgia/arthritis (9)	42	114
Study	Nation	Tumors	ICI type	Patients (male/female)	Median age(y)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (*n*)	irAE (*n*)	Non-irAE (*n*)
Teraoka 2017 [38]	Japan	NSCLC	Nivolumab	43 (27/16)	70 (50–82)	39/4	0/43	Rash (12), pyrexia (6), diarrhea (4), elevated hepatic enzyme levels (1)	19	24
Toi 2018 [39]	Japan	NSCLC	Nivolumab or pembrolizumab	137 (105/32)	68 (36–88)	134/3	18/119	Skin reaction (42), pneumonitis (14), hypothyroidism (6), hyperthyroidism (1), hepatitis (6), myositis or peripheral neuropathy (5)	66	71
Verzoni 2019 [40]	Italy	RCC	Nivolumab	389 (291/98)	65 (34–85)	350/24	2/387	Cutaneous (30), endocrine (17), hepatic (7), gastro-intestinal (19), pulmonary (4)	76	313
VonPawel 2017 [41]	Global	NSCLC	Atezolizumab	850	NA	NA	NA	NA	264	586
Bjornhart 2019 [42]	Denmark	NSCLC	Nivolumab or pembrolizumab	118 (55/63)	66 (59–71)	106/12	46/72	Pneumonitis, colitis, hypophysitis, diarrhea, arthritis, uveitis, myositis, primary AI, thyroiditis, hepatitis, allergic reaction	32	86
Otsuka 2020 [43]	Japan	Melanoma	Nivolumab	27 (9/18)	69 (31–87)	NA	23/4	Dermatological (11), gastrointestinal (2), endocrine (4), pulmonary (4), renal (1), infusion-related reaction (1)	16	12
Dick 2016 [44]	Germany	Melanoma	Ipilimumab	86 (48/38)	59 (14–83)	NA	22/64	Predominantly diarrhea, autoimmune colitis, skin toxicity, infrequently hypophysitis, autoimmune hepatitis, autoimmune pancreatitis, alopecia areata	36	50
Study	Nation	Tumors	ICI type	Patients (male/female)	Median age(y)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (*n*)	irAE (*n*)	Non-irAE (*n*)
Judd 2017 [45]	USA	RCC, HNSCC, UC, NSCLC, other	Nivolumab or pembrolizumab	160 (101/59)	65	NA	NA	Endocrinopathy, colitis, dermatitis	64	96

Table 1 (continued)

Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (years)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (*n*)	irAE (*n*)	Non-irAE (*n*)
Kim 2018 [46]	South Korea	NSCLC	Nivolumab or pembrolizumab	58 (43/15)	63.1 (49–68)	NA	NA	Thyroid dysfunction (19)	19	39
Ksienski 2018 [47]	Canada	NSCLC	Nivolumab or pembrolizumab	271 (137/134)	NA	187/54	21/250	Hypothyroid (32), dermatitis (35), colitis (18), hyperthyroid (10), hepatitis (12), arthralgias (13), pneumonitis (17), nephritis (8), adrenal insufficiency (3), diabetes (3), hypophysitis (2), pancreatitis (1), neurologic (3), cholangitis (2), myopathy (2), myositis (1), mucositis (1), palmar plantar erythrodysesthesia (1), polymyalgia rheumatica (1), vasculitis (1), idiopathic thrombocytopenic purpra (1), myocarditis (1)	116	155
Lisberg 2018 [49]	USA	NSCLC	Pembrolizumab	97 (50/47)	65 (32–83)	NA	13/84	Rash (22), fatigue (9), hypothyroidism (6), fever/chills (5), anorexia (4), pneumonitis (6), pruritus (3), abdominal pain (2), worsening dyspnea (2), joint pain (2), edema (2)	39	58
Sugano 2020 [56]	Japan	NSCLC	Nivolumab or atezolizumab or pembrolizumab	130 (98/32)	NA	99/31	NA	Interstitial lung disease (16), hypothyroidism (9), skin reaction (5), nephrotoxicity (3), encephalitis (2)	39	91
Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (years)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (*n*)	irAE (*n*)	Non-irAE (*n*)
Maher 2019 [50]	Global	UC	Nivolumab or atezolizumab or durvalumab or avelumab or pembrolizumab	1747 (1328/419)	68 (29–94)	1572/175	NA	NA	268	1479
Hua 2016 [16]	France	Melanoma	Pembrolizumab	67 (38/29)	57 (28–72)	NA	NA	Vitiligo (17)	17	50
Nakamura 2017 [17]	Japan	Melanoma	Nivolumab	35 (18/17)	NA	NA	NA	Vitiligo (9)	9	26
Nakamura 2016 [52]	Japan	Melanoma	Nivolumab	98 (52/46)	66.5 (17–93)	92/6	28/70	Vitiligo (13), hypothyroidism (11), pruritus (10), rash (7), malaise (5)	51	57

