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META-ANALYSIS

Cardiac adverse events of immune checkpoint inhibitors in oncology patients: A systematic review and meta-analysis

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Abstract

BACKGROUND

Immune checkpoint inhibitors (ICIs) are novel therapeutic agents used for various types of cancer. ICIs have revolutionized cancer treatment and improved clinical outcomes among cancer patients. However, immune-related adverse effects of ICI therapy are common. Cardiovascular immune-related adverse events (irAEs) are rare but potentially life-threatening complications.

AIM

To estimate the incidence of cardiovascular irAEs among patients undergoing ICI therapy for various malignancies.

METHODS

We conducted this systematic review and meta-analysis by searching PubMed, Cochrane CENTRAL, Web of Science, and SCOPUS databases for relevant

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interventional trials reporting cardiovascular irAEs. We performed a single-arm meta-analysis using OpenMeta [Analyst] software of the following outcomes: Myocarditis, pericardial effusion, heart failure, cardiomyopathy, atrial fibrillation, myocardial infarction, and cardiac arrest. We assessed the heterogeneity using the *I2* test and managed to solve it with Cochrane's leave-one-out method. The risk of bias was performed with the Cochrane's risk of bias tool.

RESULTS

A total of 26 studies were included. The incidence of irAEs follows: Myocarditis: 0.5% [95% confidence interval (CI): 0.1%-0.9%]; Pericardial effusion: 0.5% (95%CI: 0.1%-1.0%); Heart failure: 0.3% (95%CI: 0.0%-0.5%); Cardiomyopathy: 0.3% (95%CI: -0.1%-0.6%); atrial fibrillation: 4.6% (95%CI: 1.0%-14.1%); Myocardial infarction: 0.4% (95%CI: 0.0%-0.7%); and Cardiac arrest: 0.4% (95%CI: 0.1%-0.8%).

CONCLUSION

The most common cardiovascular irAEs were atrial fibrillation, myocarditis, and pericardial effusion. Although rare, data from post market surveillance will provide estimates of the long-term prevalence and prognosis in patients with ICI-associated cardiovascular complications.

Key Words: Atrial fibrillation; Cancer; Immune checkpoint inhibitors; Immunotherapy; Cardiovascular adverse events; Pericardial effusion

Core Tip: Cardiovascular immune-related adverse events (irAEs) are rare but potentially life-threatening complications that can occur in patients receiving immune checkpoint inhibitor (ICI) therapy. The most common ICI-associated adverse events are atrial fibrillation, myocarditis, and pericardial effusion. Risk factors for cardiovascular irAEs include treatment with combination immunotherapy, male sex, and a history of cardiac disease. Ongoing post-market surveillance is imperative to characterize long-term risks and improve outcomes among patients receiving ICIs.

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have demonstrated remarkable efficacy in various malignancies, including lung cancer, melanoma, Hodgkin's lymphoma, bladder cancer, and microsatellite instability[1]. ICIs exert their effects through blocking inhibitory receptors on tumor cells [programmed cell death 1 Ligand-1 (PD-L1)][2,3] or T-lymphocytes [programmed cell death protein-1 (PD-1) or cytotoxic T lymphocyte-associated protein-4 (CTLA-4)][4,5]. The blockade of these receptors activates the effector T cells to target neoplastic cells[2]. Many studies have demonstrated significant survival benefits of ICIs[6-8] and over 1200 trials are currently ongoing[9].

The mechanism of action of ICIs involves non-specific activation of the immune system[10]. Consequently, autoimmune inflammatory reactions frequently occur; this can ultimately lead to a broad spectrum of immune-related adverse events (irAEs) affecting both on-target and off-target organs[11]. Reactions involving the skin, gastrointestinal tract, and endocrine system are relatively common among cancer patients on ICIs[12,13]. Approximately 80% of patients treated with agents targeting CTLA-4, 70% of patients treated with anti-PD-1 drugs, and 40% of those treated with anti-PD-L1 agents develop irAEs[13,14]. Severe events are common and up to 40% of patients on ICIs require treatment discontinuation due to irAEs[10].

Cardiovascular irAEs are rare, but potentially life-threatening[15]. Although the initial trials on ICIs did not assess myocardial activity, growing evidence from case reports, case series, and cohort studies have raised awareness of unexpected cardiac toxicities associated with ICI therapy[16-18]. Dual therapy appears to markedly increase the risk of cardiovascular irAEs; using the Bristol-Myers Squibb safety database, the estimated rate of myocarditis in patients receiving combination immunotherapy (ipilimumab plus nivolumab) was 0.27% as compared to 0.06% in those receiving nivolumab monotherapy[18].

Data on other ICI-related cardiac toxicities are scarce. This study aims to provide high-class evidence on the incidence of ICI-related cardiovascular adverse events through a systematic review and meta-analysis.

MATERIALS AND METHODS

This systematic review and meta-analysis complies with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[19] and Cochrane's Handbook of Systematic Reviews of Interventions[20].

Eligibility criteria

Our analysis included interventional trials involving patients receiving an ICI in which an adverse cardiovascular event was reported. We excluded the following: Non-randomized trials, trials involving concurrent use of other anticancer interventions, animal studies, non-clinical studies, reviews, and meta-analyses. We also excluded studies without accessible data, conference abstracts, and studies for which there was no English language translation.

Literature search

We searched PubMed, Cochrane CENTRAL, SCOPUS, and Web of Science databases for possible included articles according to our eligibility criteria from May 1st, 2020 through May 15th, 2020. We retrieved articles using a combination of the following keywords: "cardiotoxicity", "adverse", "events", "myocard*", "pericard*", "neoplasm", "cancer", and "immune checkpoint inhibitor."

