Systematic Review and Meta-Analysis

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Odds ratio of programmed cell death-1 or ligand 1 inhibitor-related endocrine dysfunction in patients with lung cancer

A systematic review and meta-analysis

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Abstract

Purpose: We designed the study to investigate the incidence risk of Programmed Cell Death-1 (PD-1) or Ligand 1 (PD-L1) inhibitor-related endocrine dysfunction in patients with lung cancer.

Method: All the data were collected by 1 primary reviewer and then independently reviewed by 2 secondary reviewers according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISM) guidelines. Incidence risk of all-grade and grade 3–5 PD-1/PD-L1 inhibitors related endocrine dysfunction in patients with lung cancer were taken into account.

Results: Overall, 12 clinical trials comprising 6108 patients were identified in this systematic review and meta-analysis. The incidence risk of hypothyroidism, hyperthyroidism and adrenal insufficiency was higher in NSCLC patients receiving combination treatments. The incidence rate of all-grade of hypothyroidism was lower in PD-1/PD-L1 inhibitor subgroup compared to chemotherapy (OR = 22.62, 95%CI:9.79–52.25), while the similar result was seen in another treatment regimen (PD-1 + platinum-based chemotherapy vs platinum-based chemotherapy) (OR = 2.93, 95%CI: [2.08, 4.11). The different result can be seen in the group related to the other treatment regimen (1PD-1/PD-L1 inhibitor vs 2 PD-1/PD-L1 inhibitors) (OR = 0.40, 95%CI:0.21–0.76). All the results of the above analysis were considered to be statistical significant. Similar result could also be seen in meta-analysis related to hyperthyroidism and adrenal insufficiency.

Conclusion: The incidence risk of endocrine dysfunctions, including hypothyroidism, hyperthyroidism and adrenal insufficiency, were higher for PD-1/PD-L1 inhibitors group.

Abbreviations: CI = confidence interval, FE = fixed effect, HR = hazard ratios, ICI = immune checkpoint inhibitors, IrAEs = immune-related adverse events, NSCLC = non-small cell lung cancer, OR = odds ratio, PD-1 = programmed cell death-1, PD-L1 = programmed cell death ligand 1, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RE = random effect, RR = risk ratio.

Keywords: endocrine dysfunction, lung cancer, meta-analysis, PD-1/PD-L1

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JX, ZZ, SZ, and YL contributed equally to this work.

This study is a rearrangement analysis of results of relevant clinical trials. No ethics of human or animal was involved. So, ethical approval was not necessary.

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1. Introduction

The Programmed Cell Death 1 (PD-1) receptor had emerged as a dominant negative regulator of anti-tumor T cell effector function when engaged by its ligand—Programmed Cell Death Ligand 1 (PD-L1), expressed on the surface of cells within a tumor.[1] It was reported that PD-1 played a key role in the maintenance of immunological tolerance to self- antigens, preventing autoimmune disorders,[2–5] while immune checkpoint inhibitors (ICI), including CTLA-4 and PD-1, were able to unleash T cells to fight cancer. The first PD-1 antibody inhibitor drug, named as Nivolumab, was first administered to a patient in October 2006 in a phase 1 trial. The result of the clinical trial showed that Nivolumab had anti-tumor efficacy in non-small cell lung cancer.[6]

PD-1/PD-L1 inhibitors had marked efficacy in the treatment of advanced cancers.[7–10] With the increasing number of large clinical trials, the anti-tumor effect of PD-1/PD-L1 inhibitors in non-small cell lung cancer (NSCLC) had been increasingly confirmed.[11–22] Endocrine dysfunctions, generally referred as immune-related adverse events (IrAEs), including hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, adrenal insufficiency, and insulin-deficient diabetes, were deemed to be the most common IrAEs that had been reported in clinical trials related to PD-1/PD-L1 inhibitors or other immune checkpoint inhibitors.[11–24] Although there had been previous meta-analysis about the incidence risk of endocrine dysfunctions following the use of immune checkpoint inhibitor regimens, 6 large clinical trials which was finished in the past two years had not been included.[25] The inclusion of the results of these new clinical trials might have a profound impact on the results of the analysis, and even lead to new and much more credible analysis results. In order to clarify the incidence risk of endocrine dysfunctions for the treatment of NSCLC with PD-1/PD-L1 inhibitors, we conducted the systematic review and meta-analysis.

2. Materials and methods

2.1. Search strategy and selection criteria

A systematic search of the literature were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to identify clinical trials of PD1/PD-L1 for lung cancer patients.[26] The PRISMA checklist was provided in supplemental appendix, http://links.lww.com/MD/D448. Original articles, related to results of prospective clinical trials with PD-1/PD-L1 inhibitor regimens for lung cancer patients, including mono-therapy and combination therapy, were verified by a PubMed search. We paid our attention mainly to English studies ranged from Jan 01, 2013 to Nov 30,2018 (Keywords "PD1/PD-L1", "Nivolumab", "BMS-963558", "Pembrolizumab", "MK-3475", "Atezolizumab", "MPDL3280A", "lung cancer", "SCLC", "NSCLC", "safety", "toxicity"). We selected trials just for human beings which were shown in full text, abstract, or poster form. Four members of our team were appointed for identifying their eligibility.

The criteria for the selected data:

(1) available data of PD-1/PD-L1 related drugs in cases and controls provided;
(2) safety or toxicity was available for evaluating OR with 95% CI or other evaluable indicators such as RR, HR and so on;
(3) subjects were diagnosed with lung cancer by typical imaging changes or pathological biopsy;
(4) clinical trials or comparative studies.

We excluded trials that:

(1) involved combination regimens with other therapies and/or modalities other than PD1/PD-L1 inhibitors;
(2) serious complications not related to the purpose of the study;
(3) studies with incomplete results or data. Any discrepancy in study selection was resolved by consensus.

2.2. Data extraction and validity assessment

The extraction of the data was put into practice according to the criteria recommended by the Cochrane Collaboration.[27] The total number of lung cancer patients treated with PD-1/PD-L1 inhibitors and the number of patients with safety or toxicity problems for all grades were collected. The trial phases, tumor types, types of specific drugs, doses, and frequency of drug administration were marked. If no useful data about toxicities of related drugs was found, we would try to get in touch with the corresponding author for much more information. If some useful details were unavailable, the study would be precluded from the analysis. The primary aims were toxicities, including hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, adrenal insufficiency, and insulin-deficient diabetes. The data extraction of PD1/PD-L1 inhibitors was finished independently by two clinical oncologists, and then the comparison was made. The corresponding author of the article would be responsible for disagreements and had the right to make a final decision. Survival status comprised mortality rate of patients and complications affecting the prognosis.

