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REVIEW

Comparative risk of acute kidney injury among cancer patients treated with immune checkpoint inhibitors

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Abstract

With the development and introduction of immune checkpoint inhibitors (ICIs) in cancer patients, immune-related side effects have increasingly attracted attention. However, the risks of immune-related renal toxicity are poorly characterized. In this study, we performed a network meta-analysis (NMA) of ICI-related randomized clinical trials (RCTs) to elucidate the comparative risk

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; CKD, chronic kidney disease; CTLA-4, cytotoxic T lymphocyte-associated antigen-4.; Egfr, estimated glomerular filtration rate; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; irAKI, immune-related acute kidney injury; N1I3, 1 mg/kg nivolumab plus 3 mg/kg ipilimumab; NMA, network meta-analysis; N3I1, 3 mg/kg nivolumab plus 1 mg/kg ipilimumab; NSCLC, non-small-cell lung cancer; RCT, randomized clinical trial; RR, risk ratio; RCC, renal cell carcinoma; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PPI, proton-pump inhibitor; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

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of acute kidney injury (AKI) in cancer patients receiving different ICIs. We also sought to identify other factors potentially affecting the risk of AKI. PubMed and EMBASE were searched for peer-reviewed trial reports published between January 2000 and May 2021. Eligible studies were RCTs studying ICIs in cancer patients and reporting AKI data. We performed a frequentist NMA to evaluate the risk ratios for grade 1-5 and grade 3-5 AKI between the treatment groups. We also assessed the absolute incidence of AKI in the ICI-containing arm using traditional direct meta-analysis. Once significant heterogeneity was detected in a traditional direct meta-analysis, multivariable meta-regression analysis was applied to identify factors that significantly affected the absolute incidence of AKI. A total of 85 RCTs were included in this study. In the NMA for the risk of grade 1-5 and 3-5 AKI, ipilimumab showed a significantly higher risk than avelumab and durvalumab, whereas 1 mg/kg nivolumab plus 3 mg/kg ipilimumab (N1I3) showed a significantly higher risk than other groups. In terms of treatment ranking, durvalumab ± low-dose tremelimumab and avelumab were consistently among the top three safest treatments for grade 1-5 or 3-5 AKI, whereas N1I3, ipilimumab and tremelimumab were consistently among the top three treatments with the highest risk for grade 1-5 or 3-5 AKI. Compared with other cancers, renal cell carcinoma and urothelial carcinoma showed a significantly higher risk of AKI. The incidence of AKI was significantly higher with ICI+chemotherapy than with ICI monotherapy. In this NMA involving large-scale up-to-date ICI trials, we demonstrated the comparative safety of existing ICI drugs for grade 1-5 and grade 3-5 AKI. Based on data from the ICI arms of these trials, we also revealed several potential risk factors for immune-related AKI, including tumor type and treatment paradigm.

KEYWORDS
immune checkpoint inhibitors, acute kidney injury, cancer, immune therapy, side effects

1 | BACKGROUND

Cancer treatment with immune checkpoint inhibitors (ICIs) is an emerging and promising approach in which major breakthroughs have been achieved in clinical oncology and significantly impacted the treatment paradigm for several cancers [1–3]. The humanized antibodies in this novel class inhibit the downregulation of immune pathways (including CTLA-4, PD-1 and PD-L1) to enhance immune responses against tumors. Compared to other standard therapies, these remedies have led to improved survival by months to years in numerous clinical settings [4]. Nevertheless, ICIs might lead to inflammatory side effects by provoking the immune system, referred to as immune-related adverse events (irAEs) [5]. Various organs are affected by irAEs with ICIs, including the nervous system, gastrointestinal tract, skin, lung, liver and kidney [5].

Renal dysfunction directly caused by ICIs, referred to as immune-related renal adverse events (irRAEs), although less frequently observed than others, deserves more concern since it may result in the interruption of ICI treatment or even higher mortality [6]. ICIs are believed to disrupt the immune balance by blocking suppression signals through the CTLA-4 or PD-1/PD-L1 pathway, thus inducing the immune system to attack self-antigens in the kidney [7, 8]. With a delayed onset pattern, irAEs usually occur at a median of 16 weeks (ranging from 3 to 56 weeks) after starting ICIs [9–11]. When kidney dysfunction, sometimes as mild isolated electrolyte disorders or isolated urinalysis abnormalities, occurs in patients previously exposed to ICIs, the diagnosis of irRAE should be considered [12]. Notably, thorough screening for medical history is required to exclude confounding etiologies for renal injuries, such as sepsis, volume depletion, the use of nephrotoxic drugs or urinary tract obstruction [13]. After that, patients

suspicious for irRAE should be referred for timely renal biopsy following a full evaluation for feasibility [14].

Immune-related acute kidney injury (irAKI) is the most common manifestation observed in irRAEs [15]. However, the incidence of irAKI varies greatly in different studies, which may result from the unreliable assessment of causality based on retrospective data. Correlations between an increased incidence of irAKI and several factors have been reported, including impaired renal function at baseline, use of a proton-pump inhibitor (PPI), ipilimumab, extrarenal irAEs, ICIs in combination with chemotherapy, or a history of an autoimmune disease [6, 15-20]. However, until now, the risk factors for irAKI have not been completely elucidated. The outcome and prognosis of patients receiving immunotherapy are influenced by the ICIs-induced irAKI. Therefore, as irAKI occurs, the drugs should be stopped immediately, and supportive treatment or renal replacement should be considered when necessary. Reports on irAKI caused by ICIs or combination therapies are relatively scarce and poorly characterized. Encouragingly, the increasing number of prospective clinical trials involving ICIs provides the possibility to carry out high-quality research on irAKI.

