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Review Article

Efficacy of temsirolimus versus pazopanib in the treatment of advanced renal cell carcinoma: a meta-analysis

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Abstract: Purpose: Temsirolimus and pazopanib serve as first-line therapies for renal cell carcinoma (RCC). This meta-analysis was performed to assess and compare their efficacy, optimal treatment targets, and associated toxicities. Methods: We searched the PubMed, CNKI, Wanfang, and VIP databases for relevant literature published from 2003 to 2023. Studies were selected based on specific exclusion criteria, and eligible articles were subjected to data extraction for subsequent subgroup analysis. Results: Fourteen studies of moderate to high quality were included. In the low-risk group, the mortality rate was significantly lower in the temsirolimus group at 0.23 (95% CI, 0.15-0.31) compared to 0.44 (95% CI, 0.40-0.47) in the pazopanib group. In the high-risk group, the mortality rate was 0.73 (95% CI, 0.69-0.76) for temsirolimus and 0.67 (95% CI, 0.64-0.71) for pazopanib. Conclusion: Temsirolimus demonstrated greater efficacy in the low-risk group, while pazopanib was superior in the high-risk group for the treatment of RCC. Consideration of both efficacy and toxicity is crucial to guide drug selection for patients. TRN: CRD42024578497 (Registration date: 2024/08/21).

Keywords: Temsirolimus, pazopanib, advanced renal cell carcinoma, meta analysis, comparison

Introduction

Renal cell carcinoma (RCC), the most prevalent and lethal tumor of the urinary system [1], ranks as the eighth and tenth most common cancers among men and women in the United States, respectively [2]. The incidence of RCC escalates significantly with age, exhibiting higher rates in men than in women [3]. Projections suggest that the incidence and mortality of RCC will continue to rise, with deaths expected to surpass 300,000 by 2040 [4, 5].

Temsirolimus, an inhibitor of mTOR kinase, disrupts a signaling pathway crucial for cell growth and proliferation. Inhibiting mTOR curtails cell cycle progression and angiogenesis, thereby exerting a therapeutic effect on RCC [6]. Pazopanib, an oral inhibitor targeting the tyrosine kinase domains of the vascular endothelial growth factor receptor (VEGFR) 1-3, platelet-derived growth factor receptor (PDGFR) α and β, and stem cell factor receptor (SCF, c-KIT), has gained approval for first-line treatment of metastatic RCC (mRCC) following a Phase III registration study [7].

Although both temsirolimus and pazopanib are first-line therapies for RCC, their suitability for patients with varying physical conditions remains uncertain. A phase III trial demonstrated temsirolimus's superior efficacy over interferon-α as first-line therapy, with median overall survival (OS) of 10.9 months and progression-free survival (PFS) of 3.8 months [8], though metabolic derangements (e.g., hyperglycemia, hypercholesterolemia [9]) are frequent. In a phase IV trial, pazopanib achieved median OS of 9.3 months and PFS of 4.5 months as first-line therapy [10], with hypertension and hypothyroidism being predominant toxicities [10]. To ascertain the most effective therapeu-

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tic agents for diverse patients, we conducted a meta-analysis of pertinent literature, compared the anti-tumor efficacy of temsirolimus and pazopanib, and investigated patient survival rates, aiming to inform patient selection in RCC management.

Methods

Literature search

We conducted comprehensive searches in PubMed, Web of Science, EBSCO, CNKI, Wanfang, and ViPP from 2003 to November 2023 to identify articles detailing the treatment of RCC with temsirolimus or pazopanib. Search terms included "Temsirolimus", "Pazopanib", and "RCC". The specific PubMed query was ((("pazopanib"[MeSH Terms]) AND ("Carcinoma, Renal Cell"[MeSH]) OR ("Temsirolimus"[MeSH Terms]) AND ("Carcinoma, Renal Cell"[MeSH])). Additionally, references from the selected studies were reviewed to uncover further relevant articles.

Inclusion and exclusion criteria

Inclusion criteria: I. Individuals aged over 18; II. Patients diagnosed with advanced or mRCC, irrespective of prior targeted drug therapy, race, or gender; III. Treatment involving temsirolimus or pazopanib; IV. Studies reporting the number of deaths or mortality rates.

Exclusion criteria: I. Pregnant or breastfeeding women; II. Patients with bacterial, fungal, or active viral infections; III. Duplicates, case reports, reviews, systematic reviews, and studies with non-extractable data; IV. Animal studies; V. Studies on drug combinations; VI. Non-randomized controlled trials (RCTs) or studies with inconsistent methodologies.

Nanation method

The literature was jointly screened by two researchers based on the inclusion and exclusion criteria. In cases of disagreement, consultation with at least one additional researcher was required.

Quality evaluation

Data extraction was performed by two researchers from the included studies. In instances of disagreement, consultation with at least a third researcher was required. The quality of RCTs was assessed using the Cochrane Risk of Bias Assessment tool [11], which evaluates the following six domains: methods of randomization, concealment of allocation, blinding, completeness of outcome data, selective outcome reporting, and other potential sources of bias.