Table 1 (continued)

Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (years)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (*n*)	irAE (*n*)	Non-irAE (*n*)
Lesueur 2018 [48]	France	NSCLC	Nivolumab	104 (67/37)	60.3 (54.5–67.1)	69/35	NA	Pulmonary (4), gastrointestinal (21), dermatological (13), endocrinological (10), rheumatological (6), asthenia (19), hematological (1), others (16)	62	42
Minlee 2018 [51]	USA	Lung cancer, HL cutaneous cancer HNC, GC, UC reproductive cancer	Nivolumab or atezolizumab or pembrolizumab	114 (62/52)	NA	NA	NA	Dermatitis (20)	20	94
Osorio 2016 [53]	USA	NSCLC	Pembrolizumab	51 (21/30)	NA	NA	NA	Immune-related thyroid dysfunction (10)	10	41
Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (years)	ECOG 0–1/≥2	Previous therapy 0/≥1	IrAE type (*n*)	irAE (*n*)	Non-irAE (*n*)
Owen 2018 [54]	USA	NSCLC	Nivolumab or pembrolizumab or atezolizumab	91 (39/52)	67/22	NA	NA	Pneumonitis (9), dermatologic (6), endocrine (7), colitis (3), hepatitis (1), pancreatic insufficiency (1)	27	64
Yamazaki 2017 [59]	Japan	Melanoma	Nivolumab	24 (14/10)	63 (26–81)	24/0	16/8	Endocrine disorders (7), gastrointestinal toxicity (2), hepatotoxicity (1), pulmonary toxicity (1), skin toxicity (11)	13	10
Sanlorenzo 2015 [55]	USA	Melanoma, lung cancer, MCC, prostate cancer	Pembrolizumab	83 (52/31)	NA	NA	NA	Macular papular eruption (24), pruritus (10), hypopigmentation (7), xerosis (2), keratosis (2), facial erythema (1)	35	48
Suh 2018 [57]	South Korea	NSCLC	Nivolumab/pembrolizumab	54 (42/12)	NA	54/0	0/54		12	42

Table 1 (continued)

Study	Nation	Tumors	ICI type	Patients (male/female)	Median age (years)	ECOG 0–1/≥ 2	Previous therapy 0/≥ 1	IrAE type (*n*)	irAE (*n*)	Non-irAE (*n*)
Weber 2017 [58]	USA	Melanoma	Nivolumab	576 (349/227)	61	571/0	NA	Pruritus (99), rash (73), vitiligo (45), rash maculopapular (26), diarrhea (73), colitis (6), hypothyroidism (24), hyperthyroidism (12), hypophysitis (1), AST increased (16), ALT increased (11), γ-glutamyltransferase increased (1), hepatitis (1), liver function test abnormal (1), pneumonitis (10), blood creatinine increased (3), renal failure acute (1), tubulointerstitial nephritis (1)	255	321

NSCLC non-small cell lung cancer, *UC* urothelial cancer, *RCC* renal cell carcinoma, *HL* Hodgkin lymphoma, *HNC* head and neck carcinoma, *HCC* hepatocellular carcinoma, *GC* gastrointestinal cancer, *GBAC* gallbladder adenocarcinoma, *MCC* Merkel cell carcinoma, *irAE* immune-related adverse events, *NA* not available

