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Comparison of patients with hepatitis B virus-associated hepatocellular carcinoma: Data from two hospitals from Turkey and China

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Abstract

Aims: There are many studies on the incidence of hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC), but very little is known about the HCC features in different populations. The study aimed to compare characteristics in two cohorts of patients with HBV-associated hepatocellular carcinoma, from Turkey and China.

Methods: Data on patients with HBV-associated HCC diagnosed by imaging or liver biopsy were retrospectively collected from Shandong Provincial Hospital ($n = 578$) and Inonu University Hospital ($n = 359$) between January 2002 and December 2020, and the liver function and HCC characteristics were compared. Continuous variables were compared using Student's t-test or Mann–Whitney U test and categorical variables were compared using the $\chi 2$ test or Fisher's exact test.

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AUTHOR CONTRIBUTIONS

Brian I. Carr and Jie Li: Concept; ideas; writing. **Fajuan Rui**: Biostatistics and paper proofreading. **Volkan Ince, Sezai Yilmaz, Xinya Zhao, and Yuemin Feng**: Data collection.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

This study was approved by the Institutional Ethics Committee at the Shandong Provincial Hospital (SZRJJ:No.2021-195). Informed consent was obtained from all participants.

Results: The patients in the Turkish cohort had significantly worse Child-Pugh scores (Child-Pugh A: 38.3% vs. 87.9%; Child-Pugh B: 40.3% vs. 11.1%; Child-Pugh A: 24.1% vs. 1.0%; $p < 0.001$) and significantly higher levels of aspartate aminotransferase (66.5 vs. 36.0; $p < 0.001$), alanine aminotransferase (47.5 vs. 33.0; $p < 0.001$), total bilirubin (20.8 vs. 17.9; $p < 0.001$), and lower albumin levels (32.0 vs. 40.0; $p < 0.001$) than patients in Chinese cohort. The tumor characteristics showed the Barcelona Clinic Liver Cancer (BCLC) score (BCLC 1: 5.1% vs. 71.8%; BCLC 2: 48.7% vs. 24.4%; BCLC 3: 24.4% vs. 3.8%; BCLC 4: 21.8% vs. 0; all $p < 0.001$), maximum tumor diameter (5.0 vs. 3.5; $p < 0.001$), alpha-fetoprotein values (27.7 vs. 13.2; $p < 0.001$), and percentage of patients with portal vein tumor thrombus (33% vs. 6.1%; $p < 0.001$) were all significantly worse in the Turkish cohort compared with Chinese cohort.

Conclusions: HBV-associated HCC from the Turkish cohort had worse liver function and more aggressive clinical characteristics than patients from the Chinese cohort.

Keywords

China; Hepatocellular Carcinoma; Turkey

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and is the third most frequent cause of death from cancer globally,[1–4] likely due to its high incidence in Asia and Africa, as well as due to the advanced stage of the cancer at initial presentation. Several causes have been identified, including chronic hepatitis B, chronic hepatitis C, alcoholism, metabolic syndrome, and dietary myco-toxins such as Aflatoxin B_1.[1,5,6] The etiology varies as per the geographic location, with most Asian HCC outside Japan being due to hepatitis B virus (HBV), while in Europe and the United States, hepatitis C virus (HCV) is a prominent cause. There are many studies on the underlying cause of the geographical differences in HCC incidence, especially in relation to HBV,[7–16] but few studies on clinical patient and tumor differences in HBV-associated HCC patients between different populations.[17–23] The aim of the present retrospective study was to compare the clinical features of HBV-associated HCC patients from two different ethnic and geographic groups, HCC patients from a Chinese and Turkish hospital, since we reasoned that many ethnic and geographic differences might yield insights into either ethnic factors or practice of differing practice of medicine factors.

