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A Systematic Review and Meta-Analysis of Immune-Related Adverse Events of Anti-PD-1 Drugs in Randomized Controlled Trials

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Abstract

Objective: We aimed to evaluate immune-related adverse events occurring in clinical trials of anti-programmed cell death 1 (PD-1) drugs, compared with control treatments, including chemotherapy, targeted drugs, or placebo. Further we compared the occurrence of immune -related events in patients treated with different anti-PD-1 drugs. **Data Sources:** Randomized controlled trial (RCT) data were sourced from PubMed, Embase, and the Cochrane Central Register of Controlled Trials combined with clinicaltrials.gov. **Methods:** Randomized controlled trial of anti-PD-1 drugs compared with control treatments published between January 1, 1970 and March 1,2019, were searched and data on trial patient characteristics, and adverse events extracted, reviewed, and subjected to meta-analysis. **Results:** Eighteen Randomized controlled trials were included in our study. The Randomized controlled trials compared nivolumab (n = 12), pembrolizumab (n = 6), with chemotherapy (n = 13), targeted drugs (n = 2), or placebo (n = 3). Compared with the control group, the risk of any immune-related adverse events in patients treated with anti-PD-1 drugs was increased (RR, 2.65; 95% confidence interval, 1.84–3.83; $P < 0.00001$). Of the immune-related adverse events, the risk rates of pneumonitis (risk ratio, 2.10; 95% CI, 0.85-5.18), colitis (2.96;1.62-5.38), hypophysitis(4.79;1.54-14.89), hypothyroidism(7.87;5.36-11.57), hyperthyroidism (7.03;4.35-11.34), rash (1.58;0.98-2.54), pruritus (2.28; 1.38-3.76), and hepatitis (9.31;2.18-39.85) were increased by anti-PD-1 drugs. Further, the risk of immune-related adverse events was similar for patients treated with pembrolizumab and nivolumab ($P = 0.14$). **Conclusions:** In addition to previously reported organ-specific immune-related adverse events, we found that the risk of hyperthyroidism was also increased, in anit-PD-1-treated patients, relative to control treatments. The risk of total immune-related adverse events, was similar for pembrolizumab and nivolumab.

Keywords

anti-PD-1 drugs, immune-related adverse events, systematic review, meta-analysis

Abbreviations

Aes, adverse events; Akt, protein kinase B (PKB), also known as Akt; irAE, immune-related adverse events; PD 1, programed cell death protein 1; PD-L1, programed death-ligand 1; PD-L2, programed death-ligand 2; CI, confidence interval; NSCLC, non-small cell lung cancer; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCT, randomized controlled trial; RR, relative risk.

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Introduction

Immunotherapy, is a type of oncotherapy that boosts physiological defenses against tumors. It functions by impeding or preventing tumor cell growth, enhancing immune system-mediated tumor cell destruction, and preventing cancer from spreading to other parts of the body.

Programmed cell death protein 1(PD-1), an immunoinhibitory receptor of the CD28 family, plays a crucial role in tumor

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Box 1. PubMed search terms.

Search((((((((((((((((phase 2/3 trial) OR phase 2/3 clinical trial) OR phase II/ III clinical trial) OR phase II/III trial) OR phase 2/3 clinical study) OR phase II/ III clinical study) OR phase 2/3 study) OR phase II/III study) OR phase 2/3 randomized trial) OR phase II/III randomized trial)) OR ((((((Randomized Controlled Trial) OR Clinical Trials, Randomized) OR Trials, Randomized Clinical) OR Controlled Clinical Trials, Randomized) OR randomized controlled trial) OR RCT)) OR ((((((((((((((((Clinical Trials, Phase IV) OR Clinical Trials, Phase 4) OR Drug Evaluation, FDA Phase IV) OR Evaluation Studies, FDA Phase 4) OR Drug Evaluation, FDA Phase 4) OR Evaluation Studies, FDA Phase IV) OR phase 4 clinical trial) OR phase IV clinical trial) OR phase 4 trial) OR phase IV trial) OR phase 4 clinical study) OR phase IV clinical study) OR phase 4 study) OR phase IV study) OR phase 4 randomized trial) OR phase IV randomized trial)) OR ((((((((((((((((Clinical Trials, Phase II) OR Evaluation Studies, FDA Phase II) OR Evaluation Studies, FDA Phase 2) OR Drug Evaluation, FDA Phase II) OR Drug Evaluation, FDA Phase 2) OR phase 2 clinical trial) OR phase II clinical trial) OR phase 2 trial) OR phase II trial) OR phase 2 clinical study) OR phase II clinical study) OR phase 2 study) OR phase II study) OR phase 2 randomized trial) OR phase II randomized trial)) OR ((((((((((((((((Clinical Trial, Phase III) OR Clinical Trials, Phase 3) OR Evaluation Studies, FDA Phase III) OR Drug Evaluation, FDA Phase III) OR Drug Evaluation, FDA Phase 3) OR Evaluation Studies, FDA Phase 3) OR phase 3 clinical trial) OR phase III clinical trial) OR phase 3 trial) OR phase III trial) OR phase 3 clinical study) OR phase III clinical study) OR phase 3 study) OR phase III study) OR phase 3 randomized trial) OR phase III randomized trial))) AND (((checkpoint inhibitor) OR PD-1) OR ((((((((((JNJ-63723283) OR PDR001) OR TSR-042) OR BCD-100) OR ((Cemiplimab) OR REGN-2810)) OR ((Tislelizumab) OR BGB-A317)) OR ((Camrelizumab) OR SHR-1210)) OR ((IBI308) OR Sintilimab)) OR (((((pembrolizumab) OR pembrolizumab) OR lambrolizumab) OR keytruda) OR SCH 900475)) OR ((((((((((((nivolumab) OR Nivolumab) OR Opdivo) OR ONO-4538) OR ONO 4538) OR ONO4538) OR MDX-1106) OR MDX 1106) OR MDX1106) OR BMS-936558) OR BMS 936558) OR BMS936558) OR NIVO))

immune escape and is critical for the capacity of the immune system to control cancer growth. There are 2 known ligands for PD-1, programed cell death-ligand 1 and 2 (PD-L1 and PD-L2, also referred to as B7-H1 and B7-DC, respectively). On cells within the tumor microenvironment and in many tumors, PD-L1 is selectively expressed in response inflammatory stimuli. Blocking the interaction between PD-1 and PD-L1 can enhance the immune response in vitro and mediate preclinical antitumor activity.[1,2]

The side effects of immunotherapy, are collectively referred to as immune-related adverse events (irAE), and are a consequence of aberrant stimulation of the immune system against normal tissues.[3] There are 3 types of irAE: organ-specific immune-related adverse events including pneumonitis, hepatitis, and colitis etc; more general immune activation-related adverse events such as fatigue, diarrhea, and rash; and musculoskeletal problems like myalgia, and arthralgia among others.[4-7]

Based on previous research, to assess the risk of irAE in response to anti-PD-1 drugs, rather than all immune checkpoint inhibitors, compared with control treatments, in randomized controlled trials (RCT), we conducted a systematic review and meta-analysis. Data from both ClinicalTrials.gov and published literature were collected. Severe adverse events (grades 3–5) and fatal events were also considered, according to the National Cancer Institute Common Toxicity Criteria.

Material and Methods

This study was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. (a PRISMA checklist is included as Supplementary information S1).