Study selection, data collection, and analysis

Screening of results: We performed the screening of retrieved studies through two stages. The first stage involved the inclusion and exclusion of studies based on title and abstract review. Selected studies underwent full-text screening against the inclusion criteria. Studies that had a mismatch with a single inclusion criterion were excluded. We conducted another search through the references of the included trials to ensure that no trials were inadvertently excluded. We considered studies which included multiple treatment arms as separate studies based on the adverse event reporting and refer to them as first author last name, year of publication followed by a, b, or c in the forest plot diagrams and Table 1[3,6-8,21-42]. Figure 1 shows a PRISMA flow chart of the literature search.

Data extraction: We used a data extraction form specifically designed for this study. Three main categories of data were extracted. The first category included baseline data about the study participants, such as patients' age, gender, cancer type, and drug administered and dose. The second category included different outcome endpoints for analysis (any reported cardiovascular adverse event). The third category involved data used to assess the risk of bias among the included studies.

Quality and risk of bias assessment: This systematic review and meta-analysis were conducted in accordance with the principles of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). We included clinical trials only to ensure high-quality evidence. For assessment of the risk of bias, we used the Cochrane's Risk of Bias tool[43].

Statistical analysis

The extracted data were restricted to dichotomous outcomes, as all the data for the analysis are adverse events expressed as events/total. Using the OpenMeta[Analyst] Software, the intended scores were pooled as risk ratios (RR), and the presence of heterogeneity was assessed using two main tests[44], the I-square test (I^2) and the P value of the Chi-square test. The analysis is said to be heterogeneous if values of I^2 >

Table 1 Summary of baseline characteristics of included studies, *n* (%)

Study	*n*	ICI	Cancer type	Males	Median age (range), yr	Median follow-up (range), mo	Race, Asian	Race, Black	Tobacco users
Antonia *et al*[8], 2016a	98	Nivolumab	Small cell carcinoma of the lung	61 (62)	63 (57-68)	10.07 (NR)	NR	3 (3)	95 (97)
Antonia *et al*[8], 2016b	61	Nivolumab plus ipilimumab	Small cell carcinoma of the lung	35 (57)	66 (58-71)	12.03 (9.10-15.67)	NR	1 (2)	57 (93)
Antonia *et al*[8], 2016c	54	Nivolumab plus ipilimumab	Small cell carcinoma of the lung	32 (59)	61 (56-65)	8.68 (8.27-9.6)	NR	0	48 (89)
Antonia *et al*[21], 2017	476	Durvalumab	Stage III non-small cell lung cancer	334 (70.2)	64 (NR)	14.5 (0.2-29.9)	120 (25.2)	12 (2.5)	433 (91)
Balar *et al*[22], 2017	370	Pembrolizumab plus cisplatin	Advanced, unresectable metastatic urothelial cancer	286 (77)	74 (34-94)	5 (30-8.6)	NR	NR	NR
Barlesi *et al*[23], 2018	393	Avelumab	Advanced non-small-cell lung cancer	269 (68)	64 (59-70)	18.9 (IQR 13.2-23)	102 (26)	5 (1)	324 (82)
Bott *et al*[24], 2018	21	Nivolumab	Resectable non–small cell lung cancer	10 (48)	67 (55-84)	1.1 (0.57-1.13)	NR	NR	18 (86)
Brohl *et al*[25], 2016	31	Ipilimumab plus peginterferon	Unresectable melanoma	18 (58.1)	65 (38-83)	35.8 (19.7-50.2)	NR	NR	NR
Cho *et al*[26], 2018	33	Pembrolizumab	Relapsed thymic epithelial tumor	21 (63.6)	57 (26-78)	14.9 (IQR 6.25-20.7)	NR	NR	NR
Choueiri *et al*[3], 2018	55	Avelumab plus axitinib	Advanced clear cell renal cell carcinoma	42 (76)	60 (55–68)	13 (9.35-14.02)	6 (11)	3 (6)	NR
Chung *et al*[27], 2019	11	p53MVA vaccine combined with pembrolizumab	Advanced breast, pancreatic, hepatocellular, or head and neck cancer	NR	NR	16.26 (15.42-17.27)	NR	NR	NR
Dudnik *et al*[28], 2018	260	Nivolumab	Non-small cell lung cancer	176 (68)	67 (41-99)	8.4 (2-16.8)	NR	NR	197 (76)
Eggermont *et al*[29], 2015	475	Ipilimumab	High-risk stage III melanoma	296 (62)	51 (20-84)	7.5 (7-11.4)	NR	NR	NR
Giaccone *et al*[30], 2018	40	Pembrolizumab	Thymic carcinoma	28 (70)	57 (25-80)	8.4 (2-16.8)	4 (10)	2 (5)	NR
Herbst *et al*[31], 2020	26	Ramucirumab plus pembrolizumab	Advanced non-small-cell lung cancer	21 (78)	65 (56-72)	33.3 (IQR 27.7-39.2)	NR	1 (4)	26 (96)
Hodi *et al*[32], 2018	313	Nivolumab plus ipilimumab	Advanced melanoma	NR	NR	20 (IQR 14-26)	NR	NR	NR
Juergens *et al*[7], 2020	136	Durvalumab with or without tremelimumab and platinum-doublet	Lung cancer (unspecified)	67 (49)	61.9 (30.1-83.2)	32.8 (IQR 28.1-33.6)	8 (6)	1 (1)	NR
Loi *et al*[33], 2019	58	Pembrolizumab plus trastuzumab	Lung cancer (unspecified)	0	52 (43-92)	46.9 (48-NR)	NR	NR	NR
Maio *et al*[34], 2017	382	Tremelimumab	Malignant mesothelioma	283 (74)	66 (60-72)	19.61 (0.23-26.48)	7 (2)	3 (< 1%)	NR
Mateos *et al*[35], 2019	125	Pembrolizumab plus pomalidomide and dexamethasone	Multiple myeloma	77 (62)	65 (60-72)	25.7 (IQR 25.6-25.8)	NR	NR	NR
Motzer *et al*[36], 2019	550	Nivolumab plus ipilimumab	Advanced renal cell carcinoma	NR	NR	2 (1-3)	NR	NR	NR
Sarocchi *et al*[37], 2018	59	Nivolumab	Advanced non-small cell lung cancer	41 (NR)	69 (44-81)	8.1 (IQR 4.5-10.9)	NR	NR	51 (86)
Scherpereel *et al*[6], 2019	63	Nivolumab or nivolumab plus ipilimumab	Relapsed malignant pleural mesothelioma	47 (75)	72.3 (32.5-87)	32.4 (IQR 13.4-36.3)	NR	NR	34 (54)
Tawbi *et al*[38], 2018	94	Nivolumab plus ipilimumab	Melanoma with brain metastases	65 (69)	59 (22-81)	NR	NR	NR	NR
Ueno *et al*[39],	30	Nivolumab alone	Unresectable or recurrent	NR	NR	20.1 (IQR 19.6-	NR	NR	NR