Each domain was assigned a rating of "yes", "no", or "unclear", corresponding to a low, high, or unclear risk of bias, respectively. A study was deemed to have a low risk of bias if none or only one domain was rated as "unclear" or "no". A high risk of bias was assigned if four or more domains were judged as "unclear" or "no". Studies where two or three domains were rated as "unclear" or "no" were classified as having a moderate risk of bias [12]. Review Manager 5 (RevMan 5.2.3, Cochrane Collaboration, Oxford, U.K.) was employed to assess the quality of the studies and publication bias.

Statistical methodology

Mortality rate was analyzed as the clinical endpoint using single-arm proportion meta-an alysis (Stata 17.0), with mortality rate as the effect measure. Heterogeneity was assessed via I^2 statistics and Cochran's Q-test; random-effects models were applied for I^2 ≥50%. Publication bias was evaluated by funnel plot asymmetry, supplemented by sensitivity analyses.

Results

Literature screening process and results

We retrieved a total of 876 articles using the specified search methods. After rigorous screening based on the inclusion and exclusion criteria, 14 RCTs were selected (**Figure 1**).

Quality evaluation of included studies and their general characteristics

The risk of bias in the included studies of this meta-analysis is depicted in **Figure 2A**, **2B**. Fourteen high-quality studies were included, with two categorized as having a low risk of bias and twelve at a moderate risk of bias.

Basic information of the included studies

Data extracted from each study included: I. General study information (author, year, meth-

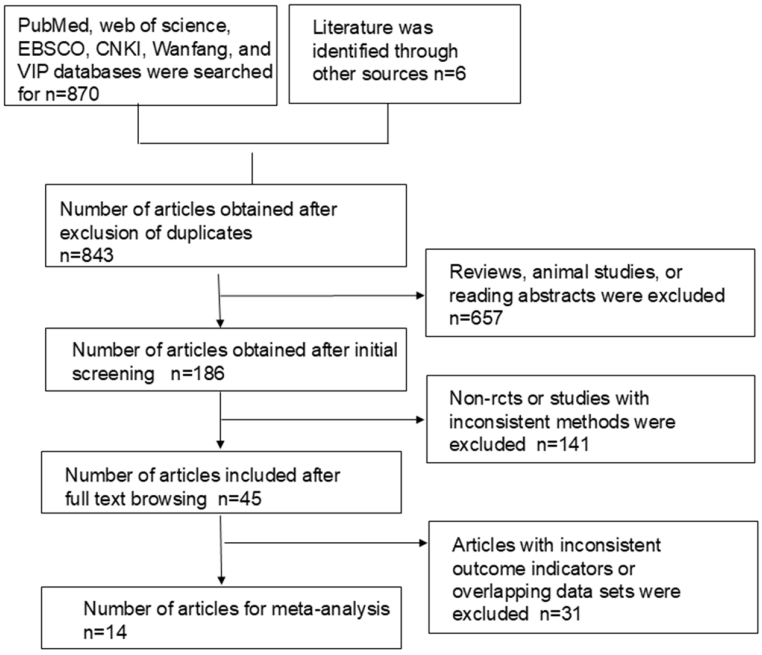

Figure 1. Literature screening process and results.

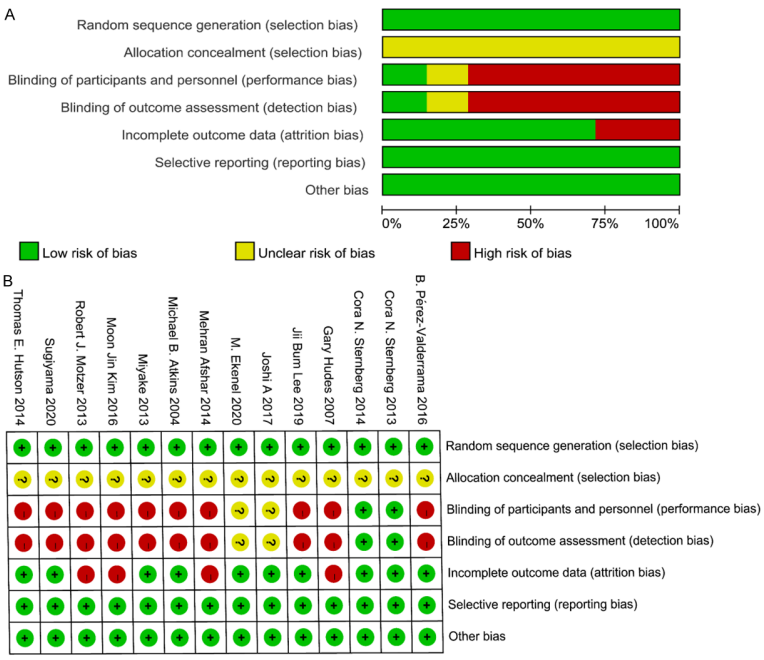

Figure 2. Risk assessment analysis. A. Cochrane Proportion chart of risk assessment; B. Cochrane Schematic of risk assessment.

odology); II. Patient numbers; III. Patient age (median and range); IV. Pretreatment protocols; V. Intervention measures and dosages. Details are provided in **Table 1**.

