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Programmed cell death protein 1 inhibitor treatment is associated with acute kidney injury and hypocalcemia: meta-analysis

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ABSTRACT

Background. The aim of this meta-analysis was to assess the risks and incidence of nephrotoxicity and electrolyte abnormalities in patients receiving programmed cell death protein 1 (PD-1) inhibitors.

Methods. We conducted a meta-analysis of clinical trials that monitored electrolyte levels and kidney functions during treatment with nivolumab or pembrolizumab by searching MEDLINE, EMBASE and the Cochrane Database from inception through April 2017. Our protocol is registered with International Prospective Register of Systematic Reviews; no.CRD42017060579.

Results. A total of 48 clinical trials with a total of 11 482 patients were included. The overall pooled risk ratios (RR) of all acute kidney injury (AKI) and all electrolyte abnormalities in patients treated with PD-1 inhibitors were 1.86 [95% confidence interval (CI) 0.95–3.64] and 1.67 (95% CI 0.89–3.12), respectively. Compared with non-nephrotoxic controls, the pooled RR of AKI in patients treated with PD-1 inhibitors was 4.19 (95% CI 1.57–11.18). Prespecified subgroup analyses demonstrated a significant association between PD-1 inhibitors and hypocalcemia with a pooled RR of 10.87 (95% CI 1.40–84.16). The pooled estimated incidence rates of AKI and hypocalcemia in patients treated with PD-1 inhibitors were 2.2% (95% CI 1.5–3.0%) and 1.0% (95% CI 0.6–1.8%), respectively. Among patients who developed AKI with PD-1 inhibitors, the pooled estimated rate of interstitial nephritis was 16.6% (95% CI 10.2–26.0%).

Conclusions. Treatment with PD-1 inhibitors is associated with a higher risk of AKI compared with non-nephrotoxic agents. It will be important to characterize the AKI patients to better understand the etiology behind the event. In addition, treatment with PD-1 inhibitors is associated with an increased risk of hypocalcemia. This study highlights a rare but serious adverse event of anti-PD-1 antibodies and we recommend, in addition to electrolytes panel, routine calcium monitoring.

Keywords: acute kidney injury, hypocalcemia, nivolumab, PD-1 inhibitor, pembrolizumab

INTRODUCTION

The kidneys are a frequent target of systemic immune-related diseases and the recent introduction of immune checkpoint inhibitors (CPIs) has raised concerns among nephrologists. The CPIs are monoclonal antibodies to the inhibitory receptors on T cells and other immune cells. The receptors targeted by CPIs are cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 pathway (PD-1/PD-Ligand-1), which function as negative immunologic regulators [1]. Inhibiting these pathways boosts the adaptive immune system's antitumor response, but with it comes a unique set of adverse events from nonspecific immunologic activation, termed immune-related adverse events (irAE).

In patients treated with the PD-1 inhibitors nivolumab and pembrolizumab, the most common irAE involve the dermatological and gastrointestinal organ systems, but cases of acute interstitial nephritis (AIN) have been reported as well [2]. A review of 13 cases from seven academic centers in the USA concluded that the great majority of cases of acute kidney injury (AKI) with CPIs are due to AIN with clinical and histologic features similar to other causes of drug-induced AIN [2]. The overall incidence (and risk) of nephrotoxicity with PD-1 inhibitors, however, is not well defined. Based on published data from Phase II and III clinical trials, the incidence of AKI has been estimated to be 1.9% with nivolumab and 1.4% with pembrolizumab [2]. However, other analyses have concluded on an incidence of PD-1 inhibitor therapy-related AKI as high as 30% [3]. In addition, electrolyte disturbances have been noted in these patients, but have not been well described beyond hyponatremia and hypokalemia [3]. There is no prior meta-analysis that has addressed this issue to the best of our knowledge. Thus, we conducted this meta-analysis to assess the risks of nephrotoxicity and electrolyte abnormalities in patients treated with PD-1 inhibitors.

MATERIALS AND METHODS

Search strategy

A systematic search of the published literature was done for clinical trials indexed in MEDLINE (1946–April 2017), EMBASE (1988–April 2017), the Cochrane Database of Systematic Reviews (2005–April 2017) and the Cochrane Central Register of Controlled Trials (from database inception through April 2017) using the search strategy described in Supplementary data 1, Item S1. Medical Subject Headings terms were applied in the search strategy. Other pertinent references were obtained via manual review of these retrieved references. Review of the abstracts and full text was done by the investigators S.M. and P.K and independently verified by C.T. Differing decisions were solved by mutual consensus.

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [4]. The PRISMA checklist is shown in Supplementary data 2. The protocol for this study is registered with International Prospective Register of Systematic Reviews (PROSPERO; no. CRD42017060579).