2019a			biliary tract cancer			20.3)			
Ueno *et al*[39], 2019b	30	Nivolumab in combination with cisplatin	Unresectable or recurrent biliary tract cancer	NR	NR	14 (6-NR)	NR	NR	NR
Usmani *et al*[40], 2019a	151	Pembrolizumab	Multiple myeloma	70 (46)	74 (70-79)	5.1 (IQR 3.4-7)	NR	NR	NR
Usmani *et al*[40], 2019b	150	Lenalidomide	Multiple myeloma	71 (47)	74 (70-78	8.2 (IQR 7-14)	NR	NR	NR
Wrangle *et al*[41], 2018	21	ALT-803, an IL-15 superagonist, in combination with nivolumab	Metastatic non-small cell lung	15 (71)	55 (46-67)	6.6 (IQR 3.4-9.6)	NR	NR	12 (57)
Yang *et al*[42], 2018a	42	Preoperative chemotherapy	Non-small cell lung cancer	21 (50)	NR	6.6 (IQR 3.4-9.6)	NR	7 (17)	NR
Yang *et al*[42], 2018b	13	Ipilimumab	Non-small cell lung cancer	5 (38)	NR	6.9 (IQR 5.5-12.0)	NR	3 (23)	NR

ICI: Immune checkpoint inhibitor; NR: Not report; IQR: Inter-quartile range.

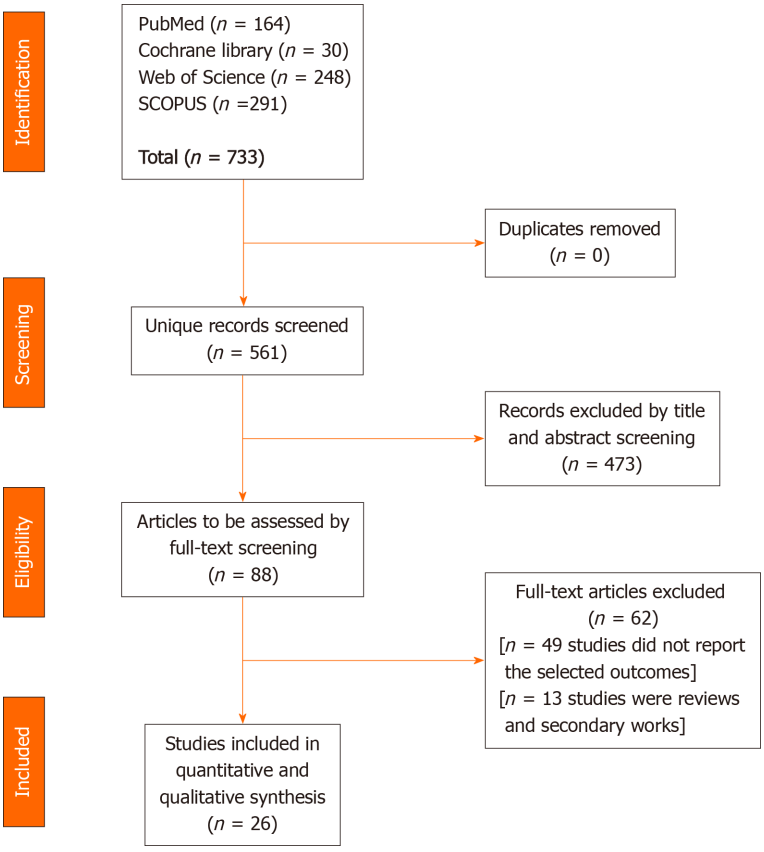

Figure 1 PRISMA diagram for our literature search.

50% and $P < 0.1$ were present, according to the Cochrane Handbook[20]. We performed the analysis of homogeneous data under a fixed-effects model, while heterogeneous data were analyzed under the random-effects model.

RESULTS

Summary of included studies

We present the analysis of 4622 cancer patients from 26 studies. Figure 1 presents a flow diagram of the number of studies at each stage of the study selection process. Males were slightly overrepresented as compared to females [2420 (52.4%) *vs* 2202

(47.6%)]. The mean age was 63.7 years. Further details pertaining to study characteristics, cancer type, ICI administered, and demographic data are illustrated in Table 1.

Results of risk of bias

The overall risk of bias was high among the included studies. Studies reported various data regarding randomization of patients, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, attrition bias, and selective reporting. The risk of bias status is summarized in Figure 2.