The studies encompassed a total of 2656 patients, with 1295 in the temsirolimus group and 1361 in the pazopanib group: The studies were divided into four subgroups based on baseline patient characteristics (e.g., ECOG performance status, tumor stage ratio, MSKCC score, Karnofsky score) and medication differences: I. High-risk patients constituted a significant proportion, with four studies on temsirolimus interventions [8, 13-15] involving 548 patients; II. High-risk patients constituted a significant proportion, with three studies featuring pazopanib interventions [7, 16, 17] involving 648 patients; III. Low-risk patients constituted a significant proportion, with three studies on temsirolimus interventions [18-20] involving 747 patients; IV. Low-risk patients constituted a significant proportion, with four studies using pazopanib interventions [21-24] involving 713 patients.

Results of meta-analysis

Temsirolimus, high-risk group: 1) Heterogeneity test. The heterogeneity test indicated that I^2=31.1% (<50%) and P>0.1 in the Q test (**Figure 3A**), suggesting no significant heterogeneity among the included studies. To ensure the accuracy and stability of the findings, a sensitivity analysis was conducted. 2) Sensitivity analysis. Sensitivity analysis of the four studies revealed that none significantly affected the outcomes of this meta-analysis, confirming the study's robust stability (**Figure 4A**). Consequently, the fixed effect model was utilized. 3) Bias test. A funnel plot was construct-

Table 1. Basic information of literature

The author	Year	Test method	Age	Number of people	Interventions and dosage	Pretreatment
Sugiyama	2020	Randomized controlled trials, Unblinded	65 (1-89)	654	25 mg of temsiolimus intravenously infused every week	Patients on temsiolimus previously
Miyake	2013	Randomized controlled trials, Unblinded	64.5 (26-83)	55	25 mg of temsiolimus intravenously infused every week	No pretreatment
Jii Bum Lee	2019	Randomized controlled trials, Unblinded	52 (17-84)	44	25 mg of temsiolimus intravenously infused every week	No pretreatment
Thomas E. Hutson	2014	Randomized controlled trials, Unblinded	60 (19-82)	259	25 mg of temsiolimus intravenously infused every week	4 Receive at least one 4-week cycle of continuous sunitinib
Michael B. Atkins	2004	Randomized controlled trials, Unblinded	55 (40-79)	36	25 mg of temsiolimus intravenously infused every week	No pretreatment
Gary Hudes	2007	Randomized controlled trials, Unblinded	58 (32-81)	209	25 mg of temsiolimus intravenously infused every week	No pretreatment
Mehran afshar	2014	Randomized controlled trials, Unblinded	62	38	25 mg of temsiolimus intravenously infused every week	Individual patients had been treated once previously
Cora N. Sternberg	2013	Randomized controlled trials, Double blind	61 (25-85)	290	Pazopanib 800 mg daily	202 Cytokine pretreatment
Cora N. Sternberg	2014	Randomized controlled trials, Double blind	60.5 (25-80)	80	Pazopanib 800 mg daily	Had previously received one cytokine-based systemic therapy
B. Pérez-Valderrama	2016	Randomized controlled trials, Unblinded	66	278	Pazopanib 800 mg daily	No pretreatment
Robert J. Motzer	2013	Randomized controlled trials, Unblinded	18+	554	Pazopanib 800 mg daily	No pretreatment
Moon Jin Kim	2016	Randomized controlled trials, Unblinded	65 (19-84)	93	Pazopanib 800 mg daily	Individual patients had previously received cytokine therapy
Joshi A	2017	Randomized controlled trials, No states	56.5 (35-76)	28	Pazopanib 800 mg daily	No pretreatment
M. Ekenel	2020	Randomized controlled trials, No states	59 (32-87)	38	Pazopanib 800 mg daily	No pretreatment

