Retrospective Cohort Study

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Effect of metformin on hepatocellular carcinoma patients with type II diabetes receiving transarterial chemoembolization: a multicenter retrospective cohort study

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Background: Diabetes is prevalent among patients with hepatocellular carcinoma (HCC) and is associated with a poor prognosis. Although the hypoglycemic drug metformin has shown antitumor effects, its potential positive effect on patients with HCC and diabetes undergoing transarterial chemoembolization (TACE) remains unclear. Therefore, this study aimed to investigate the efficacy and safety of metformin in patients with HCC and type II diabetes who are receiving TACE.

Materials and methods: This retrospective study involved 372 consecutive patients with HCC and type II diabetes across three medical centers between January 2014 and June 2021. All patients underwent TACE. Propensity score matching (PSM) was used to reduce selection bias. Cox proportional hazards regression was employed to compare all-cause death between the metformin and nonmetformin groups while competing risk regression was performed to assess cancer-specific death.

Results: Among 372 patients included in the study, 208 patients (177 male patients and 31 female patients) with a mean age of 59.6 (10.3) years received metformin, and 164 patients (139 male patients and 25 female patients) with a mean age of 60.3 (10.0) years did not. Before PSM, patients with metformin had significantly longer median overall survival (mOS) and median progression-free survival (mPFS) than those without metformin (mOS: 34 months, 95% CI: 25.6–42.4 vs. 20 months, 95% CI: 15.3–24.7; $P < 0.001$; mPFS: 11 months, 95% CI: 9.3–12.7 vs. 8 months, 95% CI: 5.9–10.1; $P < 0.001$). Similar results were observed after PSM. Multivariate regression analysis indicated that metformin was associated with a reduced risk of all-cause mortality (HR: 0.589, 95% CI: 0.454–0.763; $P < 0.001$) and tumor progression (HR: 0.667, 95% CI: 0.526–0.845; $P = 0.001$) before PSM. After excluding deaths related to other factors, metformin continued to demonstrate a reduction in cancer-specific mortality risk among the patients. Subgroup analysis further revealed that patients using metformin had lower all-cause mortality risk and tumor progression risk than those without metformin in most subgroups. Adverse event evaluation suggested that metformin could lead to elevated nausea incidence.

Conclusion: Metformin may confer survival benefits to patients with HCC and type II diabetes undergoing TACE. Metformin may simultaneously address multiple aspects of treatment in these patients.

Keywords: diabetes, efficacy, hepatocellular carcinoma, metformin, safety, transarterial chemoembolization

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Introduction

Hepatocellular carcinoma (HCC) has one of the highest incidence and mortality rates among all cancer types[1] and is the predominant histological type of liver cancer[2]. Relevant guidelines recommend different treatment strategies based on the stage of HCC. Early-stage HCC is typically managed with transplantation, liver resection, or ablation, whereas unresectable HCC often involves treatment with transarterial chemoembolization (TACE), tyrosine kinase inhibitors (TKIs), or a combination of TKIs and immunotherapy[3–5]. Although these treatment strategies effectively control HCC progression, the 5-year survival rate remains <20% for all patients with HCC and ≤50% for those with early-stage HCC[6,7]. After tumor burden, various factors, including diabetes, cardiovascular disease, and other conditions, significantly influence the survival outcomes of patients with HCC[8–10]. Therefore, addressing these variables can potentially enhance the survival outcomes of individuals diagnosed with HCC. Moreover, diabetes is a prevalent disease in the global population and contributes to an elevated risk of liver cancer and cirrhosis[11–13]. Numerous studies have substantiated that HCC patients with diabetes experience markedly lower overall survival (OS) rates than those without diabetes[14,15]. Hyperglycemia can augment the metabolism of the Wnt/β-signaling pathway. In this pathway mechanism, the Wnt gene is abnormally activated in tumor cells, which triggers the phosphorylation and activation of the Dsh protein in the cytoplasm and inhibits the activity of the vital component GSK3β in the GSK3β/APC/Axin complex. This inhibition prevents the phosphorylation and ubiquitination of β-catenin by GSK3β, thereby reducing the degradation of β-catenin via phosphorylation. The resulting increased aggregation of cytoplasmic β-catenin leads to the entry of β-catenin into the nucleus, where it interacts with the transcription factor TCF/LEF to induce tumor development in hypoxic tumor cells and ultimately foster tumor growth, proliferation, and progression[16–18].

Although TACE is the primary treatment for unresectable HCC[4,19], achieving complete embolization is challenging and creates a hypoxic tumor microenvironment[20]. The hypoxic microenvironment can, in turn, inhibit tumor immunity and promote the activation of the PI3K/AKT/mTOR pathway. This signaling pathway plays a core regulatory role in cell growth, proliferation, and survival by integrating extracellular and intracellular signals. In the PI3K/AKT/mTOR cascade, extracellular growth factors bind to their receptors to promote PI3K activation and transform PIP2 into PIP3. Next, PIP3 recruits the kinases PDK1 and AKT to the cell membrane, causing PDK1-dependent activation of AKT. This activated AKT then phosphorylates and inhibits proteins involved in apoptosis and cell cycle arrest, along with mTOR activation and the promotion of tumor occurrence and progression signaling pathway[21]. Based on these mechanisms, diabetes has been implicated in promoting tumor progression post-TACE in patients with HCC who are undergoing TACE therapy. Hence, meticulous blood sugar control is imperative for patients with HCC and diabetes.

Metformin is the first-line drug for the treatment of type II diabetes[22,23]. This hypoglycemic medication prominently lowers blood glucose levels in patients with diabetes without affecting their insulin secretion. Additionally, metformin reduces the risk of cardiovascular disease and mortality, as well as delays the progression of early-stage diabetes[24]. Recent studies have shown that metformin possesses antitumor properties. A meta-analysis of 27 eligible studies comprising 24 178 patients explored the efficacy of metformin as an adjuvant therapy in individual cancer types. The results revealed that patients with early-stage colorectal and prostate cancer could attain survival benefits from metformin use[25]. In the context of HCC, another meta-analysis of six studies including 5936 patients demonstrated that metformin significantly prolonged the OS and diminished the recurrence rate in those with type II diabetes after curative treatment[26]. The antitumor mechanism of metformin involves the activation of tumor immunity and inhibition of the PI3K/AKT/mTOR signaling pathway to suppress tumor proliferation and metastasis[21,27]. In patients with type II diabetes who are undergoing TACE, metformin can lower blood sugar levels to inhibit the Wnt/β-catenin proteins and tumor cell proliferation by impeding the PI3K/AKT/mTOR signaling pathway under hypoxic conditions, thereby improving TACE efficacy.

Based on the above observations, combining metformin with TACE can yield positive therapeutic outcomes for patients with HCC and diabetes. However, only a few studies have currently researched this aspect, and their sample sizes are relatively small[28,29]. Therefore, this study aims to investigate the clinical efficacy and safety of combining TACE with metformin in patients with HCC and diabetes.

