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META-ANALYSIS

Prognostic role of metformin in diabetes mellitus type 2 patients with hepatocellular carcinoma: A systematic review and meta-analysis

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is among the commonest malignancies associated with significant cancer-related death. The identification of chemo-preventive agents following HCC treatments with the potential to lower the risk of HCC adverse course is intriguing. Metformin, a first-line agent used in the treatment of type 2 diabetes mellitus (T2DM), has been associated with inhibition of HCC growth.

AIM

To determine whether metformin can prevent adverse events (*i.e.,* death, tumor progression, and recurrence) after any HCC treatment in T2DM patients.

METHODS

A systematic review of the published literature was undertaken focused on the role of metformin on outcomes in patients with T2DM and HCC receiving any tumor therapy. A search of the PubMed and Cochrane Central Register of Controlled Trials Databases was conducted.

RESULTS

A total of 13 studies (n = 14886 patients) were included in this review. With regard to the risk of death, a decreased risk was reported in cases receiving metformin, although this decrease was not statistically significant [odds ratio (OR) = 0.89, P =

0.42]. When only patients treated with curative strategies were considered, a more marked correlation between metformin and favorable cases was reported (OR = 0.70, *P* = 0.068). When analyzing palliative treatment, there was no statistical significance in terms of the correlation between metformin and favorable cases (OR = 0.74, *P* = 0.66). As for the risks of progressive disease and recurrence, no obvious correlation between metformin use and reduced risk was reported. When sub-analyses were performed for patients from different regions, the results for patients from Eastern countries showed a tendency for decreased risk of death in T2DM cases receiving metformin (OR = 0.69, *P* = 0.17), but the same was not seen in patients from Western countries (OR = 1.19, *P* = 0.31).

CONCLUSION

Metformin failed to show a marked impact in preventing adverse effects after HCC treatment. A trend was reported in T2DM cases receiving curative therapies in relation to the risk of death, especially in patients from Eastern regions. Great heterogeneity was reported among the different studies. Further large studies are required to definitively clarify the real impact of metformin as a chemopreventive agent for HCC.

Key Words: Hepatocellular carcinoma; Metformin; Type 2 diabetes mellitus; Death; Recurrence; Progression; Treatment

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Core Tip: The identification of chemopreventive agents following hepatocellular carcinoma (HCC) treatments with the potential to lower the risk of its adverse course is of paramount relevance. Among them, metformin has been recently examined in this setting. The present systematic review and meta-analysis aim to determine the role of metformin in preventing HCC adverse events (*i.e.*, death, tumor progression, and recurrence). Metformin only showed statistical significance as a protective factor for the risk of death in patients receiving curative therapies for HCC, but failed as a protective agent for progressive disease and recurrence. Further large studies are required to definitively clarify the real impact of metformin as a chemopreventive agent for HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC), with an estimated incidence of > 1 million cases, is among the commonest malignancies worldwide and is still associated with significant cancer-related death[1,2]. The major risk factor for developing HCC is advanced liver disease due to various etiologies such as alcohol or viral disease (hepatitis C and B). In addition, non-alcoholic steatohepatitis (NASH), associated with metabolic syndrome, obesity, and diabetes mellitus, is becoming increasingly important for HCC development. In addition, it represents the fastest-growing cause of HCC in westernized and sedentary-lifestyle regions of the world. Moreover, the comorbidities associated with nonalcoholic fatty liver disease (NAFLD) and cardiovascular diseases promote HCC development and negatively influence patients' outcomes[3-6]. Indeed, while HCC predominantly occurs in the setting of chronic liver disease and cirrhosis (80%), in up to 20% of cases, especially those with metabolic syndrome [obesity, type 2 diabetes mellitus (T2DM), and NAFLD] it emerges much earlier, during non-cirrhotic liver disease stages[7].

Several proposed mechanisms explain the relationship between NAFLD-associated comorbidities and HCC development. Among them, insulin resistance, insulin-like growth factor (IGF) related factors, chronic inflammation and proinflammatory cytokines, oxidative stress, dysbiosis of gut microbiota, intrahepatic fat accumulation, inhibition of cell apoptosis and autophagy together with enhanced angiogenesis might play a key link[8-10]. A large retrospective cohort study following over 85000 patients with NAFLD and concomitant diabetes for an average of 10 years showed that good glycemic control (hemoglobin A1c < 7%) not only results in a reduction of micro- and macrovascular diabetes-related complications but can also lower the risk of HCC by 31% [hazard ratio = 0.69; 95% confidence interval (CI): 0.62-0.78][11].

