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Original Research

The Impact of Diabetes and Glucose-Lowering Therapies on Hepatocellular Carcinoma Incidence and Overall Survival

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ABSTRACT

Purpose: The incidence of hepatocellular carcinoma (HCC) in the United Kingdom has increased 60% in the past 10 years. The epidemics of obesity and type 2 diabetes are contributing factors. In this article, we examine the impact of diabetes and glucose-lowering treatments on HCC incidence and overall survival (OS).

Methods: Data from 1064 patients diagnosed with chronic liver disease (CLD) (n = 340) or HCC (n = 724) were collected from 2007 to 2012. Patients with HCC were followed up prospectively. Univariate and multivariate logistic regression determined HCC risk factors. Kaplan-Meier curves were used to examine survival and Cox proportional hazards analysis estimated hazard ratios (HRs) for death according to use of glucose-lowering therapies.

Findings: Diabetes prevalence was 39.6% and 10.6% within the HCC and CLD cohorts, respectively. The odds ratio for having HCC in patients with diabetes was 5.55 ($P < 0.001$). Univariate analysis found an increased association of HCC with age, sex, cirrhosis, hemochromatosis, alcohol abuse, diabetes, and Child's Pugh score. In multivariate analysis age, sex, cirrhosis, Child's Pugh score, diabetes status, and insulin use retained significance. Diabetes status did not significantly affect OS in HCC; however, in people with diabetes and HCC, metformin treatment was associated with improved OS (mean survival, 31 vs 24 months; $P = .016$; HR for death = 0.75; $P = 0.032$).

Implications: Diabetes is significantly associated with HCC in the United Kingdom. Metformin treatment is associated with improved OS after HCC diagnosis. Treatment of diabetes should be appropriately reviewed in high-risk populations, with specific consideration of the potential hepatoprotective effects of metformin in HCC. (*Clin Ther.* 2022;000:1–12.) © 2022 Elsevier Inc.

Key words: diabetes, hepatocellular carcinoma, insulin, metformin.

INTRODUCTION

Type 2 diabetes (T2D) is associated with an increased risk of death from liver disease and hepatocellular carcinoma (HCC),[1] in addition to extrahepatic malignant tumors of the gastrointestinal tract, pancreas,

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breast, ovaries, endometrium, uterus, bladder, and kidneys.[1,2] Common lifestyle risk factors, including increasing age, obesity, physical inactivity, and smoking, likely contribute to the overall increased cancer risk in patients with T2D. Although the mechanistic process that links diabetes to cancer is not yet completely appreciated, such biological mechanisms as hyperglycemia, hyperinsulinemia/insulin resistance, increased bioactivity of insulin-like growth factor 1, oxidative stress, dysregulation of sex hormones, and chronic inflammation may drive the association.[3]

HCC is one of the malignant tumors whose incidence and mortality are most rapidly increasing in the general population and patients with T2D. In the United Kingdom, the age-standardized incidence rates for liver cancer have increased by 60%, and mortality rates have increased by almost half during the past decade.[4] The magnitude of the risk varies among studies but is consistently higher (odds ratio [OR] = 2–3) than age- and body mass index (BMI)–matched controls without T2D.[5,6] The risk of HCC appears to be related to T2D disease duration, with the greatest risk being in those who have had diabetes for >10 years.[7] The development of HCC in patients with T2D may also be related to a background of nonalcoholic fatty liver disease (NAFLD), often complicated by overweight/obesity. NAFLD leads to an increased risk of HCC even in the absence of cirrhosis, and a greater proportion of individuals with NAFLD have components of the metabolic syndrome.[8] There is also evidence that people with T2D are more likely to develop cirrhosis in the context of NAFLD,[8,9] putting them at higher risk of HCC. The risk of HCC in T2D is likely dependent on its interaction with obesity/BMI and may synergistically increase the risk of HCC in patients already at higher background risk of HCC, such as those with preexisting chronic liver disease (CLD).[10] In a study of >135,000 patients with NAFLD from 4 European primary care databases, the strongest independent predictor of a diagnosis of HCC or cirrhosis was a baseline diagnosis of diabetes.[11] In addition to its association with a higher incidence of cancer and HCC, T2D also adversely affects the outcome associated with increased cancer mortality.[12]