HIGHLIGHTS

- Hepatocellular carcinoma (HCC) patients with diabetes have a shorter survival time than those without diabetes.
- Metformin can prolong overall survival and progression-free survival of patients with HCC and type II diabetes who are undergoing transarterial chemoembolization (TACE).
- Metformin does not increase the incidence of severe adverse events in patients during the follow-up interval and after TACE.

Materials and methods

We retrospectively analyzed the medical records of 372 consecutive patients diagnosed with HCC and type II diabetes across three medical centers from January 2014 to June 2021. All patients underwent TACE, among which 208 received metformin (metformin group), and 164 were not administered metformin (nonmetformin group). This study received ethical approval from the ethical committee boards of the three participating institutions. The requirement for patient informed consent was waived by the boards due to the retrospective nature of this research. This study is in line with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) criteria[30] (Supplemental Digital Content 1, http://links.lww.com/JS9/C897).

Inclusion and exclusion criteria

The patients were included based on the following criteria: (1) HCC diagnosis based on biopsy, imaging (CT/MRI/ultrasonography), and/or laboratory examination results and in line with the guidelines for the diagnosis and treatment of primary liver cancer in China[31]; (2) diagnosis of type II diabetes verified by medical records examination and based on fasting plasma glucose (FPG) or A1C criteria, according to the American

Diabetes Association guidelines[32]; (3) treatment with TACE therapy; (4) classification as Child–Pugh class A or B; and (5) Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.

The patients were excluded if they met any of the criteria: (1) underwent TACE prior to study inclusion; (2) diagnosed with type I or other forms of diabetes; (3) presence of coexisting cancers; (4) contraindications to metformin use; (5) patients with missing data or lost to follow-up (Fig. 1).

Metformin administration and TACE procedure

In the patients in the metformin group, metformin dosage was initiated at 500 mg once daily for the initial 2 weeks, followed by titration to 2000 mg daily. The dose-dependent effect of metformin was analyzed according to the different cumulative durations of metformin use before TACE. The metformin dose will be increased to 2000 mg daily when the patient's blood glucose is elevated, provided that there are no grade 3 adverse events. If a grade 3 metformin-related adverse event occurs, the metformin dose will be reduced to 1000 mg daily. Furthermore, study inclusion required a minimum of 3 months of metformin use. The mean duration of metformin use was 42.6 months ± 11.5 months. In the patients in the nonmetformin group, 56 (34.1%) received insulin, and the mean duration of medication use was 40.9 months ± 9.7 months. Similarly, 25 (15.2%) patients received sulfonylurea drugs (mean duration of use: 38.4 months ± 10.6 months, 19 (11.6%) used glinide drugs (mean duration of use: 33.8 months ± 7.2 months, and 28 (17.1%) were administered other antidiabetes drugs (36.9 months ± 8.4 months). Finally, 36 (22.0%) patients did not receive any antidiabetes medication and were treated via lifestyle interventions.

All patients had a multidisciplinary consultation (radiologists, interventional radiologists specialists, hepatobiliary surgeons, and gastroenterologist) to determine whether or not to undergo TACE. TACE procedures were conducted by three highly experienced radiologists, with each having over 10 years of expertise in interventional therapy. A detailed description of the employed TACE procedure has been provided in our previous studies[33]. Briefly, percutaneous arterial puncture was performed using the Seldinger method, followed by the introduction of a 5F catheter (Cook Medical) into the hepatic artery. Subsequently, arteriography was conducted to visualize the feeding arteries of the tumors. A 3F microcatheter (Progreat, Terumo) was then inserted into the tumor-feeding arteries via the 5F catheter. Next, a mixture of lipiodol (Lipiodol Ultrafluido, Guerbet) and doxorubicin hydrochloride was emulsified at a ratio of 1 ml:2 mg. Finally, depending on the tumor size and liver function, a slow injection of 5–20 ml of the emulsion was administered into the tumor-feeding arteries until stasis occurred. Furthermore, supplemental embolization was conducted using gelatin sponge particles (300–700 μm, Cook Medical) if required.

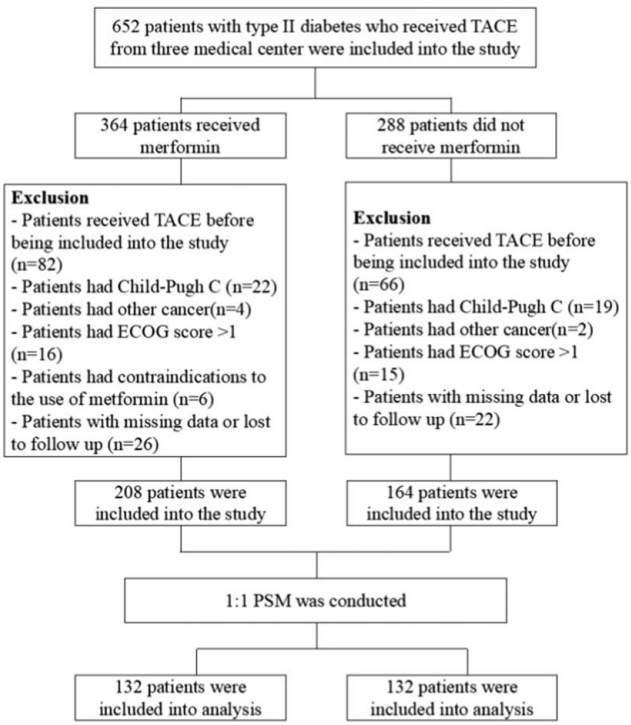

Figure 1. The flowchart of patients inclusion.

Follow-up of the patients

The patients were followed up via phone calls or scheduling hospital visits for additional examinations. The retrospective inclusion of the patients in the study was from January 2014 to June 2021. After the initial TACE, patients underwent bimonthly follow-ups for the first 6 months, followed by follow-ups every 3–4 months. In the case of disease progression during a follow-up, patients were advised to undergo repeat TACE treatment. Additionally, a patient was deemed TACE-resistant after exhibiting disease progression in two consecutive follow-up visits, and alternative treatments were recommended. The imaging, clinical, and laboratory examination data, as well as the information on post-treatment adverse events, were documented during each follow-up. Toxicities were assessed using the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events[34]. The study was concluded in June 2022.

Endpoints of the study

The study endpoints encompassed OS and progression-free survival (PFS). OS was defined as the duration from the initial TACE treatment of the patient to death from any cause. PFS was defined as the duration from the first TACE treatment of the patient to either tumor progression according to the mRECIST criteria or death[35].

Statistical analysis

Continuous variables were expressed as mean (interquartile range, IQR). Between-group comparisons of the continuous variables were performed using either the Student's *t*-test or the Mann–Whitney *U* test. Categorical variable differences were examined via either the χ^2 or Wilcoxon rank-sum tests. The Kaplan–Meier curves were employed for survival plotting, and survival comparisons were conducted utilizing the log-rank test. The Cox proportional hazards regression model was applied to identify the variables influencing patient survival. Variables with significance levels of $P < 0.05$ in the univariate regression analysis were included in the multivariable regression analysis.

Propensity score matching (PSM) was used to reduce selection bias in the study. Thirty-three variables were included into PSM

Table 1

Baseline characteristics of patients before and after matching.

