Diabetes mellitus affects long-term survival in hepatitis B virus-related hepatocellular carcinoma patients: A propensity score-matched analysis

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Abstract
Diabetes mellitus (DM) increases the risk of developing hepatocellular carcinoma (HCC), and how DM affects the prognosis of HCC have not been elucidated. The aim of this study was to compare clinicopathological characteristics and survival between hepatitis B virus (HBV)-related HCC patients with and without DM and to determine risk factors for overall survival after hepatectomy.

Among 474 patients with HBV-related HCC, 119 patients had DM. Patients were divided into the diabetic group and nondiabetic group. The short-term and long-term outcomes were evaluated by using propensity score matching analysis.

After 1:2 propensity score matching, there were 107 patients in diabetic group, 214 patients in nondiabetic group. The proportion of vessel invasion were higher in diabetic group. The overall survival rate in the diabetic group was 44.7% at 3 years, which was lower than that in the nondiabetic group (56.1%, \(P = .025\)). The multivariate analysis indicated that fasting blood glucose >7.0, capsular invasion, microvascular invasion and satellite were independent risk factor of poor prognosis in HCC.

DM dose affect the recurrence-free survival and overall survival in HBV-related HCC patients after hepatectomy. One of the more significant findings to emerge from this study is that DM induced higher proportion of major vessel invasion in HCC patients implied unfavorable prognosis.

Abbreviations: DM = diabetes mellitus, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, ICG = indocyanine green, NAFLD = non-alcoholic fatty liver disease.

Keywords: diabetes mellitus, hepatitis B virus, hepatocellular carcinoma, vessel invasion

1. Introduction
Liver cancer remains an important cancer worldwide and is responsible for over 841,000 new cases and an estimated 782,000 deaths in 2018, making it the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death.[1] The key determinants of hepatocellular carcinoma (HCC) in most high-risk HCC areas (China, Eastern Africa) is chronic Hepatitis B virus (HBV) infection. Apart from HBV, many other factors also contribute to the process of HCC, such as hepatitis C virus, aflatoxin-contaminated foodstuffs, heavy alcohol intake, smoking, and metabolic syndrome (diabetes mellitus (DM), obesity, dyslipidemia, hypertension). Recent work by Zhang et al has established that Vitamin D deficiency or insufficiency have also been linked to liver cancer.[2] Additional, virus replication, liver function and fibrosis, and even interleukin 28B polymorphisms are associated with risk of HCC.[3–6] Among these, DM was of great concern recently.

DM is a public health problem that seriously threatens human health, its incidence and mortality are rapidly growing worldwide.[7] The overall prevalence of DM was 10.4% in China, and China has become the top country with the highest number of people with DM.[8] Extensive research has shown that DM increases the risk of HCC.[9–13] Although the exact mechanism of DM in the development of HCC is still under investigation, it has previously been observed that a strong association between DM and non-alcoholic fatty liver disease (NAFLD)[14] which can process to liver cirrhosis and HCC. Now that DM was an independent risk factor for HCC, it would affect the prognosis of HCC. However, some controversies still existed about the weather DM had impacts on the short-term and long-term survival after surgical treatment. The study by Ronnie et al. indicated that DM does not influence the short-term and long-term prognosis,[15] and...
study by Wang et al suggested that DM only associated with significantly lower overall survival,\(^{16}\) while some other studies revealed that DM does affect the recurrence-free survival (RFS) and overall survival (OS) in HCC patients.\(^{17-19}\)

The presence of an association between HBV and HCC is well established, HCC also develops in diabetic patient combination of NAFLD, HBV-related HCC with DM makes this type of HCC a very different entity in terms of epidemiology, clinical, and in its management and prognosis. It has been concluded that DM increased the incidence of HCC.\(^{20}\) The evidence from epidemiological and experimental studies also suggested that HBV infection might interfere with hepatic metabolic processes such as glucose and lipid metabolism.\(^{20-22}\) Moreover, HBV also raise the risk of other malignancies, such as lymphoma.\(^{23}\) Hence, there was a need to investigate the associations between DM with short-term and long-term survival in HBV-relate HCC after hepatectomy.

2. Methods

2.1. Patients

This study was approved by the West China Hospital administration and the ethics committee. All patients were informed of the research reasons, read and signed the informed consent form. Data from all HCC patients (HCC was diagnosed based on histologic analyses) who underwent liver resection in West China Hospital of Sichuan University were retrieved in registry and follow-up database. Excluded patients included those that with type 1 diabetes, non-HBV-related disease, without regular anti-HBV therapy, mixed liver cancer, preoperative therapy such as diabetes, non-HBV-related disease, without regular anti-HBV therapy, mixed liver cancer, preoperative therapy such as hepatectomy, transarterial chemoembolization and radiofrequency ablation, and patients without hepatectomy.

