Association Between Hepatocellular Carcinoma and Type 2 Diabetes Mellitus in Chinese Hepatitis B Virus Cirrhosis Patients: A Case-Control Study

Huixian Han*, Han Deng*, Tao Han*, Haitao Zhao, Feifei Hou, Xingshun Qi

Background: Whether the presence of type 2 diabetes mellitus (T2DM) increases the risk of hepatocellular carcinoma (HCC) in hepatitis B virus (HBV) cirrhosis patients is controversial. We conducted a retrospective case-control study to evaluate this issue.

Material/Methods: We considered all patients diagnosed with HBV-related liver cirrhosis at our hospital from July 2011 to June 2014. The case (n=91) and control (n=91) groups were HBV cirrhosis patients with and without T2DM, respectively. They were matched at a ratio of 1:1 according to the individual age (±2 years) and same sex and Child-Pugh score.

Results: None of the baseline data were significantly different between the 2 groups. The percentage of HCC was similar between the 2 groups (case versus control group: 34.1% versus 46.2%, P=0.13). In the case group, sex (P=0.002), alkaline phosphatase (P<0.001), γ-glutamine transferase (P=0.001), and sodium (P=0.003) were associated with the risk of HCC. In the control group, platelet (P=0.041), alanine aminotransferase (P=0.034), aspartate aminotransferase (P=0.026), alkaline phosphatase (P=0.001), and γ-glutamine transferase (P<0.001) were associated with the risk of HCC.

Conclusions: T2DM may not be a risk factor for the presence of HCC in HBV cirrhosis.

MeSH Keywords: Carcinoma, Hepatocellular • Diabetes Mellitus • Hepatitis B Virus • Liver Cirrhosis • Risk Factors

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide [1–3]. More than 80% of cases develop in Asian and African countries, and 55% of the cases are from China alone [1–3]. Hepatitis B virus (HBV) infection is a major etiology of HCC. Notably, China has approximately 93 million HBV carriers and 30 million chronic HBV patients [4,5].

Type 2 diabetes mellitus (T2DM) is a global health problem. In 2011, almost 4.6 million deaths were attributed to diabetes, which was 8.2% of all-cause deaths in the world [6]. In 2013, the International Diabetes Federation estimated that 380 million people had diabetes worldwide [7].

Evidence supports that T2DM may be a potential risk factor for the presence of HCC, regardless of the potential etiology of liver diseases [8–11]. A majority of studies have also shown that T2DM is a potential risk factor for the presence of HCC in patients with hepatitis C virus infection [12–15]. However, the association between T2DM and HCC in chronic HBV infection remains controversial [16–22]. Herein, we conducted a case-control study to evaluate this issue.

**Material and Methods**

**Study design**

We conducted a retrospective case-control study at our hospital from July 2011 to June 2014. The inclusion criteria were: 1) patients were diagnosed with liver cirrhosis; and 2) patients were known to have positive HBV surface antigen. The exclusion criteria were: 1) patients were known to have negative HBV surface antigen; 2) patients with HBV-related cirrhosis and who had a combination of other causes (such as HCV infection, alcohol, and autoimmune hepatitis); 3) patients diagnosed with additional malignant tumors unrelated to the liver; and 4) relevant laboratory data regarding HBV surface antigen or Child-Pugh score were missing.

The case group was composed of patients with HBV cirrhosis with T2DM. The control group was patients with HBV cirrhosis without T2DM. The case and control groups were matched at a ratio of 1:1 according to the individual age (±2 years), the same sex, and Child-Pugh score. In the case of repeated admissions, we chose only the first admission that was eligible for the study.

Some relevant data were reported in our previous papers [23–33]. This study was approved by the Medical Ethics Committee of our hospital (approval number k (2016)31). Due to the retrospective nature of this study, the requirement for written informed consent was waived.

**Data collection**

The following data were collected from the electronic medical records: age, sex, ascites, hepatic encephalopathy (HE), red blood cell (RBC), hemoglobin (Hb), white blood cell (WBC), platelet (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), albumin (ALB), total bilirubin (TBIL), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), creatinine (Cr), sodium ion (Na), potassium ion (K), calcium ion (Ca), titer of HBV-DNA, diagnosis of T2DM, duration of T2DM, fasting plasma glucose (FPG), HCC, number of HCC lesions, maximum diameter of HCC lesion, and glycosylated hemoglobin (HA1C). We calculated the Child-Pugh [34] and model for end-stage of liver disease (MELD) scores [35].

**Diagnosis of liver cirrhosis**

The diagnosis of liver cirrhosis was primarily established according to the history of chronic liver diseases, clinical symptoms (e.g., decompensated events) and signs, laboratory tests (e.g., liver function and coagulation tests), and abdominal images (e.g., liver and spleen morphology). If necessary, liver biopsy was performed.

**Diagnosis of T2DM**

T2DM was diagnosed as a FPG level of >7.0 mmol/L (126 mg/dl), a plasma glucose level of >11.1 mmol/L (200 mg/dl) at 2 h in a 75-g oral glucose tolerance test, or typical T2DM symptoms together with a plasma glucose level of >11.1 mmol/L (200 mg/dl) according to the World Health Organization (WHO) diagnostic criteria in 1999.

**Evaluation of HCC**

Criteria for the diagnosis of HCC were defined by the European Association for the Study of the Liver [36]. The absence of HCC was assessed by high-quality imaging examinations (abdominal US, CT scan, or MRI). We evaluated the presence of HCC by reviewing the original electronic medical records.

