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Endocrine adverse events in patients with cancer receiving perioperative immune checkpoint blockade: a meta-analysis of randomized controlled trials

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Abstract

Background: Perioperative use of immune checkpoint blockade (ICB) improves survival in patients with early-stage cancer. Treatment-related adverse events (AEs), frequently involve the endocrine system which may increase perioperative complications and affect quality of life.

Objective: We conducted a meta-analysis to elucidate the impact of adding ICB to conventional neoadjuvant/adjuvant therapy on the incidence of endocrine AEs.

Design: A systematic review and meta-analysis of randomize-controlled trials (RCTs).

Data sources and methods: A systematic search of PubMed, Embase, Web of Science, and Cochrane library was performed for RCTs comparing groups with and without the addition of ICB to conventional perioperative therapy in patients with cancer. Outcomes included all-grade and grade 3–5 thyroiditis, hyperthyroidism, hypothyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, and hyperglycemia. The odds ratios (ORs) of all-grade and grade 3–5 endocrine were pooled using the random-effect model meta-analysis.

Results: Twenty-four RCTs comprising 12,199 patients were identified for meta-analysis. The addition of ICB was associated with higher incidence of thyroiditis [all grade: OR = 3.53 (95% confidence interval (CI): 1.88–6.64)], hyperthyroidism [all-grade: 7.18 (4.30–12.01); grade 3–5: 3.93 (1.21–12.82)], hypothyroidism [all-grade: 5.39 (3.68–7.90); grade 3–5: 3.63 (1.18–11.11)], adrenal insufficiency [all-grade: 3.82 (1.88–7.79); grade 3–5: 5.91 (2.36–14.82)], hypophysitis [all-grade: 10.29 (4.97–21.3); grade 3–5: 5.80 (1.99–16.92)], and type 1 diabetes mellitus [all-grade: 2.24 (1.06–4.74); grade 3–5: 3.49 (1.21–10.08)]. The cumulative incidence of each grade 3–5 endocrine AE was low (<1.3%). No grade 5 AEs leading to death were observed.

Conclusion: The addition of neoadjuvant/adjuvant ICB to conventional therapy was associated with an increased incidence of several endocrine AEs. Clinicians should be aware of the risk of endocrinopathy from the perioperative ICB use to facilitate risk–benefit discussion with patients with early-stage cancer.

Trial registration: The protocol of this research was registered in PROSPERO (CRD42022332624).

Keywords: adjuvant therapy, cancer immunotherapy, endocrine-related adverse events, immune checkpoint blockade, immune-related adverse events, neoadjuvant therapy

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Introduction

In recent decades, immunotherapy including immune checkpoint blockade (ICB) and cellular therapy has emerged as the 'fifth pillar' of cancer therapy, expanding the ranks of surgery, chemotherapy, radiation, and targeted therapy.[1,2] ICB has become one of the most important breakthroughs in cancer treatment, especially in patients with advanced, recurrent, and metastatic cancer.[3–5] Four different groups of ICB, including programmed cell death protein-1 (PD-1), programmed cell death ligand-1 (PD-L1), cytotoxic T lymphocyte-associated protein-4 (CTLA-4), and lymphocyte-activation gene 3 (*LAG-3*) blockade have been approved by the U.S. Food and Drug Administration for the treatment of various types of cancer. ICB was approved for advanced cancer after ipilimumab showed efficacy in patients with advanced/metastatic melanoma.[6] The incorporation of ICB into neoadjuvant or adjuvant therapy with surgery and/or radiotherapy also showed survival benefits, leading to approval in the perioperative setting in 2015.[7] Multiple clinical trials have shown perioperative ICB, either monotherapy or combined with chemotherapy, resulted in improved survival in non-small cell lung cancer, breast cancer, urothelial carcinoma, and renal cell carcinoma.[8–10] Therefore, ICB is currently used as adjuvant and neoadjuvant treatment for many resectable cancers.

ICB disrupts immunologic homeostasis by reactivating cellular immunity, increasing the incidence of treatment-related adverse events (trAEs), mostly immune toxicities known as immune-related adverse events (irAEs).[11] Endocrine adverse events (AEs), including thyroiditis, hyperthyroidism, hypothyroidism, hypophysitis, adrenal insufficiency, and type 1 diabetes mellitus, occur in approximately 10% of patients treated with ICB.[12,13] The incidence, risk, and management of irAEs has been evaluated in previous studies in patients with unresectable/metastatic cancers.[14] Severe trAEs may lead to delay or cancellation of surgery, increased postoperative complications, and even fatal events.[15,16] Endocrine AEs may necessitate life-long hormone replacement therapy and negatively affect patients' quality of life. These risks must be balanced with the potential for prolonged survival and cure among patients with early stage disease.[17] Therefore, data are needed to assess the incidence of endocrine AEs among patients receiving neoadjuvant and adjuvant ICB for curative intent.

We performed a systematic review and meta-analysis of endocrine AEs in patients receiving neoadjuvant/adjuvant therapy with ICB to evaluate the effect of the addition of ICB on the incidence of endocrine AEs, which guides clinicians providing perioperative ICB therapy for patients with early-stage cancer.

Methods

Data source and search strategy

We conducted a systematic review and meta-analysis under Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria.[18] We performed a systematic search of PubMed, EMBASE, Web of Science, and Cochrane library to identify articles up to 18 December 2022, reporting results of randomized controlled trials (RCTs) evaluating neoadjuvant and adjuvant therapy with ICB in patients with solid tumors. The search strategy is described in Supplemental Table 1. The protocol of this research was registered in PROSPERO with a registry number CRD42022332624.