In addition to being a significant risk factor for HCC development, diabetes mellitus has been linked to unfavorable prognosis in HCC patients, including recurrence of HCC after curative approaches and mortality[12]. When possible, surgery, including hepatic resection or liver transplantation, is the first line of treatment, but unfortunately, the incidence of tumor recurrence is still high. Therefore, the role of adjuvant therapy to preclude relapse is a medical need, and different chemopreventive agents following hepatic resection with the potential to lower the risk of HCC recurrence are being investigated[13].

Metformin, a first-line agent used in the treatment of T2DM, has been associated with inhibition of the growth of different cancer types[14,15]. A cohort study by Libby *et al*[16] analyzing patients with T2DM showed that new users of metformin might have a lower risk of overall incident cancer by 30% to 50% while on standard clinical doses of metformin (1500-2250 mg/d in adults).

Similarly, data from epidemiological studies suggest metformin might also lower the risk of HCC in diabetic patients [17-21]. In addition, as an adjuvant treatment for different cancers, metformin might also improve patients' survival by acting synergistically with chemo- and radiotherapy. On the other hand, data on HCC patients treated with sorafenib suggest tumor aggressiveness and therapy resistance in the case of chronic metformin use[22-25], while a recent study, using propensity score matching, suggested improved survival and reduced HCC recurrence in hepatitis B virus-induced HCC patients with T2DM receiving metformin[26]. Overall, whether metformin improves long-term outcomes in the HCC setting is still unclear. Therefore, we performed a systematic review and meta-analysis to further examine its chemopreventive role in HCC patients.

MATERIALS AND METHODS

Search sources and study design

A systematic review of the published literature was undertaken focused on the role of metformin in patients with T2DM and HCC receiving any tumor therapy. The search strategy was performed following the PRISMA guidelines[27]. The study has been registered on the International Prospective Register of Systematic Reviews (code CRD42023416686).

The specific research questions formulated in the present study included the following Patients, Intervention, Comparator, Outcome components: Patient: Patient with HCC and T2DM receiving metformin. Intervention: Any HCC therapy. Comparison: Patient with HCC with T2DM not receiving metformin. Outcome: Death, or progressive disease, or recurrence.

A search of the PubMed and Cochrane Central Register of Controlled Trials Databases was conducted using the following terms: (Recurrence or death or surv*) and (diabetes or DM2 or T2DM) and (metformin) and (HCC or hepatocellular cancer or hepatocellular carcinoma or hepatoma). The search period was from "2000/01/01" to "2022/08/11".

The systematic qualitative review included only English studies involving human patients. Published reports were excluded based on several criteria: (1) Data on animal models; (2) Lacked enough clinical details; and (3) Had non-primary source data (*e.g.*, review articles, non-clinical studies, letters to the editor, expert opinions, and conference summaries). In the case of studies originating from the same center, the possible overlap of clinical cases was examined, and the most informative study was considered eligible.

Data extraction and definitions

Following a full-text review of the eligible studies, two independent authors (Giovanardi F and Lai Q) performed the data extraction and crosschecked all outcomes. During the selection of articles and extraction of data, potential discrepancies were resolved following a consensus with a third reviewer (Mrzljak A). Collected data included the first author of the publication, year of publication, country, and the number of treated patients and those with recurrence according to the different therapies adopted.

Quality assessment

Selected studies were systematically reviewed with the intent to identify potential sources of bias. The quality of each study was assessed using the Risk of Bias In Non-randomized Studies of Interventions (Robins-I) tool[28].

Statistical analysis

Study results were expressed as odds ratio (OR) with 95%CIs. The statistical heterogeneity was evaluated with the Higgins statistic squared (I^2). I^2 values of 0%-25% were considered an index of low heterogeneity between studies, 26%-50%: Moderate heterogeneity, and ≥ 51%: High heterogeneity. The fixed-effects model was used when low or moderate (0%-50%) heterogeneity was detected between studies, while the random effects model was preferred when high heterogeneity was present. Subgroup analyses (for different types of HCC treatment and different ethnicities) were used to investigate the source of the heterogeneity.

Sensitivity analysis was used to assess the stability of the study. The funnel plot was used to evaluate publication bias. The rank correlation test and the regression test, using the standard error of the observed outcomes as predictor, were used to check for funnel plot asymmetry. A value $P < 0.05$ was considered indicative of statistical significance. The meta-analysis was performed using OpenMetaAnalyst (http://www.cebm.brown.edu/openmeta/index.html).

