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ORIGINAL ARTICLE

Treatment-related adverse events of combined anti-angiogenic and immune checkpoint inhibitors: systematic review and meta-analysis

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Abstract

Objective Immune checkpoint inhibitor (ICI) plus angiogenesis inhibitor (AI) combination therapy is a novel treatment model for multiple cancers that normalizes vascular-immune crosstalk to potentiate cancer immunity. In this review, we summarize the characteristics of adverse effects (AEs) and all fatal cases reported in clinical studies involing ICI + AI therapy.

Methods Four databases were systematically searched for eligible studies, and 28 relevant studies were selected for inclusion.

Results Of the patients included, 58.1% developed grade ≥ 3 AEs. The most common fatal AEs were cardiovascular events, severe infections, and hemorrhage. Compared with AI alone, ICI + AI therapy resulted in more cases of grade ≥ 3 proteinuria, liver injury, and fatal AEs (2.49% *vs.* 1.28%, $P = 0.0041$), especially respiratory toxicities and severe infections; however, ICI + AI therapy reduced hematological toxicity.

Conclusion We shared comprehensive and practical safety data to review the adverse events associated with ICI + AI treatment.

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Key words: combination therapy, immune checkpoint inhibitor, angiogenesis inhibitor, treatment-related adverse events, systematic review, meta-analysis

Immune checkpoint inhibitors (ICIs) are now the cornerstones of cancer therapy, with approval for use in 17 different cancer types [1, 2]. In clinical practice, the main concern when choosing an ICI is the low response rate [3]. Recent studies have indicated that the efficacy of combination therapy with ICIs and angiogenesis inhibitors (AI) is superior to monotherapy with ICIs or AIs [4–6]. AI therapy not only prunes blood vessels, which are essential for cancer growth and metastasis but also reprograms the tumor immune microenvironment [7]. For this novel therapy, whether the severity and frequency of adverse events (AEs) are synergistic or additive is unclear. To the best of our knowledge, the spectrum of treatment-related adverse events (TRAEs) associated with ICI + AI therapy has its own characteristics; however, no relevant article has summarized them. Therefore, a systematic review of such AE data is necessary to guide informed decisions in clinical trials and in clinics, for both clinicians and patients. Herein, we conducted a systematic review and meta-analysis of the incidence of all-grade AEs, grade ≥ 3 AEs, and all deaths associated with ICI + AI therapy *vs.* ICI or AI monotherapy to synthesize an accurate and comprehensive toxicity profile that can help clinicians manage patients and rapidly respond to fatal AEs.

Materials and methods

Search strategy

Relevant studies were identified using the following electronic databases: (1) PubMed, (2) Embase, (3) Web of Science, and (4) Cochrane library. The following keywords were used: "Immune Checkpoint Inhibitors," "ipilimumab," "tremelimumab," "nivolumab,"

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"pembrolizumab," "atezolizumab," "avelumab," "durvalumab," "PD-1," "PD-L1," "CTLA-4," "ICI," "anti-angiogenic," "Anti-VEGF," "ramucirumab," "bevacizumab," "TKI," "axitinib," and "sunitinib." Only studies published in English from conception of the database to November 28, 2020, were included. Further efforts to identify additional 29 studies included hand-searching of reviews and reference lists as well as attempts to contact authors. The eligibility assessment for study selection was performed independently in a blinded, standardized manner by two reviewers. Disagreements between the two reviewers were resolved by discussion and consensus.

Selection criteria

The inclusion criteria were as follows: (1) studies based on histologically or cytologically confirmed solid tumors, (2) studies on ICI + AI therapy, (3) studies including reported tabulated data on TRAEs, and (4) articles published in English. The exclusion criteria were as follows: (1) review articles, meta-analyses, and case reports, and (2) studies based on ICI + AI therapy in combination with chemotherapy.

Data extraction

A data extraction form was developed a priori, two reviewers conducted data extraction in tandem, and the final results were reviewed by a third reviewer. If overlapping data were identified, the most recent or comprehensive study was included in the analysis. Disagreements were resolved through discussions among the three reviewers. The following information was extracted from each study: (1) study name/clinical trial ID; (2) author; (3) year of publication; (4) cancer type; (5) drugs studied; (6) treatment arms; (7) trial phase; and (8) AE data including the total number of patients affected and incidence of all-grade AEs and grade ≥ 3 AEs.

Quality assessment

Two investigators independently assessed the risk of bias in the included randomized controlled trials (RCTs) using the Cochrane Collaboration's tool, which includes the following five domains: sequence generation, allocation concealment, blinding, incomplete data, and selective reporting. Blinding can't be applied in studies with specific designs (such as open-label or cross-over) for unavoidable reasons. If such reasons were clearly stated in the included studies, they were rated as "+." An RCT was judged to have a "low risk of bias," a "high risk of bias," or an "unclear risk of bias" if all domains indicated low risk, one or more domains indicated high risk or more than three domains indicated unclear risk, respectively.

Statistical analysis

The meta-analysis was conducted using Review Manager (version 5.3, The Nordic Cochrane Center) and the package "metafor" of the R-project (version 3.6.3). Pooled risk ratios (RR) with 95% confidence intervals (CI) were used to analyze the all-grade TRAEs (RR > 1 favored the combination group; RR < 1 favored the monotherapy group). Among the selected studies, only those containing both combination therapy and monotherapy groups were included in the calculation of the pooled RR, whereas all studies were included in the calculation of the pooled incidence of selected TRAEs. If a study included more than one monotherapy arm, the combination arm was compared twice with each monotherapy arm.