Inclusion criteria

The intended patient populations were all patients that received the drug pembrolizumab or nivolumab in a clinical trial setting. The included studies fulfilled the following criteria: (i) clinical trials, both randomized controlled trials (RCTs) and non-RCTs of nivolumab or pembrolizumab published as original articles, and (ii) studies that reported adverse events pertaining to AKI and/or electrolyte abnormalities after treatment with PD-1 inhibitors or studies that made available their protocols on monitoring of pertinent electrolyte levels and serum creatinine during treatment with nivolumab or pembrolizumab. Conference abstracts and observational studies were not included. Considering the cancer type for which the drug was given varied from solid cancer to hematological malignancies, information on the control drug was collected and categorized generically based on their known nephrotoxic potential during analysis phase. Clinical outcomes were AKI and electrolyte abnormalities after treatment with PD-1 inhibitors. The quality of each study was quantified via the Cochrane risk of bias tool independently by two investigators, S.M. and C.T. [5].

Data extraction

A standardized data collection template was used to extract the following information: last name of the first author, article title, study design, year of study, country of origin, year of publication, sample size, type of PD-1 inhibitors, dose of PD-1 inhibitors, indication of treatment (tumor type), age, follow-up time after treatment, definition of nephrotoxicity and definition of electrolyte abnormalities as reported in the study.

The outcome terminology AKI was used to define any adverse event reported as AKI, acute renal failure, renal failure, elevated creatinine, nephritis or tubulointerstitial nephritis. We also categorized the controls based on their known nephrotoxic potential. Control drugs like cisplatin, carboplatin, pemetrexed, temozolomide, methotrexate and ipilimumab were considered 'nephrotoxic' controls, whereas drugs like docetaxel, dacarbazine and cetuximab were considered 'non-nephrotoxic' controls. Studies that used iplimumab, a CTLA-4 inhibitor, as control were identified for further subgroup analysis.

The grading of adverse events was based on Common Terminology Criteria for Adverse Events (CTCAE) for clinical trials as reported by the individual studies; individual patient data were not available for the authors to review. Per CTCAE Version 4.0, Grade 1 AKI is creatinine level increase of

>0.3 mg/dL; creatinine 1.5–2.0 times above baseline; Grade 2 AKI is creatinine 2–3 times above baseline; Grade 3 is creatinine >3 times above baseline or >4.0 mg/dL, hospitalization indicated; Grade 4 is life-threatening consequences, dialysis indicated; and Grade 5 is death. The CTCAE criteria for other adverse outcomes relevant to this study are provided in Supplementary data, Table S1.

Statistical analysis

The data analysis was completed using the Comprehensive Meta-analysis software (Version 2.2.064; Biostat Inc.). Per study protocol, we conducted a meta-analysis of all included clinical trials for the incidence of AKI and electrolyte abnormalities and meta-analysis of RCTs for the risks of AKI and electrolyte abnormalities (a reference group composed of patients who did not receive treatment with PD-1 inhibitors). Point estimates and standard errors were derived from each included study and were combined by the generic inverse variance method of DerSimonian and Laird [6]. Given the likelihood of increased inter-observation variance; a random-effect model was applied to determine pooled incidence and pooled risk ratio (RR) with 95% confidence interval (CI) for the risks of AKI and electrolyte abnormalities. Statistical heterogeneity was evaluated utilizing Cochran's Q test. These results complemented the I^2 statistic, which quantifies the proportion of the total variation across studies due to heterogeneity rather than chance. The I^2 values of ≤25%, 26–50%, 51–75% and >75% were deemed to represent insignificant, low, moderate and high heterogeneity, respectively [7]. The presence of publication bias was screened via funnel plots of the logarithm of odds ratios versus standard errors [8].

RESULTS

Our search strategy yielded 1704 articles. Of these, 1647 were excluded based on relevance and eligibility criteria following the review of the title and abstract. The remaining 57 articles underwent full-length review. In all, nine studies were excluded for failing to meet all eligibility requirements. Of these, six were not clinical trials, and three articles did not report or monitor electrolytes or serum creatinine levels during treatment with PD-1 inhibitors. In the end, 48 clinical trials [9–56] with a total of 11 482 patients were enrolled in our systematic reviews. Figure 1 outlines our search methodology and selection process.

For risk analysis, 18 RCTs [9–11, 13, 20–23, 29, 34, 35, 37, 39–41, 48, 49, 52] were originally identified, but two studies [9, 20] had to be excluded as different doses of PD-1 inhibitors were used as controls. Of 16 RCTs, 13 [10, 11, 13, 21–23, 34, 35, 37, 39, 41, 49, 52] (Table 1) and 5 [13, 22, 23, 41, 52] (Table 2) were included in the meta-analyses assessing the risks of AKI and electrolyte abnormalities, respectively.