Overall survival

Altogether, 34 studies [14, 16, 17, 23–35, 39–54, 57, 59] contributed to the OS hereof. On account of the heterogeneity ($p < 0.00001$, $I^2 = 73\%$), a random effect model was applied for the meta-analysis. The results showed that compared with non-irAE group, irAE group had a significantly longer OS (HR = 0.49, 95% CI [0.42–0.58], $p < 0.00001$) (Fig. 3a). In the region stratification analysis, a better survival occurred in irAE group of Asia (HR = 0.27, 95% CI [0.16–0.44], $p < 0.00001$), Europe (HR = 0.55, 95% CI [0.42–0.72], $p < 0.0001$), and America (HR = 0.53, 95% CI [0.40–0.70], $p < 0.00001$) (Fig. 3b). Additionally, the irAEs correlated with longer OS, regardless of NSCLC (HR = 0.50, 95% CI [0.40–0.63], $p < 0.00001$), melanoma (HR = 0.40, 95% CI [0.26–0.61], $p < 0.0001$) or urinary cancer (HR = 0.45, 95% CI [0.31–0.67], $p < 0.0001$) (Fig. 3c). Participants treated with anti-PD-1 had a longer OS when irAEs emerged (HR = 0.43, 95% CI [0.34–0.54], $p < 0.00001$) (Fig. 3d). On the contrary, OS was not correlated with irAEs in anti-CTLA-4 subgroup (HR = 0.76, 95% CI [0.53–1.09], $p = 0.13$) (Fig. 3d). Stratification analysis on common irAEs (Fig. 3e) indicated that evident survival benefits existed in endocrine irAEs (HR = 0.50, 95% CI [0.38–0.64], $p < 0.00001$), skin irAEs (HR = 0.39, 95% CI [0.25–0.62], $p < 0.0001$) and gastrointestinal irAEs (HR = 0.58, 95% CI [0.42–0.79], $p = 0.0007$) while no favorable OS was observed in pulmonary irAEs (HR = 0.87, 95% CI [0.43–1.75], $P = 0.70$) and hepatobiliary irAEs (HR = 0.98, 95% CI [0.64–1.52], $p = 0.94$). No significant publication bias for OS was found by funnel plot (Fig. 3f).

Progression-free survival

In total, 30 studies [17, 24, 26, 27, 29–39, 42–46, 48–51, 53, 55–59] documented PFS and a random effect model was applied owing to heterogeneity ($p = 0.0002$, $I^2 = 55\%$). Compared with non-irAE group, irAE group presented a prolonged PFS (HR = 0.52, 95% CI [0.45–0.59], $p < 0.00001$) (Fig. 4a). Stratification analysis on the region showed that compared with non-irAE group, irAE group gained a longer PFS in Asia (HR = 0.38, 95% CI [0.29–0.50], $p < 0.00001$), Europe (HR = 0.51, 95% CI [0.45–0.59], $p < 0.00001$) and America (HR = 0.69, 95% CI [0.55–0.87], $p = 0.002$) (Fig. 4b). Furthermore, the irAEs were positively associated with PFS in NSCLC (HR = 0.53, 95% CI [0.46–0.60], $p < 0.00001$) and melanoma (HR = 0.47, 95% CI [0.28–0.79], $p = 0.005$) (Fig. 4c). Participants treated with anti-PD-1 had a longer PFS when irAEs emerged (HR = 0.51, 95% CI [0.43–0.60], $p < 0.00001$) (Fig. 4d). However, PFS was not correlated with irAEs in anti-CTLA-4 subgroup (HR = 0.69, 95% CI [0.35–1.39], $p = 0.31$) (Fig. 4d). Stratification analysis on common irAEs (Fig. 4e) indicated that evident

