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Epidemiological Characteristics of Advanced Hepatocellular Carcinoma in the Northern Region of Vietnam

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Abstract

Epidemiological characteristics of hepatocellular carcinoma (HCC) in Southern Vietnam has been well reported as in Globocan 2018 while data from the North has still not been fully presented. Therefore, we conducted this retrospective descriptive study on 198 advanced HCC patients treated at 3 major hospitals in Northern Vietnam to describe demographic features, HCC risk factors, and correlation among them in patients with advanced HCC. This information will lead to prevention efforts and provide information for allocating funds for treatment. The median age at diagnosis was 57 years (range: 19-86) and the male/female ratio was 8.9/1. The proportions of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection were 81.3% and 5.6%, respectively. Hepatitis C virus infection rate was significantly higher in patients <50 years old (12.5% vs 3.3%, $P = .016$). There was no significant difference in age or viral hepatitis infection status by gender. Only 7.6% of patients diagnosed with advanced HCC were asymptomatic. In conclusion, with the high rate of HBV infection among patients with advanced HCC, it is necessary for increasing prevention efforts in HBV screening. Furthermore, HCV infection should be noticed in patients with advanced HCC younger than 50 years old.

Keywords

advanced hepatocellular carcinoma, epidemiology, Vietnam, HCV, HBV

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world with 841 100 new cases in 2018 and also is the second leading cause of cancer death.[1] By gender, HCC accounts for the fifth most common cancer in males and the ninth most common cancer in females worldwide.[1] It is reported that approximately 80% of HCC cases occur in developing countries.[1] Latest data have indicated that Vietnam ranks fourth in terms of HCC incidence worldwide, after Mongolia, Egypt, and Gambia.[1] In Vietnam, HCC standardized age incidence rates (IR) are 39.0 per 100 000 people in men and 9.5 per 100 000 people in women.[1] Compared to Hanoi, Ho Chi Minh City has a significantly higher HCC IR for male (incidence rate

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ratio [IRR] = 1.22, 95% CI: 1.09-1.36) and a marginally higher rate for female (IRR = 1.21, 95% CI = 0.98-1.49).[2]

Hepatocellular carcinoma is a major health problem in Vietnam with the majority of patients being diagnosed at an advanced HCC stage, which results in poorer treatment outcomes. Hepatocellular carcinoma treatment at an advanced stage is very expensive and is an economic challenge for Vietnam's developing economy.[3,4] Although several risk factors of HCC including chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol use, diabetes, and obesity have been investigated as well as a national immunization program with HBV vaccination for infants has been implemented in Vietnam in more than 15 years, there is still an increasing trend of HCC burden. Therefore, reliable and comprehensive data on epidemiology of HCC could bring policy makers certain suggestions to strengthen the HCC prevention efforts. In this study, we aimed to describe epidemiological characteristics of patients with advanced HCC in Northern Vietnam.

Subjects and Methods

Study Population

The study took place at 3 major oncology centers in Hanoi, including Vietnam National Cancer Institute, Bach Mai Hospital, and Hanoi Medical University Hospital which are located in Northern Vietnam. At each center, we performed a retrospective medical record review on patients diagnosed with advanced HCC from 2010 to 2017.

The diagnostic criteria of HCC are based on diagnosis and treatment guideline of Vietnamese Ministry of Health and Barcelona Clinic Liver Cancer system, satisfying 1 of 3 criteria: (1) evidence of pathological diagnosis with HCC, (2) typical image of HCC on contrast-enhanced abdominal computer tomography or magnetic resonance image together with αFP level higher than 400 ng/mL, or (3) typical image of HCC on contrast-enhanced abdominal computer tomography or magnetic resonance image, with an increase in αFP (but less than 400 ng/mL) and evidence of chronic HBV or HCV infection. The advanced stage of HCC is defined as stage C or D without indication of local intervention, with the presence of portal venous thrombosis or extrahepatic metastasis.[5] Only patients treated in the hospital for advanced HCC with sufficiently documented medical records were included in this study.