	Before PSM				After PSM			
Characteristics	**Non-metformin ($n=164$)**	**Metformin ($n=208$)**	***SMD***	***P***	**Non-metformin ($n=132$)**	**Metformin ($n=132$)**	***SMD***	***P***
Age, years	59.6 ± 10.3	60.3 ± 10.0	0.067	0.525	60.0 ± 9.9	60.4 ± 10.2	0.038	0.760
Sex			0.010	0.996			0.041	0.869
Male	139 (84.8)	177 (85.1)			109 (82.6)	111 (84.1)		
Female	25 (15.2)	31 (14.9)			23 (17.4)	21 (15.9)		
Body weight, kg	70.5 (64.0–76.3)	68 (59.8–75.0)	0.241	0.028*	69.8 (63.8–75.78)	68.9 (60.2–77.6)	0.034	0.239
BMI kg/m^2	24.3 (21.8–27.1)	23.6 (21.3–25.8)	0.228	0.032*	24.1 (21.8–26.6)	23.8 (21.3–26.3)	0.069	0.351
HbA1c, %	7.96 (7.69–8.35)	7.7 (7.46–8.28)	0.388	< 0.001*	7.94 (7.68–8.32)	7.84 (7.58–8.35)	0.053	0.299
FPG, mmol/l	7.86 (7.59–8.24)	7.74 (7.39–8.18)	0.216	0.003*	7.94 (7.68–8.32)	7.84 (7.6–8.30)	0.053	0.173
2h- plasma glucose concentration, mmol/l	9.77 (9.44–10.47)	9.64 (9.35–10.35)	0.118	0.181	9.82 (9.47–10.47)	9.64 (9.33–10.26)	0.089	0.061
Hypertension	74 (45.1)	110 (52.9)	0.090	0.459	66 (50.0)	68 (51.6)	0.017	0.806
Hyperlipidemia	48 (29.3)	40 (19.2)	0.154	0.185	28 (21.2)	26 (19.6)	0.025	0.760
Diabetes duration, months	47 (31.0–63.3)	46.5 (33.0–61.0)	0.076	0.833	49.5 (32.0–63.3)	48 (33.0–61.0)	0.074	0.760
Liver cirrhosis	105 (64.0)	139 (66.8)	0.059	0.649	83 (62.9)	89 (67.4)	0.096	0.518
PSE or splenectomy			0.128	0.486			0.071	0.831
None	147 (89.6)	181 (87.0)			118 (89.4)	115 (87.1)		
PSE	13 (7.9)	17 (8.2)			10 (7.6)	12 (9.1)		
Splenectomy	4 (2.4)	10 (4.8)			4 (3.0)	5 (3.8)		
Tumor number			0.147	0.192			0.046	0.815
Single	79 (48.2)	85 (40.9)			68 (46.3)	65 (44.2)		
Multiple	85 (51.8)	123 (59.1)			79 (53.7)	82 (55.8)		
Tumor size, cm	4.5 (3.0–7.7)	4.2 (2.8–6.5)	0.052	0.360	4.5 (3–7.78)	4.2 (2.88–6.6)	0.021	0.641
TACE frequency	2 (1–4)	3 (1–5)	0.289	0.009*	2 (1–4)	3 (1–4)	0.009	0.607
Hepatitis	118 (71.9)	164 (78.9)	0.161	0.156	97 (73.5)	103 (78)	0.093	0.473
Albumin, g/l	33 (28.0–39.0)	35 (29.9–39.0)	0.213	0.077	33.4 (28.2–39.4)	35 (29.2–39.0)	0.088	0.351
ALT, U/l	36.5 (23.8–53.3)	33 (20.0–57.3)	0.124	0.447	33 (23.0–51.3)	32 (19.8–57.3)	0.081	0.577
AST, U/l	40.5 (27.8–62.0)	38 (24.0–65.3)	0.063	0.352	39 (27.0–57.3)	38 (22.0–67.3)	0.065	0.723
Creatinine, μmol/l	66.35 (57.1–79.8)	69.3 (59.0–81.0)	0.055	0.216	66.3 (56.2–79.4)	68 (58.7–84.7)	0.086	0.132
Bilirubin, μmol/l	15.2 (5.2–26.3)	15.6 (8.7–26.8)	0.010	0.428	14.6 (6.4–24.5)	15.2 (8.4–24.6)	0.017	0.683
Hemoglobin, g/l	125.5 (111.0–139.0)	128.5 (116.8–140.0)	0.093	0.203	126.5 (112.0–136.5)	128 (117.0–140.0)	0.036	0.395
Platelets, 10^9/l	125.5 (81.0–176.5)	121.5 (80.8–174.5)	0.043	0.747	127 (84.0–175.3)	129 (86.0–181.0)	0.008	0.816
Lymphocytes,10^9/l	1.1 (0.8–1.5)	1.1 (0.8–1.5)	0.096	0.801	1.11 (0.81–1.5)	1.1 (0.8–1.5)	0.072	0.616
Neutrophil, 10^9/l	3.2 (2.3–5.1)	3.1 (2.3–4.8)	0.072	0.575	3.2 (2.2–5.0)	3.1 (2.3–4.8)	0.019	0.913
Leukocyte, 10^9/l	4.9 (3.6–6.8)	4.82 (3.9–7.1)	0.022	0.822	4.98 (3.6–6.6)	5.05 (4.0–7.1)	0.095	0.331
PT, s	13.8 (12.9–14.8)	13.8 (12.8–14.7)	0.038	0.692	13.8 (12.9–14.8)	13.8 (12.6–14.7)	0.084	0.342
AFP			0.015	0.979			0.034	0.891
< 200 μg/l	117 (71.3)	147 (70.7)			94 (71.2)	96 (72.7)		
≥ 200 μg/l	47 (28.7)	61 (29.3)			38 (28.8)	36 (27.3)		
ECOG			0.212	0.070			0.057	0.816
0	153 (93.3)	181 (87.0)			123 (93.2)	121 (91.7)		
1	11 (6.7)	27 (13.0)			9 (6.8)	11 (8.3)		
Child-Pugh			0.019	0.950			0.018	0.982
A	122 (74.4)	153 (73.6)			99 (75)	100 (75.8)		
B	42 (25.6)	55 (26.4)			33 (25)	32 (24.2)		
BCLC stage			0.086	0.714			0.099	0.723
A	57 (34.8)	64 (30.8)			43 (32.6)	49 (37.1)		
B	58 (35.4)	79 (38.0)			50 (37.9)	48 (36.4)		
C	49 (29.9)	65 (31.3)			39 (29.5)	35 (26.5)		
PVTT	33 (20.1)	35 (16.8)	0.085	0.496	24 (18.2)	21 (15.9)	0.060	0.743
Extrahepatic metastasis	24 (14.6)	19 (9.1)	0.171	0.138	16 (12.1)	15 (11.4)	0.024	0.971

Categorical variables are reported as frequency and percentage; continuous variables are reported as median (25th–75th percentile).

*Statistically significant difference.