Results

Search results and study quality assessment

The initial database search yielded 1527 studies. After screening (Fig. 1), 27 studies involving 5,138 patients were included in the final analysis. Of the 27 studies, 9 were control experiments (8 RCTs; 1 retrospective study) and 18 were single-arm experiments. The rationale for the addition and exclusion of each study is summarized in Fig. 1. The ICIs administered included atezolizumab (n = 7), pembrolizumab (n = 10), nivolumab (n = 4), avelumab (n = 1), and others (n = 5). The trials involved the treatment of renal cell carcinoma (RCC; n = 8), hepatocellular carcinoma (HCC; n = 3), ovarian cancer (n = 3), cervical cancer (n = 2), other cancers (n = 8), and mixed cancer types (n = 3; Table 1).

Overall, the risk of bias across studies was relatively low; one abstract and one retrospective study were rated as having a high risk of bias. The funnel plot analysis didn't indicate any evident risk of publication bias for all-grade AEs and grade ≥ 3 AEs.

Pooled incidence of TRAEs in the ICI + AI and AI groups

Collectively, 27 studies (including 9 RCTs and 18 single-arm studies involving ICI + AI, AI, and ICI regimens) reported more than 100 different types of AEs. Overall, 4,970 (96.7%) of 5,138 patients patients ICI + AI [3052 (97.0%) of 3,146 patients], AI [1,724 (98.5%) of 1,751 patients], and ICI [194 (80.5%) of 241 patients)] from the 27 studies developed at least one AE of any grade, and 2,964 (58.1%) of 5,102 patients ICI + AI [1783 (56.8%) of 3140 patients], AI [1127 (64.4%) of 1751 patients], and ICI [54 (25.6%) of 211 patients] from 27 studies developed at least one AE of grade ≥ 3.

For the meta-analysis, we focused on AEs that were reported by at least 10% of the studies or were likely to be

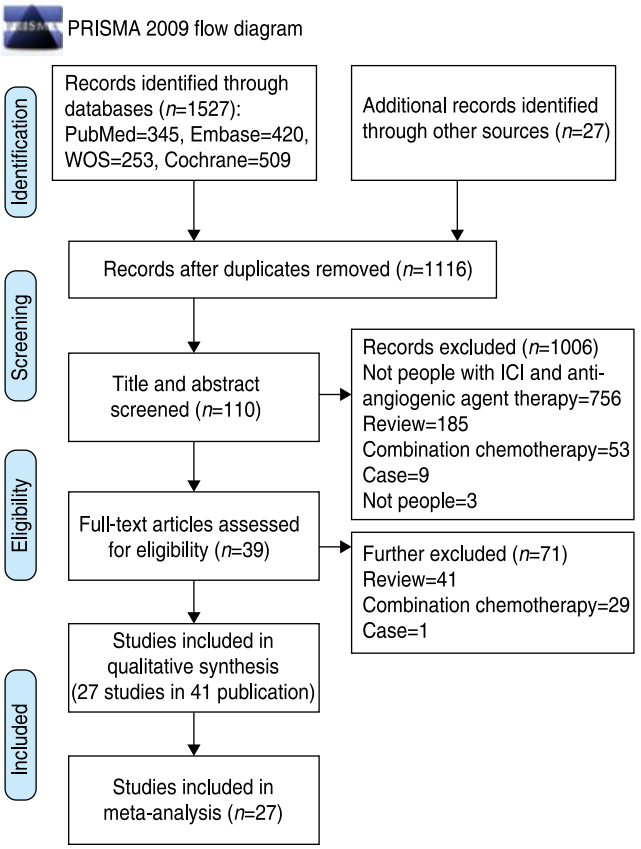


Fig. 1 Database search and study selection

TRAEs. Using these criteria, we focused on 58 AEs, which included the most clinically relevant AEs commonly seen in practice. The overall mean incidence of all-grade AEs in the ICI + AI and AI groups were 96.0% (95% CI: 94.2%–97.8%) and 98.8% (95% CI: 97.8%–99.7%), respectively, and the mean incidence of grade ≥ 3 AEs was higher in the AI group (53.9%; 95% CI: 47.4%–60.4%) than in the ICI + AI group (63.3%; 95% CI: 55.8%–70.7%). However, no significant difference in the risk of all-grade AEs and grade ≥ 3 AEs were observed between the two groups.

Common categories of AEs (grade ≥ 3) associated with ICI + AI and AI therapies

Clinicians are usually more concerned about common serious AEs; thus, we listed the top five grade ≥ 3 AEs sorted by different systems in Table 2. In the ICI + AI group, >10% of the AEs were hypertension (18.4%; 95% CI: 14.3%–22.5%), and 5%–10% AEs were rash (9.6%; 95% CI: 6.4%–12.9%), pruritus (6.9%; 95% CI: 2.8%–11%), decreased platelet count (5.6%; 95% CI: 3.40%–7.8%). Other life-threatening AEs were severe diarrhea (4.4%; 95% CI: 2.9%–5.8%), gastrointestinal hemorrhage (1.8%; 95% CI: 1.0%–4.2%), adrenal insufficiency (2.0%; 95% CI: 0.5%–3.5%), pulmonary embolism (2.1%; 95% CI: 0.7%–3.5%), and cerebrovascular accident (2.0%; 95% CI: 0.2%–3.9%). Severely abnormal biochemical indicators were increased lipase levels (5.5%; 95% CI: 2.6%–8.3%), alanine aminotransferase (ALT) elevation (5.4%; 95% CI: 3.5%–7.3%), and creatine kinase elevation (5.3%; 95% CI: 0.70%–9.9%), indicating pancreatic, liver, and cardiac damage, respectively.

