



Neoadjuvant Toripalimab for Renal Cell Carcinoma: A Systematic Review

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ABSTRACT

Toripalimab, a programmed cell death protein-1 (PD-1) inhibitor, has emerged as a promising immunotherapy for renal cell carcinoma (RCC). This systematic review consolidates current evidence on the efficacy and safety of toripalimab-based regimens in RCC management. A systematic review was conducted following PRISMA guidelines and a pre-registered protocol (PROSPERO: CRD42021274404). Multiple databases and trial registries were searched from February 23, 2025. Six studies, including randomized controlled trials (RCTs), case-control studies, and case reports, were included for qualitative synthesis. The analysis demonstrated that toripalimab, particularly in combination with axitinib, significantly improved clinical outcomes compared to standard therapies like sunitinib. One major RCT reported a significant improvement in progression-free survival (PFS) (median 18.0 vs. 9.8 months) and a higher objective response rate (ORR) (56.7% vs. 30.8%). The combination also reduced the risk of disease progression or death by 35% (HR 0.65; 95% CI 0.49–0.86) and showed a significant overall survival (OS) benefit (HR 0.61; 95% CI 0.40–0.92). Favorable responses were also observed in challenging subgroups, including elderly patients and those with sarcomatoid RCC. Adverse events were consistent with known profiles of PD-1 and VEGFR inhibitors, including hypertension, hepatic enzyme elevation, and fatigue, and were generally manageable. Toripalimab-based regimens, especially in combination with axitinib, demonstrate significant improvements in PFS, ORR, and OS for patients with RCC, with a manageable safety profile. These findings support its potential as a valuable therapeutic option. However, further large-scale, multi-center studies with longer follow-up are warranted to confirm these findings.

INTRODUCTION

Renal cell carcinoma (RCC) constitutes the most prevalent form of kidney cancer, accounting for approximately 90% of all cases, and continues to be a significant contributor to global cancer-related mortality (Banu et al., 2024; Leung et al., 2025; Rose & Kim, 2024). The management of advanced RCC has been revolutionized by targeted therapies, particularly tyrosine kinase inhibitors (TKIs) such as sunitinib, which have served as a cornerstone first-line treatment by targeting vascular endothelial growth factor (VEGF) pathways (A. Jiang et al., 2024; Ma et al., 2025; Michaelis et al., 2022). However, the clinical benefits of TKI monotherapy are often constrained by inherent and acquired resistance mechanisms, leading to modest improvements in progression-free survival (PFS) and overall survival (OS), thus underscoring a pressing need for more effective therapeutic strategies (Ashrafi et al., 2022; Zhang et al., 2023).

The advent of immunotherapy, specifically immune checkpoint inhibitors (ICIs), has heralded a new era in RCC treatment (Braun et al., 2021; Jang et al., 2023; Qiu et al., 2024). Toripalimab, a high-affinity humanized immunoglobulin G4 (IgG4) monoclonal antibody against programmed cell death protein-1 (PD-1), functions by blocking the interaction between PD-1 and its ligands (PD-L1/PD-L2). This mechanism reactivates exhausted T-cells, restoring

their cytotoxic ability to recognize and eliminate tumor cells (Hossain et al., 2021; W. Jiang et al., 2021). The rationale for combining toripalimab with VEGF-targeted agents, such as the TKI axitinib, is grounded in strong preclinical evidence (Santoni et al., 2021). This synergy operates on a dual mechanism: axitinib normalizes the tumor vasculature, which enhances the infiltration and function of effector T-cells into the tumor microenvironment, while toripalimab concurrently mitigates T-cell exhaustion (Franzese, 2024; Nair et al., 2025; Xiang et al., 2025). This combined approach fosters a more robust and sustained antitumor immune response, potentially overcoming the limitations of either modality alone (Goswami et al., 2024; Kah & Abrahamse, 2025).