Results of analysis of outcomes

Incidence of myocarditis: Twelve studies reported the incidence of myocarditis as a cardiovascular irAE. The overall effect estimate showed that the incidence of myocarditis was 0.5%; the analysis was significant (95%CI: 0.1%-0.9%) and homogeneous (I^2 = 0%, P = 0.5) (Figure 3).

Incidence of pericardial effusion: Nine studies reported the incidence of pericardial effusion as a cardiovascular irAE. The overall effect estimate showed that the incidence of pericardial effusion was 0.5%; the analysis was significant (95%CI: 0.1%-1.0%) and homogeneous (I^2 = 36.7%, P = 0.1) (Figure 4).

Incidence of heart failure: Seven studies reported the incidence of heart failure as a cardiovascular irAE. The overall effect estimate showed that the incidence of heart failure was 0.3%; the analysis was homogeneous (I^2 = 0%, P = 0.1) but not significant (95%CI: 0.0%-0.5%) (Figure 5).

Incidence of cardiomyopathy: Five studies reported the incidence of cardiomyopathy as a cardiovascular irAE. The overall effect estimate showed that the incidence of cardiomyopathy was 0.3%; the analysis was homogeneous (I^2 = 0%, P = 0.6) but not significant (95%CI: -0.1%-0.6%) (Figure 6).

Incidence of atrial fibrillation: Four studies reported the incidence of atrial fibrillation as a cardiovascular irAE. The overall effect estimate showed that the incidence of atrial fibrillation was 7.6%; the analysis was significant (95%CI: 1.0%-14.1%) and heterogeneous (I^2 = 66%, P = 0.02) (Figure 7A). Using Cochrane's leave-one-out method, we solved the heterogeneity by excluding one study (Bott *et al*). Homogeneous results revealed an incidence rate of atrial fibrillation of 4.6%. The results were not significant (95%CI: -0.2%-9.4%) (Figure 7B).

Incidence of myocardial infarction: Six studies reported the incidence of myocardial infarction as a cardiovascular irAE. The overall effect estimate showed that the incidence of MI was 0.4%; the analysis was homogeneous (I^2 = 0%, P = 0.1) but not significant (95%CI: 0.0%-0.7%) (Figure 8).

Incidence of cardiac arrest: Four studies reported the incidence of cardiac arrest as a cardiovascular irAE. The overall effect estimate showed that the incidence of cardiac arrest was 0.4%; the analysis was significant (95%CI: 0.1%-0.8%) and homogeneous (I^2 = 0%, P = 0.6) (Figure 9).

DISCUSSION

Cardiotoxicity is a rare but potentially fatal adverse effect of ICI therapy. The incidence of cardiovascular irAEs remains to be established[45]. Our meta-analysis of 26 studies including a total of 4622 ICI-treated cancer patients showed that 0.5% of cancer patients treated with ICIs developed myocarditis, 0.3% developed heart failure, and 4.6% developed atrial fibrillation. In addition, pericardial effusion occurred in 0.5% of patients, cardiomyopathy in 0.3% of patients, myocardial infarction in 0.4% of patients, and cardiac arrest in 0.4% of patients. These results are relatively consistent as evidenced by the low level of statistical heterogeneity.

The underlying pathogenesis of cardiovascular irAEs has yet to be fully elucidated. However, several mechanisms have been proposed. The most frequently postulated mechanism underlying myocarditis is that T-lymphocytes could target an antigen common to both neoplastic tissue and the heart. Indeed, in a recent report by Johnson *et al*[18] the authors described a common high-frequency T-lymphocyte sequence found in both tumor and cardiac muscles. Preclinical studies of mouse models have also shown that PD-1 and CTLA-4 deficiency is associated with myocarditis. The deletion