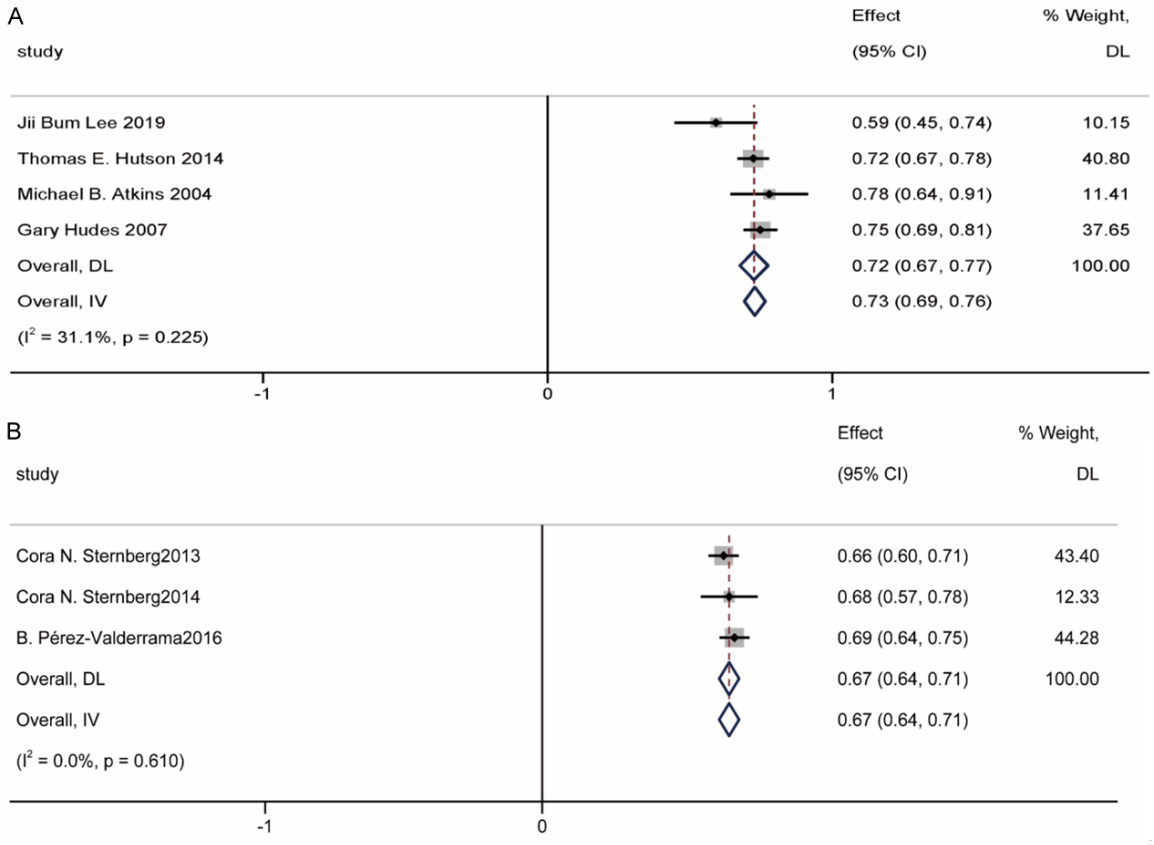

Figure 3. Forest plot analysis of the high-risk group. A. Temsirolimus treatment group; B. Pazopanib treatment group.