Study selection

To evaluate the effect of ICB on the incidence of endocrine AEs, studies meeting the following inclusion criteria were chosen for meta-analysis[19,20]: (1) RCTs reporting the efficacy and safety of neoadjuvant and/or adjuvant ICB in patients with solid tumors; (2) RCTs with an experimental arm of ICB combined with conventional neoadjuvant/adjuvant therapy and a control arm of the same conventional neoadjuvant/adjuvant therapy (such as ICB *versus* placebo/observation, ICB plus chemotherapy *versus* chemotherapy, ICB-'1' plus ICB-'2'*versus* ICB-'2'); and (3) RCT reporting the results of endocrine AEs. If multiple articles reported results of the same RCT, we chose an article that contained the most-updated information on endocrine toxicity.

Data extraction

Two investigators (SZ and YF) independently extracted data from all eligible studies. Any discrepancies between review authors were resolved by consensus. We recorded the following information of each eligible RCT: first author's name, publication year, study name, cancer type, cancer status, treatment setting (adjuvant and/or neoadjuvant), ICB subtype, treatment in each arm,

RCT design (double-blind, open-label), reported endocrine AEs, the number of patients, the number of all-grade, and grade 3–5 endocrine AEs (thyroiditis, hyperthyroidism, hypothyroidism, hypophysitis, adrenal insufficiency, type 1 diabetes mellitus, and hyperglycemia). The Cochrane Risk of Bias Tool was used to evaluate the risk of bias for each RCT.[21] TrAEs were prioritized for data extraction and meta-analysis, but irAEs were chosen if no trAEs were reported in eligible studies.

Statistical analysis

We recorded the number of patients and endocrine AEs in each treatment arm and calculated the odds ratio (OR) and corresponding 95% confidence interval (CI) of each all-grade and grade 3–5 endocrine AEs. We then performed a meta-analysis of each endocrine AE by pooling ORs using random-effects models. A p-value less than 0.05 was considered statistically significant. Funnel plots were applied to evaluate publication bias of each outcome with more than 10 studies. Subgroup analyses were conducted based on ICB class (PD-1, PD-L1, and CTLA-4 blockade) and clinical trial setting (neoadjuvant and/or adjuvant). Cochran's Q-test and I^2 statistics were used to evaluate the heterogeneity in each analysis. I^2 values of greater than 50% were considered as substantial heterogeneity in our study. We used RevMan 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) for these analyses.[22] The incidence of each AEs was calculated as the number of total events divided by the number of patients receiving ICB treatment in both experimental and control arms.

Results

Eligible studies and baseline characteristics

The systemic search identified 3602 records. After removing 1520 duplicates and 1997 records by title and abstract screening, full texts of 85 articles were reviewed in detail. Finally, 24 studies involving 12,199 patients were included for meta-analysis.[7,23–45] The PRISMA flow diagram for a systematic review is shown in Figure 1.

The characteristics of 24 included studies are summarized in Table 1. Overall, 10, 12, and 2 studies evaluated ICB in neoadjuvant, adjuvant, and neoadjuvant/adjuvant settings, respectively. Regarding ICB subtype, 6, 10, and 8 studies assessed CTLA-4, PD-1, and PD-L1 blockade, respectively. About treatment design, 5 studies compared dual ICB therapy to ICB monotherapy, 11 studies compared ICB to placebo/observation, and 8 studies compared ICB plus chemotherapy to the same chemotherapy. Most commonly evaluated cancers were malignant melanoma ($n=5$), breast cancer ($n=5$), and non-small cell lung cancer ($n=3$) (Table 1).

Meta-analysis of endocrine AEs

We performed meta-analyses of all-grade and grade 3–5 endocrine AEs: thyroiditis, hyperthyroidism, hypothyroidism, hypophysitis, adrenal insufficiency, type 1 diabetes mellitus, and hyperglycemia. The results of these meta-analyses are summarized in Figure 2 and Table 2. No grade 5 endocrine AEs were observed.

Thyroid dysfunction

The addition of ICB to conventional neoadjuvant or adjuvant therapy was associated with an increase in the incidence of all-grade thyroiditis (OR: 3.53, 95% CI: 1.88–6.64, $p<0.001$), hyperthyroidism (OR: 7.18, 95% CI: 4.30–12.01, $p<0.001$), and hypothyroidism (OR: 5.39, 95% CI: 3.68–7.90, $p<0.001$) [Table 2 and Supplemental Figure 1(A)–(C)]. For grade 3–5 thyroid dysfunction, the addition of ICB to conventional perioperative treatment significantly increased the incidence of hyperthyroidism (OR: 3.93, 95% CI: 1.21–12.82, $p=0.02$) and hypothyroidism (OR: 3.63, 95% CI: 1.18–11.11, $p=0.02$), but did not increase the incidence of thyroiditis (OR: 3.57, 95% CI: 0.42–30.58, $p=0.25$) [Table 2 and Figure 3(a)–(c)]. The incidence of grade 3–5 thyroid-related AEs in patients treated with ICB was low: 0.13% ($N=4/3191$) for thyroiditis, 0.20% ($N=12/5973$) for hyperthyroidism, and 0.19% ($N=12/6448$) for hypothyroidism.