RESULTS

Search results and study characteristics

The PRISMA flow diagram schematically depicts the article selection process (Figure 1). Among the 107 articles screened, a total of 13 studies were finally included in this review[24-26,29-38]. All the studies included in the analytic cohort were published during the last decade. Eight articles (61.5%) were from Asia, of which three (23.1%) were from Taiwan or Korea, respectively. The remaining studies were from Europe (n = 3, 23.1%) and North America (n = 2, 15.4%) (Table 1).

Qualitative assessment of the included studies

Eleven (84.6%) studies were retrospective analyses, while two (15.4%) were prospective studies. The ROBINS-I tool

Table 1 Characteristics of included studies for the risk of overall cause of death

Ref.	City	Country	Study period	Design	*N*	Therapy	DM (no metformin)	Number of events	DM (metformin)	Number of events
Chen *et al*[29], 2011	Taichung	Taiwan	June 2003 to July 2009	Retro	53	RFA	32	18	21	6
Bhat *et al*[25], 2014	Rochester	United States	January 2005 to June 2011	Retro	263	No therapy	207	133	56	37
Jang *et al*[30], 2015	Seoul	Korea	March 2003 to December 2012	Retro	48	RT	29	13	19	5
Casadei Gardini *et al*[31], 2015	Meldola	Italy	March 2008 to August 2014	Retro	42	Sorafenib	11	5	31	22
Seo *et al*[32], 2016	Seoul	Korea	January 2005 to December 2011	Retro	751	HR	218	111	533	169
Chan *et al*[33], 2017	Taipei	Taiwan	January 1995 to December 2011	Retro	4610	HR	2978	1335	1632	612
					7813	No surgery	5884	3858	1929	1437
Casadei Gardini *et al*[24], 2017	Meldola	Italy	May 2007 to September 2015	Retro	86	Sorafenib	34	26	52	45
Chung *et al*[34], 2018	Seoul	Korea	January 2009 to December 2016	Retro	63	Sorafenib + HR	23	23	40	30
					31	Sorafenib + LT	17	14	14	13
Luo *et al*[26], 2020	Nanchang	China	January 2000 to December 2013	Retro	250	HR	184	129	66	49
Cho *et al*[35], 2021	Kaohsiung	Taiwan	April 2001 to June 2016	Retro	222	HR	86	15	136	26
Tangjarusritaratorn *et al*[36], 2021	Bangkok	Thailand	January 2006 to June 2014	Prosp	327	Multiple therapies	165	84	162	60
Elsayed *et al*[37], 2021	Atlanta	United States	2014-2018	Retro	40	TARE	21	8	19	8
Hydes *et al*[38], 2022	Birmingham	United Kingdom	January 2007 to March 2012	Prosp	287	Multiple therapies	139	58	148	63
Total					14886		10028	5830	4858	2582

DM: Diabetes mellitus; Retro: Retrospective; Prosp: Prospective; RFA: Radiofrequency ablation; RT: Radiotherapy; HR: Hepatic resection; LT: Liver transplantation; TARE: Trans-arterial radio-embolization.

quality assessment showed that all the studies had a low risk of bias (Figure 2).

Review of the eligible studies

Data extracted from the selected articles are reported in detail in Tables 1-3. All the studies investigated the risk of death for any reason observed after any HCC treatment (Table 1)[24-26,29-38]. In seven (53.8%) studies, a curative therapy (*i.e.*, thermoablation, resection or transplantation) was performed[26,29,32,34,37]. The risk of progressive tumor disease was reported in four (30.8%) studies (Table 2)[24,30,31,34]. Tumor recurrence was investigated in three (23.1%) studies (Table 3)[29,33,35]. Overall, only one (7.7%) study was based on a population of patients including more than 1000 cases [33].

Death in HCC patients with T2DM receiving vs not receiving metformin

According to the data shown in Table 1, 13 studies reported post-treatment death rates in HCC patients with T2DM treated or not treated with metformin. A total of 14886 patients were considered, with 8412 (56.5%) deaths. In detail, 2582/4858 (53.1%) and 5830/10028 (58.1%) deaths were observed in the metformin group and no metformin group, respectively.