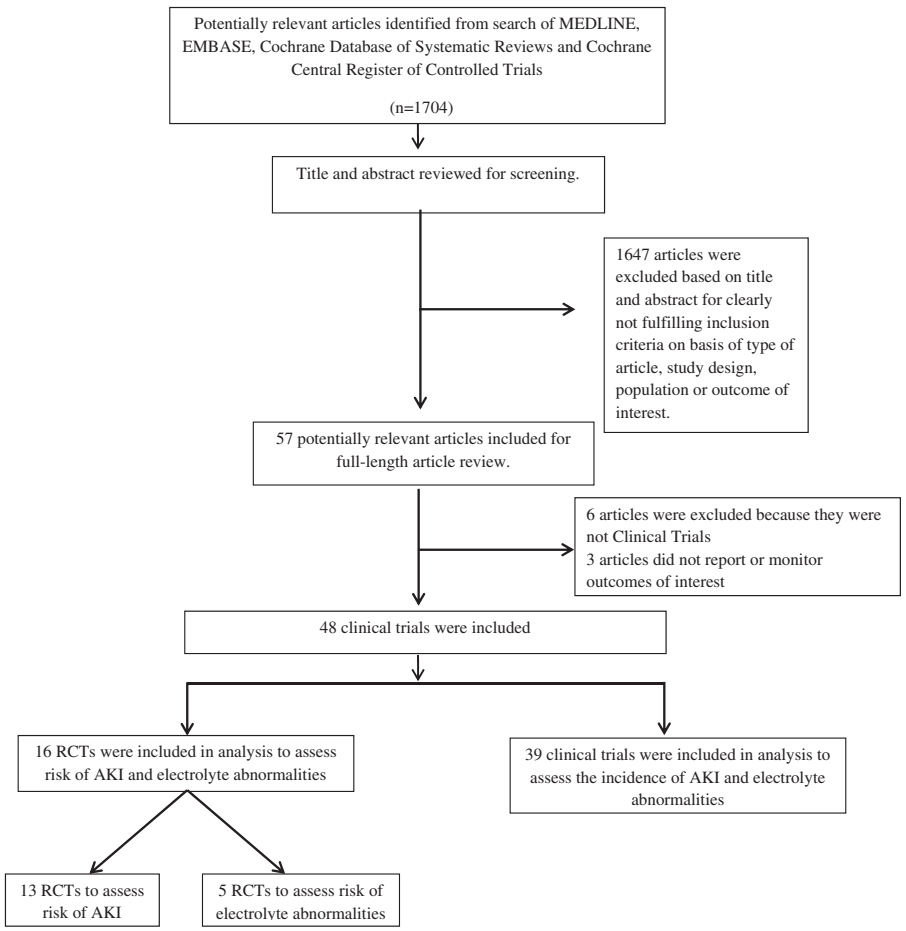

FIGURE 1: Outline of our search methodology.

Table 1. Main characteristics of the RCTs included in this meta-analysis (AKI)

Study	Phase	Drug	Control	Tumor type	Total *n*	Patients with renal events		Reported grade per CTCAE		Renal outcome definition	Follow-up (months)
						Event *n*/ drug N	Event *n*/ control *n*	Grade 1–2	Grade 3–5		
Borghaei *et al.* [10]	3	Nivolumab	Docetaxel	Nonsquamous NSCLC	582	7/287	1/268	7	–	Blood creatinine increased or acute renal failure	13.2
Brahmer *et al.* [11]	3	Nivolumab	Docetaxel	Squamous-cell NSCLC	260	5/131	2/129	4	1	Tubulointerstitial nephritis or blood creatinine increased	At least 11
Postow *et al.* [34]	2/3	Nivolumab and ipilimumab	Ipilimumab alone[a]	Melanoma	140	3.008/94 (calc)	1.012/46 (calc)	1.974 (calc)	1.034 (calc)	Creatinine increased; renal failure	At least 11
Robert *et al.* (1) [39]	3	Nivolumab	Dacarbazine	Melanoma	418	4/206	1/205	3	1	Blood creatinine increased or acute renal failure or renal failure	8.9
Weber *et al.* [48]	3	Nivolumab	Dacarbazine or paclitaxel plus carboplatin[a]	Melanoma	405	7/268	1/102	6	1	Blood creatinine increased or acute renal failure or renal failure	8.4 (IQR 7.0–9.8)
Ferris *et al.* [13]	3	Nivolumab	Single-agent therapy[a]	SCC of head and neck	361	1/236	2/111	1	–	Acute kidney injury	5.1 (0–16.8)
Hodi *et al.* [22]	2	Nivolumab and ipilimumab	Ipilimumab alone	Melanoma	140	2/94	0/46	1	1	Creatinine increased	24.5 (IQR 9.1–25.7)
Ribas *et al.* [37]	2	Pembrolizumab	Investigator choice chemotherapy[a]	Melanoma	540	2/357	0/171	2	–	Nephritis	10 (IQR 8–12)
Robert *et al.* (2) [41]	3	Pembrolizumab	Ipilimumab[a]	Melanoma	811	7/555	2/256	7	–	Blood creatinine increased	7.9
Herbst *et al.* [21]	2/3	Pembrolizumab	Docetaxel	NSCLC	991	13/682	0/309	13	–	Blood creatinine increased	13.1 (IQR 8.6–17.7)
Langer *et al.* [23]	2	Pembrolizumab plus carboplatin and pemetrexed	Carboplatin and pemetrexed alone[a]	Non-squamous NSCLC	121	8/59	5/62	6	2	Increased creatinine or acute kidney injury	10.6 (IQR 8.2–13.3)
Reck *et al.* [35]	3	Pembrolizumab	Investigator choice chemotherapy[a]	NSCLC	305	3/154	16/150	3	–	Increased blood creatinine level	11.2
Bellmunt *et al.* [52]	3	Pembrolizumab	Investigator choice chemotherapy[a]	Urothelial cancer	542	15/266	7/255	8	7	Acute kidney injury	14.1 (IQR 9.9–22.1)