2.3. Statistical analysis

We took Newcastle-Ottawa scale, proposed by the Cochrance Collaboration, to evaluate the quality of study.[28] Odds ratio (OR) value was reported to be a much more conservative evaluation parameter and might be more inclined to reveal a safety signal, as the method by which an OR is calculated provided a point estimate farther from unity than that provided by a HR. OR, and 95% confidence interval (CI) would be summarized by random effect (RE) or fixed effect (FE) models according to the actual situation of the data. $P < .05$ was deemed to be statistically significant. Most of the time, we took a RE model to deal with all the data for the existence of differences among all studies.[29] Cochrane's Q statistic and the I^2 statistic were taken to evaluate the heterogeneity among studies just as proposed by Higgins and colleagues,[30] while Harbord test was adopted to evaluate publication bias for all studies. $P < .05$ was deemed to be publication bias. The software of Review Manager 5.3 was used for data consolidation and analysis. Statistical tests were all two-sided. The study was approved by the First Hospital Affiliated with Shandong First Medical University.

3. Results

Among all the citations identified by our electronic and manual searches, 156 articles met the preliminary inclusion criteria. After screening and eligibility assessment, a total of 12 clinical trials including 6108 patients were collected.[11–22] The characteristics of them were listed in (Table 1). Trial types included 9 phase 3 studies,[11–17,21,22] 1 phase 2/3,[19] 1 phase 2,[18] 1 phase 1/2.[20] All clinical trials enrolled in the meta-analysis included at least

Table 1

Basic information and characteristics of the included studies.

NO	Name of Study	Treatment Regimen	Participants	Tumor type	Description of Study design
1	Socinski et al[11]	Atezolizumab + CP vs CP	692	Metastatic nonsquamous non-small-cell lung cancer NSCLC	An open-label, phase 3 study
2	Hellmann et al[12]	Nivolumab vs Nivolumab + Ipilimumab	299	Stage IV or recurrent NSCLC that was not previously treated with chemotherapy	An open-label, multipart, phase 3 trial
	Hellmann et al[12]	Nivolumab VS Chemotherapy			
	Hellmann et al[12]	Nivolumab+ Ipilimumab vs Chemotherapy			
3	Paz-Ares et al[13]	Pembrolizumab + CP vs Placebo + CP	558	Untreated metastatic, squamous NSCLC	A randomised, double-blind, phase 3 trial
4	Gandhi et al[14]	Pembrolizumab + PC vs Placebo + PC	616	Metastatic nonsquamous NSCLC who had received no previous treatment for metastatic disease	A double-blind, phase 3 trial
5	Govindan et al[15]	Ipilimumab + CP vs Placebo + CP	749	Stage IV or recurrent chemotherapy-naïve squamous NSCLC	A randomized, double-blind, phase 3 study
6	Antonia et al[16]	Durvalumab vs Placebo	709	Stage III Non-Small-Cell Lung Cancer.	A randomized phase 3 study
7	Reck et al[17]	Pembrolizumab vs Chemotherapy	304	Untreated advanced non-small-cell lung cancer (NSCLC)	An open-label, randomized phase 3 trial
8	Langer et al[18]	Pembrolizumab + PC vs Placebo + PC	123	Chemotherapy-naive, stage IIIB or IV, non-squamous NSCLC without targetable EGFR or ALK genetic aberrations	A randomised, phase 2 cohort of the open-label study
9	Herbst et al[19]	Pembrolizumab 2 vs Docetaxel	991	Previously treated non-small-cell lung cancer (NSCLC)	A randomised, controlled, open-label, phase 2/3 study
	Herbst et al[19]	Pembrolizumab 10 vs Docetaxel			
10	Antonia et al[20]	Nivolumab vs Nivolumab1 + Ipilimumab3	213	Limited-stage or extensive-stage SCLC, and had disease progression after at least one previous platinum-containing regimen.	A phase 1/2 multicentre, multi-arm, open-label trial
	Antonia et al[20]	Nivolumab vs Nivolumab 3 + Ipilimumab 1			
11	Brahmer et al[21]	Nivolumab vs Docetaxel	272	Advanced squamous-cell lung cancer (NSCLC)	A randomized, open-label, international, phase 3 study
12	Borghaei et al[22]	Nivolumab vs Docetaxel	582	Non-squamous non-small-cell lung cancer (NSCLC)	A randomized, open-label, international phase 3 study

Chemotherapy = carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel, CP = carboplatin plus paclitaxel, NSCLC = non–small cell lung cancer, PC = pemetrexed and a platinum-based drug, PD-1 = programmed cell death 1, PD-L1 = programmed cell death ligand 1, SCLC = small cell lung cancer.

one experimental group and one control group. The incidence risk of endocrine dysfunction would be evaluated by grades (all-grade, grade 1–2 and grade 3–5) first. Then, we divided the included data into three subgroups for meta-analysis based on the experimental and control protocols. The first treatment regimen used in 4 studies was a PD-1 inhibitor plus a platinum-based combination chemotherapy versus a platinum-based combination chemotherapy,[11,13,14,18] while the second treatment regimen used in the other 6 studies was PD-1 inhibitor versus mono-chemotherapy or combination chemotherapy.[12,15,17,19,21,22] Third, there were 2 studies that PD-1 inhibitors were used in both the experimental and control groups,[12,20] while the experimental group involved in 1 study was a PD-1 inhibitor and the control group was a placebo.[16] We used Newcastle-Ottawa scale to evaluate study quality and risk of bias in both comparison and non-comparison studies. All the enrolled studies were of high quality. The flow diagram of study inclusion was displayed in (Supplemental Fig. 7, http://links.lww.com/MD/D445). The risk of bias graph and summary were listed in (Supplemental Fig. 8, http://links.lww.com/MD/D446 and 9, http://links.lww.com/MD/D447).

3.1. Incidence risk of hypothyroidism

Ten studies of lung cancer with PD-1/PD-L1 inhibitors data were used for calculating the incidence risk of hypothyroidism by grades, which were divided into group A (all-grade of hypothyroidism),[11–14,17–22] group B (grade 1–2),[11–14,17–22] and group C (grade 3–5).[11–14,20] Then, all the data of every group were taken to make further stratification analysis according to treatment regimens. The random effect model was tried first to deal with the raw data. The forest plots of all-grade were shown in (Fig. 1).

The overall outcome of group A1 (all-grade of hypothyroidism) with the treatment regimen (PD-1 inhibitor vs mono-chemotherapy or combination chemotherapy) were summarized at the bottom of (Fig. 1A1) (OR = 22.62, 95%CI:[9.79, 52.25], $I^2 = 1\%$, $Z = 7.30$ ($P < .00001$)),[12,17,19,21,22] while the similar result of another treatment regimen (PD-1 inhibitor+platinum-based chemotherapy vs platinum-based chemotherapy) was displayed in (Fig. 1A2) (OR = 2.93, 95%CI:[2.08, 4.11],$I^2 = 0\%$, $Z = 6.18$ ($P < .00001$)).[11,13,14,18] Different from the above, the opposite result was shown in (Fig. 1A3) (OR = 0.40, 95%CI: [0.21, 0.76], $I^2 = 24\%$, $Z = 2.82$ ($P = .005$)), related to the treatment regimen (1 PD-1 inhibitor vs 2 PD-1 inhibitors). All the results of the above analysis were considered to have significant statistical differences.