**Statistical analysis**

Categorical data are expressed as frequencies (percentages) and were compared by using the chi-square test. Continuous data are expressed as mean ± standard deviation or median (range) and were compared by using the independent-samples t test. A two-sided P<0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 17.0 (SPSS Inc. Chicago, IL, USA).
Results

Characteristics of the 182 patients are summarized in Table 1. The mean age was 56.18±7.72 years. The percentage of patients with Child-Pugh class A, B, and C were 44%, 45.1%, and 11%, respectively. The mean Child-Pugh score was 7.24±1.97. Among them, 73 (40.1%) patients had HCC. A total of 58 (79.5%) HCC patients had available imaging data for measuring the number of HCC lesions; the percentage of patients with 1, 2–3, and >3 HCC lesions were 55.2%, 8.6%, and 36.2%, respectively. A total of 48 (65.8%) HCC patients had available imaging data for measuring the maximum diameter of HCC lesion; the mean maximum diameter of HCC lesion was 5.67±3.60 cm. None of the biochemical data were significantly different between the 2 groups.

In the case group, 34.1% (31/91) of patients had HCC; among them, a total of 24 (79.5%) patients had available imaging data for measuring the number of HCC lesions; the percentage of patients with 1, 2–3, and >3 HCC lesions were 58.3%, 4.2% and 37.5%, respectively; a total of 21 (67.7%) patients had available imaging data for measuring the maximum diameter of HCC lesion; the mean maximum diameter of HCC lesion was 5.59±3.60 cm. In the control group, 46.2% (42/91) of patients had HCC (P=0.13); among them, a total of 34 (83.3%) patients had available imaging data for measuring the number of HCC lesions; the percentage of patients with 1, 2–3, and >3 HCC lesions were 52.9%, 11.8%, and 35.3%, respectively (P=0.596); a total of 27 (64.3%) patients had available imaging data for measuring the maximum diameter of HCC lesion; the mean maximum diameter of HCC lesion was 5.74±3.67 cm (P=0.882).

We analyzed the characteristics of T2DM cases in Table 2. We found that sex (P=0.002), ALP (P<0.001), GGT (P=0.001), and Na (P=0.003) were associated with HCC in T2DM cases. FPG (P=0.081), HA1C (P=0.059), and duration of T2DM (P=0.065) were not significantly different between HCC and non-HCC cases.

We also analyzed the characteristics of non-T2DM cases in Table 3. We found that PLT (P=0.041), ALT (P=0.034), AST (P=0.026), ALP (P<0.001), and GGT (P<0.001) were associated with HCC in non-T2DM cases.

Discussion

In our case-control study, all of the baseline data were comparable between patients with and without T2DM. We drew a conclusion that T2DM might not be a risk factor for the presence of HCC in chronic HBV cirrhosis patients. When we compared the patient characteristics between T2DM cases with and without HCC, sex, ALP, GGT, and Na were associated with HCC; in non-T2DM cases, PLT, ALT, AST, ALP, and GGT were associated with HCC.

Our findings are different from previous evidence from New Zealand that T2DM was a potential risk factor for the presence of HCC in HBV cirrhosis patients. In 2014, Hsiang et al. conducted a retrospective study of HBV cirrhosis patients and found that T2DM was a risk factor for liver-related death and complications in hepatitis B cirrhosis patients and that T2DM was a predictor of HCC (hazard ratio=2.36, 95% confidence interval=1.14–4.85, P=0.002) [16]. In addition, a Japanese study of 156 HCC patients with chronic HBV infection suggested that T2DM might be involved in the hepatocarcinogenesis in such patients [17]. The potential mechanisms can explain the association with T2DM and HCC as follows: 1) elevated blood glucose can contribute to advanced glycation end products that can increase inflammation, which has been reported to contribute to insulin resistance [37–39]; 2) insulin resistance increases the level of insulin-like growth factor, which is associated with cancer development and cancer cell proliferation [40,41]; 3) T2DM patients have excess free radical and free radical-mediated DNA damage, which gives rise to the DNA repairing process and leads to gene mutation and subsequent chances that initiate cancer [32].

On the other hand, evidence from China appears to be very controversial [18–22]. In 2012, a Chinese Taiwanese case-control study demonstrated statistically significant synergistic interactions between T2DM and HBV infection in the development of HCC [18]. In 2015, a cohort study using the Chinese Taiwanese National Health Insurance Research Database showed that new onset diabetes predicted a significantly higher cumulative risk of HCC in HBV patients (relative risk=1.628, 95% confidence interval=1.14–2.378). Notably, this statistical association was relatively mild [19]. By contrast, another 3 Chinese studies did not establish such a significant association between T2DM and HCC. In 2010, a community cross-sectional and case-control study revealed that neither T2DM nor overweight was a risk factor for HCC in a dual HBV and HCV endemic area [20]. In 2013, a Chinese cross-sectional case-control study of 122 HBV-infected cirrhotic patients with HCC and 248 cirrhotic patients without HCC found that T2DM might be a potentially protective factor for HCC [21]. In the same year, a retrospective cohort study explored the risk factors associated with the development of HCC in 56 231 participants over 40 years old. Regardless of hepatitis B or C virus infection, T2DM, metabolic syndrome and obesity were not risk factors for developing HCC [22]. Because the precise mechanism is unknown, more prospective cohort studies are warranted.

