DOI: 10.4081/aiua.2023.11672

SYSTEMATIC REVIEW

Impact of statin on renal cell carcinoma patients undergoing nephrectomy. Does it affect cancer progression and improves survival? A Systematic Review and Meta-Analysis

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Summary ***Introduction: Renal cell carcinoma (RCC) is regarded as one of the most common malignant tumors. Various concomitant medications in RCC patients undergoing surgery are investigated to explore the potential for improving survival and preventing disease recurrence, including statin. It has been observed that these drugs induce apoptosis, thereby inhibiting tumor growth and angiogenesis. We aimed to perform a systematic review and meta-analysis to enhance the level of evidence for statin in RCC.***

Methods: A systematic literature search was conducted in several online databases, including PubMed, Scopus, and Sciencedirect, using terms relevant to the use of statins in RCC patients undergoing nephrectomy for publications published up to July 2023, according to a registered review procedure (CRD42023452318). The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias of the included study. Review Manager 5.4 was used for all analyses.

Results: Seven articles was eligible for our study. The analysis revealed that patients receiving statin had a better overall survival compared to patients who does not receive statin (HR 0.71, 95% CI 0.51-0.97, p = 0.03, I2 = 76%). However, there was insignificant difference in terms of CSS, DFS, and PFS between RCC patients receiving statin and without statin.

Conclusions: Statin has substantial benefits for improving OS. Even though the outcomes for CSS, DFS, and PFS were insignificant, the potential role of statins as a supplementary therapy in surgically treated RCC still requires further investigation.

KEY WORDS: Statin; Renal cell carcinoma; Nephrectomy; Survival rate; Outcome.

Submitted 24 August 2023; Accepted 31 August 2023

INTRODUCTION

Renal cell carcinoma (RCC) is regarded as one of the most common malignant tumors, accounting for approximately 2% of all tumors and 90% of all kidney malignancies. Renal cancer is expected to remain a major threat to global health as the global incidence of this disease has been steadily growing in recent decades (1). In order to manage the disease, surgical resection of the tumor is the cornerstone treatment. As a curative or palliative treatment, surgical therapy is performed using either partial or radical nephrectomy techniques according to the staging of the disease (2, 3). Despite the fact that surgical resection of tumors in localized disease can be curative, disease progression and mortality could be up to 20% of patients after primary treatment, and therefore any intervention to improve the oncological outcomes would be considered a significant benefit (4). Several variables including age, race, gender, stage, grade, tumor size, performance status, and blood type, have been found as independent predictors of mortality after nephrectomy for locoregional RCC. Although these risk variables may provide useful prognostic information, they typically offer limited opportunity for intervention to modify the disease's trajectory (5, 6).Unlike in metastatic RCC, targeted therapy and immunotherapy such as *Vascular Endothelial Growth Factor* (VEGF) or *mammalian-target of rapamycin* (mTOR) inhibitor are shown to have minimal benefits in an adjuvant treatment scenario for localized RCC after surgery and a high-risk profile for disease recurrence (7-9). Given the high costs and limited availability of pharmacological development and clinical implementation of targeted therapies, the technique of *drug repositioning* (DR) of selected non-anticancer drugs is being investigated (10). Various concomitant medications in RCC patients undergoing surgery are investigated to explore the potential for improving survival and preventing disease recurrence, including insulin, beta-blockers, metformin, statins, and other therapies (11). Statins are the most widely used drugs for the treatment of hypercholesterolemia, and several authors discovered the anti-tumor activities in this medication. These drugs have been observed to induce apoptosis, thereby inhibiting tumor growth and angiogenesis (12). Even though the exact mechanism is still unclear, clinical trials have been conducted to explore the potential benefits of statin in several cancers such as lung cancer, liver cancer, and colorectal cancer (13-15). Several cohorts are also currently being conducted to evaluate the impact of statins on the oncological outcomes of RCC patients having surgery (5, 16-19). The results are encouraging but often conflicting, and there are currently no strong recommendations regarding the use of statins as either neo-adjuvant or adjuvant therapy in RCC. Therefore, we aimed to perform a systematic

review and meta-analysis to enhance the level of evidence for statin in RCC.