Information Sources and Search Strategy

Before searching, we retrieved all commercial names of anti-PD-1 drugs (up to March 1, 2019) and used Medical Subject Headings to search for all of them to ensure that the search results would not be affected by a lack of terms. We searched PubMed, Embase, and the Cochrane Database for clinical trials published up to March 1, 2019. Two related concepts with the AND operator were used in the search strategy as follow: 1. "nivolumab," "pembrolizumab," "Sintilimab," "Camrelizumab," "Tislelizumab," "Cemiplimab," "PD-1," or "check inhibitors"; 2. "phase 2 clinical trial," "phase 3 clinical trial," "phase 2/3 clinical trial," "phase 4 clinical trial," or "RCTs," to ensure that no eligible studies were overlooked (Box 1). After title/abstract screening by 4 independent investigators (YKW, DJK, CKW and JC) full texts of potentially relevant studies were downloaded and the Methods and Results sections reviewed to determine whether they met the eligibility criteria. When duplicate publications from same study were found, we included only the most recent and complete reports. Then, randomized controlled trial data were sourced from publications on PubMed, Embase, and the Cochrane Central database. To make the collected data more complete, we searched for irAE of anti-PD-1 drugs on ClinicalTrials.gov, using the trial numbers in publications. For studies which did not provide complete adverse events information on ClinicalTrials.gov, we obtained information from the publication.

Study Selection and Eligibility Criteria

The aim of our study was to assess the risk of irAE following the use of anti-PD-1 drugs, compared with control groups in patients with cancer, and to compare the occurrence of irAE in patients receiving different kinds of anti-PD-1 drugs. Reviews, editorials, conference, correspondence, phase 1 trials, and non-randomized studies were excluded. Studies that met the following criteria were included in the analysis: (1) study type was prospective phase 3 RCTs involving patients with cancer;(2)-participants were patients diagnosed with cancer, regardless of age, ethnicity, sex and geographical region;(3) interventions were random assignment of participants to anti-PD-1 drugs; (4)control group included patients receiving chemotherapy, targeted drugs, or placebo; (5)outcomes were available data regarding irAEs and the number of irAE.

Data Collection Process

Data were extracted (YKW, DJK and CKW) and verified (YKW and JC) by independent reviewers. For each study, the following information was extracted: year of publication, first author, types of cancer in anti-PD1-treated and control groups, name of anti-PD-1 drugs, number of patients in each group, and number of all adverse events (data are available in Supplementary information S2). According to previous study[6] and preliminary analysis of the data collected here(Supplementary information S2), the primary outcomes of the review were organ specific irAE(pneumonitis, hepatitis, hypophysitis, hypothyroidism, hyperthyroidism and colitis)and general irAE(rash, pruritus). The secondary outcome was associated musculoskeletal problems (arthritis and myalgia).

Statistical Analyses

Data were pooled to compare the risks of irAE between patients receiving anti-PD-1 drugs and control groups. Confidence intervals for the risk ratio (RR)[8] were calculated using the Woolf method. Two models, meta-analysis with fixed-effects (Mantel–Haenszel method) and random-effects (Der Simonian and Laird method), were considered based on the heterogeneity of the included studies. Before we pooled data, we evaluated the heterogeneity of all studies. Heterogeneity among studies was assessed using Cochran's Q statistic. Inconsistency was evaluated using the I^2 statistic, which measures the total percentage of variation across studies due to heterogeneity rather than chance. An I^2 values of 0% indicates no observed heterogeneity, while values between 0% and 100% show increasing heterogeneity. Where I^2 values were <50% heterogeneity (*P* value > 0.1), pooled RR and 95% confidence interval (CI) were estimated using a fixed effects model and a random effects model was used when the assumption of homogeneity was considered invalid *(P* value < 0.1) and I^2 >50%. We added a standard continuity correction of 0.5 to each cell, when zero event studies were included.[9] If sufficient studies assessing nivolumab and pembrolizumab were available, we conducted subgroup analyses to assess the occurrence of irAE in patients treated with different anti-PD-1 drugs. We used funnel plots, Begg's rank test and Egger's regression test[10] to assess publication bias. All statistical analyses were conducted using Review Manager 5.3 (Copenhagen, Denmark), Stata 15 and Microsoft Office 2019.

Results

Initially, we identified a total of 4021citations through database searches and other sources. Of these, 18 finally underwent full text review and 19 unique trials were included for quantitative synthesis and meta-analysis. The other studies were excluded for the reasons described the flow diagram presented in Figure 1.

Quality of Included Studies

Although all included studies were RCT, the primary endpoint was survival. As adverse events are reported by clinicians who directly care for patients, studies were unmasked. Furthermore, since included studies were not designed mainly to assess adverse events, collection of adverse events information was poorly described; therefore, we considered all studies at high risk of bias with regard to blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting (Figure 2).

Study Characteristics

Of the 18 included RCTs,13 compared anti-PD-1 drugs with chemotherapy, 2 with targeted drugs, and 2 with placebo as single agents. In one trial, anti-PD-1 drug plus chemotherapy was compared with placebo plus chemotherapy. Seven RCTs were conducted in patients with non-small cell lung cancer (NSCLC), 4 in patients with melanoma, 3 in patients with carcinoma of the head and neck, and 2 each in patients with renal cell cancer and gastric or gastro-esophageal junction cancer. (Table 1).

Patients

A total of 9318 patients were randomized in the 18 phase 3 RCTs included in this meta-analysis. Of these, in trials of nivolumab,2951 patients were assigned to nivolumab, 1560 to chemotherapy, 161 to placebo, and 423 to targeted drugs (everolimus). Further, in trials of pembrolizumab, 2163 patients were assigned to pembrolizumab, 1278 to chemotherapy, 502 to placebo, 280 to placebo plus chemotherapy, and no patients to targeted drugs (Table 1). The performance status of all patients in these studies was between 0 and 2. The safety population, which included all patients who were exposed to at least 1 dose of the treatment, consisted of 9318 patients (Anti-PD-1 drugs,5114; control,4204) with NSCLC (4000), gastric or gastro-esophageal junction cancer (1061), carcinoma of the head and neck (1188), renal cell cancer (866), and melanoma (2293) (Table 1).