2 | METHODS

2.1 | Patient population

The study was conducted a retrospective study. Patients with HBV-associated HCC were admitted to Shandong Provincial Hospital and Inonu University Hospital between January 2002 and December 2020 were reviewed. The inclusion criteria were: (1) HCC diagnosed by imaging or liver biopsy; and (2) patients with HCC receiving treatment for the first time. Exclusion criteria were: (1) comorbid other malignancies; (2) previous significant extrahepatic disease such as severe cardio-cerebrovascular disease, chronic renal failure requiring dialysis, and severe chronic obstructive pulmonary disease; and (3) complicated

with various other end-stage diseases. The study was approved by Shandong Provincial Hospital Ethics Committee (SZRJJ:No.2021-195). Patient informed consent was waived when data were collected, which was approved by the Inonu Institutional Ethics Committee (IRB Approval No: 2022-3905) for a waiver from written informed consent for the deceased and deidentified patients, in accordance with local guidelines.

2.2 | Assessment

Demographic characteristics, laboratory data, and radiological information at baseline were reviewed from patient files and hospital electronic records. Data was collected on age, gender, cirrhosis, maximum tumor diameter (MTD), alpha-fetoprotein (AFP), portal vein tumor thrombus (PVTT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), and albumin.

The Child-Pugh score was calculated based on the TBIL, albumin, PT, and the clinical findings of encephalopathy and ascites. It was graded as 5–6 points for Child-Pugh-A; 7–9 points for Child-Pugh-B; and 10–15 points for Child-Pugh-C.[24] HCC was evaluated according to BCLC score: Stage A (early HCC), Stage B (intermediate HCC), Stage C (advanced HCC), and Stage D (end-stage HCC).[25]

2.3 | Statistical analysis

Kolmogorov–Smirnov test was used to assess the data for normal distribution. For continuous data, if they followed a normal distribution, they were expressed as mean ± standard deviation and tested for differences using Student's *t*-test. If not, they were shown as the median (quartile 1, quartile 3), and the differences between groups were compared using nonparametric tests. Categorical variables were shown as frequency (percentage) and compared using the $\chi 2$ test or Fisher's exact test. A two-tailed $p < 0.05$ was considered significant. Statistical analyses were performed using SPSS version 23.0 (IBM Corp, NewYork, USA).

3 | RESULTS

3.1 | Comparison of total Chinese with total Turkish HCC cohort

A total of 937 patients with HBV-associated HCC were included in the study, 578 (61.7%) in the Chinese cohort and 359 (38.3%) in the Turkish cohort. The demographic, liver function, and tumor characteristics of the two groups, Chinese and Turkish, are shown in Table 1. The Turkish patients were older (62.0 [54.0–68.0] vs. 57.0 [50.0–63.0], $p < 0.001$), had a higher percentage of males (87.2% vs. 81.1%, $p = 0.015$ and a higher percentage of patients with advanced Child-Pugh (Child-Pugh C: 21.4% vs. 1.0%, $p < 0.001$), and had a lower proportion of patients receiving antiviral therapy (48.6% vs. 74.6%, $p < 0.001$) before HCC development compared with the Chinese patients. The liver function tests in the Turkish patients were significantly worse than in the Chinese patients, as judged by higher values for serum AST (66.5 vs. 36.0, $p < 0.001$), ALT (47.5 vs. 33.0, $p < 0.001$), TBIL (20.8 vs. 17.9, $p < 0.001$), and lower albumin levels (32.0 vs. 40.0, $p < 0.001$). The proportion of cirrhosis (90.5% vs. 85.6%, $p = 0.073$) in Turkish patients was higher than in Chinese patients, but there was no significant difference. The tumor characteristics, including MTD

(5.0 vs. 3.5, $p < 0.001$), AFP levels (27.7 vs. 13.2, $p < 0.001$), and PVTT (33.0% vs. 6.1%, $p < 0.001$), were also all significantly higher in the Turkish, compared with the Chinese cohort (Table 1).