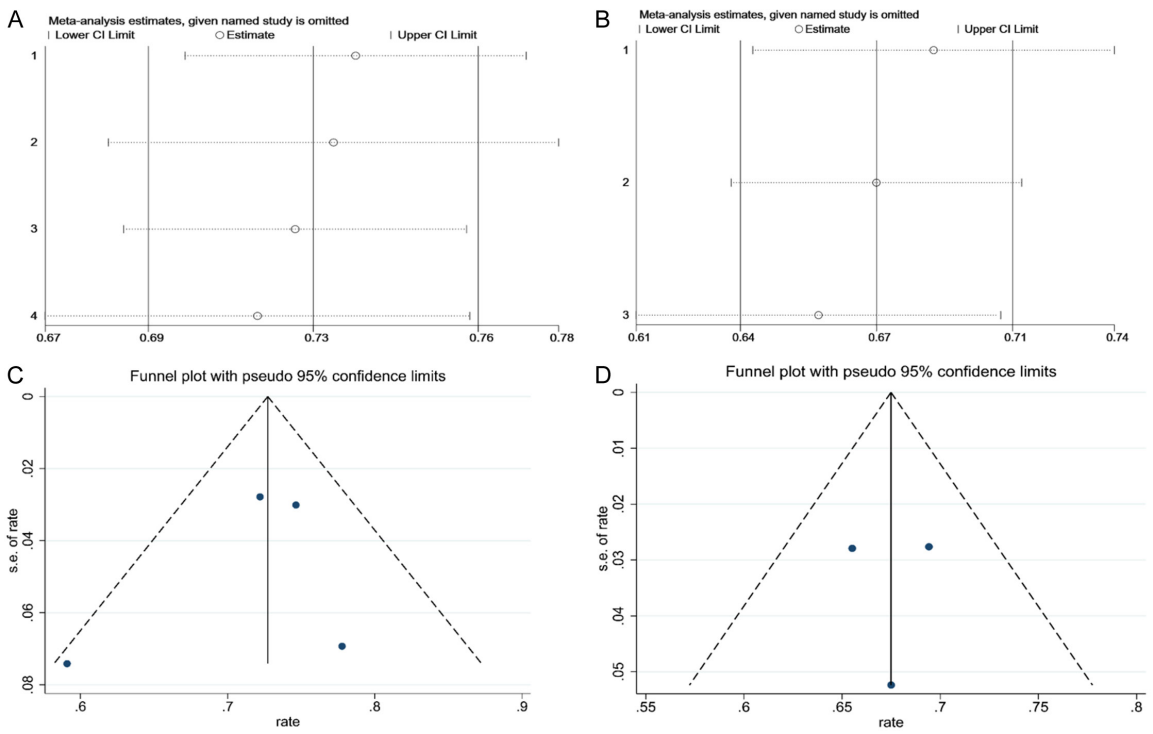

Figure 4. The sensitivity and funnel diagram of the high-risk group. A. Temsirolimus treatment groups sensitivity analysis; B. Pazopanib treatment group sensitivity analysis; C. Temsirolimus treatment group funnel diagram; D. Pazopanib treatment group funnel diagram.

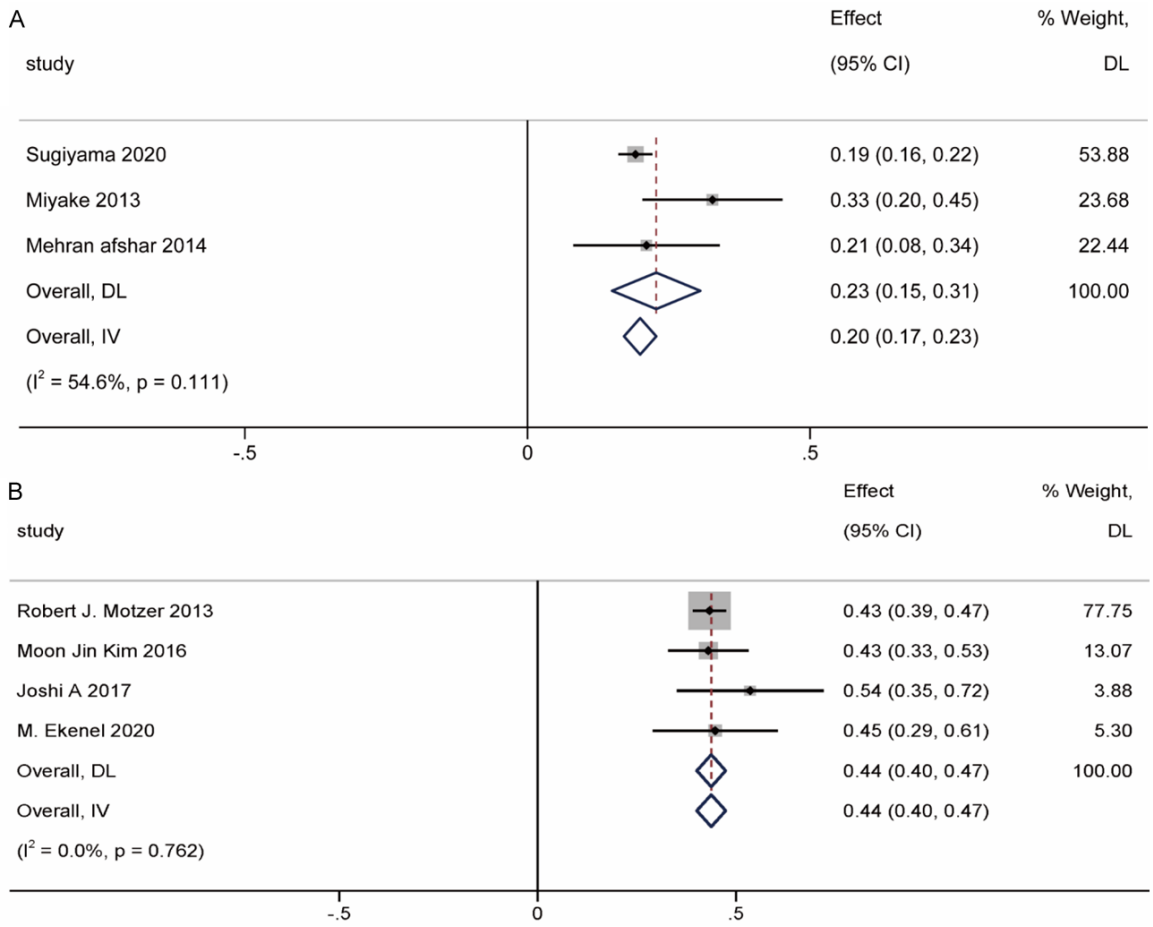

Figure 5. Forest plot analysis of the low-risk group. A. Temsirolimus treatment group; B. Pazopanib treatment group.

ed to assess the presence of publication bias in the research. The symmetry test for the funnel plot yielded P=0.594 (>0.05), indicating symmetry and suggesting the absence of publication bias in the studies (**Figure 4C**). Combining these findings, the mortality rate in the high-risk temsirolimus group was determined to be 0.73 (95% CI, 0.69-0.76) (**Figure 3A**).