In subgroup analysis according to ICB subtype, the addition of PD-1 or PD-L1 blockade was associated with a higher incidence of all-grade thyroid dysfunction. In contrast, CTLA-4 blockade was not associated with increased incidence of any all-grade thyroid AEs. None of the ICB subtypes were associated with higher incidence of grade 3–5 thyroid dysfunction (Table 2). Moderate heterogeneity among subgroups of ICB subtype was observed for all-grade hyperthyroidism ($I^2=64.6\%$) and hypothyroidism ($I^2=53.6\%$),

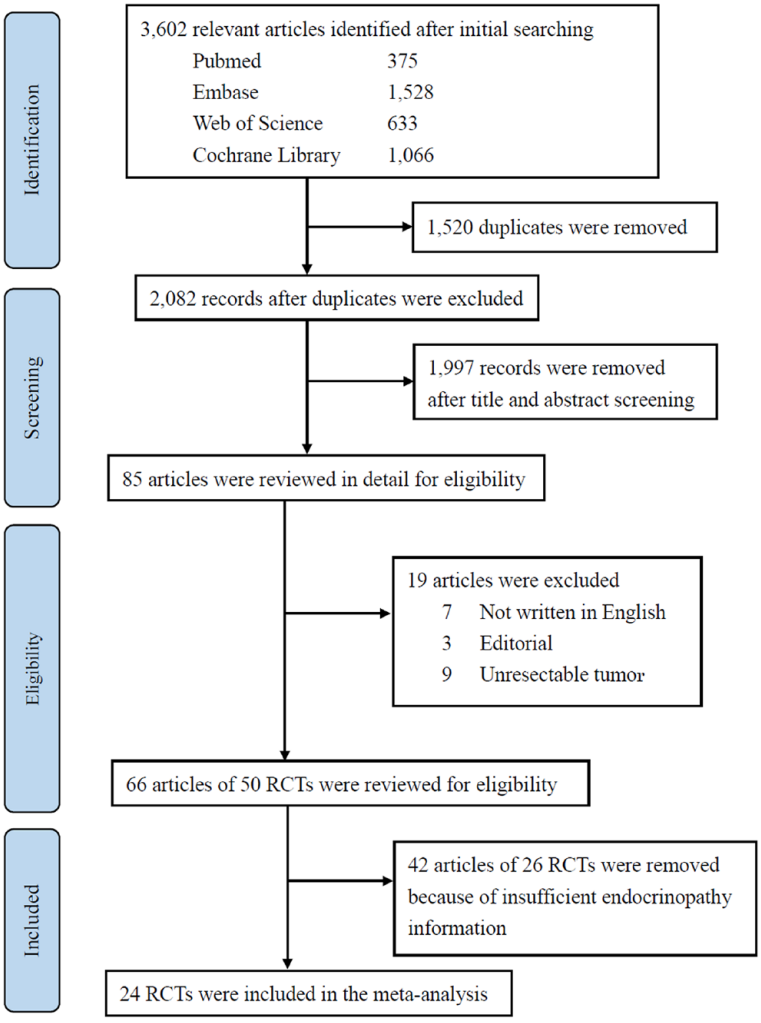

Figure 1. Flow diagram of study selection.
RCTs, randomized controlled trials.

but when analysis was limited to 18 studies of PD-1/PD-L1 blockade, heterogeneity between subgroups became low ($I^2 = 14.5\%$ for hyperthyroidism and 0% for hypothyroidism), suggesting high heterogeneity derived from discrepancy between CTLA-4 and PD-1/PD-L1 subgroups.

Adrenal insufficiency and hypophysitis

The addition of ICB resulted in a significantly higher incidence of adrenal insufficiency (all-grade: OR: 3.82, 95% CI: 1.88–7.79, $p < 0.001$; grade 3–5: OR: 5.91, 95% CI: 2.36–14.82, $p < 0.001$) and hypophysitis (all-grade: OR: 10.29, 95% CI: 4.97–21.3, $p < 0.001$; grade 3–5: OR: 5.80, 95% CI: 1.99–16.92, $p = 0.001$). The incidence of grade 3–5 adrenal insufficiency and hypophysitis in patients treated with ICB was 0.66% ($N = 31/46711$) and 1.28% ($N = 44/3434$), respectively. Subgroup analysis by ICB subtype showed that the incidence of all-grade and grade 3–5 adrenal insufficiency and hypophysitis were significantly increased by the addition of PD-1 blockade but not by the addition of CTLA-4 or PD-L1 blockade [Table 2, Figure 3(d) and (e), and Supplemental Figure 1(D) and (E)]. Heterogeneity was not high among ICB subtypes for these AEs (Table 2).

Type 1 diabetes mellitus and hyperglycemia

The addition of ICB to conventional perioperative therapy resulted in an increase in the incidence of type 1 diabetes mellitus (all-grade: OR:

Table 1. Main characteristics of the included randomized control trials.