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CHILD, Child-Pugh score; ECOG, Eastern Cooperative Oncology Group performance status; FPG, fasting plasma glucose; HbA1c, Glycosylated hemoglobin; PSE, partial splenic embolization; PT, prothrombin time; PVTT, portal vein tumor thrombus; SMD, standardized mean difference; TACE, transarterial chemoembolization.

analysis for each patient, which were list in Table 1. 1:1 ratio Nearest neighbor matching algorithm with an optimal caliper of 0.2 without replacement was used for PSM. Balance of the two matched groups was evaluated by standardized mean difference in the matching variables. Usually a maximum standardized mean difference of 0.1 is considered acceptable[36].

A competing risk model was utilized to reduce the influence of noncancer-related deaths on patient survival. All statistical

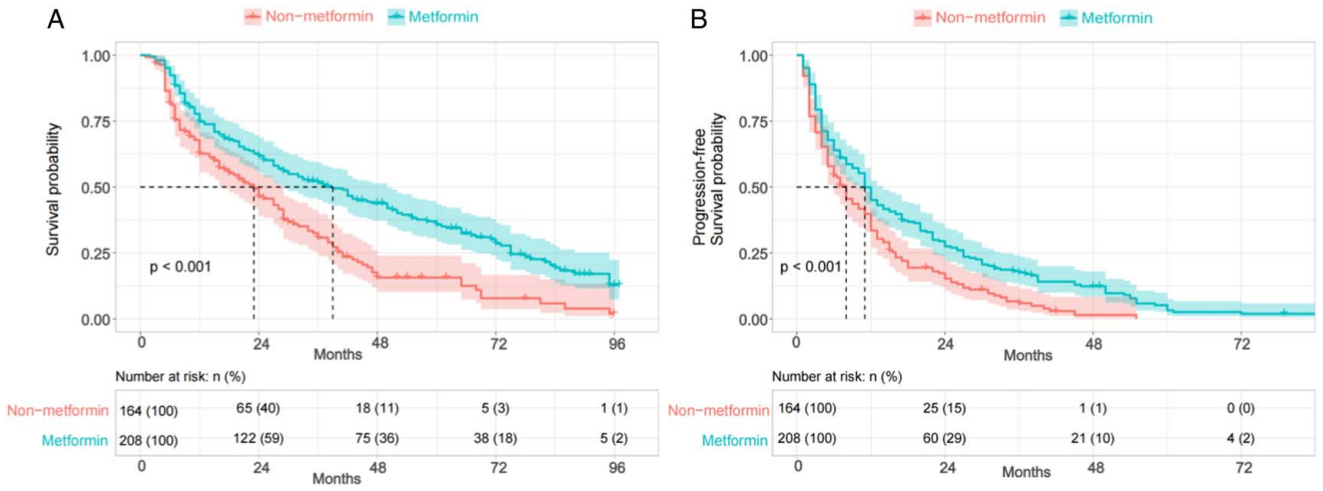

Figure 2. Kaplan–Meier survival analysis in the patients who were treated with Metformin or Non-metformin before PSM. The differences between the two groups were assessed with log-rank test. A. Kaplan–Meier estimates for overall survival (OS). B. Kaplan–Meier estimates for progression-free survival (PFS). Before PSM, the OS and PFS probability in the metformin group was significantly greater than that of the nonmetformin group ($P < 0.001$ and $P < 0.001$).

analyses were performed using R 4.0.2 software (New Zealand). A *P*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the patients

This retrospective study comprised 372 patients with HCC and type II diabetes who underwent TACE. The patients included 316 males and 56 females, with a mean age of 60 years (IQR, 53–67 years). Among them, 208 patients were prescribed metformin, while 164 were not. In the metformin group, 157 (75.5%) patients experienced all-cause mortality, with 148 (71.2%) of the deaths attributed to cancer. In the metformin group, 64 patients were diagnosed with Barcelona Clinic Liver Cancer (BCLC) stage A, 79 patients were diagnosed with BCLC stage B, and 65 patients were diagnosed with BCLC stage C. The mean tumor size was 4.2 cm (IQR: 2.8–6.5 cm). In the non-metformin group, 139 (90.2%) patients died from all causes, including 126 (76.8%) from cancer-associated causes. In the nonmetformin group, 57 patients were diagnosed with BCLC stage A, 58 patients were diagnosed with BCLC stage B, and 49 patients were diagnosed with BCLC stage C. The mean tumor size was 4.5 cm (IQR: 3.0–7.7 cm). Before PSM, there was a statistical difference in body weight, BMI, glycosylated hemoglobin (HbA1c), Fasting plasma glucose (FPG), and TACE frequency between the two groups (all $P < 0.05$). After PSM, all variables between the two groups were found to be balanced (Table 1).

Survival outcomes

Before PSM, the metformin group exhibited longer median overall survival (mOS) and median progression-free survival

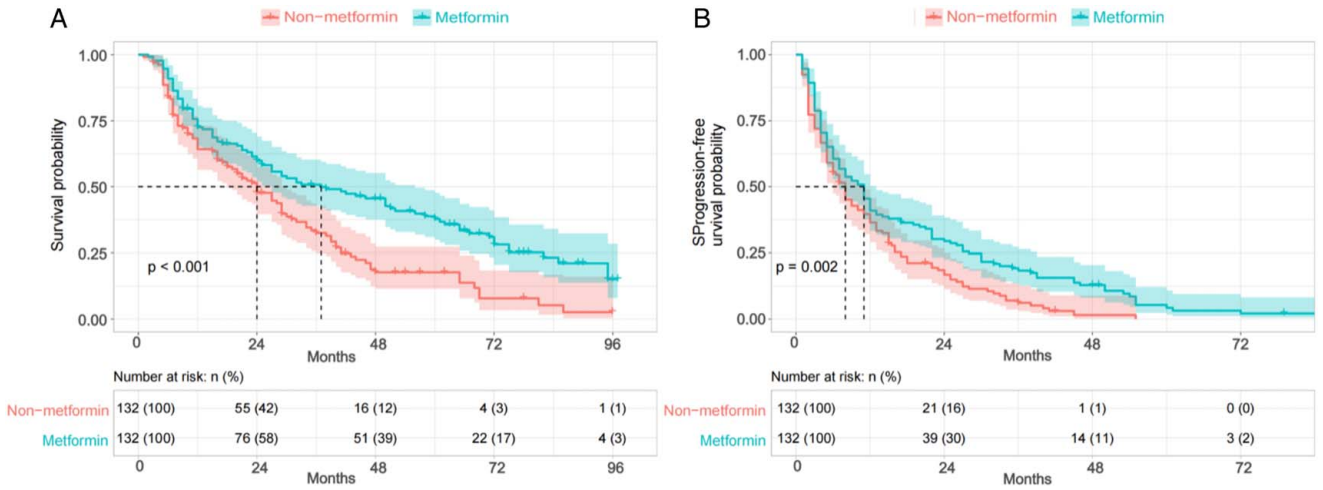

Figure 3. Kaplan–Meier survival analysis in the patients who were treated with Metformin or Non-metformin after PSM. The differences between the two groups were assessed with log-rank test. A. Kaplan–Meier estimates for overall survival (OS). B. Kaplan–Meier estimates for progression-free survival (PFS). After PSM, the OS and PFS probability in the metformin group was significantly greater than that of the nonmetformin group ($P < 0.001$ and $P = 0.03$).

