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Original article

Meta-analysis: The efficacy of metformin and other anti-hyperglycemic agents in prolonging the survival of hepatocellular carcinoma patients with type 2 diabetes

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ABSTRACT

Introduction: This study aimed to compare the therapeutic efficacy of metformin and other anti-hyperglycemic agents in hepatocellular carcinoma (HCC) patients with type 2 diabetes (T2D).
Materials: A systematic electronic search on keywords including HCC and different anti-hyperglycemic agents was performed through electronic databases including Medline and EMBASE. The primary outcome was the overall survival (OS). The secondary outcomes were the recurrence-free survival (RFS) and progression-free survival (PFS).
Results: Six retrospective cohort studies were included for analysis: Four studies with curative treatment for HCC (618 patients with metformin and 532 patients with other anti-hyperglycemic agents) and two studies with non-curative treatment for HCC (92 patients with metformin and 57 patients with other anti-hyperglycemic agents). Treatment with metformin was associated with significantly longer OS ($OR_{1\,yr}$ = 2.62, 95%CI: 1.76–3.90; $OR_{3\,yr}$ = 3.14, 95%CI: 2.33–4.24; $OR_{5\,yr}$ = 3.31, 95%CI: 2.39–4.59, all $P < 0.00001$) and RFS ($OR_{1\,yr}$ = 2.52, 95%CI: 1.84–3.44; $OR_{3\,yr}$ = 2.87, 95%CI: 2.15–3.84; all $P < 0.00001$; and $OR_{5\,yr}$ = 2.26, 95%CI: 0.94–5.45, $P = 0.07$) rates *vs.* those of other anti-hyperglycemic agents after curative therapies for HCC. However, both of the two studies reported that following non-curative HCC treatment, there were no significant differences in the OS and PFS rates between the metformin and non-metformin groups ($I^2 > 50\%$).
Conclusions: Metformin significantly prolonged the survival of HCC patients with T2D after the curative treatment of HCC. However, the efficacy of metformin needs to be further determined after non-curative therapies for HCC patients with T2D.
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1. Introduction

Hepatocellular carcinoma (HCC) is the sixth commonly diagnosed cancer and the third leading cause of cancer-related death worldwide [1]. Patients with very early and early stage HCC can receive curative treatment in the form of a hepatic resection or radiofrequency ablation therapy. While patients with medium, advanced, or end stage HCC generally receive non-curative treatment, including transhepatic arterial chemoembolization, targeted therapies, and traditional Chinese medicine [2]. However, the prognosis of HCC after these therapies is not satisfactory due to a high incidence of recurrence and progression [3,4].

Type 2 diabetes (T2D) has been proven to be a risk factor for HCC development worldwide [5]. Furthermore, T2D can promote the recurrence and progression of HCC after curative and non-curative treatments, although the mechanisms remain unclear [6]. Previous

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studies, including randomized controlled trials and multicenter retrospective studies, have reported that treatment with metformin or other anti-hyperglycemic drugs decreases the risk of HCC development in T2D patients [7–9]. However, a few retrospective cohort studies have revealed contradictory effects for anti-hyperglycemic drugs on overall survival and recurrence/progression of HCC in HCC patients with T2D [10–13]. Although a meta-analysis reported that metformin increased the overall survival rate of HCC patients with diabetes, the study contained clinical data with a high heterogeneity (I^2 = 82.9%) [14]. Therefore, there is currently no definitive clinical evidence demonstrating the efficacy of metformin and other anti-hyperglycemic treatments for HCC patients with T2D.

This meta-analysis aimed to investigate the effects of metformin and other anti-hyperglycemic agents on the overall survival, recurrence-free survival, and progression-free survival of HCC patients with T2D.

2. Materials and methods

2.1. Search strategy

We searched all of the articles in Medline, Embase, and Wanfang Data up until January 10, 2019 using keywords (metformin OR dimethylguanylguanidine) AND (carcinoma, hepatocellular OR hepatocellular carcinoma OR hepatoma).

2.2. Inclusion and exclusion criteria

We included all randomized controlled trials, cohort studies, and case–control studies if they met the following inclusion criteria: (1) focused on patients with confirmed HCC and T2D; (2) patients received T2D treatment with metformin and/or any other anti-hyperglycemic agent(s) after initial treatment for HCC; and (3) included data about HCC recurrence, disease progression, and/or mortality during the follow-up period. Publications concerning the effects of anti-hyperglycemic agents after curative or non-curative treatments for HCC were included in this analysis. The following studies were excluded: (1) non-clinical studies, animal studies, conference abstracts, or reviews; (2) preventive studies regarding metformin or other anti-hyperglycemic agents on HCC development; and (3) clinical studies without complete clinical data on overall survival (OS), recurrence-free survival (RFS), and progression-free survival (PFS).