ALP and GGT may be potential risk factors for developing HCC in HBV-related cirrhosis patients regardless of T2DM. In clinical practice, ALP and GGT are 2 common variables reflecting...
Table 1. Comparison between T2DM versus non-T2DM in all patients.

| Variables                        | Total (n=182) | T2DM (n=91) | Non-T2DM (n=91) | P value |
|----------------------------------|---------------|-------------|-----------------|---------|
| Sex (male/female), n (%)         | 182           | 144 (79.1%)/38 (20.9%) | 91               | 72 (79.1%)/19 (20.9%) | 1 |
| Age (years)                      | 182           | 56.18±7.72 (39.46–79.61) | 91               | 55.17 (39.46–78.5) | 0.369 |
| Ascites, n (%)                   | 182           | 98 (53.8%)/52 (57.1%)/46 (50.5%) | 91               | 33 (36.3%)/34 (37.4%) | 0.396 |
| HE, n (%)                        | 182           | 170 (93.4%)/85 (93.4%)/85 (93.4%) | 91               | 3 (1.1%)/2 (2.2%) | 0.801 |
| Laboratory tests                 |               |             |                 |         |
| RBC (10¹²/L)                     | 182           | 3.32±0.84 (1.55–5.65) | 91               | 3.32±0.79 (1.76–4.99) | 0.913 |
| Hb (g/L)                         | 182           | 102.5±31.18 (3.2–177) | 91               | 104.77±30.88 (48–177) | 0.336 |
| WBC (10⁹/L)                      | 182           | 5.82±5.15 (0.9–38) | 91               | 6.49±5.93 (1.3–38) | 0.076 |
| PLT (10⁹/L)                      | 182           | 98.68±63.45 (18–392) | 91               | 101.09±64.11 (23–316) | 0.61 |
| TBIL (umol/L)                    | 182           | 42.8±93.66 (3.9–809.8) | 91               | 48.10±120.26 (3.9–809.8) | 0.447 |
| ALB (g/L)                        | 181           | 32.81±6.40 (17.3–53.9) | 91               | 32.97±6.67 (18.9–47.5) | 0.725 |
| ALT (U/L)                        | 182           | 55.10±127.62 (8–1460) | 91               | 56.25±152.28 (8–1460) | 0.903 |
| AST (U/L)                        | 182           | 76.69±143.89 (11–1318) | 91               | 65.43±100.43 (12–819) | 0.292 |
| ALP (U/L)                        | 182           | 101.76±54.46 (39–322) | 91               | 103.85±54.34 (41–322) | 0.605 |
| GGT (U/L)                        | 181           | 105.56±132.26 (8–994) | 91               | 110.15±131.24 (15–713) | 0.64 |
| BUN (mmol/L)                     | 182           | 8.05±6.66 (1.54–55.01) | 91               | 8.96±6.51 (2.03–45.52) | 0.577 |
| Cr (umol/L)                      | 182           | 82.89±94.87 (28–675) | 91               | 91.73±104.42 (35–668) | 0.209 |
| K (mmol/L)                       | 182           | 4.07±0.46 (2.9–5.8) | 91               | 4.10±0.45 (3.1–5.11) | 0.332 |

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Table 1 continued. Comparison between T2DM versus non-T2DM in all patients.

| Variables                                      | Total (n=182) | T2DM (n=91) | Non-T2DM (n=91) | P value |
|------------------------------------------------|---------------|-------------|-----------------|---------|
| **Na (mmol/L)**                                |               |             |                 |         |
| No. Pts available                             | 182           | 91          | 91              |         |
| Mean±SD or frequency (percentage)             | 137.9±4.6     | 138.5±4.5   | 138.7±4.5       | 0.676   |
| Median (Range)                                | (109.2–150)   | (123.6–150) | (109.2–148.5)   |         |
| **Ca (mmol/L)**                                |               |             |                 |         |
| No. Pts available                             | 71            | 37          | 34              |         |
| Mean±SD or frequency (percentage)             | 2.1±0.23      | 2.12±0.23   | 2.14±0.23       | 0.483   |
| Median (Range)                                | (1.35–2.82)   | (1.65–2.82) | (1.35–2.76)     |         |
| **PT (second)**                                |               |             |                 |         |
| No. Pts available                             | 182           | 91          | 91              |         |
| Mean±SD or frequency (percentage)             | 16.09±3.77    | 16.03±3.69  | 15.1±3.86       | 0.848   |
| Median (Range)                                | (11–40.9)     | (11.5–35.6) | (11–40.9)       |         |
| **APTT (second)**                              |               |             |                 |         |
| No. Pts available                             | 182           | 91          | 91              |         |
| Mean±SD or frequency (percentage)             | 41.9±8.24     | 41.1±8.22   | 42.8±8.22       | 0.165   |
| Median (Range)                                | (28.2–87.3)   | (29.1–87.3) | (28.2–74.6)     |         |
| **INR**                                        |               |             |                 |         |
| No. Pts available                             | 182           | 91          | 91              |         |
| Mean±SD or frequency (percentage)             | 1.31±0.43     | 1.30±0.43   | 1.32±0.43       | 0.842   |
| Median (Range)                                | (0.81–4.19)   | (0.83–3.7)  | (0.81–4.19)     |         |
| **Titer of HBV-DNA (10^4 copies/ml)**          |               |             |                 |         |
| No. Pts available                             | 58            | 25          | 33              |         |
| Mean±SD or frequency (percentage)             | 729.5±3282.64 | 302.6±984.20| 1052.9±4268.20  | 0.393   |
| Median (Range)                                | (0.11–24000)  | (0.12–4200) | (0.11–24000)    |         |
| **Child-Pugh class, n (%)**                    |               |             |                 |         |
| A                                              | 80 (44%)      | 40 (44%)    | 40 (44%)        |         |
| B                                              | 82 (45.1%)    | 41 (45.1%)  | 41 (45.1%)      |         |
| C                                              | 20 (11%)      | 10 (11%)    | 10 (11%)        |         |
| **Child-Pugh score**                           |               |             |                 |         |
| No. Pts available                             | 182           | 91          | 91              |         |
| Mean±SD or frequency (percentage)             | 7.2±1.97      | 7.2±1.97    | 7.2±1.97        | 1       |
| Median (Range)                                | (5–14)        | (5–14)      | (5–14)          |         |
| **MELD score**                                 |               |             |                 |         |
| No. Pts available                             | 182           | 91          | 91              |         |
| Mean±SD or frequency (percentage)             | 6.7±7.22      | 7.2±7.83    | 6.2±6.56        | 0.377   |
| Median (Range)                                | (4.49–43.1)   | (4.49–43.1) | (3.39–37.57)    |         |
| **FPG (mmol/L)**                               |               |             |                 |         |
| No. Pts available                             | 88            | 88          | 0               |         |
| Mean±SD or frequency (percentage)             | 9.1±4.50      | 9.1±4.50    | NA              |         |
| Median (Range)                                | (3.9–34.7)    | (3.9–34.7)  | NA              |         |
| **HA1C (%)**                                   |               |             |                 |         |
| No. Pts available                             | 17            | 17          | 0               |         |
| Mean±SD or frequency (percentage)             | 8.3±3.07      | 8.3±3.07    | NA              |         |
| Median (Range)                                | (4.8–15.6)    | (4.8–15.6)  | NA              |         |
| **Duration (years)**                           |               |             |                 |         |
| No. Pts available                             | 76            | 76          | 0               |         |
| Mean±SD or frequency (percentage)             | 6.7±5.66      | 6.7±5.66    | NA              |         |
| Median (Range)                                | (0.00–28)     | (0.00–28)   | NA              |         |
| **HCC, n (%)**                                 |               |             |                 |         |
| No. Pts available                             | 182           | 91          | 91              |         |
| Mean±SD or frequency (percentage)             | 73 (40.1%)    | 31 (34.1%)  | 42 (46.2%)      | 0.13    |
| Median (Range)                                |                 |             |                 |         |
| **Number of HCC lesions**                     |               |             |                 |         |
| No. Pts available                             | 58            | 24          | 34              | 0.596   |
| Mean±SD or frequency (percentage)             |                 |             |                 |         |
| Median (Range)                                |                 |             |                 |         |
| **Maximum diameter of HCC lesion (cm)**       |               |             |                 |         |
| No. Pts available                             | 48            | 21          | 27              | 0.882   |
| Mean±SD or frequency (percentage)             | 5.6±3.60      | 5.5±3.60    | 5.7±3.67        |         |
| Median (Range)                                | (1.40–15.5)   | (1.5–12.2)  | (1.4–15.5)      |         |