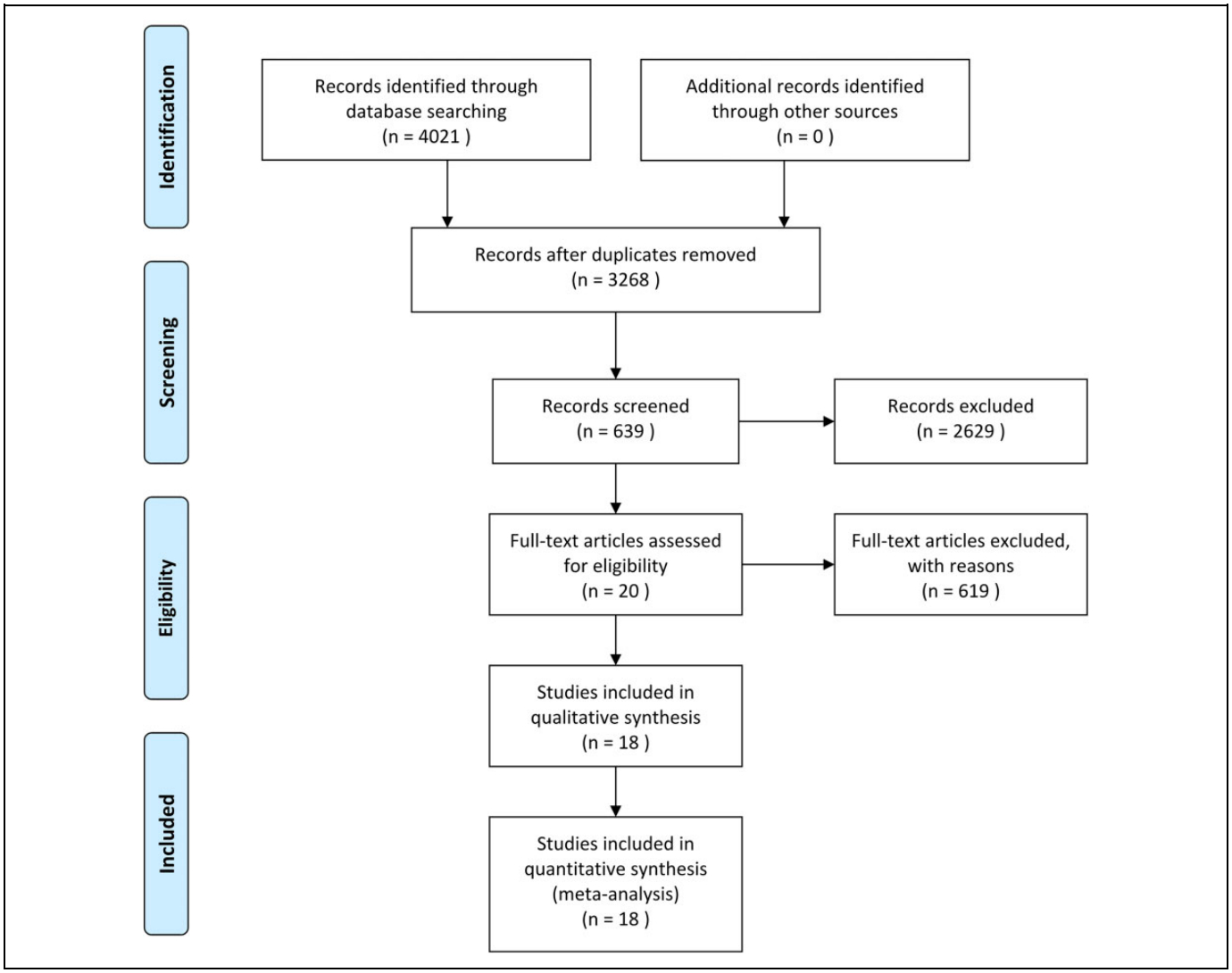

Figure 1. Flow diagram according to RISMA 2009.

The following organ specific irAE were recorded pneumonitis (n = 116), colitis(n = 42), hypophysitis(n = 21), hypothyroidism (n = 233), hyperthyroidism (n = 138) and hepatitis patients(n = 18). General immune activation-related adverse events were recorded rash (n = 394), pruritus (n = 324). (Table 1). Compared with the control group, the risk of (any irAE other than musculoskeletal problems) in patients treated with anti-PD-1 drugs was increased (RR, 2.65;95%CI 1.84-3.83; $P < 0.00001$); Further, the risk of irAE was similar for patients treated with pembrolizumab and nivolumab ($P = 0.14$) (Figure 3).

Immune-Related Adverse Events

Organ-specific immune-related adverse events.

Pneumonitis. Pneumonitis was observed in both the anti-PD-1 (n = 116 patients) and control (n = 91patients) groups. The RR values obtained for the studies ranged from 0.06 (Tomita 2017) to 15.96 (Shitara 2018). The overall pooled RR, obtained by meta-analysis using a random-effects model was 2.10(95% CI,0.85–5.18; $P = 0.11$), indicating no significant increased risk. As the observed heterogeneity was mainly attributable to the studies of nivolumab, we separately used a fixed-effects model to analyze the occurrence of pneumonitis in patients treated with pembrolizumab. Patients treated with pembrolizumab had a significantly increased risk of pneumonitis (pooled RR = 3.12; 95% CI,2.06–4.73; $P < 0.00001$) (Supplementary information S3, Figure 1); however, there was no significant risk associated with nivolumab treatment (pooled RR = 0.62; 95% CI 0.09–4.37; $P = 0.63$) (Figure 4).

Colitis. Colitis was diagnosed in 42 and 12 patients in the anti-PD-1 and control groups, respectively. The pooled RR was 2.96 (95% CI 1.62–5.38; $P = 0.0004$), indicating a significantly increased risk. Related to anti-PD1 treatment, since there was

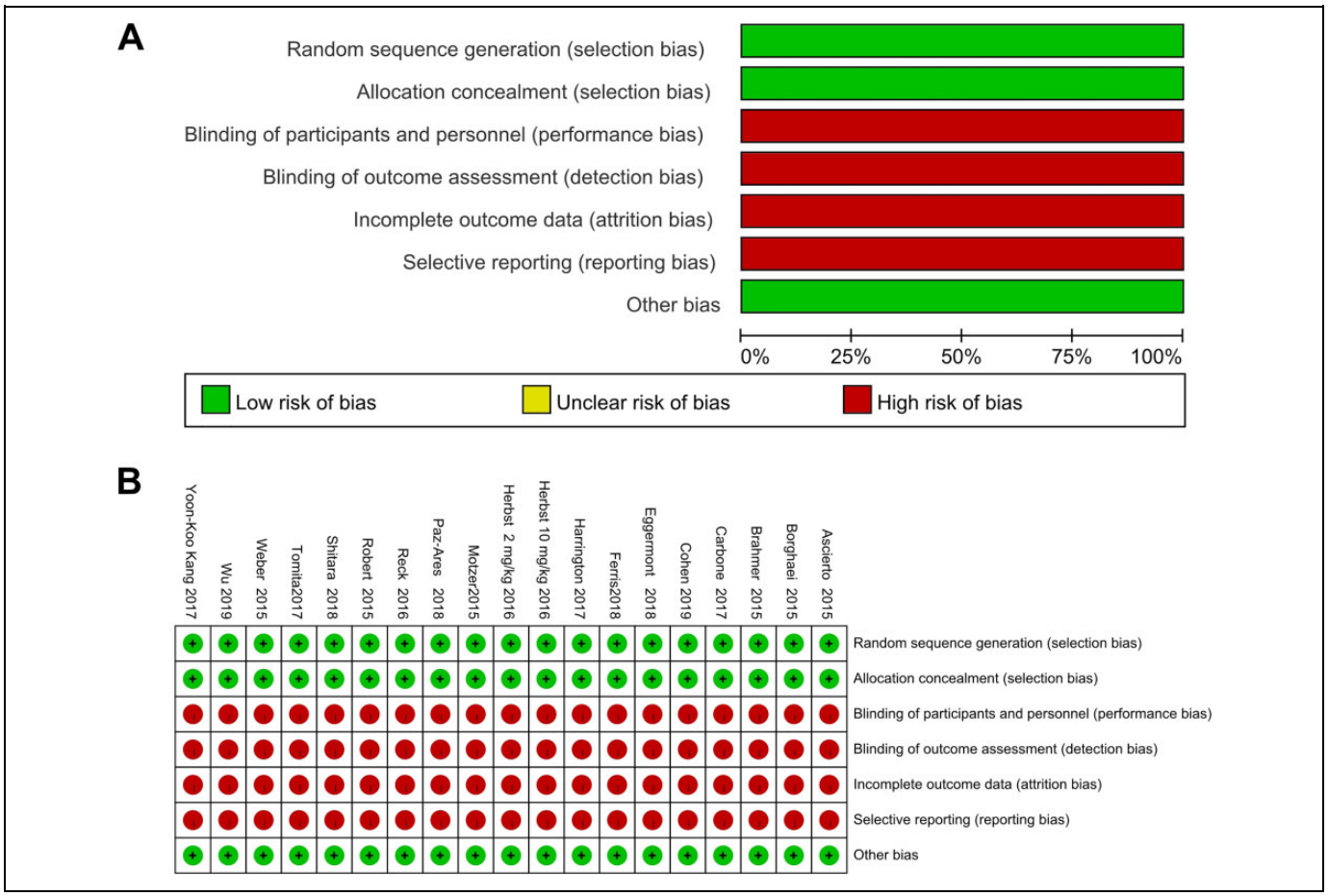

Figure 2. Graph summarizing bias risk and applicability concerns.

only 1 study of nivolumab where colitis was recorded, we did not conduct a subgroup analysis (Figure 5).