Great heterogeneity was observed among the selected studies, with an I^2 = 82.6% (P < 0.001). The summary OR (95%CI) showed a decreased risk of death in T2DM cases receiving metformin, although this value did not reach statistical significance (OR = 0.89, 95%CI: 0.67-1.18; P = 0.42) (Figure 3A). Sensitivity analysis indicated no change in the direction of

Table 2 Characteristics of included studies for the risk of progressive tumor disease

Ref.	City	Country	Study period	Design	*N*	Therapy	DM (no metformin)	Number of events	DM (metformin)	Number of events
Jang *et al*[30], 2015	Seoul	Korea	March 2003 to December 2012	Retro	48	RT	29	24	19	9
Casadei Gardini *et al*[31], 2015	Meldola	Italy	March 2008 to August 2014	Retro	42	Sorafenib	11	9	31	28
Casadei Gardini *et al*[24], 2017	Meldola	Italy	May 2007 to September 2015	Retro	86	Sorafenib	34	33	52	47
Chung *et al*[34], 2018	Seoul	Korea	January 2009 to December 2016	Retro	63	Sorafenib + HR	23	23	40	40
					31	Sorafenib + LT	17	17	14	14
Total					270		114	106	156	138

DM: Diabetes mellitus; Retro: Retrospective; RT: Radiotherapy; HR: Hepatic resection; LT: Liver transplantation.

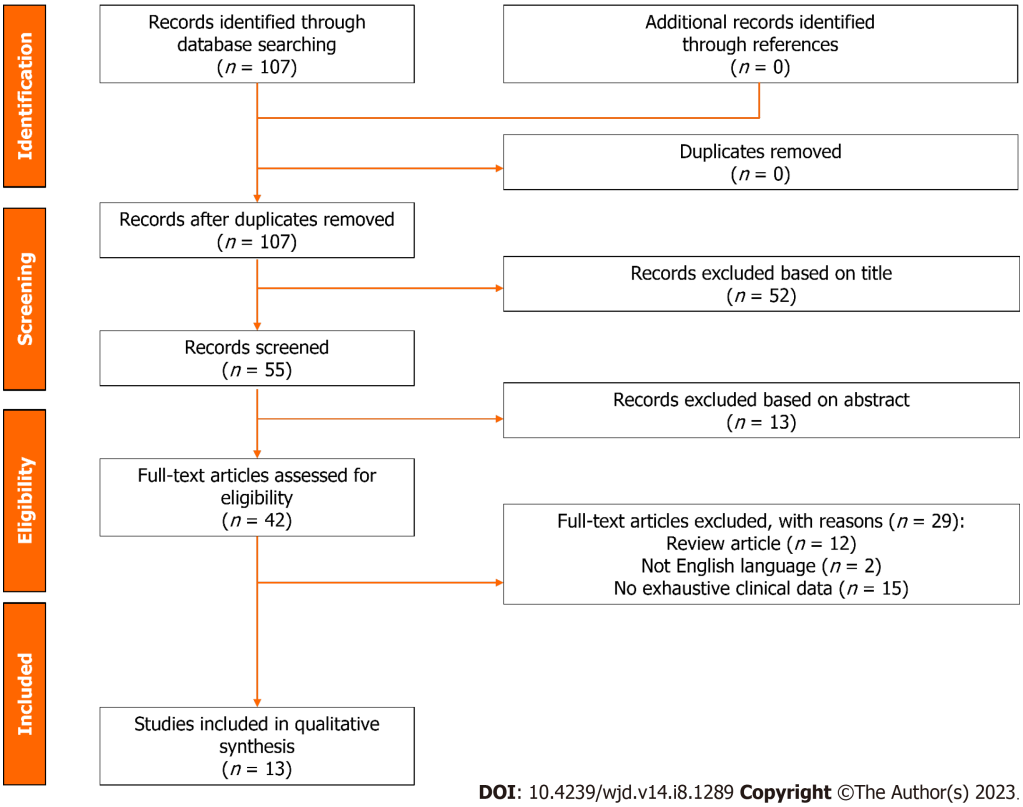

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Figure 1 PRISMA summarizing the trial flow.

effect when any one study was excluded from the meta-analysis. Funnel plot did not indicate a significant risk of publication bias (Figure 4). Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (P = 0.20 and P = 0.86, respectively).

When only patients treated with curative strategies were considered, the heterogeneity reduced; however, it remained relevant (I^2 = 67.8%, P = 0.005). The summary OR (95%CI) showed a more marked correlation between metformin and favorable cases, with an OR = 0.70 (95%CI: 0.47-1.03; P = 0.068) (Figure 3A). Despite the correlation between metformin and positive clinical course being more evident, statistical significance was not reached in this sub-analysis.