Considering that the ICI type could be one of the most significant factors affecting the risk of AKI, we first took advantage of the random controlled design and conducted this network meta-analysis (NMA) of randomized clinical trials (RCTs) to elucidate the comparative risk of AKI in cancer patients receiving different ICIs. We also examined data from the ICI arm in these RCTs to identify other factors potentially affecting the risk of AKI, such as cancer type and treatment modality.

2 | LITERATURE ACQUISITION AND DATA EXTRACTION

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. PubMed and EMBASE were searched to identify peer-reviewed, potentially eligible studies from January 1, 2000, to May 15, 2021. The literature search strategies used are shown in the Supplemental Methods. Studies were considered potentially eligible if they met all of the following criteria: 1) RCTs of cancer; 2) at least one treatment arm involved ICI-containing regimens; 3) either ICI-containing regimens or conventional therapies (including placebo, chemotherapy and targeted therapy) without ICIs as the control group; and 4) reported data of grade 1-5 or grade 3-5 AKI in each group. Studies that failed to meet the above criteria were excluded. We also excluded reviews, meta-analyses, conference abstracts, and case reports or case series.

Two independent investigators (F.L. and Z.X.W.) reviewed and selected the publications before extracting the data. Data on trial stage (phase 2 vs. phase 3), year of publication, cancer type, number of patients randomized per treatment group, regimens of the treatment and control arms, and number of AKI events per treatment group were extracted independently. AKI was defined as a >0.3 mg/dL increase or a >1.5-fold rise in serum creatinine from baseline according to the Common Terminology Criteria for Adverse Events (CTCAE). Any discrepancies were discussed by the two investigators before reaching a consensus.

3 | PIPELINE OF META-ANALYSIS OF RISK OF AKI

The risk ratio (RR) with the corresponding 95% confidence interval (CI) was used to estimate the relative risk of grade 1-5 or grade 3-5 AKI of different treatments. Mixed network comparisons between the conventional therapies and different ICI groups and among different ICI groups were conducted using the frequentist NMA model [22]. The frequentist approach was used instead of the Bayesian approach since frequentist methods are more interpretable, and no major differences were noted in the NMA results based on these methods [23]. The generalized Cochran's Q test and I^2 statistic were used to assess the level of homogeneity in the whole network [24]. A fixed-effects model was used first, and the random-effects model was used in cases of significant heterogeneity ($P < 0.10$ in Q test or $I^2 > 50\%$). The treatments were ranked based on the P-score; a P-score of 100% suggests the best treatment, whereas a P-score of 0% suggests the worst treatment [25]. To assess the consistency between direct and indirect treatment comparison results, traditional direct meta-analyses were also performed for accessible pairwise treatment comparisons. A fixed-effects model was used first, and the random-effects model was used in cases of significant heterogeneity ($P < 0.10$ in Q test or $I^2 > 50\%$).

To demonstrate the relative risk of AKI among different ICIs, we first performed drug-based NMA. Regimens containing one ICI were all classified into the corresponding ICI group (e.g., pembrolizumab monotherapy, pembrolizumab plus chemotherapy, and pembrolizumab plus targeted therapy were all denoted as the pembrolizumab group). In contrast, regimens containing two ICIs, with or without conventional therapies, were all classified into the corresponding ICI+ICI group (e.g., nivolumab plus ipilimumab alone or in combination with chemotherapy were both denoted as the nivolumab+ipilimumab group). Specifically, as the toxicity of ipilimumab was considered dose-dependent [26], the dose level of ipilimumab

(<3 mg/kg vs. ≥3 mg/kg) was considered in the regimen grouping in this drug-based NMA. Moreover, we preplanned an additional regimen-based NMA once significant heterogeneity was detected in the drug-based NMA.

We also assessed the absolute incidence of grade 1-5 or grade 3-5 AKI in the ICI-containing arm using traditional direct meta-analysis. A fixed-effects model was used first, and the random-effects model was used in cases of significant heterogeneity ($P < 0.10$ in Q test or $I^2 > 50\%$). Once significant heterogeneity was detected, multivariable meta-regression analysis was applied to identify factors that significantly affected the absolute incidence of AKI.

All P values were two-sided. Statistical analyses were performed using R version 4.1.2 (http://www.r-project.org) with the package "metafor" for the direct meta-analysis and the package "netmeta" for the frequentist NMA.