Methods

Review protocol and search strategy

This study evaluates the impact of statin on RCC patients who underwent nephrectomy on the oncological outcomes through systematic review and meta-analysis design (20), following the latest *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement in *PubMed*, *Science-direct*, and *Scopus*. The literature search followed *Medical Subject Headings* (MeSH®) Terms related to the use of statin in RCC patients who underwent nephrectomy for articles published up to July 2023. The protocol has been registered in *PROSPERO* (CRD42023452318).

Eligibility criteria for review

The inclusion criteria are (1) observational studies (2) evaluation of RCC patients who underwent open or laparoscopic. nephrectomy diagnosed with histopathological examination, (3) compare patients who receive statin and without statin (4) and reporting the outcome.

The outcomes analysed in this study were *overall survival* (OS), *cancer-specific survival* (CSS), *disease-free survival* (DFS), and *progression-free survival* (PFS). We excluded non-English studies, studies without full text, and duplicate studies.

Data extraction and risk of bias assessment

Baseline characteristics of the study were extracted by two independent authors, while the third author resolved all disagreements through a discussion. The extracted data consisting of publication details as first author name and year of publication, study design, sample size, and sample characteristics such as age, RCC grade, cell type, stage of RCC, and surgical methods were collected in spreadsheet software Microsoft Excel® 2021. The risk of bias was assessed with the *Newcastle-Ottawa Scale* (NOS), which has the domain of selection, comparison, and exposure.

Data analysis and presentation

The analysis effect size was estimated in a Forest plot with a *hazard ratio* (HR) with a 95% confidence interval (95% CI) and a p-value below 0.05 was considered statistically significant using the software *Review Manager 5.4* (*Cochrane Collaboration*).

Heterogeneity between studies was evaluated using I^2, where an I^2 value above 50% indicated high heterogeneity and a random-effects model was applied for pooled analysis.

Results

Study search

Our preliminary search found 298 results. Twenty-five full articles were retrieved for eligibility. Following the assessment of the full-text articles, sixteen were eliminated for several reasons, including differences in intervention, population, and incomplete data. The remaining seven publications were investigated further, as shown in Figure 1. The clinical characteristics of the included participants are described in Table 1.

Baseline characteristics and quality assessment

All of the included studies were retrospective cohorts. The majority of the populations of the included studies were American, ranging from 55-66 years. The type of statins that were used in the study comprised *Atorvastatin,*

