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Immune Checkpoint Inhibitors in Patients with Cancer and Chronic Kidney Disease: A Systematic Review and Meta-Analysis

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Systematic Review

Keywords: Immune checkpoint inhibitors, Chronic kidney disease, Nephritis, Immune-related adverse events, Cancer immunotherapy

Posted Date: June 15th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10006164/v1

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Additional Declarations: The authors declare no competing interests.

Abstract

Background

Immune checkpoint inhibitors (ICIs) have transformed cancer therapy, yet their efficacy and safety in patients with chronic kidney disease (CKD) remain uncertain, as this population is frequently excluded from pivotal trials. We aimed to evaluate clinical outcomes of ICI therapy in patients with cancer and CKD.

Methods

We conducted a systematic review and meta-analysis comparing outcomes of ICI therapy in patients with and without CKD. PubMed, Embase, and the Cochrane Library were systematically searched. Eligible studies included patients with CKD stages 3–5 reporting at least one efficacy or safety outcome; kidney transplant recipients were excluded. Subgroup analyses were performed for advanced CKD. Hazard ratios (HR) and risk ratios (RR) with 95% confidence intervals (CI) were pooled using random-effects models.

Results

Fourteen studies (n = 12,589 patients) were included. Patients with CKD had a significantly higher risk of nephritis (RR 2.43; 95% CI 1.11–5.33; I^2 = 0%) compared with those without CKD. No significant differences were observed in acute kidney injury (RR 1.39; 95% CI 0.93–2.08), overall survival (HR 0.97; 95% CI 0.58–1.61), or progression-free survival (HR 1.05; 95% CI 0.76–1.44). The incidence of any-grade irAEs (RR 1.01; 95% CI 0.96–1.07) and grade ≥ 3 irAEs (RR 1.07; 95% CI 0.92–1.25) was also similar between groups. However, advanced CKD was associated with worse overall survival (HR 1.42; 95% CI 1.14–1.76) and a higher incidence of any-grade irAEs (RR 1.17; 95% CI 1.01–1.34).

Conclusions

ICIs appear to be effective and generally safe in patients with moderate CKD. However, advanced CKD is a marker for increased risk of any-grade irAEs and reduced overall survival. These findings underscore the need for close monitoring and stage-stratified management in this population.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that have improved outcomes in several malignancies and are now part of standard treatment for more than 17 cancer types, used as monotherapy or in combination with chemotherapy. (1). In the United States, the proportion of patients

benefiting from ICIs increased from 1.54% in 2011 to 43.63% in 2018, with additional indications approved in subsequent years (2).

ICIs block inhibitory immune pathways, including cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 and its ligand (PD-1/PD-L1), thereby enhancing T-cell–mediated antitumor activity (3). However, this immune activation can also affect non-tumor tissues, leading to immune-related adverse events (irAEs), which occur in approximately 60% to 80% of patients. Among these, 13% to 23% experience grade 3–4 events as defined by the Common Terminology Criteria for Adverse Events. Common irAEs include endocrinopathies, hepatitis, colitis, and pneumonitis(4, 5).

Given concerns about toxicity and organ dysfunction, many ICIs clinical trials required “normal organ function” as an eligibility criterion. As a result, patients with chronic kidney disease (CKD) were excluded from most pivotal studies (6–10). However, kidney dysfunction is present in a substantial proportion of patients with cancer, with approximately 57% having an estimated glomerular filtration rate below 90 mL/min/1.73 m² and about 20% meeting criteria for stage 3 to 5 CKD (11). CKD is also associated with increased cancer mortality (12, 13) and patients with end-stage renal disease (ESRD) may have higher cancer risk and experience worse survival outcomes (12, 14, 15).

It remains unclear whether oncologic outcomes and treatment-related adverse events differ between patients with and without CKD, and whether these risks vary across CKD stages (16). Although prior studies have described the occurrence of acute kidney injury (AKI) and CKD in patients treated with ICIs, the impact of baseline CKD on survival and adverse events has not been systematically evaluated in a meta-analysis (17–19).

To address this gap, we performed a stage-stratified meta-analysis comparing clinical outcomes of ICI therapy in patients with CKD versus those without. We also conducted subgroup analyses according to CKD stage to evaluate whether outcomes differed across levels of renal impairment.

METHODS

This systematic review and meta-analysis was registered on the *International Prospective Register of Systematic Reviews* (PROSPERO) with protocol no. CRD420261306730. As this study relied exclusively on previously published data, the requirement for institutional ethics approval was waived. Data extraction, analysis, and reporting were carried out in compliance with the Cochrane Handbook for Systematic Reviews of Interventions and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20,21)

Eligibility criteria

Studies were included if they met all the following criteria: (1) conducted in patients aged ≥18 years with cancer; (2) evaluated ICI therapy; (3) included patients with CKD stages 3–5; and (4) reported at least one efficacy or safety outcome stratified by estimated glomerular filtration rate (eGFR) category.