The primary outcome was OS after curative or non-curative treatment for HCC. The secondary outcomes were RFS after curative treatment of HCC or PFS after non-curative treatment of HCC.

2.3. Data extraction and validity assessment

The available articles were reviewed and selected according to the criteria. Useful data were extracted by two investigators (JZ and YK), independently, using a standardized data extraction form that included the following information: Name of the first author, study country or region, publication year, types of anti-hyperglycemic drugs, corresponding dose and course, number of patients, number of males and females, mean age, number of hepatitis and liver cirrhosis, Child–Pugh score, tumor characteristics (number and size), Barcelona Clinic Liver Cancer (BCLC) stage, fasting glucose, and types of curative or non-curative treatments for HCC. In cases of discrepancies between the investigators during the process of article selection and data extraction, a third investigator (XFL) participated in the discussion to make the final decision. The quality of each study was assessed according to the STROBE checklist [15].

2.4. Statistical analysis

Combining the multiple outcome measures of this meta-analysis was performed using Revman 5.3 (the Nordic Cochrane Centre, Copenhagen, Denmark). Odds ratios (ORs) and 95% confidence intervals (95%CIs) were used to compare outcome variants between the metformin and non-metformin groups. An OR <1 meant a lower rate of outcome in the treatment group. Statistic heterogeneity was assessed by I^2. The combined estimates were calculated and pooled under a fixed-effects model when there was no evidence of heterogeneity (I^2 < 50%). Otherwise, the estimates were combined by a random-effects model or the results were summarized without being combined. Sensitivity analyses were also performed as a possible evaluation of the existing heterogeneity. Publication biases were evaluated by funnel plot. A P-value of <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of studies

One thousand and sixty-three pieces of abstracts were found from the literature search using the specific keywords, and 844 were identified after the removal of duplicates. A total of 82 abstracts fulfilled the inclusion criteria. From these 82 publications, 73 studies were excluded following analysis of the full text: 28 reviews, editorials, or experimental articles from rodent studies, eight conference abstracts, five studies without clinical outcomes following anti-hyperglycemic therapy, seven studies which centered on the HCC-preventative effects of an anti-hyperglycemic therapy, and 25 studies on the preventative effects of anti-hyperglycemic therapies for non-HCC cancers. There were two studies in the remaining nine that were performed by the same team and had the same theme, we chose the study with the most patients [16,17]. Finally, eight retrospective cohort studies were included in this preliminary meta-analysis [10–13,17–20] (Fig. 1).

A total of 13,985 patients from eight studies were included: 4327 HCC participants with T2D received metformin therapy in the metformin group, with a further 9658 belonging to the non-metformin group [10–13,17–20]. The choice of hypoglycemic drugs for T2D was made according to the Standards of Medical Care in Diabetes from the American Diabetes Association [12]. In the metformin group, all patients were treated with metformin in a dose range of 250–2000 mg/day for more than 3 months to control the T2D. In the non-metformin group, most patients received other anti-hyperglycemic agents, such as sulfonylurea, thiazolidinedione, alpha-glucosidase, and insulin, and three studies included patients who had used a short course of metformin (<6 months [20] and <3 [10,18]). For the initial treatment of HCC, patients from three of the studies received curative HCC treatments, including hepatic resection and radiofrequency ablation therapy [10,12,13]; patients from one study received complete tumor necrosis after stereotactic body radiotherapy or hypofractionated radiation therapy [11]; patients from one study received surgical or non-surgical treatment, but the authors did not distinguish between curative or non-curative treatment [20]; patients in another two studies received non-curative HCC targeted therapy with sorafenib [17,19]; and one study did not detail the initial treatment for the HCC [18]. Baseline comparisons between the metformin and non-metformin groups were performed in eight studies [10–13,17–20]. There were no significant differences in age, gender, hepatitis virus infection, presence of cirrhosis, Child–Pugh grading, tumor staging, fasting glucose, and the initial treatment of HCC between both of the groups. The characteristics of these patients are summarized in Table 1.