Hypophysitis. Hypophysitis events occurred almost exclusively in the anti-PD-1 group (20 of 21 total events); with one occurrence in a control group. There was significantly increased risk for patients who received anti-PD-1therapy (RR = 4.79; 95% CI,1.54–14.89; $P = 0.007$). As there was only 1 study of nivolumab that recorded hypophysitis, we did not perform a subgroup analysis. (Figure 6).

Hypothyroidism. Hypothyroidism was reported in patients treated with both anti-PD-1 (n = 233) and in controls (n = 28). Patients who received anti-PD-1 therapy had a significantly increased risk of hypothyroidism (pooled RR = 7.87; 95% CI, 5.36–11.57; $P < 0.00001$). Subgroup analysis showed that 14 patients developed hypothyroidism in the nivolumab treated group, and 2 in the control group (pooled RR = 5.21;95% CI,1.42–19.19; $P = 0.01$), while219 patients developed hypothyroidism in the pembrolizumab treated group versus 26 in the control group (pooled RR = 8.15;95% CI 5.44–12.20; $P < 0.0001$) (Figure 7).

Hyperthyroidism. Hyperthyroidism was diagnosed in 137 anti-PD-1 treated and 18 control group patients. Hence, patients who received anti-PD-1 therapy were at significant risk of hyperthyroidism (RR = 7.03; 95% CI 4.35–11.34; $P < 0.00001$).As only 1 study of nivolumab recorded hyperthyroidism, we did not perform subgroup analysis .No association of hyperthyroidism with anti-PD-1 treatment has previously been reported (Figure 8).

Hepatitis. Hepatitis was observed 18 patients treated with anti-PD-1 and 1 control group patients. The pooled RR was 9.31 (95% CI 2.18–39.85; $P = 0.003$). All patients with recorded hepatitis were in the pembrolizumab group and none in the nivolumab group. (Figure 9).

General immune activation-related adverse events.

Pruritus. Pruritis was recorded in324 patients receiving anti-PD-1 treatment and 128 administered control treatments. The estimated RR obtained by meta-analysis using a random-effects model, was 2.28 (95% CI,1.38-3.76 $P < 0.0001$). Since there was only 1 study of pembrolizumab that recorded pruritus, we did not conduct a subgroup analysis. (Figure 10)

Table 1. Characteristics of Studies Included in the Meta-Analysis.

	Cancer	Drug	Colitis		Pneumonitis		Hypothyroidism		Hyperthyroidism		Rash		Pruritus		Hepatitis		Hypophysitis	
			AE	Total	AE	Total	AE	Total	AE	Total	AE	Total	AE	Total	AE	Total	AE	Total
Robert 2015	Melanoma	Nivolumab	0	206	0	206	0	206	0	206	31	206	35	206	0	206	0	206
		Chemotherapy	0	205	0	205	0	205	0	205	6	205	11	205	0	205	0	205
Ascierto 2015	Melanoma	Nivolumab	0	206	0	206	13	206	0	206	38	206	49	206	0	206	0	206
		Chemotherapy	0	205	0	205	2	205	0	205	6	205	11	205	0	205	0	205
Borghaei 2015	Non-small cell lung cancer	Nivolumab	0	287	0	287	0	287	0	287	0	287	0	287	0	287	0	287
		Chemotherapy	0	268	0	268	0	268	0	268	0	268	0	268	0	268	0	268
Wu 2019	Non-small cell lung cancer	Nivolumab	0	337	0	337	0	337	0	337	39	337	0	337	0	337	0	337
		Chemotherapy	0	156	0	156	0	156	0	156	4	156	0	156	0	156	0	156
Brahmer 2015	Non-small cell lung cancer	Nivolumab	0	131	6	131	0	131	0	131	5	131	0	131	0	131	0	131
		Chemotherapy	0	129	0	129	0	129	0	129	8	129	0	129	0	129	0	129
Carbone 2017	Non-small cell lung cancer	Nivolumab	0	267	0	267	0	267	0	267	26	267	0	267	0	267	0	267
		Chemotherapy	0	263	0	263	0	263	0	263	15	263	0	263	0	263	0	263
Weber 2015	Melanoma	Nivolumab	0	268	0	268	0	268	0	268	0	268	43	268	0	268	0	268
		Chemotherapy	0	102	0	102	0	102	0	102	0	102	2	102	0	102	0	102
Harrington 2017	Carcinoma of the head and neck	Nivolumab	0	240	0	240	0	240	0	240	0	240	0	240	0	240	0	240
		Chemotherapy	0	121	0	121	0	121	0	121	0	121	0	121	0	121	0	121
Ferris 2018	Carcinoma of the head and neck	Nivolumab	0	236	0	236	0	236	0	236	18	236	17	236	17	236	0	236
		Chemotherapy	0	111	0	111	0	111	0	111	5	111	0	111	0	111	0	111
Yoon-Koo Kang 2017	Gastric or gastro-esophageal junction cancer	Nivolumab	2	330	1	330	1	330	2	330	19	330	30	330	0	330	10	330
		Placebo	0	161	0	161	0	161	0	161	5	161	9	161	0	161	1	161
Motzer 2015	Renal cell cancer	Nivolumab	0	406	16	406	0	406	0	406	0	406	57	406	0	406	0	406
		Target drugs	0	397	58	397	0	397	0	397	0	397	39	397	0	397	0	397
Tomita 2017	Renal cell cancer	Nivolumab	0	37	0	37	0	37	0	37	0	37	3	37	2	37	0	37
		Target drugs	0	26	5	26	0	26	0	26	0	26	6	26	7	26	0	26
Herbst 2 mg/kg 2016	Non-small cell lung cancer	Pembrolizumab (2 mg/kg)	4	339	16	339	28	339	12	339	29	339	0	339	0	339	1	339
		Chemotherapy	0	309	6	309	1	309	3	309	14	309	0	309	0	309	0	309
Herbst 10 mg/kg 2016	Non-small cell lung cancer	Pembrolizumab(10mg/kg)	2	343	15	343	28	343	20	343	44	343	0	343	0	343	1	343
		Chemotherapy	0	309	6	309	1	309	3	309	14	309	0	309	0	309	0	309
Cohen 2019	Carcinoma of the head and neck	Pembrolizumab	2	246	10	246	33	246	5	246	19	246	0	246	0	246	0	246
		Chemotherapy	1	234	3	234	2	234	1	234	34	234	0	234	0	234	0	234
Reck 2016	Non-small cell lung cancer	Pembrolizumab	3	154	9	154	12	154	14	154	0	154	0	154	0	154	1	154
		Chemotherapy	0	150	1	150	2	150	2	150	0	150	0	150	0	150	0	150
Shitara 2018	Gastric or gastro-esophageal junction cancer	Pembrolizumab	3	294	8	294	23	294	12	294	0	294	0	294	4	294	4	294
		Chemotherapy	4	276	0	276	1	276	1	276	0	276	0	276	0	276	0	276
Eggermont 2018	Melanoma	Pembrolizumab	19	509	17	509	73	509	52	509	82	509	90	509	9	509	0	509
		Placebo	3	502	6	502	14	502	6	502	54	502	51	502	1	502	0	502
Paz Ares 2018	Non-small cell lung cancer	Pembrolizumab	7	278	18	278	22	278	20	278	0	278	0	278	5	278	3	278
		Placebo	4	280	6	280	5	280	2	280	0	280	0	280	0	280	0	280