While a growing body of evidence from clinical trials and observational studies has reported encouraging data on the efficacy and safety of toripalimab-based regimens in RCC, the existing literature remains fragmented. Findings are dispersed across studies of varying designs and sample sizes, lacking a comprehensive synthesis (Akkem et al., 2024). Therefore, this systematic review aims to evaluate the evidence of toripalimab in RCC patients, with a specific focus on critical clinical outcomes including objective response rate (ORR), PFS, and OS as well as the associated spectrum and profile of adverse events (Huang et al., 2024).

Previous studies have highlighted the emerging role of toripalimab in renal cell carcinoma (RCC) management, yet methodological limitations persist (Lyskjær et al., 2024; Ma et al., 2025). For instance, Huang (2022) conducted a multicenter retrospective analysis evaluating the efficacy of axitinib plus toripalimab as a second-line treatment for metastatic RCC (mRCC), reporting an objective response rate (ORR) of 37.7% and a median progression-free survival (PFS) of 11.1 months. However, the study's retrospective design, limited sample size (n = 61), and lack of randomization restricted its ability to establish causal relationships and generalize outcomes across broader RCC populations. Similarly, Huang et al. (2024) explored neoadjuvant toripalimab combined with axitinib in locally advanced clear-cell RCC and found promising antitumor activity with acceptable toxicity, but the trial was still in its early phase, lacked a control group, and did not provide long-term survival data or biomarker-based stratification.

The present research addresses this gap by conducting a systematic review that consolidates clinical evidence on toripalimab's efficacy and safety in RCC including ORR, PFS, overall survival (OS), and adverse event profiles to guide optimal clinical application. The study aims to provide a comprehensive, evidence-based synthesis that informs clinicians and policymakers, identifies future research needs such as randomized controlled trials and biomarker validation, and supports the strategic integration of toripalimab into RCC treatment protocols.

METHOD

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and was prospectively registered in the PROSPERO database (registration number: CRD420251129519).