3.2 | Comparison of characteristics of patients with HBV-associated HCC treated with antiviral therapy between Chinese and Turkish cohorts

We further conducted a comparative analysis between Chinese and Turkish patient cohort who were given antiviral treatment (Table 2). A total of 431 patients received antiviral treatment in the Chinese cohort, whereas in the Turkish cohort, 89 patients received antiviral treatment. Compared with Chinese cohort, the Turkish cohort was older (62.0 vs. 56.0 years, $p = 0.001$), had a higher percentage of advanced Child-Pugh (Child-Pugh C: 20.8% vs. 1.5%, $p < 0.001$), and a worse liver function (all $p < 0.05$). Similarly, tumor characteristics such as MTD (4.5 vs. 3.9, $p = 0.046$), AFP level (34.6 vs. 12.5, $p < 0.001$), and PVTT (27% vs. 5.4%, $p < 0.001$) were significantly higher in the Turkish cohort than in the Chinese cohort.

3.3 | Comparison of characteristics of paitents with unresectable HCC in Chinese and Turkish cohort

The Chinese cohort contained 125 patients who had the cancer resected (21.6% of the total 578 patients and the Turkish cohort did not contain any resected cancer patients. We therefore compared the 453 unresectable Chinese patient cohort with a total of 359 unresectable cancer Turkish patient cohort, (Table 3). The results were very similar to the results in Table 1, and showed that the had higher serum AFP levels (27.7 vs. 9.5, $p < 0.001$), worse liver function (all $p < 0.05$), more aggressive tumor parameters (all $p < 0.05$), and a lower proportion of patients received antiviral therapy (48.6% vs. 74.4%, $p < 0.001$) in comparison to the unresectable patients from Chinese cohort.

3.4 | Comparison of Chinese patients with resectable and unresectable HCC

A comparison was done between the resectable and unresectable cancer in the Chinese patient cohort (Table 4). The resectable group had a significantly lower percentage of patients with cirrhosis (75.2% vs. 90.0%, $p < 0.001$), with 8.9% of patients having Child-Pugh B cirrhosis (compared with 12.5% in the nonresectable group and a significantly higher percentage of patients with normal [higher] serum albumin levels). Interestingly, the resectable group also had higher serum AFP levels (29.5 vs. 9.5, $p < 0.001$) than the unresectable group. The TBIL levels (18.0 vs. 17.9, $p = 0.795$) were similar in the two groups.

4 | DISCUSSION

The patient demographics between the two country groups were slightly different, with the Turkish patients being slightly but significantly older, and had a greater percentage of male patients. The Child-Pugh score revealed that the Turkish patients were diagnosed with more advanced liver disease, and they also had significantly higher levels of AST, ALT, TBIL, lower albumin, and thus worse liver function than the Chinese patients.

Analysis of the tumor characteristics showed that the BCLC score, the MTD, AFP values, and the percentage of patients with PVTT were all significantly worse in Turkish compared with Chinese patients. There are several possible explanations for worse liver function and more aggressive HCC characteristics in the Turkish cohort compared to the Chinese patients. The first explanation is regarding the differences in antiviral treatment between the two countries. In Turkey, the national hepatitis B vaccination program was launched in 1998 and the endemic positive rates have decreased since then.[26] Thus, there have been 25 years of neonatal HBV vaccination. However, being a large and heterogeneous country, follow-up and treatment implementation rates for patients who become HBV carriers are quite variable. It is thus common to meet HCC patients with untreated HBV in Turkey's clinics. However, the administration of antiviral treatment to Chinese patients is prevalent if they fulfill the antiviral criteria. Second, HCC monitoring approaches differ between Turkey and China, with fewer than 30% of Turkish patients undergoing surveillance during diagnosis. However, in China, nearly all chronic hepatitis B patients receive periodic evaluation, including a biannual ultrasound examination. A third explanation may be that HCC patients from Turkey had more advanced liver disease, causing more severe disease status or aggressive disease progression compared to patients from China. Finally, there may be ethnic differences in the aggressiveness of HCC in the two populations, with Turkish patients having more aggressive pheno-types than their Chinese counterparts.

