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***Retrospective Study***

**Type 2 diabetes mellitus characteristics affect hepatocellular carcinoma development in chronic hepatitis B patients with cirrhosis**

Li MY *et al.* T2DM affects prognosis in CHB patients

## **Abstract**

### **BACKGROUND**

Type 2 diabetes mellitus (T2DM) has been shown to be correlated with hepatocellular carcinoma (HCC) development. However, further investigation is needed to understand how T2DM characteristics affect the prognosis of chronic hepatitis B (CHB) patients.

### **AIM**

To assess the effect of T2DM on CHB patients with cirrhosis and to determine the risk factors.

### **METHODS**

Among the 412 CHB patients with cirrhosis enrolled in this study, there were 196 with T2DM. The patients in the T2DM group were compared to the remaining 216 patients without T2DM (the non-T2DM group). Clinical characteristics and outcomes of the two groups were reviewed and compared.

### **RESULTS**

T2DM was significantly related to hepatocarcinogenesis in this study ( $P = 0.002$ ). The presence of T2DM, being male, alcohol abuse status, alpha-fetoprotein  $> 20$  ng/mL and hepatitis B surface antigen  $> 2.0$  log IU/mL were risk factors for HCC development after multivariate analysis. T2DM duration of more than 5 years and treatment with diet control or insulin  $\pm$  sulfonylurea significantly increased the risk of hepatocarcinogenesis.

### **CONCLUSION**

T2DM and its characteristics increased the risk of HCC in CHB patients with cirrhosis. The importance of diabetic control should be emphasized for these patients.

**Key Words:** Chronic hepatitis B; Diabetes mellitus; Hepatocellular carcinoma; Prognosis; Risk factor

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**Core Tip:** This retrospective study assessed the risk factors in chronic hepatitis B (CHB) patients with type 2 diabetes mellitus (T2DM). A total of 412 CHB patients were enrolled in this study. T2DM, male sex, alcohol abuse, alpha-fetoprotein > 20 ng/mL and hepatitis B surface antigen > 2.0 log IU/mL were risk factors for hepatocellular carcinoma (HCC) development. T2DM duration and treatment were also significantly related to HCC development. Thus, T2DM and T2DM characteristics affect the prognosis of CHB patients with cirrhosis.

## INTRODUCTION

Hepatitis B virus (HBV) infection is a major public health problem worldwide<sup>[1]</sup>. It is estimated that over 257 million people are chronically infected with HBV worldwide, causing 887000 deaths annually<sup>[2]</sup>. Chronic hepatitis B (CHB) can lead to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC)<sup>[1]</sup>. CHB accounts for over 50% of HCC globally, which is the most common type of liver cancer<sup>[3]</sup>. HCC is the second-leading cause of cancer-related deaths in China<sup>[4]</sup>. Many non-HBV factors, including age, sex, alcohol consumption, smoking and type 2 diabetes mellitus (T2DM), may increase HCC risk among CHB patients<sup>[5,6]</sup>.

Currently, T2DM affects more than 440 million individuals globally<sup>[7]</sup>. China has the most people affected by T2DM with 110 million estimated T2DM diagnoses<sup>[8]</sup>. T2DM is a leading cause of death due to renal and heart complications<sup>[9]</sup> as well as an increased risk of multiple cancers<sup>[10]</sup>. Patients with T2DM have a 2.5-4.0-fold risk of developing HCC<sup>[11]</sup>. The precise mechanism of how T2DM affects the development of HCC remains

unclear, although it may be related to insulin resistance and insulin-like growth factor 1 signaling pathways<sup>[12]</sup>. Since the effect of T2DM clinical characteristics on HCC development still requires investigation, this study investigated the relationship between T2DM clinical characteristics and HCC development in T2DM patients with CHB.

## **MATERIALS AND METHODS**

### ***Study population***

This was a retrospective study consisting of consecutive CHB patients at the Fifth Affiliated Hospital of Zhengzhou University in Zhengzhou, China during the period of December 2013 to February 2021. The inclusion criteria were as follows: (1) Hepatitis B surface antigen (HBsAg) positivity for more than 6 mo; (2) Valid clinical characteristics and laboratory outcomes; (3) No hepatotrophic virus coinfection; (4) Cirrhosis present; (5) No alcoholic hepatic diseases or HCC; and (6) No type 1 DM. The final number of patients included in this study was 412. Patients were divided into a T2DM group ( $n = 196$ ) and a non-T2DM group ( $n = 216$ ). This study was conducted under compliance with the Declaration of Helsinki and was approved by the Human Ethics Committee of The Fifth Affiliated Hospital of Zhengzhou University (KY2021031).

