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Diabetes mellitus increases the risk of hepatocellular carcinoma in treatment-naïve chronic hepatitis C patients in China

Xu Li, PhD[a], Hongqin Xu, PhD[a,b], Yang Gao, MD[c], Meng Pan, MD[a], Le Wang, MD[a], Pujun Gao, PhD[a,*]

Abstract

We investigated the link between diabetes mellitus (DM) and hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) risk in treatment-naïve chronic hepatitis C (CHC) patients in China.

To examine the association between DM and HCC, we conducted a case–control study of 300 Chinese CHC patients with HCC, compared to an age- and sex-matched control group of 517 CHC patients not diagnosed with HCC.

We found that DM was more prevalent in the HCC patient group (18.7%) than in the CHC-only patient group (10.8%). We conducted logistic regression analyses adjusting for demographics features and other HCC risk factors and found that DM increased the risk of HCC development nearly 2-fold [adjusted odds ratio (AOR), 95% confidence interval (95% CI), 1.80 (1.17–2.75)]. Meanwhile, the proportion of HCC patients and CHC-only patients with liver cirrhosis were 79.3% and 46.2%, respectively, yielding an AOR of 4.62 (95% CI, 3.31–6.46). Multivariate analyses comparing the risk of HCV-related HCC development in DM patients with and without liver cirrhosis revealed that the estimated AOR (95% CI) for those with liver cirrhosis was 5.60 (2.25–13.96). However, the HCC risk decreased significantly with a later age of diabetes onset (AOR [95% CI], 0.94 [0.89–0.99]).

DM was associated with an increased risk for HCC development in treatment-naïve CHC patients in China. Furthermore, liver cirrhosis and an early DM diagnoses further increased the risks of HCC development in patients diagnosed with both CHC and DM.

Abbreviations: ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AOR = adjusted odds ratios, AST = aspartate aminotransferase, CHC = chronic hepatitis C, CHE = cholinesterase, CI = confidence interval, CT = computed tomography, DAA = direct-acting antiviral agents, GGT = gamma-glutamyl transpeptidase, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MRI = magnetic resonance imaging, NAFLD = nonalcoholic fatty liver disease, PT = prothrombin time, TBIL = total bilirubin.

Keywords: diabetes mellitus, hepatitis C virus, hepatocellular carcinoma

1. Introduction

Hepatocellular carcinoma (HCC) is a global problem, ranking as the fifth and ninth most common cancers among men and women, respectively.[1,2] Major causes of HCC include hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and excessive alcohol consumption.[3,4] Moreover, a recent report showed that chronic HCV infection contributes to 25% of HCC cases in the world.[4] Furthermore, HCC prevalence has increased over the past 20 years, and half of the increase is attributed to HCV.[5,6]

HCV infection has high comorbidity with diabetes mellitus (DM), a metabolic disorder characterized by dysregulation of blood sugar and insulin.[7–10] In addition, epidemiological studies suggested that DM confers a 2- to 3-fold increase in HCC risk in patients with CHC, regardless of whether the patient has undergone curative hepatectomy or antiviral therapy.[4,10–14] Moreover, the development of HCC may be associated with diabetes duration and antidiabetic drug treatment.[15]

However, controversy still exists as to whether DM confers risk for developing HCC after adjusting for other major HCC risk factors including viral hepatitis and alcohol-related liver disease.[16] Furthermore, the association between DM and HCV-related HCC has not been investigated in treatment-naïve patients, nor have prior studies investigated how specific diabetes-related factors affect HCC development. To address these issues, we conducted a case–control study in which we investigated the association between DM and HCC risk in treatment-naïve patients, controlling for other known HCC risk factors.

2. Methods

2.1. Patient selection

This was a cross-sectional study to investigate risk factors associated with HCC in chronic hepatitis C (CHC) patients who were hospitalized at The First Hospital of Jilin University in China from January 2005 to June 2016. In total, 1667 patients

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[a] Department of Hepatology, The First Hospital of Jilin University, Jilin University, [b] Jilin Province Key Laboratory of Infectious Disease, Laboratory of Molecular Virology, [c] Department of Neurology, The First Hospital of Jilin University, Jilin University, Changchun, China.