Among all the included patients. The patients who had been diagnosed with type 2 DM were assigned to the diabetic group, otherwise, were assigned to nondiabetic group. The decision to liver resection would be decided by preoperative risk assessment. Laboratory inspection include routine blood test, blood biochemistry, tumor marker, HBV-DNA. Indocyanine green (ICG) retention rate, abdominal ultrasonography and enhanced computed tomography or magnetic resonance imaging were performed before treatment. Patients who had Child-Pugh A liver function or selected patients with Child-Pugh B liver function, and ICG R15 <14% were considered hepatectomy.

2.2. Surgery and pathology

The operation was performed under general anesthesia, patients were placed in the supine position, hepatic inflow occlusion methods Intermittent Pringle maneuver or continuous hepatic vascular inflow occlusion were used to control surgical blood loss. Parenchymal transection of the liver was performed by Harmonic scalpel, Cavitron Ultrasonic Surgical Aspirator or Ligasure with central venous pressure was maintained <5 mm Hg.

All specimen had histological assessment. The information about tumor differentiation, tumor number, microvascular invasion, major vascular invasion, bile duct invasion, satellite nodules, Ishak score were extracted from histological reports.

2.3. Postoperative work-up and follow up

All patients underwent routine blood tests at 1, 3, and 5 days after surgery, abdominal ultrasonography was performed before out of hospital. Patients fasting blood glucose and postprandial blood glucose were monitored daily. The Dindo-Clavien classification of surgical complications was used to grade postoperative complications.\(^{25}\) Patients were followed up in outpatient department and by telephone regularly. In general, patients were requested to have follow-up by blood tests (liver function and tumor markers) and abdominal ultrasonography every 3 months. At least 1 enhanced computed tomography and/or magnetic resonance imaging was carried out every 6 months.

2.4. Statistical analysis

The primary outcome was OS and RFS. Continuous variables were compared using t tests or Mann-Whitney U and described as mean ± standard deviation. Mann-Whitney U test was used when continuous variables did not follow a normal distribution. Categorical variables were compared using \(\chi^2\) tests and expresses as percentages. A propensity score matching was carried out to overcome biases. The age, gender, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), Child-Pugh score, HBV-DNA loads were selected as covariates and a 1:2 match between the 2 groups was performed within 0.2. Potentially meaningful variables identified by univariate analysis were selected for multivariate analysis of Cox proportional risk models to determine independent risk factors of survival. Significance levels were set at .05 and all analyses were 2-tailed. Statistical analysis was performed using SPSS software (version 24). OS and RFS were calculated using the Kaplan–Meier method and compared using the log-rank test and Gehan-Breslow-Wilcoxon test. Survival analysis were performed using GraphPad Prism 8.0.1.

3. Results

3.1. Baseline characteristics

Total 745 patients were diagnosed as HCC in our center between January 2015 and May 2018. Among them, 105 patients were recurrence, 107 patients had preoperative therapy, 49 only had radiofrequency ablation, 6 patients had HCC rupture, 4 patients had mixed-type HCC. Finally, 474 patients were enrolled in the study. 119 (25.1%) patients with DM and 355 (74.9%) patients without DM. After 1:2 propensity score match, there were 107 patients in diabetic group, 214 patients in nondiabetic group. As shown in Table 2, Patients in the diabetic group had larger BMI (24.4 ± 3.0 vs 23.4 ± 3.2, \(P = .001\)), fasting blood glucose levels (8.3 ± 3.6 vs 5.1 ± 1.3, \(P < .001\)), Cys-C levels (1.05 ± 0.46 vs 0.93 ± 0.15, \(P = .006\)) and lower e-GFR (89.25 ± 21.99 vs 99.85 ± 12.12, \(P < .001\)) than those in the nondiabetic group. The proportion of Child-Pugh B patients were significantly higher in the diabetic group (6.7% vs 1.4%, \(P < .002\)). The tumor marker and ICG-R15 did not show significant difference between groups.

