REVIEW

The Impact of Adjuvant Drug Therapy on Overall Survival in Patients with Clear Cell Renal Cell Carcinoma: A Systematic Review and Meta-Analysis

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Purpose: Clear cell renal cell carcinoma (ccRCC), the dominant subtype of renal malignancy, has a rising global incidence and mortality. While surgery is the standard of care for localized cases, adjuvant therapy aims to improve outcomes in high-risk postoperative patients. To quantify the clinical value of adjuvant pharmacotherapy, this systematic review and meta-analysis assesses its effect on overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS) in patients with ccRCC.

Materials and Methods: A comprehensive search of the Web of Science, Embase, Cochrane Library, and PubMed databases was conducted for articles published up to October 2024. The search used the English keywords "clear cell renal cell carcinoma," "adjuvant drug therapy," and "randomized controlled trials," combined with a free-word search. Randomized controlled trials (RCTs) assessing the effectiveness of at least one adjuvant drug therapy in patients with ccRCC were included.

Results: The meta-analysis showed that adjuvant drug therapy did not result in a statistically significant improvement for OS or PFS compared with the control group. There was also no statistically significant difference in DFS ($P > 0.05$). This systematic review provides evidence on the impact of adjuvant targeted therapy on OS, DFS, and PFS for patients with clear cell renal cell carcinoma.
Conclusion: This study summarizes the effects of adjuvant drug therapy on OS, PFS, and DFS in ccRCC patients. The evidence from this meta-analysis can inform clinical decision-making, support risk-stratification strategies, and encourage the integration of OS-driven endpoints in future trial designs, thereby providing valuable data for the treatment of ccRCC.

Keywords: primary monosymptomatic nocturnal enuresis; genetic analysis; chromosomal abnormalities; microarray; genetic heterogeneity

INTRODUCTION

According to survey results, approximately 431,000 new cases of renal cell carcinoma are identified globally each year, making it the 16th most prevalent cancer worldwide.[1] Clear cell renal cell carcinoma (ccRCC), the most prevalent subtype, arises from the proximal convoluted tubule and accounts for approximately 70% to 80% of all RCC cases.[2] In 2023, an estimated 81,800 new kidney tumor cases and 14,890 deaths occurred in the United States, highlighting its significant public health impact.[3]
Earlier investigations into adjuvant drug therapy for ccRCC, especially those involving vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs), have demonstrated effects on tumor cell proliferation.[4] Currently, optimizing the efficacy of adjuvant therapy for localized RCC after surgery remains a challenging area in clinical research, with limited success achieved thus far.[5] However, there is insufficient evidence to demonstrate that these agents significantly prolong overall survival (OS), progression-free survival (PFS), or disease-free survival (DFS).[6,7]
Broad adoption of adjuvant therapy in locally advanced renal cell carcinoma faces multiple barriers. Key concerns include risks of unnecessary toxicity, unclear survival benefits, and economic considerations.[8] In fact, some studies have found that for patients with locally advanced RCC, adding adjuvant drug therapy not only fails to provide survival benefits but also increases the incidence of adverse events, including hypertension, rash, hand–foot syndrome, diarrhea, and fatigue.[4]
In recent years, the emergence of immunotherapy, notably anti–programmed death-1 (PD-1) antibodies, has opened a novel therapeutic avenue for ccRCC.[9] The PD-1 inhibitor pembrolizumab, in particular, has shown significant efficacy and safety in multiple clinical trials, improving postoperative DFS and OS.[10] Notably, the KEYNOTE-564 trial demonstrated that adjuvant pembrolizumab therapy significantly improved both DFS and OS in patients with ccRCC.[11,12] Based on these findings, pembrolizumab received subsequent approval as an adjuvant treatment option for postoperative RCC patients. However, a large proportion of patients experience life-altering or other serious side effects during treatment. Furthermore, with the widespread clinical application of immunotherapy, accurately assessing its long-term effects and patients' quality of life, as well as developing personalized treatment plans for patients

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Table 1. Fundamental attributes of the studies incorporated in this meta-analysis.