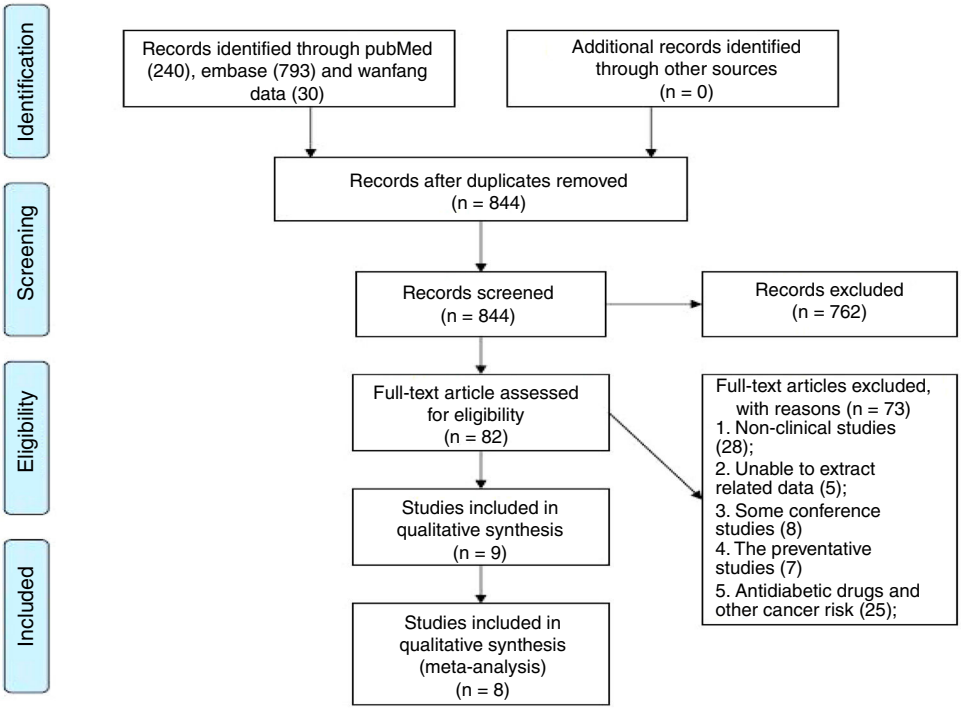

Fig. 1. PRISMA flow diagram of the literature search and selection.

3.2. Response to anti-hyperglycemic agents

During the follow-up period, insulin resistance, lactic acidosis, or hypoglycemia were not observed in the metformin and non-metformin groups from Chen's study [12], and were also not reported in the other seven studies [10,11,13,17–20]. There was no data regarding the 2-h postprandial blood glucose or hemoglobin A1c levels after anti-hyperglycemic administration. Furthermore, there was no liver function data after anti-hyperglycemic administration.

Furthermore, Chen's study showed that 31 patients died due to HCC progression, 12 patients died from severe cirrhotic complications, and two succumbed to extrahepatic diseases. However, the authors did not compare the differences in the causes of death between the metformin and non-metformin groups [12]. The other seven studies did not report on the cause of death for the HCC patients [10,11,13,17–20]. These data are shown in Table 2.

3.3. The efficacy of anti-hyperglycemic agents in the curative treatment subgroup

Combining data from the eight studies [10–13,17–20] showed there was no significant difference in 1 yr OS ($OR_{1\,yr}$ = 1.13, 95%CI: 0.43–2.94, P = 0.80), but there was a significant difference in 3 yr and 5 yr OS between the metformin and non-metformin groups ($OR_{3\,yr}$ = 1.83, 95%CI: 1.29–2.60, P = 0.0007; $OR_{5\,yr}$ = 1.63, 95%CI: 1.16–2.29, P = 0.005). It was notable that these studies showed a medium to high heterogeneity (I^2 = 86%, 76%, and 88%, respectively) (Supplementary Figure 1). We assumed that the heterogeneity mainly resulted from the initial treatment of HCC (curative or non-curative treatment). Accordingly, these studies were stratified according to their curative and non-curative treatments. In the grouping process, Bhat et al. [18] did not indicate the type of initial treatment for the HCC and Chan et al. [20] divided the patients into surgical and non-surgical groups, but did not distinguish between curative and non-curative treatments, and as such the two were excluded from the curative treatment group. Finally, the curative treatment group had four studies [10–13] and the non-curative treatment group had two studies [17,19].

The 1 yr, 3 yr, and 5 yr OS in the patients from the metformin group with curative treatment were significantly longer than that of the non-metformin group ($OR_{1\,yr}$ = 2.62, 95%CI: 1.76–3.90; $OR_{3\,yr}$ = 3.14, 95%CI: 2.33–4.24; $OR_{5\,yr}$ = 3.31, 95%CI: 2.39–4.59, all P < 0.00001). There was a low heterogeneity in the curative treatment subgroup (I^2 = 0%, 0%, and 20%, respectively) (Table 3 and Fig. 2).

Similarly, the 1 yr, 3 yr, and 5 yr RFS in the patients receiving curative treatment for HCC in the metformin group were significantly longer than the non-metformin group ($OR_{1\,yr}$ = 2.52, 95%CI: 1.84–3.44; $OR_{3\,yr}$ = 2.87, 95%CI: 2.15–3.84; all P < 0.00001; and $OR_{5\,yr}$ = 2.26, 95%CI: 0.94–5.45, P = 0.07). There was a low–middle heterogeneity between them (I^2 = 0%, 33%, and 75%) (Table 4 and Fig. 3).