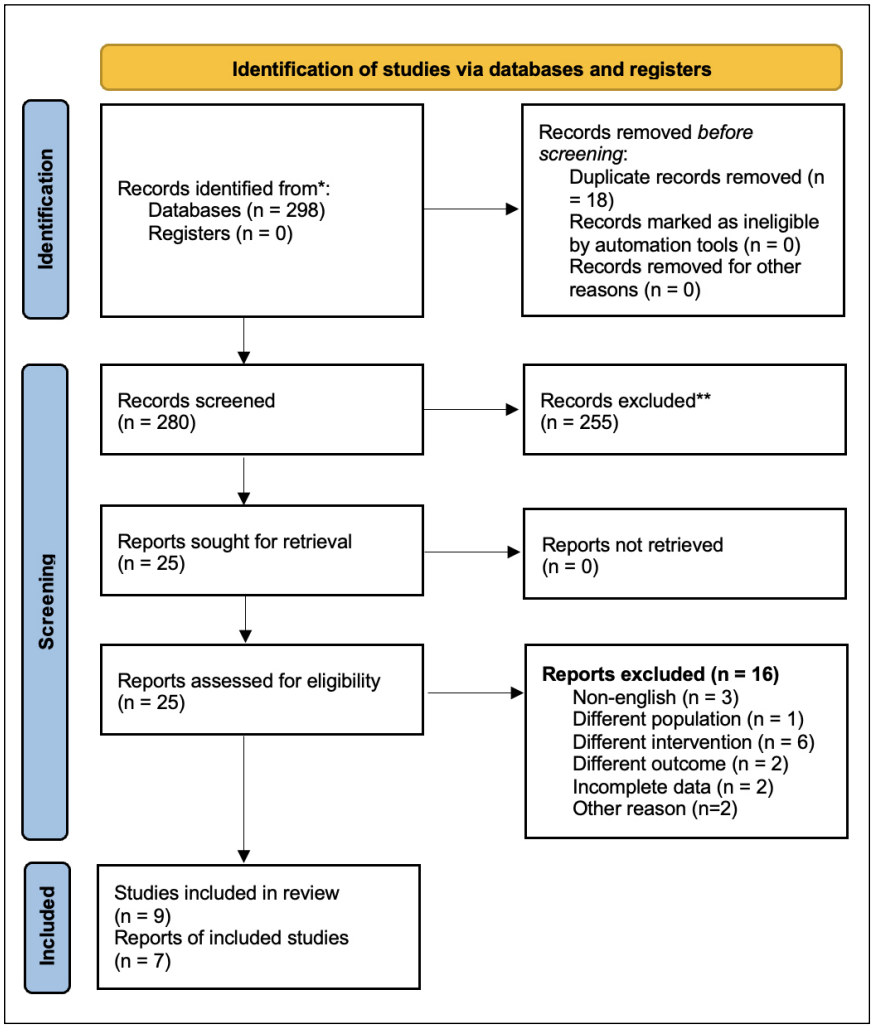


Figure 1.
Identification of included studies.

Table 1.
Baseline characteristics of the included study.

Author	Country	Study Type	Sample size (n)	Intervention	N	Age (years)	Follow Up (month) Median (IQR)	Nephrectomy (n)	Cancer histology	Outcome analyzed	Adjusted variable in multivariate analysis
Choi, 2012	Korea	Retrospective cohort	115	Statin Non Statin	21 94	58.95 ± 12.33 65.24 ± 6.82	40	Radical and Partial (115)	Clear Cell, Papillary, Chromophobe, Collecting Duct, Sarcomatoid	PFS, RFS	Age, gender, BMI
Hamilton, 2013	America	Retrospective cohort	2608	Statin Non Statin	708 1900	66 (59-72) 59 (50-68)	36	Radical (1580) Partial (1028)	Clear Cell, Papillary, Chromophobe, Unclassified	Progression, overall mortality	Age, gender, race, type of surgery, commorbidity, renal function, tumor stage, year of surgery, local and systemic symptoms
Kaffenberg, 2014	America	Retrospective cohort	916	Statin Non Statin	270 646	60.8 (51.3-69.3)	42.5 (19.1-67.1)	Radical (584) Partial (332)	Clear Cell, Non-Clear Cell	DSS, OS	Age, ASA score, staging, nodes, metastatic status, blood group, corrected hypercalcemia
Viers, 2015	America	Retrospective cohort	2357	Statin Non Statin	630 1727	66 (59-73) 61 (52-70)	93.6 (63.6-134.4)	Radical (1727) Partial (630)	Clear Cell, Papillary, Chromophobe, Clear Cell, Mucinous-Spindle Cell. Translocation-Associated Collecting Duct, NOS	PFS, CSS, OS	Age, gender, type of surgery, smoking status, tumor stage, tumor grade, sarcomatoid differentiation
Haddad, 2015	America	Retrospective cohort	850	Statin Non Statin	342 508	62 (19-92) 55 (20-87)	25 (7.8-52.3)	Radical (384) Partial (466)	Clear cell, Non-Clear Cell	RFS,OS	Tumor stage, tumor grade, lymphovascular invasion, LDL, TG
Nayan, 2016	Canada	Retrospective cohort	839	Statin Non Statin	259 634	66 ± 16 57 ± 18	47 (20-80)	Radical (477) Partial (259)	Clear Cell, Papillary, Chromophobe, Unclassified	DFS, CSS, OS	Age, gender, type of surgery, tumor stage
Berquist, 2017	America	Retrospective cohort	283	Statin Non Statin	180 103	57.5 ± 15	68 (50-90)	Radical (204) Partial (77)	Clear Cell, Papillary, Chromophobe RCC, Other histology	DFS	Tumor stage and grade
Neumann, 2019	Germany	Retrospective cohort	388	Statin Non Statin	207 39	64.26 (17.12-90.32)	57.93 (0-237.18)	Radical Partial	Clear Cell	OS	Commedication, tumor stage,
Haide, 2019	Germany	Retrospective cohort	104	Statin Non Statin	41 63	62 (53-70	35.4 (12.3-73.3)	Radical Partial	Clear Cell, Non-Clear Cell	CSS	Tumor stage, hypertension