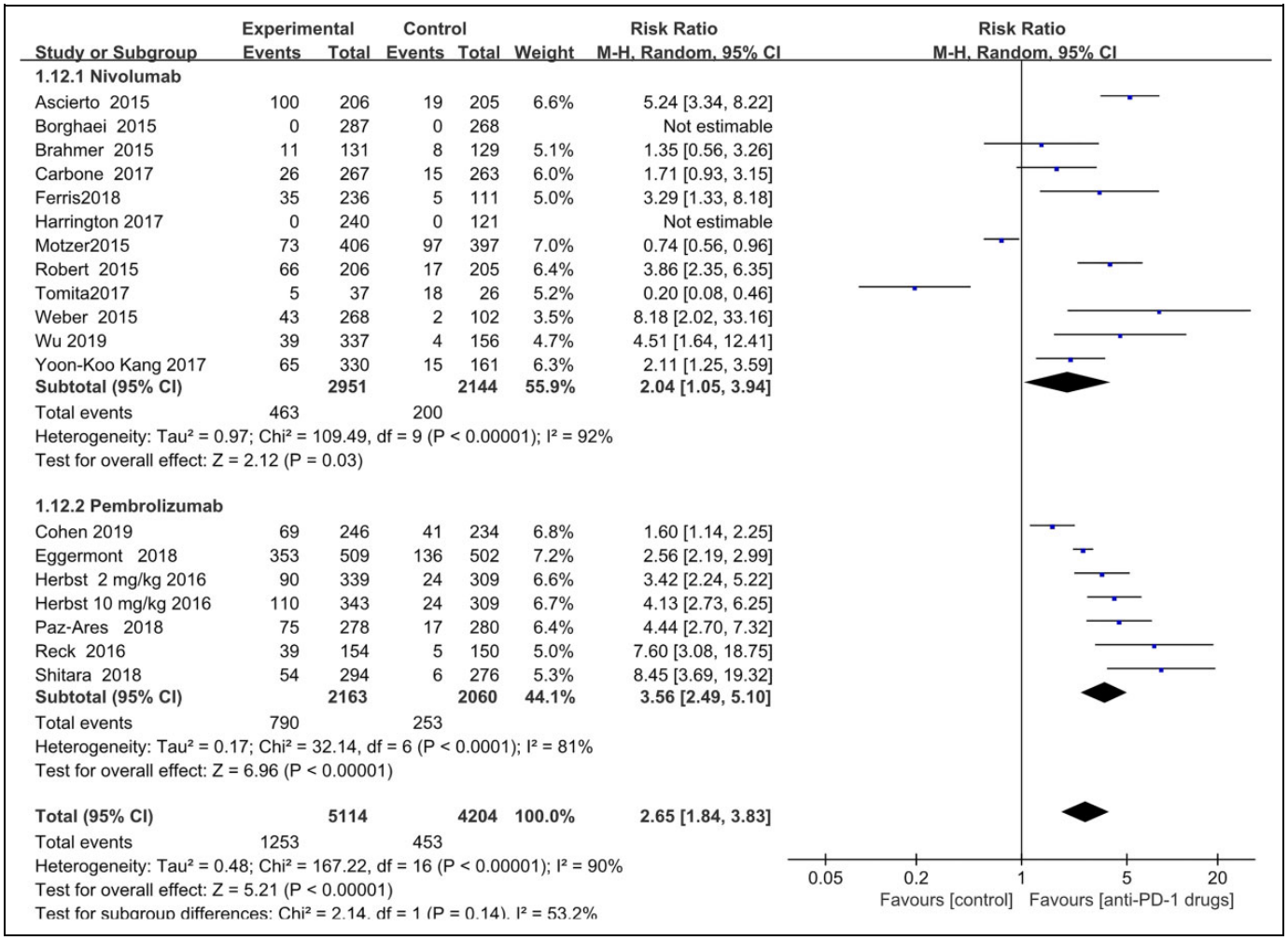

Figure 3. Forest plot of total immune-related adverse events.

Rash. Rash was observed in 394 patients receiving anti-PD-1 treatment and 250 control group patients. The pooled RR, according to random-effects model meta-analysis was 1.58 (pooled 95% CI,0.98–2.54; $P = 0.06$). In subgroup analysis, 220 patients were diagnosed with rash in the nivolumab treated group and 134 in the control groups (RR = 1.66; 95% CI 0.79–3.50; $P = 0.18$), indicating no significant increase in the risk of rash events in the nivolumab-treated subgroup. Further, no statistically significant risk was detected for patients who received pembrolizumab (pooled RR = 1.42; 95% CI 0.76–2.68; $P = 0.27$) .These results are not consistent with previously published data[6](Figure 11).

Musculoskeletal problems. There were 133 and 144 patients with recorded musculoskeletal problems. The pooled RR, calculated using random-effects model meta-analysis, was 0.89 (95% CI,0.37–2.21; $P = 0.78$), hence, there was no significant risk of musculoskeletal problems (Supplementary information S3, Figure 2).[11-30]

Publication Bias

The distribution of the irAE on both sides of the funnel plot is symmetrical. Further Begg's ($P = 0.967$) and Egger's ($P = 0.493$;95%CI,-2.077279-4.12382) suggested that there was no publication bias. (Figure 12 funnel plot generated using Stata 15).

Discussion

In this study, we completed a systematic comparison of immune-related adverse events between patients receiving anti-PD-1 drugs and other treatments, using data from 18 RCTs, including 9318 treated patients. We found the that patients treated with anti-PD-1 drugs had significantly higher risks for organ-specific irAE(hepatitis, hypophysitis, hypothyroidism, hyperthyroidism and colitis) than those in control groups; however, the data included in the statistical analysis were not serious adverse events.