3.4. The efficacy of anti-hyperglycemic agents in the non-curative treatment subgroup

Due to the high heterogeneity, there were no conclusive data about OS or PFS in the non-curative subgroup of the two studies [17,19] (Tables 3 and 4 and Supplementary Figure 2). Accordingly, we did a descriptive analysis: The HCC patients from these two studies received sorafenib treatment and all belonged to BCLC B or C. Casadei Gardini et al. [17] reported that patients were treated with sorafenib (400 mg twice daily) for HCC until HCC progression, unacceptable toxicity, or death. Chung et al. [19] reported that the patients were treated with sorafenib for a median of 10.2 months (range: 2–76 months), without providing dose clarification.

Additionally, Casadei Gardini et al. [17] reported that the treatment of HCC patients with sorafenib and metformin resulted in a median OS of 6.6 months (95%CI: 4.6–8.7) as compared to 16.6 months (95%CI: 14.5–25.5) with insulin (P = 0.0001), and a median PFS of 1.9 months (95%CI: 1.8–2.3) as compared to 8.5 months (95%CI: 5.3–11.4) with insulin (P < 0.0001). Chung et al. [19] reported that the median OS of patients on sorafenib treatment was

Table 1
Characteristics of hepatocellular carcinoma (HCC) patients with T2D before initial treatment of HCC.

Ref.	Country/ region and publication time	Group (types of drug × cases, dose, course)	No. of patient	Gender (male *vs.* female)	Mean age (yr)	No. of hepatitis (HBV infection *vs.* HCV infection)[a]	No. of liver cirrhosis	Child–Pugh grading, (A/B/C/D)	No. of tumor, solitary	Tumor size, (≤5 cm/>5 cm)	BCLC, (0/A/B/C/D)	Fasting glucose, mg/dL[b]	Initial treatment for HCC
Kang et al. [13][c]	South Korea (2018)	Metformin (metformin × 45, NA, NA)	45	35 *vs.* 10	60.8	35 (31 *vs.* 4)	NA	45/0/0/0	45 (100%)	45/0	NA	NA	Curative therapy: hepatic resection
		Non-metformin (metformin <12 months or other antidiabetic drugs × 225, NA, NA)	225	179 *vs.* 46	58.4	195 (183 *vs.* 12)	NA	225/0/0/0	225 (100%)	225/0	NA	NA	
Seo et al. [10]	South Korea (2016)	Metformin (metformin × 533[d] + sulfonylurea × 464 + thiazolidinedione × 98 + others × 246, NA, 647days[e])	533	421 *vs.* 112	60	423 (311 *vs.* 112)	320	NA	NA	NA	NA	121 (104.5, 151.5)	Curative therapy: hepatic resection
		Non-metformin (metformin × 65[d] + sulfonylurea × 202 + thiazolidinedione × 28 + others × 91, NA, 468days[e])	218	177 *vs.* 41	60	187 (131 *vs.* 56)	141	NA	NA	NA	NA	119 (103.5, 150)	
Jang et al. [11][c]	South Korea (2015)	Metformin (metformin × 19, 1000 mg/d, NA)	19	14 *vs.* 5	NA	19 (14/5[f])	NA	18/1[g]	NA	13/6	0/12/7[h]	NA	Curative therapy: stereotactic body radiotherapy or hypofractionated radiotherapy
		Non-metformin (diabetes mellitus × 29: sulfonylurea × 16 + thiazolidinedione × 3 + meglitinide × 1 + alpha-glucosidase × 1 + insulin × 8 + non-diabetes mellitus × 28: no anti-hyperglycemic treatment, NA, NA)	57	43 *vs.* 14	NA	57 (43/14[f])	NA	54/3[g]	NA	37/20	0/36/21[h]	NA	
Chen et al. [12]	China Taiwan (2011)	Metformin (metformin × 21[i], 750 mg/d, NA)	21	9 *vs.* 12	64.2	18 (7 *vs.* 11[j])	NA	10.2 ± 4.5[k]	18 (85.7%)	10/0	NA	164.0 ± 45.4	Curative therapy: radiofrequency ablation
		Non-metformin (sulfonylurea and/or insulin[i], NA, NA)	32	12 *vs.* 20	67.4	31 (12 *vs.* 19[j])	NA	9.7 ± 3.4[k]	24(75.0%)	13/0	NA	153.9 ± 58.6	

Table 1 (*Continued*)