Study, Year	Country	Total (n)	Disease Stage	Follow-up, median (m)	Treatment	Control	Outcome Indicators
Albiges, 202217	USA	53/55	Advanced	Unclear	Nivolumab + Ipilimumab	Sunitinib	OS/PFS
Shah, 201918	USA	410/411	Advanced/Metastatic	45.0/44.2	Nivolumab	Everolimus	OS/PFS
Rini, 201419	USA	400/391	Advanced	Unclear	Temsirolimus + Bevacizumab	Interferon + Bevacizumab	OS/PFS
Grunwald, 202320	Germany	243/229	Advanced/Metastatic	26.6	Lenvatinib + Pembrolizumab	Sunitinib	OS/PFS
Choueiri, 20245	USA	496/498	Unclear	57.2	Pembrolizumab	Placebo	OS
Chamie, 201721	USA	433/431	High risk	54.1/54.0	Girentuximab	Placebo	OS/DFS
Lara, 202422	USA	351/348	High-risk	8.2 years	Everolimus	Placebo	OS
Rini, 201223	USA	82/69/75	Unclear	Unclear	Sorafenib + AMG386	Placebo	PFS
Motzer, 202324	USA	405/411	High-risk	37.0	Nivolumab + Ipilimumab	Placebo	DFS
Ravaud, 201625	France	309/306	High-risk	5.4 years	Sunitinib	Placebo	OS/DFS

Abbreviations: USA, United States; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

with different risk levels, are pressing issues to be addressed.

In addition, adjuvant drug therapy also includes other inhibitors of the VEGF pathway, such as sunitinib and sorafenib. Sunitinib is a standard-of-care, first-line treatment for metastatic RCC. As a TKI targeting the VEGFR, it can effectively manage RCC.[13,14] Choueiri et al. found that sunitinib treatment in patients with metastatic RCC effectively improves median PFS and median OS.[15] However, studies indicate that in locally advanced ccRCC patients at high recurrence risk post-nephrectomy, sunitinib treatment significantly extended median DFS compared with placebo, though with substantially higher toxicity rates.[2,16]

Despite the clinical promise of some adjuvant drug therapies in ccRCC, concerns about unnecessary toxicity and uncertain overall survival benefits persist as critical barriers to their widespread adoption.[8] Notably, no prior meta-analysis has comprehensively evaluated the OS benefits of adjuvant therapies across all major drug