In the AI group, >10% of the AEs were hypertension (16.7%; 95% CI: 14.3%–19.2%), 5%–9% AEs were decreased platelet counts (7.6%; 95% CI: 2.4%–12.9%), palmar-plantar erythrodysesthesia syndrome (PPE) (6.0%; 95% CI: 3.5%–8.6%), and anemia (5.7%; 95% CI: 3.5%–7.8%). Severely abnormal biochemical indicators were aspartate aminotransferase (AST) elevation (2.5%; 95% CI: 1.3%–3.6%) and ALT elevation (2.3%; 95% CI: 1.4%–3.3%), indicating liver injury.

Characteristics and incidence of fatal AEs (grade 5) in the ICI + AI and AI groups

(1) Eleven studies, including 2,991 patients, reported fatal AEs in the ICI + AI group, with a total of 57 deaths. The overall incidence of fatal AEs was 2.50% (57/2291). As shown in Table 3, fatal hemorrhage at any site [n = 13 (0.57%)], cardiovascular toxicities [n = 12 (0.52%)], and severe infection [n = 10 (0.44%)] accounted for more than half of the fatal AEs. Other important fatal AEs included respiratory, gastrointestinal, and hepatic toxicities, such as pneumonitis [n = 6 (0.26%)], ulcer perforation [n = 4 (0.17%)], and hepatic injury [n = 4 (0.17%)]. Myasthenia gravis and adrenal insufficiency led to 6 (0.26%) and 1 death, respectively.

(2) In the AI group, 5 studies reported at least 1 fatal AE, with a total of 20 reported deaths. The overall incidence of fatal AEs was 1.28% (20 of 1,566). The most common cause of fatal AEs in the AI group was cardiovascular toxicity [n = 8 (0.51%)], including cardiac arrest [n = 3 (0.19%)) and sudden death [n = 3 (0.19%)]; and hepatic toxicities and hemorrhage were both observed in 4 [0.26%] cases; together accounting for 80% of fatal AEs. Sudden death and cardiac arrest are common causes of medical disputes in China and thus need attention. Informing about the risk in advance rather than acting after its occurrence usually helps reduce medical disputes. As shown in Table 3 , the ICI + AI group had a significantly higher risk of fatal AEs than the AI group [57 (2.50%) *vs.* 20 (1.28%), P = 0.0041], especially with regard to respiratory toxicities [8 (0.35%) *vs.* 1 (0.06%), P = 0.04] and severe infection [10 (0.44%) *vs.* 0 (0.00%), P < 0.01].

The total number of fatal AEs in the ICI + AI group (n = 59) was slightly higher than the total number of deaths (n = 57); the percentage values were calculated from 57. One study [10] reported four treatment-related deaths that occurred in 451 patients (one patient had cerebral infarction, one patient had adrenal insufficiency and hypotension, one patient had multiple organ dysfunction

Table 1 Study characteristics

Study	NCT number	Phase	Cancer	Treatment arm	Monotherapy arm	Patients (*n*)	Number of all-grade AEs	Number of grade 3 AEs
[8]	IMmotion150	II	RCC	[a]atezolizumab+bevacizumab	[b]sunitinib	101/100	101/99	67/71
[8]	IMmotion150	II	RCC	[a]atezolizumab+bevacizumab	[a]tezolizumab	101/103	101/101	67/43
[9]	NCT02684006	Ib	RCC	[c]avelumab+axitinib	[b]sunitinib	434/439	432/436	309/314
[10]	NCT02420821	III	RCC	[a]atezolizumab+bevacizumab	[b]sunitinib	451/446	411/429	187/245
[11]	NCT02853331	III	RCC	[d]pembrolizumab+axitinib	[b]sunitinib	429/425	422/423	325/300
[12]	-	-	LUAD	ICI + AI	AI	25/49	23/39	3/3
[13]	NCT03434379	III	HCC	[a]atezolizumab+bevacizumab	[e]sorafenib	329/156	323/154	201/95
[14]	NCT02337491	II	glioblastoma	[f]pembrolizumab+bevacizumab	pembrolizumab	50/30	50/30	-
[15]	ORIENT-32	III	HCC	[g]sintilimab+bevacizumab	[e]sorafenib	380/185	376/181	217/93
[16]	NCT02715531	IB	HCC	[a]atezolizumab+bevacizumab	atezolizumab	60/58	57/52	41/24
[16]	NCT02715531	IB	HCC	atezolizumab+bevacizumab	None	104	91	55
[17]	-	-	glioblastoma	ipilimumab+bevacizumab	None	20	20	7
[18]	CheckMate 016	I	RCC	nivolumab+sunitinib	None	33	33	27
[18]	CheckMate 016	I	RCC	nivolumab+pazopanib	None	20	20	14
[19]	NCT02133742	Ib	RCC	pembrolizumab+axitinib	None	52	52	34
[20]	NCT02443324	Ia/b	mixed	pembrolizumab+ramucirumab	None	92	75	22
[21]	NCT02501096	II	endometrial cancer	pembrolizumab+lenvatinib	None	53	51	36
[22]	NCT02636725	II	sarcomas	pembrolizumab+axitinib	None	33	33	13
[23]	NCT02873962	II	ovarian cancer	nivolumab+bevacizumab	None	38	34	9
[24]	NCT02921269	II	cervical cancer	atezolizumab+bevacizumab	None	11	11	4
[25]	NCT02821000	1b	melanoma	toripalimab+axitinib	None	33	32	13
[26]	-	1b/II	mixed	pembrolizumab+lenvatinib	None	137	133	94
[27]	NCT03136627	Ib	RCC	nivolumab+tivozanib	None	25	25	20
[28]	EPOC1706	II	gastric cancer	pembrolizumab+lenvatinib	None	29	29	14
[29]	NCT02496208	I	urothelial carcinoma	nivolumab+cabozantinib	None	24	24	18
[30]	BTCRC-GU14-003	Ib/II	RCC	pembrolizumab+bevacizumab	None	60	60	27
[31]	-	II	cervical cancer	camrelizumab+apatinib	None	45	43	32
[32]	NCT01633970	Ib	ovarian cancer	atezolizumab+bevacizumab	None	20	19	7
[33]	NCT02853318	II	ovarian cancer	pembrolizumab+bevacizumab	None	40	33	13
[34]	NCT02942329	Ib	mixed	SHR-1210+apatinib	None	33	-	-