Studies were excluded if they: (1) were conference abstracts without an available full; (2) involved overlapping study populations; (3) employed ineligible study designs; or (4) enrolled kidney transplant recipients. No restrictions were applied regarding publication date or geographical location.

Outcome assessments

Primary outcomes were overall survival (OS), progression-free survival (PFS), and incidence of AKI. Secondary outcomes included the incidence of irAEs and tumor response metrics. AKI was conceptually defined using serum creatinine thresholds consistent with Kidney Disease: Improving Global Outcomes (KDIGO) recommendations,(22) and studies employing conceptually overlapping definitions were considered eligible for inclusion in pooled analyses. Outcomes were pooled in meta-analyses when reported by at least three studies.

Search strategy and data extraction

A systematic literature search was conducted in PubMed, Embase, and Cochrane Central Register of Controlled Trials, with no restrictions on publication date, up to January 1, 2025. The full search strategy used is available in the registered protocol. Duplicates were removed using Zotero reference management software. Titles and abstracts were screened, and full-text articles were evaluated for eligibility. Data were extracted using a standardized Excel template by two independent reviewers, with any disagreements resolved through discussion and consensus. When data were available only in graphical format, they were extracted using WebPlotDigitizer (Rohatgi A. WebPlotDigitizer version 5.2. Automeris; 2024)

Quality assessment

We evaluated the risk of bias of the included studies with the Newcastle-Ottawa scale (NOS), which is based on three domains: selection of study groups, comparability of the groups, and ascertainment of either the exposure or outcome of interest. Based on the graded assessments, studies are classified as “good quality”, “fair quality” or “poor quality” (23).

Overall quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (24). For each outcome, the quality of evidence was classified as 'high', 'moderate', 'low', or 'very low', based on risk of bias, inconsistency, imprecision, publication bias, and the magnitude of the effect estimate.

Statistical analysis

Random-effects models were used to pool hazard ratios (HRs) and risk ratios (RRs) with corresponding 95% confidence intervals (CIs). A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using R software, version 4.2.2 (R Foundation for Statistical Computing). When HRs were not directly reported, they were estimated by reconstructing individual

participant data (IPD) from published Kaplan–Meier curves using the method described by Guyot et al. (2012) based on graphical digitization and algorithmic reconstruction procedures.(25)

Assessment of heterogeneity

Heterogeneity was assessed by visually inspecting forest plots, calculating the I^2 statistic, and performing Cochran's Q test, with p-values > 0.10 and I^2 <25% considered indicative of low heterogeneity. (26) The heterogeneity variance (τ^2) was estimated using the restricted maximum-likelihood (REML) method. Leave-one-out analyses were conducted to investigate potential sources of variability by systematically removing individual studies from the pooled estimates. Pre-specified subgroup analyses were performed when data availability permitted, defined as a minimum of three studies per subgroup. (27)

Stage-stratified analysis

The main analysis compared outcomes between patients with CKD (eGFR <60 mL/min/1.73 m^2) and those without CKD (eGFR ≥60 mL/min/1.73 m^2; CKD stages 1–2). When sufficient data were available, pre-specified subgroup analyses compared outcomes between patients with moderate CKD (stages 3a–3b; estimated glomerular filtration rate [eGFR] 30–59 mL/min/1.73 m^2) and those without CKD (eGFR ≥60 mL/min/1.73 m^2), as well as between patients with advanced CKD (stages 4–5; eGFR <30 mL/min/1.73 m^2, including dialysis) and those without advanced CKD (eGFR ≥30 mL/min/1.73 m^2).

RESULTS

Study Cohort and Characteristics

Our systematic search yielded 2,031 records. Following duplicates removal and screening of titles and abstracts, 180 studies were selected for full-text review. The main reasons for exclusion were the lack of reported outcomes for the CKD population.. Ultimately, 14 (28–41) studies comprising 12,589 patients were included in the final analysis. Of these patients, 2,910 (23%) had baseline CKD. The complete study selection process is detailed in the PRISMA flow diagram (Figure 1).

Five studies were conducted in the United States (28,31,39–41) and two in Japan.(30,38); the remaining studies were conducted across India, Turkey, the Netherlands, China, United Kingdom, Germany and France. The proportion of male participants ranged from 55% to 86.7%, and while the reported mean or median age ranged from 60 to 80 years, it was close to 65 years in most cohorts.