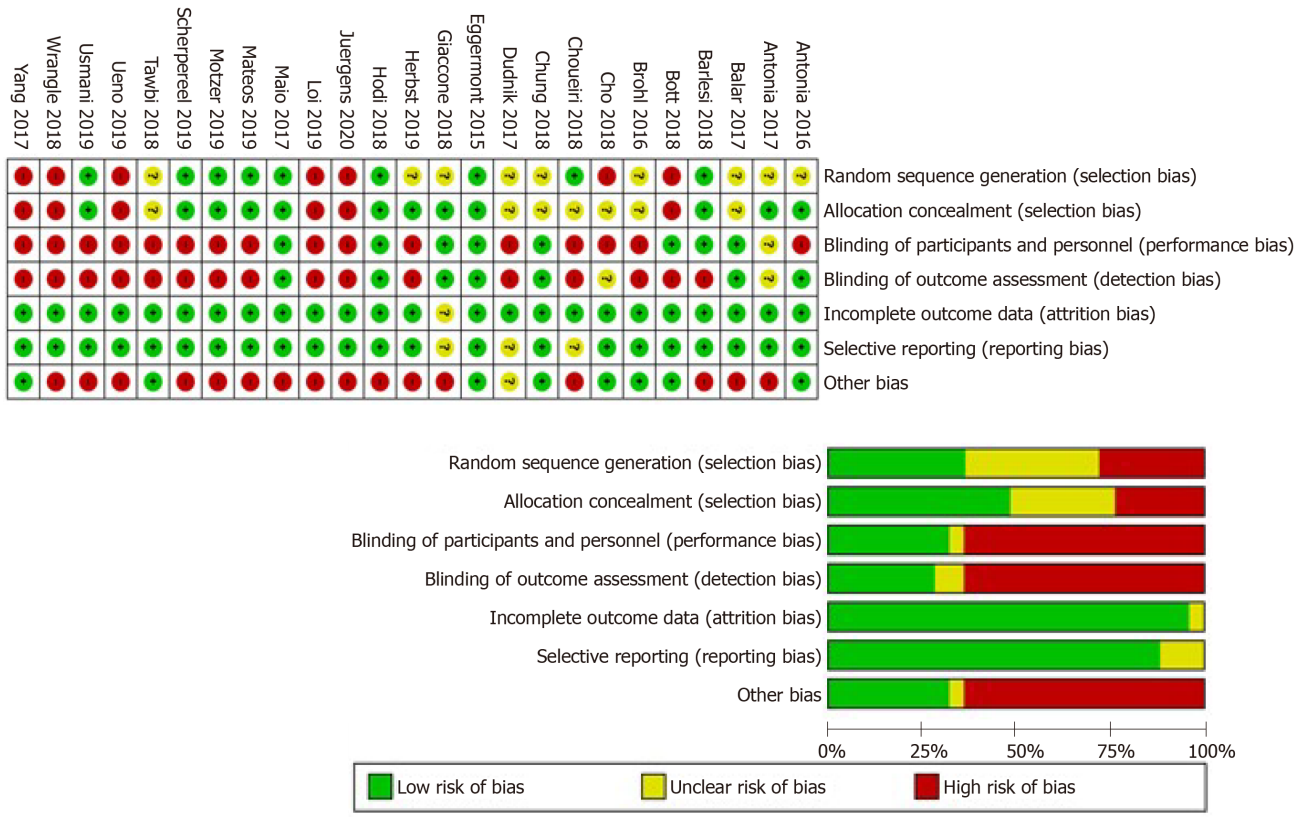

Figure 2 Results of risk of bias assessment among included trials.

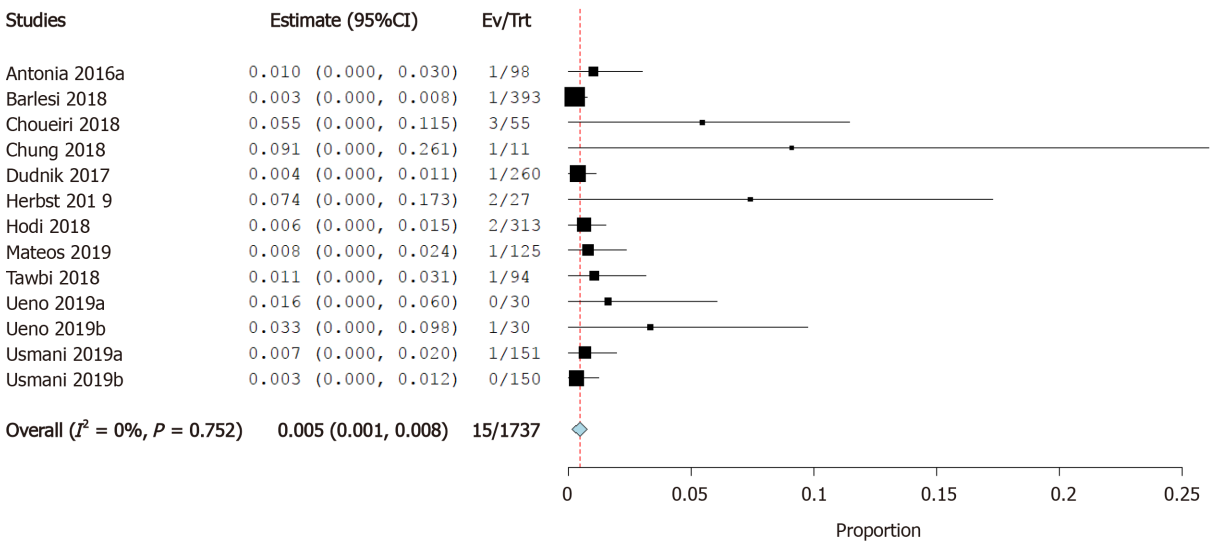

Figure 3 Incidence of myocarditis. CI: Confidence interval.

of the PD-1 and CTLA-4 axes induces autoimmune myocarditis, indicating that the PD-1/PD-L1 interaction and CLTA-4 play important roles in protecting against T-lymphocyte-mediated inflammation[46-48]. Injury usually occurs within first three months of initiating ICI; however, late presentation is not uncommon[49,50].

T-lymphocyte-mediated inflammation may also be implicated in the pathogenesis of ICI-related atrial fibrillation. In one recent case report, histopathologic analysis of a patient with atrial fibrillation displayed patchy infiltrations of lymphocytes in the sinoatrial and atrioventricular nodes[18]; this suggests that T-lymphocytes are intricately involved in the development of atrial fibrillation and other ICI-induced conduction disorders. In addition, it has been hypothesized that the increased risk of atrial fibrillation among patients taking ICIs may be attributed to the direct connection

