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INPLASY

Evolving epidemiology and improving safety of rechallenge in immune checkpoint inhibitor-associated acute kidney injury: an updated meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 December 2025 and was last updated on 19 December 2025.

INTRODUCTION

Review question / Objective We aimed to provide a definitive, contemporary synthesis of the epidemiology, management outcomes, and specifically the safety profile of ICI rechallenge following Immune checkpoint inhibitors- acute kidney injury(ICIs-AKI).

Rationale Immune checkpoint inhibitors (ICIs) have transformed cancer therapy but are complicated by immune-related adverse events, including acute kidney injury (AKI). As clinical experience matures and treatment durations lengthen, initial estimates of ICI-AKI incidence and the perceived risks of resuming therapy may become outdated.

Condition being studied Patients with cancer treated by Immune checkpoint inhibitors.

METHODS

Search strategy 1)Intervention: "Immune checkpoint inhibitors," "PD-1 inhibitors," "PD-L1 inhibitors," "CTLA-4 inhibitors," and specific drug names (e.g., "ipilimumab," "nivolumab," "pembrolizumab," "atezolizumab," "durvalumab," "avelumab," "cemiplimab," "toripalimab," "tislelizumab"). 2)Outcome: "Acute kidney injury," "nephrotoxicity," "nephritis," "renal failure," "renal insufficiency," "acute interstitial nephritis," "granulomatous interstitial nephritis." 3)Study Design: "Cohort studies," "observational studies," "clinical trials," "real-world evidence."

Participant or population Patients with cancer treated by Immune checkpoint inhibitors.

Intervention Immune checkpoint inhibitors.

Comparator Other chemotherapy.

Study designs to be included Randomized controlled trials (RCTs), prospective cohort studies, and retrospective cohort studiesCohort studies," "observational studies," "clinical trials," "real-world evidence.

Eligibility criteria Inclusion Criteria: 1)Population: Adult patients (aged ≥ 18 years) with histologically confirmed solid tumors or hematologic malignancies. 2)Intervention: Treatment with at least one ICI (anti-CTLA-4, anti-PD-1, or anti-PD-L1) either as monotherapy or in combination with other ICIs or chemotherapy. 3) Comparisons: For incidence analysis: a defined denominator of patients exposed to ICIs. For recovery analysis: patients receiving corticosteroids versus those who did not. For rechallenge analysis: patients rechallenged with ICIs versus those who discontinued therapy. 4)Outcomes: Studies must report at least one of the following: (1) the incidence of ICI-associated AKI (ICI-AKI); (2) rates of renal recovery following AKI; or (3) the incidence of recurrent AKI upon ICI rechallenge. 5)Study Design: Randomized controlled trials (RCTs), prospective cohort studies, and retrospective cohort studies (including large-scale registry analyses).

Exclusion Criteria: 1)Case reports, case series involving fewer than 10 patients, reviews, editorials, and conference abstracts lacking full quantitative data. 2)Animal studies or in vitro experiments. 3)Studies where AKI was not explicitly defined or where the etiology was clearly attributed to non-ICI causes (e.g., contrast-induced nephropathy, sepsis) without adjudication for ICI causality. 4)Duplicate cohorts**.**

Information sources Data extraction was performed independently by two reviewers using a standardized, pilot-tested data extraction form in Microsoft Excel. The following variables were extracted: 1)Study Characteristics: First author, year of publication, country/region, study design (single-center vs. multicenter vs. registry), data source, and follow-up duration. 2)Patient Baseline Characteristics: Total sample size, median/mean age, sex distribution, baseline renal function (serum creatinine or eGFR), tumor types, and comorbidities (hypertension, diabetes mellitus). 3)Treatment Details: Type of ICI (monotherapy vs. combination), concomitant medications (PPIs, NSAIDs). 4)Outcome Data: 5)Incidence of ICI-AKI: Defined according to the KDIGO criteria (increase in serum creatinine ≥ 0.3 mg/dL within 48 hours or ≥ 1.5 times baseline) or Common Terminology Criteria for Adverse Events (CTCAE). We specifically extracted data on ICI-associated AKI rather than all-cause AKI whenever adjudicated data were available. 6)Renal Recovery: Defined as the return of serum creatinine to baseline or $\le$ Grade 1 AKI. We extracted the number of patients recovering in steroid-treated vs. non-steroid-treated groups. 7)Recurrence: Defined as a new episode of AKI occurring after the resumption of ICI therapy in patients who had previously recovered from an ICI-AKI event.