Eastern Cooperative Oncology Group (ECOG)(42) performance status was reported in five studies (29,31,33,35,40). In these reports, most patients had ECOG 0 or 1. Renal cell carcinoma and melanoma were each included in five studies. Other solid tumors included lung, bladder, and head and neck cancers. Hematologic malignancies were also included. Detailed study characteristics are presented in Table 1.

Endpoints

There were no significant differences between patients with or without CKD in OS (HR 0.97; 95% CI 0.58 to 1.61; p = 0.893; I^2 = 56%; Figure 2A) or PFS (HR 1.05; 95% CI 0.76 to 1.44; p = 0.780; I^2 = 0%; Figure 2B).

Patients with CKD had a higher risk of nephritis (RR 2.43; 95% CI 1.11 to 5.33; p = 0.026; I^2 = 0%; Figure 3A) compared to those without CKD. There was no significant difference in AKI incidence (RR 1.39; 95% CI 0.80 to 2.41; p = 0.106; I^2 = 48.2%; Figure 3B).

The incidence of grade ≥3 (RR 1.07; 95% CI 0.81 to 1.42; p = 0.385; I^2 = 23.4%; Figure 4A) and any-grade irAes (RR 1.01; 95% CI 0.93 to 1.10; p = 0.640; I^2 = 17.5%; Figure 4B) did not differ between groups.

Tumor response outcomes could be pooled only for the advanced CKD subgroup due to insufficient data for other groups.

Sensitivity Analysis

For OS and PFS, leave-one-out analyses were consistent with the primary results. No single study changed the heterogeneity, direction or statistical significance of the pooled estimates.

In leave-one-out analysis AKI incidence, exclusion of Stein et al. reduced heterogeneity to 0%, identifying it as a source of between-study variability. The pooled estimate remained unchanged. For nephritis, exclusion of Seydel et al. and Tiu et al. also reduced heterogeneity to 0% without altering the effect estimate.

For grade ≥3 irAEs, exclusion of Seydel et al. reduced heterogeneity to 0% without affecting the pooled result. For any-grade irAEs, exclusion of Ishihara et al. (ICI–ICI cohort) eliminated heterogeneity, and the overall estimate remained unchanged. Forest plots for all leave-one-out analyses are available in Supplementary Figure 1.

Moderate CKD subgroup analysis

There were no significant differences between patients with moderate CKD and those without CKD in OS (RR 1.01; 95% CI 0.89 to 1.15; p = 0.3291; I^2 = 10%; Supplementary Figure 2A), rates of grade ≥3 (RR 1.06; 95% CI 0.90 to 1.25; p = 0.468; I^2 = 0%; Supplementary Figure 2B) or any-grade irAEs (RR 1.02; 95% CI 0.96 to 1.08; p = 0.574; I^2 = 28.3%; Supplementary Figure 2C).

Advanced CKD subgroup analysis

Patients with advanced CKD had worse OS (HR 1.42; 95% CI 1.14 to 1.76; p = 0.002; I^2 = 20.7%; Supplementary Figure 3A) and a higher incidence of any-grade irAEs (RR 1.17; 95% CI 1.01 to 1.34; p = 0.032; I^2 = 60.4%; Supplementary Figure 3B) compared with patients without advanced CKD.

Patients with and without advanced CKD showed no significant differences in PFS (RR 0.95; 95% CI 0.55 to 1.64; p = 0.849; I^2 = 35%; Supplementary Figure 3C), incidence of grade ≥3 irAEs (RR 1.24; 95% CI 0.88 to 1.76; p = 0.224; I^2 = 5.5%; Supplementary Figure 3D), objective response rate (RR 1.21; 95% CI 0.66 to 2.21; p = 0.543; I^2 = 47.6%; Supplementary Figure 3E), and disease control rate (RR 1.10; 95% CI 0.87 to 1.39; p = 0.438; I^2 = 0%; Supplementary Figure 3F).

Quality assessment and certainty of evidence

Eleven studies (79%) were rated as high quality (NOS ≥7), and three (21%) were classified as moderate quality (scores 5–6); none were low quality. Selection and outcome domains were consistently well scored. Comparability was the main limitation, largely due to single-arm designs in which CKD versus non-CKD comparisons were performed as subgroup analyses. The complete assessment and scoring for each study are available in Supplementary Table 3.

Using the GRADE framework, the certainty of evidence was rated as very low across all outcomes, including overall survival, progression-free survival, nephritis, acute kidney injury, and grade ≥3 immune-related adverse events. This was primarily driven by the observational and predominantly retrospective nature of the included studies, with residual confounding and limited comparability between CKD and non-CKD groups, further compounded by inconsistency across studies and imprecision of the estimates, as confidence intervals frequently crossed the line of no effect and encompassed both potential benefit and harm. Publication bias was not formally assessed using funnel plots, as there were fewer than ten studies available per outcome.