Child-Pugh Score

The score employs 5 clinical measures of liver disease, including ascites status, bilirubin, albumin level, prothrombin time, and encephalopathy condition.[6] Each measure is scored 1 to 3, with 3 indicating most severe derangement. A total score of 5 to 6 is considered Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease).

Research Methods

Medical charts of eligible patients were abstracted by medical doctors who were trained about study protocol and data collection. Obtained epidemiological information included age, gender, HBV and HCV infection status, alcohol use, reason for hospitalization, and liver function prior to treatment according to Child Pugh score. Patients were confirmed to be infected with HBV when positive with HBsAg and infected with HCV when positive with anti HCV. Alcohol use is defined as having up to 1 drink per day for women and up to 2 drinks per day for man.

Data Analysis

Differences in demographic features and HCC risk factors between males and females and between patients diagnosed at <50 and ≥50 years of age were calculated using χ^2 test or Fisher exact test when appropriate. Analyses were carried out using SPSS version 20.0 software.

Results

Epidemiological Characteristics

During the period from January 2010 to December 2017, a total of 198 patients with advanced HCC met our study inclusion criteria. The median age of diagnosis with HCC was 57 years old and age at diagnosis ranged from 19 to 86 years old. The most common age-group was older than 50 (75.8%), whereas the proportion of patients younger than 40 years old accounted for only 8.6%. The majority of the patients were males (89.9%) and the male/female ratio was 8.9/1. Most patients were symptomatic (92.4%), while only 7.6% were asymptomatic and diagnosed during medical checkup. Of all, 72.2% of patients had well-compensated liver function (Child-Pugh A), 15.2% had moderate-compensated (Child-Pugh B), and 12.6% had decompensated liver function (Child-Pugh C; Tables 1 and 2).

Liver Cancer Risk Factors

Most patients with advanced HCC were infected with HBV (81.3%), while HCV infection proportion was low (5.6%). The proportion of patients infected with both HBV and HCV was only 2.5%. Alcohol use was recorded in 15.7% of patients with advanced HCC. Patients with both HBV infection and alcohol abuse disorder accounted for10.6%, HCV infection and alcohol abuse disorder was 0.5%, and none of the patients were coinfected with HBV and HCV and alcohol use (Tables 1 and 2).

Epidemiological Factors by Genders and Ages

We found no differences in age, HBV status, HCV status, HBV-HCV co-infection by gender (Table 1). However, the proportion of alcohol use significantly differed between men and women ($P = .048$), with no women having reported alcohol abuse. When we assessed demographic features and risk

Table 1. Epidemiological Factors by Genders.

Characteristic	Total (N = 198)	Male (n = 178)	Female (n = 20)	*P* Value[a]
Age-group, no (%)				
<50	48 (24.2)	40 (22.5)	8 (40.0)	.083
≥50	150 (75.8)	138 (77.5)	12 (60.0)	
Alcohol use, no (%)				
Yes	31 (15.7)	31 (17.4)	0 (0)	**.048**
No	167 (84.3)	147 (82.6)	20 (100)	
HBV, no (%)				
Yes	161 (81.3)	145 (81.5)	16 (80.0)	.771
No	37 (18.7)	33 (18.5)	4 (20.0)	
HCV, no (%)				
Yes	11 (5.6)	10 (5.6)	1 (5.0)	1
No	187 (94.4)	168 (94.4)	19 (95.0)	
HBV and HCV, no (%)				
Yes	4 (2.0)	4 (2.2)	0 (0)	1
No	194 (98.0)	174 (97.8)	20 (100.0)	
None HBV and HCV, no (%)				
Yes	31 (15.7)	28 (15.7)	3 (15.0)	1
No	167 (84.3)	150 (84.3)	17 (85.0)	
Alcohol use and none HBV, HCV, no (%)				
Yes	9 (4.5)	9 (5.1)	0 (0)	.602
No	189 (95.5)	169 (94.9)	20 (100)	
HBV and alcohol use, no (%)				
Yes	21 (10.6)	21 (11.8)	0 (0)	.138
No	177 (89.4)	157 (88.2)	20 (100.0)	
HCV and alcohol use, no (%)				
Yes	1 (0.5)	1 (0.6)	0 (0)	1
No	197 (99.5)	177 (99.4)	20 (100)	
Child-Pugh				
A	143 (72.2)	127 (71.3)	16 (80.0)	.486
B	30 (15.2)	28 (15.7)	2 (10.0)	
C	25 (12.6)	23 (12.9)	2 (10.0)	
Reason for hospital admit				
Regular health check	15 (7.6)	14 (7.9)	1 (5.0)	1
Symptomatic	183 (92.4)	164 (92.1)	19 (95.0)	