Ref.	Country/ region and publication time	Group (types of drug × cases, dose, course)	No. of patient	Gender (male *vs.* female)	Mean age (yr)	No. of hepatitis (HBV infection *vs.* HCV infection)[a]	No. of liver cirrhosis	Child–Pugh grading, (A/B/C/D)	No. of tumor, solitary	Tumor size, (≤5 cm/>5 cm)	BCLC, (0/A/B/C/D)	Fasting glucose, mg/dL[b]	Initial treatment for HCC
Chung et al. [19]	South Korea (2018)	Metformin (metformin × 40, NA, NA)	40	36 *vs.* 4	59.4	32 (29 *vs.* 3)	NA	NA	NA	NA	0/0/1/39/0	NA	Non-curative therapy: sorafenib
		Non-metformin (insulin × 17, NA, NA)	23	23 *vs.* 0	61.8	18 (17 *vs.* 1)	NA	NA	NA	NA	0/0/1/22/0	NA	
Casadei Gardini et al. [17]	Italy (2017)	Metformin (metformin × 52, NA, NA)	52	46 *vs.* 6	69	25 (2 *vs.* 23)	NA	262/17/0/0	NA	NA	0/0/14/38/0	NA	Non-curative therapy: sorafenib
		Non-metformin (insulin × 34, NA, NA)	34	31 *vs.* 3	69	9 (1 *vs.* 8)	NA	262/17/0/0	NA	NA	0/0/15/19/0	NA	
Chan et al.-1[l] [20]	China Taiwan (2016)	Metformin (metformin × 1632, NA, NA)	1632	1176 *vs.* 456	64	959 (552 *vs.* 407)	785	NA	NA	NA	NA	NA	Hepatectomy (partial, segmental or lobectomy)
		Non-metformin (metformin <6 months or other antidiabetic drugs × 2978, NA, NA)	2978	2170 *vs.* 808	64	1788 (962 *vs.* 826)	1562	NA	NA	NA	NA	NA	
Chan et al.-2[l] [20]	China Taiwan (2016)	Metformin (metformin × 1929, NA, NA)	1929	1210 *vs.* 719	66	786 (328 *vs.* 458)	1073	NA	NA	NA	NA	NA	Non-surgery
		Non-metformin (metformin <6 months or other antidiabetic drugs × 5884, NA, NA)	5884	3813 *vs.* 2071	66	2606 (1032 *vs.* 1574)	3343	NA	NA	NA	NA	NA	
Bhat et al. [18]	The United States (2014)	Metformin (NA, NA, NA)	56	45 *vs.* 11	62	17 (5 *vs.* 12)	NA	NA	NA	NA	0/11/4/23/1	NA	NA
		Non-metformin (NA, NA, NA)	207	160 *vs.* 47	65.5	67 (6 *vs.* 61)	NA	NA	NA	NA	0/26/15/96/25	NA	

[a] The criteria of hepatitis B virus HBV and hepatitis C virus HCV infection were not mentioned in original articles.
[b] Data are median values (and interquartile ranges) or means ± standard deviations.
[c] Data after propensity score matching.
[d] Using metformin for ≤90 days was categorized as the non-metformin group or >90 days was categorized as the metformin group.
[e] The medium prescription of hypoglycemic agents.
[f] The total number of HBV and HCV *vs.* the total number of non-B and non-C hepatitis.
[g] Child–Pugh: A *vs.* B + C.
[h] Barcelona Clinic Liver Cancer: 0 + A/B + C/D.
[i] In all patients, 33 patients received sulfonylurea and 10 patients received insulin treatment simultaneously.
[j] No. of HBsAg (+) cases *vs.* anti-HCV antibody (+) cases.
[k] Data about model for end-stage liver disease score.
[l] Chan-1: the data of surgical group; Chan-2: the data of non-surgical group (with sorafenib treatment).

Table 2
The number and cause of death of hepatocellular carcinoma (HCC) patients with T2D after metformin or non-metformin treatments.

Ref.	Group	Number of deaths/total	Causes of death	Median follow-up time (mo.)
Kang et al. [13] [a]	Metformin and non-metformin groups	118/885 (13.3%)	NA	62
Seo et al. [10]	Metformin	NA	NA	NA
	Non-metformin	NA	NA	NA
Jang et al. [11] [b]	Metformin	5/19 (26.3%)	NA	15
	Non-metformin	13/57 (22.8%)	NA	15
Chen et al. [12]	Metformin, non-metformin, and non-diabetes groups	45/135 (33.3%)	31 deaths were related to HCC progression, 12 to cirrhosis complication, and 2 were unrelated to liver disease.	32.2
Chung et al. [19] [c]	Metformin	245/304 (80.6%)	NA	10.2
	Non-metformin	245/304 (80.6%)	NA	10.2
Casadei Gardini et al. [17]	Metformin	NA	NA	NA
	Non-metformin	NA	NA	NA
Chan et al.-1 [20]	Metformin	612/1632 (37.5%)	NA	NA
	Non-metformin	1335/2978 (44.8%)	NA	NA
Chan et al.-2 [20]	Metformin	1437/1929 (74.5%)	NA	NA
	Non-metformin	3858/5884 (65.6%)	NA	NA
Bhat et al. [18]	Metformin	37/56 (66.1%)	NA	NA
	Non-metformin	133/207 (64.3%)	NA	NA

[a] Data before propensity score matching.
[b] Data after propensity score matching.
[c] The total number of patients in metformin group, non-metformin group, and non-diabetes group.

Table 3
Overall survival of hepatocellular carcinoma (HCC) patients with T2D after metformin or non-metformin treatment for HCC.