When only patients treated with palliative strategies were considered, the heterogeneity was high (I^2 = 90.8%, P < 0.001). The summary OR (95%CI) did not show statistical significance in terms of the correlation between metformin and favorable cases, with an OR = 0.74 (95%CI: 0.19-2.85; P = 0.66). A sub-analysis focused on the region in which the studies were published was also performed. In patients from Eastern countries, great heterogeneity was observed among the studies, with an I^2 = 67.9% (P < 0.001). The summary OR (95%CI) showed a decreased risk of death in T2DM cases

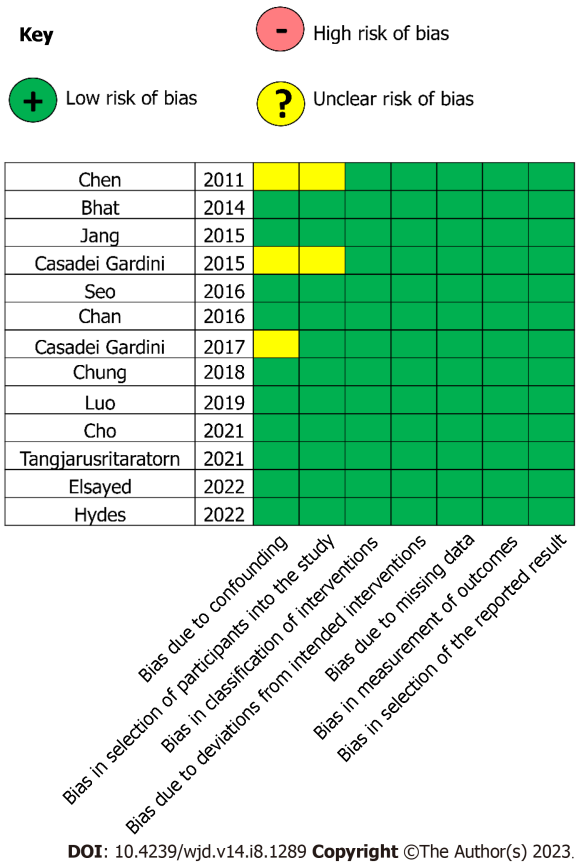

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Figure 2 Results of the risk of bias in non-randomized studies of interventions tool for the extracted articles.

receiving metformin, although this value did not reach statistical significance (OR = 0.69, 95%CI: 0.40-1.17; P = 0.17). In Western patients, heterogeneity was not present (I^2 = 0; P = 0.60). Also in this case, the summary OR (95%CI) did not show any correlation between metformin and favorable cases (OR = 1.19, 95%CI: 0.85-1.65; P = 0.31).

Progressive disease in HCC patients with T2DM receiving vs not receiving metformin

According to the data shown in Table 2, four studies reported post-treatment progressive disease rates in HCC patients with T2DM treated or not treated with metformin[24,30,31,34]. A total of 270 patients were considered, with 244 (90.4%) patients having progressive disease. In detail, 138/156 (88.5%) and 106/114 (93.0%) patients with progressive disease were observed in the metformin and no metformin group, respectively.

Low heterogeneity was observed among the selected studies, with an I^2 = 16.0% (P = 0.31). The summary OR (95%CI) showed a decreased risk of progressive disease in T2DM cases receiving metformin, although this correlation did not reach statistical significance (OR = 0.47, 95%CI: 0.16-1.37; P = 0.17) (Figure 3B).

Recurrence in HCC patients with T2DM receiving vs not receiving metformin

According to the data shown in Table 3, three studies reported post-treatment recurrence rates in HCC patients with T2DM receiving or not receiving metformin[29,33,35]. A total of 12698 patients were considered, with 6130 (48.3%) recurrences. In detail, 1777/3718 (47.8%) and 4353/8980 (48.5%) recurrences were observed in the metformin and no metformin group, respectively. Great heterogeneity was observed among the selected studies, with an I^2 = 95.8% (P < 0.001). The summary OR (95%CI) showed no evident correlation between metformin use and reduced risk of recurrence (OR = 0.95, 95%CI: 0.57-1.58; P = 0.85) (Figure 3B).

DISCUSSION

HCC, even after potentially curative treatment, is still associated with significant mortality. Therefore, identifying adjuvant agents that might decrease this risk is important. As T2DM imposes a significant risk for HCC, the role of metformin in this setting is of relevance. Data including information on 14886 patients with T2DM and HCC included in 13 studies, regardless of the treatment option used, showed a numerical decrease in the death rate in those on metformin, although no statistical significance was reported. When the survival results were analyzed for T2DM patients treated with curative strategies, similar results were reported, although the suggested correlation between the use of metformin and favorable prognosis was close to statistical significance (P = 0.068).