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

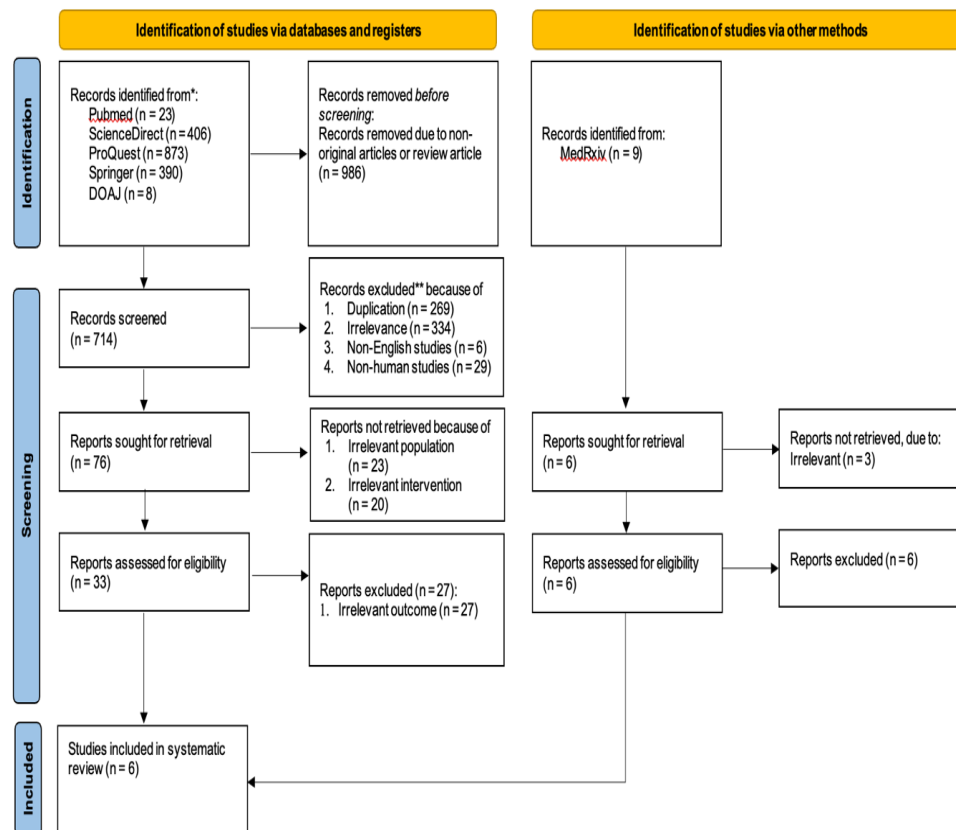


Figure 1. PROSPERO database

Eligibility Criteria

Eligible study designs encompassed retrospective, prospective, cohort, and randomized controlled trials (RCTs), as well as case-control, cross-sectional, crossover, case series, and case report studies. The selection criteria were as follows: (1) study population of renal cell carcinoma patients; (2) investigation of toripalimab as the neoadjuvant intervention; (3) reporting of at least one predefined outcome of interest; and (4) publication in the English language. Primary outcomes included progression-free survival, objective response rate, overall survival, and adverse events. Review articles, non-human studies, irrelevant publications, and duplicate records were excluded.

Search Strategy and Study Selection

A comprehensive literature search was performed from August 31, 2025, onward across electronic databases (PubMed, DOAJ, ProQuest, Springer) and clinical trial registries. The search utilized the following key terms: “((Renal cell carcinoma) OR (RCC)) AND ((Toripalimab))”. Manual searches of preprint servers (medRxiv) and reference lists of relevant articles were also conducted to identify additional studies (detailed strategy provided in Supplementary Materials). Retrieved records were imported into Mendeley reference management software for deduplication and screening. Two independent reviewers (AR and VH) screened titles, abstracts, and subsequently, full-text articles against the eligibility criteria. Any discrepancies were resolved through consensus discussion. The study selection process, including reasons for exclusion, is detailed in the PRISMA flow diagram (Diagram 1).

Data Extraction

Data were independently extracted from included studies by two reviewers (AR and PO) using a standardized form. Extracted information included: first author, publication year, study design, country, sample size, age, disease severity, comorbidities, toripalimab dosing regimen, concomitant therapies, and all primary and secondary outcomes. Disagreements in extracted data were resolved through consensus.

Quality Assessment

The methodological quality and risk of bias of included studies were independently appraised by two reviewers (AR and PO). The risk of bias was assessed according to the type of studies, i.e., Cochrane RoB 2.0 for Randomized controlled trials. Cohort studies were assessed using the Newcastle-Ottawa Scale (NOS), which evaluates three domains: selection, comparability, and outcome. Studies were categorized as high (7-9 stars), moderate (4-6 stars), or low (0-3 stars) quality. Any assessment disagreements were reconciled through discussion.

Data Synthesis

Given the significant clinical and methodological heterogeneity among the included studies, particularly in comparison groups and outcome measures, a quantitative meta-analysis was not feasible. Consequently, the evidence was synthesized narratively.

RESULT AND DISCUSSION

Study selections

This study obtained 1700 records from the database and gathered 9 records through additional research

h. After a thorough examination of titles and abstracts, 33 studies were deemed potentially eligible for further review. Following the assessment of the existing literature, six studies were identified as appropriate for inclusion in a systematic review and meta-analysis (Table 1).