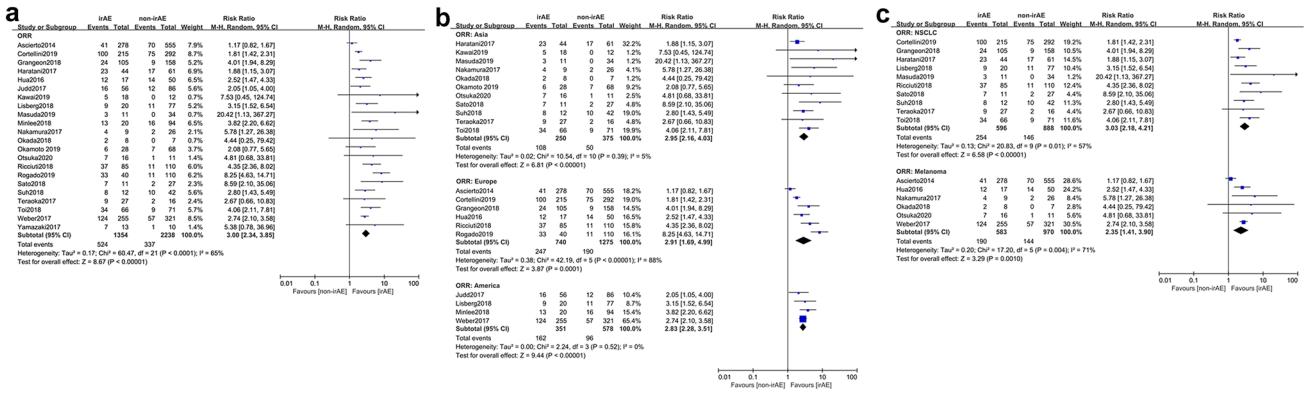

Fig. 2 Analyses of irAEs for ORR. **a** ORR of the study; **b** stratification analysis of trial regions; **c** stratification analysis of tumor

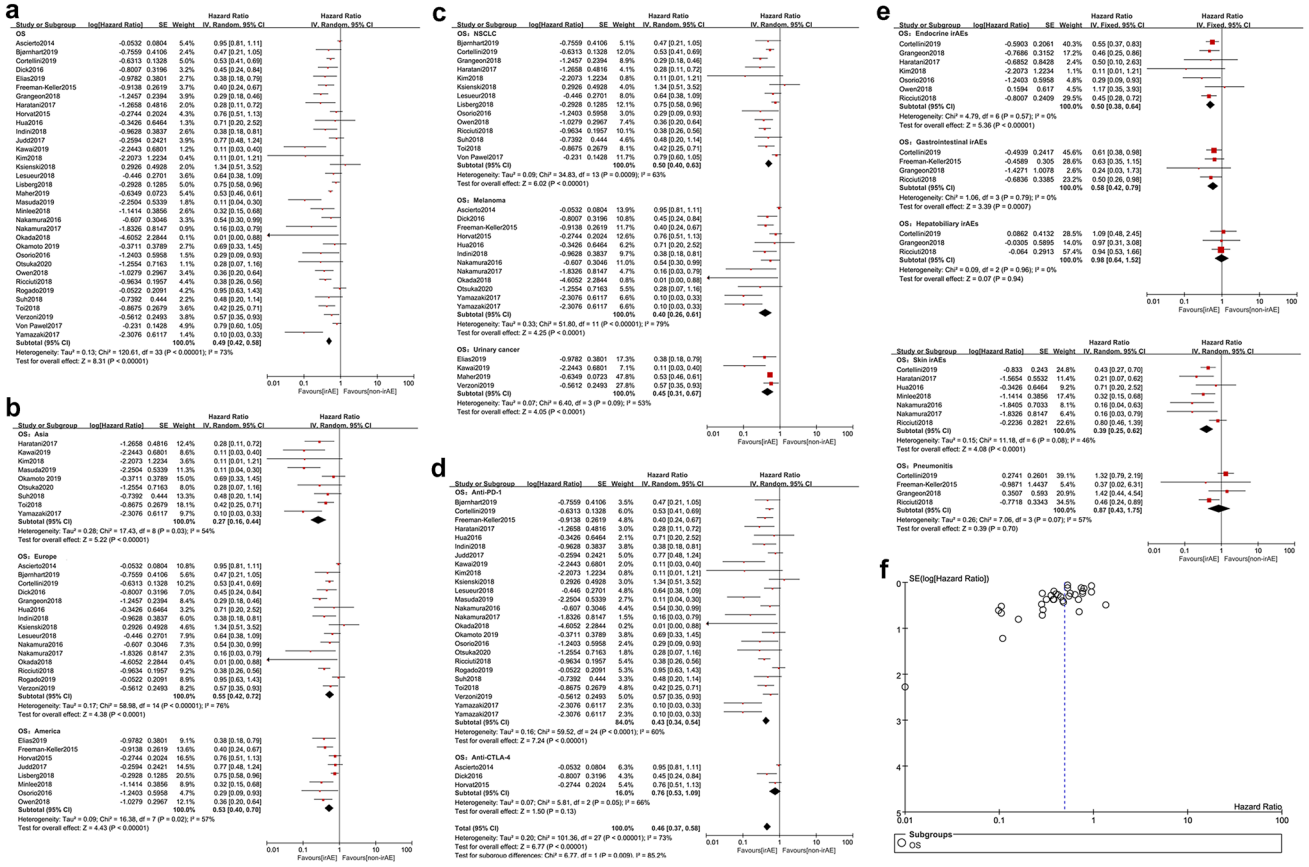

Fig. 3 Analyses of irAEs for OS. **a** OS of the study; **b** stratification analysis of trial regions; **c** stratification analysis of tumors; **d** stratification analysis of ICI types; **e** stratification analysis of common irAEs; **f** funnel plot