First author	Year	Study	Cancer	Cancer status	Study setting	ICB added in the experimental group	Control/baseline treatment	Analyzed endocrine irAE	Patients		Reference
									ICB	Control	
Amaria	2018	NCT02519322	Melanoma		Neoadjuvant	Ipilimumab	Nivolumab	Hyperthyroidism, hypothyroidism, hypophysitis, hyperglycemia	11	12	23
Bajorin	2021	CheckMate 274	Urothelial	Muscle-invasive	Adjuvant	Nivolumab	Placebo	Thyroiditis, hyperthyroidism, hypothyroidism, adrenal insufficiency, type 1 diabetes mellitus	351	348	24
Bellmunt	2021	IMvigor010	Urothelial	Muscle-invasive	Adjuvant	Atezolizumab	Observation	Hyperthyroidism, hypothyroidism, hypophysitis, type 1 diabetes mellitus, hyperglycemia	390	397	25
Cascone	2021	NEOSTAR	NSCLC		Neoadjuvant	Ipilimumab	Nivolumab	Hypothyroidism	21	23	26
Choueiri	2021	KEYNOTE-564	Renal		Adjuvant	Pembrolizumab	Placebo	Thyroiditis, hyperthyroidism, hypothyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus	488	496	27
Cloughesy	2019	Ivy Consortium	Glioblastoma		Neoadjuvant	Pembrolizumab	Adjuvant pembrolizumab	Hyperthyroidism, hypothyroidism	16	16	28
Eggermont	2015	EORTC 18071	Melanoma	Stage III	Adjuvant	Ipilimumab	Placebo	Hypothyroidism, hypophysitis	471	474	7
Eggermont	2020	EORTC 1325-MG/ KEYNOTE-054	Melanoma	Resected Stage III	Adjuvant	Pembrolizumab	Placebo	Thyroiditis, hyperthyroidism, hypothyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus	509	502	29
Felip	2021	IMpower010	NSCLC	Stage IB–IIIA	Adjuvant	Atezolizumab	BSC following adjuvant chemotherapy	Hyperthyroidism, hypothyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus	495	495	30
Forde	2022	CheckMate 816	NSCLC	Stage IB–IIIA	Neoadjuvant	Nivolumab	platinum-doublet chemotherapy	Hyperthyroidism, hypothyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus	176	176	31
Gianni	2022	NeoTRIP	Breast		Neoadjuvant	Atezolizumab	CBDCA + nabPTX	Thyroiditis, hyperthyroidism, hypothyroidism	138	140	32
Kaseb	2022	NCT03222076	Hepatocellular		Neoadjuvant and adjuvant	Ipilimumab	Nivolumab	Hyperthyroidism, hypothyroidism, adrenal insufficiency, hyperglycemia	14	13	33
Kelly	2021	CheckMate 577	Esophageal or GEJ	Resected stage II or III	Adjuvant	Nivolumab	Neoadjuvant CRT, surgery, adjuvant placebo	Hyperthyroidism, hypothyroidism	532	260	34
Loibl	2019	GeparNuevo	Breast		Neoadjuvant	Durvalumab	Placebo + nabPTX, EC	Hyperthyroidism, hypothyroidism, hypophysitis, hyperglycemia	92	82	35

(Continued)

Table 1. (Continued)

First author	Year	Study	Cancer	Cancer status	Study setting	ICB added in the experimental group	Control/baseline treatment	Analyzed endocrine irAE	Patients		Reference
									ICB	Control	
Luke	2022	KEYNOTE-716	Melanoma	Stage IIB or IIC	Adjuvant	Pembrolizumab	Placebo	Thyroiditis, hyperthyroidism, hypothyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus	483	486	36
Mittendorf	2020	IMpassion031	TNBC		Neoadjuvant	Atezolizumab	Placebo + nabPTX followed by CPA + ADR	Hyperthyroidism, hypothyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus	164	167	37
Monk	2021	JAVELIN Ovarian 100	Ovarian	Stage III or IV	After debulking surgery or neoadjuvant	Avelumab	Chemotherapy followed by observation	Thyroiditis, hyperthyroidism, hypothyroidism, adrenal insufficiency, type 1 diabetes mellitus, hyperglycemia	328	334	38
Moore Nanda	2021 2020	IMagyn050 I-SPY2	Ovarian Breast	Stage III or IV Stage II or III	After debulking surgery or neoadjuvant Neoadjuvant	Atezolizumab Pembrolizumab	Placebo + paclitaxel + carboplatin + bevacizumab PTX, AC	Hyperthyroidism, hypothyroidism, adrenal insufficiency, type 1 diabetes mellitus, hyperglycemia Hyperthyroidism, hypothyroidism, adrenal insufficiency, hypophysitis, hyperglycemia	642 69	644 181	39, 40
Park	2022	NCT02520453	Esophageal		Adjuvant	Durvalumab	Placebo after CCRT	Hyperthyroidism, hypothyroidism, adrenal insufficiency, hyperglycemia	45	41	41
Rahma	2021	NRG-GI002	Rectal	Stage II or III	Neoadjuvant	Pembrolizumab	Neoadjuvant FOLFOX, CRT (with capecitabine)	Hyperthyroidism, hypothyroidism	81	83	42
Schmid	2022	KEYNOTE-522	Breast		Neoadjuvant and adjuvant	Pembrolizumab	Placebo + CBDCA + PTX, AC/EC, placebo	Thyroiditis, hyperthyroidism, hypothyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus	783	389	43
Schoenfeld	2020	NCT02919683	Oral cavity		Neoadjuvant	Ipilimumab	Nivolumab	Hyperthyroidism, hypothyroidism, type 1 diabetes mellitus, hyperglycemia	15	15	44
Zimmer	2020	IMMUNED	Melanoma	Resected stage IV	Adjuvant	Ipilimumab	Nivolumab	Thyroiditis, hyperthyroidism, hypothyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, hyperglycemia	55	56	45

AC, adriamycin + cyclophosphamide; ADR, adriamycin; BSC, best supportive care; CBDCA, carboplatin; CCRT, concomitant chemoradiotherapy; CPA, cyclophosphamide; CRT, chemo-radiotherapy; EC, epirubicin + cyclophosphamide; FOLFOX, 5-fluorouracil + oxaliplatin; GEJ, gastroesophageal junction; ICB, immune checkpoint blockade; irAE, immune-related adverse event; nabPTX, nab-paclitaxel; NSCLC, non-small cell lung cancer; PTX, paclitaxel; TNBC, triple negative breast cancer.