### ***Data collection***

Patient data were obtained from the electronic medical record database of the hospital. The prothrombin time and international normalized ratio were measured by an ACL TOP coagulation analyzer (Instrumentation Laboratory, Beckman Coulter, Sydney, NSW, Australia). The platelet count was monitored by an LH 750 Automated Hematology Analyzer (Instrumentation Laboratory, Beckman Coulter). Alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, albumin, total bilirubin and creatinine levels were measured using an AU5800 Clinical Chemistry Analyzer (Instrumentation Laboratory, Beckman Coulter). The serum HBV-DNA level was quantified by polymerase chain reaction using a Roche LightCycler (Roche

Diagnostics, Basel, Switzerland). HBsAg and hepatitis B e-antigen were determined using an AutoLumo A2000Plus Chemiluminescence Detector (Autobio, Zhengzhou, China).

### *Statistical analysis*

Continuous variables were expressed as medians (the first to third quartiles), and the Mann-Whitney *U* test was used to assess continuous variables. The  $\chi^2$  test or Fisher's test was used to analyze categorical variables. The incidence of HCC was analyzed by the Kaplan-Meier method and log-rank test. Cox regression was used to screen and identify factors associated with mortality and hepatocarcinogenesis. Multivariate logistic regression analysis was also performed to identify potential factors associated with T2DM. The model for end-stage liver disease score was calculated according to the standard formula<sup>[13]</sup>. The following cutoffs of analyzed factors were based on previous reports and included age of 65 years<sup>[14]</sup>, HBsAg of 2.0 log IU/mL<sup>[15]</sup>, and HBV-DNA of 20000 IU/mL<sup>[16]</sup>.  $P < 0.05$  was considered statistically significant. All statistical analyses were performed with the SPSS software package (version 22.0; IBM Corp., Armonk, NY, United States).

## **RESULTS**

### *Baseline characteristics*

A total of 412 CHB patients with cirrhosis were enrolled in this study, including 196 patients with pre-existing T2DM at baseline and 216 patients without T2DM at baseline. Their characteristics are summarized in Table 1. Compared to patients in the non-T2DM group, patients in the T2DM group had significantly lower prothrombin time [11.8 (10.8-14.1) *vs* 10.4 (9.6-11.3), respectively,  $P < 0.001$ ] and international normalized ratio [1.05 (0.96-1.24) *vs* 0.94 (0.87-1.01), respectively,  $P < 0.001$ ]. Since nucleos(t)ide analogue (NUC) may affect HCC development, we compared the preparation of NUC between groups. We found that the proportion of different HBV therapies between two groups did not differ significantly (Supplementary Table 1). Therefore, the HBV therapy may

not affect the risk of HCC in this study. The other baseline characteristics did not show significant differences between the two groups.

### ***T2DM characteristics***

In the T2DM group, 22.4% (44/196) of patients had been diagnosed with T2DM for less than 2.0 years, 21.4% (42/196) of patients had been diagnosed with T2DM for 2.1-5.0 years, 26.5% (52/196) of patients had been diagnosed with T2DM for 5.1-10.0 years, and 29.6% (58/196) of patients had been diagnosed with T2DM for more than 10.0 years. Among all the T2DM patients, 57.1% (112/196) were treated with metformin with or without sulfonylurea treatment, 25.5% (50/196) were treated with insulin with or without sulfonylurea treatment, and 17.3% (34/196) controlled T2DM with diet alone.

### ***Factors associated with hepatocarcinogenesis***

The factors related to hepatocarcinogenesis were assessed (Table 2). The analyzed factors included age, sex, smoking status, alcohol abuse status, dyslipidemia, T2DM, ascites, esophagogastric varices, alpha-fetoprotein (AFP), HBsAg, hepatitis B e-antigen, HBV-DNA, and antiviral treatment. The univariate analysis showed that sex ( $P < 0.001$ ), smoking status ( $P = 0.013$ ), T2DM ( $P = 0.002$ ) and ascites ( $P = 0.016$ ) were significantly related to hepatocarcinogenesis. Then, the multivariate analysis was conducted to analyze the factors associated with hepatocarcinogenesis. The results showed that sex [hazard ratio (HR) = 3.47, 95% confidence interval (CI): 1.36-8.89,  $P = 0.010$ ], alcohol abuse status (HR = 1.38, 95%CI: 0.80-1.68,  $P = 0.008$ ), T2DM (HR = 6.73, 95%CI: 2.77-16.36,  $P < 0.001$ ), AFP (HR = 3.89, 95%CI: 1.06-14.27,  $P = 0.041$ ) and HBsAg (HR = 4.10, 95%CI: 1.52-11.12,  $P = 0.005$ ) were significantly related with hepatocarcinogenesis.