Although there are many publications on HBV in various countries, as well as the incidence of HCC across countries,[27,28] comparisons of HCC characteristics in HBV patients between countries or ethnic groups are few.[19,21–23] The highest HCC incidence in the world has been reported from Mongolia,[29] whose HCC patients were younger and have more females than that reported in HCC patients from Europe or the USA. An 8329 HBV patient study from the US Veterans Affairs administration showed higher incidence rates in Asian Pacific islanders that in whites or African-Americans,[19] who had similar HCC rates. In a US study of HCC on Asian-Americans versus non-Asian-Americans, the Asian-Asian American patients with HCC presented with a higher incidence of history of HBV, lower Child and MELD scores, and an early stage of HCC.[21] Ethnic differences were also found in a study from New York city among different Asian American groups.[22] In another study from New York, physicians treating Asian and African immigrants acknowledged in a survey that less than 70% of patients with an HBV diagnosis were recommended HCC surveillance during follow-up.[30] A comparison of hepatitis types and treatment and HCC incidence in multiple Mediterranean countries showed a wide range of HBV association, but also no comparison of the HCCs.[13]

Due to the confounding influences of HBV management and severity between the two study groups reported here, it is difficult to be confident of the explanation for the more advanced HCCs in the Turkish patients. However, there are likely significant differences between Asian and non-Asian patients with HCC. In the two international randomized studies comparing Sorafenib versus placebo for HCC treatment (SHARP study in Europe and the United States, Asia-Pacific study) with similar entry criteria, the survival in the untreated placebo arm (SHARP study patients) was greater than in the Asia-Pacific placebo-treated patients.[31,32] In the Asia Pacific study, the median overall survival was 6.5 months in the sorafenib group compared with 4.2 months in the placebo group By contrast, in the SHARP

trial, the median overall survival was 10.7 months in the sorafenib group and 7.9 months in the placebo group. This shows the need to employ varying treatment methods in different ethnic groups because therapeutic benefits in one ethnic group may not apply to another.

This study investigates and compares the clinical profiles of HBV-associated HCC patients between Turkish and Chinese cohorts. Our study underscores the impact of medical patterns on the clinical performance of patients. However, we must acknowledge some limitations of our study. First, we did not record data on metabolic profiles such as the prevalence of diabetes mellitus and obesity and HBV genotypes, which could potentially introduce some bias in analysis. Second, the sample size in the two cohorts was relatively small, which limited the generalizability of our results.

In conclusion, our study found that HBV-associated HCC patients from Turkish cohort had worse liver function and more aggressive characteristics compared with patients from the Chinese cohort. Our study highlights the critical importance of administering timely antiviral therapy and implementing regular surveillance for HCC in HBV-infected individuals. In the future, larger prospective studies are needed to further investigate the factors that impact the prognosis of such patients, which will assist clinicians to improve management strategies.

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DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included in the article.

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Key points

Significant findings of the study

This retrospective study showed that compared with the Chinese cohort, patients with hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) in Turkish cohort had poorer liver function (serum aspartate aminotransferase, alanine aminotransferase, total bilirubin, and lower albumin levels) and more aggressive clinical characteristics (maximum tumor diameter, alpha-fetoprotein levels, and portal vein tumor thrombus).

What this study adds

A comparison of the characteristics of two cohorts of patients with HBV-associated HCC from Turkey and China provides data to understand the differences in HBV-HCC between the two countries.

TABLE 1

Comparison of baseline data on HBV-associated HCC patients between Chinese and Turkish cohorts.