Pazopanib, high-risk group: 1) Heterogeneity test. The heterogeneity test revealed that I^2=0.0% (<50%) and P>0.1 in the Q test (**Figure 3B**), indicating no significant heterogeneity among the studies selected. To maintain scientific rigor, a sensitivity analysis was performed. 2) Sensitivity analysis. Sensitivity analysis of the three studies showed that none significantly impacted the results of this meta-analysis, indicating good stability (**Figure 4B**); thus, the fixed-effect model was adopted. 3) Bias test. A funnel plot was created to assess the presence of publication bias. The symmetry test for this plot showed P=0.991 (>0.05), confirming a symmetrical distribution and indicating no publication bias in the included studies (**Figure 4D**). Summarizing, the mortality rate in the high-risk group treated with pazopanib was 0.67 (95% CI, 0.64-0.71) (**Figure 3B**).

Temsirolimus, low-risk group: 1) Heterogeneity test. The heterogeneity test for three studies on low-risk patients treated with temsirolimus showed I^2=54.6% (>50%), and P>0.1 in the Q test (**Figure 5A**), indicating moderate heterogeneity. Therefore, sensitivity analysis was conducted to explore the causes. 2) Sensitivity analysis. Analysis identified that the first study contributed to the heterogeneity of the results (**Figure 6A**). After reviewing and discussing, the potential reasons include: (1) disparities in medical standards over different years; (2) differences in the patient population, as the first study involved unresectable or mRCC, contrasting with the other two. Despite these factors,

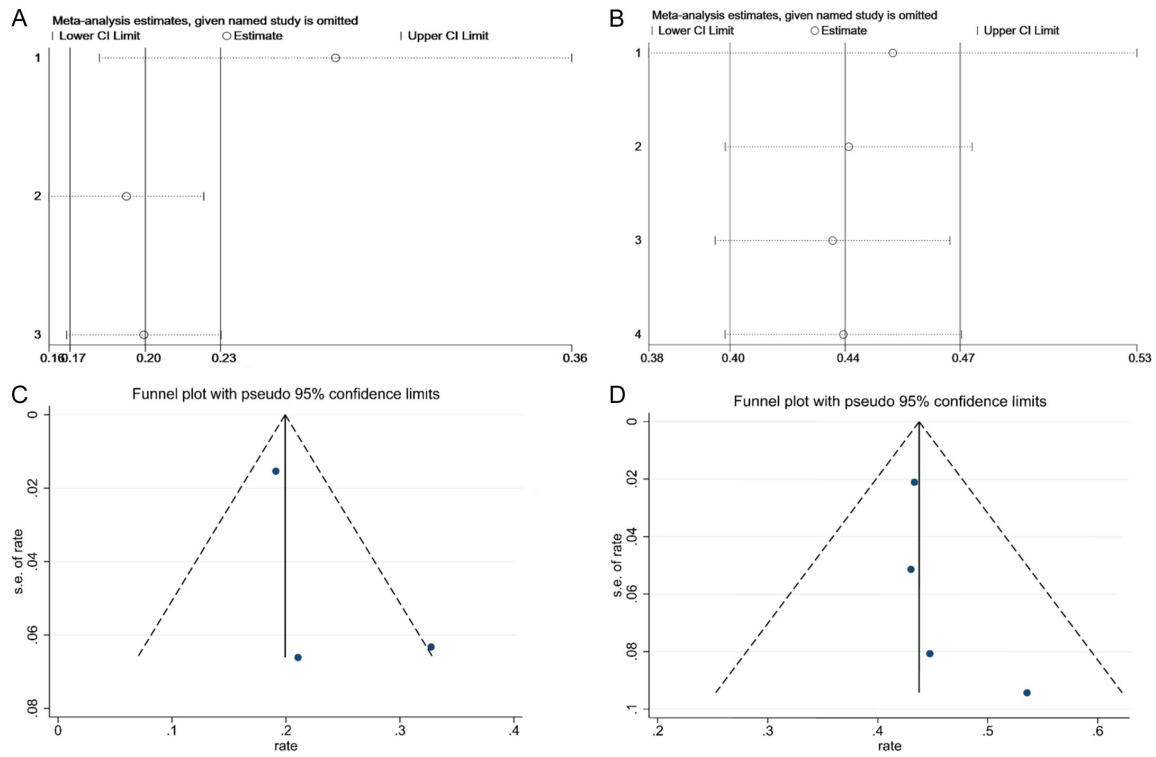

Figure 6. The sensitivity and funnel diagram of the low-risk group. A. Temsirolimus treatment group sensitivity analysis; B. Pazopanib treatment group sensitivity analysis; C. Temsirolimus treatment group funnel diagram; D. Pazopanib treatment group funnel diagram.

the analysis confirmed that the study still maintained reasonable stability; hence, the random-effects model was used. 3) Bias test. A funnel plot was constructed to examine publication bias. The symmetry test resulted in P=0.436 (>0.05), suggesting symmetry and no publication bias in the studies (**Figure 6C**). From this summary, the mortality rate for temsirolimus treatment in the low-risk group was 0.23 (95% CI, 0.15-0.31) (**Figure 5A**).