[a] atezolizumab 1200mg + bevacizumab 15mg/kg; [b] sunitinib 50mg; [c] avelumab 10mg/kg + axitinib 5mg; [d] pembrolizumab 200mg + axitinib 5mg; [e] sorafenib 400mg; [f] pembrolizumab + bevacizumab; [g] sintilimab 200mg + bevacizumab 15mg/kg; LUAD: lung adenocarcinoma cells

syndrome and post-radiation ulcer with cecum perforation, and one patient had sepsis and pneumonia). The total number of fatal AEs in the AI group was 20; the percentage values were calculated from 20.

Characteristics and risk of all-grade and grade ≥ 3 TRAEs in the ICI + AI versus AI groups in RCT studies

The meta-analysis included nine studies based on all-grade AEs, grade ≥ 3 AEs, fatal AEs, and dose modifications/interruptions. Of these, five studies compared the ICI + AI group with the AI group, three studies compared the ICI + AI group with the ICI group, and one study compared the ICI + AI group with both the AI and ICI groups.

The ICI + AI group had a higher risk in grade ≥ 3 TRAEs [RR, 1.70; (95%CI: 1.33–2.18)] (Fig. 3b) than the ICI group. However, compared to the AI group, the ICI + AI group showed no significant differences in the risk of all-grade [RR, 0.90; (95%CI: 0.97–1.01)] (Fig. 2a), grade ≥ 3 [RR, 1.00; (95%CI: 0.89–1.13)] (Fig. 3a) and fatal AEs [RR, 0.96; (95%CI: 0.59–1.58)] (Fig. 4). Compared to the ICI group, the ICI + AI group also showed no significant differences in the risk of all-grade [RR, 1.12; (95%CI: 0.94-1.32)] (Fig.2b). The ICI + AI group had similar incidences of drug discontinuation and dose modification to the AI group (RR, 1.47; 95% CI: 0.89–2.43), (RR, 0.92; 95% CI: 0.65–1.31) (Fig. 5a and 5b).

In other words, compared with AI, adding ICI to AI didn't increase the total incidence of AEs. However, analysis of the top 20 reported AEs (hypertension, fatigue, diarrhea, PPE, decreased platelet count, decreased appetite, dyspepsia, pruritis, proteinuria, hypothyroidism,

Table 2 Incidences of the most common grade ≥ 3 adverse events in the ICI + AI *vs* AI groups

Outcome	ICI + AI	AI
	Incidence (95% CI)	Incidence (95% CI)
General		
Fatigue	0.039 (0.025-0.052)	0.045 (0.031-0.058)
Weight loss	0.028 (0.019-0.037)	0.004 (0.002-0.007)
Fever	0.014 (0.004-0.025)	-
Asthenia	0.013 (0.001-0.025)	0.029 (0.019-0.040)
Decreased appetite	0.012 (0.006-0.018)	0.013 (0.004-0.022)
Gastrointestinal		
Diarrhea	0.044 (0.029-0.058)	0.039 (0.028-0.049)
Gastrointestinal hemorrhage	0.018 (0.001-0.042)	-
Colitis	0.013 (0.004-0.022)	-
Vomiting	0.010 (0.001-0.019)	0.011 (0.005-0.016)
Stomatitis	0.008 (0.004-0.013)	0.016 (0.007-0.025)
Nausea	0.007 (0.002-0.012)	0.007 (0.001-0.013)
Cutaneous		
Rash	0.096 (0.064-0.129)	0.005 (0.001-0.009)
Pruritis	0.069 (0.028-0.110)	-
PPE	0.044 (0.032-0.055)	0.060 (0.035-0.086)
Mucosal inflammation	0.006 (0.001-0.013)	-
Endocrine dysfunction		
Proteinuria	0.037 (0.025-0.048)	0.007 (0.002-0.012)
Adrenal insufficiency	0.020 (0.005-0.035)	-
Hyperthyroidism	0.006 (0.002-0.014)	-
Hypothyroidism	0.003 (0.001-0.005)	0.004 (0.001-0.009)
Pain		
Myalgia	0.024 (0.001-0.057)	-
Headache	0.022 (0.003-0.041)	-
Abdominal pain	0.014 (0.008-0.020)	0.013 (0.001-0.017)
Arthralgia	0.012 (0.007-0.018)	0.004 (0.001-0.007)
Oral pain	0.009 (0.006-0.041)	-
Respiratory		
Pulmonary embolism	0.021 (0.007-0.035)	-
Dyspnea	0.011 (0.001-0.026)	-
Cough	0.010 (0.002-0.018)	-
Pneumonia	0.010 (0.004-0.017)	-
Dysphonia	0.003 (0.001-0.007)	-
Cardiovascular		
Hypertension	0.184 (0.143-0.225)	0.167 (0.143-0.192)
Cerebrovascular accident	0.020 (0.002-0.039)	-
Hematologic		
Decreased platelet count	0.056 (0.340-0.078)	0.076 (0.024-0.129)
Leukopenia	0.030 (0.005-0.055)	-
Anemia	0.016 (0.006-0.026)	0.057 (0.035-0.078)
Neutropenia	0.010 (0.002-0.021)	0.010 (0.002-0.021)
Biochemical abnormalities		
Increased lipase	0.055 (0.026-0.083)	-
ALT elevation	0.054 (0.035-0.073)	0.023 (0.014-0.033)
Creatine kinase elevation	0.053 (0.007-0.099)	-
AST elevation	0.047 (0.029-0.064)	0.025 (0.013-0.036)
GGT elevation	0.040 (0.001-0.086)	-