Characteristic	**Turkey (*n* = 359)**	**China (*n* = 578)**	***p*-Value**
Age (years)	62.0 (54.0–68.0)	57.0 (50.0–63.0)	<0.001
Male gender, *n*/*N* (%)	313/359 (87.2)	469/578 (81.1)	0.015
Antiviral therapy, *n*/*N* (%)	89/183 (48.6)	431/578 (74.6)	<0.001
History of alcohol consumption	14/175 (8.0)	81/221 (36.7)	<0.001
Cirrhosis, *n*/*N* (%)	209/231 (90.5)	356/416 (85.6)	0.073
MTD (cm)	5.0 (3.0–9.0)	3.5 (2.5–6.0)	<0.001
AFP (ng/mL)	27.7 (6.1–373.1)	13.2 (3.8–55.7)	<0.001
PVTT, *n*/*N* (%)	67/203 (33.0)	25/412 (6.1)	<0.001
AST (IU/L)	66.5 (38.0–126.0)	36.0 (27.0–50.0)	<0.001
ALT (IU/L)	47.5 (30.0–87.3)	33.0 (24.0–45.0)	<0.001
TBIL (mg/dL)	20.8 (13.7–39.3)	17.9 (13.8–24.0)	<0.001
Albumin (g/L)	32.0 (26.0–39.0)	40.0 (36.1–43.8)	<0.001
Platelets ($\times 10^9$)	152.0 (95.8–234.0)	121.0 (78.0–175.3)	<0.001
Child-Pugh			<0.001
A, *n*/*N* (%)	79/206 (38.3)	277/315 (87.9)	
B, *n*/*N* (%)	83/206 (40.3)	35/315 (11.1)	
C, *n*/*N* (%)	44/206 (21.4)	3/315 (1.0)	
BCLC			<0.001
A, *n*/*N* (%)	10/197 (5.1)	94/131 (71.8)	
B, *n*/*N* (%)	96/197 (48.7)	32/131 (24.4)	
C, *n*/*N* (%)	48/197 (24.4)	5/131 (3.8)	
D, *n*/*N* (%)	43/197 (21.8)	0/131 (0)	

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona clinic liver cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MTD, maximum tumor diameter; PVTT, portal vein tumor thrombus; TBIL, total bilirubin.

TABLE 2

Comparison of baseline data on HBV-associated HCC patients treated with antiviral therapy between Chinese and Turkish cohorts.

Characteristic	Turkey (*n* = 89)	China (*n* = 431)	*p*-Value
Age (years)	62.0 (52.5–66.5)	56.0 (51.0–62.0)	0.001
Male gender, *n*/*N* (%)	77/89 (86.5)	346/431 (80.3)	0.169
History of alcohol consumption, *n*/*N* (%)	4/81 (4.9)	52/142 (36.7)	<0.001
Cirrhosis, *n*/*N* (%)	79/89 (88.8)	319/357 (89.4)	0.872
MTD (cm)	4.5 (2.9–7.7)	3.9 (2.4–6.0)	0.046
AFP (ng/mL)	34.6 (7.6–290.3)	12.5 (3.9–55.3)	<0.001
PVTT, *n*/*N* (%)	24/89 (27.0)	19/354 (5.4)	<0.001
AST (IU/L)	68.0 (36.0–117.0)	36.0 (27.0–50.0)	<0.001
ALT (IU/L)	43.0 (29.5–94.5)	32.0 (24.0–44.8)	<0.001
TBIL (mg/dL)	20.5 (13.6–41.0)	18.0 (14.3–24.1)	0.041
Albumin (g/L)	31.0 (24.5–38.0)	39.8 (36.2–43.8)	<0.001
Platelets ($\times 10^9$)	123.0 (80.5–204.5)	117.0 (77.0–172.0)	0.196
Child-Pugh			<0.001
A, *n*/*N* (%)	41/89 (38.2)	175/196 (89.3)	
B, *n*/*N* (%)	33/89 (41.0)	18/196 (9.2)	
C, *n*/*N* (%)	15/89 (20.8)	3/196 (1.5)	
BCLC			<0.001
A, *n*/*N* (%)	6/86 (4.5)	44/60 (73.3)	
B, *n*/*N* (%)	47/86 (50.0)	14/60 (23.3)	
C, *n*/*N* (%)	18/86 (24.2)	2/60 (3.3)	
D, *n*/*N* (%)	1586 (21.3)	0/60 (0)	

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona clinic liver cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MTD, maximum tumor diameter; PVTT, portal vein tumor thrombus; TBIL, total bilirubin.