Table 2

Univariable and multivariable Cox regression analysis for OS.

Variables	Univariable analysis HR (95% CI)	*P*	Multivariable analysis HR (95% CI)	*P*
[a]Age, years	0.989 (0.977–1.000)	0.054		
Female sex (vs. Male)	0.832 (0.592–1.169)	0.298		
[a]Body weight, kg	1.000 (0.988–1.013)	0.955		
[a]BMI kg/m^2	0.991 (0.957–1.026)	0.620		
[a]HbA1c, %	1.296 (1.059–1.586)	0.012*	1.173 (0.949–1.450)	0.141
[a]FPG, mmol/l	1.310 (1.021–1.681)	0.033*	1.128 (0.852–1.495)	0.400
[a]2h- plasma glucose concentration	0.938 (0.832–1.058)	0.298		
Hypertension (vs. No)	1.115 (0.842–1.477)	0.448		
Hyperlipidemia (vs. No)	1.106 (0.736–1.662)	0.627		
[a]Diabetes duration, months	0.997 (0.991–1.002)	0.232		
Liver cirrhosis (vs. No)	2.174 (1.695–2.788)	< 0.001*	1.420 (1.050–1.920)	0.03*
PSE or splenectomy (vs. None)				
PSE	0.795 (0.498–1.269)	0.336		
Splenectomy	0.712 (0.336–1.387)	0.318		
Tumor number (vs. Single)	1.013 (0.799–1.285)	0.915		
[a]Tumor size, cm	1.139 (1.104–1.174)	< 0.001*	1.013 (0.973–1.054)	0.538
TACE frequency	0.829 (0.785–0.875)	< 0.001*	0.859 (0.811–0.910)	< 0.001*
Hepatitis (vs. Yes)	0.650 (0.497–0.849)	0.002*	0.893 (0.649–1.227)	0.485
[a]Albumin, g/l	0.968 (0.956–0.979)	< 0.001*	0.984 (0.971–0.997)	0.017*
[a]ALT, U/l	1.001 (0.999–1.002)	0.328		
[a]AST, U/l	1.001 (1.000–1.002)	0.121		
[a]Creatinine, μmol/l	1.002 (1.000–1.005)	0.070		
[a]Bilirubin, μmol/l	1.003 (0.999–1.006)	0.062		
[a]Hemoglobin, g/l	0.991 (0.986–0.996)	< 0.001*	0.994 (0.988–1.001)	0.059
[a]Platelets, 10^9/l	1.002 (1.000–1.004)	0.026*	0.998 (0.996–1.000)	0.053
[a]Lymphocytes, 10^9/l	0.999 (0.980–1.019)	0.946		
[a]Neutrophil, 10^9/l	1.018 (1.004–1.032)	0.009*	1.004 (0.985–1.024)	0.665
[a]Leukocyte, 10^9/l	1.116 (1.065–1.169)	< 0.001*	1.067 (1.009–1.128)	0.023*
[a]PT, s	1.030 (1.005–1.055)	0.017*	1.046 (1.015–1.079)	0.004*
AFP ≥ 200 μg/l	1.760 (1.364–2.270)	< 0.001*	1.185 (0.894–1.572)	0.238
ECOG (vs. 0)	1.925 (1.318–2.812)	0.001*	1.086 (0.653–1.806)	0.750
Child-Pugh (vs. grade A)	1.064 (0.811–1.396)	0.655		
BCLC stage (vs. A)				
B	1.442 (1.067–1.949)	0.017*	2.039 (1.458–2.850)	< 0.001*
C	5.441 (3.953–7.489)	< 0.001*	3.133 (1.658–5.923)	0.001*
PVTT	7.429 (5.394–10.231)	< 0.001*	3.209 (1.908–5.396)	< 0.001*
Extrahepatic metastasis	4.155 (2.853–6.052)	< 0.001*	1.585 (0.940–2.672)	0.001*
Metformin	0.554 (0.434–0.707)	< 0.001*	0.589 (0.454–0.763)	< 0.001*

*Statistically significant difference.

[a]Per 1 unit increase.

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CHILD, Child-Pugh score; ECOG, Eastern Cooperative Oncology Group performance status; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HR, hazard ratio; PSE, partial splenic embolization; PT, prothrombin time; PVTT, portal vein tumor thrombus; TACE, transarterial chemoembolization.

(mPFS) than the nonmetformin group (mOS: 34 months, 95% CI: 25.6–42.4 months vs. 20 months, 95% CI: 15.3–24.7 months; mPFS: 11 months, 95% CI: 9.3–12.7 months vs. 8 months, 95% CI: 5.9–10.1 months, both $P < 0.001$) (Fig. 2). After PSM, the metformin group demonstrated extended mOS and mPFS compared to the nonmetformin group (mOS: 37 months, 95% CI: 21.6–52.4 months vs. 24 months, 95% CI: 18.0–30.0 months; mPFS: 11 months, 95% CI: 8.3–13.7 months vs. 8 months, 95% CI: 6.0–10.0 months, both $P < 0.05$) (Fig. 3).

In the univariable regression analysis before PSM, factors including glycosylated hemoglobin (HbA1c), FPG, liver cirrhosis, tumor size, TACE frequency, hepatitis, albumin, hemoglobin, platelet, neutrophil, leukocyte, prothrombin time (PT), α-fetoprotein (AFP) level, BCLC stage, ECOG score, extrahepatic metastasis, portal vein tumor thrombus (PVTT), and metformin use were identified as independent predictors for OS. In the multivariable regression analysis, liver cirrhosis (vs. noncirrhosis, HR: 1.420, 95% CI: 1.050–1.920, $P = 0.023$), TACE frequency (HR: 0.859, 95% CI: 0.811–0.910, $P < 0.001$), albumin (HR: 0.984, 95% CI: 0.971–0.997, $P = 0.017$), leukocyte (HR: 1.067, 95% CI: 1.009–1.128, $P = 0.023$), PT (HR: 1.046, 95% CI: 1.015–1.079, $P = 0.004$), BCLC stage (stage B vs. stage A: HR: 2.039, 95% CI: 1.458–2.850, $P < 0.001$; stage C vs. stage A: HR: 3.133, 95% CI: 1.658–5.923, $P = 0.001$), PVTT (HR: 3.209, 95% CI: 1.908–5.396, $P < 0.001$), and metformin use (HR: 0.589, 95% CI: 0.454–0.763, $P < 0.001$) were determined as independent predictors for OS (Table 2).

In the univariable regression analysis for PFS before PSM, FPG, hyperlipidemia, liver cirrhosis, patients with splenectomy, tumor number, tumor size, TACE frequency, albumin, hemoglobin, neutrophil count, leukocyte, AFP level, BCLC stage, ECOG score, extrahepatic metastasis, and metformin use were detected as independent predictors for PFS. In the multivariable regression analysis, factors such as TACE frequency (HR: 0.914,

Table 3

Univariable and multivariable Cox regression analysis for PFS.