Table 3 Cases and fatality rates of treatment-related deaths in clinical trials of ICI + AI and AI groups

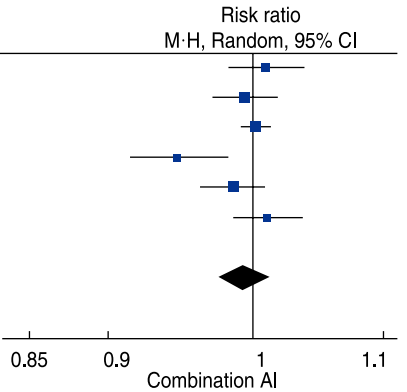
Cause of death	Number (%)		
	ICI + AI 57 (2.49)	AI 20 (1.28)	*P* value (0.0041)
Respiratory	8 (0.35)	1 (0.06)	0.04
Pneumonia	6 (0.26)	1 (0.06)	0.08
Respiratory distress	1 (0.04)	0 (0.00)	0.20
Respiratory failure	1 (0.04)	0 (0.00)	0.20
Cardiovascular	12 (0.52)	8 (0.51)	0.48
Sudden death	4 (0.17)	3 (0.19)	0.45
Cardiac arrest	2 (0.09)	3 (0.19)	0.19
Myocarditis	2 (0.09)	0 (0.00)	0.12
Myocardial infarction	1 (0.04)	1 (0.06)	0.39
Hypotension	1 (0.04)	0 (0.00)	0.20
Thromboembolic event	1 (0.04)	0 (0.00)	0.20
Heart failure	0 (0.00)	1 (0.06)	0.11
Hemorrhage	13 (0.57)	4 (0.26)	0.08
Gastrointestinal hemorrhage	6 (0.26)	1 (0.06)	0.08
Intracranial hemorrhage	4 (0.17)	2 (0.13)	0.36
Pulmonary hemorrhage	1 (0.04)	0 (0.00)	0.20
Esophageal varices hemorrhage	1 (0.04)	0 (0.00)	0.20
Hematemesis	1 (0.04)	0 (0.00)	0.20
Peritoneal hemorrhage	0 (0.00)	1 (0.06)	0.11
Gastrointestinal	6 (0.26)	1 (0.06)	0.08
Ulcer perforation	4 (0.17)	1 (0.06)	0.17
Necrotizing pancreatitis	1 (0.04)	0 (0.00)	0.20
Bowel obstruction	1 (0.04)	0 (0.00)	0.20
Hepatic	8 (0.35)	4 (0.26)	0.30
Liver injury	4 (0.17)	2 (0.13)	0.36
Hepatic cirrhosis	2 (0.09)	2 (0.13)	0.35
Hepatic failure	2 (0.09)	0 (0.00)	0.12
Cerebrovascular	1 (0.04)	0 (0.00)	0.20
Cerebral infarction	1 (0.04)	0 (0.00)	0.20
Sever infectious	10 (0.44)	0 (0.00)	< 0.01
Sepsis	5 (0.22)	0 (0.00)	0.03
Bacterial peritonitis	2 (0.09)	0 (0.00)	0.12
Empyema	1 (0.04)	0 (0.00)	0.20
Necrotizing fasciitis	1 (0.04)	0 (0.00)	0.20
Bacteremia	1 (0.04)	0 (0.00)	0.20
Other	3 (0.13)	2 (0.13)	0.49
Myasthenia gravis	1 (0.04)	0 (0.00)	0.20
Adrenal insufficiency	1 (0.04)	0 (0.00)	0.20
MODS	1 (0.04)	0 (0.00)	0.20
General physical health deterioration	0 (0.00)	1 (0.06)	0.11
Malignant neoplasm progression	0 (0.00)	1 (0.06)	0.11

stomatitis, arthralgia, mucosal inflammation, rash, elevated liver enzymes, dysphonia, anemia, constipation, headache, neutropenia), revealed differences between them. When ICI was added to AI, some AEs increased in line with our speculation; however, other AEs decreased beyond our expectations. (1) For all-grade AEs, ICI + AI group displayed significantly higher rates of dysphonia

a

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M·H, Random, 95% CI
David1	101	101	99	100	15.3%	1.01 [0.98, 1.04]
Finn	323	329	154	156	16.9%	0.99 [0.97, 1.02]
Motzer	432	434	436	439	21.3%	1.00 [0.99, 1.01]
Rinia	411	451	429	446	13.0%	0.95 [0.92, 0.98]
Rinib	413	429	415	425	16.7%	0.99 [0.96, 1.01]
Zhengguang	376	380	181	185	16.7%	1.01 [0.99, 1.04]
Total (95% CI)		2124		1751	100.0%	0.99 [0.97, 1.01]
Total events	2056		1714			