Table 2.
Quality assessment using Newcastle-ottawa scale.

Author	Selection	Comparability	Exposure	Score
Berquist, 2017	***	**	***	8
Haddad, 2015	****	**	**	8
Choi, 2012	***	*	*	5
Hamilton, 2013	****	**	**	8
Kaffenberger, 2014	***	**	***	8
Nayan, 2016	****	**	****	9
Neumann, 2019	***	**	***	8
Viers, 2015	***	**	***	8
Haide, 2019	***	**	***	8

Simvastatin, Lovastatin, Pravastatin, Rosuvastatin, Fluvastatin, and *Cerivastatin*. The techniques used for surgical resection were varied such as open, laparoscopic, and robotic approach. The follow-up of the studies ranged from 25 to 93 months. The risk of bias assessed using NOS revealed a moderate score ranging from 5 to 9, with a median of 7 as presented in Table 2.

Impact of statin on overall survival

Six articles were included in the analysis of overall survival using the random-effect model, as presented in Figure 2.

Figure 2.
Impact of statin on Overall Survival.

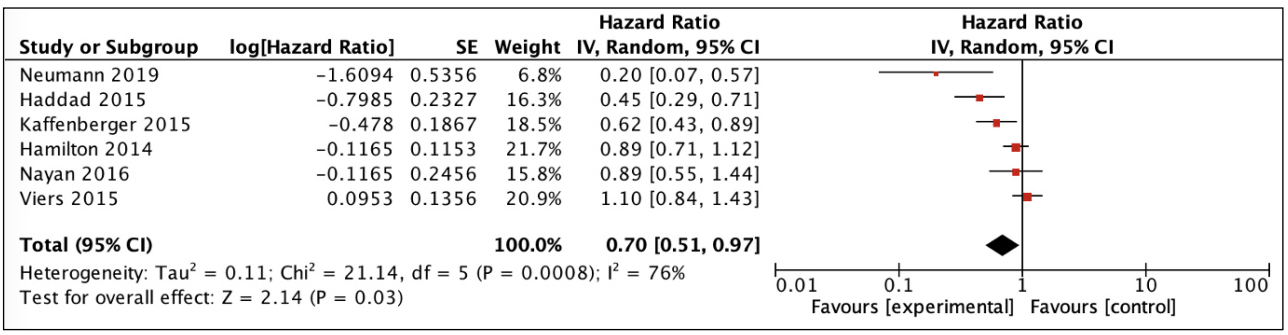


Figure 3.
Impact of statin on cancer-specific survival.

