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Comparison of Clinical Features of Hepatitis B and C Virus-Related Hepatocellular Carcinoma

Ganchudur Luvsan [1], Taivanbaatar Erdenebileg [2], Adilsaikhan Mendjargal [3], Gan-Erdene Baatarjav [4], Otgonbayar Damdinbazar [5], Bayarmaa Enkhbat [6], Baatarkhuu Oidov [7], Shiirevnyamba Avirmed [1,8]

[1]Department of Surgery, Mongolia-Japan Hospital and School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [2]Department of Hepatobiliary and Pancreatic Surgery, National Cancer Center of Mongolia, Ulaanbaatar, Mongolia; [3]Department of Surgery, Mongolia-Japan Hospital, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [4]Department of Surgery, Second General Hospital of Mongolia, Ulaanbaatar, Mongolia; [5]Division of Sciences and Technology, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [6]Department of Pathology, School of Biomedicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [7]Department of Infectious Diseases, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [8]Graduate School, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia

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Corresponding Author
Shiirevnyamba Avirmed, MD., PhD
Department of Surgery, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, 14210 Mongolia
Tel: + 976-9400-0269
E-mail: shiirevnyamba@mnums.edu.mn

Objective: To compare the clinical characteristics of hepatitis B virus-related hepatocellular carcinoma (HBV group) and C virus-related hepatocellular carcinoma (HCV group). **Methods:** By a single century, we analyzed the clinical characteristics of 23 patients with hepatitis B virus-related hepatocellular carcinoma (HBV group) and 34 with hepatitis C virus-related hepatocellular carcinoma (HCV group). **Results:** The patients in the HBV group (mean age 61.1 year) were about 6 years younger than those in the HCV group (mean age 67.1 year). Liver function, as measured by indocyanine green retention at 15 min, was better in the HBV group (17.5 %) than in the HCV group (25.4 %). A higher proportion of the HBV group (55 %) than the HCV group (44 %) had clinical stage I. T-factor differed significantly between the groups: 53 % of the HBV group were T3 - 4 compared with 41 % of the HCV group. Furthermore, a higher proportion of the HBV group was graded 2 - 3 for tumor thrombus in the portal vein (20.3 %) and had poorly differentiated hepatocellular carcinoma (7 %) compared with the HCV group (7.1 % and 5 % respectively). Univariate analysis identified poor prognostic factors for hepatocellular carcinoma as HBV, age < or = 50 year, clinical stage II-III, a high AFP level, higher number of tumors, larger tumor size, tumor thrombus in the portal vein 2 - 3 and in the hepatic vein 2 - 3. On multivariate analysis, poor prognostic factors were a high AFP level, a higher number of tumors, and tumor thrombus in the portal vein 2 - 3 and in the hepatic vein 2 - 3, but not HBV, age, clinical stage, or tumor size. In the multiple logistic regression models on the hepatitis infection, the OR for ASAT was 2.01 (95 % CI 1.41 - 6.91), statistically significant ($p < 0.05$). **Conclusion:** These results suggest that HBV itself is not a stronger prognostic factor than HCV.

Keywords: Hepatitis, Carcinoma, Virus, Neoplasms, Antigens, Blood-Borne Infections

Introduction

Hepatocellular carcinoma (HCC) has risen to become the fifth most common cancer and the third leading cause of cancer-related deaths in the world and continues to increase progressively in incidence, being a major global health problem [1 - 3]. The two most important risk factors for HCC are the hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. It has been reported that approximately 54 % of HCC cases are attributed to HBV infection whilst 31 % are attributed to HCV infection (170 million) globally [4, 5]. The incidence rate of HCC in Mongolia is the highest in the world with 54.1 cases per 100.000 population. The high incidence rate of HCC closely reflects a high prevalence rate of HBV or HCV infection. According to previous studies, the prevalence of HBV is 10.6 % whilst the it is 9.9 % for HCV [6, 7].