calc, calculated from a reported percentage; IQR, interquartile range; *n*, number; NSCLC, non-small-cell lung cancer; SCC, squamous cell carcinoma.
[a]Control drugs with known nephrotoxic profile.

Association between AKI and PD-1 inhibitors

A total of 13 studies [10, 11, 13, 21–23, 34, 35, 37, 39, 41, 49, 52] (Table 1) were included in the meta-analyses assessing the association between AKI and PD-1 inhibitors. The overall pooled RR of AKI in patients treated with PD-1 inhibitors versus control was 1.86 (95% CI 0.95–3.64; $I^2 = 48\%$, Figure 2A).

Compared with non-nephrotoxic controls, the pooled RR of AKI in patients treated with PD-1 inhibitors was 4.19 (95% CI 1.57–11.18; $I^2 = 0\%$, Figure 2B). Of these, 9.6% (3/31) AKI were reported as Grade 3–4. Three studies used ipilimumab as control [22, 34, 41]. The overall pooled RR of AKI in patients treated with PD-1 inhibitors versus non-ipilimumab control was 1.76 (95% CI 0.73–4.21; $I^2 = 59\%$). When ipilimumab was used as control, the pooled RR of AKI in patients treated with PD-1 inhibitors was 2.13 (95% CI 0.61–7.44; $I^2 = 0\%$).

Subgroup analysis by type of PD-1 inhibitors demonstrated pooled RR of AKI of 3.28 (95% CI 1.15–9.35; $I^2 = 0\%$) following nivolumab treatment. The data on the risk of AKI following pembrolizumab treatment was limited. One RCT [21] demonstrated increased risk of AKI with pembrolizumab with odds ratio of 24.47 (95% CI 1.46–410.77). Compared with nephrotoxic controls, the pooled RR of AKI in patients treated with PD-1 inhibitors was 1.11 (95% CI 0.46–2.64; $I^2 = 56\%$) (Supplementary data, Figure S1). In all, 26.2% of these AKIs were reported to be of Grade 3–4.

Association between electrolyte abnormalities and PD-1 inhibitors

A total of five RCTs [13, 22, 23, 41, 52] (Table 2) were included in the meta-analyses assessing the association between electrolyte abnormalities and PD-1 inhibitors. The overall pooled RR of electrolyte abnormalities in patients treated with PD-1 inhibitors was 1.67 (95% CI 0.89–3.12; $I^2 = 25\%$, Figure 2C). Sensitivity analysis excluding two studies [22, 41] (using ipilimumab as control) was also performed. The overall pooled RR of electrolyte abnormalities in patients treated with PD-1 inhibitors versus non-ipilimumab control was 1.05 (95% CI 0.53–2.10; $I^2 = 17\%$). When ipilimumab was used as control, the pooled RR of electrolyte abnormalities in patients treated with PD-1 inhibitors was 3.91 (95% CI 1.22–12.56; $I^2 = 0\%$).

Prespecified subgroup analyses by type of electrolyte abnormalities demonstrated a significant association between PD-1 inhibitors and hypocalcemia (two studies with pembrolizumab treatment) with pooled RR of 10.87 (95% CI 1.40–84.16). The data on the risk of hypocalcemia with nivolumab treatment was limited. As mentioned previously, the pooled incidence of hypocalcemia with PD-1 inhibitors was 1.0% (95% CI 0.6–1.8%). In addition, hypocalcemia with PD-1 inhibitor therapy reached severe degree (Grade 3 or higher) in 13.0% of the cases (95% CI 3.3–39.4%; $I^2 = 0\%$).