Heterogeneity: Tau²=0.00; Chi²=22.55, df=5 (*P*=0.0004); I²=78%
Test for overall effect: Z=0.67 (*P*=0.50)



b

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M·H, Random, 95% CI
David2	101	101	101	103	31.9%	1.02 [0.99, 1.05]
Di huang	23	25	39	49	23.4%	1.16 [0.96, 1.39]
Lee	41	60	24	59	13.3%	1.68 [1.18, 2.39]
Nayak	50	50	30	30	31.3%	1.00 [0.95, 1.05]
Total (95% CI)		236		241	100.0%	1.12 [0.94, 1.32]
Total events	215		194			

Heterogeneity: Tau²=0.02; Chi²=53.22, df=3 (*P*=0.00001); I²=94%
Test for overall effect: Z=1.27 (*P*=0.20)

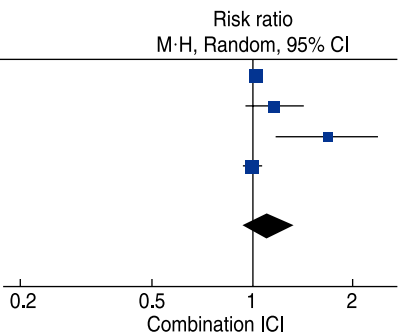
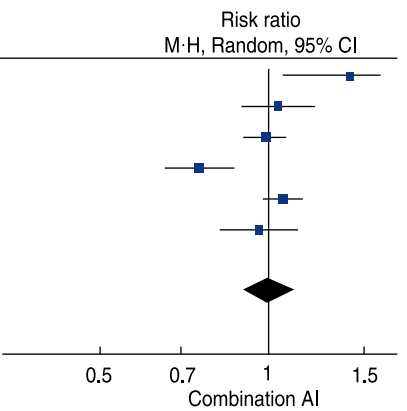


Fig. 2 Risk of all-grade AEs in combination therapy vs. monotherapy (a) show all-grade AEs in combination therapy vs. AI therapy. (b) show all-grade AEs in combination therapy vs. ICI therapy.

a

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M·H, Random, 95% CI
David1	60	101	42	100	9.9%	1.41 [1.07, 1.87]
Finn	211	329	95	156	16.5%	1.05 [0.91, 1.22]
Motzer	309	434	314	439	20.1%	1.00 [0.92, 1.08]
Rinia	187	451	245	446	17.2%	0.75 [0.66, 0.87]
Rinib	325	429	300	425	20.2%	1.07 [0.99, 1.16]
Zhengguang	217	380	93	158	16.1%	0.97 [0.83, 1.13]
Total (95% CI)		2124		1724	100.0%	1.00 [0.89, 1.13]
Total events	1309		1089			

Heterogeneity: Tau²=0.02; Chi²=25.85, df=5 (*P*<0.0001); I²=81%
Test for overall effect: Z=0.05 (*P*=0.96)



b

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M·H, Random, 95% CI
David2	67	101	43	103	85.7%	1.59 [1.22, 2.08]
Di huang	3	25	3	49	2.6%	1.96 [0.43, 9.02]
Lee	22	60	8	59	11.6%	2.70 [1.31, 5.58]
Total (95% CI)		186		211	100.0%	1.70 [1.33, 2.18]
Total events	92		54			

Heterogeneity: Tau²=0.00; Chi²=1.97, df=2 (*P*=0.37); I²=0%
Test for overall effect: Z=4.20 (*P*<0.0001)

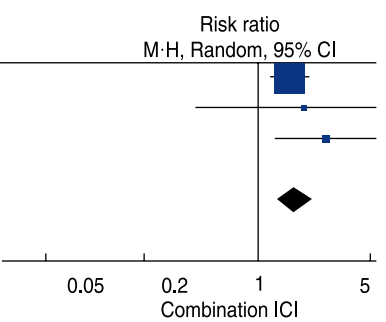


Fig. 3 Risk of grade ≥ 3 AEs in combination vs monotherapy (a) show grade ≥ 3 AEs in combination therapy vs. AI therapy. (b) show grade ≥ 3 AEs in combination therapy vs. ICI therapy