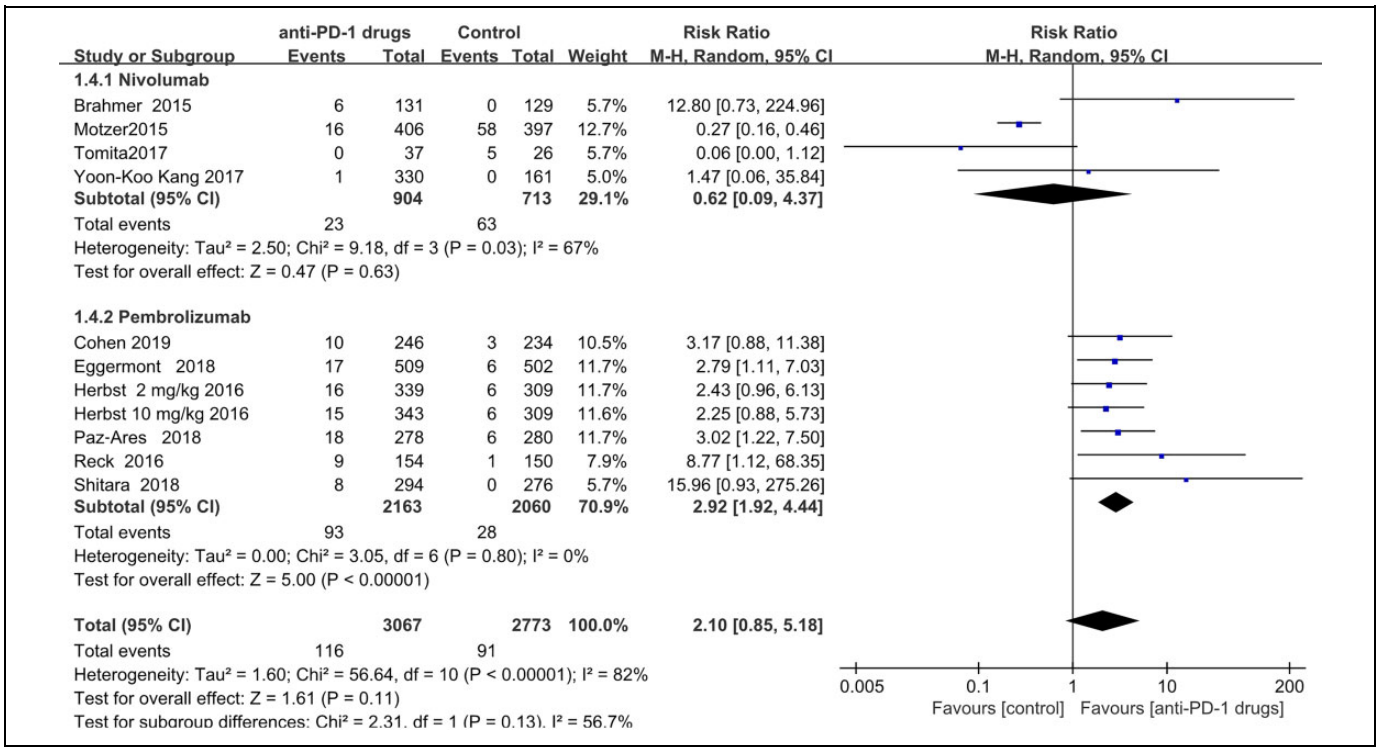

Figure 4. Forest plot of pneumonitis.

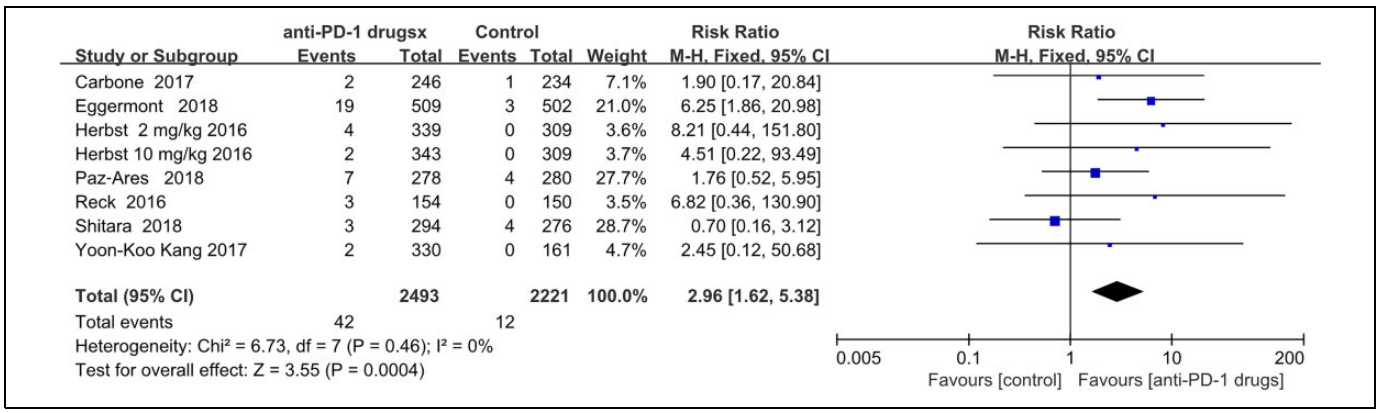

Figure 5. Forest plot of colitis.

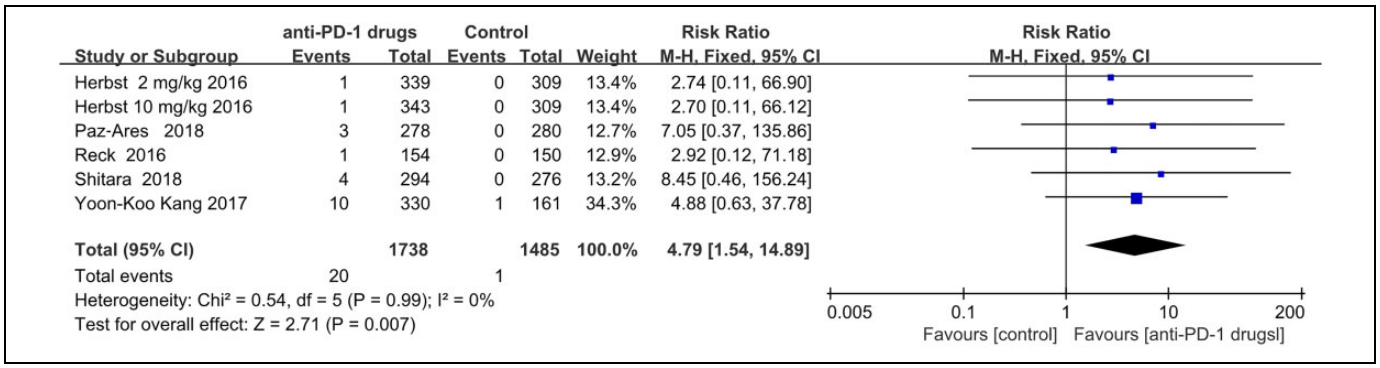

Figure 6. Forest plot of hypophysitis.