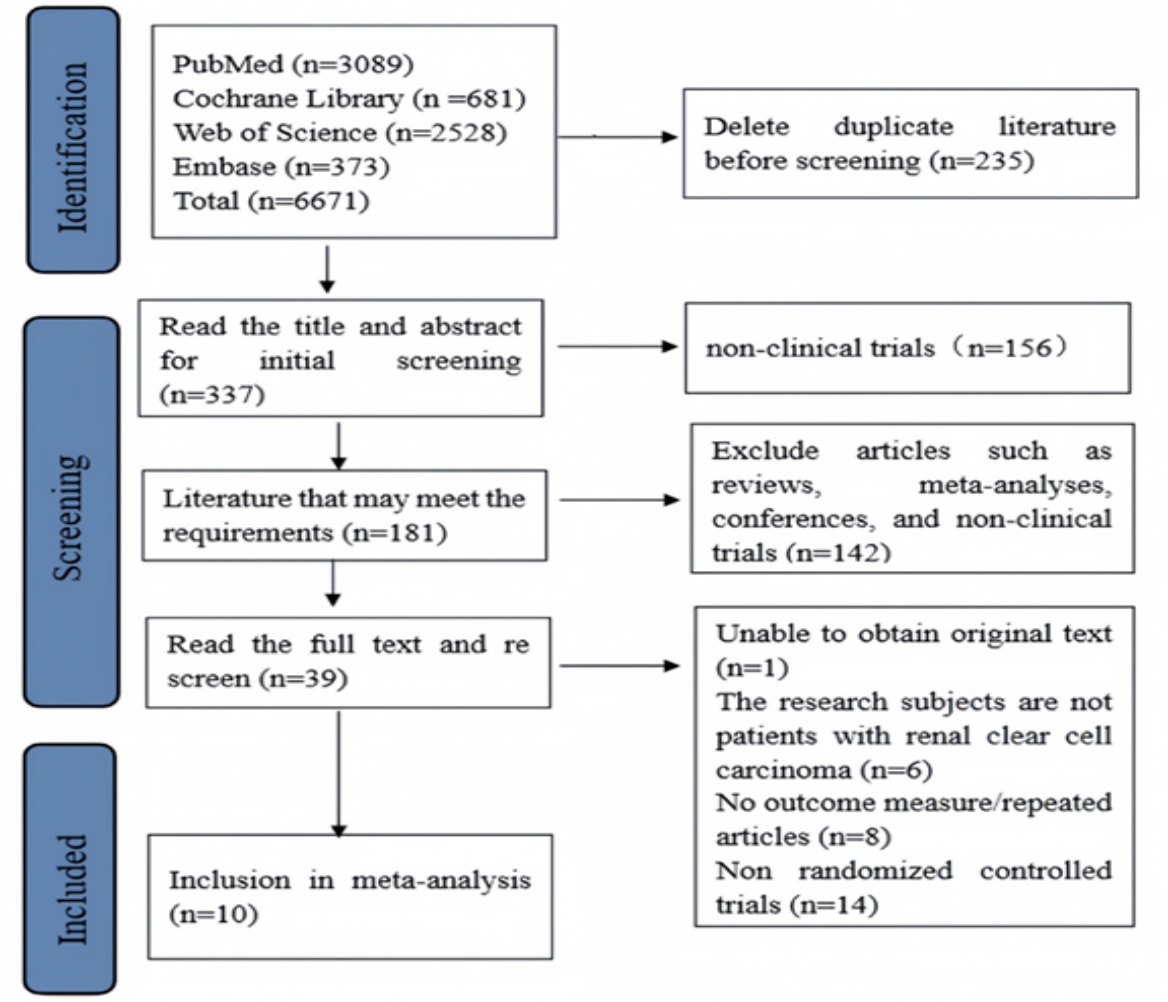

Figure 1. Study selection flowchart.

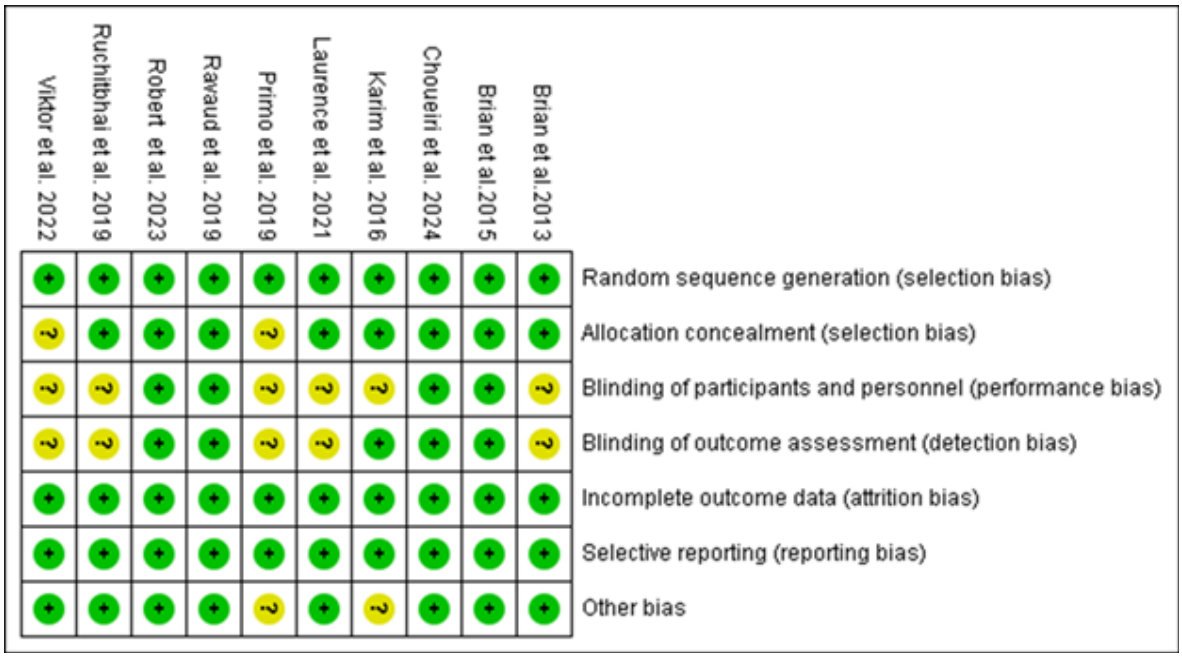

Figure 2. Risk of bias for each study.

classes in ccRCC. To address this critical unmet need, this study presents a comprehensive systematic review and meta-analysis of published randomized controlled trials. The aim is to evaluate the impact of various adjuvant drug therapies on survival outcomes in ccRCC patients, thereby informing clinical decision-making and guiding future research.

MATERIALS AND METHODS

Search Strategy

This systematic review and meta-analysis was conducted by searching the Web of Science, Cochrane Library, Embase, and PubMed databases for studies published up to October 21, 2024. The search used the following English keywords: "clear cell renal cell carcinoma", "adjuvant drug therapy", and "randomized controlled trials", which were combined with a free-word search. The search strategy utilized Boolean operators (AND/OR) and truncation symbols to ensure comprehensive retrieval. We included randomized controlled trials (RCTs) that evaluated the efficacy of at least one adjuvant therapy in patients with ccRCC. The primary endpoint was OS; secondary endpoints were PFS and DFS. We also examined the citations listed in the retrieved articles to uncover other potentially relevant studies.