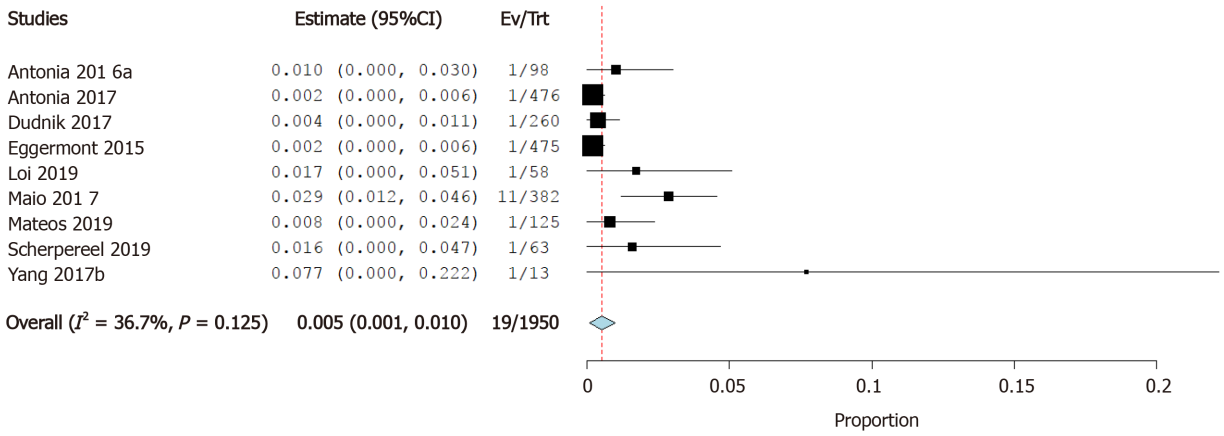

Figure 4 Incidence of pericardial effusion. CI: Confidence interval.

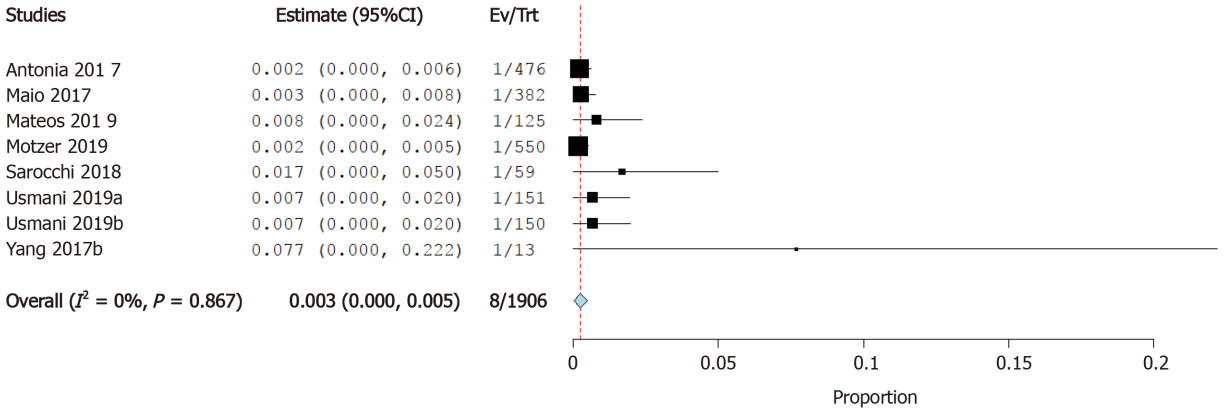

Figure 5 Incidence of heart failure. CI: Confidence interval.

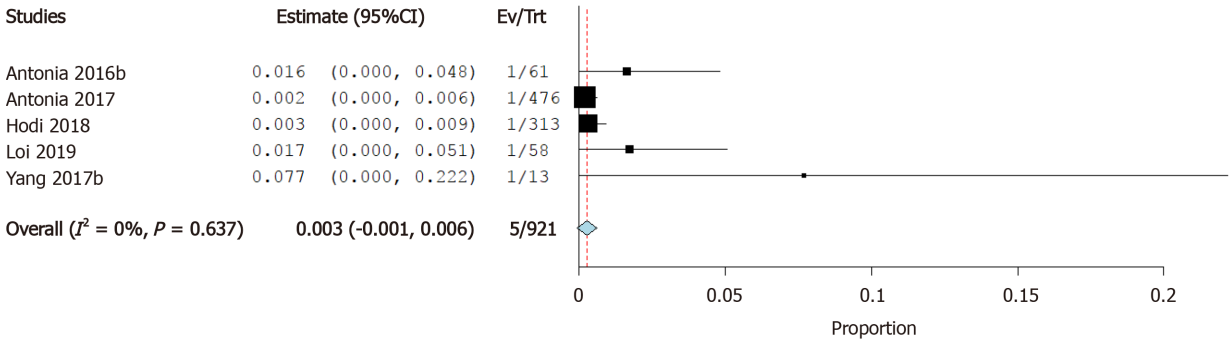

Figure 6 Incidence of cardiomyopathy. CI: Confidence interval.

between the sinoatrial node and the autonomic nervous system, which make the atria sensitive indicators of any disruptive processes in the body[10].

T-lymphocyte-related inflammatory processes are also suspected in pericardial effusion[51] and myocardial infarction[52]. Lyon *et al*[52] suggested that the development of ICI-induced myocardial infarction could be due to the activation of an inflammatory reaction that triggers atherosclerotic coronary plaque formation and acute infarction. Conversely, Nykl *et al*[53] argued that the PD-1 inhibitory effect of ICIs leads to coronary vasospasm and ST-segment elevation. The mechanism by which coronary vasospasm develops is unclear but could be associated with systemic inflammatory response syndrome[43].