survival benefits existed in endocrine irAEs (HR = 0.57, 95% CI [0.47–0.70], $p < 0.00001$), skin irAEs (HR = 0.48, 95% CI [0.38–0.60], $p < 0.00001$) and gastrointestinal irAEs (HR = 0.67, 95% CI [0.51–0.88], $p = 0.004$), whereas no favorable PFS was observed in pulmonary irAEs (HR = 0.80, 95% CI [0.59–1.09], $p = 0.17$) and hepatobiliary irAEs (HR = 0.95, 95% CI [0.65–1.38], $p = 0.78$). No significant publication bias for PFS was found by funnel plot (Fig. 4f).

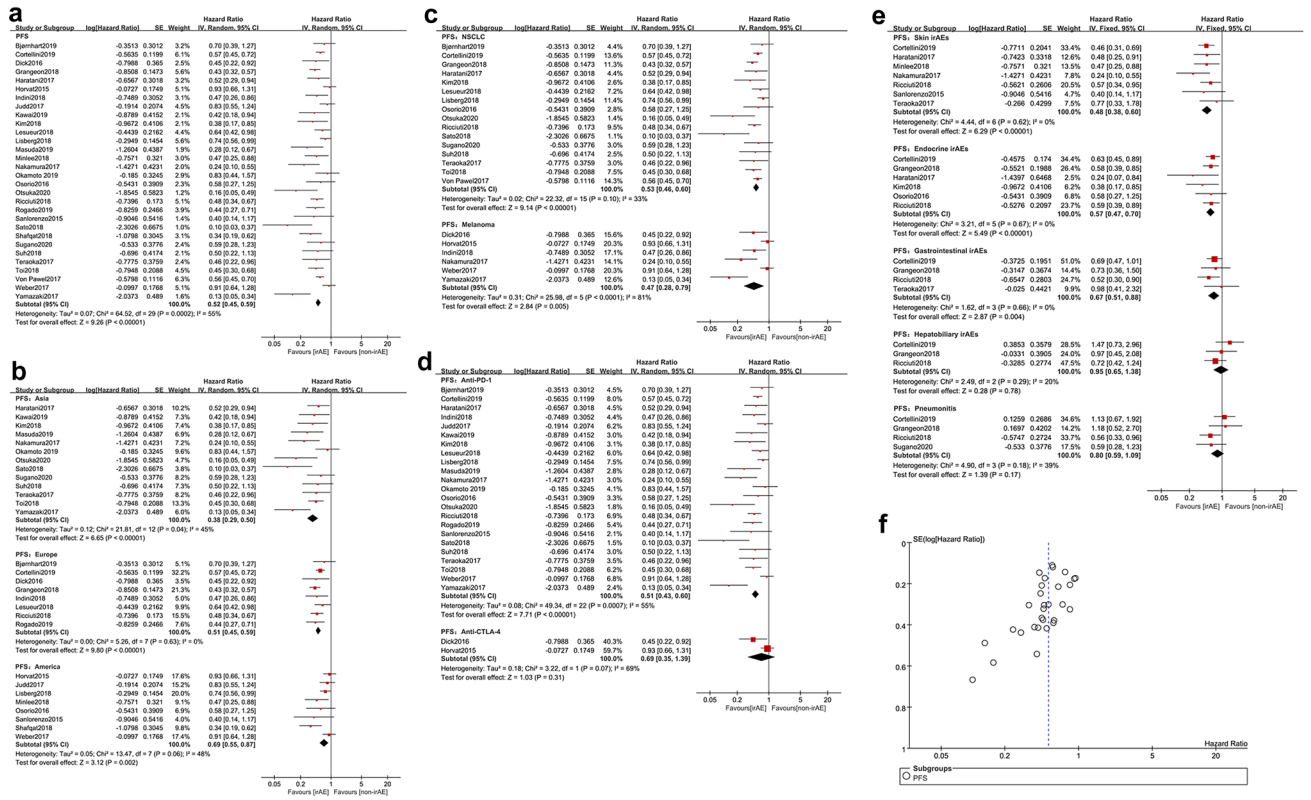

Fig. 4 Analyses of irAEs for PFS. **a** PFS of the study; **b** stratification analysis of trial regions; **c** stratification analysis of tumors; **d** stratification analysis of ICI types; **e** stratification analysis of common irAEs; **f** funnel plot

Minor or chronic irAEs

Altogether, 23 studies [16, 17, 23, 24, 26–31, 33–35, 37, 39, 42, 47–50, 56, 58, 59] reported some relatively minor or chronic irAEs, such as connective tissue diseases and neurological irAEs. However, only the outcomes of patients with these irAEs were presented, by which we found patients with connective tissue diseases tended to generate better survival statistics (Table 2). However, such severe irAEs may require systemic glucocorticoid therapy, which then become chronic disease and also partially lead to the cessation of ICIs. Unfortunately, no survival data were available for neuromuscular irAEs. Hence, further studies are required to clarify the correlation.

Severity of irAEs

