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The effect of metformin administration on cancer-specific survival, overall survival, progression-free survival, and disease progression in renal cell carcinoma patients; a systematic review and meta-analysis

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ABSTRACT

Introduction: The increase in the incidence of renal cell carcinoma (RCC) has been reported worldwide. The anti-cancer impacts of metformin on the various types of cancer have been observed in clinical studies. Therefore, this study aims to survey the effect of metformin use on RCC patients using systematic review and meta-analysis methods.

Materials and Methods: In this research, Cochrane, Web of Science, PubMed, Scopus databases, and Google Scholar web browser were searched using standard keywords. Data were analyzed with STATA 14 software. The significance level of tests $P<0.05$ was considered.

Results: The improvement in the progression-free survival (PFS) (HR: 0.72 [95% CI: 0.54, 0.94], $P=0.169$, $I^2=37.8\%$) and cancer-specific survival (CSS) (HR: 0.36 [95% CI: 0.18, 0.75], $P=0.339$, $I^2=7.5\%$) was observed in eight studies with 10404 patients affected by RCC. However, no significant statistical effect was observed on the improvement in the disease progression (OR: 1.10 [95% CI: 0.85, 1.42], $P=0.326$, $I^2=0\%$) and cancer overall survival (OS) (HR: 0.72 (95% CI: 0.51, 1.01), $P=0.153$, $I^2=43.1\%$).

Conclusion: This study showed metformin administration improved CSS and PFS in RCC patients. More studies are warranted on the effect of metformin on the improvement in disease progression and OS of cancer.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID= CRD42022369108; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022369108).

Implication for health policy/practice/research/medical education:
The results of this study indicated that metformin affects the improvement in cancer-specific survival (CSS) and progression-free survival (PFS) of the disease in patients with renal cell carcinoma (RCC). The usefulness of this drug was proved in this study. In contrast, no advantage or significant impact was observed in the disease progression and overall survival of cancer improvement. There were limited number of studies on this subject. In addition, in each of the reviewed studies, the effect of metformin on some of the following cases of CSS, overall survival, PFS, and disease progression was not mentioned, therefore, it is recommended further researchers on this aspect of metformin.

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Meta-analysis

Introduction

Renal cell cancer (RCC) is the most common type of renal cancer, which includes about 85% of all renal cancers (1). The highly proliferative and metastatic renal tumor cells account for 3.8% of all new cancers (2). The incidence of this cancer in Europe and the US is significantly higher than in Asian countries and lower in Japan and India (3,4).

The incidence of RCC in men is more than in women (5). The other risk factors for this disease include smoking (6), obesity (7), and high blood pressure (8). Considering the death of about half of these patients within 5-years after diagnosis (9), the importance of investigating this subject has increased.

Metformin, a biguanide anti-hyperglycemic agent, can be effective in patients with type 2 diabetes (T2D) treatment for more than 30 years (10). Some studies have shown the anti-tumor effects of this drug in cancers, including breast, colorectal, lung, prostate, and endometrial (11, 12). Although there is much evidence of the clinical use of metformin in other tumors, no published clinical study has been reported in the field on the effect of metformin on the results of renal cell carcinoma (RCC) patients systematically (13). This meta-analysis aims to survey the effect of metformin use on RCC.

Materials and Methods

Study design

In this study, the relationship between metformin and RCC in patients with T2D is to be investigated.

Search strategy

In this meta-analysis, Google Scholar web browser and Scopus, Cochrane, Web of Science, and PubMed databases were searched without time and language restrictions. The search strategy phase was performed using the standard keywords "cancer-specific survival, overall survival, progression-free survival, disease progression, metformin, renal cell carcinoma" and the search was updated to 10.10.2022. Keywords were searched using Boolean operators "AND" and "OR". Reference lists of all primary studies were screened in a manual search. For example, the search strategy in the PubMed database is given below: ((Cancer-Specific Survival [Title/Abstract] OR Overall Survival [Title/Abstract] OR Progression-Free Survival[Title/Abstract] OR Disease Progression[Title/Abstract]) AND (Metformin[Title/Abstract])) AND (Renal Cell Carcinoma[Title/Abstract]).

PICO components

Population: Patients with T2D, Intervention: Metformin, Comparison: Patients who do not use metformin, Outcomes; cancer-specific survival, overall survival, progression-free survival, and disease progression.

Inclusion criteria

Studies that investigated the relationship between metformin and RCC were included in the meta-analysis.