Even though there are histological similarities in the resulting carcinomas, studies suggested quite distinct oncogenic pathways and histories between HBV and HCV. In the case of HBV infection, the expression of viral proteins that transactivate human oncogenes could be the main factor for hepatocarcinogenesis in addition to chronic inflammation. HBV infection usually occurs from genes of an infected mother. The risk of transmission is 70 to 90 % from women seropositive for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen [8]. Whilst, in HCV infection, chronic inflammation seems to play the main role in oncogenesis, thus, cirrhosis almost always accompanies HCV-related HCC [9, 10].

Numerous studies indicated that there are genetic, immune-associated as well as environmental factors that can be strongly related to HCC manifestations [11 - 13]. The cross-sectional study enrolled 188 patients by Munaf et al demonstrated the prevalence of HCV- and HBV-related HCC in Pakistan. Here, patients with HCV were more likely to develop HCC at an advanced age (52.4 ± 11.952.4 ± 11.9 vs. 40.7 ± 12.0940.7 ± 12.09 years), with highly raised serum AFP levels (≥ 400ng/ml ≥ 400ng/ml) 78. 2% (HBV 67.1 %), large tumor size (HCV-66 % > 5 cm, HBV-59.3 %), and presence of portal vein thrombosis (8.06 %, HBV 1.56 %). Moreover, the HCV-HCC group was more likely to be cirrhotic (OR = 0.245, 95 % CI: 0.117, 0.516) and had more than two times higher rate of solitary macrovascular involvement (OR = 2.533, 95 % CI: 1.162, 5.521) as compared with HBV associated HCC [14]. Another study by Sun et al. characterized genome-scale profiles of HBV and HCV-infected HCC by comparing their gene expression pattern, methylation profiles, and copy number variations from the publicly accessible data of The Cancer Genome Atlas

Program (TCGA). It has been confirmed that HLA-A, STAT1, and OAS2 genes were highly enriched and up-regulated discovered in the HCV-infected HCC [15].

There are still controversies about HCC surveillance due to the different research protocols as well as management strategies. We aimed, in this study, to determine HBV and HCV clinical features of Mongolian patients with HCC who enrolled in the National Cancer Center of Mongolia and Mongolia-Japan Hospital of MNUMS.

Materials and Methods

Subjects

A total of 56 patients with histologically confirmed HCC who were diagnosed in the Mongolia- Japan Hospital of the Mongolian National University of Medical Sciences were enrolled in this study. All patients provided informed consent and completed structured questionnaires.

This was a retrospective study. Patients' characteristics were extracted from medical records. In our study, patients were included if they (1) had pathologically confirmed HCC (2) underwent hepatectomy, and (3) have medical data for hepatitis viral infection status of HBsAg and HCV- Ab. Patients were excluded if (1) they had an additional carcinoma, (2) they were HCV-Ab positive, or (3) their clinical data were not complete. To control the bias, patients were included in the study consecutively. The flow chart is shown in Additional file 1: Figure S1. A total of 175 patients with HCC, who underwent hepatectomy were enrolled. Among them, 107 patients were positive for HBsAg and negative for HCV-Ab for at least 6 months [16]. A total of 68 cases were negative for HBsAg and negative for HCV-Ab. The study was approved by the medical ethics committee. In our study, HCC was diagnosed with pathological evidence and the stage of HCC was determined according to the TNM classification. TNM staging was defined according to the American Joint Committee on Cancer TNM Staging for Liver Tumors as follows: (1) Primary tumor (T): (TX) Primary tumor cannot be assessed; (T0) no evidence of primary tumor; (T1) solitary tumor without vascular invasion; (T2) solitary tumor with vascular invasion or multiple

tumors less than 5 cm in size; (T3a) multiple tumors more than 5 cm in size; (T3b) single tumor or multiple tumors of any size, involving a major branch of the portal vein or hepatic vein; and (T4) tumor(s) with direct invasion of adjacent organs, other than the gallbladder, or with perforation of visceral peritoneum.

(2) Regional lymph nodes (N): (NX) regional lymph nodes cannot be assessed; (N0) no regional lymph node metastasis and (N1) regional lymph node metastasis. (3) Distant metastasis (M): (M0) no distant metastasis and (M1) distant metastasis.