The Kaplan-Meier survival curves showed that the hepatocarcinogenesis probability of the T2DM group and non-T2DM group was significantly different (Figure 1). The median hepatocarcinogenesis times for the T2DM group and non-T2DM group were 30 mo and 34 mo, respectively. We then analyzed the relationship between T2DM and hepatocarcinogenesis among all subgroups (Figure 2). T2DM and hepatocarcinogenesis

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were significantly correlated in the following subgroups: Males (HR = 2.04, 95%CI: 1.08-3.84,  $P = 0.028$ ); non-smokers (HR = 10.73, 95%CI: 3.12-36.98,  $P < 0.001$ ); patients without alcohol abuse (HR = 2.49, 95%CI: 1.27-4.87,  $P = 0.008$ ); patients with HBsAg > 2.0 log IU/mL (HR = 5.47, 95%CI: 2.36-12.65,  $P < 0.001$ ); and patients not treated with antiviral medication (HR = 3.29, 95%CI: 1.44-7.54,  $P = 0.005$ ).  
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### ***T2DM characteristics and hepatocarcinogenesis***

Since T2DM was shown to be associated with hepatocarcinogenesis in CHB patients, we analyzed the relationship between T2DM characteristics and hepatocarcinogenesis in CHB patients with T2DM. We found that patient age over 65-years-old ( $P < 0.001$ ), male sex ( $P = 0.049$ ), AFP > 20 ng/mL ( $P = 0.002$ ), HBsAg > 2.0 log IU/mL ( $P = 0.001$ ) or receipt of antiviral treatment ( $P = 0.007$ ) were significantly correlated with hepatocarcinogenesis in the T2DM group (Table 3). Among T2DM characteristics, T2DM duration of more than 5 years (HR = 6.74, 95%CI: 2.36-19.29,  $P < 0.001$ ), insulin  $\pm$  sulfonylurea therapy (HR = 1.45, 95%CI: 0.26-7.96,  $P = 0.041$ ) and diet control only (HR = 10.70, 95%CI: 2.91-39.31,  $P < 0.001$ ) were significantly correlated with hepatocarcinogenesis in the T2DM group.

### **DISCUSSION**

T2DM is a major public health problem in China<sup>[17]</sup>. It has been suggested that T2DM is a risk factor of HCC development, liver disease progression and mortality in CHB patients<sup>[18]</sup>. However, it remains controversial whether T2DM is related to HCC development. Results from the current study suggested that the presence of T2DM significantly increased the risk of HCC development in CHB patients with cirrhosis. Cox regression analysis showed that sex, alcohol abuse status, T2DM, AFP and HBsAg were significantly related with hepatocarcinogenesis. The T2DM characteristics, including duration and treatment, were found to be significantly related with hepatocarcinogenesis.



In the present study, the incidence of hepatocarcinogenesis was significantly correlated to sex ( $P = 0.010$ ), alcohol abuse status ( $P = 0.008$ ), T2DM ( $P < 0.001$ ), AFP ( $P = 0.041$ ) and HBsAg ( $P = 0.005$ ). A recent study showed that gamma-glutamyltranspeptidase ( $\gamma$ -GTP) levels were related with the risk of HCC among HBV patients on NUC therapy<sup>[19]</sup>. But in this study, the level of  $\gamma$ -GTP did not differ between two groups in both univariate and multivariate analysis ( $P = 0.692$ ;  $P = 0.530$ ). Thus, whether  $\gamma$ -GTP levels affect the prognosis of CHB patients still needs to be further verified. The Kaplan-Meier survival curves showed that the probability of hepatocarcinogenesis<sup>12</sup> in the T2DM group was significantly different than that in the non-T2DM group. These results suggested that T2DM was an independent risk factor for HCC development. These findings were consistent with prior studies<sup>[20,21]</sup>. The subgroup analysis showed that the effect of T2DM on HCC development was stronger in CHB patients in the subgroups of male, non-smoker, no alcohol abuse, HBsAg  $> 2.0$  log IU/mL and no antiviral treatment. This difference may be due to the limited number of patients, which still needs to be validated in further studies.