Table 3 Characteristics of included studies for the risk of hepatocellular carcinoma recurrence

Ref.	City	Country	Study period	Design	*N*	Therapy	DM (no metformin)	Number of events	DM (metformin)	Number of events
Chen *et al* [29], 2011	Taichung	Taiwan	June 2003 to July 2009	Retro	53	RFA	32	18	21	12
Chan *et al* [33], 2017	Taipei	Taiwan	January 1995 to December 2011	Retro	4610	HR	2978	1615	1632	698
					7813	No surgery	5884	2668	1929	982
Cho *et al* [35], 2021	Kaohsiung	Taiwan	April 2001 to June 2016	Retro	222	HR	86	52	136	85
Total					12698		8980	4353	3718	1777

DM: Diabetes mellitus; Retro: Retrospective; RFA: Radiofrequency ablation; HR: Hepatic resection.

The results mentioned were promising but never reached statistical significance, showing that the real protective effect of metformin is questionable. Unfortunately, the present study could not definitively clarify this potential protective effect due to several confounding factors related to tumor burden and the severity of cirrhosis, which are not well described in the studied population. Therefore, it was impossible to perform a meta-regression focused on these aspects.

Moreover, there was no specific investigation on the HCC-related death concerning the timing of curative treatment (1-, 2-, 5-year period), or the metformin dose, which also limited data interpretation. Specific studies exploring these aspects showed a positive effect of metformin. For example, use of metformin in high doses before cancer diagnosis reduced the likelihood of death in colorectal patients comparing T2DM and non-T2DM patients not receiving metformin [39].

Due to these promising results, metformin has also been used in non-diabetic cancer patients, and available data suggest its benefits in terms of Ki-67 reduction (positive effects on tumor cell proliferation and apoptosis) and insulin level reduction when given to non-diabetic breast cancer patients in standard doses[40,41]. Whether the suppressive effect of metformin on cancer is caused by a direct preventive effect or is due to the cancer-diabetes association, relying on lowering hyperglycemia and insulin levels, remains unclear[42]. An interesting clinical study suggests metformin has a preventive role in colorectal precancerous lesions in non-diabetic patients even when used in very low doses (250 mg/d) [43]. The actual mechanism behind the metformin anti-tumor effect is still intriguing. In the case of HCC, activating adenosine monophosphate-activated protein kinase and increasing p53 gene expression, which then induces the senescence of cancer cells, might be the key player in the anti-tumor role[44]. Besides inhibition of the mechanistic target of rapamycin signaling, effects on insulin and IGF-1 are also interesting potential pathways[45,46]. Data regarding metformin use in non-diabetic HCC patients is lacking. Also, in the present meta-analysis, all the enrolled cases had a diagnosis of T2DM. The correlation between metformin and HCC appears intriguing for numerous reasons related to the connection of T2DM and metabolic associated fatty liver disease/NASH and obesity, together with the potential lowering of hyperglycemia and hyperinsulinemia known factors in HCC development.

The effects of metformin on tumor progression and tumor recurrence are best studied in pancreatic cancer. A recently published meta-analysis including 38772 patients with T2DM and pancreatic adenocarcinoma showed a significant survival benefit of those taking metformin during early and mixed stages of the disease, for patients receiving surgical treatment but not for those at an advanced stage or those receiving chemotherapy[47]. Similar improvements in survival were described earlier by Li *et al*[48] and related only to patients with locally advanced pancreatic cancer and coexisting T2DM when taking metformin.

In the present study, patients with T2DM and HCC receiving metformin had a decreased risk of progressive disease, although this correlation did not reach statistical significance (OR = 0.47, 95%CI: 0.16-1.37; P = 0.17). In addition, the role of metformin on tumor recurrence showed no evident correlation between its use and reduced risk of recurrence (OR = 0.95, 95%CI: 0.57-1.58; P = 0.85). The negative results might relate to the previously reported biases deriving from the high rate of heterogeneity observed among the studies. Moreover, only a few studies explored the role of metformin on tumor progression and recurrence, with a consequently limited number of cases investigated.