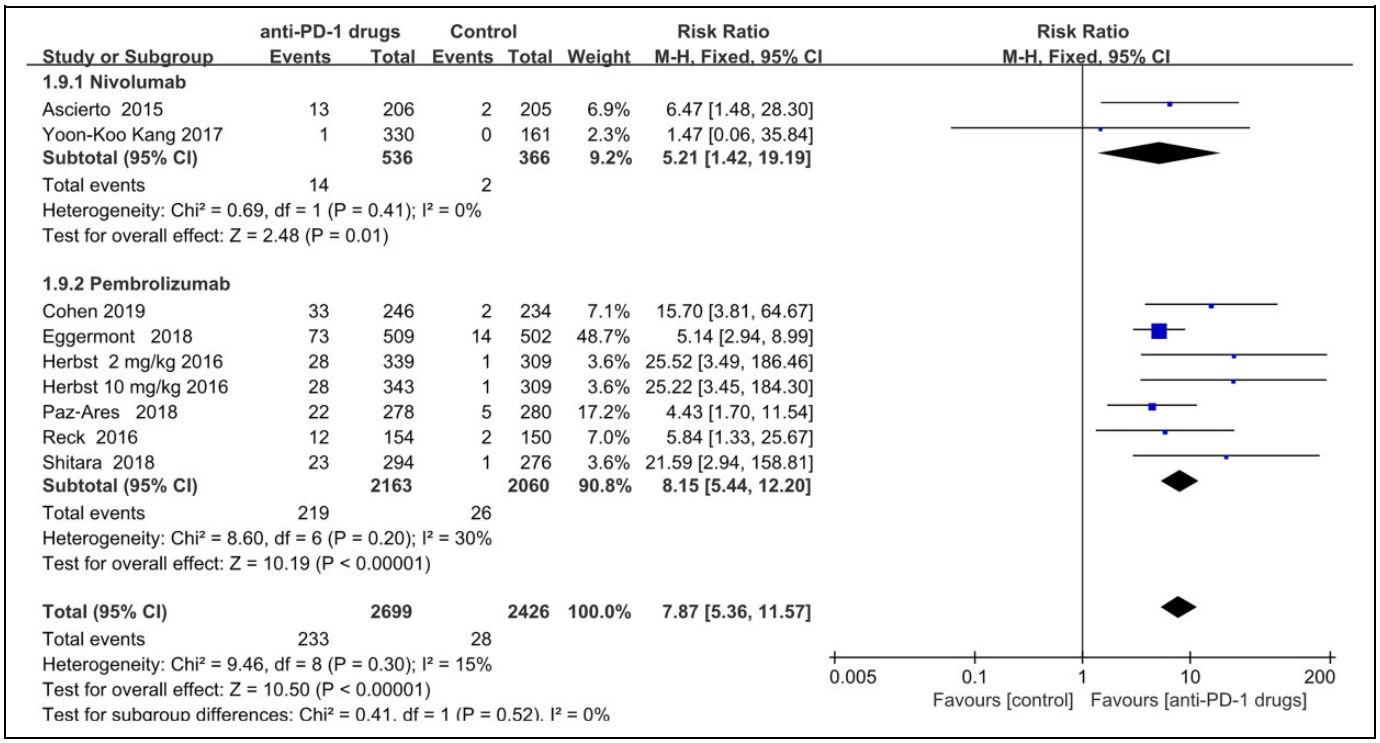

Figure 7. Forest plot of hypothyroidism.

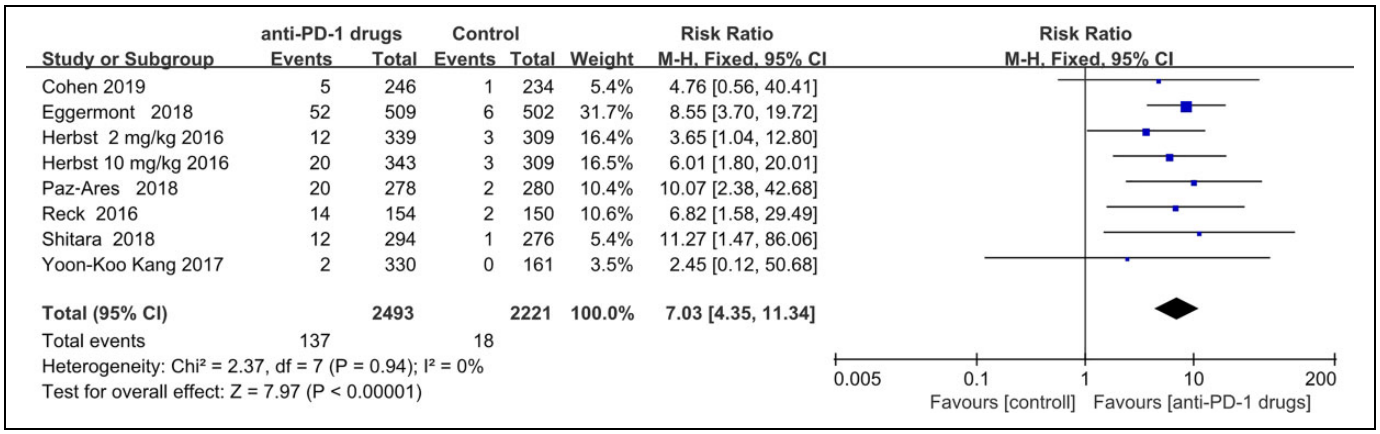

Figure 8. Forest plot of hyperthyroidism.

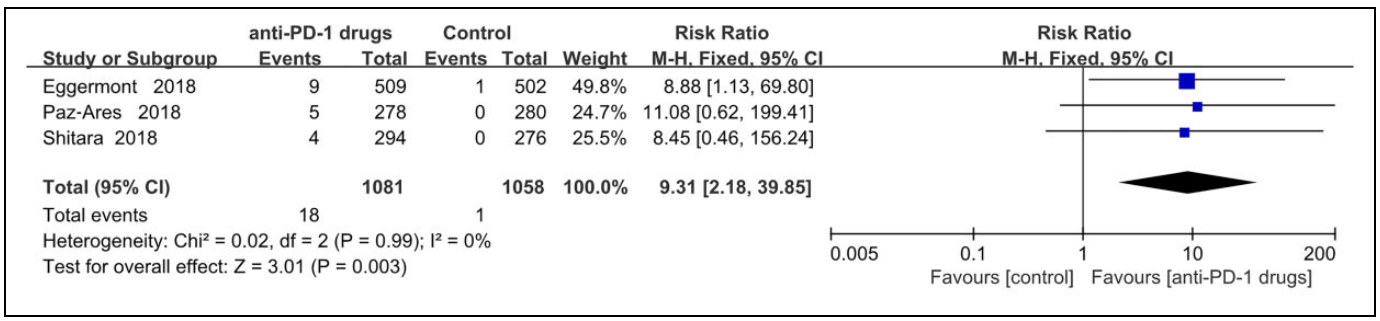

Figure 9. Forest plot of hepatitis.

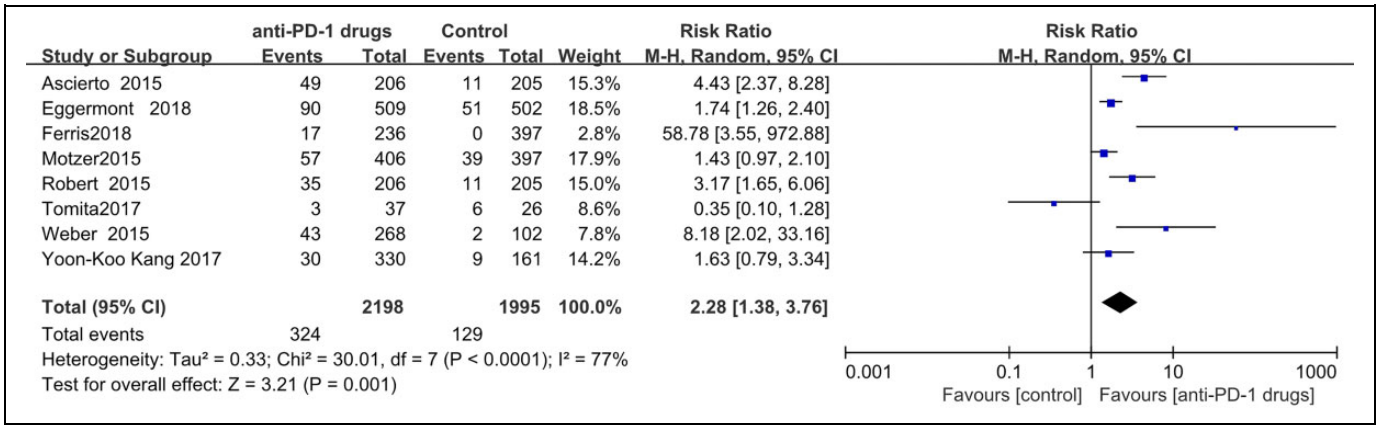

Figure 10. Forest plot of pruritus.