Inclusion and Exclusion Criteria

Two researchers conducted an independent literature review, ultimately reaching a consensus through collab-

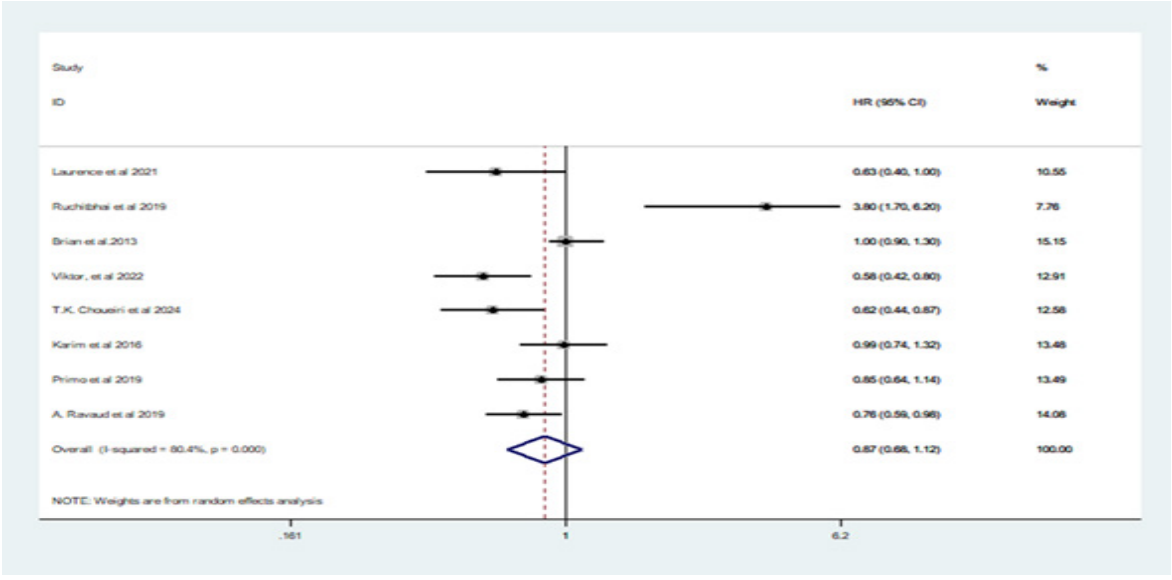

Figure 3. The forest plot visualizes the correlation between adjuvant therapies and the oncologic outcomes observed in patients with ccRCC.

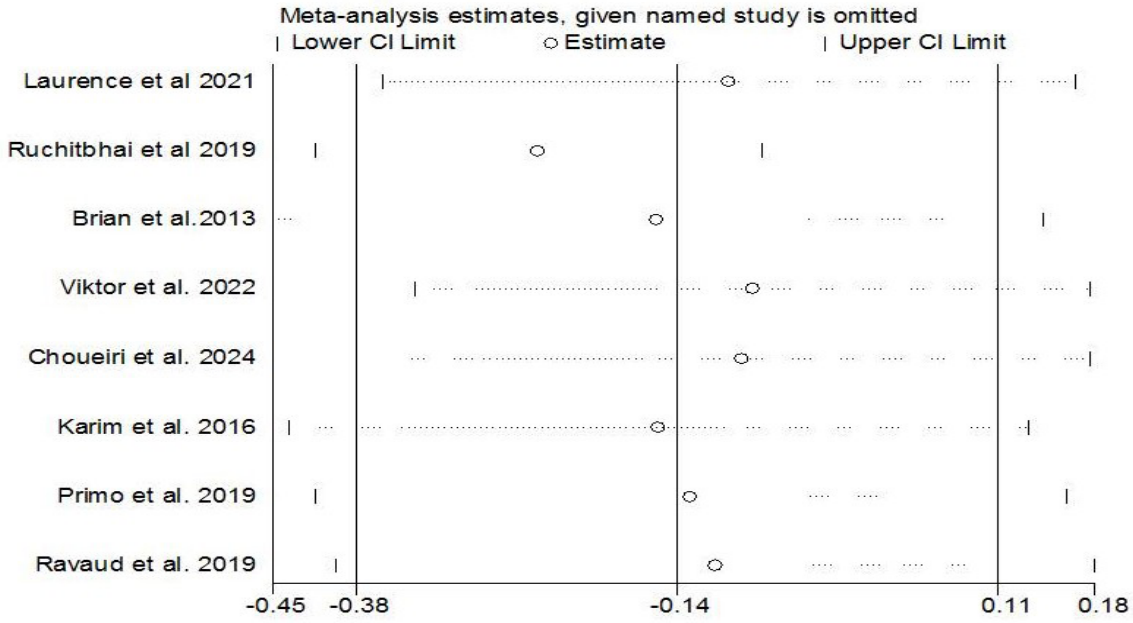

Figure 4. Sensitivity analysis of overall survival.