[*] Correspondence: Pujun Gao, Department of Hepatology, The First Hospital of Jilin University, No. 71 Xinmin Street, Changchun 130021, China (e-mail: gpj0411@163.com).

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with chronic HCV infection (CHC), as diagnosed by the presence of anti-HCV antibodies and HCV RNA in the serum for ≥6 months, were recruited for inclusion in our study. We excluded 110 patients because of incomplete information, and we excluded 476 patients according to other exclusion criteria which were described in detail in the next paragraph. There were 300 patients remaining with HCC and 781 patients with CHC only. After matching for sex and age in the HCC group, 517 patients constituted the control sample group.

Subjects were excluded due to the following criteria: coinfection with human immunodeficiency virus or HBV; history or evidence of any other type of cancer; history or evidence of infection with other hepatitis types; presence of other liver disease, such as nonalcoholic fatty liver disease (NAFLD) or alcoholic liver disease; and treatment with direct-acting antiviral agents (DAA) or interferon for CHC.

2.2. Diagnosis of HCC and liver cirrhosis

HCC was diagnosed based on 1 of 3 methods: biopsy; images from both a computerized tomography (CT) scan and magnetic resonance imaging revealing a nodule with arterial hypervascularization, followed up by portal washout scan; or a single positive imaging technique associated with alpha-fetoprotein levels >400 ng/mL.

Liver cirrhosis was diagnosed using either liver biopsy or combined clinical findings, biochemistry, and radiology.

The Independent Institutional Review Board of The First Hospital of Jilin University approved the study protocol and the recruitment of human subjects. We obtained written informed consent from each patient upon enrollment in the study.

2.3. Fibrosis-4 (FIB-4) score and AST to platelet ratio index (APRI)

The FIB-4 score was calculated by the following formula[17]:

$$\text{FIB}-4 = [\text{age (years)} \times \text{AST (U/L)}]/[\text{platelet count (PLT)}\ (10^9/\text{L}) \times \text{ALT (U/L)}^{1/2}]$$

APRI was calculated by this formula[18]:

$$\text{APRI} = (\text{AST(U/L)}/\text{upper limit of normal})/\text{PLT}\ (10^9/\text{L}) \times 100$$

Upper limit of AST = 40 U/L.

2.4. Study variables

We analyzed the following demographic, lifestyle, and health-related variables in this study: sex, age, HCV antibody, liver cirrhosis, gallstones, family history of HCC, cigarette smoking, presence of DM, the age at diagnosis of DM, and the duration and the treatment method of diabetes (metformin or non-metformin). Furthermore, we examined the following biochemical parameters: alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), albumin (ALB), cholinesterase (CHE), prothrombin time (PT), platelet count (PLT), FIB-4 score, APRI, and glucose.

2.5. Statistical analysis

Continuous variables were shown as the mean (25th and 75th percentiles), whereas categorical variables were displayed as numbers and percentages. To determine the significance of our findings, we employed a Chi-square test for categorical variables. For normally distributed continuous variables, we employed an independent sample *t* test. All tests were 2-tailed. We employed multivariate logistic regression to adjust for possible confounding effects among the variables. Additionally, we calculated the adjusted odds ratios (AORs) and 95% confidence intervals (CIs) for these comparisons. We used SPSS, version 13.0 software (SPSS, Inc., Chicago, IL) to perform the statistical analyses. We considered *P* values of <0.05 to be statistically significant.

3. Results

3.1. Patient demographics and clinical characteristics

Demographics and clinical features of the research subjects are summarized in Table 1. We obtained complete diagnostic records

Table 1

Demographic and clinical characteristics of cases and controls.