Moderate heterogeneity could be only seen in (Fig. 1A3) ($I^2 = 24\%$, $P = .27$).[12,20] Harbord test statistic did not suggest obvious publication bias in funnel plot (Supplemental Fig. 1A1–3, http://links.lww.com/MD/D439). Then, the incidence risks of grade 1–2 and grade 3–5 hypothyroidism were taken into account. The results of the incidence rates related to all-grade and grade 1–2 were almost the same. The details of the meta-analysis

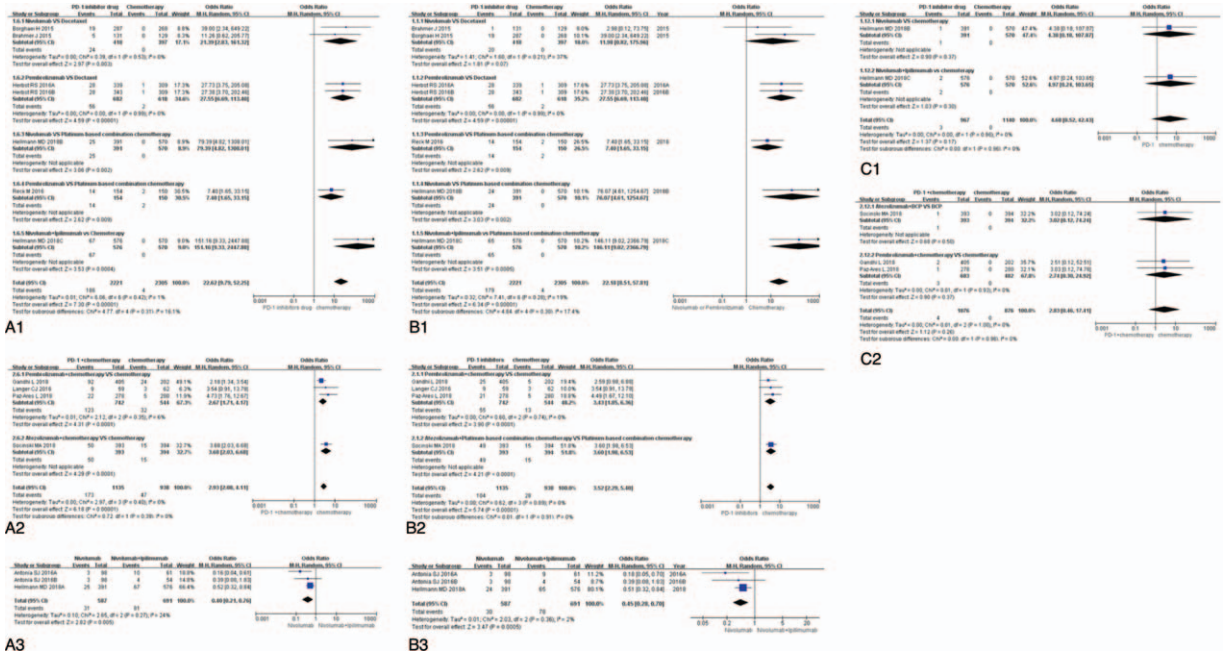

Figure 1. Forest plot of meta-analysis: Incidence of Hypothyroidism During Treatment With Different PD-1 Inhibitor Regimens; Incidence rates are represented by boxes and whiskers indicate binomial exact 95% CIs; Model results are shown for each class of therapy as a polygon using the fitted value and 95% prediction interval. Random effect model was used for all the data. A1: Incidence of overall grades of hypothyroidism during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); A2: Incidence of overall grades of hypothyroidism during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy); A3: Incidence of overall grades of hypothyroidism during treatment with treatment regimen (1 PD-1 inhibitor drug vs 2 or more PD-1 inhibitor drugs); B1: Incidence of grade 1–2 hypothyroidism during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); B2: Incidence of grade 1–2 hypothyroidism during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy); B3: Incidence of grade 1–2 hypothyroidism during treatment with treatment regimen (1 PD-1 inhibitor drug vs 2 or more PD-1 inhibitor drugs); C1: Incidence of grade 3–5 hypothyroidism during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); C2: Incidence of grade 3–5 hypothyroidism during treatment with treatment regimen (PD-1 inhibitor drug + chemotherapy vs chemotherapy).

for grade 1–2 were summarized in (Fig. 1B).[11–14,17–22] Harbord test statistic The funnel plots for grade 1–2 were provided in (Supplemental Fig. 1B1–3, http://links.lww.com/MD/D439). However, The analysis outcomes of the grade 3–5 incidence risk were considered to have no statistically significant differences.[11–14,20] The forest plot and funnel plot were listed in (Fig. 1C) and (Supplemental Fig. 1C1–2, http://links.lww.com/MD/D439) separately.

3.2. Incidence risk of hypophysitis

The incidence risk of hypophysitis for all-grade in 5 studies were reported.[13,14,17,19,22] A total of 11 cases of all-grade hypophysitis were observed among 2404 patients. The overall outcome of all grade of hypophysitis with the treatment regimen (PD-1 inhibitor vs mono-chemotherapy or combination chemotherapy) were summarized at the bottom of (Fig. 2A1) (OR = 5.05, 95%CI:[0.87, 29.40], $I^2 = 0\%$, Z = 1.80 ($P = .07$)),[13,14,17,19,22] while similar result of the treatment regimen (PD-1/PD-L1 inhibitor + platinum-based chemotherapy vs platinum-based chemotherapy) was displayed in (Fig. 2A2) (OR = 3.47, 95%CI:[0.39, 30.65], $I^2 = 0\%$, Z = 1.12 ($P = .26$)). [13,14,17,19,22] The similar results of stratification for grade 1–2 were provided in (Fig. 2B1 and B2). Since only 1 patient was reported with a grade 3 degree thyroiditis, no meta-analysis was performed.[13] All the results of the above analysis, even in further stratification analysis, were considered to have no statistical significance. Harbord test statistic did not suggest obvious publication bias in funnel plot (Supplemental Fig. 2A1 and 2A2, http://links.lww.com/MD/D440, Supplemental Figure 2B1 and 2B2, http://links.lww.com/MD/D440).

3.3. Incidence risk of hyperthyroidism

A total of 9 studies related to NSCLC with PD-1/PD-L1 inhibitors were taken to make further analysis about hyperthyroidism by grades, which were divided into group A (all-grade of hyperthyroidism),[11,13,14,15,17–19,20,22] group B (grade 1–2),[11,13–15,17–19,20,22] and group C (grade 3–5).[11,13,19] Then, all the data of every group were taken to make further stratification analysis about hyperthyroidism according to treatment regimens. The random effect model was adopted to deal with the raw data. The forest plots of all were shown in (Fig. 3).