Otherwise, no significant associations between PD-1 inhibitors and other electrolyte abnormalities including hyponatremia, hypokalemia, hypomagnesemia, hypercalcemia and hypophosphatemia were found (Figure 2C). Overall 28.8% (15/52) of reported electrolyte abnormalities were of Grade 3 or higher. Even though no significant association could be made with hyponatremia, >53% (8/15) of those reported as Grade

Table 2. Main characteristics of the RCTs included in this meta-analysis (electrolytes)

Study	Phase	Drug	Control	Tumor type	Total *n*	Age, years (range)	Electrolyte outcome definition	Patients with electrolyte events		Reported grade per CTCAE		Follow-up, months (range)
								Event *n*/drug N	Event *n*/control *n*	Grade 1–2	Grade 3–5	
Ferris *et al.* [13]	3	Nivolumab	Standard single-agent therapy	SCC of the head and neck	347	60 (28–83)	Hypercalcemia	3/236	1/111	–	3*	5.1 (0–16.8)
							Hyponatremia	2/236	3/111	–	2	
							Hypophosphatemia	2/236	1/111	–	2	
Hodi *et al.* [22]	2	Nivolumab and ipilimumab	Ipilimumab alone	Melanoma	140	64 (27–87)	Hypokalemia	3/94	0/46	3	–	24.5 (9.1–25.7)
							Hyponatremia	5/94	0/46	4	1	
Bellmunt *et al.* [52]	3	Pembrolizumab	Investigator choice chemotherapy	Urothelial cancer	542	67 (29–88)	Hyponatremia	15/266	18/255	10	5	14.1 (9.9–22.1)
Langer *et al.* [23]	2	Pembrolizumab plus carboplatin and pemetrexed	Carboplatin and pemetrexed alone	Non-squamous NSCLC	121	54–70	Hypocalcemia	3/59	0/62	2	1	10.6 (8.2–13.3)
							Hypokalemia	6/59	2/62	5	1	
Robert *et al.* (2) [41]	3	Pembrolizumab	Ipilimumab	Melanoma	811	61 (18–89)	Hypocalcemia	8/555	0/256	8	–	7.9
							Hypomagnesemia	5/555	2/256	5	–	

n, number; NSCLC, non-small-cell lung cancer; SCC, squamous cell carcinoma.