Variable	HCC, N = 300	CHC-only, N = 517	*P*
Male, N (%)	165 (55.0)	256 (49.5)	0.131
Age, y	63.69 (59.00, 69.00)	62.97 (59.00, 69.00)	0.149
Cigarette smoking, N (%)	58 (19.3)	89 (17.2)	0.447
Family history of HCC, N (%)	1 (0.3)	0 (0.0)	0.189
Diabetes, N (%)	56 (18.7)	56 (10.8)	0.002
Gallstone, N (%)	79 (26.3)	139 (26.9)	0.863
Liver cirrhosis, N (%)	238 (79.3)	239 (46.2)	<0.001
AST, IU/L	90.45 (42.38, 109.38)	90.19 (37.40, 100.55)	0.010
ALT, IU/L	66.07 (30.85, 78.95)	107.99 (29.00, 112.00)	0.024
GGT, IU/L	128.24 (38.00, 142.43)	87.79 (25.20, 89.50)	<0.001
ALP, IU/L	141.91 (79.00, 148.25)	101.09 (67.00, 114.15)	<0.001
TBIL, μmol/L	63.83 (16.93, 45.95)	38.24 (14.50, 36.25)	0.003
ALB, g/L	32.64 (27.40, 37.68)	35.24 (29.40, 39.10)	0.001
CHE, IU/L	3777.16 (2069.25, 5129.50)	5083.03 (2876.00, 6959.00)	<0.001
PT, s	13.21 (11.50, 14.28)	13.00 (11.15, 13.80)	0.001
Glucose, mmol/L	6.10 (4.80, 6.49)	5.78 (4.80, 5.94)	0.291
PLT, 10^9/L	109.36 (68.00, 132.75)	111.30 (74.00, 140.00)	0.190

Continuous variables are expressed as median (25th, 75th percentiles).

ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHC = chronic hepatitis C, CHE = cholinesterase, GGT = gamma-glutamyl transpeptidase, HCC = hepatocellular carcinoma, PLT = platelet count, PT = prothrombin time, TBIL = total bilirubin.

Table 2

Univariate and multivariate analyses of variables associated with HCV-related HCC.

Variable	HCC, N = 300	CHC-only, N = 517	P*	AOR (95% CI)†	P‡
Sex			0.131	1.48 (1.09–2.01)	0.012
Female, N (%)	135 (45.0)	261 (50.5)			
Male, N (%)	165 (55.0)	256 (49.5)			
Age			0.070	—	—
≤50	13 (4.3)	39 (7.5)			
>50	287 (95.7)	478 (92.5)			
Diabetes			0.002	1.80 (1.17–2.75)	0.007
No, N (%)	244 (81.3)	461 (89.2)			
Yes, N (%)	56 (18.7)	56 (10.8)			
Cigarette smoking			0.447	—	—
No, N (%)	242 (80.7)	428 (82.8)			
Yes, N (%)	58 (19.3)	89 (17.2)			
Family history of HCC			0.189	—	—
No, N (%)	299 (99.7)	517 (100)			
Yes, N (%)	1 (0.3)	0 (0.0)			
Liver cirrhosis			<0.001	4.62 (3.31–6.46)	<0.001
No, N (%)	62 (20.7)	278 (53.8)			
Yes, N (%)	238 (79.3)	239 (46.2)			
FIB-4	9.26 (4.14, 11.56)	7.36 (3.13, 9.08)	<0.001	—	—
APRI	2.88 (0.95, 3.59)	2.64 (0.83, 3.04)	0.039	—	—
Gallstone			0.863	—	—
No, N (%)	221 (73.7)	378 (73.1)			
Yes, N (%)	79 (26.3)	139 (26.9)			

AOR = adjusted odds ratio, APRI = AST to Platelet Ratio Index, CHC = chronic hepatitis C, CI = confidence interval, FIB-4 = fibrosis 4, HCC = hepatocellular carcinoma, HCV = hepatitis C virus.

* *P*-value for univariate analysis.

† Adjusted for sex, age, cigarette smoking, APRI, FIB-4, liver cirrhosis, gallstones, and diabetes.

‡ *P*-value for multivariate analysis.

for all 817 study participants. Of all of our study participants, 517 had a diagnosis of CHC only (CHC-only patients), and 300 were newly diagnosed with HCV-related HCC (HCC patients). The HCC patient group was comprised of 55.0% males, and the mean age was 63.69 (59.00, 69.00) years. The control group (CHC) was sex- and age-matched to the HCC group, with 49.5% males and a mean age of 62.97 (59.00, 69.00) years. We found no significant differences between the 2 groups with regard to demographic characteristics including cigarette smoking, family history of HCC, and gallstones. Notably, the prevalence of DM was significantly higher in HCC patients than in CHC-only patients (18.7% vs 10.8%; $P = 0.002$). Likewise, the prevalence of liver cirrhosis was significantly higher in HCC patients compared to the CHC-only patients (79.3% vs 46.2%; $P < 0.001$).