ALB – albumin; ALP – alkaline phosphatase; ALT – alanine aminotransferase; APTT – activated partial thromboplastin time; AST – aspartate aminotransferase; BUN – blood urea nitrogen; Ca – calcium ion; Cr – creatinine; Duration – the duration of T2DM; FPG – fasting plasma glucose; GGT – γ-glutamine transferase; HE – hepatic encephalopathy; HCC – hepatocellular carcinoma; HA1C – glycosylated hemoglobin; HB – hemoglobin; INR – international normalized ratio; K – potassium ion; MELD – model for end-stage liver disease; Na – sodium ion; NA – not available; PLT – platelet; PT – prothrombin time; Pts – patients; RBC – red blood cell; T2DM – type 2 diabetes; TBIL – total bilirubin; WBC – white blood cell.
| Variables               | HCC (n=31)                                                                 | Non-HCC (n=60)                                                                 | P value |
|-------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------|
|                         | No. Pts available | Mean±SD or frequency (percentage) | Median | No. Pts available | Mean±SD or frequency (percentage) | Median |
| Sex (male/female), n (%) | 30 (96.8%)/1 (3.2%) | 60 | 42 (70%)/18 (30%) | 0.002 |
| Age (years)             | 31 | 56.49±7.29 | 55.82 (39.46–70.8) | 60 | 55.24±8.09 | 55.07 (40.6–78.5) | 0.474 |
| Ascites, n (%)          | 31 | No | 18 (58.1%) | 34 (56.7%) | 0.64 |
|                         | 60 | Mild | 1 (3.2%) | 5 (8.3%) | 0.002 |
|                         | 60 | Moderate to severe | 12 (38.7%) | 21 (35%) |
| HE, n (%)               | 31 | No | 29 (93.5%) | 56 (93.3%) | 0.743 |
|                         | 60 | Grade I–II | 3 (5%) | 1 (1.7%) | 0.002 |
| Laboratory tests        | RBC (10^12/L) | 31 | 3.53±0.91 | 3.72 (1.76–4.99) | 60 | 3.22±0.72 | 3.3 (1.82–4.7) | 0.096 |
|                         | Hb (g/L) | 31 | 113.13±33.52 | 119 (48–177) | 60 | 100.45±28.77 | 104 (51–155) | 0.063 |
|                         | WBC (10^9/L) | 31 | 6.59±6.30 | 5 (2.6–38) | 60 | 6.45±5.78 | 4.1 (1.3–29.1) | 0.913 |
|                         | PLT (10^9/L) | 31 | 117.29±66.25 | 105 (27–281) | 60 | 92.72±61.88 | 75 (23–316) | 0.083 |
|                         | TBIL (umol/L) | 31 | 45.92±85.09 | 19.1 (8–396.1) | 60 | 49.23±135.56 | 18.3 (3.9–809.8) | 0.902 |
|                         | ALB (g/L) | 31 | 33.35±6.96 | 33 (19.2–47.5) | 60 | 32.78±6.57 | 32.75 (18.9–45.6) | 0.705 |
|                         | ALT (U/L) | 31 | 44.58±28.42 | 36 (10–153) | 60 | 62.28±186.67 | 25 (8–1460) | 0.602 |
|                         | AST (U/L) | 31 | 63.45±64.96 | 48 (16–368) | 60 | 66.45±115.06 | 30 (12–819) | 0.894 |
|                         | ALP (U/L) | 31 | 140.21±68.46 | 126 (48.7–322.2) | 60 | 85.07±32.67 | 77 (41–170) | <0.001 |
|                         | GGT (U/L) | 31 | 187.94±171.68 | 123 (36–713) | 60 | 69.97±80.42 | 50 (15–542) | 0.001 |
|                         | BUN (mmol/L) | 31 | 8.1±5.57 | 6.24 (3.58–31.51) | 60 | 9.4±6.95 | 7.5 (2.03–45.52) | 0.368 |
|                         | Cr (umol/L) | 31 | 70.5±45.17 | 57.1 (39–263) | 60 | 102.72±127.30 | 62.4 (35–668) | 0.083 |
|                         | K (mmol/L) | 31 | 4.15±0.4 | 4.1 (3.15–5.04) | 60 | 4.08±0.48 | 4.09 (3.1–5.11) | 0.523 |
|                         | Na (mmol/L) | 31 | 135.96±4.38 | 136.8 (123.6–143.2) | 60 | 138.82±4.20 | 139.35 (130.6–150) | 0.003 |