4 | OVERVIEW OF CHARACTERISTICS OF ELIGIBLE TRIALS

A total of 85 randomized trials met the selection criteria and were included in this study (Supplementary Figure S1). The trial characteristics are summarized in Supplementary Table S1. A total of 51,141 patients were enrolled in these trials. Fifteen different tumor types were examined, predominantly non-small-cell lung cancer (NSCLC, $n = 25$), melanoma ($n = 11$), renal cell carcinoma (RCC), urothelial carcinoma, gastroesophageal cancer and head and neck cancer ($n = 7$ for all). Most ($n = 61$) of the trials were phase 3 trials. The most commonly studied ICIs included pembrolizumab ($n = 31$), atezolizumab ($n = 15$), nivolumab and ≥3 mg/kg ipilimumab ($n = 9$ for both). Forty trials assessed ICI monotherapy, and 23 investigated ICI+chemotherapy. Among the 24 trials involving an ICI+chemotherapy arm, 8 (33%) trials involved cisplatin-containing regimens. Eight trials studied durvalumab+low-dose tremelimumab, four studied 3 mg/kg nivolumab plus 1 mg/kg ipilimumab (N3I1), and three investigated 1 mg/kg nivolumab plus 3 mg/kg ipilimumab (N1I3).

5 | RELATIVE RISK OF GRADE 1-5 OR 3-5 AKI FOR DIFFERENT TREATMENT GROUPS

We included 71 randomized trials investigating the comparison of an ICI group with conventional therapy or comparisons between different ICI groups to establish a network for multiple treatment comparisons (Figure 1). Given that no significant evidence of heterogeneity was detected ($P = 0.999$ in Q test and $I^2 = 0\%$ for grade 1-5 AKI; $P = 0.997$ in Q test and $I^2 = 0\%$ for grade 3-5 AKI), the fixed-effects model was applied while the regimen-based NMA was waived.

Figure 2 summarizes the results of multiple treatment comparisons in the frequentist NMA. In terms of grade 1-5 AKI, conventional therapy was significantly safer than pembrolizumab (RR, 0.66 [95% CI, 0.49-0.91]), atezolizumab (RR, 0.58 [95% CI, 0.35-0.96]), ≥3 mg/kg ipilimumab (RR, 0.37 [95% CI, 0.16-0.84]), and N1I3 (RR, 0.14 [95% CI, 0.05-0.42]). Ipilimumab showed a significantly higher risk than avelumab (RR, 2.83 [95% CI, 1.14-7.07]) and durvalumab (RR, 3.05 [95% CI, 1.18-7.91]). N1I3 showed a significantly higher risk than nivolumab (RR, 5.27 [95% CI, 1.80-15.45]), pembrolizumab (RR, 4.72 [95% CI, 1.53-14.56]), atezolizumab (RR, 4.10 [95% CI, 1.24-13.59]), avelumab (RR, 7.46 [95% CI, 2.33-23.89]), and durvalumab (RR, 8.04 [95% CI, 2.44-26.50]), whereas durvalumab+low-dose tremelimumab and N3I1 were significantly safer than N1I3 (RR, 0.07 [95% CI, 0.01-0.75] and RR, 0.19 [95% CI, 0.06-0.64], respectively). For grade 3-5 AKI, conventional therapy was significantly safer than pembrolizumab (RR, 0.66 [95% CI, 0.48-0.93]), atezolizumab (RR, 0.57 [95% CI, 0.33-0.97]), ipilimumab (RR, 0.40 [95% CI, 0.17-0.90]), and N1I3 (RR, 0.18 [95% CI, 0.06-0.56]). Durvalumab was significantly safer than atezolizumab (RR, 0.45 [95% CI, 0.20-1.00]), whereas ipilimumab showed a significantly higher risk than durvalumab (RR, 3.17 [95% CI, 1.16-8.67]). In addition, durvalumab+low-dose tremelimumab was significantly safer than N1I3 (RR, 0.08 [95% CI, 0.01-0.95]), while N1I3 showed a significantly higher risk than nivolumab (RR, 4.11 [95% CI, 1.30-12.99]), pembrolizumab (RR, 3.73 [95% CI, 1.14-12.22]), avelumab (RR, 5.02 [95% CI, 1.38-18.23]), and durvalumab (RR, 7.04 [95% CI, 1.95-25.42]).

As shown in Figure 2, in terms of safety for grade 1-5 AKI, durvalumab+low-dose tremelimumab ranked first (P-score, 0.84), followed by durvalumab (0.82), avelumab (0.78), conventional therapy (0.76), nivolumab (0.55), N3I1 (0.53), pembrolizumab (0.46), atezolizumab (0.39), pembrolizumab plus 1 mg/kg ipilimumab (0.31), tremelimumab (0.29), ipilimumab (0.22), and N1I3 (0.04). Regarding safety for grade 3-5 AKI, durvalumab ranked first (P-score, 0.86), followed by durvalumab+low-dose tremelimumab (0.85), conventional therapy (0.77), avelumab (0.68), nivolumab (0.56), pembrolizumab (0.49), N3I1 (0.45), atezolizumab (0.40), pembrolizumab plus 1 mg/kg ipilimumab (0.31), tremelimumab (0.31), ipilimumab (0.25), and N1I3 (0.06).