The incidence of cardiovascular irAEs is affected by many risk factors. Patients

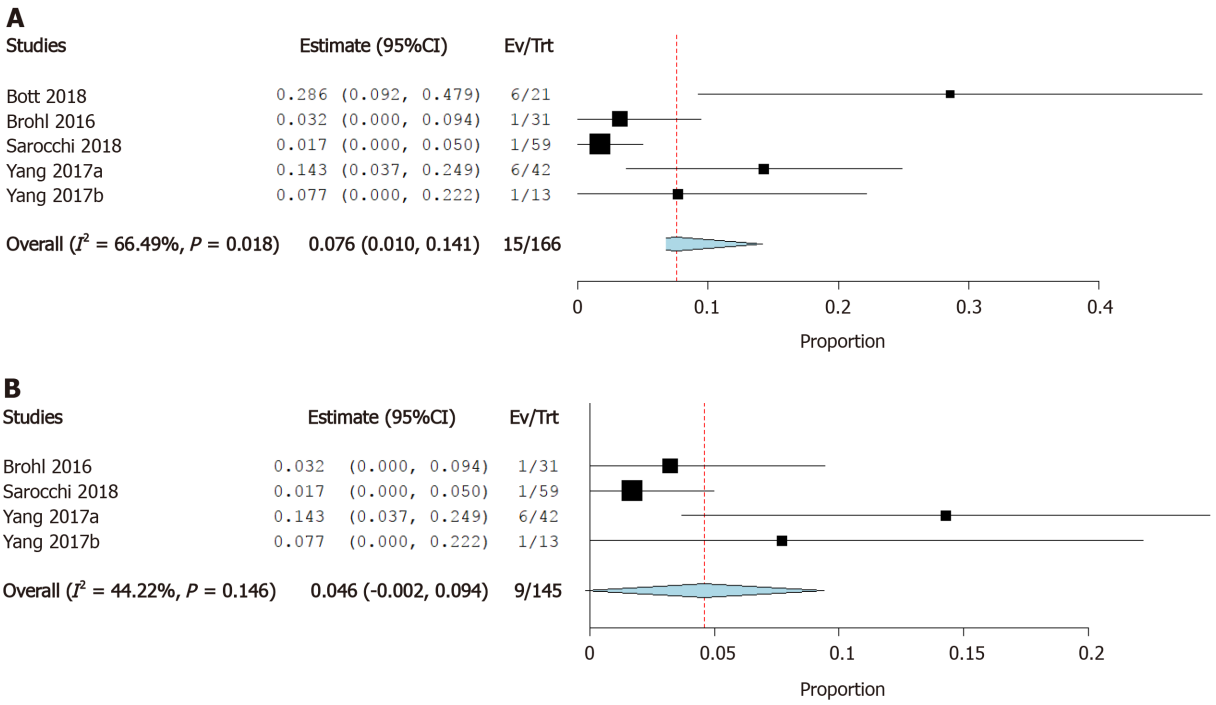

Figure 7 Incidence of atrial fibrillation. A: Incidence of atrial fibrillation with heterogeneity; B: Incidence of atrial fibrillation after correction with Cochrane's leave-one-out method. CI: Confidence interval.

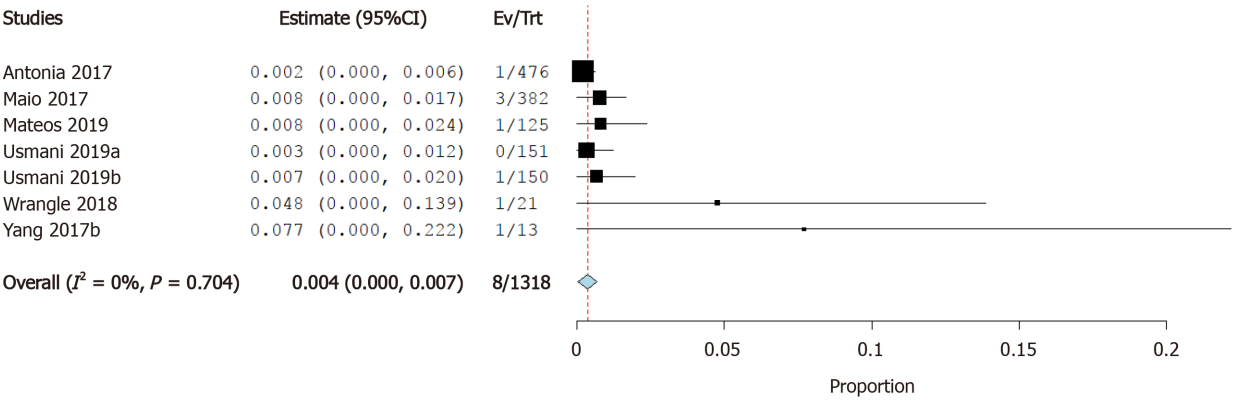

Figure 8 Incidence of myocardial infarction. CI: Confidence interval.

treated with combination therapy were more susceptible to cardiac complications as compared to those treated with ICI monotherapy[49]. In addition, male patients are at higher risk of developing cardiovascular irAEs. A retrospective analysis showed that 77% of cases with ICI-related cardiac toxicity were males[48]. In addition, another multicenter study found that 23 out of 35 irAEs (71%) occurred in male patients[54]. However, data is limited and based on retrospective analyses of a small number of cases (65 cases). Furthermore, concomitant cardiovascular disease is a potential risk factor for cardiovascular irAEs[55].

Cardiovascular irAEs are classified into four grades by the Society for Immunotherapy of Cancer[56]. The management of patients with cardiovascular irAEs differs based on the grade and severity of the symptoms. Grade I is usually asymptomatic and requires neither treatment nor discontinuation of immunotherapy. Grade II is characterized by mild cardiac symptoms that should be controlled by holding cancer immunotherapy and management of the coexisting cardiac disease and its risk factors. Grade III cardiovascular symptoms are significant and require the withdrawal of ICI therapy as well as urgent initiation of high-dose prednisone (1-2 mg/kg). Grade IV cardiovascular irAEs are life-threatening conditions characterized by decompensated cardiac function with moderate-to-severe symptoms; corticosteroid therapy is the first-line treatment. The addition of intravenous immunoglobulins,