DISCUSSION

This systematic review and meta-analysis, encompassing 14 studies and 12,589 patients with cancer, evaluated outcomes associated with immune checkpoint inhibitor (ICI) therapy in individuals with and without chronic kidney disease (CKD). CKD was associated with an increased incidence of nephritis. However, no significant differences were observed in overall survival (OS), progression-free survival (PFS), acute kidney injury (AKI), or the rates of grade ≥3 or overall immune-related adverse events (irAEs). In subgroup analyses, advanced CKD was associated with reduced OS and a higher incidence of any-grade irAEs, while PFS, objective response rate (ORR), disease control rate (DCR), and severe irAEs remained comparable between groups.

ICIs are large monoclonal antibodies (~150 kDa) that are not cleared through glomerular filtration but instead undergo intracellular lysosomal degradation and FcRn-mediated recycling. (39,43). These elimination pathways are largely independent of kidney function, providing a biological rationale for the absence of dose adjustment requirements in patients with CKD, including those with advanced disease or receiving dialysis. (44,45). This pharmacokinetic profile likely explains the preserved antitumor efficacy and comparable rates of systemic toxicity observed across CKD stages.

Our findings suggest that the antitumor efficacy of ICIs remains preserved in patients with CKD. OS and PFS were similar between patients with and without CKD in the overall analysis. In the advanced CKD subgroup, PFS, ORR, and DCR were comparable to those observed in patients without advanced CKD. The worse OS observed in advanced CKD is more consistent with competing risks of mortality and a higher comorbidity burden than a reduced efficacy of ICIs, as stage 4–5 CKD and ESRD are independently associated with high baseline morbidity and mortality in oncology populations(14).

We observed no significant differences in the incidence of grade ≥3 irAEs or overall irAEs between CKD and non-CKD cohorts. Reported rates of irAEs in CKD populations were comparable to those observed in clinical trials of patients without significant organ dysfunction. However, advanced CKD was associated with a higher incidence of any-grade irAEs without a corresponding increase in severe irAEs. This pattern may reflect the complex immune alterations associated with progressive kidney disease. Advanced CKD is characterized by heightened systemic inflammation, expansion of proinflammatory monocyte subsets, increased circulating cytokines such as IL-6 and TNF-α, and features of immunosenescence. Concurrent T-cell dysfunction and depletion may limit the progression of immune activation into severe toxicity. (47,49–51) Dialysis exposure may further contribute through oxidative stress and persistent inflammatory activation. (50–52) Together, these factors may lower the threshold for developing mild irAEs while attenuating the likelihood of severe manifestations. (53,54).

Our meta-analysis revealed that cancer patients with CKD demonstrated a significantly increased risk of nephritis. In the cohort by Seydel et al., nephritis was the most frequent irAE among patients with CKD (8.2% vs. 1.3% in non-CKD), despite comparable ICI exposure (36). The authors suggested that one potential explanation is that underlying kidney dysfunction lowers the threshold for detecting immune-mediated injury, resulting in earlier clinical recognition. In contrast, patients without CKD may develop subclinical renal inflammation that does not lead to measurable creatinine elevation. (55–58). This “unmasking” phenomenon is consistent with broader observations that irAEs preferentially affect organs with pre-existing disease. (50,55,59). In CKD, the kidney may represent an immunologically primed target due to chronic inflammation and impaired regulatory mechanisms at which immune activation translates into measurable creatinine elevation. (50,59–61).

In contrast, the lack of significant difference in AKI incidence likely reflects the multifactorial etiology of kidney injury in cancer patients. As demonstrated by Tiu et al., the 17.5% AKI rate in CKD patients receiving ICIs aligns with expected rates in cancer patients with CKD receiving any antineoplastic therapy, and the rates of new-onset kidney failure (6–10%) fall within the range expected for progression to ESRD in the general CKD population (39). Contributors include volume depletion, nephrotoxic medications, tumor-related factors, and progression of underlying CKD. The heterogeneity observed across studies further supports the influence of clinical variables such as cancer type, treatment regimens, and concomitant exposures on AKI risk.

Studies contributing to the AKI analysis showed moderate heterogeneity, with individual studies demonstrating variable effect sizes, further suggesting that patient selection, cancer types, ICI regimens

(monotherapy versus combination therapy), and concomitant nephrotoxic exposures may modify risk (39,62).

Several limitations should be acknowledged. All included studies were observational and retrospective, limiting causal inference. Subgroup analyses were constrained by incomplete reporting, precluding detailed evaluation of treatment- and cancer-specific effects. In a subset of studies, hazard ratios were reconstructed from Kaplan–Meier curves using established digitization methods. Although this approach may introduce some estimation imprecision, it is widely accepted in meta-analytic methodology when individual patient-level data are unavailable and allowed for a more comprehensive synthesis of the evidence. Finally, the limited number of studies per outcome precluded formal assessment of publication bias.