TABLE 3

Comparison of baseline data among patients with unresectable HCC of China and Turkey.

Characteristic	Turkey (*n* = 359)	China (*n* = 453)	*p*-Value
Age (years)	62.0 (54.0–68.0)	57.0 (51.0–63.0)	<0.001
Male gender, *n*/*N* (%)	313/359 (87.2)	365/453 (80.6)	0.012
Antiviral therapy, *n*/*N* (%)	89/183 (48.6)	337/453 (74.4)	<0.001
History of alcohol consumption, *n*/*N* (%)	14/175 (8.0)	44/96 (45.8)	<0.001
Cirrhosis, *n*/*N* (%)	209/231 (90.5)	262/291 (90.0)	0.960
MTD (cm)	5.0 (3.0–9.0)	2.2 (1.6–4.6)	0.034
AFP (ng/mL)	27.7 (6.1–373.1)	9.5 (3.5–33.7)	<0.001
AST (IU/L)	66.5 (38.0–126.0)	34.0 (26.0–48.0)	<0.001
ALT (IU/L)	47.5 (30.0–87.3)	31.0 (23.0–42.0)	<0.001
TBIL (mg/dL)	20.8 (13.7–39.3)	17.9 (13.9–24.1)	<0.001
Albumin (g/L)	32.0 (26.0–39.0)	38.7 (34.5–41.9)	<0.001
Platelets ($\times 10^9$)	152.0 (95.8–234.0)	108.0 (73.0–154.0)	<0.001
Child-Pugh			<0.001
A, *n*/*N* (%)	79/206 (38.3)	164/191 (85.9)	<0.001
B, *n*/*N* (%)	83/206 (40.3)	24/191 (12.5)	
C, *n*/*N* (%)	44/206 (21.4)	3/191 (1.6)	
BCLC			<0.001
A, *n*/*N* (%)	10/197 (5.1)	94/131 (71.8)	
B, *n*/*N* (%)	96/197 (48.7)	32/131 (24.4%)	
C, *n*/*N* (%)	48/197 (24.4)	5/131 (3.8)	
D, *n*/*N* (%)	43/197 (21.8)	0/131 (0)	

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; MTD, maximum tumor diameter; TBIL, total bilirubin.

TABLE 4

Comparison of baseline data among resectable and unresectable HCC in Chinese cohort.

Characteristic	Resectable (*n* = 125)	Unresectable (*n* = 453)	*p*-Value
Age (years)	55.0 (48.0–63.0)	57.0 (51.0–63.0)	0.214
Male gender, *n* (%)	104 (83.2)	365 (80.6)	0.506
Antiviral therapy, *n* (%)	94 (75.2)	337 (74.4)	0.855
History of alcohol consumption, *n*/*N* (%)	37/125 (29.6)	44/96 (45.8)	0.013
Cirrhosis, *n*/*N* (%)	94/125 (75.2)	262/291 (90.0)	<0.001
MTD (cm)	3.8 (2.5–6.0)	2.2 (1.6–4.6)	0.159
AFP (ng/mL)	29.5 (5.2–224.7)	9.5 (3.5–33.7)	<0.001
AST (IU/L)	38.0 (28.3–54.8)	34.0 (26.0–48.0)	0.018
ALT (IU/L)	37.0 (25.3–53.8)	31.0 (23.0–42.0)	0.001
TBIL (mg/dL)	18.0 (13.6–23.2)	17.9 (13.9–24.1)	0.795
Albumin (g/L)	42.8 (39.6–46.0)	38.7 (34.5–41.9)	<0.001
Platelets ($\times 10^9$)	164.0 (113.0–218.0)	108.0 (73.0–154.0)	<0.001
Child-Pugh			0.240
A, *n*/*N* (%)	113/124 (91.1)	164/191 (85.9)	0.240
B, *n*/*N* (%)	11/124 (8.9)	24/191 (12.5)	
C, *n*/*N* (%)	0/124 (0)	3/191 (1.6)	

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; MTD, maximum tumor diameter; TBIL, total bilirubin.