There is increasing evidence that certain glucose-lowering therapies may modify cancer risk and outcomes. A recent meta-analysis suggests that treatment with metformin may be associated with a lower risk of HCC and may beneficially influence HCC prognosis, whereas treatment with insulin or sulfonylureas appears to be associated with a higher HCC risk.[13,14] There is similar evidence of a reduction in the incidence of liver cancer with thiazolidinediones, with more potent protective effects occurring with a higher cumulative dose and longer duration of treatment.[15,16] Metformin particularly appears to have antineoplastic and tumor-suppressing activity for a number of tumor types and thus appears to have a chemopreventive and chemotherapeutic effect.[17] Newer therapies, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide (GLP)-1 receptor agonists, have only been licensed and used in the last few years so their longer-term effects of hepatocarcinogenesis in people are not yet known. The aims of this study were to determine whether, and to what extent, diabetes represents a risk factor for HCC, to assess the impact of concomitant diabetes on overall survival from HCC, and to examine the influence of various glucose-lowering therapies on HCC survival.

PARTICIPANTS AND METHODS

Data Collection

Data were collected as part of a larger biomarker study. The study received approval by the South Birmingham Research Ethics Committee (Reference 06/Q2707/182). We conducted a single-institution study at University Hospital Birmingham, a regional referral center within the United Kingdom. Data were collected from patients seen with a diagnosis of CLD (defined as NAFLD, alcohol-related liver disease, chronic hepatitis B virus [HBV] or chronic hepatitis C virus [HCV], genetic hemochromatosis, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, or another cause of metabolic liver disease) or HCC from January 2007 to March 2012. Patients with a diagnosis of HCC were followed up prospectively to the end of the study.

Demographic, Biochemical, and Clinical Data

We collected data on demographic characteristics (age, sex, and ethnicity), liver biochemistry (liver enzymes and markers of liver synthetic function and serum α-fetoprotein), risk factors for HCC and CLD, including diabetes, severity of liver disease (Child's Pugh classification), HCC stage, treatment received, and survival. A diagnosis of cirrhosis was made using histologic analysis or imaging or via the presence of features of decompensation or portal hypertension.

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HBV and HCV infections were defined by the presence of hepatitis B surface antigen or anti-HCV, respectively. Alcohol abuse was defined as drinking >20 g/d of alcohol for women or >30 g/d of alcohol for men. HCC was diagnosed by imaging (computed tomography or magnetic resonance imaging) or lesional liver biopsy with histopathologic confirmation. All cases were reviewed in a specialist regional liver unit by experienced radiologists and histopathologists as part of a weekly multidisciplinary meeting.

Diabetes and Glucose-Lowering Therapies

A diagnosis of diabetes was taken from the patient's medical records and, where relevant, details of glucose-lowering therapy (oral agents and subcutaneous insulin) were recorded. Unfortunately, we did not have access to data to allow differentiation between type 1 and type 2 diabetes. Treatment of diabetes was analyzed by reviewing all drugs taken within the course of the patients' disease to determine whether treatment had been administered and at what time point. For patients to be categorized as users, they were required to have been taking the drug for at least 6 months. Patients were categorized according to the different types of antidiabetes treatment: (1) metformin, (2) sulfonylureas, or (3) insulin. The study was conducted before the use of more contemporary glucose-lowering therapies, such as SGLT2 inhibitors and GLP-1 receptor agonists.

Statistical Analysis

The Mann-Whitney *U* test and χ^2 test were used to compare continuous and categorical data, respectively. Univariate and multivariate analyses were performed using logistic regression to determine factors associated with HCC using the CLD group as controls. Kaplan-Meier analysis was used to compare survival for patients with and without diabetes, in addition to different diabetic treatments. Cox proportional hazards analysis was used to estimate the hazard ratio (HR) for death for patients with HCC receiving different glucose-lowering treatments. Propensity score analysis was used to examine the impact of demographic characteristics, liver disease severity, and performance status on this relationship.

RESULTS

Demographic Details and Comorbidities

Overall Population

The cohort consisted of 1064 individuals (724 with HCC and 340 CLD controls). The study flowchart is shown in Figure 1. The mean (SD) age of all patients within this study was 60.1 (14) years. The patient population was of mixed ethnicity: 79% of patients were White, 12% Asian Indian, 3% Afro Caribbean, 3% Asian Oriental, and 4% other ethnic origin.