Pazopanib, low-risk group: 1) Heterogeneity test. The heterogeneity test for the four studies on advanced RCC treated with pazopanib indicated I^2=0.0% (<50%) and P>0.1 (**Figure 5B**), demonstrating no significant heterogeneity among the studies. A sensitivity analysis was subsequently performed to assess the accuracy and stability of the findings. 2) Sensitivity analysis. Sensitivity analysis of the four studies confirmed that none significantly affected the results of this meta-analysis, indicating robust stability (**Figure 6B**). Based on these results, the fixed-effect model was employed. 3) Test of bias. A funnel plot was constructed to examine potential publication bias. The symmetry test for this plot showed P=0.314 (>0.05), confirming that the funnel plot was symmetrical and indicating no publication bias in the studies (**Figure 6D**). In summary, the mortality rate for pazopanib in the low-risk group was 0.44 (95% CI, 0.40-0.47) (**Figure 5B**).

Discussion

Based on global ARCC phase III trials, the mTOR inhibitor temsirolimus is currently regarded as a first-line agent for patients with low-risk or non-clear cell mRCC [25]. Pazopanib has also been employed as a first-line TKI-targeted therapy for mRCC in a randomized phase III study [26]. Both medications are now primary treatments for RCC. By reviewing various studies, summarizing their findings, and conducting a meta-analysis, this research aims to identify the most appropriate patient populations for these drugs and provide scientific guidance for their clinical use.

This study presents a meta-analysis of the anti-tumor efficacy of temsirolimus and pazopanib in treating advanced RCC, primarily through

analyzing and comparing patient mortality rates.

According to our meta-analysis results, among high-risk patients with advanced RCC, the mortality rate for those treated with temsirolimus [8, 13-15] was 0.73 (95% CI, 0.69-0.76); for pazopanib [7, 16, 17], it was 0.67 (95% CI, 0.64-0.71). This suggests superior efficacy of pazopanib over temsirolimus in patients with poor physical conditions. The FLIPPER trial revealed that pazopanib serves as an effective and rational first-line treatment for patients with high-risk metastatic renal cell carcinoma (median PFS 4.5 months, median OS 9.3 months) [10], consistent with our team's findings. This aligns with pivotal temsirolimus trial outcomes [8]. The therapeutic efficacy of pazopanib primarily stems from its inhibition of tyrosine kinase receptors, including vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), thereby blocking tumor angiogenesis and suppressing tumor growth and metastasis [7]. Furthermore, the TemPa trial indicated that pazopanib demonstrates at least equivalent efficacy to temsirolimus. When selecting between these regimens, pazopanib should be prioritized as first-line therapy in high-risk patients (median PFS 5.2 months for pazopanib vs. 2.7 months for temsirolimus) [27]. However, it is noteworthy that crossover therapy in some study participants may confound the results. Additionally, a retrospective study in hypertensive and diabetic patients highlighted a significantly elevated risk of chronic kidney disease progression during tyrosine kinase inhibitor treatment for renal cell carcinoma [28]. Given that hypertension is a predominant adverse effect of pazopanib [10], preexisting comorbidities and drug-related toxicities may attenuate its clinical benefits.

For the low-risk group, the mortality rate for patients treated with temsirolimus [18-20] was 0.23 (95% CI, 0.15-0.31); for those treated with pazopanib, it was 0.44 (95% CI, 0.40-0.47) [21-24]. This indicates greater efficacy of temsirolimus compared to pazopanib in patients with better physical conditions. Temsirolizumab exerts its antitumor activity by inhibiting mTOR kinase, thereby disrupting signaling pathways critical for cellular growth and proliferation, and suppressing tumor cell survival. This mechanism demonstrates pronounced efficacy during the tumorigenic phase of neoplastic progression [6], further corroborating our research findings.

A randomized, open-label, phase III trial [29] compared the efficacy of temsirolimus, reporting a progression-free survival (PFS) of 10.7 months (95% CI, 8.5-13.0). Similarly, a study by Thomas E. Hutson [30] examined the efficacy of pazopanib in advanced RCC, recording a PFS of 13 months (95% CI, 11-15) for 225 patients. These studies demonstrate that both temsirolimus and pazopanib can extend PFS. However, the limited number of studies and differences in study duration constrain the accuracy of these comparisons. To reach definitive conclusions, further large-scale, well-designed randomized controlled trials are necessary.