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.
[a]We compared the difference between male and female using χ^2 test or Fisher exact test.
$p < 0.05$ for statistically significant difference are in bold.

factors for HCC by 2 age groups (<50 vs ≥50), no significant differences were observed in terms of HBV infection, alcohol use, coinfection with HCV-HBV, concomitant HBV infection—alcohol use, and HCV infection—alcohol use (Table 2). The proportion of HCV was significantly higher in younger group ($P = .016$).

Discussion

The incidence of HCC varies by geographic region. The median age at diagnosis in our study was 57 years old (ranged from 18-86 years old), similar to those of Asia and Africa countries where the HCC rates were high.[7] Recent data have shown that the median age of patients with HCC in countries with a high incidence is usually 10 to 20 years younger than those with low incidence.[7] According to the data from Asia-Pacific (AP) trial (in Asia) and Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial (in Europe and in North America), the median age were 51 and 67, respectively.[8,9] The difference in diagnostic age among these countries might be due to the variation in the epidemiology of HBV prevalence, which is a major cause of HCC. In Asian countries, patients are usually found to be infected with HBV during the first few years of life and are at risk of developing HCC after 20 to 40 years. Therefore, HCC tends to be diagnosed at a younger age in Asia compared to Western countries.[10]

The majority of advanced HCC cases were among males (89.9%), and this gender difference is consistent with HCC worldwide statistics.[11] Liver disease is reported to develop more easily in patients with high levels of testosterone and low levels of estrogen.[11] Estrogen inhibits inflammation through interleukin 6 and thereby reducing the damage of liver cells, while testosterone increases the pathways through the androgen receptor and thereby promoting the development of hepatocytes.[12]

Among patients with advanced HCC in our study, the proportion of HBV infection was very high (81.3%), while the rate of HCV infection was only 5.7%. The proportion of HBV in

Table 2. Epidemiological Factors by Age.[a]

Characteristic	Total (N = 198)	Age < 50 (n = 48)	Age ≥ 50 (n = 150)	*P* Value[b]
Alcohol use, no (%)				
Yes	31 (15.7)	8 (16.7)	23 (15.3)	.825
No	167 (84.3)	40 (83.3)	127 (84.7)	
HBV, no (%)				
Yes	161 (81.3)	39 (81.2)	122 (81.3)	.99
No	37 (18.7)	9 (18.8)	28 (18.7)	
HCV, no (%)				
Yes	11 (5.6)	6 (12.5)	5 (3.3)	**.016**
No	187 (94.4)	42 (87.5)	145 (96.7)	
HBV and HCV, no (%)				
Yes	5 (2.5)	3 (6.2)	2 (1.3)	.093
No	193 (98.0)	45 (93.8)	148 (98.7)	
None HBV and HCV, no (%)				
Yes	31 (15.7)	6 (12.5)	25 (16.7)	.489
No	167 (84.3)	42 (87.5)	125 (83.3)	
Alcohol use and none HBV-HCV				
Yes	9 (4.5)	2 (4.2)	7 (4.7)	.885
No	189 (95.5)	46 (95.8)	143 (95.3)	
HBV and alcohol use, no (%)				
Yes	21 (10.6)	6 (12.5)	15 (10.0)	.624
No	177 (89.4)	42 (87.5)	135 (90.0)	
HCV and alcohol use, no (%)				
Yes	1 (0.5)	0 (0)	1 (0.7)	1
No	197 (99.5)	48 (100)	149 (99.3)	
Child-Pugh				
A	143 (72.2)	111 (74.0)	32 (66.7)	.605
B	30 (15.2)	21 (14.0)	9 (18.8)	
C	25 (12.6)	18 (12.0)	7 (14.6)	
Reason for hospital admit				
Regular health check	15 (7.6)	2 (4.2)	13 (8.7)	.530
Symptomatic	183 (92.4)	46 (95.8)	137 (91.3)	