Ref.	Group	No. of patient	1 yr	3 yr	5 yr	Mean survival (mo.)	*P*
Kang et al. [13]	Metformin	45	NA	44	37	80.4	0.028
	Non-metformin	225	NA	204	157	76.8	
Seo et al. [10]	Metformin	533	477	379	274	92.4	<0.01
	Non-metformin	218	169	96	50	51.6	
Jang et al. [11] [a]	Metformin	19	17	13	NA	30.1	0.022
	Non-metformin	57	45	19	NA	18.0	
Chen et al. [12]	Metformin	21	20	9	5	37.1	0.024
	Non-metformin	32	23	9	1	24.5	
Chung et al. [19]	Metformin	40	21	4	NA	12.1	0.96
	Non-metformin	23	12	0	NA	11.8	
Casadei Gardini et al. [17]	Metformin	52	17	2	NA	9.3	0.0001
	Non-metformin	34	27	6	NA	20.5	
Chan et al.-1 [20]	Metformin	1632	NA	1519	1204	96	<0.0001
	Non-metformin	2978	NA	2646	1973	84	
Chan et al.-2 [20]	Metformin	1929	NA	1603	1000	62.4	0.4925
	Non-metformin	5884	NA	4617	2792	55.2	
Bhat et al. [18]	Metformin	56	35	25	11	22.8	0.77
	Non-metformin	207	137	75	55	32.4	

[a] Data after propensity score matching.

12.1 months in the metformin group, similar to the 11.8 months of the insulin group ($P = 0.96$), and the median PFS of patients on sorafenib treatment was 4.5 months in the metformin group, similar to the 4.1 months of the insulin group ($P = 0.63$). Therefore, these two studies indicated that treatment with metformin did not significantly prolong the OS and PFS when compared to insulin therapy in HCC patients on sorafenib.

3.5. Publication bias assessment

The publication bias in the study was assessed using a funnel plot of the 3 yr OS rate for curative treatment in all of the studies. There was no obverse publication bias in this meta-analysis (Supplementary Figure 3).

4. Discussion

This meta-analysis revealed that anti-hyperglycemic therapies after curative treatment for HCC significantly reduced the risk of cancer recurrence and improved the OS of HCC patients with T2D. This study provides a comprehensive assessment of the efficacy of anti-hyperglycemic drugs on cancer recurrence and OS after the curative treatment of HCC patients with T2D.

Despite advances in surgery, chemotherapy, and radiotherapy, there is still no effective adjuvant treatment for preventing HCC recurrence and prolonging the OS. Recent studies have shown that HCC patients with T2D, before or after HCC treatment, are associated with an increased risk of HCC recurrence and a shorter OS [8,9]. These observations have shed some light on the potential role of anti-hyperglycemic therapies in preventing HCC recurrence and prolonging OS. However, this hypothesis has not been demonstrated by any prospective randomized controlled trials. Therefore,

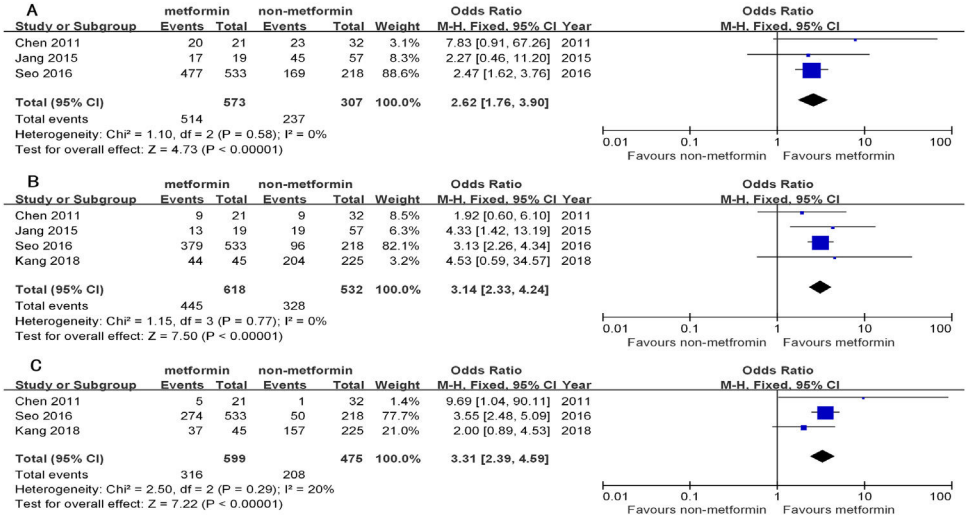

Fig. 2. The overall survival of hepatocellular carcinoma (HCC) patients with type 2 diabetes (T2D) between the metformin and non-metformin groups after curative treatment for HCC. (A) Meta-analysis of the 1 yr results (lacking the study by Kang). (B) Meta-analysis of the 3 yr results. (C) Meta-analysis of the 5 yr results (lacking the study by Jang).