Clinical features

Clinical and pathological data on all patients, including age, gender, preoperative alpha-fetoprotein (AFP), tumor size, tumor number, capsule, and tumor differentiation were collected. Follow-up was conducted using a telephonic interview. The postoperative survival of the two groups was observed. The effects of HBV- and NBNC on the clinicopathological features and prognosis of HCC were analyzed.

Statistical analysis

Statistical analysis was performed using the chi-square test to compare discrete variables and the t-test for continuous variables between HBV and HCV-related HCC. The student's t-test and Chi-square test was used to examine the correlation between different etiologies and clinical and pathological variables. The multiple logistic regression model was conducted to predict risk factors for hepatitis infection. P-values less than 0.05 were considered statistically significant. Statistical analysis was performed using the SPSS software (version 13; SPSS Inc., Chicago, IL, USA).

Ethical statement

This study was approved by the Ethics Committee of the Ministry of Health of Mongolia (No. 2020/3-05), and the institutional review board of the Mongolian National University of Medical Sciences. All participants were native Mongolians and aged > 18 years.

Results

The mean age of the participants in our study was 62.92 ± 9.38 years. Most of the patients with HBV were male (73.9 %) while most of the HCV patients were female (70.6 %). With respect to socioeconomic factors, 46 (80.7 %) of those had secondary

Table 1. General characteristics of study population.

Variables	HBV (n = 23)	HCV (n = 34)	Total (n = 57)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age, years	61.14 ± 8.51	67.06 ± 7.38	62.92 ± 9.38	0.009
BMI, kg	24.45 ± 4.71	24.99 ± 3.79	25.30 ± 3.82	0.832
Gender	N (%)	N (%)	N (%)	
Male	17 (73.9)	10 (29.4)	27 (47.4)	0.002
Female	6 (26.1)	24 (70.6)	30 (52.6)	
Smoking				
Yes	11 (47.8)	6 (17.6)	17 (29.8)	0.032
No	12 (52.2)	28 (82.4)	40 (70.2)	
Alcohol				
No	13 (56.5)	26 (76.5)	39 (68.4)	0.194
Yes	10 (43.5)	8 (23.5)	18 (31.6)	
Education				
Middle	18 (78.2)	28 (82.4)	46 (80.7)	0.966
College	5 (21.8)	6 (17.6)	11 (19.3)	
Family members				
< 4	13 (56.5)	18 (52.9)	31 (54.4)	0.821
> =5	10 (43.5)	16 (45.1)	26 (45.6)	

Table 2. Comorbidities.

Variables	HBV (n = 23)	HCV (n = 34)	Total (n = 56)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Viral Hep, years	5.39 ± 5.20	8.18 ± 7.04	7.05 ± 6.46	0.092
	N (%)	N (%)	N (%)	
Tumor				
Yes 1	2 (9.1)	4 (11.7)	6 (89.3)	0.135
No 2	20 (90.9)	30 (88.3)	50 (10.7)	
Cardiovascular				
Yes 1	5 (21.7)	3 (8.8)	8 (14.4)	0.247
No 2	18 (78.3)	31 (91.2)	49 (85.9)	
Diabetes				
Yes 1	3 (13.0)	2 (5.8)	5 (8.8)	0.383
No 2	20 (86.9)	32 (94.2)	52 (91.2)	
Ascites				
Yes 1	1 (4.3)	2 (5.9)	3 (5.3)	0.931
No 2	22 (95.7)	32 (94.1)	54 (94.7)	
Jaundice				
Yes	4 (18.2)	3 (8.8)	7 (12.5)	0.414
No	18 (81.8)	31 (91.2)	49 (87.5)	

Table 3. Laboratory measurements.