orative discussion. Subsequently, the complete texts of the eligible articles were examined for definitive inclusion and the extraction of relevant data. Studies were included if they met the following criteria: (1) all patients were diagnosed with ccRCC through pathological examination; (2) patients received regular treatment and follow-up; (3) ccRCC patients received adjuvant drug therapy; (4) sufficient data were available to analyze patient OS, including the hazard ratio (HR) and its 95% confidence interval (CI). The main exclusion criteria were: (1) inadequate data for analysis; (2) conference abstracts, commentaries, letters to the editor, editorials, and articles in non-translatable languages; (3) redundant data.

Data Extraction

Data extraction was independently performed by two reviewers using a standardized electronic data extraction table created in Excel. The extracted information included: study characteristics (first author, publication

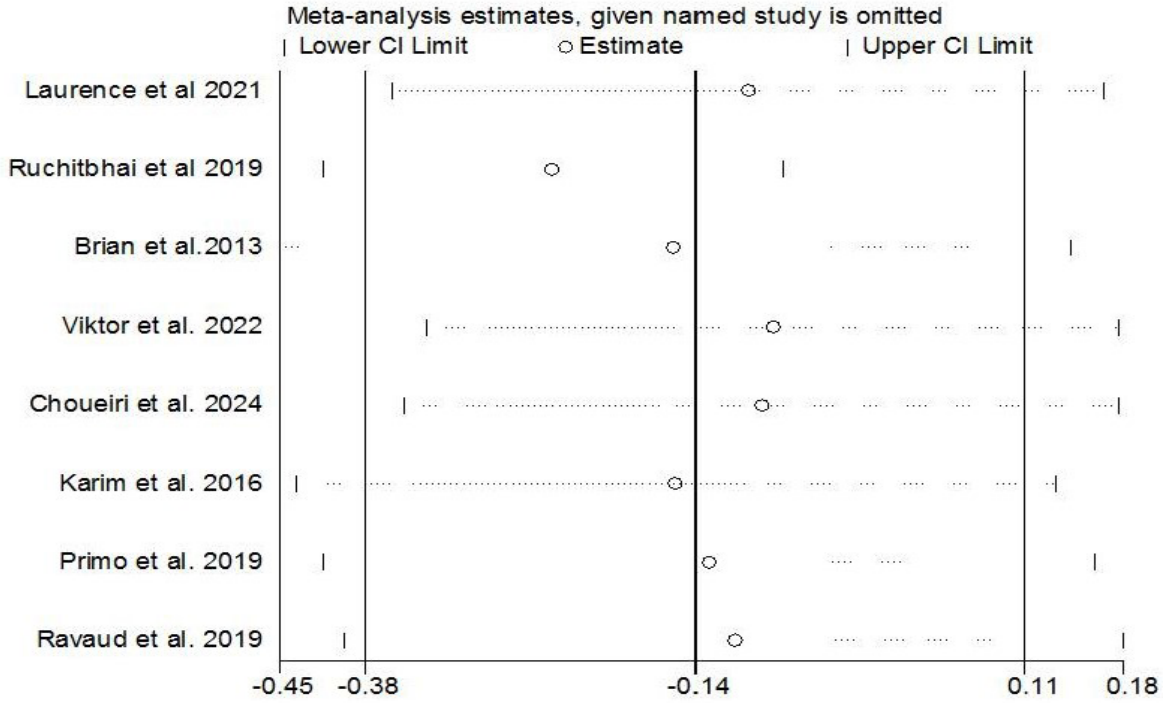

Figure 5. The forest plot displays the link between adjuvant therapies and the oncologic results in individuals with ccRCC.