Comparison of Patients With HCC and CLD (Controls)

Table 1 summarizes the baseline characteristics of patients with HCC compared with CLD controls. Patients with HCC were a mean of 11 years older than those with CLD (63.6 [12.7] vs 52.8 [13.7] years). Most participants were male (81% in the HCC cohort and 63% in the CLD control group). A number of comorbid diseases were present within both groups because of the nature of the population selection. HBV infection was present in 14% and 20%, HCV infection in 24% and 33%, alcohol-related liver disease in 37% and 28%, and NAFLD in 8% and 10% of the HCC group and CLD controls, respectively. In total, 71% and 47% of patients with HCC and CLD controls, respectively, had a diagnosis of cirrhosis. There was a significant difference in the disease prevalence of diabetes between the HCC cohort and the CLD controls (39% vs 11%; $P < 0.001$).

Comparison of Patients With and Without Diabetes

Table 2 summarizes the baseline characteristics of patients with and without diabetes. For the HCC and CLD groups combined, patients with diabetes were a mean of 9 years older (66.1 [9.7] vs 57 [14.7] years) than those without diabetes, with a similar sex distribution between the 2 groups (81% and 72% male in those with vs without diabetes). Ethnicity distribution was also comparable. Comorbidities differed in distribution within the 2 groups. HBV was seen in 9% and 19%, HCV in 19% and 30%, hemochromatosis in 7% and 2%, primary biliary cholangitis in 2% and 6%, and NAFLD in 18% and 5% of patients with and without diabetes, respectively (all $P < 0.05$); metabolic disease was found more commonly in people with diabetes, and viral hepatitis was found more commonly in people without diabetes. The frequency of alcohol abuse was similar between groups (35% and 34% in those with

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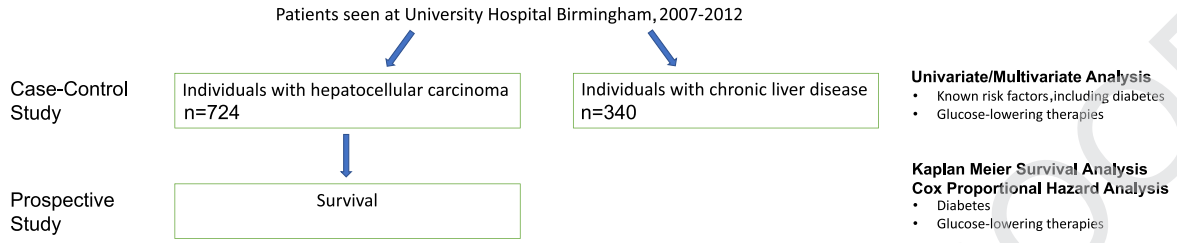

Figure 1. Study flowchart.

Table 1. Summary of baseline characteristics of patients with HCC compared with chronic liver disease controls.*

Characteristic	HCC (n = 724)	Control (n = 340)	Total (N = 1064)	Odds Ratio (95% CI)	*P* Value
Male sex	583 (80.5)	215 (63.2)	798 (75)	2.4 (1.7–3.2)	<0.05
Age, mean (SD), y	63.6 (12.7)	52.8 (13.7)	60.1 (14.0)	–	<0.05
BMI, mean (SD), kg/m^2	30.0 (5.0)	30.1 (5.1)	29.9 (5.0)	–	0.871
Ethnicity				–	
White	600 (82.9)	245 (72.1)	845 (79.4)		<0.05
Asian Indian	74 (10.2)	50 (14.7)	124 (11.7)		<0.05
Asian Oriental	13 (1.8)	11 (3.2)	24 (2.3)		0.113
Afro Caribbean	17 (2.4)	15 (4.4)	32 (3.0)		0.086
Other	20 (2.7)	19 (5.6)	39 (3.7)		<0.05
Comorbidities					
Diabetes	287 (39.6)	36 (10.6)	323 (30.4)	5.6 (3.8–8.1)	<0.05
HBV	100 (13.8)	69 (20.3)	169 (15.8)	0.63 (0.44–0.9)	<0.05
HCV	173 (3.9)	111 (32.7)	284 (26.7)	0.65 (0.47–0.87)	<0.05
Hemochromatosis	33 (4.6)	6 (1.8)	39 (3.7)	2.6 (1.1–7.9)	<0.05
Primary biliary cholangitis	22 (3.0)	26 (19.4)	48 (4.5)	0.38 (0.2–0.72)	<0.05
Alcohol abuse	270 (37.3)	96 (28.2)	366 (34.4)	1.6 (1.2–2.1)	<0.05
NAFLD	61 (8)	33 (9.7)	94 (9)	0.86 (0.54–1.4)	0.568
Cirrhosis	512 (70.7)	161 (47.4)	673 (63.3)	2.7 (2.04–3.5)	<0.05
Liver parameters					
AFP, mean (SD)	20,161 (229,987)	5.0 (8.1)	13,482 (188,253)	–	0.107
AST, mean (SD)	75.7 (65.3)	51 (46.9)	67.7 (61.0)	–	<0.05
Child's Pugh score				–	
A	438 (60.5)	289 (85.0)	727 (68.3)		<0.05
B	126 (17.4)	40 (11.8)	166 (15.6)		<0.05
C	25 (3.5)	4 (1.2)	29 (2.7)		<0.05
D	0	0	–		–
Unknown	135 (18.7)	7 (2.1)	142 (13.4)		<0.05

AFP = α-fetoprotein; AST = aspartate aminotransferase; BMI = body mass index; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NAFLD = nonalcoholic fatty liver disease.