Table 4
Recurrence-free survival or progression-free survival of hepatocellular carcinoma (HCC) patients with T2D after metformin or non-metformin treatment for HCC.

Ref.	Group	No. of patient	1 yr	3 yr	5 yr	Median recurrence or progression-free survival (mo.)	*P*
Studies about HCC patients who received curative treatment[a]							
Kang et al. [13]	Metformin	45	39	30	25	56.4	NA
	Non-metformin	225	182	127	108	46.8	
Seo et al. [10]	Metformin	508	415	331	253	100.8	<0.01
	Non-metformin	202	125	72	41	24.0	
Jang et al. [11][b]	Metformin	19	10	6	NA	10.8	0.045
	Non-metformin	57	17	6	NA	18.0	
Chen et al. [12]	Metformin	21	15	5	2	33.9	0.045
	Non-metformin	32	16	4	2	18.1	
Studies about HCC patients who received non-curative treatment[c]							
Chung et al. [19]	Metformin	40	7	NA	NA	4.7	0.63
	Non-metformin	23	3	NA	NA	4.3	
Casadei Gardini et al. [17]	Metformin	52	4	NA	NA	9.3	<0.0001
	Non-metformin	34	12	NA	NA	20.5	
Chan et al.-1 [20]	Metformin	1632	1612	1235	1439	6.4	<0.0001
	Non-metformin	2978	2562	1819	1204	4.7	
Chan et al.-2 [20]	Metformin	1929	1906	1410	997	62.4	0.1182
	Non-metformin	5884	4483	3796	3292	75.6	

[a] Recurrence-free survival for HCC patients received curative treatment.
[b] Data after propensity score matching.
[c] Progression-free survival for HCC patients received non-curative treatment.

this meta-analysis provides important data on the beneficial effects of anti-hyperglycemic therapies on the survival of HCC patients after curative treatment.

In this study, we first combined eight retrospective studies to determine the 1 yr, 3 yr, and 5 yr OS rates [10–13,17–20]. However, they had a high heterogeneity (I^2 = 86%, 76%, and 88%, respectively). This heterogeneity could have stemmed from many factors, including the different durations of the T2D, the different extents of insulin resistance, and the different initial therapies and stages of the HCCs among these studies. To decrease the heterogeneity as much as possible, we subsequently stratified these studies into curative and non-curative treatments for HCC. This stratification decreased the heterogeneity to 0%, 0%, and 20% for 1 yr, 3 yr, and 5 yr OS and 0%, 33%, and 75% for 1 yr, 3 yr, and 5 yr RFS in the curative treatment subgroup. However, the heterogeneity for OS and PFS in the non-curative treatment subgroup did not significantly decrease (I^2 = 88% and 76% for 1 yr and 3 yr OS, and 81% for 1 yr PFS, there were no 5 yr OS and 3 yr and 5 yr PFS reported in the non-curative treatment). The relatively higher heterogeneity of the 5 yr RFS may relate to the following three points: (1) the 5 yr-sample sizes of the HCC patients decreased; (2) the BCLC staging could have affected the time of HCC recurrence during the follow-up, unfortunately, only one study reported the BCLC-staging data in the curative treatment subgroup [11] and probably different BCLC staging existed among the studies; and (3) the different Child–Pugh grading among the studies might have influenced the recurrence of HCC patients. In the non-curative group, the high heterogeneity may have originated from the difference in the doses and duration of the sorafenib treatment for HCC.

The results from the current study revealed that metformin therapy significantly reduced the risk of HCC recurrence and prolonged OS of HCC patients after curative treatment when compared with other anti-hyperglycemic agents. Clinically, HCC recurrence within 2 yr after a curative operation is generally due to primary tumor diffusion. After 2 yr, the recurrence is usually is multicentric [21]. Given that metformin treatment decreases the risk of HCC development in T2D patients [22] and inhibits HCC cell proliferation [23], we speculate that metformin therapy may not only