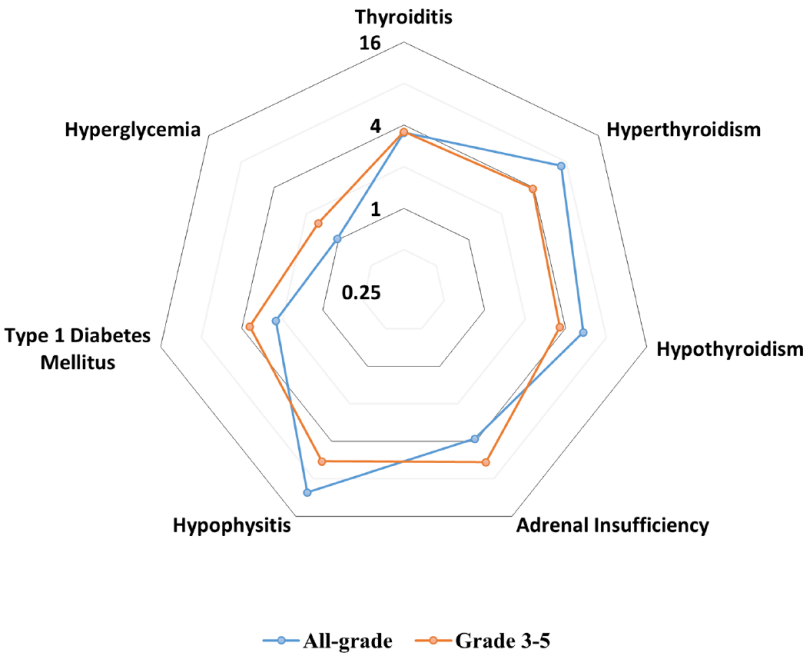

Figure 2. Radar chart illustrating pooled odds ratios of endocrine adverse events associated with immune checkpoint blockade. Seven axes represent the log-transformed odds ratio of each endocrinopathies. The incidence of all-grade adverse events is represented in blue, whereas grade 3–5 adverse events are plotted in orange.

2.24, 95% CI: 1.06–4.74, $p=0.03$; grade 3–5: OR: 3.49, 95% CI: 1.21–10.08, $p=0.02$). Moderately high heterogeneity among ICB subtypes was found for all-grade type 1 diabetes mellitus ($I^2=52.5\%$). On the other hand, the incidence of both all-grade and grade 3–5 hyperglycemia was not significantly increased by the addition of ICB (all-grade: OR: 1.03, 95% CI: 0.76–1.39, $p=0.87$; grade 3–5: OR: 1.55, 95% CI: 0.77–3.10, $p=0.22$). The incidence of grade 3–5 type 1 diabetes mellitus and hyperglycemia in patients treated with ICB was 0.44% ($N=22/4948$) and 1.18% ($N=20/1688$), respectively. The summary of subgroup analysis based on ICB subtype is shown in Table 2, Figure 3(f) and (g), and Supplemental Figure 1(F) and (G).

Subgroup analysis based on clinical trial setting

We next conducted subgroup analyses based on clinical trial setting (neoadjuvant and adjuvant therapy). Only a single small study included patients who received ICB in the neoadjuvant setting, therefore this result should be interpreted with caution. The addition of ICB in the adjuvant setting was associated with a significant increase in the incidence of grade 3–5 type 1 diabetes mellitus (OR: 5.10, 95% CI: 1.52–17.05, $p=0.008$), but this increase was not seen in the neoadjuvant setting (OR: 0.31, 95% CI: 0.01–8.28, $p=0.49$) with moderate subgroup differences ($I^2=56.3\%$, $p=0.12$). Otherwise, no significant subgroup heterogeneity between neoadjuvant and adjuvant groups was observed for all-grade and grade 3–5 endocrinopathies (Supplemental Table 2).

Comparison of dual ICB with ICB monotherapy

We also compared the incidence of endocrine AEs from dual ICB (PD-1 and CTLA-4 blockade) to that from PD-1 blockade alone. As shown in Supplemental Table 3, the incidence of all-grade and grade 3–5 endocrine AEs was not significantly different between patients on dual ICB and those on ICB monotherapy although the number of RCTs included in an analysis of each endocrine AE was low (all grade: $n=1$–5, grade 3–5: $n=1$–2).