Patients in the HCC group had elevated levels of AST, GGT, ALP, TBIL, and PT compared to the CHC group. Conversely, ALT, ALB, and CHE levels were higher in the CHC-only group compared to the HCC group. The 2 groups had similar glucose and PLT levels.

3.2. Factors associated with HCC development in CHC patients

Our univariate analyses suggested that patients who developed HCC had a higher incidence of liver cirrhosis and diabetes (Table 2). Meanwhile, patients who developed HCC had higher levels of FIB-4 and APRI. In addition, sex, age, cigarette smoking, FIB-4, APRI, liver cirrhosis, gallstones, and diabetes were then considered for multivariate analysis. After adjusting for potential confounders, the independent factors most strongly associated with HCC were sex (male), liver cirrhosis, and DM (Table 2). DM was associated with a nearly 2-fold higher risk of HCC [AOR (95% CI), 1.80 (1.17–2.75); $P = 0.007$], and liver cirrhosis was associated with a 4- to 5-fold higher risk of HCC [AOR (95% CI), 4.62 (3.31–6.46); $P < 0.001$].

3.3. Association between diabetes duration, treatment, or age at diabetes diagnosis and risk of HCC development

Because we found that diabetes was a major risk factor associated with HCC, we further analyzed the association between HCC risk and the following DM-related factors: the age at DM diagnosis; the length of time over which the patient had DM; the method of DM treatment; and other health and lifestyle factors. Table 3 summarizes the results of analyses comparing HCC and CHC-only (control) patients with diabetes patients. A total of 56 HCC patients and 56 controls recalling a prior history of DM were enrolled. Univariate analyses indicated that factors associated with a greater risk of HCC development in treatment-naïve CHC companied by DM patients included: younger age at DM diagnosis ($P = 0.007$); having lived with DM for >5 years ($P = 0.023$); and liver cirrhosis ($P < 0.001$).

We also performed multivariate analyses examining the roles of sex; age at DM diagnosis; duration of DM treatment; type of DM treatment; and liver cirrhosis. CHC patients diagnosed with DM at an older age had a lower risk of HCC development (AOR, 0.94; 95% CI, 0.89–0.99; $P = 0.016$). CHC patients with liver cirrhosis had a much higher risk of HCC development [AOR (95% CI), 5.60 (2.25–13.96); $P < 0.001$]. Conversely, we did not find that the length of time over which CHC patients had diabetes affected the risk of HCC development. Moreover, we found no correlation between the type of DM treatment and risk of HCC development.

Table 3

Association between diabetes duration, treatment, or age at diabetes diagnosis and risk of HCC development.

Variables	HCC patients, N = 56	Controls, N = 56	P^*	AOR (95% CI)†	$P^‡$
Sex			0.705	—	—
Female, N (%)	27 (48.2)	29 (51.8)			
Male, N (%)	29 (51.8)	27 (48.2)			
Age at diabetes diagnosis	54.89 (50.00, 61.50)	59.03 (52.00, 64.75)	0.007	0.94 (0.89–0.99)	0.016
Duration of diabetes			0.023	—	—
≤5 years, N (%)	24 (42.9)	36 (64.3)			
>5 years, N (%)	32 (57.1)	20 (35.7)			
Diabetes treatment			0.508	—	—
Nonmetformin, N (%)	50 (89.3)	52 (92.9)			
Metformin, N (%)	6 (10.7)	4 (7.1)			
Cigarette smoking			0.105	—	—
No, N (%)	45 (80.4)	51 (91.1)			
Yes, N (%)	11 (19.6)	5 (8.9)			
Gallstone			0.670	—	—
No, N (%)	40 (71.4)	42 (75.0)			
Yes, N (%)	16 (28.6)	14 (25.0)			
Liver cirrhosis			<0.001	5.60 (2.25–13.96)	<0.001
No, N (%)	9 (16.1)	29 (51.8)			
Yes, N (%)	47 (83.9)	27 (48.2)			

Continuous variables are expressed as median (25th, 75th percentiles).

AOR = adjusted odds ratio, CI = confidence interval, HCC = hepatocellular carcinoma.

* *P*-value for univariate analysis.

† Adjusted for sex, age at DM diagnosis, duration of DM treatment, type of DM treatment, and liver cirrhosis.