Exclusion criteria

Case-report studies; not having enough data for analysis; lack of full text of some studies; Low quality of studies based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist; Studies that examined the effect of metformin and another drug at the same time.

Qualitative assessment

Two researchers independently evaluated the quality of the studies based on the standard STROBE checklist (14). This checklist has 22 parts that cover different parts of a report. If the total score is between 1 and 15, it is low quality, if it is between 16 and 30, it is medium quality, and if it is between 31 and 44, it is considered high quality. The cut-off point of the Strobe checklist in the current study was 15.

Data extraction

In the data extraction stage, two researchers separately extracted the data required for meta-analysis from the analyzed studies. For this purpose, the researchers designed a checklist that included author's name, number of men and women, year of publication, type of study, average age, country, sample size, OR (HR) between metformin use and RCC, etc. In order to resolve the difference between the data extracted by the two previous researchers, the third researcher evaluates the data impartially.

Statistical analysis

Odds ratio (OR) or hazard ratio (HR) was conducted to examine the relationship between metformin use and RCC. To combine the results of different studies, the logarithm of OR (HR) of each study was used. The heterogeneity of the studies was evaluated using the I^2 index and Cochrane's Q-test. Data were analyzed using STATA 14 software. The significance level of the tests was considered $P<0.05$.

Results

In the first stage, 301 articles were searched. After reviewing the titles of the studies, 134 duplicate studies were excluded. The abstracts of 167 articles were reviewed and 44 other articles were excluded in the full text review stage. The full text of 123 articles was evaluated and another 115 articles were excluded based on the exclusion criteria. Finally, 8 articles that had the desired quality entered the meta-analysis phase (Figure 1).

Table 1 shows one case-control study and seven cohort studies out of eight published ones from 2013 to 2022. The total number of samples was 10 404 cases, which 7000 men and 3404 women were among them.

Metformin use by patients with RCC resulted in improvement progression-free survival (PFS) (HR: 0.72;

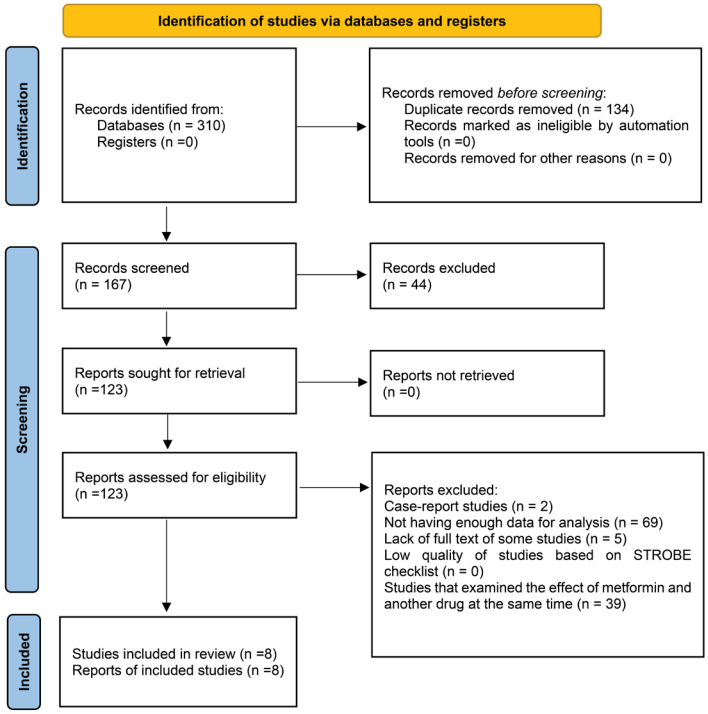

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

95% CI: 0.54, 0.94) and cancer-specific survival (CSS) (HR: 0.36; 95% CI: 0.18, 0.75) (Figures 2A and 2B). However, it had no significant effect on the improvement in the disease progression and overall survival (OS) of cancer (HR: 0.72; 95% CI: 0.51, 1.01) (Figures 2C and 2D).

Discussion

In eight studies with a total of 10 404 people, we concluded that the use of metformin improves CSS and PFS in patients with RCC. The anticancer activity of metformin has two aspects. On the one hand, its direct effect on tumor cells and on the other hand, its indirect effect on the host based on the reduction of blood glucose and insulin and anti-inflammatory effects (22,23). Following, the meta-analyses published in the field of "the effect of metformin on urology field cancers" will be discussed and reviewed.