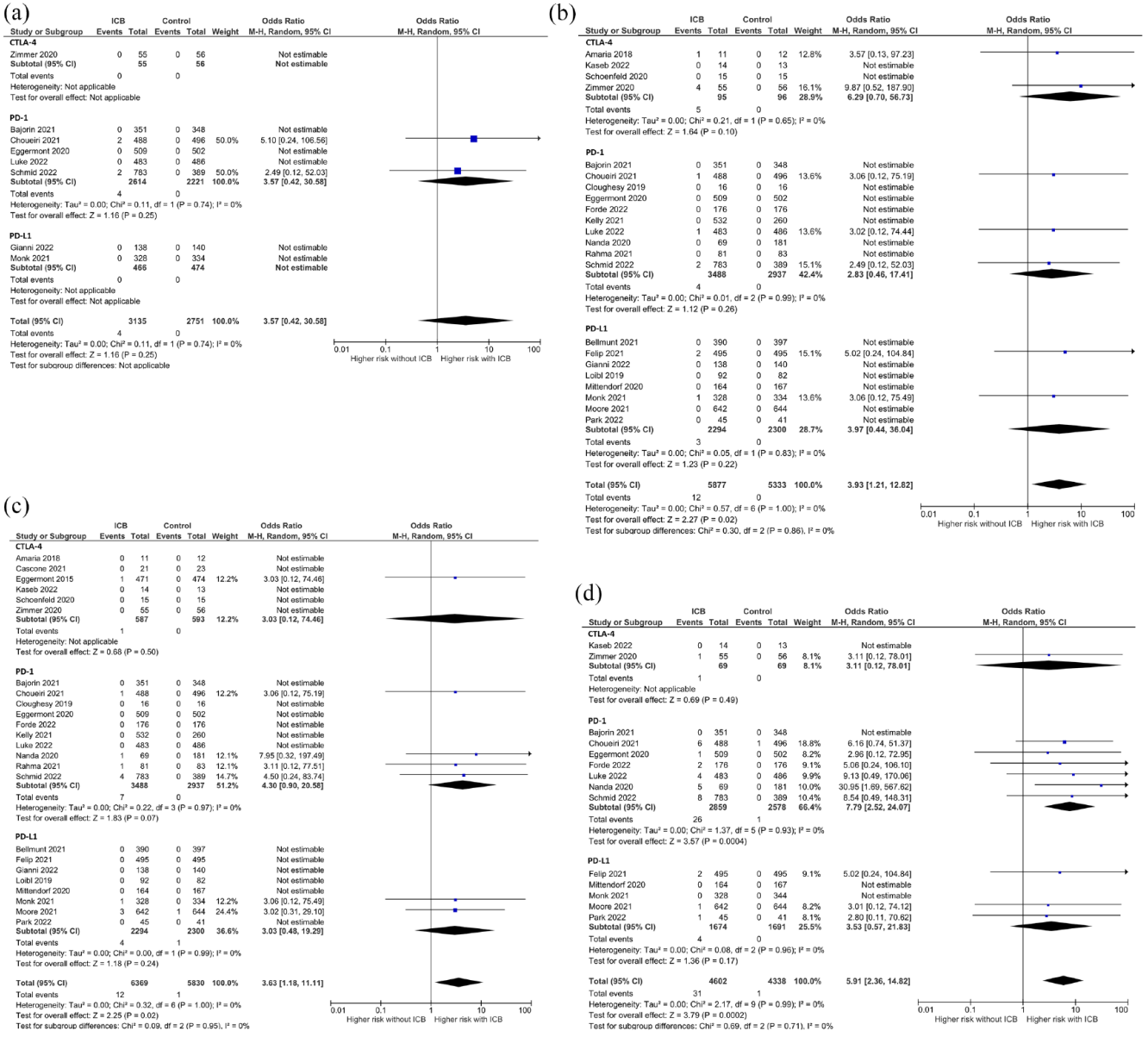

Figure 3. (Continued)

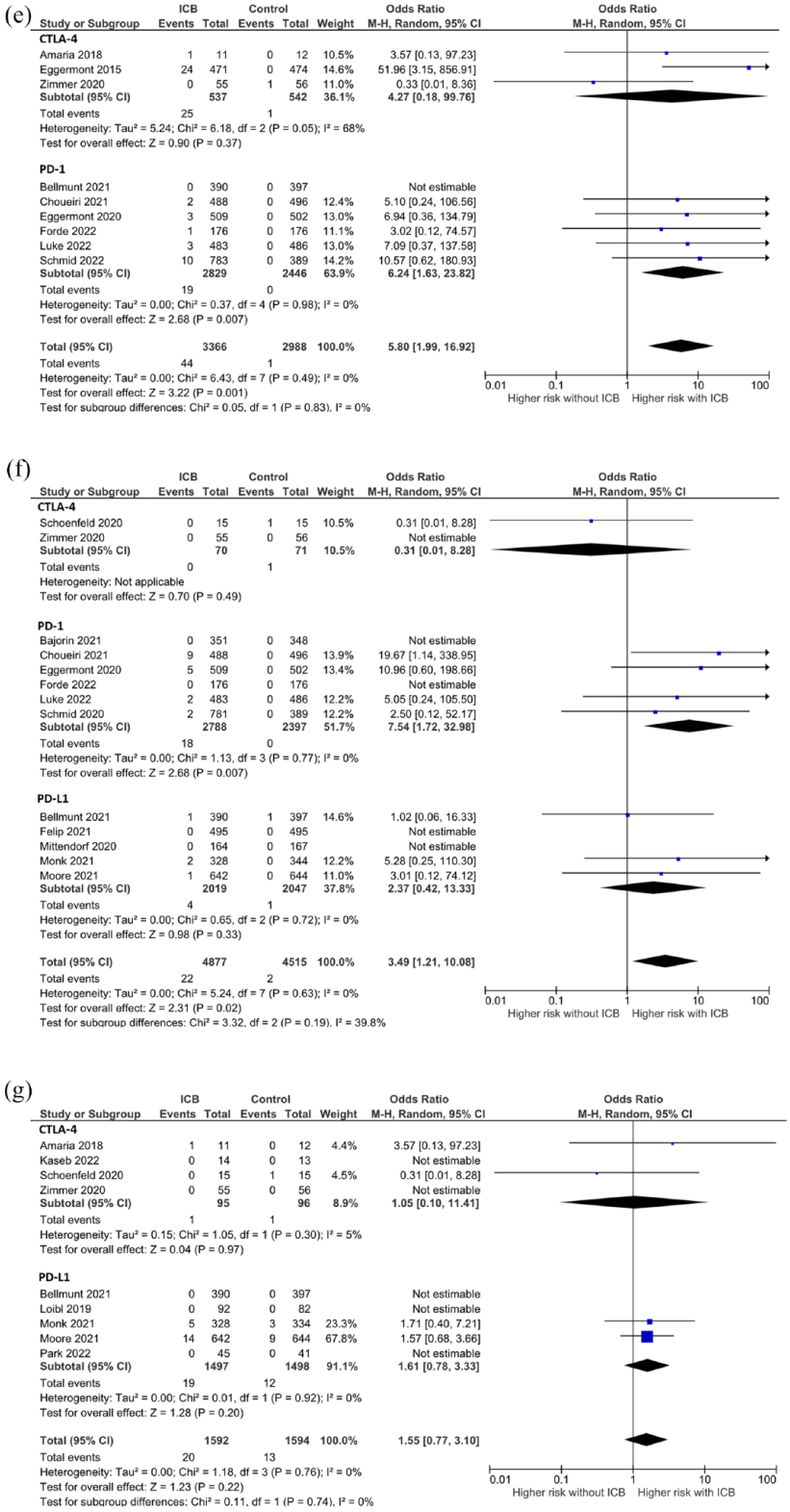

Figure 3. Forest plot of grade 3–5 endocrine adverse events with subgroup analyses based on ICB subtype. (a) Thyroiditis. (b) Hyperthyroidism. (c) Hypothyroidism. (d) Adrenal insufficiency. (e) Hypophysitis. (f) Type 1 diabetes mellitus. (g) Hyperglycemia.
CI, confidence interval; CTLA-4, T lymphocyte-associated protein 4; ICB, immune checkpoint blockade; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1.