A total of three studies [40, 45, 47] illustrated the relationship between the severity of irAEs and efficacy. On account of the heterogeneity ($p = 0.009$, $I^2 = 79\%$), a random effect model was applied for the meta-analysis. The results showed that compared with high-grade irAE group, low-grade irAE group tended to harbor a longer OS (HR = 1.48, 95% CI [0.53–4.14], $p = 0.46$) (Fig. 5). It is possible that severe irAEs on the body damage offset the immune efficacy.

Discussion

At present, the correlation between irAEs and efficacy remains controversial. To our best knowledge, this is a comprehensive study on the correlation between efficacy and irAEs of ICIs. This study revealed that irAE group enjoyed a better survival benefit than non-irAE group. Regarding to the types of irAEs, the survival benefit for patients with irAEs was observed in patients presenting skin, endocrine organ or gastrointestinal tract irAEs. With respect to the severity of irAEs, low-grade irAEs tended to be actively associated with efficacy. The occurrence of irAEs was significantly associated with a favorable efficacy of PD-1 inhibitors rather than CTLA-4 inhibitors.

Currently, the mechanism of irAEs is not completely elucidated. ICIs activate immune system against tumor, and provoke inflammatory side effects termed irAEs [60]. It is evidenced that irAEs may be triggered by an antigen common to both tumor and normal tissue, and then the release of T cells would attack both tissues, generating both response