The overall outcome of group A1 (all-grade of hyperthyroidism) with the treatment regimen (PD-1/PD-L1 inhibitor vs mono-chemotherapy or combination chemotherapy) were summarized at the bottom of (Fig. 3A1) (OR = 5.39, 95%CI:[2.58, 11.27], $I^2 = 0\%$, Z = 4.47 ($P < .000001$)), [17,19,22] while similar result of the treatment regimen (PD-1/PD-L1 inhibitor + platinum-based chemotherapy vs platinum-based chemotherapy) was displayed in (Fig. 3A2) (OR = 2.93, 95%CI:[2.08, 4.11], $I^2 = 0\%$, Z = 6.18 ($P < .00001$)).[11,13–15,18] Statistically significant different result could also be seen in (Fig. 3A3) (OR = 0.23, 95%CI:[0.07,0.76], $Tau^2 = 0.00$, $I^2 = 0\%$, Z = 2.41 ($P = .02$)), related to the treatment regimen (1 PD-1/PD-L1 inhibitor vs 2 PD-1/PD-L1 inhibitors).[20]

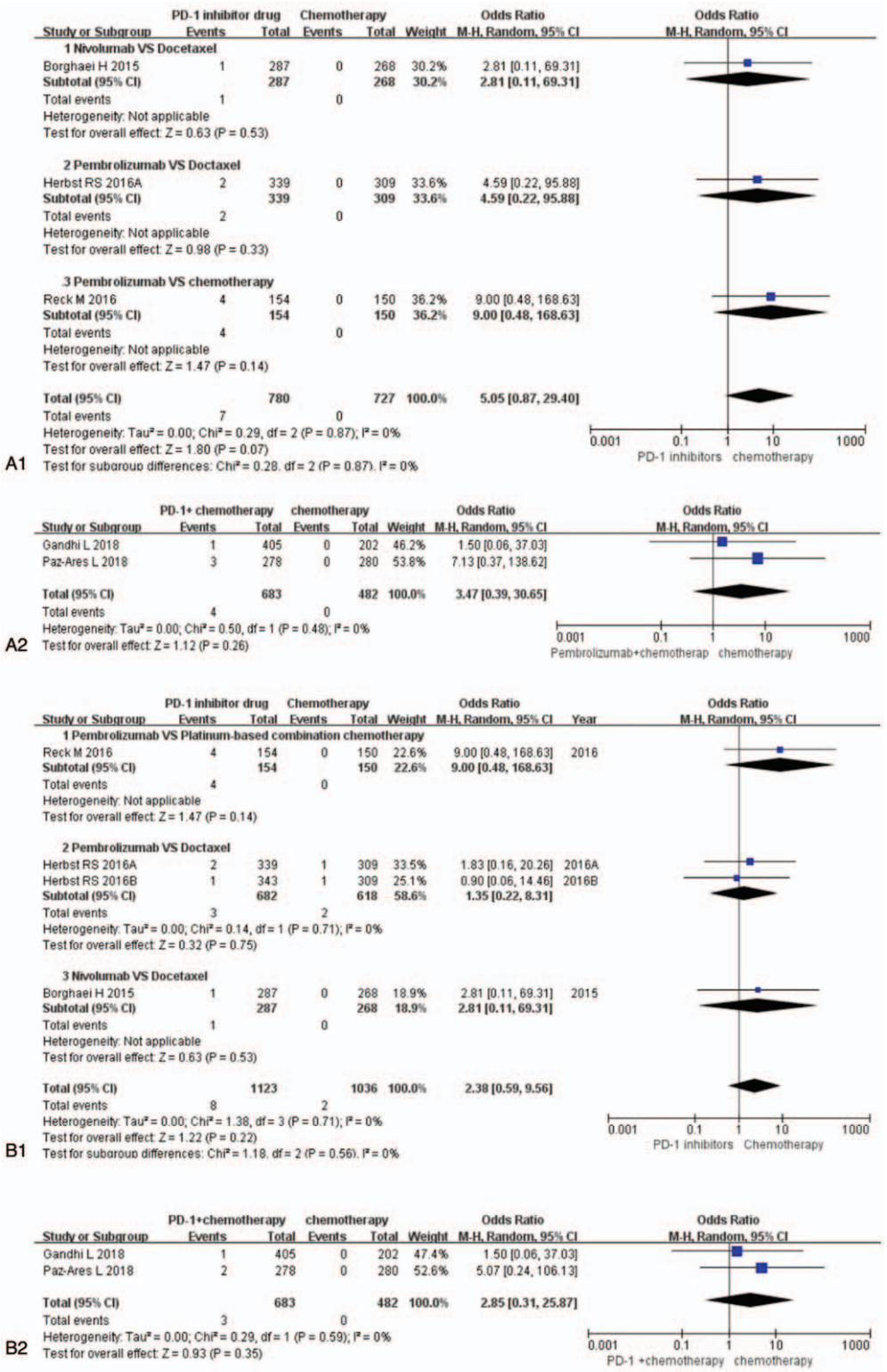

Figure 2. Forest plot of meta-analysis: Incidence of Thyroiditis During Treatment With Different PD-1 Inhibitor Regimens; Incidence rates are represented by boxes and whiskers indicate binomial exact 95% CIs; Model results are shown for each class of therapy as a polygon using the fitted value and 95% prediction interval. Random effect model was used for all the data. A1: Incidence of overall grades of thyroiditis during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); A2: Incidence of overall grades of thyroiditis during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy); B1: Incidence of grade 1–2 thyroiditis during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); B2: Incidence of grade 1–2 thyroiditis during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy).