Variables	Univariable analysis HR (95% CI)	*P*	Multivariable analysis HR (95% CI)	*P*
[a]Age, years	0.991 (0.981–1.001)	0.068		
Female sex (vs. Male)	0.973 (0.726–1.304)	0.854		
[a]Body weight, kg	1.008 (0.996–1.019)	0.192		
[a]BMI kg/m^2	1.016 (0.985–1.047)	0.321		
[a]HbA1c, %	1.154 (0.952–1.398)	0.144		
[a]FPG, mmol/l	1.292 (1.026–1.627)	0.029*	1.038 (0.805–1.338)	0.776
[a]2h- plasma glucose concentration	0.926 (0.835–1.026)	0.141		
Hypertension (vs. No)	1.044 (0.816–1.337)	0.730		
Hyperlipidemia (vs. No)	1.607 (1.164–2.219)	0.004*	1.259 (0.899–1.764)	0.180
[a]Diabetes duration, months	0.997 (0.993–1.002)	0.294		
Liver cirrhosis (vs. No)	1.582 (1.266–1.977)	< 0.001*	1.113 (0.868–1.427)	0.399
PSE or splenectomy (vs. None)				
PSE	0.974 (0.656–1.445)	0.895		
Splenectomy	0.472 (0.257–0.866)	0.015*	0.565 (0.304–1.053)	0.072
Tumor number (vs. Single)	1.421 (1.147–1.761)	0.001*	1.116 (0.844–1.474)	0.441
[a]Tumor size, cm	1.128 (1.093–1.164)	< 0.001*	1.002 (0.964–1.041)	0.927
TACE frequency	0.892 (0.855–0.931)	< 0.001*	0.914 (0.872–0.958)	< 0.001*
Hepatitis (vs. Yes)	0.821 (0.645–1.047)	0.112		
[a]Albumin, g/l	0.975 (0.965–0.986)	< 0.001*	0.979 (0.966–0.991)	0.001*
[a]ALT, U/L	1.001 (0.999–1.001)	0.826		
[a]AST, U/l	1.000 (0.999–1.001)	0.661		
[a]Creatinine, μmol/l	1.002 (0.996–1.003)	0.785		
[a]Bilirubin, μmol/l	1.003 (0.998–1.003)	0.753		
[a]Hemoglobin, g/l	0.994 (0.990–0.999)	0.015*	0.998 (0.993–1.004)	0.539
[a]Platelets, 10^9/l	1.001 (1.000–1.003)	0.146		
[a]Lymphocytes, 10^9/l	0.993 (0.974–1.012)	0.457		
[a]Neutrophil, 10^9/l	1.023 (1.008–1.038)	0.003*	1.011 (0.991–1.032)	0.289
[a]Leukocyte, 10^9/l	1.086 (1.042–1.133)	< 0.001*	1.039 (0.991–1.090)	0.113
[a]PT, s	1.021 (0.994–1.048)	0.131		
AFP ≥ 200 μg/l	1.607 (1.274–2.027)	< 0.001*	1.295 (1.005–1.667)	0.045*
ECOG (vs. 0)	2.015 (1.426–2.846)	< 0.001*	1.229 (0.754–2.002)	0.407
Child-Pugh (vs. grade A)	1.169 (0.920–1.484)	0.201		
BCLC stage (vs. A)				
B	1.514 (1.169–1.961)	0.002*	1.671 (1.189–2.349)	0.003*
C	4.643 (3.482–6.192)	< 0.001*	2.680 (1.443–4.978)	0.002*
PVTT	4.169 (3.116–5.576)	< 0.001*	1.574 (0.975–2.539)	0.063
Extrahepatic metastasis	4.456 (3.177–6.250)	< 0.001*	1.976 (1.204–3.241)	0.007*
Metformin	0.654 (0.526–0.813)	< 0.001*	0.667 (0.526–0.845)	0.001*

*Statistically significant difference.

[a]Per 1 unit increase.

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CHILD, Child-Pugh score; ECOG, Eastern Cooperative Oncology Group performance status; FPG, fasting plasma glucose; HbA1c, Glycosylated hemoglobin; HR, hazard ratio; PSE, partial splenic embolization; PT, prothrombin time; PVTT, portal vein tumor thrombus; TACE, transarterial chemoembolization.

95% CI: 0.872–0.958, $P < 0.001$), albumin (HR: 0.979, 95% CI: 0.966–0.991, $P = 0.001$), AFP level (vs. <200 μg/l: HR: 1.295, 95% CI: 1.005–1.667, $P = 0.045$), BCLC stage (stage B vs. stage A: HR: 1.671, 95% CI: 1.189–2.349, $P = 0.003$; stage C vs. stage A: HR: 2.680, 95% CI: 1.443–4.978, $P = 0.002$), extrahepatic metastasis (HR: 1.976, 95% CI: 1.204–3.241, $P = 0.007$), and metformin use (HR: 0.667, 95% CI: 0.526–0.845, $P = 0.001$) were found to be independent predictors for PFS (Table 3).

Outcomes of competing risk analysis

Noncancer-related mortality was reported in seven patients in the metformin group and 13 in the nonmetformin group. Moreover, the cumulative incidences of cancer-specific death in the metformin group were consistently lower than those in the nonmetformin group before and after PSM (both $P < 0.05$ in Gray's test) (Fig. 4). In the multivariable competing risk regression analysis for cancer-specific deaths before PSM, certain factors emerged as independent predictors for cancer-specific survival. These factors included TACE frequency (HR: 0.877, 95% CI: 0.834–0.922, $P < 0.001$), albumin (HR: 0.981, 95% CI: 0.970–0.994, $P = 0.003$), creatinine (HR: 1.003, 95% CI: 1.001–1.005, $P = 0.011$), bilirubin level (HR: 1.003, 95% CI: 1.001–1.005, $P = 0.013$), BCLC stage (stage C vs. stage A: HR: 3.418, 95% CI: 1.539–7.593, $P = 0.002$), and metformin use (HR: 0.749, 95% CI: 0.577–0.971, $P = 0.029$) (Table 4).

Subgroup analyses

In the subgroup analysis before PSM, male patients, those without hypertension, those without hyperlipidemia, those with liver cirrhosis, those without partial splenic embolization (PSE) or