These findings support the use of ICIs in patients with CKD, including those receiving dialysis, without dose adjustment, while emphasizing the need for vigilant monitoring for immune-related toxicities in this higher-risk population. Additionally, we provide a biologically grounded interpretation linking CKD-associated immune dysregulation with the observed pattern of increased mild irAEs without a corresponding rise in severe toxicity, a relationship that has not been systematically explored in prior studies. Taken together, our findings suggest that CKD should be viewed not as a contraindication but as a modifier of immune-related risk in patients receiving ICIs, warranting tailored monitoring strategies rather than therapeutic exclusion.

Declarations

Acknowledgments

Not applicable.

Declaration of conflicting interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical considerations

Not applicable. This study is a meta-analysis of previously published research and did not require formal ethics committee approval.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

Authors' contributions

RS conceived the study idea, coordinated the team's activities, performed data collection, conducted the statistical analysis, and was a major contributor in writing the manuscript. MF performed data extraction, reconstructed hazard ratios, wrote the methodology section, and conducted the statistical analysis of hazard ratios. DA performed study screening, collaborated on the statistical analysis, and wrote the abstract. VA conducted study screening and performed the NOS and GRADE quality assessments. RM performed data extraction, contributed to the statistical analysis, and generated the figures. IA performed data extraction, created Table 1, and contributed to the writing. LB performed the NOS and GRADE quality assessments. JD provided overall supervision for the study, wrote the discussion section, collaborated on the abstract, and critically revised the manuscript. All authors read and approved the final manuscript.

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Table

Table 1 is available in the Supplementary Files section.