3.2. Pathological characteristics

As shown in Table 2, Patients in the diabetic group had larger tumor diameters (5.0 ± 2.9 vs 4.1 ± 2.4, \(P = .014\)). The proportion of portal invasion and bile duct invasion (8.4% vs 0.5%, \(P = .000\); 3.7% vs 0.5%, \(P = .026\)) were higher in diabetic group.
Table 1
Baseline characteristics of all patients before and after propensity score matching.

|                | Before Propensity Matching | After Propensity Matching |
|----------------|----------------------------|---------------------------|
|                | Nondiabetic (n = 355)      | Diabetic (n = 119)        | P value |
|                | Nondiabetic (n = 214)      | Diabetic (n = 107)        | P value |
| Gender         |                           |                           | .126    | .219    |
| Male           | 292 (82.3%)                | 105 (88.2%)               | .000    | .000    |
| Female         | 63 (17.7%)                 | 14 (11.8%)                | .000    | .000    |
| Age (years)    | 53.1 ± 1.13                | 58.7 ± 0.7                | .000    | .000    |
| BMI (kg/m2)    | 23.4 ± 3.0                 | 24.4 ± 3.2                | .002    | .002    |
| Child-Pugh A   | 350 (98.6%)                | 111 (93.3%)               | .000    | .000    |
|               | 5 (1.4%)                   | 8 (6.7%)                  | .000    | .000    |
| ALBI grade     |                           |                           | .415    | .356    |
| 1              | 275 (77.5%)                | 86 (72.3%)                | .529    | .356    |
| 2              | 79 (22.3%)                 | 32 (26.9%)                | .574    | .356    |
| 3              | 1 (0.2%)                   | 1 (0.8%)                  | .000    | .000    |
| HGB (g/L)      | 141.5 ± 18.6               | 142.1 ± 18.1              | .721    | .858    |
| WBC (×10⁹/L)   | 5.50 ± 2.1                 | 5.81 ± 2.0                | .137    | .841    |
| PLT (×10⁹/L)   | 138.2 ± 63.6               | 135.6 ± 58.9              | .680    | .242    |
| PT (s)         | 12.23 ± 1.0                | 12.13 ± 1.5               | .507    | .533    |
| INR            | 1.04 ± 0.13                | 1.05 ± 0.14               | .514    | .731    |
| ALT (IU/L)     | 47.1 ± 62.6                | 48.3 ± 68.9               | .866    | .902    |
| FBG (mmol/L)   | 5.1 ± 1.3                  | 8.3 ± 3.6                 | .000    | .000    |
| e-GRF (mg/min/1.73m²) | 99.85 ± 12.12 | 89.25 ± 21.99 | .000 | .018 |
| CysC (mg/L)    | 0.93 ± 0.15                | 1.05 ± 0.46               | .006    | .003    |
| Cre (μmol/L)   | 69.0 ± 13.1                | 83.4 ± 67.0               | .022    | .006    |
| HBV-DNA ( copies) | 3.4 ± 1.7                 | 3.6 ± 1.5                 | .464    | .078    |
| APP (ng/ml)    | 105 (29.7%)                | 27 (22.9%)                | .151    | .100    |
| PIVKA-II (mAU/ml)      | 85 (56.0%)                 | 19 (31.7%)                | .520    | .356    |
| ICG-R15 (%)     | 6.6 ± 6.9                  | 7.1 ± 5.5                 | .074    | .284    |

Nondiabetic = protein induced by vitamin K antagonist-II, PLT = platelet, PT = prothrombin time, TB = total bilirubin, WBC = white blood cell.

Table 2
Pathologic characteristics of HCC in patients after propensity score matching.

|                | Nondiabetic (n = 214) | Diabetic (n = 107) | P value |
|----------------|-----------------------|--------------------|---------|
| Tumor size (cm)| 4.1 ± 2.4             | 5.0 ± 2.9          | .014    |
| Tumor number   | 2                     | 9                  | .926    |
| 1              | 178 (83.2%)           | 89 (83.2%)         | .000    |
| 2              | 20 (9.3%)             | 9 (8.4%)           | .000    |
| ≥3             | 16 (7.5%)             | 9 (8.4%)           | .775    |
| Differentiation|                       |                    |         |
| Poor           | 78 (36.4%)            | 39 (36.4%)         | .000    |
| Moderate       | 134 (62.6%)           | 66 (61.7%)         | .000    |
| Well           | 2 (0.9%)              | 2 (1.9%)           | .000    |
| Capsular invasion| 79 (36.9%)           | 44 (41.1%)         | .465    |
| Microvascular invasion| 46 (21.5%)       | 31 (29.0%)         | .139    |
| Portal vein invasion| 1 (0.5%)            | 9 (8.4%)           | .000    |
| Hepatic vein invasion| 0 (0.0%)             | 1 (0.9%)           | .157    |
| Bile duct invasion| 1 (0.3%)             | 4 (3.7%)           | .026    |
| satellite nodules| 15 (7.0%)             | 13 (12.1%)         | .124    |
| cirrhosis      | 91 (42.5%)            | 56 (52.3%)         | .096    |

HCC = hepatocellular carcinoma.