Table 2. Comparison between HCC versus non-HCC in T2DM patients.
cholestasis. The severity of cholestasis might be higher in liver cirrhosis with HCC than in liver cirrhosis without HCC. An electron microscopic cytochemistry study showed that the reaction ratio of nucleolar ALPase in HCC cells indicated approximately 5-fold higher frequency than in the normal cells. This phenomenon means that a high level of ALPase was associated with cancer cell proliferation in nucleolar localization. ALP affects tumor proliferation and progression [42].

In 2015, a study showed that GGT was an independent predictive factor for the overall survival of HCC patients [43]. It might be mediated by the functions of the oxidative stress pathways in cellular responses [44]. Indeed, ALP has been included in the Chinese University Prognostic Index, which can predict the prognosis of HCC [45]. In 2014, Xu et al. reported that elevated ALP and GGT levels were predictors for the prognosis of HCC [46].

Na may be a potential risk factor for developing HCC in HBV-related cirrhosis patients with T2DM. In clinical practice, serum Na is a prognostic indicator in patients with cirrhosis. A prospective study that compared the predictive accuracy of the different models indicated that the MELD-Na score was superior to the MELD score for the prognostic assessment of HCC [47]. This phenomenon indirectly indicates that Na might be associated with HCC.

### Table 2 continued. Comparison between HCC versus non-HCC in T2DM patients.

| Variables                              | HCC (n=31)                                      | Non-HCC (n=60)                                      | P value |
|----------------------------------------|------------------------------------------------|-------------------------------------------------|---------|
| No. Pts available                      | Mean±SD or frequency (percentage)              | Mean±SD or frequency (percentage)                |         |
| Ca (mmol/L)                            | 6                                              | 2.02±0.27 (1.65–2.4)                             | 2.14±0.22 (1.79–2.82) | 0.233   |
| PT (second)                            | 31                                             | 15.78±4.17 (11.8–35.6)                          | 16.17±3.45 (11.5–31.8) | 0.643   |
| APTT (second)                          | 31                                             | 41.60±6.54 (32–65.9)                            | 40.91±9.01 (29.1–87.3) | 0.707   |
| INR                                    | 31                                             | 1.27±0.49 (0.89–3.7)                            | 1.32±0.40 (0.83–3.22) | 0.644   |
| Titer of HBV-DNA (10^4 copies/ml)      | 8                                              | 34.59±54.24 (0.29–140)                          | 428.74±1182.74 (0.12–4200) | 0.361   |
| Child-Pugh class, n (%)                | 31                                             | 14 (45.2%)                                      | 26 (43.3%)                           | 0.872   |
| A                                      | 13 (41.9%)                                     | 13 (41.9%)                                      | 28 (46.7%)                           |         |
| C                                      | 4 (12.9%)                                      | 4 (12.9%)                                       | 6 (10%)                              |         |
| Child-Pugh score                       | 31                                             | 7.29±2.18 (5–14)                                | 7.22±1.88 (5–12)                   | 0.867   |
| MELD score                             | 31                                             | 5.89±8.46 (–2.45–43.1)                          | 7.90±7.47 (–4.19–26.4)             | 0.248   |
| FPG (mmol/L)                           | 28                                             | 9.01±5.77 (4.31–34.47)                          | 9.25±3.31 (3.92–21.14)             | 0.813   |
| HA1C (%)                               | 6                                              | 8.9±3.20 (4.8–13.5)                             | 7.97±3.10 (4.9–15.6)              | 0.569   |
| Duration (years)                       | 25                                             | 6.38±5.93 (0–22)                                | 6.99±5.56 (0–28)                  | 0.658   |

ALB – albumin; ALP – alkaline phosphatase; ALT – alanine aminotransferase; APTT – activated partial thromboplastin time; AST – aspartate aminotransferase; BUN – blood urea nitrogen; Ca – calcium ion; Cr – creatinine; Duration – the duration of T2DM; FPG – fasting plasma glucose; GGT – γ-glutamine transferase; HE – hepatic encephalopathy; HCC – hepatocellular carcinoma; HA1C – glycosylated hemoglobin; HD – hemoglobin; INR – international normalized ratio; K – potassium ion; MELD – model for end-stage liver disease; Na – sodium ion; NA – not available; PLT – platelet; PT – prothrombin time; Pts – patients; RBC – red blood cell; T2DM – type 2 diabetes; TBIL – total bilirubin; WBC – white blood cell.
# Table 3. Comparison between HCC versus no-HCC in Non-T2DM patients.