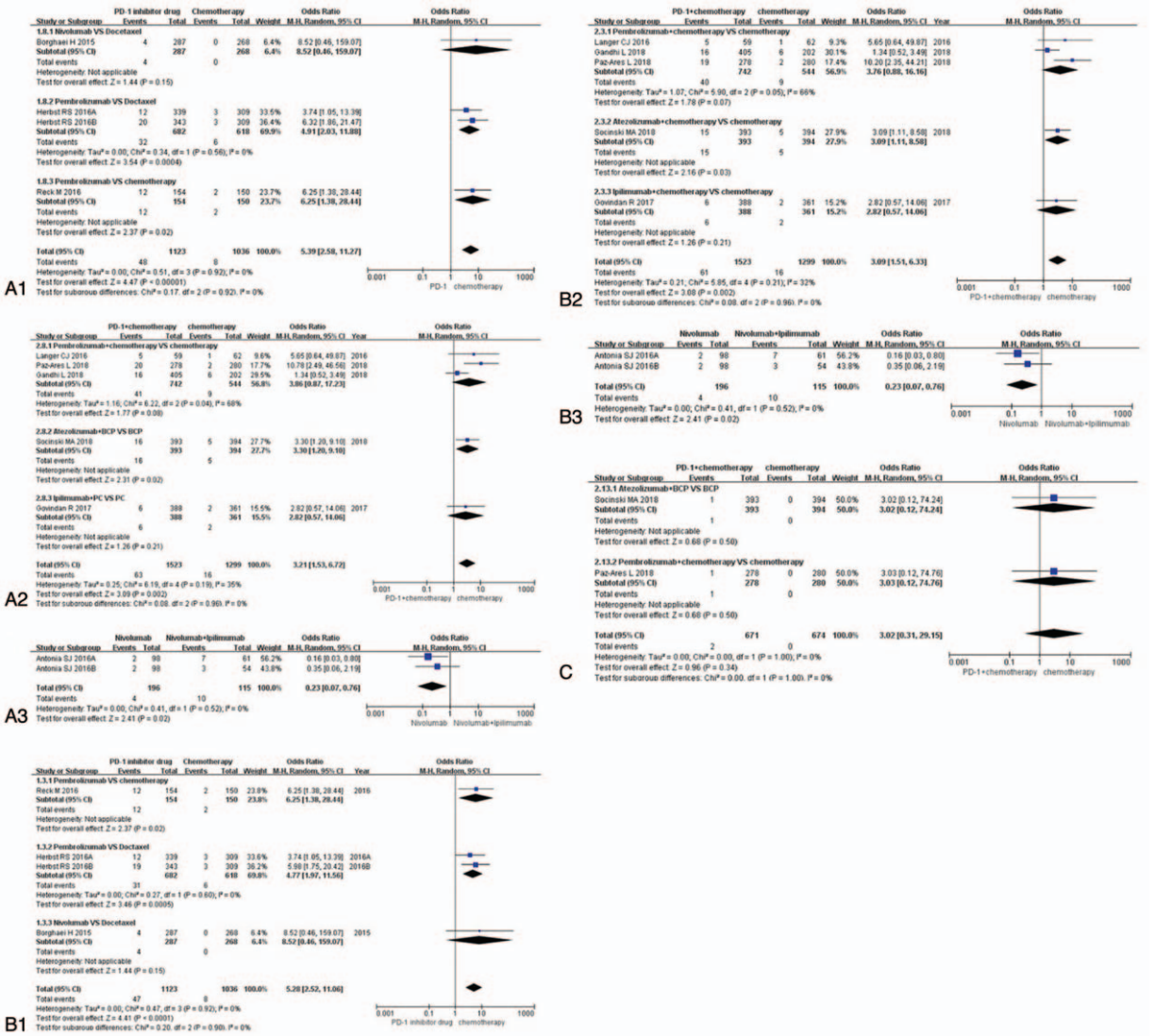

Figure 3. Forest plot of meta-analysis: Incidence of Hyperthyroidism During Treatment With Different PD-1 Inhibitor Regimens; Incidence rates are represented by boxes and whiskers indicate binomial exact 95% CIs; Model results are shown for each class of therapy as a polygon using the fitted value and 95% prediction interval. Random effect model was used for all the data. A1: Incidence of overall grades of hyperthyroidism during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); A2: Incidence of overall grades of hyperthyroidism during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy); A3: Incidence of overall grades of hyperthyroidism during treatment with treatment regimen (1 PD-1 inhibitor drug vs 2 or more PD-1 inhibitor drugs); B1: Incidence of grade 1–2 hyperthyroidism during treatment with treatment regimen (PD-1 inhibitor drug s chemotherapy); B2: Incidence of grade 1–2 hyperthyroidism during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy); B3: Incidence of grade 1–2 hyperthyroidism during treatment with treatment regimen (1 PD-1 inhibitor drug vs 2 or more PD-1 inhibitor drugs); C: Incidence of grade 3–5 hyperthyroidism during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy).

No heterogeneity were found among the results of the above analysis (Fig. 3A) ($I^2=0\%$).[11,13–15,17–19,20,22] Harbord test statistic did not suggest obvious publication bias in funnel plot (Supplemental Fig. 3A1–3, http://links.lww.com/MD/D441).

Then, the incidence risk of grade 1–2 hyperthyroidism was calculated. The results of the incidence risk related to all-grade and grade 1–2 were similar to each other (Fig. 3B), [11–14,17–22] while the analysis result of grade 3–5 was considered to have no statistical significance (Fig. 3C). The details of the meta-analysis for grade 1–2 and grade 3–5 were summarized in (Fig. 3B)[11–14,17–22] and (Fig. 3C) separately.[11,13] The funnel plots of grade 1–2 and grade 3–5 were shown in (Supplemental Figs. 3B1–3 and C1–3, http://links.lww.com/MD/D441).

3.4. Incidence risk of adrenal insufficiency

The incidence risk of adrenal insufficiency for all-grade in 6 studies were reported.[11,12,14,15,19,20] A total of 46 cases of all-grade adrenal insufficiency were observed among 5487 patients. The incidence risk of adrenal insufficiency for the chemotherapy regimen was higher than the PD-1/PD-L1 inhibitor regimen. The overall outcome of all-grade of adrenal insufficiency with the treatment regimen (PD-1/PD-L1 inhibitor vs mono-chemotherapy or combination chemotherapy) were summarized at the bottom of (Fig. 4A1) (OR = 7.98, 95%CI:[1.78, 35.77], $I^2=0\%$, $Z=2.71$ ($P=.007$)),[12,19] while the result of the treatment regimen (PD-1 inhibitor + platinum-based chemotherapy vs platinum-based chemotherapy) with no statistical significance