Variables	HBV (n = 23)	HCV (n = 34)	Total (n = 56)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
ASAT	121.41 ± 130.31	66.38 ± 43.34	88.72 ± 98.74	0.081
ALAT	105.66 ± 92.68	54.13 ± 40.26	74.93 ± 70.57	0.018
PLT	207.0 ± 70.72	188.79 ± 46.02	196.14 ± 57.39	0.283
Creatinine	78.15 ± 17.23	79.38 ± 37.18	78.89 ± 30.52	0.867
Total bilirubin	14.07 ± 5.91	14.83 ± 9.13	14.53 ± 7.94	0.704
INR	1.09 ± 0.11	1.12 ± 0.21	1.11 ± 0.18	0.538
Glucose	6.38 ± 2.53	6.45 ± 3.45	6.42 ± 3.09	0.938

Table 4. Multiple logistic regression for HBV.

Variables	OR	95%CI	p-value
Age, years	1.21	1.01 - 4.51	0.061
Viral hepatitis, years	1.51	0.94 - 6.10	0.098
BMI, kg	1.29	0.21 - 3.61	0.612
ASAT	2.16	0.95 - 6.81	0.058
ALAT	1.12	1.06 - 9.26	0.049
Gender			
Female	1.00	Reference	
Male	1.03	0.18 - 2.91	0.601
Alcohol			
No	1.00	Reference	
Yes	1.05	0.02 - 4.61	0.921

Table 5. Multiple logistic regression for HCV.

Variables	OR	95% CI	p-value
Age, years	1.09	0.91 - 4.51	0.083
Viral hepatitis, years	1.24	0.22 - 2.52	0.062
BMI, kg	1.13	1.37 - 11.4	0.783
ASAT	1.92	1.02 - 3.93	0.060
ALAT	2.83	1.06 - 13.10	0.054
Gender			
Female	1.00	Reference	
Male	1.14	0.04 - 11.14	0.841
Alcohol			
No	1.00	Reference	
Yes	1.46	0.19 - 2.82	0.672

Table 6. Multiple logistic regression for hepatitis infection.

Variables	OR	95% CI	p-value
Age, years	1.34	0.24 - 2.68	0.064
Viral hepatitis, years	1.68	1.84 - 8.41	0.091
BMI, kg	1.29	0.92 - 9.49	0.210
ASAT	2.01	1.41 - 6.91	0.041
ALAT	3.14	1.18 - 7.94	0.091
Gender			
Female	1.00	Reference	
Male	1.09	0.13 - 9.95	0.682
Alcohol			
No	1.00	Reference	
Yes	1.18	0.58 - 6.94	0.386

education while 11 patients had higher education (Table 1).

Comorbidities of HBV and HCV patients was shown in (Table 2). We had not detected any statistical significance in both group regarding the other diagnosis such as diabetes, tumor as well as cardiovascular diseases.

Lab results of liver function tests (AST and ALT) were 121.41 ± 130.31 and 105.66 ± 92.68 in HBV patients. On the other hand, HCV patients had 66.38 ± 43.34 and 54.13 ± 40.26, which is significantly lower than HBV (Table 3).

(Table 4) shows, the multiple logistic regression model for HBV. In the model, the ORs for ASAT and ALAT were 2.16 and 1.12, respectively ($p = 0.058$, $p = 0.049$).

The adjusted odds ratios from the multiple logistic regression model for HCV were shown in (Table 5). The highest OR, 2.83 was observed for ALAT ($p = 0.054$). The ORs of BMI and ASAT were 1.13 and 1.92, respectively, none of them were statistically significant ($p = 0.783$, $p = 0.060$). Moreover, the OR for alcohol intake was 1.46 ($p = 0.672$). In (Table 6), the results from the multiple logistic regression model on both HBV and HCV infection. The OR for ASAT was 2.01 (95 % CI 1.41 - 6.91), statistically significant ($p < 0.05$).

Discussion

Hepatocellular carcinoma (HCC) is the most prevalent primary malignant tumor in the liver and the third most common cause of cancer death worldwide [17, 18]. The major causative factors are HBV and HCV.

HBV is a DNA virus that causes the malignant transformation of hepatocytes with gene integration into chromosomes [19 - 21]. In acute HBV, after the appearance of viral markers, serum AST and ALT levels begin to increase, and jaundice can appear.