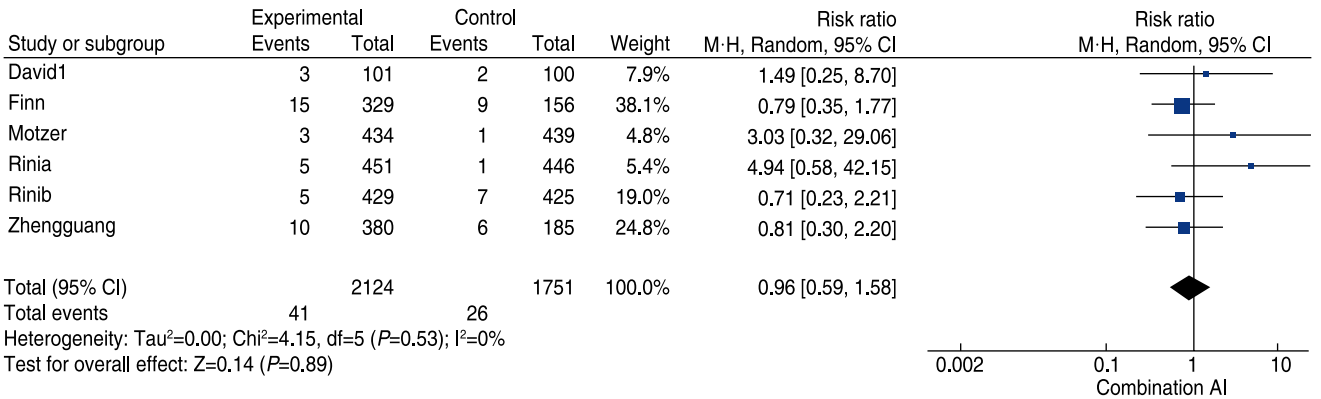


Fig. 4 Risk of treatment-related deaths in combination therapy vs. monotherapy

(21.90% *vs* 3.40%; 95% CI: 2.86–12.46, $P < 0.001$), proteinuria (20.40% *vs* 7.90%; 95% CI: 1.67–4.80, $P = 0.0001$), pruritis (17.00% *vs* 6.00%; 95% CI: 2.18–3.40, $P < 0.001$), arthralgia (18.40% *vs* 8.00%; 95% CI: 1.72–3.17, $P < 0.001$), ALT elevation (19.70% *vs* 12.50%; 95% CI: 1.35–2.01, $P < 0.001$), AST elevation (20.10% *vs* 14.40%; 95% CI: 1.12–1.69, $P = 0.002$), fatigue (33.6% *vs* 27.3%; 95% CI: 1.02–1.64, $P = 0.04$), and headache (16.8% *vs* 13.7%; 95% CI: 1.01–1.52, $P = 0.04$). In contrast, the ICI + AI group reported lower rates of PPE (16.6% *vs* 35.9%; 95% CI: 0.08–0.50, $P < 0.0006$), neutropenia (1.2% *vs* 16.6%; 95% CI: 0.05–0.13, $P < 0.001$), decreased platelet counts (4.9% *vs* 15.5%; 95% CI: 0.09–0.97, $P = 0.04$), anemia (5.7% *vs* 20.4%; 95% CI: 0.22–0.36, $P < 0.001$), mucosal inflammation (12.1% *vs* 22.0%; 95% CI: 0.32–0.92, $P = 0.02$), stomatitis (15.9% *vs* 22.4%; 95% CI: 0.44–0.99, $P = 0.04$) and dyspepsia (5.1% *vs* 16.6%; 95% CI: 0.16–0.53, $P < 0.001$). (2) For grade ≥ 3 AEs, the ICI + AI group induced significantly higher rates of proteinuria (3.0% *vs* 0.9%; 95% CI: 1.42–7.18, $P = 0.005$) and liver enzymes (ALT elevation (8.0% *vs* 2.5%; 95% CI: 2.17–5.12, $P < 0.001$) and AST elevation (5.9% *vs* 2.6%; 95% CI: 1.29–3.20, $P = 0.002$)) but had lower rates of fatigue (2.4% *vs* 4.4%; 95% CI: 032–0.93, $P = 0.03$), neutropenia (0.3% *vs* 6.1%; 95% CI: 0.02–0.16, $P < 0.001$), anemia (0.8% *vs* 5.8%; 95% CI: 0.08–0.30, $P < 0.001$), and decreased platelet count (0.3% *vs* 24.5%; 95% CI: 0.02–0.21, $P < 0.001$) (Table 4).

Discussion

The overall response rate to ICI remains suboptimal [3]. AI drugs have been shown to synergize with ICIs in multiple cancers. However, TRAEs resulting from the combination of these two modalities aren't fully understood. Although the toxicity profile of this new treatment is favorable, a unique set of AEs including fatal hemorrhage, liver injury, severe infection, and pneumonitis has been observed. To help clinicians better understand the safety data of ICI + AI therapy and learn more about the toxicity of this new regimen, we conducted this systematic review and meta-analysis. To the best of our knowledge, our meta-analysis is the largest and most comprehensive study on the TRAEs associated with ICI + AI therapy.

Compared with traditional chemotherapy, AI or ICI + AI treatment has shown advantages in safety and efficacy in many cancer types [9, 11, 16, 18, 35–37]. However, more than 90% of patients suffered all-grade AEs, and grade ≥ 3 AEs were reported in more than 50% of cancer patients. From the standpoint of patients and clinicians, we cannot ignore TRAEs and should pay attention to toxicity monitoring and control.

In the analysis of the top 20 reported all-grade AEs, we observed that adding ICI to AI increased the incidence rates of proteinuria, liver injury, dysphonia, pruritis, arthralgia, fatigue, and headache. This reminds clinicians of the following when using ICI + AI therapy: (1) For symptoms that may lead to serious organ injury and adverse clinical outcomes, such as proteinuria (20.40%), liver injury [AST elevation (20.10%)], and ALT elevation (19.70%), monitoring of these AEs and medication optimization are suggested. (2) Symptoms that may affect a patient's quality of life, such as dysphonia (increased from 3% to 22%), pruritus (increased from 6% to 17%), arthralgia (increased from 8% to 18%), fatigue (increased from 27% to 33%), and headache (increased from 13% to 16%), should be shared with patients before they accept ICI + AI treatment, and symptomatic treatment and management need to be strengthened during treatment [3]. Interestingly, compared to the AI group, the ICI + AI group had lower rates of PPE, hematologic toxicity (neutropenia, decreased platelet counts, anemia), mucosal inflammation, and stomatitis. The mechanisms involved are currently unclear, probably because in the ICI + AI group, AIs (such as bevacizumab and axitinib) [9, 16] had lower blood, skin, and mucosal toxicities than those used