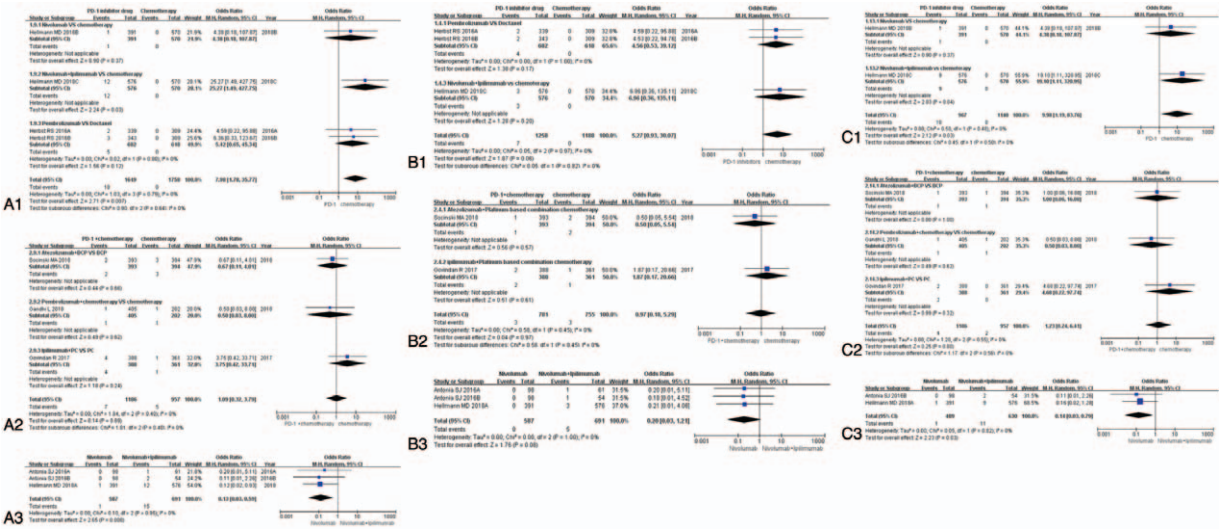

Figure 4. Forest plot of meta-analysis: Incidence of Adrenal insufficiency During Treatment With Different PD-1 Inhibitor Regimens; Incidence rates are represented by boxes and whiskers indicate binomial exact 95% CIs; Model results are shown for each class of therapy as a polygon using the fitted value and 95% prediction interval. Random effect model was used for all the data. A1: Incidence of overall grades of Adrenal insufficiency during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); A2: Incidence of overall grades of Adrenal insufficiency during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy); A3: Incidence of overall grades of Adrenal insufficiency during treatment with treatment regimen (1 PD-1 inhibitor drug vs 2 or more PD-1 inhibitor drugs); B1: Incidence of grade 1–2 Adrenal insufficiency during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); B2: Incidence of grade 1–2 Adrenal insufficiency during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy); B3: Incidence of grade 1–2 Adrenal insufficiency during treatment with treatment regimen (1 PD-1 inhibitor drug vs 2 or more PD-1 inhibitor drugs); C1: Incidence of grade 3–5 Adrenal insufficiency during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); C2: Incidence of grade 3–5 Adrenal insufficiency during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy); C3: Incidence of grade 3–5 of Adrenal insufficiency during treatment with treatment regimen (1 PD-1 inhibitor drug vs 2 or more PD-1 inhibitor drugs).

was displayed in (Fig. 4A2) (OR = 1.09, 95%CI:[0.32, 3.79], I^2 = 0%, Z = 0.14 (*P* = .89).[11,14,15] The results of stratification for treatment regimen (1 PD-1/PD-L1 inhibitor vs 2 PD-1/PD-L1 inhibitors) were provided in (Fig. 4A3),[12,20] which displayed lower incidence risk of Nivolumab compared to Nivolumab plus Ipilimumab (OR = 0.13, 95%CI:[0.03, 0.59]).

However, when we took all the data of grade 1–2 degree adrenal insufficiency into account, no statistical significant analysis results was found. The details of all the results were summarized in (Fig. 4B1–3). Then, we paid our attention to the analysis of grade 3–5 degree adrenal insufficiency. The overall outcome of the treatment regimen (PD-1/PD-L1 inhibitor vs mono-chemotherapy or combination chemotherapy) were summarized at the bottom of (Fig. 4C1) (OR = 9.98, 95%CI:[1.19, 83.76],I^2 = 0%, Z = 2.12 (*P* = .03)),[12] while the different result of the treatment regimen (1 PD-1/PD-L1 inhibitor vs 2 PD-1/PD-L1 inhibitors) was displayed in (Fig. 4C3) (OR = 0.14, 95%CI:[0.03, 0.79], I^2 = 0%, Z = 2.23 (*P* = .03)).[12,20] Both of them were displayed with statistical significance. There was no difference in the incidence risk of adrenal insufficiency between PD-1/PD-L1 inhibitor combined with a platinum-based combination chemotherapy and platinum-based combination chemotherapy (Fig. 4C2).[11,14,15] No heterogeneity were found among all the results of the above analysis (Fig. 3) (I^2 = 0%).[11,12,14,15,19,20] Harbord test statistic did not suggest obvious publication bias in funnel plots (Supplemental Fig. 4A1–3, http://links.lww.com/MD/D442, Supplemental Fig. 4B1–3, http://links.lww.com/MD/D442 and Supplemental Fig. 4C1–3, http://links.lww.com/MD/D442).

3.5. Incidence risk of hypophysitis and I mellitus

The incidence risk of hypophysitis for all-grade in 5 studies were reported,[11,13,14,17,19] while there were 5 studies related to insulin deficient diabetes (I Mellitus) too.[11,14,17,19,22] The details of the meta-analysis for incidence risk of hypophysitis and I mellitus were summarized at the bottom of each figure (Figs. 5 and 6). The results of stratification for treatment regimen (PD-1 inhibitor + platinum-based chemotherapy vs a platinum-based chemotherapy) were provided in (Fig. 5A2),[11,13,14] which displayed lower incidence risk of chemotherapy group compared to combination group (OR = 5.62, 95%CI:[1.01, 31.18], Z = 1.98 (*P* = .05)). No other similar or statistical significant analysis results were found among all the enrolled data. No heterogeneity were found among all the results of the above analysis (Figs. 5 and 6) (I^2 = 0%).[11,13,14,17,19,22] Harbord test statistic did not suggest obvious publication bias in funnel plots (Supplemental Fig. 5, http://links.lww.com/MD/D443 and Supplemental Fig. 6, http://links.lww.com/MD/D444).

4. Discussion

PD-1/PD-L1 inhibitors played an increasingly important role in anti-tumor therapy.[8] It was reported that PD-1/PD-L1 inhibitor series drugs could unleash anti-tumor immunity and then inhibit tumor growth and improve survival prognosis for some patients with advanced NSCLC,[16,17,31–33] even for neoadjuvant therapy for early stage lung cancer patients.[34,35] PD-1/PD-L1 inhibitors brought good clinical benefits, along with significant toxic side effects, especially when combined with platinum-based chemotherapy.[11–22,31–33] So, we performed this meta-analysis to examine endocrine dysfunction related to the use of PD-1/PD-L1 inhibitors in patients with NSCLC. When we finished the meta-analysis, we found that the combined group had a higher incidence rate of endocrine dysfunction than the mono-therapy group, which some of them were considered to have statistical