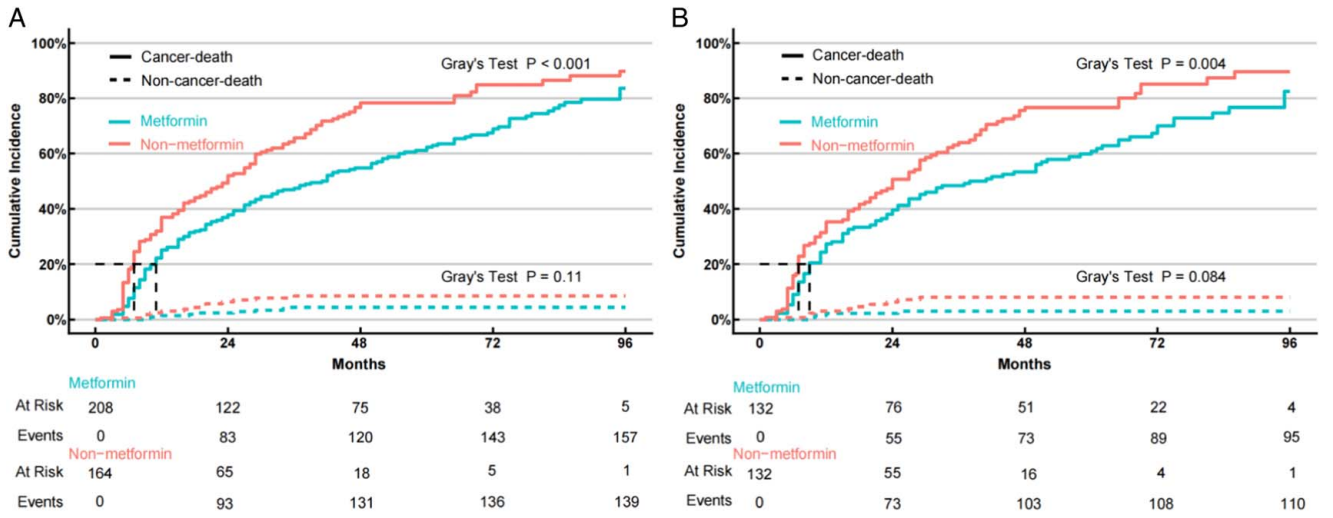

Figure 4. The cumulative incidence of the cancer-specific death with noncancer death as a competing risk in the patients who were treated with Metformin or Non-metformin A. before PSM and B. after PSM. The differences were assessed with the Gray's test. The cumulative incidence of cancer-specific death in the metformin group was significantly lower than that of the nonmetformin group ($P < 0.001$ and $P = 0.027$).

splenectomy, those with single or multiple tumors, those with or without hepatitis, those with AFP levels <200 μg/l or ≥200 μg/l, those with an ECOG score of 0, those classified as Child–Pugh class A or B, those with BCLC stage A, B, or C, those without PVTT, and those without extrahepatic metastasis showed survival benefits (Supplementary Figure S1A, Supplemental Digital Content 2, http://links.lww.com/JS9/C898) and a higher tumor control rate (Supplementary Figure S1B, Supplemental Digital Content 2, http://links.lww.com/JS9/C898) with metformin treatment compared to those who did not receive metformin.

The subgroup analysis after PSM exhibited comparable results to those before PSM. For example, male patients, those without hypertension, those without hyperlipidemia, those with liver cirrhosis, those without PSE or splenectomy, those with a single tumor, those with hepatitis, those with AFP levels <200 μg/l or ≥200 μg/l, those with an ECOG score of 0, those classified as Child–Pugh class A, those with BCLC stage A, those without PVTT, and those without extrahepatic metastasis experienced survival benefits (Supplementary Figure S2A, Supplemental Digital Content 2, http://links.lww.com/JS9/C898) and a higher tumor control rate (Supplementary Figure S2B, Supplemental Digital Content 2, http://links.lww.com/JS9/C898) with metformin administration compared to those who were not prescribed metformin.

Adverse events analysis

Adverse events in the patients were analyzed from their inclusion in the study to the study end and after TACE. During the follow-up period, patients in the metformin group exhibited a higher risk of nausea (46.7 vs. 32.5%, $P = 0.005$), diarrhea (24.5 vs. 15.4%, $P = 0.027$), and fatigue (70.4 vs. 47.9%, $P < 0.001$) than those in the nonmetformin group (Supplementary Table S1, Supplemental Digital Content 2, http://links.lww.com/JS9/C898). However, no such significant differences in adverse events were observed after TACE (all $P > 0.05$) (Supplementary Table S2, Supplemental Digital Content 2, http://links.lww.com/JS9/C898).

Discussion

The survival prognosis for cancer patients with diabetes is inferior to that for those without diabetes[37,38]. Therefore, controlling blood sugar levels is particularly crucial in this patient population. The hypoglycemic drug metformin can decrease the synthesis of liver glucose and intestinal glucose absorption, thereby enabling patients with diabetes to maximize their utilization of endogenous insulin and reduce the levels of fasting and postprandial blood glucose. Moreover, metformin exhibits antitumor effects and can effectively hinder tumor cell growth. In this study, we investigated the effectiveness of combining metformin with TACE for treating HCC. Our results revealed that metformin significantly enhances the survival of patients with HCC and type II diabetes undergoing TACE.

The mOS for patients with unresectable HCC after TACE is 26–32 months, while the time to tumor progression is 5.5–13.5 months[39–41]. In this study, the mOS and mPFS of the patients who did not receive metformin were 20 months and 8 months, respectively. Furthermore, the mPFS in the non-metformin group of this study exceeded the mPFS results obtained in the SPACE trial[41], possibly due to the inclusion of 58 (34.3%) patients with BCLC stage A in the current study. Additionally, patients receiving metformin demonstrated a median survival of 35 months, significantly higher than that of those not receiving metformin. This finding suggested that metformin provides survival benefits to patients with HCC and type II diabetes undergoing TACE.

We further conducted a multivariate Cox regression analysis to eliminate the influence of confounding factors, and the results indicated that metformin reduces the risk of all-cause death. Given that numerous complications associated with diabetes, particularly cardiovascular-related issues, pose a threat to patient survival[42], a competitive risk model analysis was also undertaken in this study. In this model, nontumor-related death was used as a competing factor to determine whether metformin still confers survival benefits. The analysis indicated that metformin continues to reduce the risk of tumor-related death in patients

Table 4

Univariable and multivariable competing risk regression analysis for cancer-specific survival.