Figure 3 shows the direct and indirect results for 19 accessible head-to-head treatment comparisons. Overall, the direct meta-analysis results showed excellent consistency with the corresponding NMA results (i.e., similar RRs for direct meta-analysis and NMA), except

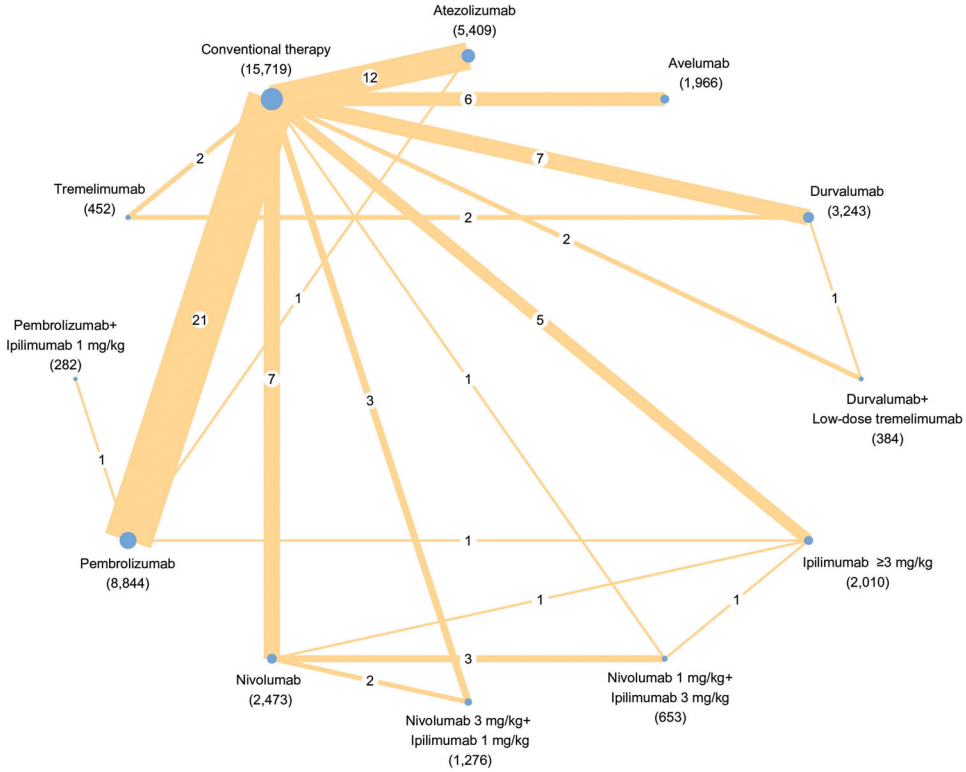

FIGURE 1 Network plot of the pairwise treatment comparisons in the network meta-analyses of the risks for AKI. Seventy-one randomized trials investigating the comparison of an ICI group with conventional therapy or comparisons between different ICI groups were included. Considering that the risk of AKI for PD-(L)1 inhibitors are not dose-dependent, PD-(L)1 inhibitors at different dosages were combined, except for the combination of PD-(L)1 blockade and CLTA-4 blockade. The circle size is proportional to the total number of patients (in parentheses) who received the given treatment. The width of the lines is proportional to the number of studies that involved the given treatment comparison, which is shown on top of the lines. To be noted, as some studies are multi-arm trials, the 71 eligible trials involved a total of 79 comparisons between different treatment and control groups.
Abbreviations: AKI, acute kidney injury; ICI, immune checkpoint inhibitor.

for the comparisons between atezolizumab and pembrolizumab and between ipilimumab and pembrolizumab, both involving only one relevant trial.

6 | ABSOLUTE INCIDENCES OF GRADE 1-5 OR 3-5 AKI AND RISK FACTORS

By including the ICI arm of the 85 eligible randomized trials, the pooled incidence rates of grade 1-5 and grade 3-5 AKI in the ICI-containing group were 1.4% (95% CI, 1.3-1.5) and 1.1% (95% CI, 0.9-1.2), respectively (Figure 4). Considering that significant heterogeneity was detected for both grade 1-5 AKI ($P < 0.001$ in Q test and $I^2 = 38\%$) and grade 3-5 AKI ($P = 0.053$ in Q test and $I^2 = 24\%$), we further performed multivariable meta-regression analysis to identify factors that significantly were associated with the absolute incidence of AKI.

As shown in Figure 5, cancer type, treatment modality and ICI type significantly impacted the incidence rates of grade 1-5 and grade 3-5 AKI. Compared with small-cell lung cancer, RCC and urothelial carcinoma showed significantly higher risks of grade 1-5 AKI (effect size, +1.49% [95% CI, 0.60-2.37] and +2.13% [95% CI, 1.23-3.02], respectively) and grade 3-5 AKI (effect size, +1.22% [95% CI, 0.38-2.07] and +1.94% [95% CI, 1.08-2.80], respectively). The incidence rates of grade 1-5 and grade 3-5 AKI were significantly higher with ICI+chemotherapy than with ICI monotherapy (effect size, +0.74% [95% CI, 0.33-1.14] and +0.62% [95% CI, 0.24-1.00], respectively). Moreover, N1I3 showed significantly higher risks of grade 1-5 and grade 3-5 AKI than durvalumab+low-dose tremelimumab (effect size, +1.26% [95% CI, 0.02-2.50] and +1.37% [95% CI, 0.16-2.57], respectively). Durvalumab±low-dose tremelimumab and avelumab were among the top three treatments with the lowest incidence rates of grade 1-5 and grade 3-5 AKI, whereas N1I3, N3I1 and tremelimumab were among the top three treatments with the highest incidence rates of grade 1-5 and grade 3-5 AKI.