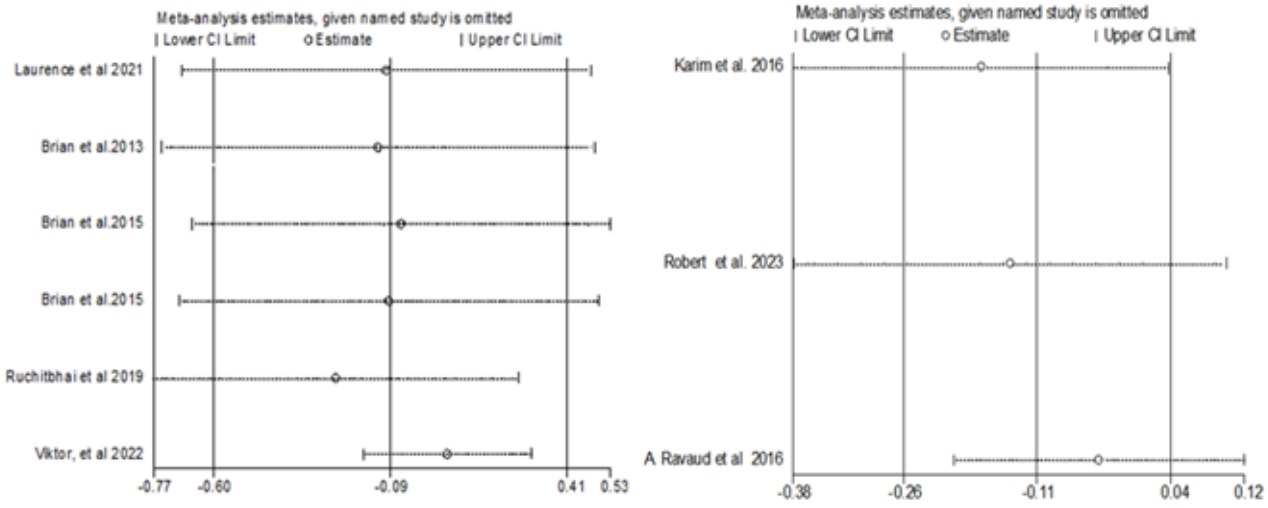

Figure 6. Sensitivity analysis of progression-free survival and disease-free survival.

year, country of origin, study design), patient demographics (sample size, cancer staging), and intervention details (drug name, dosage, treatment duration). The main outcome measures were the HR and 95% CI for OS, PFS, and DFS.

Risk of Bias Assessment

We utilized the Cochrane Collaboration's risk of bias tool to evaluate the articles for their quality and potential bias risks. The tool assesses several domains, including whether the control group was randomized, the allocation plan was concealed, the outcome assessment was blinded, follow-up was complete, and whether other potential sources of bias were present.

Statistical Analysis

A meta-analysis was carried out employing STATA software version 14.0 and Review Manager version 5.4. The HR along with its 95% CI was extracted from the selected studies. The I^2 statistic was used to measure heterogeneity. Data were pooled using a fixed-effects model if $I^2 < 50\%$ (indicating low heterogeneity) or a random-effects model if $I^2 \geq 50\%$. Funnel plots were used to visually assess publication bias, and Egger's linear regression test was used to statistically test for plot asymmetry.

RESULTS

Study Selection and Characteristics

The initial search yielded 6,671 potentially relevant studies. After removing duplicates and irrelevant articles based on titles and abstracts, 337 publications were screened. Of these, 298 were excluded. The full texts of the remaining articles were assessed, resulting in the final inclusion of 10 studies in our meta-analysis.[5,17–25] The study selection process is illustrated in (**Figure 1**). All ten studies were randomized controlled trials or phase III studies, and each incorporated a control group. In total, 5,328 patients with ccRCC were enrolled across these studies. The adjuvant drug treatments included in the trial evaluation were nivolumab, ipilimumab, temsirolimus, bevacizumab, lenvatinib, pembrolizumab, girentuximab, everolimus, sunitinib, and sorafenib. The studies were conducted primarily in the USA (n = 8), Germany (n = 1), and France (n = 1). Among these, two studies directly investigated TKIs as primary treatment, with additional mentions in combination therapies. Immunotherapy was explored in eight studies, including three with nivolumab, one with pembrolizumab, and two involving ipilimumab in combination regimens. (**Table 1**) summarizes the key characteristics of the studies analyzed.

