Clinical characteristics and outcome of hepatocellular carcinoma in alcohol related and cryptogenic cirrhosis: a prospective study

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BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is becoming a leading cause of chronic liver disease. Hepatocellular carcinoma (HCC) is one of its complications. Although the pathophysiology is unclear, it is reasonable to expect that cryptogenic cirrhosis related HCC (cryptogenic HCC) behaves differently to other types of HCC. This study prospectively compared patients with cryptogenic HCC and those with HCC related to alcoholic cirrhosis.

METHODS: A total of 150 consecutive patients with HCC (89 cryptogenic HCC and 61 alcohol related HCC) referred to our unit over a 23-month period were studied. Their demographic data, liver function, tumor characteristics and outcomes were compared.

RESULTS: Alcohol related HCC was seen only in males. Compared with cryptogenic HCC, alcohol related HCC had significantly higher aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio (1.7 vs 1.4, *P*=0.002), model for end-stage liver disease score (13 vs 11, *P*=0.018) and Child's score (7 vs 6, *P*=0.037). No significant difference was seen in platelet counts, serum sodium and AST to platelet ratio index. Single nodular tumors were more common in cryptogenic HCC, while diffuse type tumors and macroscopic vascular invasion were common in alcohol related HCC. In patients who could not be offered any treatment because of advanced tumors or poor liver function, alcohol related HCC had a significantly lower median survival (5.3 months) compared with cryptogenic HCC (9.3 months, *P*=0.034).

CONCLUSIONS: Compared with cryptogenic HCC, alcohol related HCC had worse liver function and aggressive tumor morphology at presentation, and a higher proportion was untreatable. In patients who could not be treated, median survival was lower in patients with alcohol related HCC than in those with cryptogenic HCC.

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KEY WORDS: hepatocellular carcinoma; liver diseases; alcoholic; fatty liver

Introduction

Hepatitis B and C are the leading causes of hepatocellular carcinoma (HCC) worldwide.[1] Viral hepatitis leads to HCC as a complication of cirrhosis or as a result of direct integration of viral DNA into the host genome.[1] Alcohol is another leading cause of cirrhosis and HCC, and although the exact mechanism is not understood, chromosomal loss, oxidative stress, decreased retinoic acid levels in the liver, altered DNA methylation and genetic susceptibility may play a role.[2] Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are becoming increasingly prevalent in the Asian continent and are already a leading cause of chronic liver disease in the region.[3-5] NASH is now believed to account for most cases of cryptogenic cirrhosis worldwide.[6] Unlike in alcoholic liver disease, HCC can complicate NASH even in the absence of cirrhosis.[7, 8] Although, here too, the pathophysiology is unclear, it is reasonable to expect that NASH related HCC behaves differently to alcohol and hepatitis related HCC.

In Sri Lanka the most common causes of cirrhosis are alcohol related and cryptogenic (probably NASH-re-

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lated). Hepatitis B, C and hemachromatosis are uncommon.[9] The present study compares tumor morphology, clinical characteristics and outcomes of patients with alcohol related HCC and cryptogenic cirrhosis related HCC (cryptogenic HCC).

Methods

One hundred and fifty consecutive patients with alcohol related and cryptogenic HCC referred to our clinic from January 2011 to December 2012 were included in the study. All data were collected prospectively. HCC was diagnosed according to the American Association for the Study of Liver Diseases (AASLD) guidelines.[10] Biopsy from the lesion was done in only 4 patients with atypical imaging. A detailed history was taken to assess the degree of alcohol consumption. Patients who had a history of consuming alcohol above the accepted safe limits (Asian standards: <14 units of alcohol per week in men and <7 units per week in women) prior to the diagnosis of cirrhosis were considered as having alcoholic cirrhosis. There were 61 patients in the alcohol related HCC group, and their median abstinence from alcohol on presentation to our unit was 7 months. Patients who did not drink alcohol above the safe limits had no history of contributory drug or herbal product use and did not have hepatitis B and C, autoimmune disease, hemachromatosis, Wilson's disease, and alpha-1 antitrypsin deficiency were considered to have cryptogenic HCC. However a liver biopsy had not been performed for the diagnosis of cryptogenic cirrhosis. There were 89 patients in the cryptogenic HCC group.