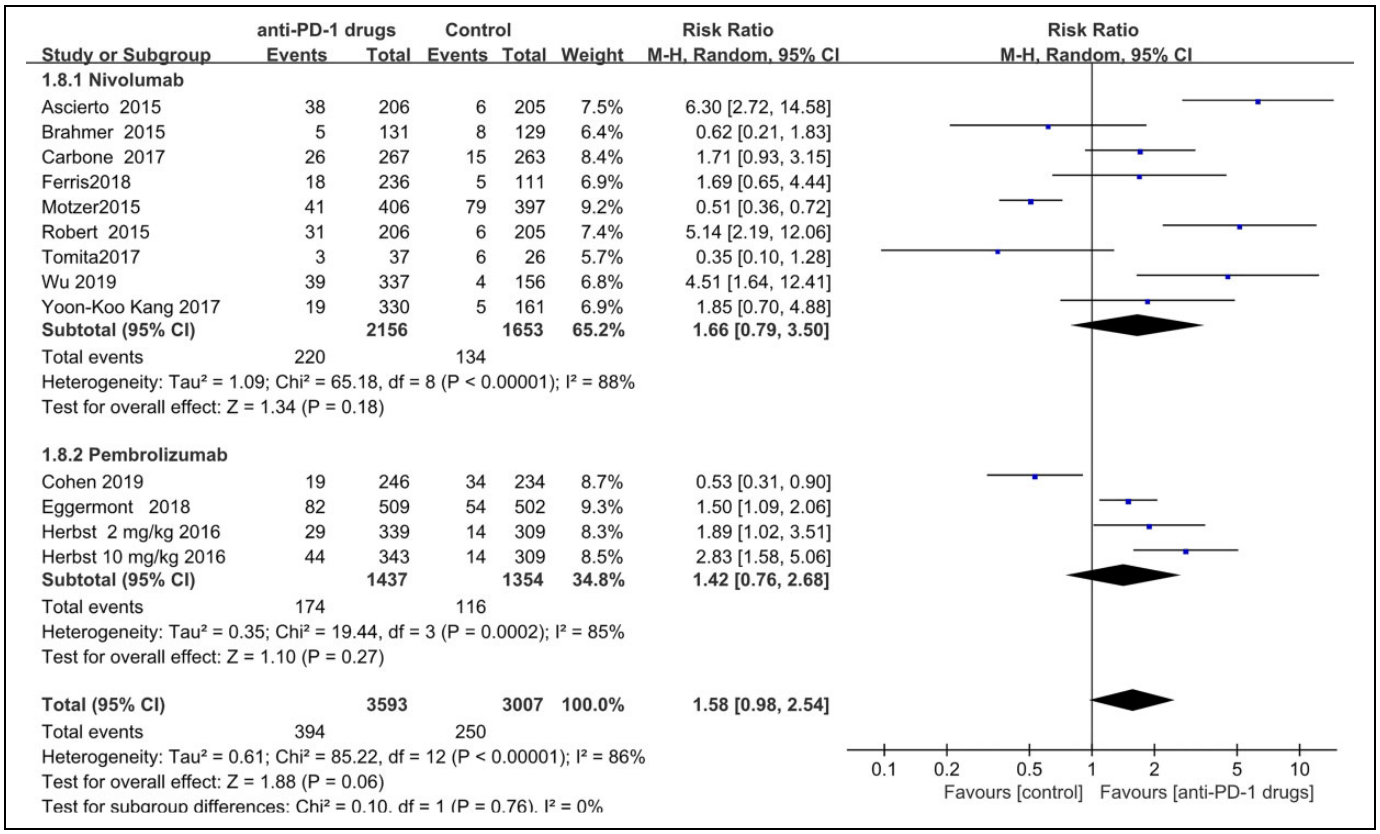

Figure 11. Forest plot of rash.

Mechanisms of the action of anti-PD-1 drugs involve enhancement of patient immune function, through active or passive methods.[31] We conducted a subgroup analysis of total irAE between pembrolizumab and nivolumab, and found that the risk was similar between the 2 drugs. It can help clinicians who choose the 2 types of anti-PD-1drugs based on their therapeutic effects, rather than with the aim of reducing irAE in the future.

We found that risk of hyperthyroidism, was a significantly and markedly increased in patients receiving anti-PD-1 drugs. Based on the findings of a previous study[32] combined with the results of this review, we consider anti-PD-1drug have bidirectional effects on thyroid function, as they can cause hypothyroidism or hyperthyroidism. This finding could help clinicians to identify and correctly address thyroid function related irAE when treating patients with anti-PD-1 drugs.

Our results regarding the risk of rash were inconsistent with those of a previous study.[6] The risk of rash was not increased. Since we included more anti-PD-1 drug studies, any differences in the results presented here with those of previous

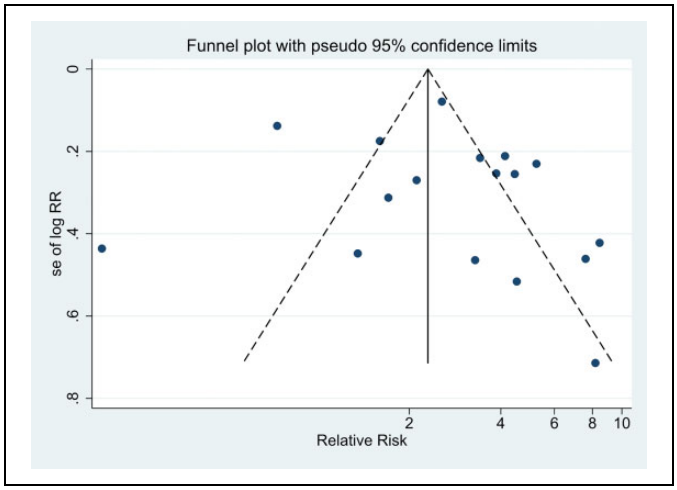

Figure 12. Funnel plot to assess potential publication bias.

reviews could be attributed to that factor. Furthermore, we found that the risk of musculoskeletal problems was similar between anti-PD-1drugs and other therapies. We speculate that the researchers who conducted the RCT may not have been fully informed about the risk of musculoskeletal problems as irAE, leading to inaccurate diagnosis and recording of these events.

Study Strengths and Limitations

The strengths of this study are that all included studies were randomized controlled trial and that it was focused on anti-PD-1 drugs, rather than all immune checkpoint inhibitors, making the studies included in this review less heterogenous than those in previously published analyses, and our results more reliable. In addition, we performed subgroup analyses of patients treated with pembrolizumab and nivolumab, to increase the specificity of our irAE data. Moreover, compared with a previous review,[6] this review updated data from previous RCT and data from additional RCT conducted over the last 2 years.

Conclusion

Consistent with previous reports, the risk of organ-specific irAE in patients treated with anti-PD-1 drugs was higher than that for those administered control treatments. The results of this review, demonstrated that, compared with control groups, the risk of hyperthyroidism is also increased in patients receiving anti-PD-1 treatment; however, the risk of rash as a general immune activation-related adverse event was not increased. The overall risk of irAE was similar for patients treated with pembrolizumab and nivolumab.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Our study did not require an ethical board approval because it is a systematic review and meta-analysis and it did not contain human or animal trials.

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Supplemental Material

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