And the proportion of microvascular invasion was higher in diabetic group (29% vs 21.5%), although no significant difference was found between 2 group. The tumor number, differentiation, microvascular invasion, satellite, and cirrhosis did not differ by DM.

3.3. Intraoperative and postoperative results

Comparing the 2 group, we found that more intraoperative blood loss occurred in diabetic group (316.6 ± 287.1 vs 211.0 ± 251.0 ml, P = .001), which may lead to more proportion of blood transfusion (8.4% vs 2.3%, P = .012). Diabetic patients had longer postoperative hospital stay (8.3 ± 7.3 vs 6.4 ± 5.1, P < .001), more drainage (1724.5 ± 2916.6 vs 376.9 ± 476.5, P < .001) and lower albunin levels (32.3 ± 6.2 vs 46.9 ± 6.6, P < .001). Among 7 patients with grade IV complications in diabetic group, there were 3 patients had liver failure, 4 patients had respiratory failure. (Table 3)

3.4. Survival and risk factors in HCC patients

Median follow-up time for the entire cohort was 24.0 months (95% CI 22.1–25.9). The results of survival analysis were consistent before (Fig. 1A, B) and after (Fig. 1C, D) propensity score matching. The RFS was significantly better in the nondiabetic group than in the diabetic group (P = .026). The 1-, 3-year RFS were 63.9% and 41.0% in nondiabetic group, 59.8% and 26.8% in diabetic group after propensity score matching (Fig. 1C). The OS was significantly better in the nondiabetic group than in the diabetic group (P = .025). The 1-, 3-year OS were 79.4% and 56.1% in nondiabetic group, 73.2%...
and 44.7% in diabetic group after propensity score matching (Fig. 1D).

The multivariate analysis (Table 4) indicated that fasting blood glucose > 7.0 (HR: 1.489, 95% CI, 1.004–2.208, P = .048), capsular invasion (HR: 1.553, 95% CI, 1.061–2.273, P = .024), macrovascular invasion (HR: 1.552, 95% CI, 1.045–2.304, P = .029) and satellite (HR: 1.861, 95% CI, 1.066–3.249, P = .029) were independently associated with OS (Table 4).

4. Discussion

A strong relationship between DM and HCC has been reported in the literatures,[9–13,26,27] even in the chronic HBV infected patients, DM was a risk factor of HCC development and affected the all-cause mortality.[10] However, the reports on the effects of diabetes on perioperative and postoperative prognosis of HBV-related HCC patients are rare and the controversies still exist. We study set out with the aim of assessing the effects of diabetes on prognosis of HCC in HBV patients. Patients with diabetes do have more intraoperative bleeding, worse liver function postoperatively, longer postoperative hospital stay and more serious complications.

Table 3

|                      | Nondiabetic (n = 214) | Diabetic (n = 107) | P value |
|----------------------|----------------------|-------------------|---------|
| Blood loss (mL)      | 211.0 ± 251.0        | 316.6 ± 297.1     | .001    |
| Blood transfusion    | 5 (2.3%)             | 9 (8.4%)          | .012    |
| POD inpatient time (d)| 6.4 ± 5.1           | 8.3 ± 7.3         | .000    |
| Drainage (ml)        | 376.9 ± 476.5        | 1724.5 ± 2916.6   | .000    |
| ALT (IU/L)           | 345.4 ± 481.0        | 389.3 ± 400.9     | .116    |
| TB (µmol/L)          | 28.4 ± 14.0          | 24.3 ± 14.4       | .001    |
| ALB (g/L)            | 33.7 ± 4.7           | 32.3 ± 4.7        | .018    |
| AFP > 400 (ng/mL)    | 9 (4.2%)             | 7 (6.5%)          | .365    |

Compliations

| Grade | Nondiabetic (%) | Diabetic (%) | P value |
|-------|-----------------|--------------|---------|
| Grade I | 172 (80.4%)   | 82 (76.6%)   | .000    |
| Grade II | 39 (18.2%)    | 11 (10.3%)   | .116    |
| Grade III | 0 (0.0%)      | 5 (4.7%)     | .521    |
| Grade IV | 3 (1.4%)      | 7 (6.5%)     | .365    |
| Grade V | 0 (0.0%)       | 2 (1.9%)     | .012    |

AFP = alpha-fetoprotein, ALB = albumin, ALT = alanine aminotransferase, POD = post operation day, TB = total bilirubin.