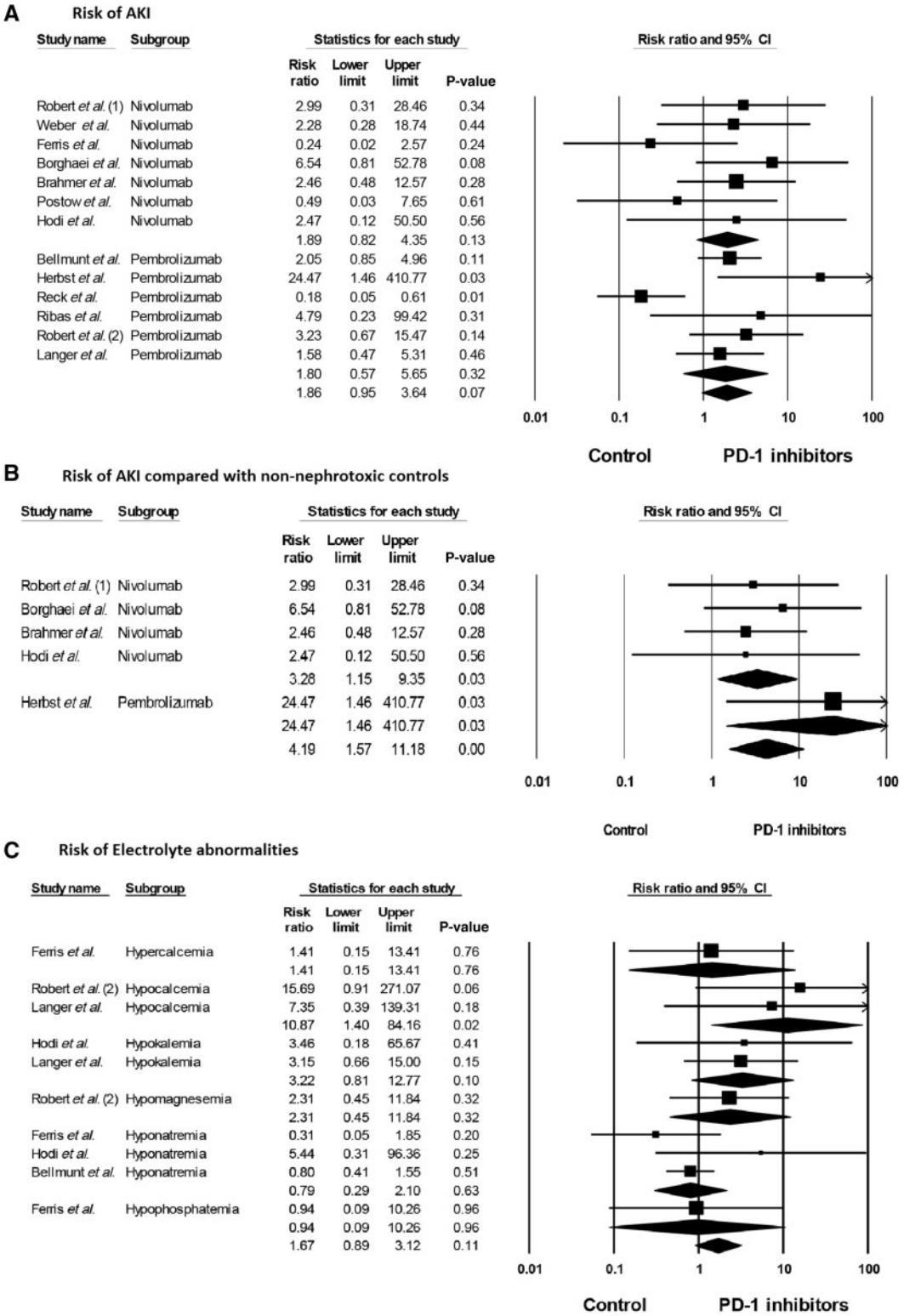

FIGURE 2: Forest plot of included studies comparing the risk of AKI in patients treated with PD-1 inhibitors versus non-PD-1 inhibitors **(A)**, risk of AKI in patients treated with PD-1 inhibitors versus non-nephrotoxic controls **(B)** and risk of electrolyte abnormalities in patients treated with PD-1 inhibitors versus non-PD-1 inhibitors **(C)**. Square data markers represent RRs and horizontal lines represent the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

Table 3. Incidence rates of AKI and electrolyte abnormalities with PD-1 inhibitors

AKI/electrolyte abnormalities	Nivolumab [*n*% (95% CI)]	Pembrolizumab [*n*% (95% CI)]	Overall [*n*% (95% CI)]
AKI	2.2 (1.4–3.5)	2.0 (1.1–3.5)	2.1 (1.5–3.0)
Hyponatremia	1.0 (0.5–2.3)	1.3 (0.6–3.2)	1.2 (0.7–2.1)
Hypokalemia	1.1 (0.6–1.9)	1.0 (0.3–3.3)	1.1 (0.6–1.8)
Hyperkalemia	0.5 (0.2–1.0)	1.0 (0.5–2.1)	0.7 (0.4–1.2)
Hypomagnesemia	0.3 (0.1–0.8)	0.8 (0.4–1.5)	0.6 (0.4–1.0)
Hypocalcemia	0.9 (0.4–2.1)	1.1 (0.5–2.4)	1.0 (0.6–1.8)
Hypercalcemia	0.7 (0.3–1.3)	0.6 (0.3–1.4)	0.6 (0.4–1.1)
Hypophosphatemia	2.3 (1.2–4.2)	0.4 (0.2–1.1)	1.3 (0.8–2.2)

3–5 were from hyponatremia. Only one case of hypocalcemia and three cases of hypercalcemia were reported among all cases with Grade 3–5 derangements. Of note, one case of hypercalcemia was specifically reported to be of Grade 5 (death).

Incidence rates of AKI and electrolyte abnormalities with PD-1 inhibitors

Of the 48 clinical trials [9–56], 39 studies [9–15, 18–24, 27–31, 33–41, 43, 44, 46, 48–54, 56] were included in the analysis to assess the incidence of AKI. The pooled incidence of all AKI with PD-1 inhibitors was 2.2% (95% CI 1.5–3.0%; $I^2 = 68\%$) (Supplementary data, Figure S2). Of these, 19% of AKI were of Grade 3–4 and no deaths were observed. Subgroup analyses by type of PD-1 inhibitors demonstrated a pooled incidence of AKI of 2.3% (95% CI 1.4–3.6%; $I^2 = 63\%$) following nivolumab treatment and 2.0% (95% CI 1.1–3.5%; $I^2 = 75\%$) following pembrolizumab treatment.

Of those AKI events that were specifically reported as 'interstitial nephritis' or 'nephritis' [11, 37, 52] the pooled estimated rate of interstitial nephritis was 16.6% (95% CI 10.2–26.0%; $I^2 = 0\%$). Subgroup analyses by type of PD-1 inhibitors demonstrated an estimated rate of interstitial nephritis of 15.0% (95% CI 8.3–25.5%; $I^2 = 0\%$) following nivolumab treatment and 21.6% (95% CI 8.7–44.4%; $I^2 = 40\%$) following pembrolizumab treatment among those who developed AKI. Of note, three out of the five reported cases of interstitial nephritis were reported as Grade 3 or higher.

Of the 48 clinical trials [9–56], 39 studies [9–14, 16–27, 30–35, 37, 39, 41–47, 50, 52–56] were included in the analysis to assess the incidence of electrolyte abnormalities. The pooled incidences of reported electrolyte abnormalities with PD-1 inhibitors including hyponatremia, hypokalemia, hyperkalemia, hypomagnesemia, hypocalcemia, hypercalcemia and hypophosphatemia were 1.2% (95% CI 0.7–2.1%; $I^2 = 66\%$), 1.1% (95% CI 0.6–1.8%; $I^2 = 52\%$), 0.7% (95% CI 0.4–1.2%; $I^2 = 0\%$), 0.6% (95% CI 0.4–1.0%; $I^2 = 0\%$), 1.0% (95% CI 0.6–1.8%; $I^2 = 42\%$), 0.6% (95% CI 0.4–1.1%; $I^2 = 0\%$) and 1.3% (95% CI 0.8–2.2%; $I^2 = 51\%$), respectively. Though the incidence of electrolyte abnormalities was low, 28.8% (15/52) of reported electrolyte abnormalities were of Grade 3 or higher. Table 3 summarizes the pooled incidence of AKI and electrolyte abnormalities categorized by type of PD-1 inhibitors.