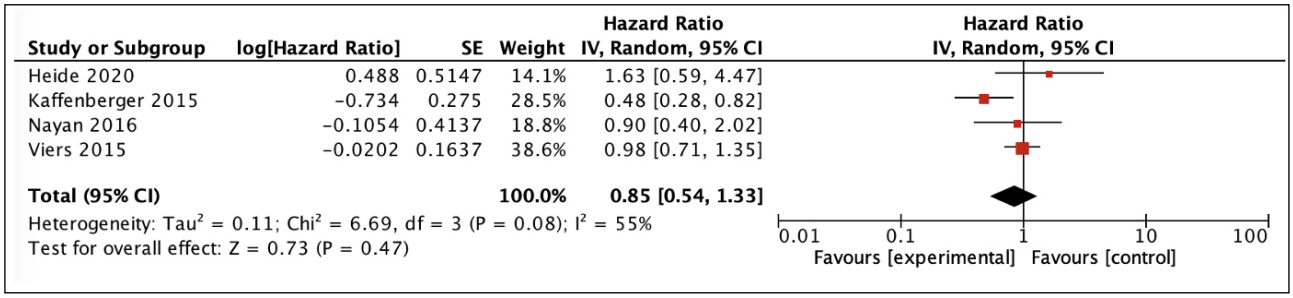


Figure 4.
Impact of statin on disease-free survival.

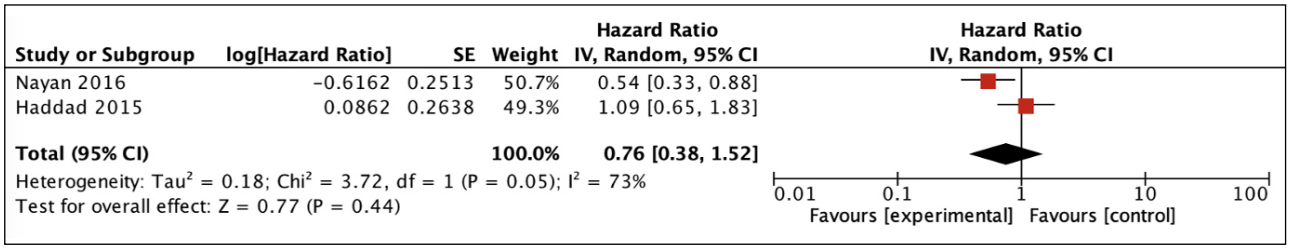
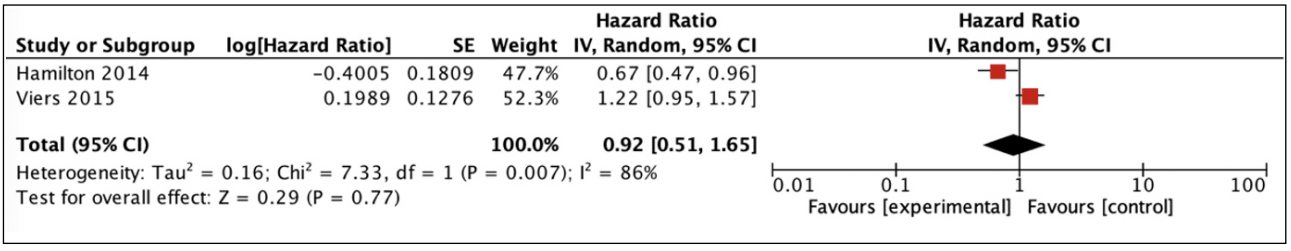


Figure 5.
Impact of statin on progression-free survival.



The meta-analysis revealed that RCC patients receiving statin had better overall survival compared to patients who did not receive statin (HR 0.71, 95% CI 0.51-0.97, p = 0.03, I^2 = 76%).

Impact of statin on cancer-specific survival, disease-free survival, and progression-free survival

Four studies were included in the analysis of CSS.

The meta-analysis using the random-effects model in Figure 3 revealed that there was an insignificant difference in terms of CSS between RCC patients receiving statin and those without statin (HR: 0.85 95% CI 0.54-1.33, p = 0.47, I^2 = 55%). Analysis of DFS was performed using two studies.

The meta-analysis result using the random-effects model in Figure 4 showed that there was an insignificant difference in terms of DFS between RCC patients receiving statin and without statin (HR: 0.76 95% CI 0.38-1.52; p = 0.44, I^2 = 73%). Based on the result from the Forest plot shown in the Figure 5, there was an insignificant difference in PFS between RCC patients receiving statin and those without statin (HR: 0.92 95% CI 0.51-1.65; p = 0.77, I^2 = 86%).