Figure 1. (A) recurrence-free survival (RFS) and (B) overall survival (OS) in patients before propensity score matching; (C) recurrence-free survival (RFS) and (D) overall survival (OS) in patients after propensity score matching.
complications. It’s worth noting that patients in diabetic group had large abdominal effusion after hepatectomy. This result may be explained by the fact that diabetic kidney disease is common in DM patients. Our study also showed that diabetic patients had lower e-GFR and higher Cys-C levels.[23] Hyperglycemia is a fundamental cause of diabetic kidney disease complications.[23] The albuminuria causes an extra loss of albumin from the urine, and hypoproteinemia led to a massive abdominal effusion. On the other hand, diabetes are associated with NASH and NAFLD,[14,30] which contributed to the progression of liver inflammation and decompensation.[12,31,32]

It is notable that tumors in diabetic patients tended to have a higher incidence of microvascular invasion (although no statistic significance), portal vein invasion and bile duct invasion than nondiabetic patients, which had not been found by previous studies.[13-19] The vessels invasion was an important factor leading to early recurrence and poor long-term survival after surgery. Several reports have shown that hyperglycemia changed basement membrane size and composition in both the micro- and macrovascular, which increased vascular permeability and fragility.[33-35] Hence, it could conceivably be hypothesized that vascular dysfunction enable cancer prone to invasion and metastasis. And these aggressive characteristics of HCC in diabetic patients prompted poorer prognosis. Further research should be undertaken to investigate the real impacts that DM on the mechanisms underlying invasion and metastasis in HCC.

Prior studies have shown that the 3-year RFS rate after hepatectomy in HCC patients with DM range from 22.2% to 44.5%, 3-year OS rate range from 54.3% to 75% in Asia.[13-18] And the 3-year OS in Caucasian patients with NAFLD was about 40% to 76.7%.[16-18] In our study, the 3-year OS rate was found to be 50.6% before propensity score matching, lower than that of previously reported rates in Asian. There might be several explanations for this finding. First, part of patients in these studies were non-HBV HCC, especially in some low-risk areas, metabolic diseases and alcohol abuse are likely predominated causes. Second, HBV infection is a major cause of HCC in China. In our study, all the patients were HBV-related HCC and receive antiviral therapy after surgery. The effects of DM were more pronounced in patients with effective viral suppression.[11] Several studies also concluded that among HBV infection patients, patients with DM had lower OS than patients without DM.[20,27,39] These findings suggested that the coexistence of HBV infection and diabetes may have synergistic effect on the prognosis of tumor. Lastly, race was not the main factor affecting the prognosis of HCC.

Multivariate analysis demonstrated similar risk factors, such as capsular invasion, macrovascular invasion and satellite, which were associated with OS in HCC patients. Furthermore, fasting blood glucose ≥ 7.0 was an independent risk factor for long-term survival in this study. It is reported that an increase of plasma glucose levels by 1 mmol/L, significantly increased the probability of HCC and cirrhosis (adjusted HR of 1.04).[27] An intensive control of blood glucose is required in HCC patients. Antioxidant treatment to control the causes of HCC is significant. The results of many studies have also suggested that antioxidants may be used as adjuvants in chronic liver diseases.[44] Both HBV infection[41] and DM[42] are associated with increased levels of oxidative stress, induced several inflammatory responses, causing persistent liver injury, which acts on progressive diseased state, placed the liver into a state of vulnerability to the development of HCC. Oxidative stress usually induced chronic inflammation and fibrosis of the liver, resulting in activation of macrophages to produce a variety of proinflammatory cytokines, such as IL-1β, IL-6, IL-17, CXCL-8, and TNF-α.[43] Therefore, antioxidant treatment to control the causes of HCC is significant. The results of many studies have also suggested that antioxidants may be used as adjuvants in chronic liver diseases.[44]

Some limitations do exist in our study. Although propensity score matching was performed to eliminate selection biases, not all the possible biases were considered in this study. Because of the nature of retrospective study, the diagnosis of DM and assessment of blood glucose control were defined by retrospective inspection of medical records and laboratory tests. The details (eg, diabetes medications, blood glucose level in daily life, diabetes duration and family history) of DM were not collected. Due to small sample size in single center, the generalizability of these results is subject to certain limitations. In spite of its limitations, the study certainly adds to our understanding of the differences between HBV-related HCC in Patients with and without DM.
This study confirms that DM is associated with worse short-term and long-term outcomes and DM may contributed to the invasion and metastasis of HCC. The complex interaction between HBV and host metabolism in hepatic disease progression warrants further study.

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