| Variables                  | HCC (n=42) | No. Pts available | Mean±SD or frequency (percentage) | Median (range) | Non-HCC (n=49) | No. Pts available | Mean±SD or frequency (percentage) | Median (range) | P value |
|----------------------------|------------|-------------------|-----------------------------------|----------------|----------------|-------------------|-----------------------------------|----------------|---------|
| Sex (male/female), n (%)   | 42         | 37 (88.1%)/5 (11.9%) | 35 (71.4%)/14 (28.6%)              | 0.070          | 49             | 35 (71.4%)/14 (28.6%) | 0.070                                          |
| Age (years)                | 42         | 57.49±7.09        | 57.46 (40.08–69.33)               | 49             | 56.02±8.09     | 56.05 (42.49–79.61)            | 0.365                                           |
| Ascites, n (%)             | 42         | 21 (50%)          | 25 (51%)                          | 49             | 17 (34.7%)     | 17 (34.7%)                  | 0.729                                           |
| HE, n (%)                  | 42         | 3.51 (1.63–6.65)  | 3.16±0.82 (1.55–5.19)             | 49             | 4.34±3.20      | 3.8 (0.9–19.6)               | 0.068                                           |
| No                         | 42         | 4.4 (1.1–30.7)    | 4.4                               | 49             | 3.8            | 3.8 (0.9–19.6)               | 0.05                                            |
| Grade I–II                 | 1 (2.4%)   | 111.5 (3.2–160)   | 91 (37–165)                       | 0.092          | 49             | 3.16±0.82 (1.55–5.19)         | 0.068                                           |
| Grade III–IV               | 1 (2.4%)   | 6.06±4.94         | 6.06±4.94 (1.1–30.7)              | 49             | 3.16±0.82      | 3.16±0.82 (1.55–5.19)         | 0.068                                           |
| Laboratory tests           |            |                   |                                   |                |                |                                |                                                 |
| RBC (10¹²/L)               | 42         | 3.49±0.90         | 3.51 (1.63–6.65)                  | 49             | 3.16±0.82      | 2.98 (1.55–5.19)              | 0.068                                           |
| Hb (g/L)                   | 42         | 106.31±32.8       | 106.31±32.8 (3.2–160)             | 49             | 95.16±29.67    | 95.16±29.67 (3.2–160)         | 0.092                                           |
| WBC (10⁹/L)                | 42         | 6.06±4.94         | 6.06±4.94 (1.1–30.7)              | 49             | 4.34±3.20      | 4.34±3.20 (1.1–30.7)          | 0.05                                            |
| PLT (10⁹/L)                | 42         | 111.5±79.37       | 111.5±79.37 (22–392)              | 49             | 83.16±41.12    | 83.16±41.12 (22–392)          | 0.041                                           |
| TBIL (umol/L)              | 42         | 44.71±58.11       | 44.71±58.11 (7.5–241.1)           | 49             | 31.32±53.74    | 31.32±53.74 (7.5–241.1)       | 0.257                                           |
| ALB (g/L)                  | 42         | 33.49±6.43        | 33.49±6.43 (20.1–53.9)            | 49             | 31.90±5.85     | 31.90±5.85 (20.1–53.9)        | 0.22                                            |
| ALT (U/L)                  | 42         | 79.45±138.82      | 79.45±138.82 (9–827)              | 49             | 32.08±20.30    | 32.08±20.30 (9–827)           | 0.034                                           |
| AST (U/L)                  | 42         | 136.19±248.44     | 136.19±248.44 (17–1318)           | 49             | 46.61±46.70    | 46.61±46.70 (17–1318)         | 0.026                                           |
| ALP (U/L)                  | 42         | 123.40±65.62      | 123.40±65.62 (46–392)             | 49             | 79.31±32.24    | 79.31±32.24 (46–392)          | <0.001                                          |
| GGT (U/L)                  | 42         | 161.69±173.07     | 161.69±173.07 (24–994)            | 49             | 47.73±40.08    | 47.73±40.08 (24–994)          | <0.001                                          |
| BUN (mmol/L)               | 42         | 7.15±8.04         | 7.15±8.04 (1.54–55.01)            | 49             | 7.135±5.41     | 7.135±5.41 (1.54–55.01)       | 0.991                                           |
| Cr (umol/L)                | 42         | 65.05±31.64       | 65.05±31.64 (33–221)              | 49             | 81.73±104.99   | 81.73±104.99 (33–221)         | 0.295                                           |
| K (mmol/L)                 | 42         | 4.11±0.54         | 4.11±0.54 (3.26–5.8)              | 49             | 3.97±0.41      | 3.97±0.41 (3.26–5.8)          | 0.168                                           |
Table 3. Comparison between HCC versus no-HCC in Non-T2DM patients.

| Variables                        | HCC (n=42) | Non-HCC (n=49) | P value |
|----------------------------------|------------|----------------|---------|
| No. Pts available               |            |                |         |
| Mean±SD or frequency (percentage)|            |                |         |
| Na (mmol/L)                     | 42         | 137.68±5.57    | 139     | 0.409  |
| (109.2–143.7)                   |            |                | 130.4–148.5 |       |
| Ca (mmol/L)                     | 13         | 2.17±0.22      | 2.06    | 0.086  |
| (1.89–2.76)                     |            |                | 1.35–2.41|       |
| PT (second)                     | 42         | 15.76±4.41     | 15.3    | 0.385  |
| (11–40.9)                       |            |                | 11.8–27.5|       |
| APTT (second)                   | 42         | 41.04±7.40     | 44      | 0.052  |
| (28.2–61.7)                     |            |                | 29.7–74.6|       |
| INR                             | 42         | 1.28±0.50      | 1.35    | 0.439  |
| (0.81–4.19)                     |            |                | 0.86–2.53|       |
| Titer of HBV-DNA (10^4 copies/ml)|            | 92.22 ±149.28 | 1957.08 ±5884.11 | 0.210 |
| (1–470)                         |            |                | 0.11–24000|      |
| Child-Pugh class, n (%)         | 42         | 19 (45.2%)     | 21 (42.9%) | 0.551 |
| A                               |            |                |         |
| B                               |            | 20 (47.6%)     | 21 (42.9%) |       |
| C                               |            | 3 (7.1%)       | 7 (14.3%) |       |
| Child-Pugh score                | 42         | 7.24±1.95      | 7.25    | 0.987  |
| (5–14)                          |            |                | 5–12   |       |
| MELD score                      | 42         | 5.80±5.63      | 6.66   | 0.536  |
| (–3.39–19.63)                   |            |                | –2.57–37.57|      |