As previously reported, the present study has some limitations. First, studies examining the effect of metformin in HCC patients have been carried out exclusively in T2DM patients. No specific studies investigating non-diabetic cases have been published, therefore identifying a potential new area of interest to be explored with specific prospective research. Second, the heterogeneity of the studies limits our ability to clarify the real effect of metformin, mainly on outcomes (*i.e.*, recurrence and progressive disease) with a limited number of enrolled cases. Therefore, more studies are needed specifically focused on these aspects, to better clarify whether the role of metformin is marginal for the risk of post-curative recurrence. Third, despite the potential effect on death prevention after curative therapies, many confounders were reported, requiring a meta-regression to clarify the real positive effect of metformin. Unfortunately, in many cases, the data needed to perform such an analysis is insufficient or lacking. New studies to clarify these aspects or an individual participant data meta-analysis are required. Other relevant aspects not explorable in the extracted studies are the metformin dose, HCC-related death, and the time-to-event data to perform inferential analyses. Also, in this case, the publication of new studies on these aspects or an individual participant data meta-analysis are needed. Lastly, HCC

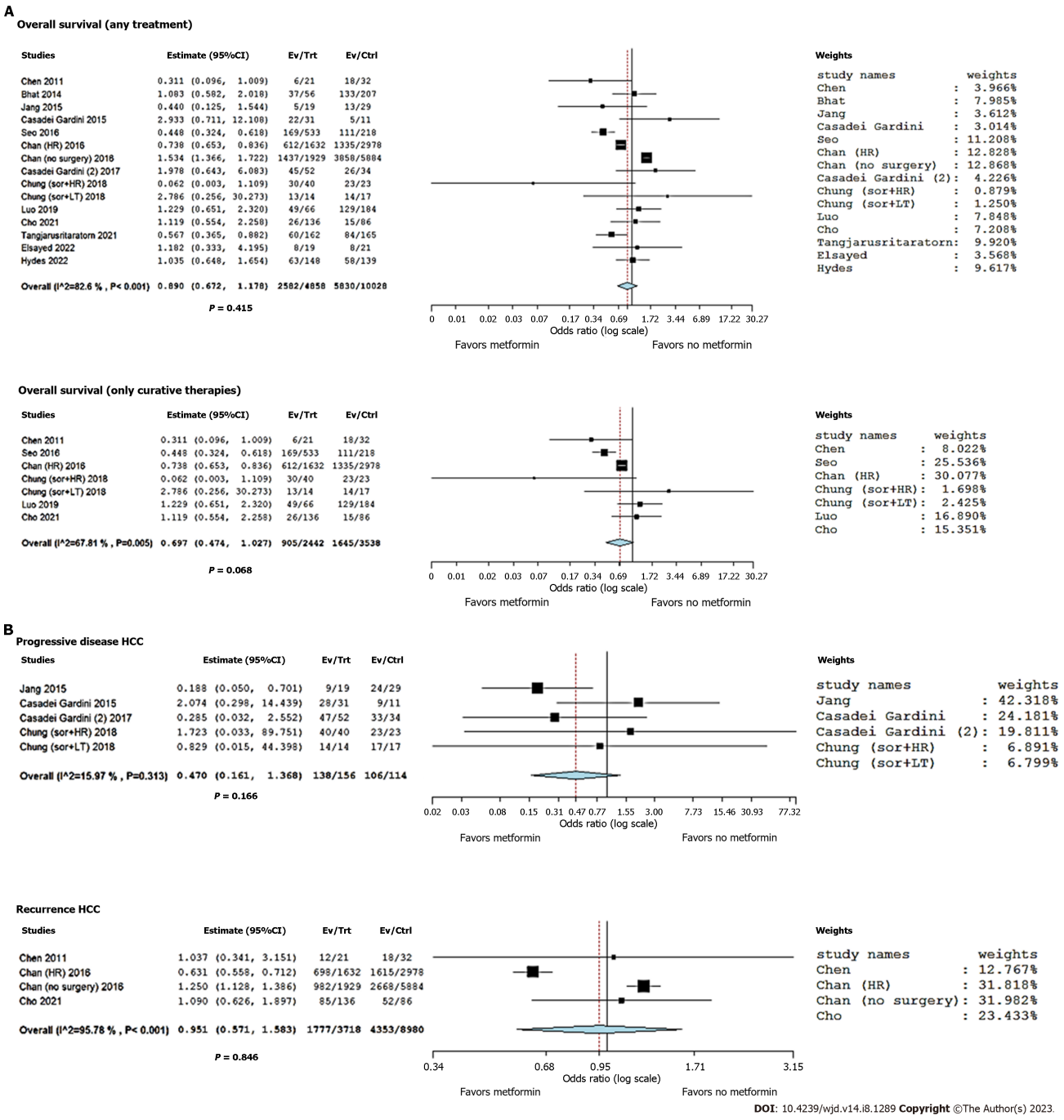

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Figure 3 Forest plots and meta-analyses results. A: The occurrence of death after any hepatocellular carcinoma (HCC) treatment and only after curative therapies: Metformin *vs* no metformin in type 2 diabetes mellitus (T2DM) patients; B: The occurrence of progressive tumor disease and HCC recurrence after any HCC treatment: Metformin *vs* no metformin in T2DM patients. HCC: Hepatocellular carcinoma.

patients often present an underlying liver disease, with different degrees of severity. Metformin is contraindicated in patients which severe liver injury, therefore adding a potential bias in the results reported.