* Data are presented as number (percentage) of participants unless otherwise indicated.

Q3

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Table 2. Summary of baseline characteristics of patients with and without diabetes.*

Characteristic	Diabetes (n = 323)	No Diabetes (n = 741)	Total (N = 1064)	Odds Ratio (95% CI)	*P* Value
HCC	287 (88.9)	437 (59.0)	724 (68.1)	–	<0.05
Male sex	263 (81.4)	535 (72.2)	798 (75)	1.7 (1.2 -2.4)	<0.05
Age, mean (SD), y	66.1 (9.7)	57 (14.7)	60.1 (14.0)	–	<0.05
Ethnicity				–	
White	262 (81)	583 (78)	845 (79.4)		0.422
Asian Indian	44 (13)	80 (11)	124 (11.7)		0.221
Asian Oriental	5 (2)	19 (3)	24 (2.3)		0.366
Afro Caribbean	4 (1)	28 (4)	32 (3.0)		<0.05
Other	8 (3)	31 (4)	39 (3.7)		0.20
Comorbidities					
HBV	30 (9)	139 (19)	169 (15.9)	0.44 (0.28–0.68)	<0.05
HCV	62 (19)	222 (30)	284 (26.7)	0.56 (0.40–0.77)	<0.05
Hemochromatosis	21 (7)	18 (2)	39 (3.7)	2.8 (1.4–5.6)	<0.05
Primary biliary cholangitis	5 (2)	43 (6)	48 (4.5)	0.26 (0.08–0.65)	<0.05
Alcohol abuse	112 (35)	254 (34)	366 (34.4)	1.0 (0.76–1.34)	0.944
NAFLD	59 (18)	35 (5)	94 (8.8)	4.5 (2.8–7.2)	<0.05
Cirrhosis	225 (70)	448 (61)	673 (63.3)	1.5 (1.1–2.0)	<0.05
Liver parameters					
AFP, mean (SD)	9179 (52,239)	15,327 (222,433)	13,482 (188,253)	–	0.632
AST, mean (SD)	63.6 (53.9)	69.4 (63.8)	67.7 (61.0)	–	0.151
Child's Pugh Score				–	
A	225 (70)	502 (68)	72 (68.3)		0.56
B	46 (14)	120 (16)	166 (15.6)		0.462
C	4 (1)	25 (3)	29 (2.7)		0.058
D	0	0	–		
Unknown	48 (15)	94 (13)	142 (13.4)		0.374

AFP = α-fetoprotein; AST = aspartate aminotransferase; BMI = body mass index; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NAFLD = nonalcoholic fatty liver disease. Q4
*Data are presented as number (percentage) of participants unless otherwise indicated.

and without diabetes, respectively). The prevalence of cirrhosis was higher in people with diabetes (70% vs 61% in those with vs without diabetes; $P < 0.05$).

Glucose-Lowering Therapies in Patients With Diabetes

Some patients were treated with lifestyle intervention only (diet and exercise). Metformin was the most commonly prescribed drug in 53%, subcutaneous insulin in 39%, and sulfonylureas in 36% of all patients. No significant differences were found in the diabetes therapies used between group, including the prescription of insulin (41% of the HCC group vs 25% of CLD controls; $P = 0.069$) (Table 3). The use of lifestyle intervention alone, however, was more common in patients with HCC compared with CLD controls (30% vs 14%; $P = 0.046$).

Factors Associated With the Incidence of HCC: Case-Control Data

Demographic and Clinical Risk Factors

Patients with HCC and CLD controls were subjected to univariate analysis on factors known to increase the risk of HCC. The presence of diabetes produced an OR

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Table 3. Summary of treatment for patients with diabetes with and without HCC.