Effects of high-dose versus low-dose PD-1 inhibitors on rates of AKI and hypocalcemia

Doses of PD-1 inhibitors of each included study are available in Supplementary data, Tables S2 and S3. In nivolumab high dose was defined based on average median dose of >1.5 mg/kg/week dose and in pembrolizumab >2.325 mg/kg/week dose. Meta-regression showed no significant impact of dose of PD-1 inhibitors (high dose versus low dose) on the rates of AKI ($P = 0.85$ for nivolumab treatment and $P = 0.68$ for pembrolizumab treatment, shown in Supplementary data, Figures S7 and S8, respectively). However, when compared with low-dose PD-1 inhibitors, meta-regression analysis demonstrated significant positive correlation between incidence of hypocalcemia in patients treated with high-dose PD-1 inhibitors (slope = +2.45, $P = 0.02$ for nivolumab treatment and slope = +1.63, $P = 0.03$ and for pembrolizumab treatment, shown in Supplementary data, Figures S9 and S10, respectively). We were not able to include four studies in this analysis as the median/average weight was not available and the patients had not received weight-based drug dosing (Supplementary data, Tables S2 and S3).

Evaluation for publication bias

We found no publication bias as assessed by the funnel plots (Supplementary data, Figures S3 and S4) and Egger's regression asymmetry test with $P = 0.43$ and 0.24 for the risks of AKI and electrolyte abnormalities in patients treated with PD-1 inhibitors, respectively.

Study quality

The risk of bias of the 13 trials included is presented in Supplementary data, Figures S5 and S6. Overall, the study quality was reasonable, but there was unclear reporting in several domains, including blinding of participants and personnel (performance bias) and blinding of outcome assessment (detection bias).

DISCUSSION

In this systematic review, we found a significant, 4-fold increased risk of AKI after treatment with a PD-1 inhibitor compared with non-nephrotoxic agents. The pooled estimated incidence rate of AKI was 2.2% (95% CI 1.5–3.0%). Interstitial nephritis is considered to be a leading cause, but many reported kidney events could not be related to this etiology with a high degree of certainty in this study due to variability in data reporting. However, based on those studies that did provide verifiable data, the estimated incidence rate of AIN among AKI cases with PD-1 inhibitor therapy is 16.6% (95% CI 10.2–26.0%).

Kidney injury in oncologic patients can have diverse implications, one of them being a potential for limiting future chemotherapeutic treatment options. An understanding of the mechanism of AKI in patients treated with PD-1 inhibitors and the patient population at greatest risk can be helpful in predicting and preventing AKI episodes. Even though patients on chemotherapy may develop AKI from other potential etiologies like prerenal, associated with poor oral intake and diarrheal illness or concurrent nephrotoxic drug use among other causes, there are also some case reports of glomerulonephritis

associated with immune CPIs. Reports of lupus-like membranous nephropathy [57] and minimal change disease [58] have been reported with the CTLA-4 inhibitor ipilimumab and recently a case of minimal change disease was reported with pembrolizumab [59]. But AIN remains the dominant finding seen on the kidney biopsy of those presenting with AKI and PD-1 drug use.

Clinically, it has been reported that patients with PD-1 related AIN present similar to other causes of AIN, with evidence of pyuria and sub-nephrotic range proteinuria [2]. Diagnostic clues of eosinophilia, rash and fever are less commonly seen. Cortazar *et al.* reported that 60% of the patients also had concurrent evidence of extrarenal irAE at the time of the renal manifestation [2]. The time frame of presentation of AKI also appears to be delayed, usually 6–12 months after initial drug administration. In our current study, which involved only clinical trials, by design, we were limited in the information available to us for review. The time of onset of AKI in relation to the duration of drug exposure was not available for us. We did find that the AKI events were independent of the drug dose received. This is interesting as most protocols after an AKI event suggest steroid initiation followed by drug initiation at a lower dose. It can be contemplated that the risk of a subsequent AKI event may not necessarily change with dose reduction in such cases. Furthermore, we did not have data regarding the AKI patient's proteinuria status, urine sediment and concurrent use of other nephrotoxic medication or presence of other factors clinical factors that could cause kidney injury, like volume depletion from diarrhea. We also did not find any association with the PDL-1 status of the underlying cancer cells with AKI events.