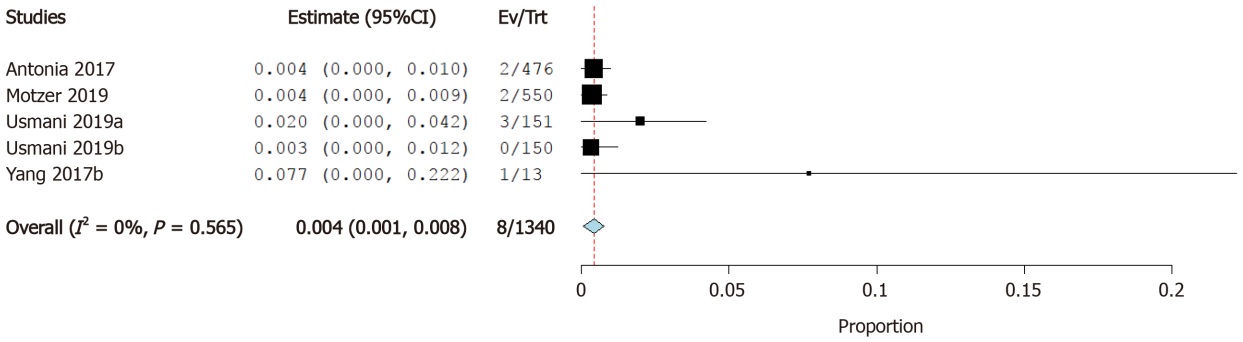

Figure 9 Incidence of cardiac arrest. CI: Confidence interval.

infliximab, or anti-thymocyte globulin should be considered as second-line treatments for patients with grade IV cardiovascular irAEs[10,56].

Long-term data regarding the prognosis of patients with cardiovascular irAEs are limited. However, the available findings suggest a high fatality rate. In a systematic review that included 99 patients with cardiovascular irAEs, the fatality rate was 35%[50,57]. In addition, observational studies report a 50% rate of major adverse cardiac events in ICI-associated myocarditis, which is significantly higher than that of non-ICI-related myocarditis[58,59].

This study represents an attempt to estimate the overall incidence of cardiovascular irAEs in cancer patients receiving ICI therapy. The quality of the included studies ranged from low to moderate according to the Cochrane Risk of Bias Assessment tool[43]. The main limitation of our analysis is that the included studies were not primarily designed to investigate the incidence of ICI-induced cardiac adverse events. In addition, there was a high risk of bias resulting from the difficulty in blinding and randomization of some studies. The definitions to determine adverse events were slightly different across all studies. We did not consider medication dose, which may influence the severity of adverse effects. Furthermore, although some trials noted an increased risk of cardiovascular irAEs among males, patients receiving multiple ICIs, and patients with pre-existing cardiovascular disease, raw data were not available to perform further subgroup analysis[48,49,54,55]. It is also important to note that malignancy in and of itself is a risk factor for coronary artery disease and other cardiovascular comorbidities and hence it is difficult to differentiate a concomitant cardiovascular irAE[60]. It is therefore reasonable to perform cardiovascular magnetic resonance to distinguish a pre-existing cardiovascular disease from a cardiovascular irAE[58,60]. Nevertheless, we believe this analysis provides a valuable framework for further studies on ICI-associated cardiovascular events.

CONCLUSION

Cardiovascular irAEs are rare but potentially life-threatening complications that can occur in patients receiving ICI therapy. Our analysis revealed that the most frequent ICI-associated adverse events are atrial fibrillation, myocarditis, and pericardial effusion. Risk factors for cardiovascular irAEs include treatment with combination immunotherapy, male sex, and a history of cardiac disease. Data on the prognosis of cardiac irAEs are limited. Ongoing post-market surveillance is therefore imperative to characterize long-term risks and improve outcomes among patients receiving ICIs.

ARTICLE HIGHLIGHTS

Research background

Immune checkpoint inhibitors (ICIs) are novel antineoplastic agents that are used with increasing frequency throughout the developed world. However, although ICIs have demonstrated remarkable efficacy for the treatment of many malignancies, a range of adverse events have been reported.

Research motivation

Cardiovascular adverse events have been associated with numerous anticancer agents. ICIs have been available for nearly a decade, however, and yet the rate of cardiovascular ICI-related adverse events (irAEs) remains to be definitively established.

Research objectives

We reviewed the medical literature in order to identify, quantify, and characterize the risk of cardiovascular irAEs.

Research methods

We conducted a systematic review and meta-analysis by searching PubMed, Cochrane CENTRAL, Web of Science, and SCOPUS databases for relevant interventional trials reporting cardiovascular irAEs. We performed a single-arm meta-analysis using OpenMeta [Analyst] software of the following outcomes: Myocarditis, pericardial effusion, heart failure, cardiomyopathy, atrial fibrillation, myocardial infarction, and cardiac arrest. A total of 26 studies were included.

Research results

New-onset atrial fibrillation was the most common cardiovascular irAE observed among patients taking ICIs, occurring in 4.6% of individuals included in the analysis. Other relatively common cardiovascular adverse events included pericardial effusion and myocarditis, both of which occurred in 0.5% of patients receiving ICI therapy. The mechanism underlying cardiovascular irAEs remains to be definitively established, but it has been hypothesized that T-lymphocyte-mediated inflammation causes direct myocardial injury and disrupts sinoatrial node activity.

Research conclusions

Cardiovascular irAEs—including atrial fibrillation, pericardial effusion, and myocarditis—are uncommon but potentially life-threatening complications of ICI therapy. Mechanisms of pathogenesis and patient- and ICI-associated risk factors warrant further investigation.

Research perspectives

Cardiovascular irAEs represent rare but potentially life-threatening complications of ICIs. Data from post-market surveillance will play a vital role in clarifying the risk of cardiovascular irAEs. Based on the available evidence, however, close cardiac monitoring of patients receiving ICIs may be warranted.

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