Treatment	No. (%) of Patients			*P* Value
	Diabetes With HCC (n = 287)	Diabetes Without HCC (n = 36)	Total (N = 323)	
Diet	86 (30)	5 (14)	91 (28.2)	0.046
Metformin	148 (52)	23 (64)	171 (52.9)	0.218
Thiazolidinedione	17 (6)	1 (2.8)	1 (5.6)	0.501
DPP4 inhibitor	5 (1.7)	2 (5.6)	7 (2.2)	0.181
Sulfonylureas	105 (37)	12 (33)	117 (36.2)	0.722
Insulin	11 (41)	9 (25)	126 (39.0)	0.069

DPP4 = dipeptidyl-peptidase 4; HCC = hepatocellular carcinoma.

Table 4. Odds ratios for incident HCC according to demographic, lifestyle and clinical risk factors.

Variable	Odds Ratio (95% CI)	*P* Value
Univariate Analysis		
Age	1.08 (1.06–1.09	<0.001
Sex	2.40 (1.80–3.20)	<0.001
Alcohol abuse	1.55 (1.17–2.05)	0.002
Diabetes	5.55 (3.81–8.08)	<0.001
Hemochromatosis	2.70 (1.12–6.50)	0.027
Cirrhosis	2.69 (2.06–3.51)	<0.001
Child's Pugh score	1.37 (1.24–1.51)	<0.001
Multivariate Logistic Regression		
Age	1.06 (1.04–1.07)	<0.001
Sex	2.66 (1.86–3.78)	<0.001
Cirrhosis	1.92 (1.39–2.65)	<0.001
Child's Pugh score	1.49 (1.32–1.69)	<0.001
Diabetes	1.78 (1.03–3.06)	0.038
Insulin use	3.74 (1.52–9.21)	0.004

of 5.55 (95% CI, 3.81–8.08; $P < 0.001$). Other factors with ORs reaching significance included age, sex, cirrhosis, hemochromatosis, alcohol abuse, and Child's Pugh score (Table 4). NAFLD was not significantly associated with HCC risk (OR = 0.86; 95% CI, 0.55–1.34). Multivariate logistic regression was performed to identify whether the role of diabetes in HCC retained independence when additional variables were added to the model. All factors that had significance within univariate analysis were added to the model. Factors that maintained significance were age, sex, cirrhosis, Child's Pugh score, diabetes, and insulin (Table 4).

Effects of Glucose-Lowering Therapies on the Presence of HCC

Univariate analysis was also performed to examine the relationship between treatment of diabetes and HCC. In univariate analysis, all treatments had an increased OR for the presence of HCC. However, when adjusted for diabetes, only insulin and diet retained an increased OR to a significant level ($P < 0.05$) (Table 5). Multivariate analysis allowed adjustment for the effects of all diabetic treatments within the same model, along with the presence of diabetes itself. When the model contained either diet or insulin alongside

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Table 5. Odds ratios for incident hepatocellular carcinoma according to diabetic treatment.

Treatment	Odds Ratio (95% CI)	*P* Value
Univariate Analysis		
Diet	9.53 (3.83–23.71)	<0.001
Diet adjusted for diabetes	3.04 (1.14–8.14)	0.027
Metformin	3.77 (2.4–6.0)	<0.001
Metformin adjusted for diabetes	0.65 (0.29–1.43)	0.282
Sulfonylureas	4.97 (2.69–9.17)	<0.001
Sulfonylureas adjusted for diabetes	1.45 (0.69–3.04)	0.329
Insulin	7.5 (3.76–14.9)	<0.001
Insulin adjusted for diabetes	2.52 (1.13–5.6)	0.023
Multivariate Analysis Including Presence of Diabetes and All Major Treatment Options		
Diabetes	1.75 (0.68–4.52)	0.247
Diet	5.52 (1.77–17.30)	0.003
Metformin	0.83 (0.36–1.91)	0.655
Sulfonylureas	2.32 (1.01–5.37)	0.049
Insulin	4.04 (1.58–10.33)	0.004

diabetes, the independent effect of the 2 factors entered into the model was maintained. However, when both insulin and diet were added together to the model, the significance of diabetes was lost (Table 5).

Survival Analysis for Patients With HCC: Prospective Data

The median follow-up time for people with HCC was 25 months (range, 0–139 months). Kaplan-Meier curve analysis found no difference in survival when comparing people with and without diabetes ($P = 0.56$) (Figure 2). The percentage of patients with cirrhosis (71% in both groups) and features of hepatic decompensation at the time of HCC diagnosis was comparable between groups, as was the Barcelona Clinic Liver Cancer stage and broad treatment category (palliative or curative intent) (Supplemental Table I).