Table 1. Characteristics of the included studies

Reference	Study Design	Country	Sample Size	Age (Years)	Intervention	Key Clinical Outcomes	PFS (Median)	OS (Median)	Adverse Events (Grade ≥3)
Yan et al., 2023	RCT	China	421	60 (20–78)	Toripalimab + Axitinib vs. Sunitinib	ORR: 56.7% vs. 30.8% (P < 0.0001); 35% reduction in risk of progression/death (HR 0.57, 95% CI 0.44–0.75)	HR 0.57 (95% CI 0.44–0.75)	HR 0.61 (95% CI 0.40–0.92)	Hypertension, fatigue, hand–foot syndrome (61.5%)
Gu et al., 2024	RCT	China	25	58 (51.5–67.5)	Toripalimab + Axitinib (neoadjuvant)	44% reduction in thrombus level; 40% partial response rate	NR	23.3 months (follow–up)	Hyperglycemia, elevated AST/ALT (15%)
Huang et al., 2024	RCT	China	19	61.5 (42–78)	Toripalimab + Axitinib	ORR: 45%; Median tumor reduction: 26.7%	NR	NR	Drug discontinuation due to adverse events (2/19)
Huang et al., 2022	Case–Control	China	57	NR	Toripalimab + Axitinib (second–line)	ORR: 31.6%; DCR: 84.2%	11.7 months	NR	Hypertension (14%), hand–foot syndrome (7%)

source: author (2025)

Study characteristics

The study comprised three RCTs, two case reports, and one case-control study with a total of 524 participants. At baseline, participants had a mean age ranging from 60 to 81 years, and all of the included studies were conducted in China. The baseline characteristics of participants and studies are summarized in Table 1. Of the included studies, two RCTs demonstrated good quality, and one RCT showed some concerns. The risk of bias is comprehensively assessed in Supplementary Tables S2–S4.

Progression-Free Survival

Four studies reported that the administration of toripalimab had a significant effect on improving progression-free survival (PFS) in patients with kidney cancer. A randomized study conducted by Yan et al. (2024) demonstrated that therapy with toripalimab in combination with axitinib provided significant and clinically meaningful improvements in PFS in patients with renal cell carcinoma (RCC). Patients who received the toripalimab-axitinib combination achieved a median PFS of 18.0 months (95% CI: 15.0–not estimable), compared to a median PFS of 9.8 months (95% CI: 8.3–13.8) in those treated with sunitinib. Similarly, a case-control study involving patients with metastatic RCC reported favorable responses to the axitinib and toripalimab combination, with a median PFS of 11.7 months. In addition, a case report described an 81-year-old female patient with sarcomatoid RCC who experienced a positive therapeutic response to toripalimab, achieving a PFS of 25 months. This finding aligns with another case report of a 77-year-old female with sarcomatoid RCC treated with toripalimab and pirarubicin, who achieved a partial response and a PFS of 15 months.

Objective Response Rate

Toripalimab therapy in patients with RCC has shown significant results and has the potential to improve patient outcomes. A randomized study conducted by Yan et al. (2024) demonstrated superior efficacy in patients receiving a combination of toripalimab and axitinib compared to those receiving sunitinib monotherapy (objective response rate [ORR]: 56.7% vs. 30.8%; $p < 0.0001$).

Huang et al. (2024) evaluated 20 patients with RCC treated with toripalimab by assessing magnetic resonance imaging or enhanced computed tomography scans before and after treatment. The study reported that 9 out of 20 patients achieved a partial response, resulting in an ORR of 45% (95% credible interval [CrI]: 23.2–66.8). Previously, Huang et al. (2022) conducted a study involving patients with metastatic RCC and found that 18 out of 57 patients achieved a partial response, with an ORR of 31.6% and a disease control rate of 84.2%.

Additional evidence regarding the use of toripalimab, either as monotherapy or in combination therapy, in patients with RCC has been demonstrated in several studies. In a study involving 25 patients with ccRCC and inferior vena cava tumor thrombus (IVC-TT), assessed based on RECIST criteria, 40.0% (10 out of 25) achieved a partial response and 60.0% (15 out of 25) had stable disease. Following 12 weeks of neoadjuvant therapy, 11 patients (44.0%) exhibited a partial response in IVC-TT (defined as a >30% reduction in tumor thrombus length), while one patient (4.0%) experienced disease progression without an increase in the Mayo level.