Figures

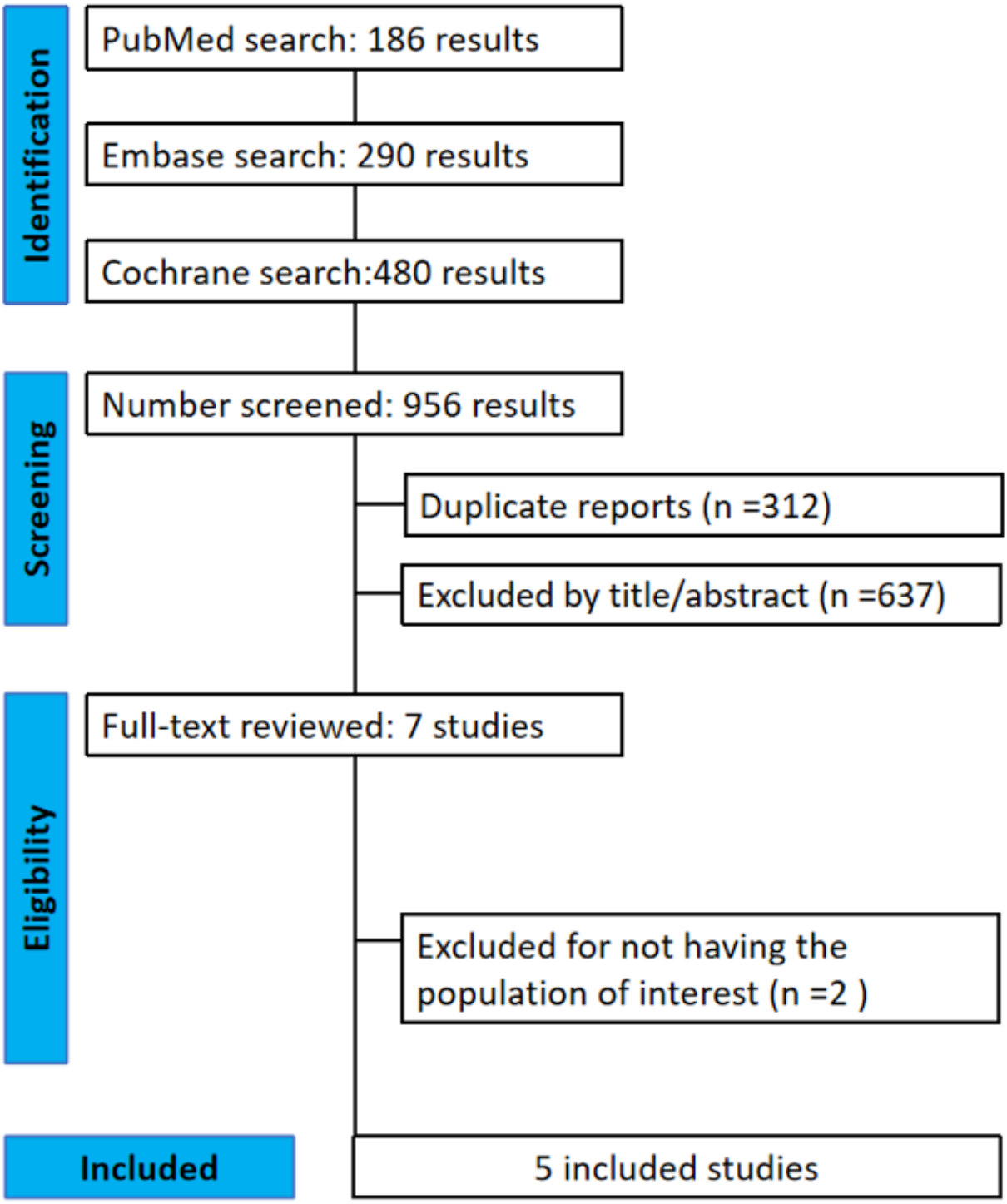


Figure 1

PRISMA 2020 Flowchart

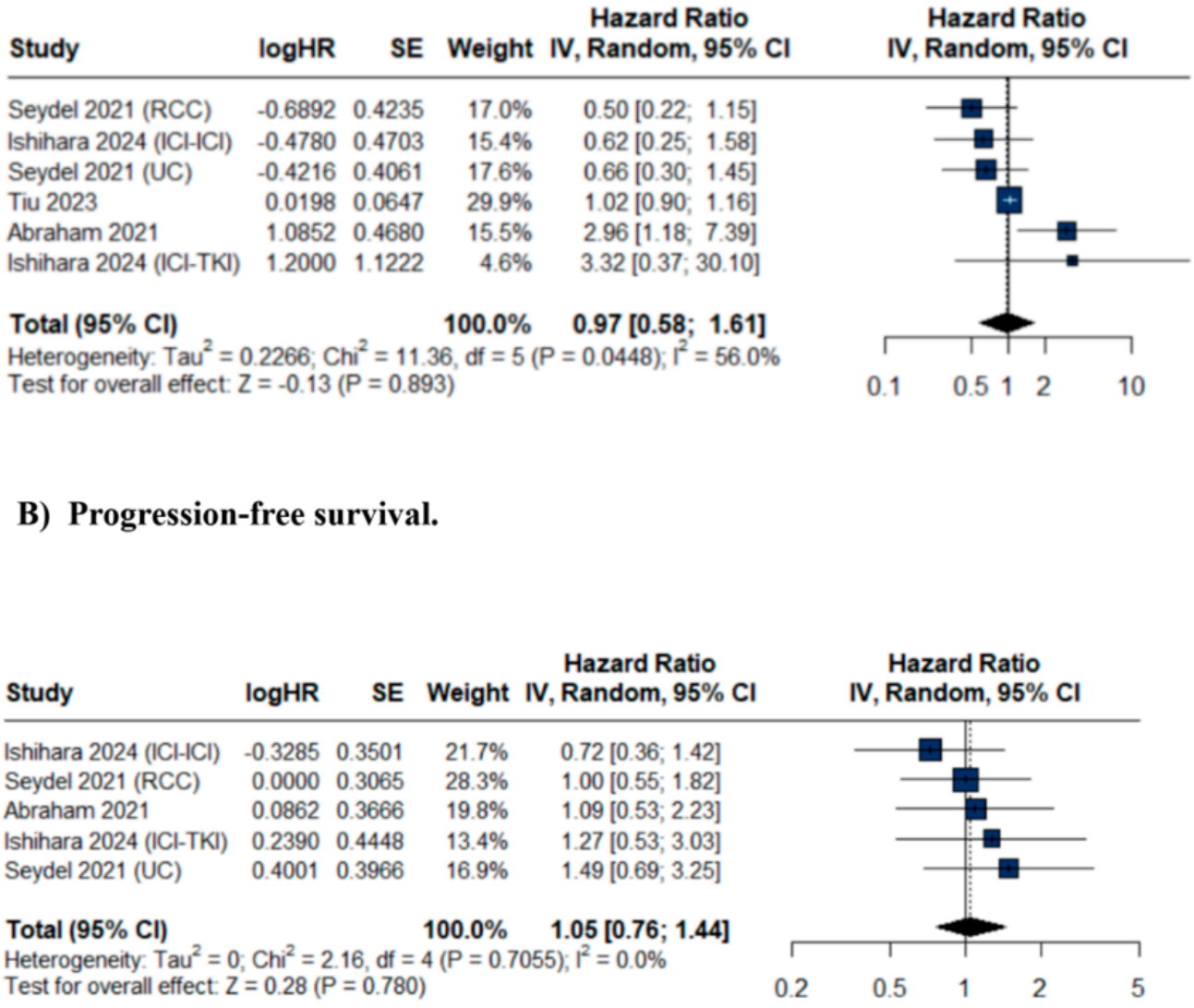


Figure 2

Survival outcomes comparing patients with chronic kidney disease (CKD) versus those without CKD.