ALB – albumin; ALP – alkaline phosphatase; ALT – alanine aminotransferase; APTT – activated partial thromboplastin time; AST – aspartate aminotransferase; BUN – blood urea nitrogen; Ca – calcium ion; Cr – creatinine; GGT – γ-glutamine transferase; HE – hepatic encephalopathy; HCC – hepatocellular carcinoma; Hb – hemoglobin; INR – international normalized ratio; K – potassium ion; MELD – model for end-stage liver disease; Na – sodium ion; NA – not available; PLT – platelet; PT – prothrombin time; Pts – patients; RBC – red blood cell; T2DM – type 2 diabetes; TBIL – total bilirubin; WBC – white blood cell.

There were some limitations in this study. First, we conducted a retrospective study. Second, in some patients, the data regarding HBV surface antigen or Child-Pugh score were lacking. Third, the number of patients was relatively small. Fourth, there was a relatively high percentage of HCC in our study. Fifth, some reports suggested that anti-diabetic agents can affect the risk of developing HCC [48,49], but these retrospective studies failed to examine this issue due to the absence of relevant data.

Conclusions

In conclusion, it appears that T2DM is not a risk factor for the presence of HCC in chronic HBV cirrhosis patients. A well-designed, prospective, case-control study should be conducted to explore this association in the future.

Conflict of interest

None.
References:

1. Forner A, Llovet JM, Bruix J: Hepatocellular carcinoma. Lancet, 2012; 379: 1245–55
2. El-Serag HB. Hepatocellular carcinoma. N Engl J Med, 2011; 365: 1118–27
3. Parkin DM, Bray F, Ferlay J, Pisani P: Global cancer statistics, 2002. Cancer J, 2005; 55: 74–108
4. Wang SS, Fan JG, Zhang Z et al: The global burden of liver disease: The major impact of China. Hepatology, 2014; 60: 2099–108
5. Lu FM, Zhehong H: Management of hepatitis B in China. Chin Med J (Engl), 2009; 122: 3–4
6. IDF Diabetes Atlas Group: Update of mortality attributable to diabetes for the IDF Diabetes Atlas: estimates for the year 2011. Diabetes Res Clin Pract, 2013; 100: 277–99
7. IDF Diabetes Atlas Group: Update of mortality attributable to diabetes for the IDF Diabetes Atlas: Estimates for the year 2013. Diabetes Res Clin Pract, 2015; 109: 461–65
8. Jha DK, Mittal A, Gupta SP et al: Association of type 2 diabetes mellitus with hepatocellular carcinoma occurrence – a case control study from Kathmandu Valley. Asian Pac J Cancer Prev, 2012; 13: 5979–97
9. Liu TL, Trogdon J, Weinberger M et al: Diabetes is associated with clinical decompensation events in patients with cirrhosis. Dig Dis Sci, 2016; 61: 3335–45
10. Polesel J, Zucchetto A, Montella M et al: The impact of obesity and diabetes mellitus on the risk of hepatocellular carcinoma. Ann Oncol, 2009; 20: 351–57
11. Wang C, Wang X, Gong G et al: Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: A systematic review and meta-analysis of cohort studies. Int J Cancer, 2012; 130: 1639–48
12. Dyal HK, Aguilar M, Bartos G et al: Diabetes mellitus increases risk of hepatocellular carcinoma in chronic hepatitis C virus patients: A systematic review. Dig Dis Sci, 2016; 61: 636–45
13. Ektiefe L, Chouinard P, Bendersky N et al: Diabetes mellitus is an independent prognostic factor for major liver-related outcomes in patients with cirrhosis and chronic hepatitis C. Hepatology, 2014; 60: 823–31
14. Konishi I, Hisa Y, Shigematsu S et al: Diabetes pattern on the 75 g oral glucose tolerance test is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus. Liver Int, 2009; 29: 1194–201
15. Wang CS, Yao WJ, Chang TT et al: The impact of type 2 diabetes on the development of hepatocellular carcinoma in different viral hepatitis statuses. Cancer Epidemiol Biomarkers Prev, 2009; 18: 2054–60
16. Hsiang JC, Gane EJ, Bai WW, Gerred SJ: Type 2 diabetes: A risk factor for liver cirrhosis. Gastroenterol Res Pract, 2015; 2015: 109. 461–65
17. Amano K, Kagaysuchi T, Kuromatsu R et al: Time trends of clinical characteristics in hepatocellular carcinoma patients with chronic hepatitis B virus infection: A field survey between 2000 and 2012. Mol Clin Oncol, 2014; 2: 927–34
18. Ko WH, Chiu SY, Yang KC, Chen HH: Diabetes, hepatitis virus infection and hepatocellular carcinoma: A case-control study in hepatitis endemic area. Hepatol Res, 2012; 42: 774–81
19. Fu SC, Huang YW, Wang TC et al: Increased risk of hepatocellular carcinoma in chronic hepatitis B patients with new onset diabetes: A nationwide cohort study. Aliment Pharmacol Ther, 2015; 10: 591–99
20. Tung HB, Wang JH, Tseng PL et al: Neither diabetes mellitus nor overweight is a risk factor for hepatocellular carcinoma in a dual HBV and HCV endemic area: Community cross-sectional and case-control studies. J Atheroscler Thromb, 2015; 12: 1220–9
21. Gao C, Fang L, Zhao HC et al: Potential role of diabetes mellitus in the progression of cirrhosis to hepatocellular carcinoma: A cross-sectional case-control study from Chinese patients with HBV infection. Hepatobiliary Pancreat Dis Int, 2013; 12: 385–93
22. Chen CT, Chen JY, Wang JH et al: Diabetes mellitus, metabolic syndrome and obesity are not significant risk factors for hepatocellular carcinoma in an HBV- and HCV-endemic area of Southern Taiwan. Kaohsiung J Med Sci, 2013; 29: 451–59
23. Peng Y, Qi X, Dai J et al: Child-Pugh versus MELD score for predicting the in-hospital mortality of acute upper gastrointestinal bleeding in liver cirrhosis. Int J Clin Exp Med, 2015; 8: 751–57
24. Zhu C, Qi X, Li H et al: Correlation of serum liver fibrosis markers with severity of liver dysfunction in liver cirrhosis: A retrospective cross-sectional study. Int J Clin Exp Med, 2015; 8: 5989–98
25. Dai J, Qi X, Peng Y et al: Association between D-dimer level and portal venous system thrombosis in liver cirrhosis: A retrospective observational study. Int J Clin Exp Med, 2015; 8: 15296–301
26. Qi X, Li H, Chen J et al: Serum liver fibrosis markers for predicting the presence of gastroesophageal varices in liver cirrhosis: A retrospective cross-sectional study. Gastroenterol Res Pract, 2015; 2015: 274534
27. Qi X, Peng Y, Li H et al: Diabetes is associated with an increased risk of in-hospital mortality in liver cirrhosis with acute upper gastrointestinal bleeding. Eur J Gastroenterol Hepatol, 2015; 27: 476–77
28. Qi X, Han G, Ye C et al: Splenectomy causes 10-fold increased risk of portal venous system thrombosis in liver cirrhosis patients. Med Sci Monit, 2016; 22: 2528–50
29. Qi X, Liu X, Zhang Y et al: Serum liver fibrosis markers in the prognosis of liver cirrhosis: A prospective observational study. Med Sci Monit, 2016; 22: 2720–30
30. Zhang X, Qi X, De Stefano V et al: Epidemiology, risk factors, and in-hospital mortality of venous thromboembolism in liver cirrhosis: A single-center retrospective observational study. Med Sci Monit, 2016; 22: 969–76
31. Deng H, Qi X, Zhang Y et al: Diagnostic accuracy of contrast-enhanced computed tomography for esophageal varices in liver cirrhosis: A retrospective observational study. J Evid Based Med, 2016 [Epub ahead of print]
32. Deng H, Qi X, Peng Y et al: Diagnostic accuracy of APRI, AAR, FIB-4, FI, and king scores for diagnosis of esophageal varices in liver cirrhosis: A retrospective study. Med Sci Monit, 2015; 21: 1961–77
33. Wang R, Qi X, Peng Y et al: Association of umbilical hernia with volume of ascites in liver cirrhosis: A retrospective observational study. J Evid Based Med, 2016 [Epub ahead of print]
34. Pugh RN, Murray-Lyon IM, Dawson JL et al: Transection of the oesophagus for bleeding oesophageal varices. Br J Surg, 1973; 60: 646–49
35. Kamath PS, Kim WR. Advanced Liver Disease Study Group: The model for end-stage liver disease (MELD). Hepatology, 2007; 45: 797–805
36. Bruix J, Sherman M, Llovet JM et al: Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol, 2001; 35: 421–30
37. Shikata K, Ninomiya T, Kiyohara Y: Diabetes mellitus and cancer risk: Review of the epidemiological evidence. Cancer Sci, 2013; 104: 9–14
38. Rabe K, Lehrke M, Parhofer KG, Broedl UC: Advokine and insulin resistance. Mol Med, 2008; 14: 741–51
39. Shoelson SE, Lee J, Goldfine AB: Inflammation and insulin resistance. J Clin Invest, 2006; 116: 1793–801
40. Nussbaum T, Samarlin I, Ehemann V et al: Autoimmune insulin-like growth factor-II stimulation of tumor cell migration is a progression step in human hepatocarcinogenesis. Hepatology, 2008; 48: 146–56
41. Arcidiacono B, Iiritano S, Nocera A et al: Insulin resistance and cancer risk: An overview of the pathogenetic mechanisms. Exp Diabetes Res, 2012; 2012: 789174
42. Yamamoto K, Awogbi T, Okuyama K, Takahashi N: Nuclear localization of alkaline phosphatase in cultured human cancer cells. Med Electron Physiol, 2006; 116: 409–18
43. Arcidiacono B, Iiritano S, Nocera A et al: Insulin resistance and cancer risk: An overview of the pathogenetic mechanisms. Exp Diabetes Res, 2012; 2012: 789174
44. Pompella A, Corti A, Paolicelli A et al: Gamma-glutamyltransferase, redox regulation and cancer drug resistance. Curr Opin Pharmacol, 2007; 7: 360–66
45. Leung TW, Tang AM, Zee B et al: Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: A study based on 926 patients. Cancer, 2005; 103: 94–107
46. Xu XS, Wan Y, Song SD et al: Model based on gamma-glutamyltransferase and alkaline phosphatase for hepatocellular carcinoma prognosis. World J Gastroenterol, 2014; 20: 10944–52
47. Huo Ti, Hsia CY, Huang YH et al: Selecting a short-term prognostic model for hepatocellular carcinoma: Comparison between the model for end-stage liver disease (MELD), MELD-sodium, and five cancer staging systems. J Clin Gastroenterol, 2009; 43: 773–81

48. Seo YS, Kim YJ, Kim MS et al: Association of metformin use with cancer-specific mortality in hepatocellular carcinoma after curative resection: A nationwide population-based study. Medicine, 2016; 95: e3527

49. Bosetti C, Franchi M, Nicotra F et al: Insulin and other antidiabetic drugs and hepatocellular carcinoma risk: A nested case-control study based on Italian healthcare utilization databases. Pharmacoepidemiol Drug Saf, 2015; 24: 771–78