Table 4 Significantly different adverse effects (all-grade and grade ≥ 3) associated with ICI + AI vs AI

Items	ICI + AI group (event/total)	AI group (event/total)	RR (95% CI)	*P* value	Heterogeneity	
					I^2 (%)	*P* value
All-grade adverse effects						
Dysphonia	288/1314	44/1310	5.97 (2.86–12.46)	< 0.001	82	0.004
Proteinuria	267/1310	89/1127	2.83 (1.67–4.80)	0.0001	78	0.004
Pruritis	297/1744	94/1566	2.72 (2.18–3.40)	< 0.001	0	0.42
Arthralgia	261/1415	113/1410	2.34 (1.72–3.17)	< 0.001	51	0.11
ALT elevation	235/1192	128/1020	1.65 (1.35–2.01)	< 0.001	0	0.72
AST elevation	239/1192	147/1020	1.38 (1.12–1.69)	0.002	14	0.31
Fatigue	79/235	66/242	1.29 (1.02–1.64)	0.04	0	0.59
Headache	238/1415	193/1410	1.24 (1.01–1.52)	0.04	23	0.07
PPE	290/1744	562/1566	0.20 (0.08–0.50)	0.0006	97	< 0.001
Mucosal inflammation	171/1415	310/1410	0.54 (0.32–0.92)	0.02	88	< 0.001
Neutropenia	16/1314	218/1310	0.08 (0.05–0.13)	< 0.001	0	0.48
Decreased platelet count	59/1192	158/1020	0.29 (0.09–0.97)	0.04	92	< 0.001
Anemia	75/1314	267/1310	0.28 (0.22–0.36)	< 0.001	0	0.42
Stomatitis	225/1415	316/14410	0.66 (0.44–0.99)	0.04	83	0.0005
Dyspepsia	67/1314	217/1310	0.29 (0.16–0.53)	< 0.001	78	0.01
Grade 3 adverse effects						
Proteinuria	36/1209	9/1027	3.19 (1.42–7.18)	0.005	9	0.33
ALT elevation	95/1192	26/1020	3.33 (2.17–5.12)	< 0.001	0	0.42
AST elevation	70/1192	27/1020	2.03 (1.29–3.20)	0.002	7	0.34
Fatigue	41/1744	69/1566	0.55 (0.32–0.93)	0.03	41	0.16
Neutropenia	4/1314	80/1310	0.06 (0.02–0.16)	< 0.001	0	0.43
Anemia	11/1314	76/1310	0.16 (0.08–0.30)	< 0.001	0	0.46
Decreased platelet count	4/1314	76/1310	0.07 (0.02–0.21)	< 0.001	13	0.32

in the AI group (such as sunitinib and sorafenib) [15, 38], as shown in Table 1.

This meta-analysis showed that the ICI + AI group had a significantly higher risk of fatal AEs than the AI group, especially for respiratory toxicities and severe infections. Moreover, cardiovascular events, hemorrhage, and liver injury were the most common fatal AEs in both groups. Based on our results, we suggest that (1) for both ICI + AI and AI groups, clinicians need to closely monitor the symptoms or signs associated with hemorrhage, blood pressure (BP), ECG recordings, and liver function of patients; (2) for the ICI + AI group, clinicians need additional monitoring of symptoms or signs associated with respiratory system toxicity (e.g., dyspnea, dyspnea, and cough) [39] and indices of severe infection (such as C-reactive protein, procalcitonin, blood lactate, and index of fungal infection) [40]. Such knowledge is essential for identifying potentially fatal AEs, and early recognition and prompt treatment of fatal AEs are warranted; and (3) some fatal AEs, such as adrenal insufficiency, necrotizing pancreatitis, myasthenia gravis, cardiac arrest, thromboembolic events, and myocarditis, are relatively rare and tend to be overlooked by clinicians. If clinicians can keep these rare fatal AEs in mind, the rate of missed diagnoses can be reduced.

Moreover, what is particularly interesting is that the incidence of severe infections in the ICI + AI group was significantly higher than that in the AI group. We speculated that PD1/PDL1 inhibitors activate immune killer cells, which is beneficial for anti-tumor therapy; however, activation of the immune system may amplify microorganisms associated with immune damage. For example, vaccination of patients with COVID-19 with cancer will cause CRS, a vaccine-related adverse event, and anti-PD1 blockade is a potential contributor [41].

This study had some limitations. First, in RCTs, the AIs used in the ICI + AI group were different from those used in the AI group, which may have influenced the comparison results. Furthermore, the type of cancer was limited in the present study, and it is uncertain whether the results are consistent with those of other cancer types. Finally, although the number of cases was large, it was not sufficient to represent the real world and special patients. It is necessary to continue follow-up research reports to further improve ICI + AI adverse reaction cognition.

Conclusion

Clinicians should pay close attention to monitoring AEs associated with ICI + AI treatment. Understanding the characteristics of severe or fatal AEs is necessary because prompt diagnosis and optimal treatment of severe AEs are important to improve patient survival.

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Conflicts of interest
The authors indicated no potential conflicts of interest.

Author contributions
All authors contributed to data acquisition and interpretation and reviewed and approved the final version of this manuscript.

Data availability statement
Not applicable.

Ethical approval
Not applicable.

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