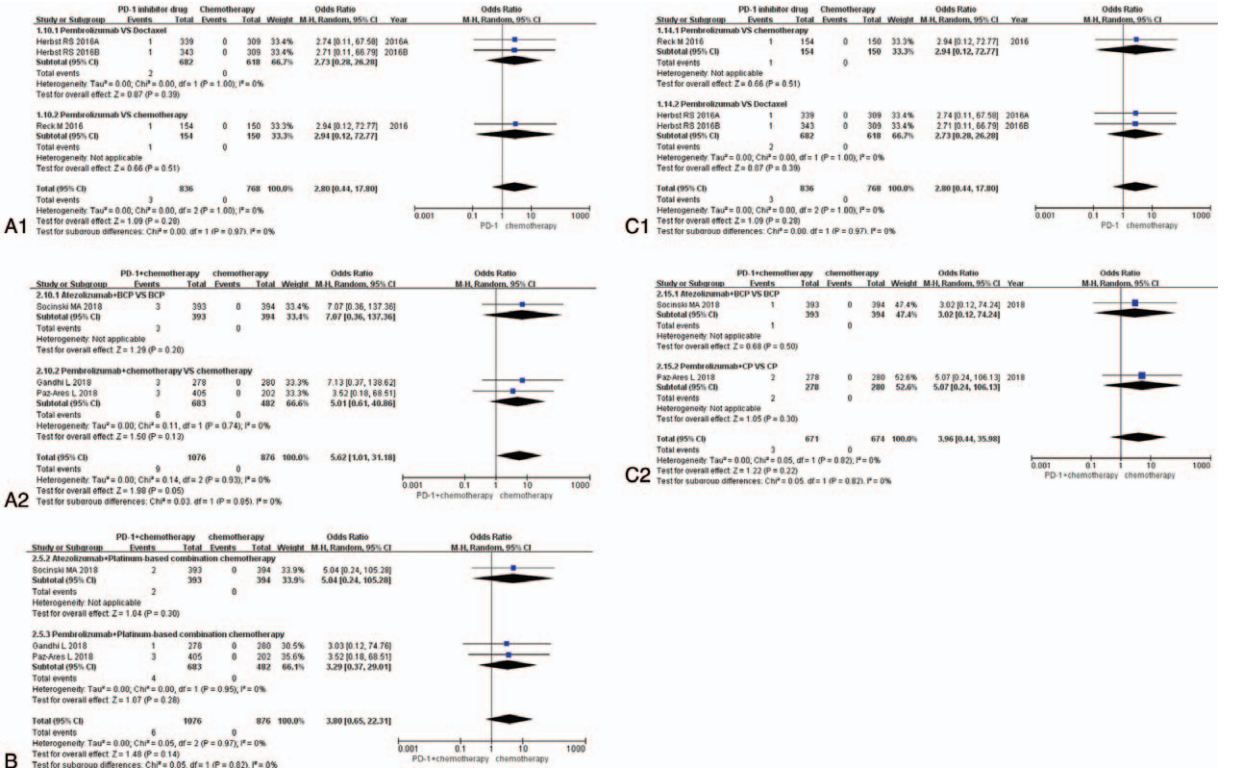

Figure 5. Forest plot of meta-analysis: Incidence of Hypophysitis During Treatment With Different PD-1 Inhibitor Regimens; Incidence rates are represented by boxes and whiskers indicate binomial exact 95% CIs; Model results are shown for each class of therapy as a polygon using the fitted value and 95% prediction interval. Random effect model was used for all the data. A1: Incidence of overall grades of hypophysitis during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); A2: Incidence of overall grades of hypophysitis during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy); B: Incidence of grade 1–2 hypophysitis during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy); C1: Incidence of grade 3–5 hypophysitis during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); C2: Incidence of grade 3–5 hypophysitis during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy).

significance (Fig. 1A and B; Fig. 3A and B; Fig. 4A1, A3, B1, C1, and C3; Fig. 5A2). It was the first time for endocrine dysfunction following the use of PD-1/PD-L1 inhibitors in patients with lung cancer to be evaluated by a comprehensive systematic review and meta-analysis. Much more subgroups and stratification, including treatment regimens and levels of endocrine disorders, were taken into account. More phase 3 clinical studies on NSCLC were included. All of the included studies were of higher quality and had a lower risk of bias (Supplemental Fig. 8, http://links.lww.com/MD/D446 and 9, http://links.lww.com/MD/D447).

Among all endocrine-related complications, unlike previous reports related to other malignant tumors, hypothyroidism is the most common complication (Figs. 1–6) in NSCLC patients,[25,36] but the level was often limited to grade 1–2, and rare at grade 3–5. We found that a higher incidence risk of hypothyroidism among NSCLC patients who received combination therapy (PD-1/PD-L1 + chemotherapy) or PD-1/PD-L1 inhibitors (2 or more PD-1/PD-L1 inhibitors) compared with those who just received PD-1/PD-L1 inhibitors or chemotherapy.[11–22] There were statistically significant differences for the meta-analysis of all-grade and grade 1–2 (Fig. 1A and B).[11–14,17–22] Since the incidence risk of grade 3–5 hypothyroidism was lower, no statistically significant difference could be found (Fig. 1C).[11–14,20] The incidence risk of hypothyroidism was significantly higher in the PD-1/PD-L1 inhibitor group than the chemotherapy group (Fig. 1A1), and the results were statistically significant; therefore, we hypothesized that hypothyroidism may be an endocrine toxicity caused primarily by PD-1/PD-L1 inhibitors. This was subsequently confirmed in the combination of chemotherapy with the PD-1/PD-L1inhibitor group (Fig. 1A2) and the multiple PD-1/PD-L1 inhibitor group (Fig. 1A3). Similar results could also be seen in grade 1–2 level of hypothyroidism (Fig. 1B).

According to previous reports, thyroid disorders have emerged as one of the most common adverse events associated with immune checkpoint inhibitor (ICI) therapy.[36–38] Furthermore, ICI may rarely lead to life-threatening thyroid storm.[39] Another endocrine disorder thyroiditis associated with the thyroid gland has also been included in the meta-analysis evaluation.[13,14,17,19,22] However, after systematic evaluation and meta-analysis, no statistical differences were found among the subgroups. No significant correlation was found between the incidence risk and the use of PD-1/PD-L1 inhibitors (Fig. 2).[13,14,17,19,22] Therefore, we concluded that thyroiditis was only a treatment complication with a low incidence and might not be significantly associated with the use of PD-1/PD-L1 inhibitors.

Another thyroid-related endocrine disorder, hyperthyroidism, had also been assessed. [11,13–15,17–20,22] Its incidence risk trend was similar to hypothyroidism. Compared with those who just received PD-1/PD-L1 inhibitors or chemotherapy (Fig. 3), a higher incidence risk of hyperthyroidism for NSCLC patients

who received combination therapy (PD-1/PD-L1 + chemotherapy) or PD-1/PD-L1 inhibitors (2 or more PD-1/PD-L1 inhibitors). In addition to the grade 3–5 hyperthyroidism (Fig. 3C),[11,13,19] there were significant statistical differences among others (Fig. 3A and B).[11,13–15,17–20,22] Therefore, we could conclude that hyperthyroidism was another common endocrine dysfunction caused by PD-1/PD-L1 inhibitors. However, up to now, although hyperthyroidism and hypothyroidism had been reported in many clinical trials related to PD-1/PD-L1 inhibitors or other ICIs, the specific mechanism of triggering hyperthyroidism and hypothyroidism had not been clarified.[11–22,24,36–38]