Discussion

This meta-analysis includes seven retrospective cohorts investigating oncological outcomes in the form of OS, DFS, CSS, and PFS in statin administration in surgically treated RCC patients (5, 11, 16-19, 21). The pooled analysis revealed that RCC patients receiving statin had a better OS compared to patients who did not receive statin, while there are no differences in DFS, CSS, and PFS. Overall survival is a critical parameter for evaluating the efficacy, safety, and clinical benefits of a cancer intervention. The effect of statins on improving OS has been explored in many tumors in urology, including patients with RCC, although investigations in RCC patients having nephrectomy were limited to a retrospective cohort and the results were contradictory. Based on the results of combined observational studies, we discovered higher overall survival in RCC patients who received statin therapy compared to those without statins. The results of this meta-analysis are consistent with the previous meta-analysis by *Nayan et al.* which reported that statins were significantly associated with an improvement in OS in all patients kidney cancer patients with HR of 0.74 (22). Our finding also aligns with a recent meta-analysis conducted

by *Luo et al.* (23), who incorporated 35 studies to evaluate on the beneficial effects of statins in various urological cancers and discovered a significant improvement in OS in patients with RCC and bladder cancer. However, *Wu et al.* (24) observed no significant difference in OS in RCC patients, but their analysis only included American cohorts, which can be biased if generalized in the global population. The strength of the current analysis is that this review mainly focused on RCC patients undergoing surgical treatment, whereas prior meta-analyses included all RCC patients, surgical or non-surgical (22). Statin improves the OS of RCC patients undergoing surgery by several mechanisms. One possible mechanism of statins in improving the OS of cancer patients is by inhibiting the proliferation and progression of RCC and inducing apoptosis of cancer cells thereby directly improving OS (11). Another possible mechanism is lowering cholesterol levels by blocking the active site of the HMG-CoA reductase enzyme, reducing the risk of coronary artery blockage and deadly cardiovascular events such as myocardial infarction or stroke which indirectly improves OS (17). Tumor cells can activate the coagulation process by releasing procoagulants, tissue factors, and fibrinolytic proteins, or by invading the vessel wall. In cancer patients including RCC, increased blood hypercoagulation can occur which causes an increased risk of arterial thrombosis and thromboembolic events, whereas one of the ways statins reduce death is by preventing thrombosis (17). Furthermore, our study tried to evaluate comprehensively the synergistic effect of statin in RCC patients receiving targeted therapy. *McKay et al.* (25) discovered that patients who had targeted therapies and concomitant statins had improved OS compared to non-statin patients (25.6 *versus* 18.9 months, respectively) with insignificant differences in drug-related toxicity. Although statin has been proven to improve the OS, this parameter has a weakness because it can be affected by bias from external factors and confounding factors.

There is currently no high level of evidence demonstrating the advantage of adjuvant radiation therapy, VEGFR, or mTOR inhibitors for improving survival, and these treatments are not recommended in adjunctive contexts due to unfavorable tolerability. Given that a third of RCC patients will develop recurrence or advancement after nephrectomy, any adjunctive therapies to reduce the progression and improve cancer-related survival were considered a substantial benefit.

In this study, we assessed the effects of statin as adjunctive therapy on several other oncology outcomes including PFS, DFS, and CSS. Based on the results of the combined analysis, we found that statins had an insignificant effect on CSS in RCC patients undergoing nephrectomy procedures ($p = 0.47$). These results differ from a meta-analysis study by *Nayan et al.*, which found that statins were significantly associated with improved cancer-specific survival (HR 0.67) (26). The discrepancy could be attributed to several factors, including the inclusion of non-surgically treated RCC in the earlier review. According to the literature, the outcome of CSS in patients with surgically treated and non-surgically treated RCC differs, therefore combining the populations may have resulted in bias. After performing a combined analysis using Forest plots, we found that statins had no significant effect on DFS and PFS in RCC patients undergoing nephrectomy. These results are in accordance with a meta-analysis by *Nayan et al.* which included 2 studies, with the result that there was no relationship between statin administration in PFS and DFS in RCC patients in general (22).