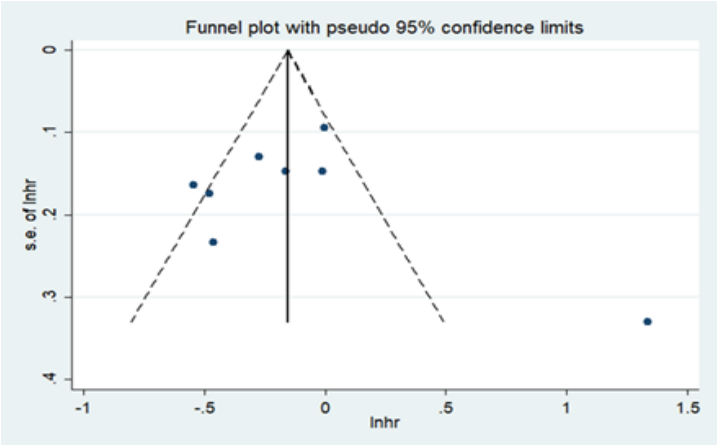

Figure 7. Publication bias of overall survival.

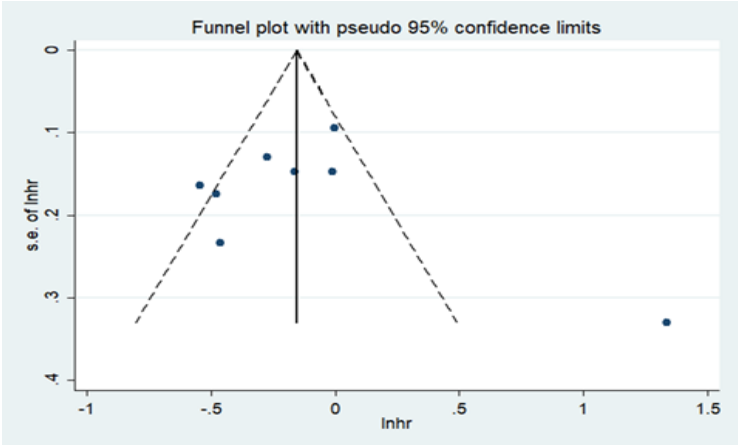

Figure 8. Publication bias of progression-free survival.

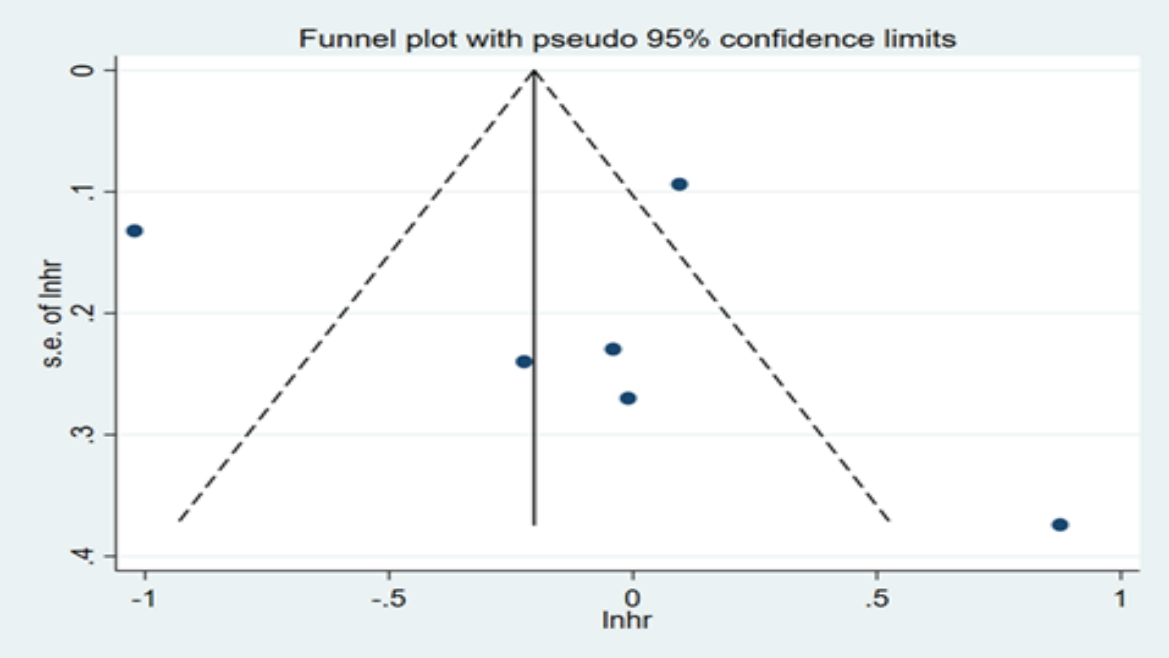

Figure 9. Publication bias of disease-free survival.

Quality Assessment Results

Upon identification, the report, abstract, and complete text of each study were thoroughly scrutinized. Subsequently, the quality of the publications was rigorously screened and evaluated utilizing the Cochrane risk of bias assessment tool. The outcomes of this literature quality evaluation are depicted in (**Figure 2**). Notably, two studies lacked data on OS, and one study exclusively reported PFS without providing information on OS or DFS.