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.
[a]Cut-off: 50 years old.
[b]We compared the difference between age <50 and age ≥50 using χ^2 test or Fisher exact test.
$p < 0.05$ for statistically significant difference are in bold.

our study was significantly higher than those reported in other Asian countries, and there were no differences in age–sex ratio.[8] The rate of HBV and HCV infection in the AP trial was 73% and 8%, respectively, while according to global data, 53% of HCC are related to HBV and 25% are related HCV infection.[13] In Southeast Asia, these prevalence is 65% and 18%, respectively.[13] In Vietnam, there have been very few international publications of data on the association between primary HBV infection and HCC. The prevalence of viral hepatitis in a number of reports indicates that there is a difference between the 2 regions, the North and the South of Vietnam, while our study population is in the North.[2] One report found that the odds ratio of developing HCC in HBV-infected patients was lower in Ho Chi Minh City than in Hanoi (OR = 37.8, 95% CI = 11.6-121.4 vs OR = 61.7, 95% CI = 30.0-128.0) and similar to those with HCV-infected and HBV-free patients, (OR = 6.8, 95% CI: 2.1-22.1 vs OR = 38.1, 95% CI: 2.8-1443.0).[2] Hepatitis B virus causes primary liver cancer through 2 pathways, 1 direct and 1 indirect. Direct pathway involves the integration of the virus's DNA into the chromosomes of the liver cells, while indirect pathway is through necrotic inflammation and recreation, thereby increasing the accumulation of genetic mutations and fibrosis in the liver.[10,14,15] Some studies have shown that different genotypes of HBV pose different risks of HCC. In Asia, genotype C is associated with a higher risk of HCC than genotype B.[16] In Vietnam, the prevalence of hepatitis B with genotype B was over 75.3% and the genotype C accounted for 11.7% in one report of general population, while other hospital-based studies showed the predominance of genotype C.[17-20] More studies evaluating the HBV' genotypes should be performed in patients with HCC to clarify this problem.[20] In Vietnam, since 2002, the vaccination of hepatitis B in the expanded vaccination program for children under 1 year of age has been a positive sign in reducing the incidence of hepatitis B and thereby reducing the incidence of HCC. Unfortunately, the hepatitis B vaccination coverage rate was only 60% in 2013, so hepatitis B remains the main cause of HCC in Vietnam, especially in the North in the next 2 decades.[21]

The proportion of hepatitis C infection in our study population was only 5.7%. People with chronic hepatitis C often

develop HCC on a cirrhotic liver, the risk of primary liver cancer in the group anti-HCV positive is 20 times higher than that in the negative group.[22] As the RNA of the HCV is fully replicated in the cytoplasm, the mechanism of liver cancer development is mainly through indirect pathways, such as chronic inflammation and hepatocellular injury due to oxidizing shock.[23] We did not find differences in HCV infection proportion between sexes. However, in the group aged <50, the proportion of hepatitis C was higher than that in the group aged older than 50 (12.5% vs 3.3%, $P = .016$).