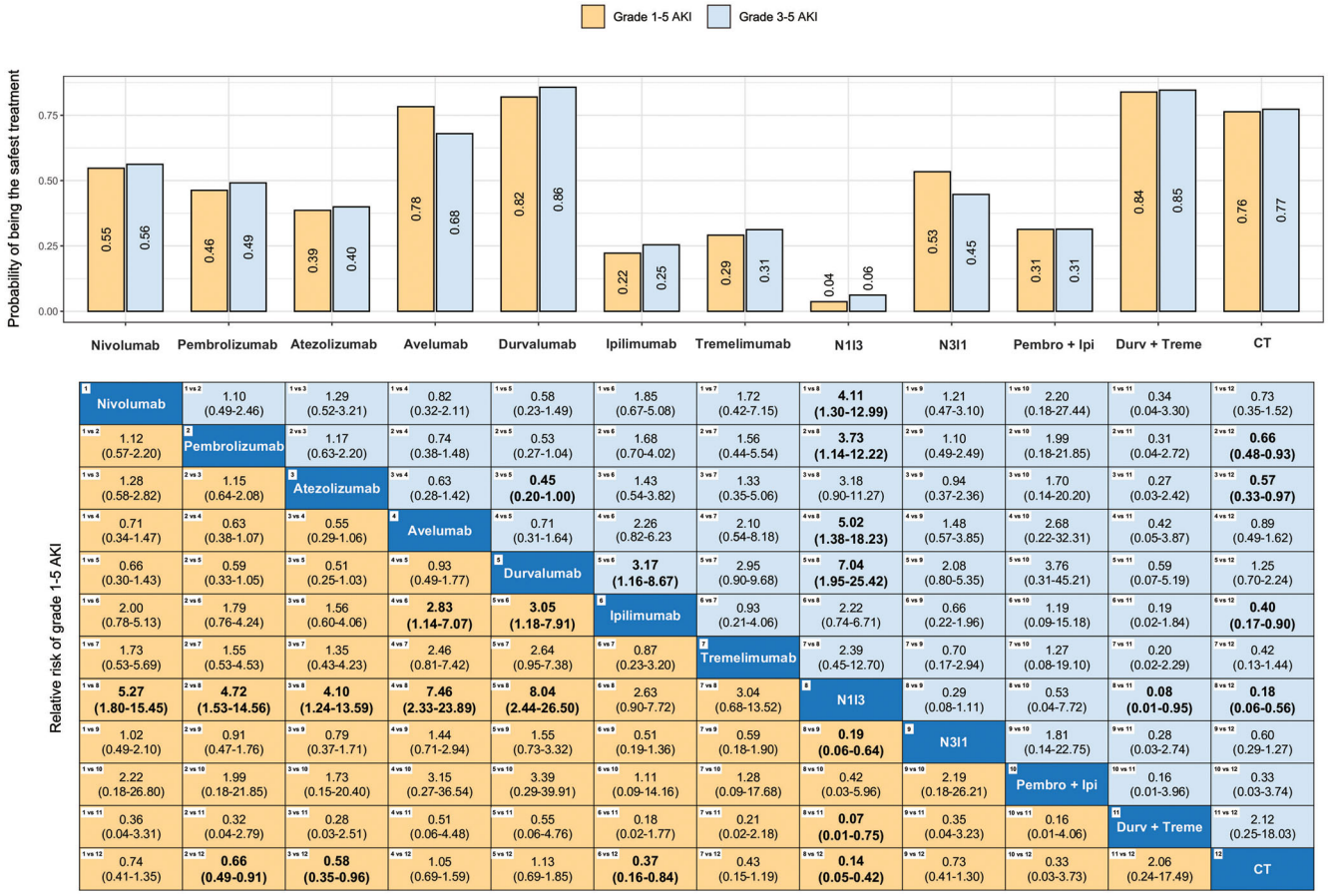

FIGURE 2 Risk ratios and 95% confidence intervals for AKI in pairwise treatment comparisons and the best safety ranking for each treatment. The colored table shows the risk ratio and 95% confidence interval for comparison of different treatment groups. For grade 1-5 AKI, the risk ratio and 95% confidence interval in each cell indicate the result of the row versus column treatments in the network meta-analysis. The following conditions indicate statistically significant results: 1) Significantly safer: the upper limit of the 95% CI below 1; 2) significantly higher risk: the lower limit of the 95% CI above 1. For grade 3-5 AKI, the risk ratio and 95% confidence interval in each cell indicate the result of the column versus row treatments in the network meta-analysis. Significant results are in bold. The treatments were ranked based on the P-score; a P-score of 100% suggests the best treatment, whereas a P-score of 0% suggests the worst treatment. A greater P-score indicates a better safety ranking. Abbreviations: AKI, acute kidney injury; N1I3, 1 mg/kg nivolumab plus 3 mg/kg ipilimumab; N3I1, 3 mg/kg nivolumab plus 1 mg/kg ipilimumab; Pembro+Ipi, pembrolizumab plus 1 mg/kg ipilimumab; Durv+Treme, durvalumab plus low-dose tremelimumab; CT, conventional therapy.