Results of the Meta-Analysis for Outcomes

Overall Survival

Eight studies provided data on OS for patients with ccRCC who underwent adjuvant drug therapy.5,17–22,25 The pooled analysis of these studies showed no statistically significant improvement in OS with adjuvant therapy compared with the control group (pooled HR: 0.87, 95% CI: 0.68–1.12) (**Figure 3**). Sensitivity analysis revealed that excluding one study in each iteration did not significantly alter the pooled estimate, indicating the robustness of the results (**Figure 4**).

Subgroup Analysis

Progression-Free Survival (PFS)

A meta-analysis was conducted on five studies reporting PFS.17–20,23 Compared with the control group, the pooled analysis showed no significant improvement in PFS for the experimental group (HR 0.91, 95% CI 0.55–1.51) (**Figure 5**).

Disease-Free Survival (DFS)

A meta-analysis was performed on three studies for DFS.21,24,25 In contrast to the control group, the DFS of the experimental group did not exhibit statistically significant changes (HR = 0.90, 95% CI = 0.77–1.04, *P* = 0.310) (**Figure 5**). Sensitivity analysis demonstrated that excluding any individual study in each iteration had no impact on the results, thus confirming the robustness of the findings (**Figure 6**).

Publication Bias

Additionally, we conducted a funnel plot analysis on the retrieved data to assess publication bias. The funnel plots for OS, PFS, and DFS exhibited some degree of symmetry **(Figure 7–Figure 9**). Furthermore, Egger's test did not reveal significant publication bias for OS (*P* = 0.769), PFS (*P* = 0.786), or DFS (*P* = 0.615).

DISCUSSION

In this systematic review and meta-analysis, we evaluated the effect of adjuvant drug therapy on survival outcomes in patients with ccRCC. Our pooled analysis did not demonstrate a statistically significant improvement in OS or PFS for patients receiving adjuvant therapy compared to controls. Similarly, DFS was not significantly improved. Although our primary analysis did not find a statistically significant improvement in OS and PFS, the trend favored adjuvant therapy. This trend suggests a potential clinical benefit, which could translate to improved quality of life and more time for subsequent treatments, but this requires confirmation in future studies.

Our findings are consistent with several individual trials that found no significant OS benefit with adjuvant TKI therapy compared to placebo.[8,26,27] Our analysis also showed no significant improvement in DFS for ccRCC patients receiving adjuvant therapy. This aligns with the results of the CheckMate 914 trial, which found that adjuvant nivolumab plus ipilimumab did not improve DFS compared to placebo.24 Similarly, a meta-analysis by Yiu et al. also found no DFS benefit for adjuvant sorafenib, sunitinib, or pazopanib.[4]

Our results may differ slightly from other meta-analyses due to variations in the included studies, search dates, and analytical methods.[28–30] Therefore, while our meta-analysis did not confirm a statistically significant

survival benefit, the role of adjuvant therapy in ccRCC remains an important area of investigation. Further research is needed to identify patient subgroups who may benefit most, to optimize drug selection, and to mitigate adverse effects.

This study has several limitations. We acknowledge that heterogeneity in study protocols (e.g., variable dosing regimens and control groups) and the limited demographic and racial diversity of the trial populations (predominantly Caucasian cohorts) may limit the comparability and generalizability of our results. Future trials should standardize protocols, diversify enrollment, and prioritize OS endpoints to enhance applicability and refine adjuvant therapy strategies in ccRCC.

CONCLUSIONS

In conclusion, this meta-analysis did not find a statistically significant improvement in overall survival, progression-free survival, or disease-free survival for patients with ccRCC receiving adjuvant drug therapy compared with a control group. Despite the non-significant findings, these results highlight the ongoing challenges in adjuvant therapy for ccRCC and underscore the need for better-designed trials and patient selection strategies to guide future treatment plans.

SUMMARY

After kidney cancer surgery, extra drug treatments are sometimes used to prevent cancer from returning. Our review of ten studies found that these drugs did not show a clear overall benefit in helping patients live longer or stay cancer-free.

ACKNOWLEDGEMENTS

Author Contributions: Dong Lan and Jianhua Lan designed the study and performed the experiments. Jianhui Du and Wenqiang Yuan collected the data. Qiao Ying and Guohua Huang analyzed the data. Dong Lan and Jianhua Lan prepared the manuscript. All authors read and approved the final manuscript.

Data Availability: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Ethical Approval: Not applicable.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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