Various statin mechanisms for reducing cancer progression and death in RCC patients have been discussed in the literature. Statins have previously been proven in vitro and in vivo to reduce proliferation, angiogenesis, and tumor invasion, thereby reducing cancer growth (27). Data suggests that in general statin reduces cancer growth by two possible mechanisms, including cholesterol-dependent and cholesterol-independent pathways. Statins limit mevalonate production and the generation of downstream lipid isoprenoid intermediates in the HMG-CoA pathway. The latter chemical regulates angiogenesis, apoptosis, and inflammation. In the cholesterol-independent process, interactions with proteasomes and lymphocyte-function antigen 1 agents have impacts on invasion, cell adhesion, inflammation, and proliferation. The latest evidence suggests that statins can decrease RCC cell growth by prompting cell cycle arrest and apoptosis in a dose and time-dependent manner. Furthermore, statins suppress the phosphorylation of AKT, mTOR, and ERK, resulting in decreased RCC cell motility (28).

Although there are various mechanisms through which statins have been shown to prevent cancer progression, in this meta-analysis, we discovered that statins did not provide substantial benefits in preventing cancer progression. The insignificant results in this study could be attributed to lower statin bioavailability due to liver metabolism and variations in lipid metabolism in RCC (29). Statins are selectively absorbed by the liver, with less than 5% of the provided dose reaching the systemic circulation, resulting in limited statin penetrating RCC cells (28).

Furthermore, lipid metabolism in RCC differs from that of other cancers. RCC has much lower expression of cholesterol synthase proteins including *HMG-CoA reductase* (HMGCR) than adjacent normal tissues (30). In fact, the major mechanism of statins is HMGCR downregulation. This might explain the reason that statins have a lower impact on RCC than on other forms of cancer. Statin plasma levels depend on dose, statin type, and liver function. The higher the dose the higher level of statin in the plasma. Lipophilic statin (atorvastatin, simvastatin, lovastatin, fluvastatin, and pitavastatin) tends to have higher uptake in the liver than hydrophilic statin (pravastatin and rosuvastatin) which can affect the liver function and rising the creatinine kinase level (28). Statin plasma levels are higher in altered liver function patients due to reduced statin metabolism and transport activities (31).

In general, this review provided evidence of the beneficial effect of statin on improving the OS of surgically treated RCC patients. Despite the insignificant result of CSS, DFS, and PFS, the potential role of statins as adjunctive therapy in surgically treated RCC still needs to be explored. This meta-analysis provides support for future prospective and randomized controlled studies to evaluate the potential benefit of statins in extending the survival of surgically treated RCC patients, especially when

considering the limited efficacy and toxicity of targeted therapies in adjunctive settings.

There are several limitations to this review. This review was confined only to retrospective cohort studies, which cannot establish causality. Furthermore, there was significant heterogeneity among the studies due to variation of histological subgroups, surgical technique, intervention protocol, and RCC stage, which we could not further analyze using subgroups analysis due to the lack of data. Moreover, the several included studies were conducted on small sample size and in a single institution. Therefore, larger cohorts, and multi-institutional or population-based research are necessary.

Conclusions

In the context of limited recommendations for adjunctive immunotherapy or targeted therapy for improving OS of surgically treated RCC patients, the present review highlights the substantial benefits of statin for improving OS in this population. Even though the outcomes for CSS, DFS, and PFS were insignificant, the potential role of statins as a supplementary therapy in surgically treated RCC still requires further investigation. To confirm the beneficial effects of statin on surgically treated RCC more evidence from prospective and clinical studies may be required.

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Conflict of interest: The authors declare no potential conflict of interest.