Main outcome(s) (1) the incidence of ICI-associated AKI (ICI-AKI); (2) rates of renal recovery following AKI; or (3) the incidence of recurrent AKI upon ICI rechallenge.

Quality assessment / Risk of bias analysis The methodological quality of included observational studies was assessed using the Newcastle-Ottawa Scale (NOS)4. This tool evaluates studies across three domains: selection of the study groups (0–4 stars), comparability of the groups (0–2 stars), and ascertainment of the outcome (0–3 stars). Studies scoring $\ge$ 7 stars were classified as "high quality," 4–6 stars as "moderate quality," and < 4 stars as "low quality." For the few included RCTs (if any), the Cochrane Risk of Bias Tool (RoB 2) was utilized. Two reviewers independently performed the assessment, with discrepancies resolved by discussion.

Strategy of data synthesis All statistical analyses were performed using R statistical software (version 4.3.2) utilizing the meta and metafor packages, which are considered the gold standard for high-level meta-analyses.

2.7.1 Incidence and Proportions:

For single-arm analyses (incidence of AKI, recurrence rate), we calculated pooled event rates. Due to the anticipation of low event rates in some subgroups and variance instability near 0 or 1, we applied the Freeman-Tukey double arcsine transformation to stabilize variances before pooling. The pooled proportions and their 95% confidence intervals (CIs) were then back-transformed for reporting.

2.7.2 Comparative Outcomes:

For dichotomous outcomes comparing two groups (e.g., steroid vs. non-steroid for recovery), we calculated Odds Ratios (ORs) with 95% CIs. We used the Mantel-Haenszel method for pooling if event counts were sufficient; otherwise, the Peto method was considered for rare events.

2.7.3 Model Selection:

Given the inherent clinical and methodological heterogeneity across the included studies (ranging from single-center cohorts to global registries), we employed a Random-Effects Model (DerSimonian-Laird method) for all primary analyses. This model

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assumes that the true effect size varies between studies, providing a more conservative and generalizable estimate than a fixed-effect model5.
2.7.4 Heterogeneity Analysis:
Heterogeneity was quantified using the I2 statistic and assessed for significance using the Cochran Q test. I2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively.

Subgroup analysis 2.7.5 Subgroup Analysis and Meta-Regression: To investigate sources of heterogeneity and test our hypothesis regarding age-related risks, we performed pre-specified Subgroup Analyses stratified by: 1)Age: Elderly (≥ 65 years) vs. Non-elderly (< 65 years). 2)Study Design: Registry/Database studies vs. Clinical Cohorts. 3)Treatment Type: Monotherapy vs. Combination therapy.Interaction tests were performed to determine statistically significant differences between subgroups (Pinteraction < 0.05). Univariable meta-regression was also conducted to assess the impact of continuous covariates (e.g., baseline creatinine, percentage of female participants) on ICI-AKI incidence.

Sensitivity analysis 2.7.6 Sensitivity Analysis: We evaluated the robustness of our findings through a "Leave-One-Out" sensitivity analysis, iteratively removing one study at a time to determine if any single study disproportionately influenced the pooled effect size. This was particularly crucial to assess the impact of the newly included large-scale study by Chuang et al. on the overall results.

Language restriction No language restriction.

Country(ies) involved China.

Keywords Immune checkpoint inhibitors; Acute kidney injury; Immune-related adverse events (irAEs); Rechallenge safety; Renal recovery; Meta-analysis.

Contributions of each author
Author 1 - danyang zhang - collected data, analyzed, and drafted the manuscript.
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