Table 2. OR of endocrine AEs with subgroup analysis based on ICB subtype.

ICB subgroup	Overall			CTLA-4 blockade			PD-1 blockade			PD-L1 blockade			Subgroup difference	
Endocrine AEs	No. studies	OR (95% CI)	*p*	No. studies	OR (95% CI)	*p*	No. studies	OR (95% CI)	*p*	No. studies	OR (95% CI)	*p*	I^2 (%)	*p*
All-grade														
Thyroiditis	8	3.53 (1.88–6.64)	**<0.001**	1	9.87 (0.52–187.9)	0.13	5	3.23 (1.64–6.35)	**<0.001**	2	5.13 (0.60–44.15)	0.14	0	0.74
Hyperthyroidism	22	7.18 (4.30–12.01)	**<0.001**	4	1.99 (0.54–7.33)	0.30	10	11.21 (5.89–21.32)	**<0.001**	8	6.25 (2.69–14.50)	**<0.001**	**64.6**	0.06
Hypothyroidism	24	5.39 (3.68–7.90)	**<0.001**	6	1.70 (0.51–5.68)	0.39	10	5.72 (4.21–7.77)	**<0.001**	8	8.02 (3.11–20.71)	**<0.001**	**53.6**	0.12
Adrenal insufficiency	14	3.82 (1.88–7.79)	**<0.001**	2	1.58 (0.18–13.56)	0.67	7	6.91 (2.10–22.73)	**0.001**	5	2.64 (0.85–8.18)	0.09	0.2	0.37
Hypophysitis	12	10.29 (4.97–21.3)	**<0.001**	3	9.15 (0.78–106.86)	0.08	7	8.96 (3.35–23.96)	**<0.001**	2	2.85 (0.29–27.58)	0.37	0	0.66
Type 1 diabetes mellitus	13	2.24 (1.06–4.74)	**0.03**	2	1.01 (0.10–10.01)	1.00	6	6.17 (1.81–21.03)	**0.004**	5	1.28 (0.45–3.61)	0.64	**52.5**	0.12
Hyperglycemia	10	1.03 (0.76–1.39)	0.87	4	2.12 (0.42–10.63)	0.36	1	2.01 (0.44–9.23)	0.37	5	1.0 (0.66–1.52)	0.99	0	0.49
Grade 3–5														
Thyroiditis	2	3.57 (0.42–30.58)	0.25	–	–	–	2	3.57 (0.42–30.58)	0.25	–	–	–	–	–
Hyperthyroidism	7	3.93 (1.21–12.82)	**0.02**	2	6.29 (0.70–56.73)	0.10	3	2.83 (0.46–17.41)	0.26	2	3.97 (0.44–36.04)	0.22	0	0.86
Hypothyroidism	7	3.63 (1.18–11.11)	**0.02**	1	3.03 (0.12–74.46)	0.50	4	4.30 (0.90–20.58)	0.07	2	3.03 (0.48–19.29)	0.24	0	0.95
Adrenal insufficiency	10	5.91 (2.36–14.82)	**<0.001**	1	3.11 (0.12–78.01)	0.49	6	7.79 (2.52–24.07)	**<0.001**	3	3.53 (0.57–21.83)	0.17	0	0.71
Hypophysitis	8	5.80 (1.99–16.92)	**0.001**	3	4.27 (0.18–99.76)	0.37	5	6.24 (1.63–23.82)	**0.007**	–	–	–	0	0.83
Type 1 diabetes mellitus	8	3.49 (1.21–10.08)	**0.02**	1	0.31 (0.01–8.28)	0.49	4	7.54 (1.72–32.98)	**0.007**	3	2.37 (0.42–13.33)	0.33	39.8	0.19
Hyperglycemia	4	1.55 (0.77–3.10)	0.22	2	1.05 (0.10–11.41)	0.97	–	–	–	2	1.61 (0.78–3.33)	0.20	0	0.74

CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte antigen 4; ICB, immune checkpoint blockade; OR, odds ratio; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand 1.
P values less than 0.05 and I^2 values 50 or more are bolded in the table.

Risk of bias and publication bias

According to the Cochrane risk-of-bias tool, 12, 8, and 4 RCTs were judged at a low, moderate, and high risk of bias, respectively. Twelve RCTs with open-label design were at high risk of bias in outcome measurement. A summary of the risk of bias assessment is presented in Supplemental Figure 2. Funnel plots evaluating publication bias showed a symmetrical distribution, suggesting there was no obvious publication bias among the studies (Supplemental Figure 3).

Discussion

With this meta-analysis, we investigated the effect of the addition of ICB to conventional neoadjuvant/adjuvant therapy on the incidence of endocrine toxicities in patients with solid tumors. Incorporating ICB as a part of perioperative therapy significantly increased the incidence of all-grade and grade 3–5 thyroid dysfunction, hypophysitis, adrenal insufficiency, and type 1 diabetes mellitus. Because these AEs often require life-long hormone replacement therapy, our work supports risk and benefit discussion with patients who receive neoadjuvant/adjuvant ICB therapy.