It has been demonstrated that HBV is hyperendemic in several Asia– Pacific countries and contributes greatly to the mortality from chronic liver disease, liver cirrhosis, and HCC in these countries [22]. In the study by Merican et al, 73 % of patients in China with chronic hepatitis and 78 % and 71 % of those with cirrhosis and HCC, respectively, are HBsAg positive. Whilst 8 - 10 % of males and 6 - 8 % of females are HBsAg positive, with HBsAg also found in 30% of patients with cirrhosis and 50 – 75 % of those with HCC in Thailand [23]. The study by Choi et al demonstrated that the incidence and mortality of hepatocellular carcinoma (HCC) have decreased over time in South Korea, where the hepatitis B virus (HBV) is endemic. Differences in patient characteristics and outcomes were compared between chronological cohorts: cohort A (2000 - 2004, n = 1,157) vs. B (2005 - 2009, n = 1,678) vs. C (2010 - 2015, n = 1,456), and HBV-related patients showed significantly improved survival (12.7 vs. 20.4 vs. 64.5 months, $p < 0.001$) associated with the use of antiviral treatments [24]. The data from our study confirmed that patients with HBV - HCC were significantly younger than HCV - HCC. Moreover, HBV-HCC patients had smoking behaviors and the majority were males. The liver function test revealed that HBV patients had significantly higher AST and ALT levels (121.41 ± 130.31 and 105.66 ± 92.68).

On the other hand, chronic HCV infection is estimated to affect more than 150 million people worldwide and to cause major health problems by causing liver cirrhosis and cancer. It is the second leading cause of cancer mortality worldwide [25 - 27]. Sievert et al showed that approximately 49.3 - 64.0 million adults in Asia, Australia, and Egypt are anti-HCV positive. Authors revealed that nosocomial infection, blood transfusion as well as injection drug use were identified as common risk factors in the region. Genotype 1 was common in Australia, China, Taiwan, and other countries in North Asia, while genotype 6 was found in Vietnam and other Southeast Asian countries. In India and Pakistan, genotype 3 was predominant, while genotype 4 was found in Middle Eastern countries such as Egypt, Saudi Arabia, and Syria [28]. Botheju et al also showed that HCV prevalence among the general population at 0.7 % (95 % CI: 0.7 - 0.8 %) in Kazakhstan, 2.0 % (95 % CI: 1.7 - 2.4 %) in Kyrgyzstan, 2.6 % (95 % CI: 1.7 - 3.6 %) in Tajikistan, and 9.6 % (95 % CI: 5.8 - 14.2 %) in Uzbekistan [29]. In the retrospective study of Lee et al, among 376 patients, it was found that 27 % of the cohort had cirrhosis and 25 % of patients had HCC and 1 % had lymphoma. The median AST and ALT levels were 82 and 48 U/L, respectively [30]. In our study, these levels were 66.38 ± 43.34 and 54.13 ± 40.26, respectively.

Prior studies have shown that the influencing factors hepatitis infection are multiple, including male gender, old age, hepatitis B vaccine dose, malnutrition, diabetics and low albumin level [31]. But the results of these studies are inconsistent. Alanine aminotransferase (ALAT) level is an important factor in the decision to initiate the treatment of CHB because the elevated ALAT levels indicate immune-mediated inflammation to eliminate HBV-infected hepatocytes and a higher rate of hepatitis B virus e antigen (HBeAg) seroconversion [32]. Further, some studies reported that there was alteration of the liver functions which could be linked to hepatitis virus infection or liver damage [33]. In our study, we conducted the multiple logistic regression to predict the factors, ASAT and ALAT were associated significantly with both HBV and HCV infection.

The limitation of our study is that the sample size was small. Therefore, more subjects in future study should provide stronger statistical analysis. Moreover, other hepatic cirrhosis evaluations such as MRI as well as liver biopsy should be included in future studies.

Conflict of interest

The authors have no conflict of interest.

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