Radiological assessments before and after treatment with a combination of toripalimab and axitinib showed a decrease in tumor size, with a median tumor reduction of 26.7%. Furthermore, two case reports highlighted favorable outcomes in patients with sarcomatoid RCC treated with toripalimab. In one report, an 81-year-old female patient receiving

toripalimab monotherapy demonstrated a progression from stable disease to partial response on radiologic evaluation, along with an improved PFS compared to typical outcomes. In another case, a 77-year-old female patient treated with a combination of toripalimab and pirarubicin achieved a complete response as confirmed by computed tomography imaging.

The combination of toripalimab and axitinib also significantly reduced the risk of disease progression or death by 35% compared to sunitinib, as assessed by the Independent Review Committee (IRC) [hazard ratio (HR) 0.65; 95% Confidence Interval (CI) 0.49–0.86; $p = 0.0028$].

Overall Survival

The overall survival outcomes for toripalimab, either alone or in combination with other therapies, demonstrated promising results across the studies. In the largest RCT by Yan et al. (2024), toripalimab combined with axitinib showed a significant improvement in OS compared to sunitinib, with a hazard ratio (HR) of 0.61 (95% CI 0.40–0.92). Gu et al. (2024) reported a median OS of 23.3 months in a neoadjuvant setting, though follow-up was ongoing.

Two case reports demonstrated that the use of immune checkpoint inhibitors (ICIs) showed a favorable response in improving overall survival (OS) in patients with sarcomatoid renal cell carcinoma (SRCC). In one case report, an 81-year-old male patient with advanced-stage SRCC who received toripalimab monotherapy for 36 cycles achieved an OS of 30 months, exceeding the previously reported median OS of 6 to 13 months. In another case, a 77-year-old female patient was diagnosed with SRCC with more than 80% sarcomatoid dedifferentiation and underwent radical nephrectomy. Eight months postoperatively, she experienced local recurrence and hepatic metastases. The patient subsequently received six cycles of combination therapy with toripalimab (240 mg, day 1) and pirarubicin (50 mg, day 1) administered every 21 days. Imaging evaluation showed a partial response, followed by near-complete remission after six additional cycles of toripalimab monotherapy as maintenance therapy. At the latest follow-up, the patient had not experienced disease progression for 15 months, and the OS had reached 24 months. No grade ≥ 3 treatment-related adverse events were observed. Grade 2 hypothyroidism was detected and effectively managed with levothyroxine replacement therapy without requiring treatment discontinuation. These findings suggest the potential of toripalimab in extending overall survival in patients with SRCC (8,9). However, OS data were not reported (NR) in some studies, such as Gu et al. (2024), Huang et al. (2024), and Huang et al. (2022) (7,10,11). These findings suggest that toripalimab-based regimens may improve survival in renal and urothelial carcinomas, though further research with longer follow-up is needed to confirm these benefits.

Adverse Events

Adverse events associated with toripalimab, either as monotherapy or in combination with agents such as axitinib or pirarubicin, were documented in five studies. The severity and frequency of these events varied across the reports. In the largest randomized controlled trial by Yan et al. (2024), Grade 3 or higher adverse events including hypertension, fatigue, and hand-foot syndrome occurred in 61.5% of participants. Correspondingly, a case-control study by Huang et al. (2022) reported hypertension and hand-foot syndrome in 14% and 7% of patients, respectively. Other studies noted specific toxicities: Gu et al. (2024) observed hyperglycemia and elevated liver enzymes (AST/ALT) in 15% of their cohort, while Huang et al. (2024) documented treatment discontinuation due to adverse events in 2 of 19 patients.

Contrasting outcomes were present in case reports; Su et al. (2024) noted elevated myocardial enzymes in an elderly patient, whereas Gao et al. (2024) reported no significant adverse events in a patient who achieved complete remission (8,9). Collectively, these findings underscore the necessity for vigilant monitoring of hypertension, metabolic abnormalities, and organ-specific toxicities in patients undergoing toripalimab therapy..