Thyroid AEs are among the most common endocrine toxicities related to ICB therapy.[46] Consistent with our previous finding, this study showed an increase in thyroiditis, hyperthyroidism, and hypothyroidism associated with the addition of ICB.[47] Subgroup analysis revealed hyperthyroidism and hypothyroidism to be more likely with addition of PD-1 or PD-L1 blockade than with CTLA-4 blockade. Although our work did not focus on the incidence of endocrine AEs from dual checkpoint blockade, this is consistent with prior data that dual CTLA-4 and PD-1 blockade had the highest incidence of thyroid issues, followed by PD-1, PD-L1, and CTLA-4 blockade in advanced disease.[11,48] The difference in the incidence of thyroid dysfunction based on ICB subtype may derive from expression of PD-1 ligands including PD-L1 and PD-L2 on normal thyroid tissue.[49]

In our study, ICB was associated with a significantly higher incidence of both all-grade and grade 3–5 hypophysitis and adrenal insufficiency. Subgroup analysis revealed an increase in the incidence of hypophysitis and adrenal insufficiency associated with addition of PD-1 blockade, but not CTLA-4 blockade statistically. The reliability of these results is limited by the small number of studies utilizing CTLA-4 blockade included in the subgroup analysis. Hypophysitis has been described as more frequently associated with CTLA-4 blockade than with PD-1 or PD-L1 blockade in studies evaluating patients with advanced disease.[50,51] CTLA-4 expression on the pituitary gland has been implicated in CTLA-4 blockade-induced hypophysitis, but the association between the PD-1–PD-L1 axis and hypophysitis has not been fully explored yet.[52,53] Adrenocorticotropic hormone (ACTH) deficiency is occasionally seen in patients treated with PD-1 blockade; therefore, expression of PD-1 on ACTH-secreting cells may be involved in the pathogenesis of hypophysitis induced by PD-1 blockade.[54] These AEs require prolonged hormone replacement therapy, which causes a significant burden and impairs quality of life, particularly in patients with early-stage disease. Therefore, further study is warranted to elucidate the pathophysiology and incidence of hypophysitis and adrenal insufficiency associated with ICB.

Type 1 diabetes mellitus is an endocrine AE oftentimes associated with PD-1/PD-L1 blockade.[54,55] In our study, the addition of ICB was associated with a higher incidence of type 1 diabetes, particularly with the addition of PD-1 blockade, consistent with previous research in the advanced disease setting.[55,56] The finding of our study supports further research investigating risk factors, incidence, and pathophysiology of immune-related diabetes mellitus to guide discussion about the risk of neoadjuvant/adjuvant ICB therapy.

Unlike irAEs involving other organ systems, where steroids are often used as first-line treatment, managing endocrine AEs may require a unique approach. For endocrine AEs, high-dose steroids usually play a limited role, and endocrine organ failure from ICB is often irreversible, requiring lifelong treatment with hormone replacement or insulin therapy.[57,58] Patients receiving neoadjuvant and adjuvant ICB have potentially curable cancer; however, they may experience a negative impact in their quality of life as a result of an endocrine AE. Hypophysitis and type 1 diabetes mellitus may be life-threatening if unrecognized. Clinicians should strive for early detection of ICB-mediated endocrinopathies through vigilant monitoring of signs and symptoms and serial laboratory surveillance.

Our study has several limitations. First, the effect of each ICB subtype on endocrinopathies was not compared head-to-head because the aim of this study was to investigate the effect of the addition ICB to conventional neoadjuvant/adjuvant therapy on the incidence of endocrine AEs. Subgroup analyses based on ICB subtype may give an insight on differences in the incidence of endocrine AEs among ICB mechanisms; however, this subgroup analysis was based on a small number of RCTs, limiting the statistical power to assess some subgroups, particularly CTLA-4 blockade. The number of studies was insufficient to compare the incidence of endocrine AEs according to cancer type or individual ICB agent (nivolumab, pembrolizumab, etc.). Additionally, risk factors associated with the development of endocrine AEs, such as genetic predisposition, were not reported in the studies included in this meta-analysis; therefore, the impact of patients' risk factors on the analysis cannot be estimated. Further studies utilizing individual patient data could elucidate risk factors for development of endocrine AEs associated with use of ICB. Lastly, the included RCTs did not include information on the association between endocrine AEs and surgical delays and cancellations; thus, our study was unable to perform an analysis investigating the impact of endocrine AEs on the surgery itself. The occurrence of endocrine AEs in the neoadjuvant setting may affect the surgical schedule, which could lead to worse surgical outcomes. Future studies are needed to evaluate the impact of these AEs on surgery delays and cancellations.

Conclusion

Addition of ICB to conventional neoadjuvant/adjuvant therapy for treatment of solid tumors was associated with an increase in the incidence of a variety of endocrine AEs. Patients receiving ICB in the perioperative setting have an elevated risk of thyroid dysfunction, hypophysitis, adrenal insufficiency, and type 1 diabetes mellitus. Clinicians utilizing neoadjuvant and adjuvant ICB for treatment of early stage cancer must balance the risk of irreversible endocrinopathy with the potential for cure and guide risk–benefit discussion with patients given the risk of life-long complications from endocrine AEs associated with ICB.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Susu Zhou: Data curation; Formal analysis; Investigation; Resources; Visualization; Writing – original draft.

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Theresa Shao: Investigation; Writing – review & editing.

Matthew Harrington: Investigation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

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Supplemental material

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