7 | DISCUSSION AND PERSPECTIVES

Due to the emergence of immune checkpoint therapies, many cancer treatment paradigms have been changed [1, 27, 28]. As large-scale applications of various ICIs have become increasingly available, clinicians should pay more attention to drug-related kidney impairment since ICI-induced AKI has emerged as a major toxicity among cancer patients [3]. Although several agents that target immune checkpoints were found to be useful in clinical trials [15], few studies have systematically compared the frequency or risks of renal damage. Liu et al. [29] performed an NMA of the risk of immune-related renal toxicity associated with ICIs. In Liu's analysis, different ICIs targeting the same checkpoint were classified into the same group; for instance, different PD-L1 inhibitors were all classified into the PD-L1 group. In contrast, by including a greater number of up-to-date ICI trials, our NMA was able to treat each ICI drug as a single group. Therefore, for the first time, we depict the comparative safety of the existing ICI drugs for grade 1-5 and grade 3-5 AKI. We found that durvalumab±low-dose tremelimumab and avelumab were consistently among the top three safest treatments for grade 1-5 or grade 3-5 AKI, whereas N1I3, single-agent ipilimumab and tremelimumab were consistently among the top three treatments with the highest risk for grade 1-5 or grade 3-5 AKI. These findings substantially extend the knowledge from Liu's analysis

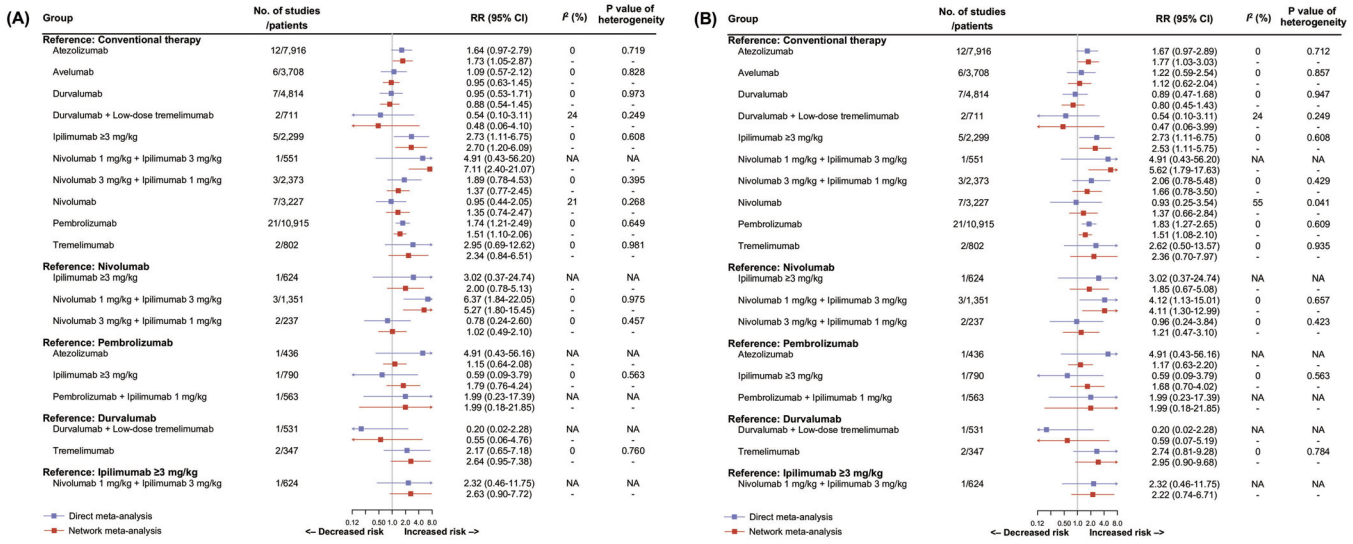

FIGURE 3 Direct versus indirect results for 19 accessible head-to-head treatment comparisons for grade 1-5 AKI (A) and grade 3-5 AKI (B). $I^2 > 50\%$ or $P < 0.10$ in Q test for heterogeneity indicate significant heterogeneity in direct meta-analyses. Abbreviations: AKI, acute kidney injury; RR, risk ratio; CI, confidence interval; NA, not applicable for the analysis of heterogeneity as only one study was included; "-". not performed for NMA.

FIGURE 4 Incidence rates of grade 1-5 and grade 3-5 AKI in and baseline characteristics of the 85 trials with an ICI-containing arm. $I^2 > 50\%$ or $P < 0.10$ in Q test for heterogeneity indicate significant heterogeneity in direct meta-analyses. *Cancer types involved in less than 5 trials were denoted as "Other". #Other ICI-containing combination regimens rather than ICI+chemotherapy and ICI+ICI were denoted as "ICI+other". Abbreviations: AKI, acute kidney injury; ICI, immune checkpoint inhibitor; GEC, gastroesophageal cancer; HNSCC, head and neck cancer; NSCLC, non-small-cell lung cancer; CC, renal cell carcinoma; SCLC, small-cell lung cancer; UC, urothelial cancer; N1I3, 1 mg/kg nivolumab plus 3 mg/kg ipilimumab; N3I1, 3 mg/kg nivolumab plus 1 mg/kg ipilimumab; Pembro+Ipi, pembrolizumab plus 1 mg/kg ipilimumab; Durv+Treme, durvalumab plus low-dose tremelimumab.