Table 2 Outcome of minor or chronic irAEs

Study	Rheumatic or neuromuscular irAEs (*n*)	Outcome	Treatment of irAEs	IrAE response to treatment
Ascierto 2014 [23]	Vasculitis (1)	Therapy discontinued (1)	Therapy discontinued (1)	NA
Cortellini 2019 [24]	Rheumatologic, neuromuscular	OS HR 0.61 [0.38–0.97], $P=0.04$ PFS HR 0.84 [0.57–1.23], $P=0.37$	NA	NA
Grangeon 2018 [26]	Arthralgia (5), psoriasis (1)	NA	NA	NA
Horvat 2015 [28]	Uveitis (8)	Therapy discontinued (1)	Systemic corticosteroids (1), therapy discontinued (1)	Improved
	Neurotoxicity (1)	Therapy discontinued (1)	Therapy discontinued (1)	NA
	Arthritis (1)	NA	Systemic corticosteroids (1)	Improved
Haratani 2017 [27]	Polyarthritis (1), myasthenia gravis (1)	NA	NA	NA
Indini 2018 [29]	Arthralgias (11), myasthenia with myositis (1), headache (2), paresthesia (2), peripheral sensory neuropathy (8), peripheral motor neuropathy (1), uveitis (1)	NA	NA	NA
Kawai 2019 [30]	Myasthenia gravis (1)	NA	NA	NA
Masuda 2019 [31]	Myalgia (1), peripheral motor neuropathy (1)	NA	NA	NA
Okamoto 2019 [33]	Myositis (1), rheumatoid arthritis (1)	NA	NA	NA
Ricciuti 2018 [34]	Uveitis (1), arthritis (7), polymyalgia rheumatica (1), dermatomyositis (1)	NA	NA	NA
Rogado 2019 [35]	Arthritis (3)	Therapy discontinued (1)	Therapy discontinued (1)	NA
	Myositis (1)	NA	NA	NA
Shafqat 2018 [37]	Arthralgia/arthritis (9)	NA	Prednisone (5)	NA
Study	Rheumatic or neuromuscular irAEs (n)	Outcome	Treatment of irAEs	IrAE response to treatment
Toi 2018 [39]	Myositis or peripheral neuropathy (5)	PR (4), SD (1)	NA	NA
	Rheumatoid factor positive	PFS HR 0.61 [0.38–0.97], $P=0.04$	NA	NA
Bjornhart 2019 [42]	Arthritis (24)	OS HR 0.35 [0.11–1.12], $P=0.08$ PFS HR 0.51 [0.22–1.17], $P=0.11$	NA	NA
	Uveitis, myositis	NA	NA	NA
Ksienski 2018 [47]	Arthralgias (8) (caused by nivolumab)	OS (month) NR (8.27-NR) vs 10.1 (8.3–14.2), $P=0.44$	NA	NA
	Arthralgias (5) (caused by pembrolizumab)	OS (month) NR (NR-NR) vs 13.5 (10.6-NR), $P=0.42$	NA	NA
	Neurologic (3), myopathy (2), myositis (1), polymyalgia rheumatica (1), vasculitis (1)	NA	NA	NA
Lisberg 2018 [49]	Joint pain (2)	NA	NA	NA

Table 2 (continued)

Study	Rheumatic or neuromuscular irAEs (*n*)	Outcome	Treatment of irAEs	IrAE response to treatment
Sugano 2020 [56]	Ocular myasthenia gravis (1)	NA	NA	NA
Maher 2019 [50]	Musculoskeletal pain, rhabdomyolysis, Muscle spasms	NA	NA	NA
Hua 2016 [16]	Arthralgia (11)	NA	NA	NA
Lesueur 2018 [48]	Rheumatological (6)	NA	NA	NA
Nakamura 2017 [17]	Psoriasis (1)	Therapy discontinued (1)	NA	NA
Weber 2017 [58]	Arthralgia (39)	NA	NA	NA
Yamazaki 2017 [59]	Arthralgia (3)	NA	NA	NA

NA not available, *NR* not reached

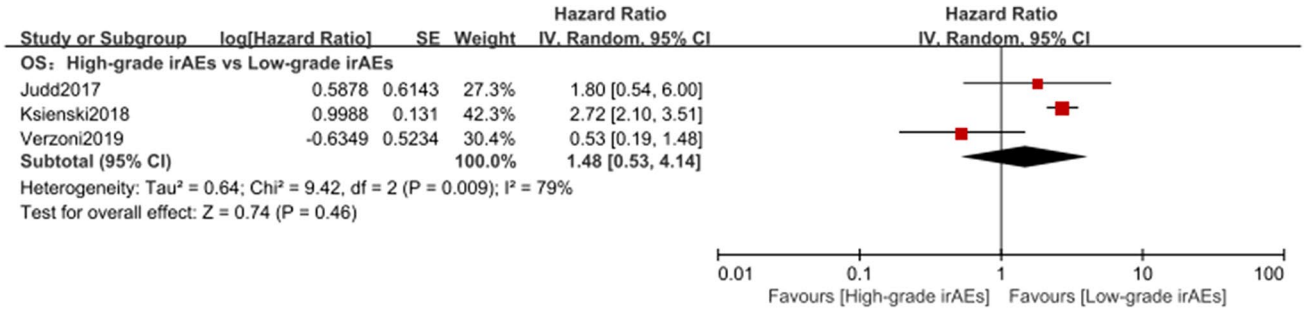

Fig. 5 Analysis on the severity of irAEs for OS

and toxicity [61]. Consequently, on the basis of the antigen mimicry theory, it is logical that more severe irAEs are, the better the prognosis is. However, this study indicated that the severity of irAEs was not associated with efficacy. This may be attributed to the increasing risk of death, which may counteract the immune efficacy. Therefore, further studies are required to illustrate the mechanism behind irAEs.