From a mechanistic perspective, PD-1 is expressed after activation by T cells, B cells, natural killer T cells, activated monocytes and dendritic cells [60]. Its ligand PDL-1 is expressed in the kidney tubules, especially the proximal tubule segments. No PDL-1 expression has been detected in the glomeruli [61]. Their role in the kidney appears to be in modulating peripheral immune tolerance of kidney cells against T cells; in the absence of PD-1 the autoreactive T cells have been found to be activated in mice models [62]. PD-1 knockout mice have spontaneously developed a chronic systemic inflammatory response akin to lupus with proliferative arthritis and glomerulonephritis with Immunoglobulin G 3 (IgG3) and complement C3 deposition [62]. Interestingly, the spectrum of findings in these knockout mice depended on the background genes of the mice [62]. Currently, only one human case report of glomerulonephritis has been reported in PD-1 drug use [59].

The delayed nature of the AIN presentation with PD-1 drugs has stirred some debate as it is unlike the other well-known drug-related hypersensitivity reactions. The possibility of loss of tolerance and reactivation of previously silenced drug-specific T cells has been contemplated, which play an important role in and can lead to drug-induced interstitial nephritis [2, 63, 64]. Progressive silencing and eventually eradication of the activated T cell clone has been commonly described in high-grade chronic infections like human immunodeficiency virus, hepatitis B virus and hepatitis C virus [65]. Tumor cells appear to utilize a similar mechanism in evading detection and destruction by our body's immune surveillance system. It is the rekindling of precisely these exhausted T cells in the tumor microenvironment that is targeted by PD-1 inhibitors [66]. Thus, any concurrent (or prior) use of medications with well-known hypersensitivity reaction potential will need to be considered in any patients presenting with AKI while on PD-1 inhibitor therapy.

When it comes to electrolyte disorders, hyponatremia related to hypophysitis has been the most common and well-described electrolyte abnormality with CPIs use [67] and Wanchoo *et al.* in their review of the Food and Drug Administration adverse event database also noted higher reporting of hyponatremia and hypokalemia when compared with other electrolytes [3]. Our meta-analysis, on the other hand, shows a significant association between pembrolizumab and hypocalcemia. Although the overall reported incidence of hypocalcemia was low at 1%, severe hypocalcemia, defined as Grade 3 or higher by CTCAE criteria, was reported in 13% of cases of PD-1 inhibitor-related hypocalcemia. Furthermore, in our study we also found that PD-1-related hypocalcemia is dose-dependent. Interestingly, a Grade 5 event was also reported for hypercalcemia. The exact mechanism of PD-1 inhibitors affecting the calcium metabolism is unclear as we did not have data available from the clinical trials regarding the parathyroid hormone (PTH) and vitamin D levels. It is possible that incidence of hypocalcemia could be related to other causes such as severity of the renal injury, but again we lack this information. Recently, a case of hypoparathyroidism with undetectable PTH levels has been reported in a patient that received combination therapy with ipilimumab and nivolumab [68]. This raises the possibility of loss of T cell self-regulation in these patients resulting in development of autoimmunity. Polymorphisms of immune checkpoint genes have been linked with various autoimmune diseases [69, 70]. Clinically, this is an important finding, and we recommend routine calcium monitoring in these patients during treatment.

Although only clinical trials that used PD-1 inhibitors were included in our meta-analysis, there are some limitations that bear mention. First, there were moderate heterogeneities in the meta-analysis assessing the risk of AKI with PD-1 inhibitors. The potential sources of these heterogeneities include the differences in the definition and severity of AKI and controls. When we included only studies with non-nephrotoxic agents as controls, we found significant increased AKI risk following PD-1 inhibitors without significant heterogeneity. Second, although the findings of our meta-analysis suggest interstitial nephritis as an important cause of PD-1 inhibitors-associated AKI, estimates could be compromised if kidney biopsies were not performed routinely on AKI patients. Information on the total number of kidney biopsies performed was not available for the authors to review and hence not accounted for here. Therefore, the pooled risk estimate for interstitial nephritis should be viewed with caution. Future studies are warranted to systematically study the renal pathology of AKI patients treated with PD-1 inhibitors. Lastly, the association between the use of PD-1 inhibitors and hypocalcemia emerged in studies with pembrolizumab and cannot be inferred upon nivolumab or

other immune CPIs, for which separate studies will be required [23, 41].

Immune CPIs, particularly PD-1/PD-L1 inhibitors, are projected to be leading anticancer drugs on the market by the end of this decade. The use of PD-1 inhibitors has led to significant improvements in survival and overall prognosis in many cancer types, including melanoma, non-small-cell lung cancer, kidney cancer and bladder cancer. However, there is evolving knowledge of immunotherapy-related nephrotoxicity and electrolyte disorders with these agents. This systematic review, therefore, adds important information on a relevant side effect profile, and timely recognition of these toxicities can help with proper management of patients undergoing treatment with immune checkpoint inhibitors.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

AUTHORS' CONTRIBUTIONS

All authors had access to the data and played essential roles in writing of the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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