In the anti-tumor treatment process, whether it was chemotherapy or immunotherapy, adrenal insufficiency was a treatment-related complication with low incidence risk.[11–22,24,36–38] After dividing the data into subgroups according to the treatment plan and the level of toxicities, we took meta-analysis to deal with all the data and found that the incidence risk of adrenal insufficiency in the PD-1/PD-L1 treatment group was significantly higher than that in the chemotherapy group (OR = 7.98, 95%CI[1.78, 35.77]; Fig. 4A1),[12,19] furthermore, a higher incidence risk could be found in PD-1 combination group compared with 1 PD-1/PD-L1 inhibitor group (OR = 0.13, 95%CI[0.03, 0.59]; Fig. 4A3).[12,20] In our data set, among NSCLC patients treated with Nivolumab plus Ipilimumab, the incidence rate (2.08%) was obvious higher than other enrolled studies.[12] A similar incidence risk trend was seen in the meta-analysis of grade 3–5

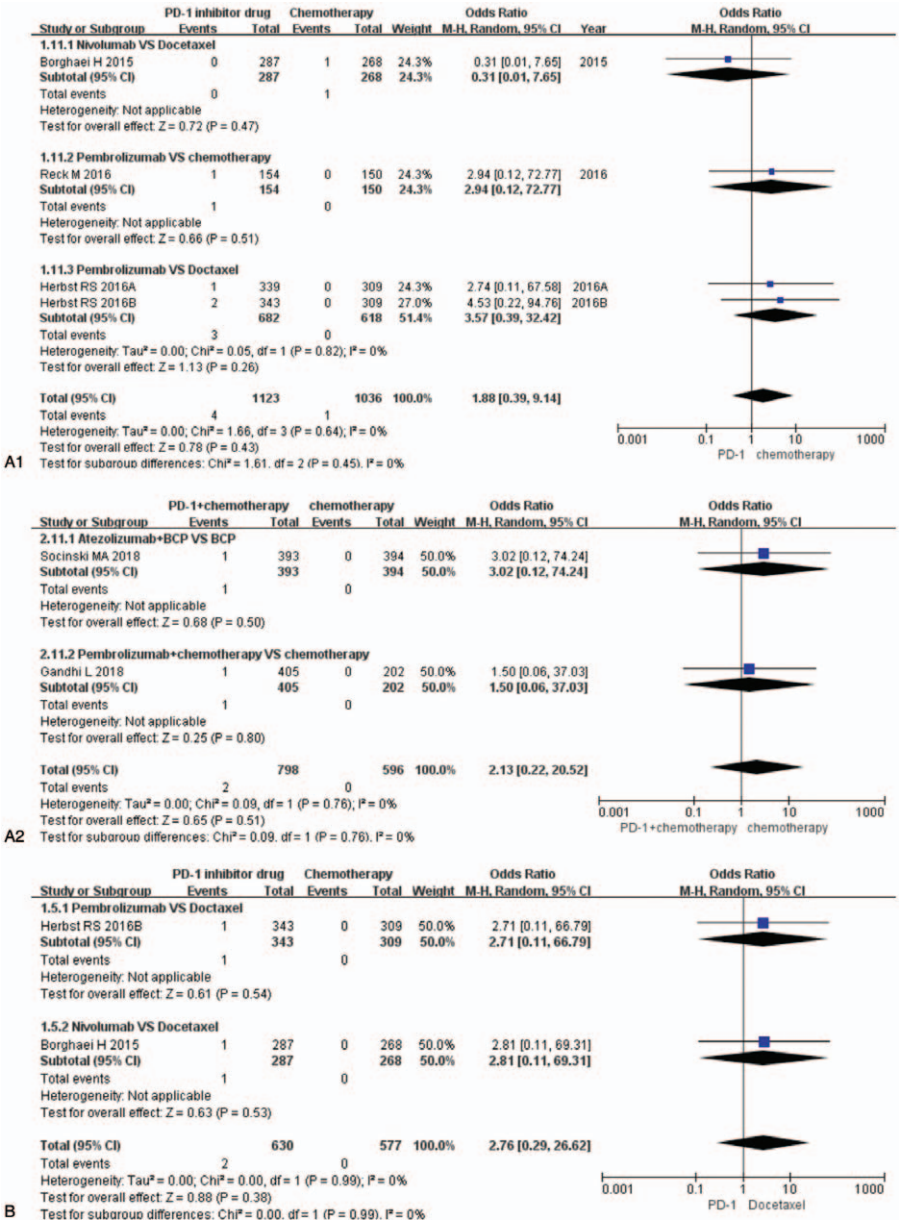

Figure 6. Forest plot of meta-analysis: Incidence of I Mellitus During Treatment With Different PD-1 Inhibitor Regimens; Incidence rates are represented by boxes and whiskers indicate binomial exact 95% CIs; Model results are shown for each class of therapy as a polygon using the fitted value and 95% prediction interval. Random effect model was used for all the data. A1: Incidence of overall grades of mellitus during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy); A2: Incidence of overall grades of mellitus during treatment with treatment regimen (PD-1 inhibitor drug+ chemotherapy vs chemotherapy); B: Incidence of grade 1–2 mellitus during treatment with treatment regimen (PD-1 inhibitor drug vs chemotherapy).

adrenal insufficiency (Fig. 3).[11,12,14,15,20] Although adrenal insufficiency was often reported in the field of immunoppressive anti-tumor therapy, the specific mechanism of occurrence had not been fully understood. When severe adrenal insufficiency occurred, the preferred treatment method for it was to stop anti-tumor therapy drugs, and then give symptomatic treatment.[11,12,14,15,20,36,37–39]

Hypophysitis had emerged as one of the most common endocrine dysfunctions induced by Ipilimumab, and sometimes, it could be life threatening.[40,41] However, in this study, although we collected data on two clinical trials of Ipilimumab, no reports of complications of hypophysitis were found.[12,20] As the low incidence of hypophysitis in patients with lung cancer in our study, we did not get results of statistically significant differences (Fig. 5).[11,13,14,17,19] Though, the incidence risk of hypophysitis was higher in PD-1/PD-L1 inhibitor plus chemotherapy group than that of mono-chemotherapy (OR = 5.62, 95%CI[1.01, 31.18]), the P value ($P = .05$) was considered to have no statistical significance.[11,13,14] According to the above data, we hypothesized that the occurrence of hypophysitis was not only related to anti-tumor drugs, but also may be related to tumor type.[12,20,40,41]

PD-L1 is expressed in the islets of people with type 1 diabetes and is up-regulated by interferons -α and -γ via IRF1 induction.[42] However, the pathogenesis of PD-1/PD-L1 inhibitor associated insulin-deficient diabetes remained unclear. In many clinical trials, only the occurrence of such events had been reported, but the pathogenesis had not been elaborated.[11,14,17,19,22,24] We put the data collected on PD-1/PD-L1 related insulin-deficient diabetes into comprehensive and stratification analysis, but no statistically significant results were obtained (Fig. 6).[11,14,17,19,22,24] We guessed that such a result might be related to the low incidence of the disease and less data included in the study.

5. Conclusions

The incidence risk of endocrine dysfunctions, including hypothyroidism, hyperthyroidism and adrenal insufficiency, were higher for PD-1/PD-L1 inhibitors group.

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