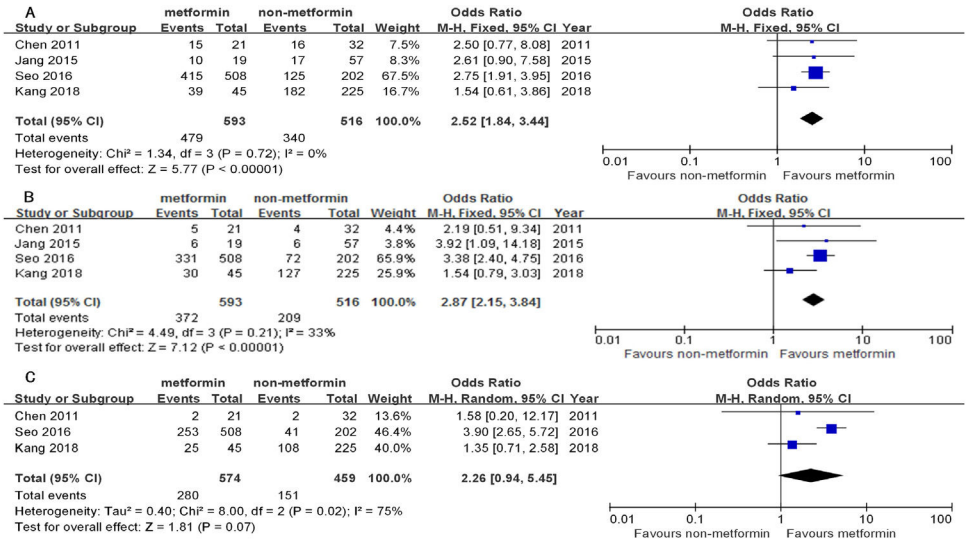

Fig. 3. The recurrence-free survival of HCC patients with T2D in the metformin and non-metformin groups after curative HCC treatment. (A) Meta-analysis of the 1 yr results. (B) Meta-analysis of the 3 yr results. (C) Meta-analysis of the 5 yr results.

inhibit HCC cell proliferation to prevent primary tumor cell diffusion, but also suppress multicentric HCC growth *de novo* to some extent. Furthermore, since most malignant cells depend on glucose for metabolism, metformin treatment can decrease blood glucose levels and, potentially, inhibit energetic metabolism in HCC cells. Moreover, metformin can control T2D, thereby improving liver function [24] that may contribute to an increase in the OS of HCC patients. However, neither the liver function changes nor the cause of death data for the HCC patients were compared between the different anti-hyperglycemic agents, which should be a focus of further study. On the other hand, through its receptors, insulin can activate the Ras-mitogen-activated protein kinase pathway, which may promote the growth and progression of HCC [25].

In the non-curative group, metformin treatment showed no significant difference compared with other anti-hyperglycemic drugs after non-curative therapy in this population. We speculate that residual tumor and the limited survival time (about 1 yr) after non-curative therapy may have hidden the efficacy of the metformin therapy. Furthermore, one basic study indicated that chronic treatment with metformin increased tumor aggressiveness and resistance to sorafenib in advanced HCC [17].

Metformin is a biguanide class of drug. It works by decreasing the glucose production by the liver and increasing the insulin sensitivity of body tissues. Metformin is generally well tolerated. Common side effects of metformin include diarrhea, nausea, and abdominal pain. It has a low risk of causing hypoglycemia. A high blood lactic acid level is a concern if the medication is prescribed inappropriately and in overdose. Insulin is a peptide hormone produced by the pancreatic islet β-cells. It regulates blood glucose levels by promoting the transportation of blood glucose into the liver, fat, and skeletal muscle cells. Furthermore, it strongly inhibits the glucose production and secretion by the liver. Hypoglycemia and increased insulin resistance are major concerns for patients with T2D using insulin. In this meta-analysis, these side effects were not reported following metformin and non-metformin treatments.

The main limitation of this meta-analysis was a lack of data from prospective randomized controlled trials. All of the data in this study were derived from retrospective cohorts, and hence, there was no T2D patients avoiding anti-hyperglycemic therapy. Ideally, a large-scale randomized, placebo-controlled trial is needed to determine the effect of anti-hyperglycemic therapies on HCC patients with T2D after curative HCC treatment. However, it might be considered unethical to perform such a randomized clinical trial, because anti-hyperglycemic therapy is indicated for these patients according to different international guidelines [26,27]. Another limitation of this study was a lack of sufficient data after non-curative treatments for HCC. There were only two studies that indicated that metformin did not improve the OS in these patients [17,19]. Furthermore, information on the baseline severity of T2D, liver disease (cirrhosis, Child–Pugh score, MELD, *etc.*), HCC stage (BCLC or TNM), and cause of death (liver disease progression, HCC progression, or T2D related and non-liver related complications) were incomplete in some of the studies included in this meta-analysis, and hence, it is difficult to draw strong conclusions.

In conclusion, our data indicates that metformin treatment significantly improves the OS of HCC patients with T2D after curative therapies. Before or after the curative treatment of HCC, patients should be monitored regularly for their blood glucose for consideration of metformin therapy. Further studies should explore the efficacy and safety of metformin in HCC patients without T2D, including HCC patients with insulin resistance and non-alcoholic fatty liver disease (NAFLD), as well as HCC patients with advanced or end stage disease.

Abbreviations

HCC	hepatocellular carcinoma
T2D	type 2 diabetes
OS	overall survival
RFS	recurrence-free survival
PFS	progression-free survival
BCLC	Barcelona Clinic Liver Cancer
NAFLD	non-alcoholic fatty liver disease

Informed patient consent

Not applicable.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.aohep.2019.11.008.

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