The impact of glucose-lowering therapies on overall survival was also examined. Metformin was associated with a beneficial effect on survival, with a mean survival of 31 months versus 24 months for other glucose-lowering therapies ($P = 0.016$) (Figure 3A). Metformin had a lower HR for death (HR = 0.75; 95% CI, 0.57–0.98; $P = 0.032$) in contrast to other glucose-lowering therapies (insulin HR = 0.90; 95% CI, 0.69–1.19; $P = 0.453$; sulfonylureas HR = 0.81; 95% CI, 0.60–1.09; $P = 0.155$). The survival benefit from metformin lost statistical significance, however, after a propensity score analysis that adjusted for Child's Pugh score, performance status, tumor burden (solitary or multifocal), age, and sex (HR = 0.80; 95% CI, 0.61–1.04; $P = 0.098$). Although no other treatment option had a significant effect on survival (Figure 3B and 3C), metformin taken in combination with insulin was associated with an increase in survival time compared with those patients taking insulin alone; mean survival was 31.2 months in the combined group versus 21.4 months in the insulin alone group ($P = 0.008$) (Figure 3D).

DISCUSSION

Main Findings

In this cohort of patients with HCC and a CLD control group, we found a significant association between diabetes and HCC. The absence of any pharmacologic glucose-lowering therapy (ie, dietary management) was significantly associated with developing HCC, as was insulin use in a multivariate model, although we did not have the available data to analyze how this relates to glycemic control or diabetes duration. Metformin use was not associated with HCC incidence. In those individuals who developed HCC, treatment with metformin was associated with a longer overall survival: a >30% prolongation in median survival time compared with other glucose-lowering therapies. The

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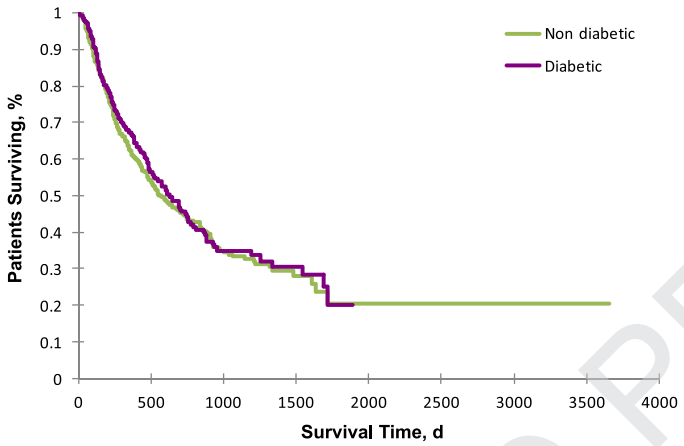

Figure 2. Kaplan-Meier analysis found no survival difference for patients with hepatocellular carcinoma with or without diabetes ($P = 0.561$, log-rank test).