The meta-analysis by Hu et al included nine studies with 1 270 179 patients with bladder cancer and showed that metformin use is relationship with an increase in recurrence-free survival (HR = 0.55, 95% CI = 0.35–0.88), PFS improvement (HR = 0.70, 95% CI = 0.51–0.96), and long-term CSS (HR = 0.57, 95% CI=0.40–0.81). Although, it was not relationship with a decrease in the incidence of bladder cancer (HR = 0.82, 95% CI = 0.61–1.09) or OS of this disease (HR = 0.83, 95% CI = 0.47–1.44) (24) , which is consistent with the result of our research.

The results of the survey by Li et al on 254 329 patients affected by kidney cancer showed that metformin use could improve OS (HR = 0.64, 95% CI: 0.52–0.79) and CSS (HR = 0.61, 95% CI: 0.44–0.85). The administration of metformin contributed to a decrease in the risk of death in patients with kidney cancer (HR = 0.71, 95% CI: 0.56–0.89) (25). Another study in the kidney cancer field indicated an effective impact on DP improvement (HR = 0:80; 95%

Table 1. Basic information contained in the reviewed studies

Author, year of publication	Type of study	Country	Sample size	Number of females	Number of males	Mean age (year)
Becker C, 2017 (15)	Case–control	UK	3506	1407	2099	<90
Psutka SP, 2015 (13)	Cohort	USA	283	88	195	67
Santoni M, 2022 (16)	Cohort	Italy, Spain, USA	304	80	224	65
Hamieh L, 2017 (17)	Cohort	USA	4736	1373	3363	61.5
Nayan M, 2017 (18)	Cohort	Canada	158	45	113	64
Fiala O, 2021 (19)	Cohort	Czech Republic	343	88	255	65
Ari Hakimi A, 2013 (20)	Cohort	USA	784	235	549	62
Cheng JJ, 2016 (21)	Cohort	Singapore	290	88	202	59.4