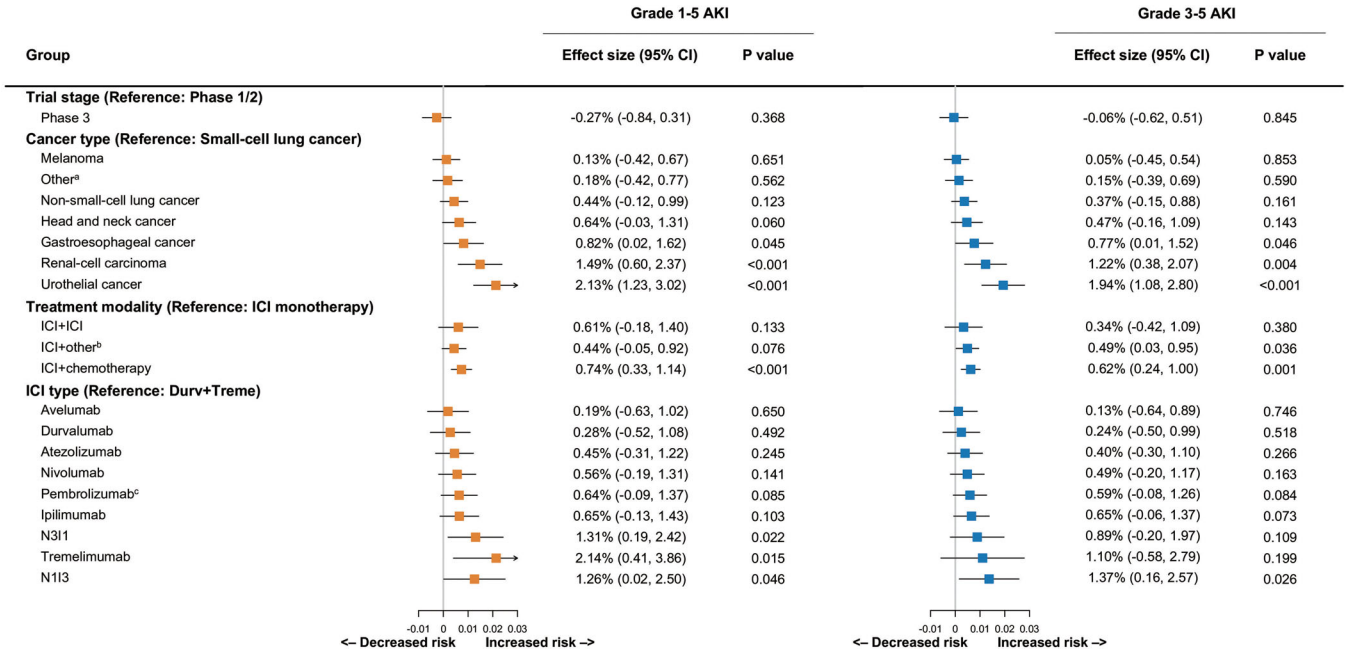

FIGURE 5 Meta-regression analyses showing the impacts of baseline trial characteristics on grade 1-5 and grade 3-5 AKI in the ICI-containing arm. [a]Cancer types involved in less than 5 trials were denoted as "Other". [b]Other ICI-containing combination regimens rather than ICI+chemotherapy and ICI+ICI were denoted as "ICI+other". [c]The only one study involving pembrolizumab plus ipilimumab was included in this group in meta-regression analyses. Abbreviations: AKI, acute kidney injury; ICI, immune checkpoint inhibitor; N1I3, 1 mg/kg nivolumab plus 3 mg/kg ipilimumab; N3I1, 3 mg/kg nivolumab plus 1 mg/kg ipilimumab; Durv+Treme, durvalumab plus low-dose tremelimumab.

by revealing that not all anti-PD-L1+anti-CTLA-4 combinations are associated with a higher risk of AKI. This might change clinicians' treatment combination paradigm options for tumor immunotherapy. Moreover, we used NMA to show the relative risk of AKI between ICIs without head-to-head comparisons. For instance, for the first time, we demonstrated that durvalumab was significantly safer than atezolizumab in terms of grade 3-5 AKI.

It was reported that the incidence rate of AKI following ICI therapy varies from 1% to 29% [9, 12, 14, 30, 31]. The reason for the large difference in the incidence of AKI remains to be elucidated, but several possible explanations have been proposed, including cancer type, comorbidities, treatment paradigms or concomitant medications [18]. By investigating 85 randomized trials, our meta-analysis indicated that the pooled incidence rates of grade 1-5 and grade 3-5 AKI in the ICI-containing group were 1.4% and 1.1%, respectively, which is less frequent than other irAEs. The strict inclusion and exclusion criteria of clinical trials might explain to some extent why the incidence of AKI was lower than those reported in retrospective studies. Additionally, patients with irAEs in other organs might receive corticosteroid therapy during AKI. Thus, the majority of patients did not exhibit ICI-induced nephrotoxicity. Studies on ICI-induced nephrotoxicity consist primarily of case series of patients diagnosed after a kidney biopsy. Nephrotoxicity might have been underestimated in these patients. Moreover, Baker et al. [10] reported that mortality was higher in patients with AKI following ICIs, suggesting that oncologists and nephrologists assessing these patients should collaborate to routinely address kidney dysfunction after ICI therapy.