‡ *P*-value for multivariate analysis.

4. Discussion

To our knowledge, our study is the first to examine the association between DM and HCC in treatment-naïve CHC patients in China. We demonstrated that DM confers a nearly 2-fold increase in the risk of HCC development in treatment-naïve CHC patients in China, consistent with results from other studies.[10,19] Likewise, a population-based study using data from the SEER-Medicare database detected a 2- to 3-fold increased risk of HCC in CHC patients with DM, regardless of other major HCC risk factors.[10] Similarly, a European study following 541 CHC patients revealed that the incidence of HCC over 5 years was 11.4% for patients with DM and 5.0% for patients without DM.[19] Likewise, a large cohort study revealed a higher incidence of HCC over 10 years among patients with DM than among those without DM.[16]

We suggest that the biological association between DM and HCV-related HCC may be associated with the elevated insulin levels caused by insulin resistance (IR) in fat, liver, and muscle tissue in DM patients.[20] Elevated insulin levels could increase insulin-like growth factor-1 (IGF-1), which may contribute to carcinogenesis in liver and other tissues.[21–27] In agreement with this hypothesis, epidemiological studies have demonstrated that IR is a critical determinant for cancer incidence and prognosis.[27]

In addition to altered insulin signaling, DM may impact the risk of HCC via several other mechanisms. Chronic hyperglycemia may cause oxidative stress and cellular damage.[23] DM might also impact the progress of liver cirrhosis. Liu et al reported that the presence DM increased the risk for decompensation events (including HCC) compared to patients with cirrhosis only,[28] a finding supported by other earlier studies.[29–31] In addition, although successful HCV eradication with antiviral therapy reduced HCC risk,[32,33] hyperglycemia, and other unfavorable predictors of antiviral treatment efficacy[34,35] may indirectly promote HCC development. Finally, metabolic syndrome, of which DM is a component, increases the risk of nonalcoholic steatohepatitis (NASH), which can lead to HCC.[36,37]

Notably, we found that an early age of DM onset conferred increased risk for HCC development. As stated above, DM-mediated HCC development could be mediated through inflammation, cellular proliferation, apoptosis inhibition, and generation of tumor-causing mutations. Our current result suggests that the biological progression discussed above might change with age, a possibility requiring a more detailed study. Interestingly, although the association between the duration of DM and HCC risk was significant in univariate analyses, it was not significant in our multivariate analyses, in line with an earlier report by Hassan et al.[15]

In the present study, we found no significant difference in HCC risk between patients treated for DM with metformin and without metformin. Metformin, which is an insulin sensitizer, could not only reduce the levels of circulating insulin but also the levels of glucose in patients with IR and hyperinsulinemia.[38–41] In addition, some observational studies[42] hypothesized that metformin aids in improving the responses to antiviral treatment including peg-IFN (PEG-IFN) alfa-2a plus ribavirin (RBV) in patients with naïve genotype 1 (G1) CHC. This indicated that metformin might decrease the incidence of liver cancer in patients with CHC. However, our results conflicted with previous studies.[40,43,44] The reason might be that the patients included in our study were treatment-naïve therefore metformin might not improve responses to antiviral treatment. Second, a side effect of metformin is liver injury which had been reported in previous studies.[45,46] Though it was not as common as other side effects, such as gastrointestinal upset and metabolic acidosis, we do not know whether injury might enlarge in CHC patients and play a role in the development of HCV-related HCC. Third, most existing studies regarding HCV-related HCC, including ours, included very few patients treated with metformin. Therefore, we had a limited ability to assess the associations with HCC, and the results should be interpreted with caution.

Several limitations to our study should be noted. The number of cases in our study was not large, leading to a small number of subjects for the subgroup analyses. The case numbers were limited by our desire to exclude patients undergoing antiviral drug therapy and patients with liver injury induced by other factors, such as alcoholic liver disease and NAFLD. Therefore, our insignificant findings with respect to diabetes duration and treatment type may be a reflection of these low numbers.

In conclusion, we found that DM increased the risk of HCC development among treatment-naïve CHC patients in China. Our findings also suggested that, for patients dually diagnosed with CHC and DM, an early age of DM diagnosis and liver cirrhosis may enhance the risk of developing HCC.

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