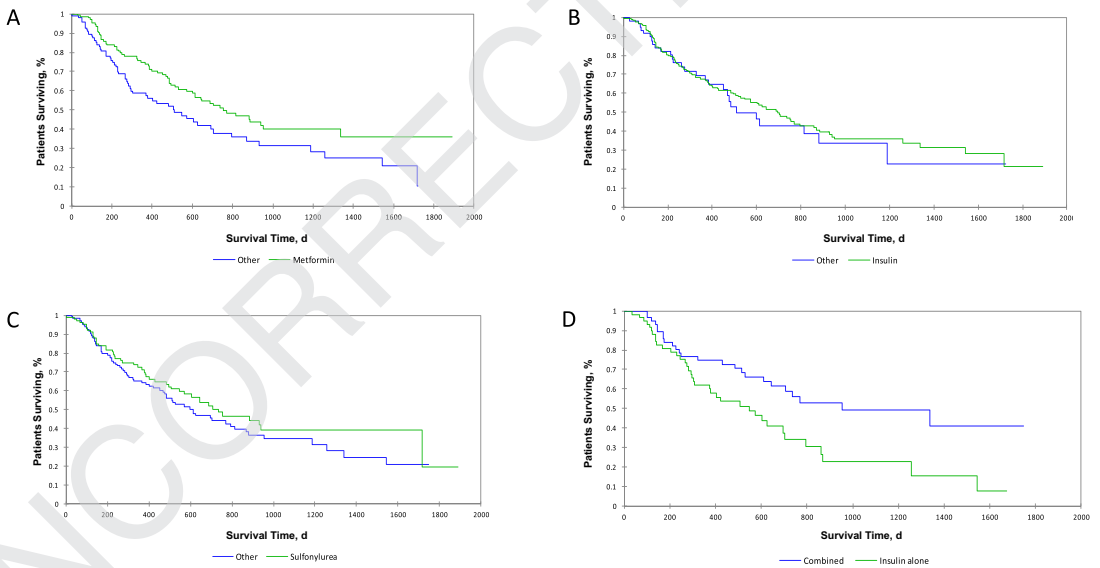

Figure 3. Kaplan-Meier analysis of survival for patients with hepatocellular carcinoma (HCC) prescribed (A) metformin ($P = 0.016$), (B) insulin ($P =$ nonsignificant), and (C) sulfonylureas ($P =$ nonsignificant) compared with other diabetic treatments and (D) patients with HCC prescribed insulin and metformin combined compared with insulin alone ($P = 0.008$). Q5

beneficial association of metformin use and survival lost statistical significance, however, after propensity score analysis.

Comparison to the Existing Literature

These findings support the substantial body of evidence that has identified diabetes as a significant risk factor for liver cancer.[1,5–7,18,19] We did not, however, observe any difference in survival according to diabetes status among individuals with HCC in contrast with other major studies, and disease stages in terms of cirrhosis severity and Barcelona Clinic Liver Cancer staging were comparable between groups at the time of diagnosis.[12]

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This study adds to our understanding of the influence of glucose-lowering therapies on the development of cancer, including HCC. Metformin was first found to be associated with reduced cancer risk in people with diabetes in 2005, with the adjusted OR reducing proportionately with increasing duration of exposure and cumulative dose dispensed.[20] Several meta-analyses have found an attenuated risk of developing liver cancer in metformin users of 50% to 60%, although significant heterogeneity was observed.[6,13,14,21] A nationwide study of nearly 100,000 patients with HCC with matched controls found that each incremental year increase in metformin use resulted in a 7% reduction in HCC risk.[22] The preventive role of metformin against incident HCC has been contested, however, as is the case in this study.[7,23–25] A meta-analysis identified that the protective effects observed for metformin use were not supported by randomized control trial data.[23] Furthermore, a retrospective cohort study of nearly 96,000 people with T2D did not find that users of metformin benefited from protection against all cancers, including HCC, compared to those taking sulfonylureas.[24] However, we observed a significant association between metformin use and improved survival from HCC, and these findings are consistent with the existing literature.[26–28] In contrast, use of insulin and insulin secretagogues (eg, sulfonylureas) has been associated with an increased risk of liver cancer (and other cancers, including colorectal, lung, stomach, and pancreatic), consistent with the findings presented in this article.[6,13,21,29] Whether these relationships are causal, influenced by the duration or severity of diabetes, or associated with obesity remains unclear. The relationship of the risk with glycemic control in T2D is also not fully understood, although 1 study highlighted the additional risk observed in the group with poor metabolic control.[30]

Despite having been used for nearly a century,[31] metformin is still recommended in all guidelines as first-line therapy for T2D.[32] The mechanism of its glucose-lowering action may be mediated through its ability to activate the adenosine monophosphate–activated protein kinase (AMPK) in peripheral insulin-sensitive tissues, stimulating skeletal muscle glucose uptake and inhibiting hepatic gluconeogenesis. However, the upstream regulator of AMPK is liver kinase B1 (LKB1), a tumor suppressor gene, and it appears that metformin can suppress tumor formation and inhibit cell growth by inhibiting the mechanistic target of rapamycin pathway through an LKB1-AMPK–dependent mechanism.[33] This negative correlation between AMPK activity and proliferation of HCC (assessed with Ki-67 level, a proliferation marker, and tumor size) has been found in cell lines, rodent models, and clinical samples.[34] The molecular pathway appears to involve phosphorylation and inactivation of Sirtuin1, the p53 deacetylase, promoting p53 acetylation and apoptosis of HCC cells.[35]

Of note, we found that the prevalence of HCV infection was lower in patients with diabetes (19%) than in those without (30%). This finding is not consistent with the literature, which has found that HCV can increase insulin resistance.[36]