The risk of AKI following ICIs varies by type of cancer, and patients with genitourinary cancers are at a higher risk for AKI [17, 32-34]. Our data also showed that RCC exhibited a significantly higher risk of AKI than other cancers. Patients with renal cancer frequently undergo urinary surgery, which might lead to renal dysfunction. However, prior nephrectomy was not associated with a greater risk of AKI or estimated glomerular filtration rate (eGFR) loss following ICIs [35]. Leppert et al. [28] suggested that nephrectomy was associated with postoperative AKI, yet data on its long-term link to deteriorating kidney function were inconclusive. According to the study, there was no risk of eGFR loss or chronic kidney disease (CKD) following nephrectomy if post-surgical AKI had not occurred. Therefore, other underlying mechanisms might be associated with a high risk for AKI in RCC patients. Previous research revealed that the presence of immune cell infiltration was higher in RCC than in other cancer types

[36], thus indicating the induction of a stronger immune adverse effect after receiving ICI treatment.

Based on our study, anti-CTLA-4 monotherapy, such as ipilimumab, exhibited a significantly higher AKI risk than anti-PD-1 monotherapy. According to a previous study [37], CTLA-4 regulates the early stage of T-cell activation. Instead, PD-1 functions mainly in the late course of T cell activation. Thus, anti-CTLA-4 may cause higher toxicity than anti-PD-1 due to its upstream and less specific effect. In addition, the risk of immune-related toxicity for an anti-CTLA-4 drug is associated with its drug dosage [26]. A higher target concentration could induce more side events.

Moreover, our data suggested that the risk of AKI in anti-PD-L1 therapy was lower than in anti-PD-1, which was consistent with previous literature[14, 19]. PD-1 can interact with both PD-L1 and PD-L2 [38, 39]. It is speculated that selective inhibition of PD-L1, not PD-L2 ligand, is attributed to the low toxicity since the interaction between PD-1 and PD-L2 may be crucial for immune tolerance in certain organs. These might explain why durvalumab±low-dose tremelimumab was consistently among the top three safest treatments, while N1I3 and other CTLA-4 targeted therapy was associated with higher risks. Moreover, as aforementioned, the risk of immune-related toxicity of an anti-CTLA-4 drug is associated with its drug dosage[26]. Therefore, these might explain why the durvalumab (anti-PD-L1)±low-dose tremelimumab (anti-CTLA-4) treatment combination was found to be safer than nivolumab (anti-PD-1)+high dose ipilimumab (anti-CTLA-4), single-agent ipilimumab (anti-CTLA-4) and tremelimumab (anti-CTLA-4).

Gupta et al. [11] reported that a lower baseline eGFR, PPI use and extrarenal irAEs were related to a higher risk of ICI-induced AKI. Hypertension and cerebrovascular disease were associated with a high risk of AKI, according to Meraz et al. [12]. The difference in previous studies resulted from the inability to adjust for cancer type, treatment paradigm and other vital causes. We discovered correlations between cancer type, treatment modality, and ICI type and the occurrence of AKI after ICI treatment.

This study had some limitations. Our meta-analysis relies on trial-level data rather than individual-patient-level data, and we could not establish a predictive model for the risk of AKI. In addition, based on the clinical trial level, individual characteristics such as basic renal function, other drugs such as steroid therapy, concomitant diseases and the long-term outcomes of these patients were not available in this meta-analysis. Thus, more studies are needed to elucidate the impact of these variables on the risk of AKI.

8 | CONCLUSIONS

In this NMA involving large-scale up-to-date ICI trials, we demonstrated the comparative safety of the existing ICI drugs for grade 1-5 and grade 3-5 AKI. Durvalumab±low-dose tremelimumab showed the highest safety regarding ICI-induced AKI, while N1I3 exhibited the most nephrotoxicity. Based on reported data from the ICI arms of these trials, we also revealed several potential risk factors for immune-related AKI, such as tumor type and treatment paradigm. RCC and urothelial carcinoma showed significantly higher risks of AKI. The addition of chemotherapy increased the risk of ICI-induced AKI, providing a foundation for the clinical identification of high-risk groups. Our findings could help clinicians improve their recognition and management of immune-related AKI in patients with cancer.

AUTHOR CONTRIBUTIONS

Conception and design: F. Liu, G.-Y. Cai, X.-M. Chen. Development of methodology: Z.-X. Wang, Z. Zhang, J.-Q. Chen. Acquisition of data: Z.-X. Wang, Z. Zhang, J.-Q. Chen, X.-F. Li, Y. Yang. Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Z.-X. Wang, F. Liu, D.-H. Chen, L.L Wu: Writing, review and/or revision of the manuscript: F. Liu, Z.-X. Wang, X.-F. Li: Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): X.-Y. Liu, S.-J. Han, F.-M. Wang, W.-L. Wahafu. Study supervision: Y.-B. Gao, S.-C. Ren, N.-Z. Xing

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding authors upon reasonable request.

ETHICS APPROVAL AND CONSENT

This is a meta-analysis based on public use data; thus, ethics approval and consent were waived.

CONSENT FOR PUBLICATION

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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