A) Overall survival.

B) Progression-free survival.

CI: confidence interval; CKD: chronic kidney disease; HR: hazard ratio; ICI: immune checkpoint inhibitor; IV: inverse variance; logHR: logarithm of hazard ratio; RCC: renal cell carcinoma; SE: standard error; TKI: tyrosine kinase inhibitor.

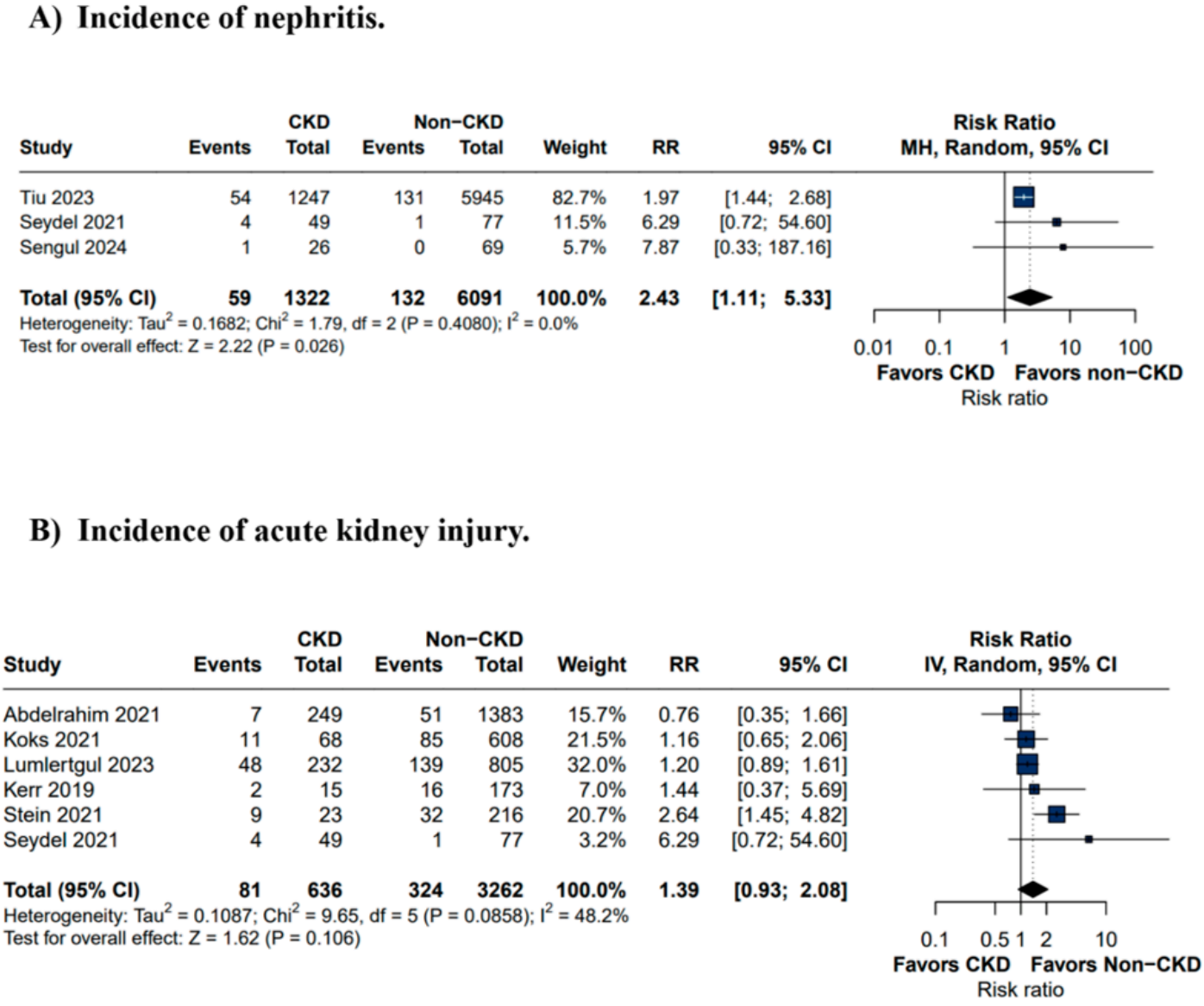


Figure 3

Incidence of renal adverse events in patients with chronic kidney disease (CKD) versus those without CKD.