Importance of the Study

The prevalence of liver disease is increasing markedly, with 4-fold increases in the UK standardized mortality rate since 1970.[37] Although much of this overall mortality relates to excess alcohol, the exponential increase in the prevalence of overweight and obesity, and in parallel T2D, cannot be overlooked. With 63% of UK adults now classified as overweight or obese, NAFLD (ie, hepatic steatosis associated with obesity, T2D, and other components of the metabolic syndrome) is becoming increasingly common. NAFLD represents a disease spectrum that includes simple steatosis (fatty infiltration), nonalcoholic steatohepatitis, fibrosis, and cirrhosis. In the next decade, NAFLD is predicted to become the primary cause of liver transplantation.[38] It is estimated that 40% to 70% of people with T2D have NAFLD, a risk factor for HCC, so considering the current obesity/T2D epidemic, the high prevalence of NAFLD may partly explain the doubling of rates of HCC in the last few decades and their projected increase by 38% by 2035.[39] The frequent coexistence of NAFLD and T2D likely also contributes to the higher incidence and risk of mortality from liver cancer and cirrhosis that is approximately 2-fold higher in patients with T2D.[40–43] Furthermore, additional risk factors may also be evident, with a synergistic effect. The risk of developing CLD, including cancer, is supraadditive when obesity and excess alcohol intake coexist,[44] whereas T2D magnifies the risk of cirrhosis, liver cancer, and liver-related deaths for people with other causes of liver disease, including viral hepatitis.[10,45] Increased recognition of the significant role of diabetes in the development of

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end-stage liver disease and liver cancer is therefore a priority.

Clinical Implications

Clearly, the liver-related complications are significant in T2D, but because the absolute risk of HCC remains small, these complications are not currently screened for. There is no universally accepted algorithm to screen for NAFLD-related liver fibrosis in individuals with obesity, metabolic syndrome, and T2D, with discordance among international guidelines.[46–48] The American Diabetes Association recommends that patients with T2D/prediabetes with elevated liver enzyme levels or fatty liver on ultrasonography should be evaluated for the presence of nonalcoholic steatohepatitis and liver fibrosis.[49] Additional studies on the cost-effectiveness of case finding for liver fibrosis in this setting are required, which may provide a positive step forward in improving HCC screening in this higher risk cohort. Given the balance of evidence generally in favor of a chemopreventive role against HCC (and other malignant tumors) among patients with diabetes and improved survival, metformin should be continued in patients even with cirrhosis (excluding those with decompensation) to provide this benefit.

Study Strengths and Limitations

To the best of our knowledge, this is the first prospective UK study to look at diabetes as a risk factor for liver cancer survival and the first prospective UK study to examine the role of diabetic therapies on cancer risk and survival in the specific setting of HCC. A significant strength is that the data were collected prospectively with a 5-year follow-up. We acknowledge some limitations to the study, which are partly a reflection of the period in which the data were first collected. Most significantly we were unable to assess whether the relationships observed between diabetes and HCC were independent of body mass index and the presence of NAFLD because at the time of data collection only a few participants had body mass index data recorded and a significant proportion were noted as having an unknown cause of liver disease, many of which in hindsight probably had NAFLD. Unfortunately, we were unable to access this data retrospectively. Furthermore, data on glycemic control, specific diabetes subtype (most likely >90% had T2D), and disease duration were also not available in most people with diabetes so we could not examine the impact of this on the observed effects of diabetes therapies on HCC incidence and survival. This limitation may be particularly pertinent to the relationship between insulin and HCC incidence because this relationship may be confounded by poorer glycemic control or longer disease duration. Similarly, for those not receiving any glucose-lowering treatment, this finding most likely reflected chronic poor/suboptimal glycemic control. The study was undertaken before widespread prescription and availability of more contemporary glucose-lowering therapies, such SGLT2 inhibitors and GLP-1 receptor agonists (that may also modulate liver steatosis with or without fibrosis); therefore, their impact on HCC could not be assessed.

CONCLUSIONS

We found a significant association between HCC and diabetes but highlight the significant improvement in overall survival in those people with HCC treated with metformin. These data highlight an emerging, but thus far frequently overlooked, epidemiologically significant complication of the diabetes and obesity pandemics. The study findings raise important questions about the value of closer screening for CLD, cirrhosis, and even HCC in people with diabetes and the potentially hepatoprotective effects of metformin.

DISCLOSURE

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Theresa J. Hydes was involved with study design, performed data analysis and interpretation, and edited the manuscript. Daniel J. Cuthbertson was involved with study design and data interpretation and wrote the manuscript. Suzanne Graef was involved in study design, data analysis, and interpretation. Sarah Berhane provided statistical advice. Mabel Teng and Anna Skowronska helped with data collection, analysis, and interpretation. Pushpa Singh, Sofi Dhanaraj, and Abd Tahrani helped with data collection. Philip J. Johnson was involved in study concept and design and data interpretation and edited the manuscript.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2021.12.011.

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