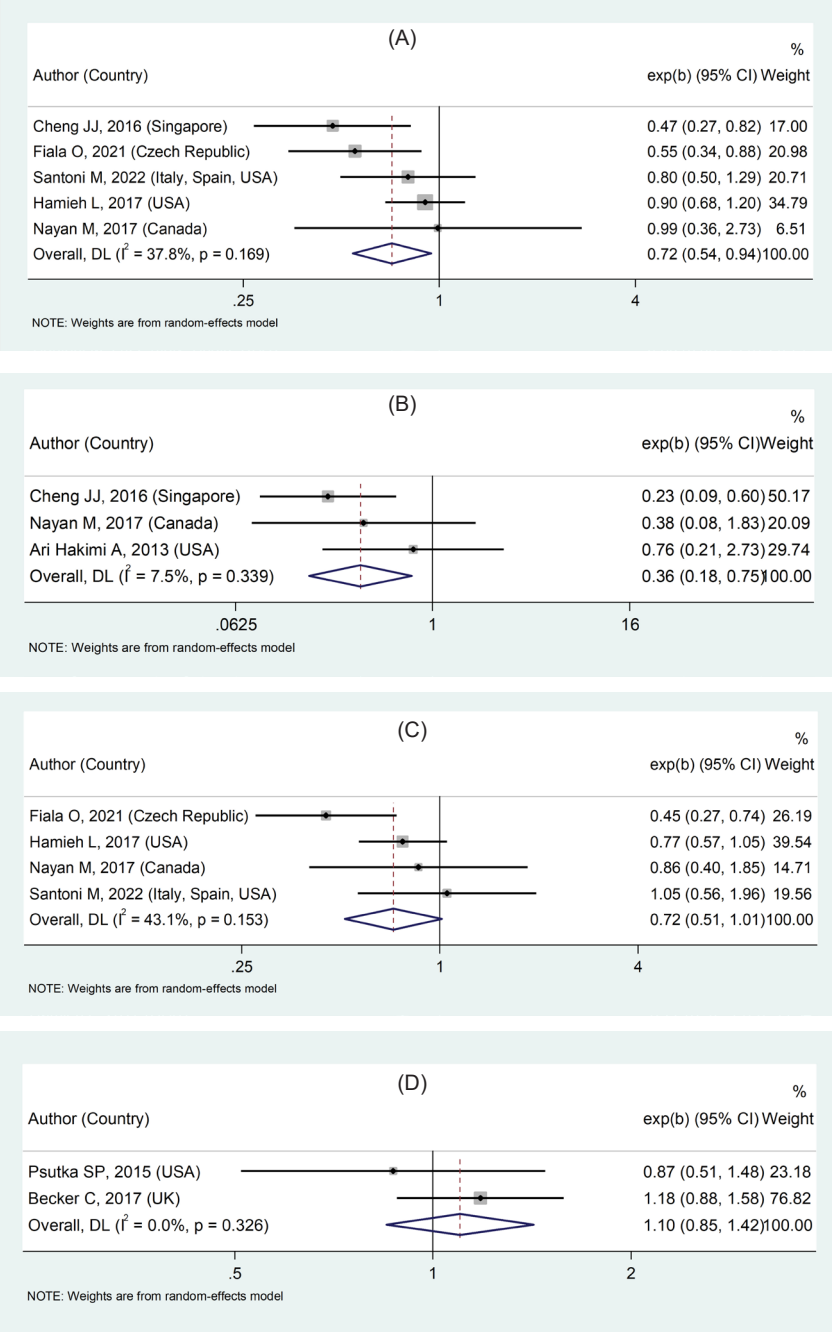

Figure 2. (A) Graph of the effect of metformin on progression-free survival (PFS) and its 95% CI in RCC patients. (B) Graph of the effect of metformin on cancer-specific survival (CSS) and its 95% CI in RCC patients. (C) Graph of the effect of metformin on overall survival (OS) and its 95% CI in RCC patients. (D) Graph of the effect of metformin on disease progression and its 95% CI in RCC patients.

CI: 0.65-0.98) (26). The pieces of evidence demonstrate the beneficial and positive effects of metformin use on patients with renal cancer, which can prove this drug's role in improving various tumors.

The recent meta-analysis by Liu et al included 12 studies and 1 552 773 patients and surveyed the long-term effect of metformin use on bladder cancer. The results of this study showed that the use of metformin can decrease the incidence of bladder cancer (OR = 0.45, 95% CI: 0.37–0.56) and increase recurrence-free survival (HR = 0.56, 95% CI: 0.41–0.76). Although, it had no significant protective effect on OS (HR = 0.93, 95% CI: 0.67–1.28), CSS (HR = 0.73, 95% CI: 0.47–1.16), and PFS (HR = 0.78, 95% CI: 0.53–1.15) (27). There is a controversy in the published meta-analysis results on the impact of metformin on bladder cancer. Factors such as type of study, age group of patients, and duration of metformin use and its dosage are involved in this controversy.

In the meta-analysis of Xiao et al, the relationship between metformin administration and the prognosis of

prostate cancer in 13 cohort studies with 177 490 patients was studied. The pooled HRs for OS and CSS were 0.79 (95% CI: 0.63–0.98) and 0.76 (95% CI: 0.57–1.02), respectively (28). The meta-analysis by He et al aimed to survey the relationship between metformin and prostate cancer, and 30 cohort studies including 1 660 795 patients were included in this study. Based on the results of metformin therapy, the improvements in OS (HR = 0.72, 95% CI: 0.59–0.88), CSS (HR = 0.78, 95% CI: 0.64–0.94), and recurrence-free survival (HR = 0.60, 95% CI: 0.42–0.87) in prostate cancer were observed compared to the non-metformin therapy. Furthermore, metformin use did not contribute to a decrease in the incidence of prostate cancer (HR = 0.86, 95% CI: 0.55–1.34) (29).

The results of the study by Yao et al, regarding meta-analysis of prostate cancer showed that the recurrence risk of patients who use metformin is lower and their disease-specific survival and OS (HR = 0:74; 95% CI: 0.61-0.90), CSS (HR = 0:74; 95% CI: 0.61-0.91), and OS (HR = 0:76; 95% CI: 0.65-0.90) have been improved (26). Metformin could improve the OS rate of patients with prostate cancer. There is still a challenge in the field of the metformin effect on CSS and more studies are necessary.

Conclusion

The results of this study indicated that metformin affects the improvement in CSS and progression-free survival of the disease in patients with RCC. The usefulness of this drug was proved in this study. In contrast, no advantage or significant impact was observed in the disease progression and OS of cancer improvement. According to the limited number of studies and since, in each of the reviewed studies, the effect of metformin on some of the following cases of CSS, OS, progression-free survival, and disease progression was not mentioned, therefore, it is recommended further researchers on this aspect of metformin.

Limitations of the study

There was no information on the effect of metformin on RCC based on subgroups, including gender, age group, duration of metformin administration, and dose of this drug. No analysis was presented based on these subgroups in this study.

Authors' contribution

Conceptualization: MF, DS, TJ, ZA and HN.
Methodology: DS, and SHA.
Formal analysis: DS and MF.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no conflict of interest regarding the contents of this article.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (ID: CRD42022369108, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022369108). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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