A) Incidence of nephritis.

B) Incidence of acute kidney injury.

AKI: acute kidney injury; CI: confidence interval; CKD: chronic kidney disease; IV: inverse variance; MH: Mantel–Haenszel; RR: risk ratio; SE: standard error.

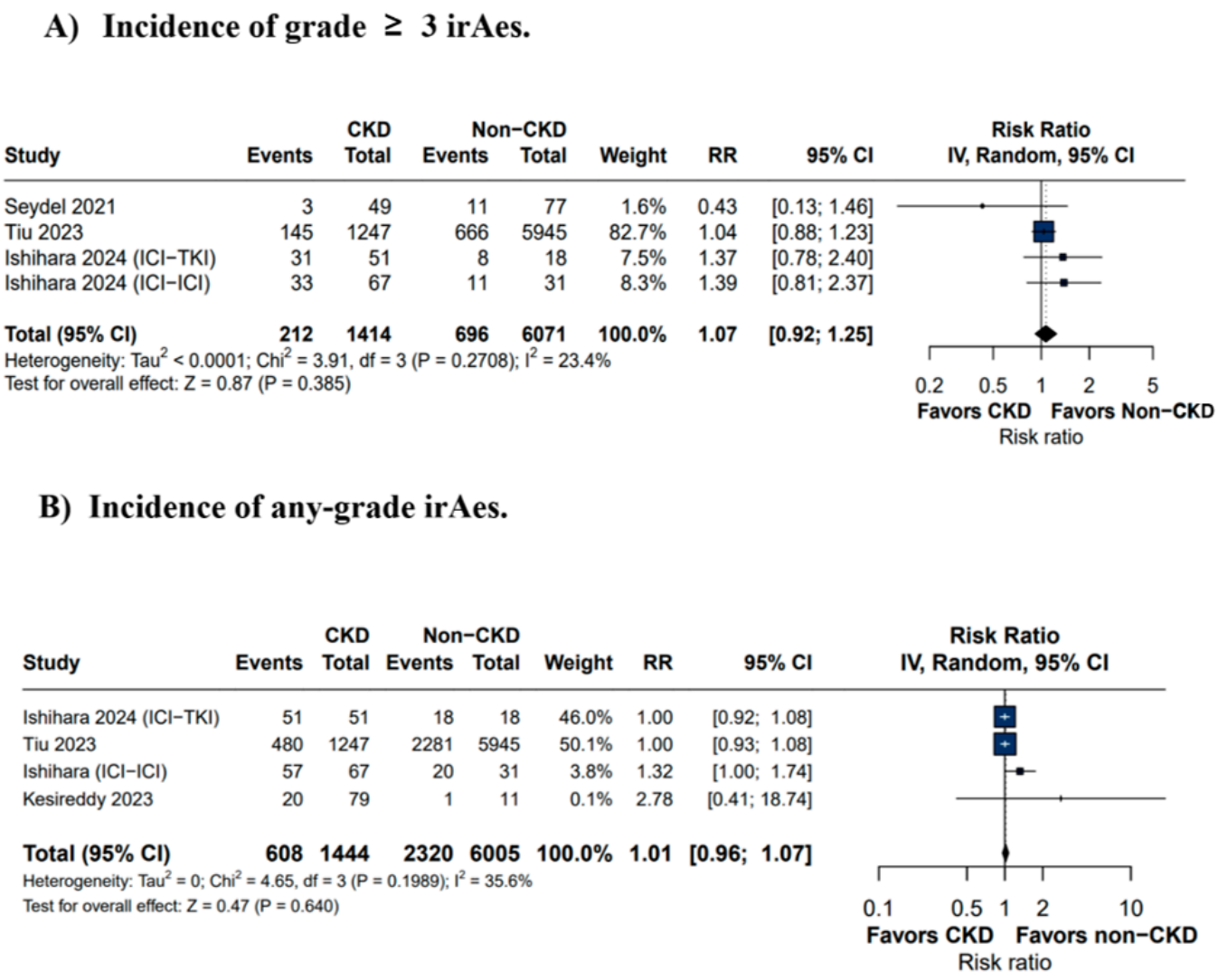


Figure 4

Incidence of irAes in patients with chronic kidney disease (CKD) versus those without CKD.

A) Incidence of grade ≥ 3 irAes.

B) Incidence of any-grade irAes.

CI: confidence interval; CKD: chronic kidney disease; irAes: immune-related Adverse events; IV: inverse variance; RR: risk ratio; SE: standard error.

Supplementary Files

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- SupplementalMaterialJournalofOncoNephrology.docx

- Table1JournalofOncoNephrology.docx