We found the proportion of HCV and HBV co-infection was very low at 2%. In a meta-analysis of 32 case–control studies of the effects of HBV and HCV on the development of primary liver cancer suggests that for patients with HBV-only, the risk of developing HCC was17.3, for patients with HCV infection the risk of HCC was 22.5.[24] However, for patients with co-infection of HBV and HCV the risk was 165.[24] The mechanism of co-infection on the development of primary liver cancers is unclear because of the limited number of research on this issue.

The percentage of alcohol use of patients in our study was 15.7%. The relationship between alcohol consumption and liver cancer has been demonstrated in many studies, but the consumption threshold and the timing of consumption were not well defined.[25-27] Drinking alcohol causes HCC directly by hepatocellular toxicity or indirectly through cirrhosis. Alcohol is the leading cause of liver oxidation, hepatitis, and cirrhosis.[28] Prevalence of alcohol dependence in Vietnam was from 28.3% to 44% as found in other socioeconomic studies,[29] higher than in Asian countries, such as Japan (7.2%).[30] Surprisingly, 100% alcohol use in our study was males, with significant differences ($P = .048$). A study was conducted to compare the differences in cancer incidence among Vietnamese in Hanoi and Vietnamese in the United States to assess the impact of living environment on the incidence of cancer in the Vietnamese population.[31] For liver cancer, Vietnamese people in the United States have a higher incidence than those live in Hanoi.[31]

In the study group, only 7.6% of patients were diagnosed with periodic health checkups, while the remaining 92.4% had obvious clinical signs. This is the general condition of Vietnam, where the majority of patients come to the hospital in the late stage of disease. In one report in 2009 in Vietnam, the proportion of patients admitted to the hospital in the late stage accounted for 87.9%.[29] The proportion of early diagnosis was low due to inadequate economic status and low awareness of the disease. The percentage of respondents in one study who knew more than 4 signs of cancer awareness was only 22.3%, with 19.7% of people asked did not know the early signs of cancer; a high proportion of patients seek traditional medicine before coming to the hospital. In our study, the percentage of patients with liver function level Child-Pugh B and C at the time of diagnosis were quite high (15.2% and 16.2%, respectively). For patients with this liver function, the therapeutic results of existing treatments for advanced HCC were limited.

Although this is the first study to evaluate some of the epidemiologic features of advanced phase HCC in northern Vietnam, our study was limited to no further analysis of the factors other than HBV, HCV, and alcohol use. The levels of alcohol consumption had not been mentioned in our study. Other risk factors such as aflatoxin, hereditary syndromes, were not covered in this study and require further epidemiological studies to assess these factors. Another limitation is that the number of patients in our study was limited to 198 patients, taken from 3 major hospitals in Hanoi, which did not cover all of Northern Vietnam. However, it is difficult to obtain full information about HCC at provinces other than Hanoi. Therefore, data analysis in 3 large hospitals receiving treatment for the majority of patients in the North is acceptable.

Conclusions

Our data have shown that advanced stage HCC is strongly associated with HBV infection. Therefore, efforts in HBV prevention and screening could contribute to HCC control in Vietnam. Moreover, our study observed a significantly higher proportion of HCV among patients younger than 50 years of age compared to the age-group of 50 and above. Further studies should be conducted to evaluate this phenomenon in more details, which could be helpful in the prevention of HCC. In our study, a majority of patients with advanced HCC did not seek medical care until they had obvious clinical symptoms or poor liver function. This raises the urgent need for preventive and surveillance programs to diagnose patients with HCC at an earlier stage in parallel with the improvement of diagnostic and therapeutic quality to reduce both morbidity and mortality.

Authors' Note

Le Van Quang and Nguyen Thi Thu Huong are equal contributors and co-primary authors. The protocol of this study was approved by the Human Research Ethics Committee at Hanoi Medical University in Vietnam (approval no. 129/HĐĐĐĐHYHN 04 October 2017). All patients provided written informed consent prior to enrollment in the study.

Declaration of Conflicting Interests

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