It is notable that T2DM characteristics were associated with hepatocarcinogenesis in this study. In cirrhotic CHB patients with T2DM, patients who were over 65-years-old or male, who had AFP  $> 20$  ng/mL or HBsAg  $> 2.0$  log IU/mL or who received antiviral treatment had a significantly increased risk of hepatocarcinogenesis. T2DM duration of more than 5 years was found to be significantly correlated to the incidence of hepatocarcinogenesis. It had a 6.74-fold increased risk for HCC compared to in T2DM patients with a duration of less than 5 years.

Moreover, T2DM patients who were treated with only diet control or insulin  $\pm$  sulfonylurea therapy were at a higher risk for HCC development. However, it is still unknown whether different treatment strategies affect HCC development. It has been reported that the use of insulin can elevate the risk of HCC<sup>[9,22]</sup>. On the contrary, metformin treatment was reported to be associated with a reduced risk of HCC<sup>[12]</sup>. A large-scale study also showed that<sup>8</sup> the use of metformin among DM patients can significantly reduce the HCC risk in chronic hepatitis C patients<sup>[23]</sup>. The underlying

mechanism has not been fully understood, but it may be related with the anti-proliferative and immune modulation effect of metformin<sup>[24]</sup>. Although evidence suggests that sulfonylureas can increase the risk of HCC<sup>[12,25]</sup>, we found that the use of metformin with or without sulfonylurea had a significantly lower risk of HCC. These results suggest that good diabetic management and appropriate therapy are crucial in cirrhotic CHB patients with T2DM. <sup>3</sup> There are some limitations for this study. This is a single center retrospective study, and the sample size was small. Some details of T2DM patients were not collected, which limited further analysis. Thus, the results need to be validated in larger multicenter studies in the future.

## **CONCLUSION**

In conclusion, T2DM was found to be related to a poor CHB prognosis. Analysis suggested that patients who were male, who abused alcohol or who had AFP > 20 ng/mL and HBsAg > 2.0 log IU/mL were at a higher risk for poor outcomes. T2DM characteristics, including T2DM duration of more than 5 years, diet control and insulin ± sulfonylurea therapy, significantly increased the risk of hepatocarcinogenesis. These findings confirmed the importance of diabetic management in CHB patients with cirrhosis. The exact mechanism of how T2DM affects HCC development still warrants further study.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Type 2 diabetes mellitus (T2DM) has been shown to be correlated with hepatocellular carcinoma (HCC) development. However, the T2DM characteristics that affect HCC are unknown.

### ***Research motivation***

T2DM affects more than 440 million individuals globally. T2DM is a leading cause of death due to renal and heart complications as well as an increased risk of multiple cancers. Understanding the correlation between T2DM and HCC will benefit patients.

### ***Research objectives***

This study aimed to investigate the relationship between T2DM clinical characteristics and HCC development in pre-existing T2DM patients with chronic hepatitis B (CHB).

### ***Research methods***

Among 412 CHB patients enrolled in this study, there were 196 patients with T2DM. The patients were divided into the T2DM group and the non-T2DM group ( $n = 216$ ). Clinical characteristics and outcomes of the two groups were compared.

### ***Research results***

T2DM was found to be significantly related to hepatocarcinogenesis in this study. After multivariate analysis, T2DM, male sex, alcohol abuse status, alpha-fetoprotein (AFP) > 20 ng/mL and hepatitis B surface antigen (HBsAg) > 2.0 log IU/mL were risk factors for HCC development. T2DM duration and therapy significantly increased the risk of hepatocarcinogenesis.

### ***Research conclusions***

T2DM was found to be related to a poor CHB prognosis. Male sex, alcohol abuse status, AFP > 20 ng/mL and HBsAg > 2.0 log IU/mL were also significantly related with poor outcomes. T2DM characteristics, including T2DM duration more than 5 years and treatment of diet control or insulin  $\pm$  sulfonylurea significantly increased the risk of hepatocarcinogenesis.

### ***Research perspectives***

These findings confirmed the importance of diabetic management in CHB patients. The exact mechanism of how T2DM affects HCC development still warrants further study.

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