Both temsirolimus and pazopanib are first-line treatments for RCC, but they are associated with varying degrees of side effects. In a phase III study by Hudes et al. [8], 626 previously untreated mRCC patients with poor prognosis were randomized to receive temsirolimus (25 mg weekly), IFN-α, or a combination of temsirolimus (15 mg weekly) and IFN-α. The most common adverse effects of temsirolimus included asthenia (51%), rash (46%), anemia (45%), nausea (37%), and anorexia (32%). Grade 3 or 4 toxicities in the temsirolimus group included asthenia (11%), dyspnea (9%), pain (5%), and infection (5%). The most frequent grade 3 or 4 laboratory adverse events were anemia (20%), hyperglycemia (11%), hyperlipidemia (3%), neutropenia (3%), and elevated serum creatinine (3%). Additionally, a phase III study of pazopanib by Sternberg et al. [26] involved 435 patients with locally advanced or metastatic renal cell carcinoma who were randomly assigned in a 2:1 ratio to receive pazopanib or placebo. The most common adverse effects in the pazopanib group were diarrhea (52%), hypertension (40%), hair color change (38%), nausea (26%), anorexia (22%), and vomiting (21%). Grade 3 or 4 adverse events occurred in 33% and 7% of pazopanib-treated patients, respectively, with hypertension (4%) and diarrhea (4%) being the most frequent grade 3 or 4 events. Arterial thrombotic events occurred in 3% of pazopanib-treated patients, including myocardial infarction/ischemia (2%), cerebrovascular accident (<1%), and transient ischemic attack (<1%). Most laboratory abnormalities in the pazopanib group were grade 1/2. Given pazopanib's significant hepatotoxicity

[21], caution is advised when prescribing it to patients with compromised liver function. The side effects of temsirolimus and pazopanib require further validation through large-sample randomized trials.

To mitigate the side effects of temsirolimus, adjunctive combination therapies with other drugs can be utilized. During temsirolimus treatment, hypoglycemic agents such as metformin (500 mg/day) [31] or insulin can alleviate hyperglycemia. Diphenhydramine is also administered to relieve nausea and vomiting, and its effectiveness may increase when given over a 24-hour period [31]. Ruiz-Morales et al. demonstrated that the newer drugs cabozantinib and nivolumab could improve clinical outcomes following the progression of pazopanib treatment [32], offering a novel approach to mitigating side effects post-pazopanib therapy.

However, our meta-analysis has several limitations. In the subgroup analysis, the I^2 for the subgroup that responded well to temsirolimus was >50%, indicating moderate heterogeneity. Sensitivity analysis was conducted to identify the sources of heterogeneity. Discussion revealed that the study by Sugiyama et al. [20] differed from the others [18, 19] in terms of timing, potentially leading to higher survival rates due to improved care levels. Additionally, Sugiyama et al. [20] included patients with unresectable or metastatic RCC, while the others focused on metastatic cases [18, 19]. Variations in patient populations among the studies could lead to different research outcomes. Two [19, 20] of the three studies involved Japanese patients, suggesting that regional differences might also influence results. Future research will concentrate on reducing the side effects of these drugs and evaluating the impact of combination therapies with other medications to guide clinical practice and enhance the quality of life for patients with RCC.

Michael Staehler's research demonstrates differential efficacy of pazopanib as first-line therapy: median PFS was 4.5 months in treatment-naïve patients [10] versus 6.7 months in those with prior targeted therapy exposure [33]. This suggests potential confounding in our analysis. Crucially, the primary studies included in our meta-analysis did not stratify outcomes by prior treatment status [18], precluding subgroup analysis on this variable - a recognized limitation of our work. Furthermore, inherent heterogeneity in real-world evidence (RWE) must be acknowledged when comparing clinical outcomes, whether intra- or inter-study [34]. As this study aims to reflect real-world practice, and targeted therapies constitute first-line treatment for advanced renal cell carcinoma, excluding pretreated patients would compromise clinical relevance. We therefore retained data from cohorts including pretreated individuals (e.g., Mehran Afshar et al. [17, 18]), consistent with methodologies in seminal RWE studies [34-36]. Notably, Byoung Chul Cho's work indicates that prior targeted therapy exposure did not significantly compromise pazopanib efficacy outcomes [37], suggesting limited impact of these patients on overall results and mitigating concerns regarding data inclusion.

Conclusion

This meta-analysis demonstrates significant risk-stratified heterogeneity in the anti-neoplastic efficacy between pazopanib and temsirolimus. Specifically, pazopanib exhibits superior tumor control in high-risk patient cohorts, while temsirolimus demonstrates enhanced therapeutic outcomes in low-risk populations, thereby providing evidence-based recommendations for risk-adapted therapeutic selection. We systematically analyzed Grade 3/4 adverse events for both agents: Pazopanib was predominantly associated with hypertension (7%), managed via dose adjustment and antihypertensive therapy, whereas temsirolimus primarily induced anemia (20%) and hyperglycemia (11%), necessitating close monitoring and prophylactic interventions. However, due to the limitations of this study, more high-quality research is needed to validate these findings.

Disclosure of conflict of interest

None.

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