With regard to skin irAEs of ICIs, this study demonstrated that patients with skin irAEs enjoyed a significantly prolonged survival. The mechanism behind irAEs is that T cell infiltration triggers an inflammatory side effect, and also provokes an anti-tumor effect [62]. A typical instance is vitiligo and its skin pigment loss is positively associated with the efficacy of ICIs [15–17, 63]. Meanwhile, vitiligo is a unique side effect of melanoma. Unfortunately, due to data deficiency, this study did not explore any correlation between different irAEs with certain cancer.

Gastrointestinal irAEs were also positively associated with efficacy of ICIs in this study. But some studies pointed out that there were no evident survival benefits from colitis or diarrhea [14–16, 38]. Nevertheless, it was documented that gastrointestinal irAEs predicted improved OS and PFS [63]. The discrepancy may attribute to the diversity of baseline intestinal flora [64, 65].

An exceptional evidence is that no increasing efficacy coupled with pulmonary and hepatobiliary irAEs in our study. This may be attributed to the importance of involved organ. The reasons may be as follows: first, pneumonia and hepatobiliary irAEs are generally severe, even fatal, which counteracts the efficacy of ICIs [66]; second, the major agent was anti-PD-1 in this study which had the highest incidence of pneumonia and hepatobiliary irAEs, thus abating the survival benefits [67]; finally, the majority of the individuals were advanced NSCLC who accompanied with basic lung disease, which would attenuate the therapeutic effect to some extent.

Concerning the correlation between the irAEs of CTLA-4 inhibitor and efficacy, this study failed to discover the positive outcome. CTLA-4 inhibitor activates T cells at an earlier stage of their development and might thus directly

disrupt central tolerance without affecting the tumor immune response, while PD-1/PD-L1 inhibits activate T cells in the effect stage [68, 69]. Thus, patients treated with CTLA-4 inhibitor developed more severe irAEs. We make an attempt to interpret this phenomenon as follows: one is that anti-CTLA-4 therapy mediated the higher severity and mortality of irAEs than those of PD-1/PD-L1 inhibitor [66, 67], which compromised the effect to some degree; the other is that the therapeutic course of CTLA-4 was only within 4 cycles (12 weeks) in included studies and its efficacy was not as good as expected [70].

We analyzed the common irAEs, but some chronic or rare irAEs cannot be ignored. In the case of chronic irAEs, because of its chronic nature, these irAEs may affect patients' quality of life. In our study, although patients with rheumatic irAEs tend to have better survival benefits, such severe irAEs may require systemic glucocorticoid therapy, which then become chronic disease and also partially lead to the cessation of ICIs. A study [71] showed that a majority of patients experienced long courses of immunotherapy, but only a minority of them needed the discontinuation of ICIs. Therefore, more studies are expected to focus on the quality of life in patients with rheumatic irAEs.

Comprehensive analysis was accomplished in this study as for the correlation between irAEs and immune efficacy. In addition, stratification analyses were performed based on the region of studies, type of tumors, ICIs and irAEs as well as severity of irAEs. If ICI efficacy is positively correlated with side effects, irAEs could be defined as a simple, economical and easily observed predictor of efficacy.

There have been previous studies similar to ours. A systematic review and meta-analysis reported by Xiaoxiang Zhou et al. [72] analyzed the association between irAEs and ICI efficacy. However, they did not conduct the analyses on the correlation between irAEs and efficacy for ORR. Additionally, they did not conduct stratified analysis of tumor types and regions. However, in our study, more participants and trials were included, and more comprehensive stratified analyses were conducted.

Limitations

Although this study involved comprehensive data (included 40 studies encompassing 8,641 participants), it was confronted with the following two limitations: only 9 prospective studies were available and just 4 studies with monotherapy of anti-CTLA-4/anti-PD-L1 were included. Thereby, more large-scaled prospective studies are recommended.

Conclusion

IrAEs, especially in skin, endocrine organ or gastrointestinal tract, triggered by ICIs implied significant survival benefits.

Author contributions Conceptualization: XX and LZ; methodology: LZ and JL; software: LZ; validation: all authors; formal analysis: LZ, FC and XX; data curation: LZ; writing—original draft preparation: LZ, QW and XX; writing—review and editing: all authors; visualization: LZ; supervision: XX.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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