CONCLUSION

In conclusion, no definitive answer can be given on the real protective effect of metformin in diabetic patients receiving therapies for HCC. A trend for a protective effect regarding death after curative treatments has been reported. However, many confounders exist, reducing the relevance of the reported results. More studies are needed to resolve these relevant confounders.

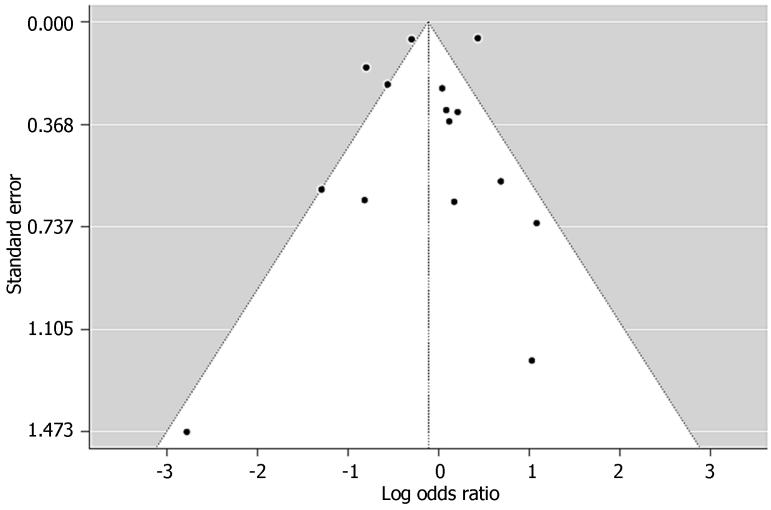

Figure 4 Funnel plot of the studies selected in the present meta-analysis.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is a common malignancy associated with significant cancer-related death. Therefore, it is important to identify chemopreventive potential to lower the risk of an HCC adverse course. Metformin has been associated with a lower risk of HCC development, but its role in prevention of death, tumor progression, and recurrence after any HCC treatment in type 2 diabetes mellitus (T2DM) patients is still inconclusive.

Research motivation

Metformin is a first-line therapeutic option for T2DM, with expanded re-purposing in the treatment of different cancer types. Whether it can improve long-term outcomes in the HCC setting is still unclear. Therefore, we performed a systematic review and meta-analysis to further explore its chemopreventive role in HCC patients.

Research objectives

We focused on the role of metformin in patients with T2DM and HCC in terms of outcomes (death, or progressive disease, or recurrence) receiving any tumor therapy. Moreover, we performed subgroup analyses (including different types of HCC treatment and different ethnicities).

Research methods

We performed a systematic review *via* a search of PubMed and Cochrane Central Register of Controlled Trials Databases of the published literature focused on the role of metformin in patients with T2DM and HCC receiving any tumor therapy.

Research results

We included 13 studies (n = 14886 patients) in this review. A decreased risk was reported in cases receiving metformin, although this value did not reach statistical significance [odds ratio (OR) = 0.89, P = 0.42]. When only patients treated with curative strategies were considered, a more marked correlation between metformin and favorable cases was reported (OR = 0.70, P = 0.068). In the case of a palliative treatment, there was no correlation between metformin and favorable cases (OR = 0.74, P = 0.66). With regard to the risk of progressive disease and recurrence, no obvious correlation between metformin use and reduced risk was reported. Moreover, there was a tendency for a decreased risk of death with metformin use in patients from Eastern countries (OR = 0.69, P = 0.17), but the same was not seen in patients from Western countries (OR = 1.19; P = 0.31).

Research conclusions

Metformin failed to have a relevant impact on preventing adverse effects after HCC treatment. A trend was reported in T2DM cases receiving curative therapies in relation to the risk of death.

Research perspectives

Further large studies are required to definitively clarify the real impact of metformin as a chemopreventive agent for HCC.

FOOTNOTES

Author contributions: Lai Q and Mrzljak A contributed to the conception and design of the study; Giovanardi F and Lai Q contributed to the acquisition of data; Lai Q and Giovanardi F analyzed and interpreted the data; Mrzljak A and Cigovski Berkovic M drafted the article; Lai Q critically revised the manuscript; and all authors approved the final version.

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