Variables	Univariable analysis HR (95% CI)	*P*	Multivariable analysis HR (95% CI)	*P*
[a]Age, years	0.988 (0.976–1.000)	0.052		
Female sex (vs. Male)	0.815 (0.589–1.127)	0.220		
[a]Body weight, kg	0.998 (0.987–1.010)	0.780		
[a]BMI kg/m^2	0.986 (0.954–1.018)	0.390		
[a]HbA1c, %	1.267 (1.049–1.530)	0.014*	1.000 (0.806–1.240)	>0.999
[a]FPG, mmol/L	1.242 (0.969–1.592)	0.087		
[a]2h- plasma glucose concentration	0.939 (0.839–1.051)	0.280		
Hypertension (vs. Yes)	0.899 (0.678–1.192)	0.460		
Hyperlipidemia (vs. Yes)	0.671 (0.438–1.028)	0.067		
[a]Diabetes duration, months	0.998 (0.993–1.004)	0.520		
Liver cirrhosis (vs. No)	1.802 (1.399–2.321)	<0.001*	1.064 (0.786–1.440)	0.690
PSE or splenectomy (vs. None)				
PSE	0.685 (0.446–1.053)	0.084		
Splenectomy	0.726 (0.380–1.388)	0.330		
Tumor number (vs. Single)	1.032 (0.986–1.316)	0.780		
[a]Tumor size, cm	1.107 (1.057–1.160)	<0.001*	1.035 (0.994–1.078)	0.094
TACE frequency	0.851 (0.811–0.894)	<0.001*	0.877 (0.834–0.922)	<0.001*
Hepatitis (vs. Yes)	0.711 (0.543–0.933)	0.014*	0.896 (0.647–1.242)	0.510
[a]Albumin, g/l	0.973 (0.962–0.984)	<0.001*	0.981 (0.970–0.994)	0.003*
[a]ALT, U/l	1.001 (0.999–1.002)	0.410		
[a]AST, U/l	1.001 (0.999–1.002)	0.310		
[a]Creatinine, μmol/l	1.003 (1.001–1.005)	0.009*	1.003 (1.001–1.005)	0.011*
[a]Bilirubin, μmol/l	1.003 (1.000–1.006)	0.024*	1.003 (1.001–1.005)	0.013*
[a]Hemoglobin, g/l	0.994 (0.989–0.999)	0.036*	0.996 (0.991–1.001)	0.140
[a]Platelets, 10^9/l	1.001 (1.000–1.003)	0.069		
[a]Lymphocytes, 10^9/l	1.000 (0.997–1.003)	0.910		
[a]Neutrophil, 10^9/l	1.017 (1.006–1.028)	0.002*	1.009 (0.999–1.019)	0.086
[a]Leukocyte, 10^9/l	1.081 (1.023–1.143)	0.006*	1.041 (0.987–1.097)	0.140
[a]PT, s	1.026 (0.998–1.056)	0.071		
AFP ≥200 μg/l	1.695 (1.303–2.205)	<0.001*	1.334 (0.997–1.784)	0.052
ECOG (vs. 0)	1.619 (1.072–2.446)	0.022*	1.239 (0.738–1.689)	0.180
Child-Pugh (vs. grade A)	1.001 (0.766–1.308)	0.990		
BCLC stage (vs. A)				
B	1.254 (0.960–1.637)	0.097		
C	3.629 (2.558–5.418)	<0.001*	3.418 (1.539–7.593)	0.002*
PVTT	5.934 (3.952–8.910)	<0.001*	2.015 (0.965–4.210)	0.062
Extrahepatic metastasis	2.397 (1.450–3.963)	0.001*	1.985 (1.186–2.914)	0.360
Metformin	0.656 (0.518–0.831)	<0.001*	0.749 (0.577–0.971)	0.029*

*Statistically significant difference.

[a]Per 1 unit increase.

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CHILD, Child-Pugh score; ECOG, Eastern Cooperative Oncology Group performance status; FPG, fasting plasma glucose; HbA1c, Glycosylated hemoglobin; HR, hazard ratio; PSE, partial splenic embolization; PT, prothrombin time; PVTT, portal vein tumor thrombus; TACE, transarterial chemoembolization.

even after excluding the effects of other causes of death. Metformin has also been proven to reduce cardiovascular disease risk in patients with type II diabetes[43]. In the present study, the number of patients in the metformin group with cardiovascular disease-related mortality was lower than that of those in the nonmetformin group, consistent with the previous study findings. All these results imply that metformin offers multiple survival benefits for patients with type II diabetes receiving TACE.

Although nonmetformin anti-diabetic medications can lower blood sugar, no studies have confirmed their anticancer effects. Previous studies have shown that Glucagon-like peptide-1 receptor agonists (GLP-1RAs)[44–46] and thiazolidinediones[47,48] could reduce the risk of incident HCC and hepatic decompensation compared to other antidiabetes medications in patients with T2DM. However, few studies have focused on the survival of GLP-1RAs and thiazolidinediones in HCC patients with T2DM. GLP-1RAs and thiazolidinediones have been proven to alleviate the inflammatory environment and suppress HCC cell growth in mice and in vitro models[49,50]. Therefore, GLP-1RAs and thiazolidinediones might have efficacy in controlling tumor growth and prolonging survival in HCC patients with T2DM. In contrast, sulfonylureas and insulin can increase the risk of HCC in patients with T2DM because sulfonylureas are insulin secretagogues[51,52]. Insulin can promote oncogenesis either directly or indirectly by increasing IGF-1 activity, resulting in abnormal stimulation of multiple cellular signaling cascades, enhancing growth factor-dependent cell proliferation, and affecting cell metabolism[53]. Overall, nonmetformin drugs have mixed effects on HCC, and it is unclear whether they have antitumor effects. Further research is warranted in the future.

Prior studies have established that tumor burden, hepatic reserve function, and etiology are influential factors in the

survival of patients with HCC[54–56]. However, the impact of metformin on prolonging OS and PFS in this patient cohort remains unclear. Consequently, we performed a subgroup analysis to investigate this aspect. The findings revealed a significant extension of OS and PFS among patients receiving metformin in most subgroups. Moreover, the results suggested that metformin exerts a comprehensive positive effect on the survival of patients with HCC and type II diabetes.

The adverse events linked to metformin use have been reported to include fever, nausea, vomiting, diarrhea, fatigue, and acidosis[57,58]. The evaluation of the adverse events in the patients of the current study yielded similar results. During the follow-up examinations and after TACE, patients receiving metformin exhibited an increased incidence of nausea, diarrhea, and fatigue, as well as elevated lactate levels compared to those not taking metformin. Nevertheless, most patients recovered with the use of relevant medications or after receiving optimal care, indicating that metformin use in patients with liver cancer who are undergoing TACE treatment is safe.

Although the current study demonstrated promising findings, it has several limitations that should be acknowledged. First, the retrospective nature of this study introduces an inherent selection bias. Second, this study involves a relatively small number of centers (i.e. three centers). Finally, we did not include data on patients without diabetes for additional comparison. Thus, future investigations should involve prospective studies and larger sample sizes, while also integrating this patient subgroup to enhance our understanding.

Conclusions

Metformin effectively extends the survival of patients with liver cancer and type II diabetes, with the elevation of metformin treatment-related side effects being manageable with appropriate treatment and care. These study findings offer valuable guidance to clinicians on the treatment options for this specific patient population.

Ethical approval

Ethical approval for this study was provided by the Ethical Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China on 16 July 2022 (Number reference: UHCT-IEC-SOP-016-03-03).

Consent

Patient informed consent was waived by the boards due to the retrospective nature of the study.

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Author contribution

C.Z. and H.Z.: conceptualization; L.C., L.W., L.Z., B.S., W.W., Y.L., and L.Z.: data curation; L.C. and L.W.: formal analysis; C.Z.: funding acquisition; L.C., L.W., T.S., and L.Z.: investigation; C.Z., B.L., and L.W.: methodology; C.Z.: project administration; L.C., L.W., and L.Z.: resource; L.W. and L.C.: software; C.Z., B.L., and H.Z.: supervision; C.Z., B.L., and H.Z.: validation; L.C., L.Z., and L.W.: visualization; L.C., L.W., L.Z., and T.S.: writing – original draft; C.Z., B.L., and H.Z.: writing – review and editing.

Conflicts of interest disclosure

All authors declare no conflict of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Chinese Clinical Trial Registry.
2. Unique identifying number or registration ID: ChiCTR1 800018621.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.chictr.org.cn/showproj.html?proj=31360.

Guarantor

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Data availability statement

The data used in the study can be available from the corresponding author (Chuansheng Zheng, hqzcsxh@sina.com).

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Presentation

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