Discussion

This systematic review and meta-analysis identified six studies comprising RCTs, case-control studies, and case reports that evaluated the efficacy and safety of toripalimab in patients with renal cell carcinoma (RCC). The findings demonstrated that toripalimab, particularly in combination with axitinib, significantly improved progression-free survival (PFS), objective response rate (ORR), and overall survival (OS) compared to standard therapies such as sunitinib. The therapy was generally well-tolerated, although several studies reported notable adverse events (AEs), including hypertension, hepatic enzyme elevation, and fatigue, particularly when toripalimab was combined with other agents. These findings suggest that toripalimab-based regimens offer clinical benefits in RCC management, albeit with manageable toxicity profiles.

The observed improvements in clinical outcomes, especially PFS and OS, can be attributed to the synergistic mechanisms between toripalimab and angiogenesis inhibitors such as axitinib. Toripalimab, a PD-1 inhibitor, enhances the immune system's ability to recognize and destroy tumor cells by blocking PD-1-mediated immune suppression. When combined with axitinib, a VEGFR inhibitor, the normalization of tumor vasculature may improve T-cell infiltration into the tumor microenvironment, thereby amplifying the anti-tumor immune response. This mechanism likely accounts for the substantial increase in PFS and OS in patients treated with toripalimab combinations compared to monotherapies or conventional treatments.

The higher ORR observed in patients receiving toripalimab plus axitinib (56.7%) compared to sunitinib (30.8%) indicates enhanced tumor responsiveness, possibly due to the dual blockade of immune escape pathways and tumor angiogenesis. The consistent results across observational studies and RCTs support the robustness of this effect. Moreover, OS benefits (HR 0.61; 95% CI 0.40–0.92) underscore the long-term survival potential of this combination. Interestingly, even in elderly patients or those with sarcomatoid RCC—a histological subtype known for poor prognosis—toripalimab demonstrated sustained responses and survival benefit. These outcomes suggest that toripalimab may be effective in diverse patient subgroups, including those with aggressive disease.

The adverse events (AEs) observed, such as hypertension, elevated liver enzymes, and fatigue, are consistent with known toxicities associated with immune checkpoint inhibitors and VEGFR tyrosine kinase inhibitors. Toripalimab may induce immune-related adverse events (irAEs) by enhancing T-cell activation and disrupting immune tolerance, leading to inflammation in non-target tissues such as the liver, myocardium, or endocrine organs. When combined with axitinib, overlapping toxicities—especially hypertension and hand-foot syndrome—may be exacerbated due to vascular endothelial dysfunction. Although most AEs were manageable, some cases required treatment discontinuation, indicating the need for close monitoring and timely intervention during therapy.

This review has several limitations. First, the heterogeneity in study designs (RCTs,

observational studies, case reports) and small sample sizes in some included studies may limit the generalizability of the findings. Second, all studies were conducted in China, raising concerns about external validity in broader populations. Third, some studies lacked mature OS data or long-term follow-up, which is critical in evaluating the durability of immune-based therapies. Finally, publication bias and selective reporting cannot be entirely excluded, especially with the inclusion of case reports. Future large-scale, multi-center RCTs with longer follow-up are warranted to confirm these findings and to better define the patient populations that would benefit most from toripalimab-based therapies.

CONCLUSION

In conclusion, this systematic review consolidates evidence indicating that toripalimab, particularly in combination with the angiogenesis inhibitor axitinib, represents a significant advancement in the treatment of renal cell carcinoma (RCC). The regimen demonstrates superior efficacy over standard therapies like sunitinib, evidenced by statistically significant and clinically meaningful improvements in key oncological outcomes: progression-free survival, objective response rate, and overall survival. Notably, these benefits were observed even in challenging patient subgroups, such as the elderly and those with aggressive sarcomatoid histology. The safety profile of toripalimab-based therapy, while associated with manageable adverse events like hypertension, fatigue, and hepatic enzyme elevation consistent with its drug class, necessitates vigilant monitoring. Toripalimab-based combinations emerge as a potent and promising therapeutic strategy for RCC. However, future large-scale, multi-center randomized controlled trials with extended follow-up are essential to validate these findings and confirm long-term survival benefits.

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