All patients underwent liver function assessment. Upper gastrointestinal endoscopy was done in all newly diagnosed cirrhotics. The presence of portal vein invasion was diagnosed when an enhancing tumor extension was detected in the main or sectoral portal vein branch. All these patients underwent portal vein Doppler to assess the flow within the thrombus. Management decisions were taken at a multi-disciplinary meeting. Decisions regarding liver transplantation, surgical resection, ablation, trans-arterial chemoembolization or sorafenib therapy were made according to tumor morphology, background liver status and functional index. Patients were followed up in a special combined medical and surgical clinic.

The majority of our patients with treatable disease underwent combined treatment. As the follow-up period was relatively short and multiple treatment combinations were used, the actual numbers treated with each combination was small. We therefore selected patients with Barcelona clinic liver cancer (BCLC) stages C and D who could not be given any active treatment, and compared survival in these patients (alcohol related versus cryptogenic).

Values of continuous variables were presented as median and range. Differences between the two groups were compared by the Chi-square test, Fisher's exact test or the Mann-Whitney *U* test where appropriate. Cumulative survival and recurrence rates were calculated using the Kaplan-Meier method and the difference between survivals was evaluated using the log-rank test. A *P* value of less than 0.05 was considered statistically significant.

Results

Of the 150 patients with HCC, 61 were alcohol related and 89 were cryptogenic originated. Alcohol related HCC was seen only in males. The two groups were not different in age or body mass index at presentation. Baseline liver functions were different in the two groups (Table 1). Alcohol related HCC had a significantly higher aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio (1.7 vs 1.4, *P*=0.002), a MELD score (13 vs 11, *P*=0.018), and a Child's score (7 vs 6, *P*=0.037). There was no significant difference in platelet count, serum sodium levels or AST to platelet ratio index (APRI) between the two groups. When tumor characteristics were compared, there was no difference in median tumor diameter or alpha-fetoprotein levels between the two

Table 1. Comparison of liver status in alcohol related and cryptogenic HCC

Variables	Alcohol related HCC (*n*=61)	Cryptogenic HCC (*n*=89)	*P* value
Age (yr)	63 (45-75)	62 (12-88)	0.887
Gender (male)	61 (100%)	72 (80.9%)	**<0.001**
Body mass index (kg/m^2)	23.1 (15.1-40.0)	23.2 (15.2-36.8)	0.821
Presence of diabetes	32 (52.5%)	64 (71.9%)	0.050
Presence of hypertension	7 (11.5%)	12 (13.5%)	0.113
MELD score	13 (5-21)	11 (4-22)	**0.018**
Child's score	7 (5-14)	6 (5-12)	**0.037**
AST (U/L)	66 (15-354)	58 (21-320)	0.317
ALT (U/L)	33 (9-131)	41 (10-585)	0.061
APRI	42.3 (10.7-840.0)	43.6 (6.6-169.1)	0.527
Platelet count (×10^9/L)	145 (10-364)	161 (39-652)	0.678
Presence of ascites	17 (27.9%)	23 (25.8%)	0.431
Bilirubin (mg/dL)	1.6 (0.3-8.3)	1 (0.2-13.7)	**0.046**
INR	1.3 (1.0-3.5)	1.2 (1.0-2.8)	**0.020**
Sodium (mmol/L)	135 (122-145)	138 (121-145)	0.265
AST/ALT ratio	1.7 (0.52-8.20)	1.4 (0.24-4.08)	**0.002**
Albumin (mg/dL)	3.2 (2.2-4.4)	3.5 (1.9-4.8)	**0.004**

MELD: model for end-stage liver disease; AST: aspartate aminotransferase; ALT: alanine aminotransferase: APRI: AST to platelet ratio index; INR: international normalized ratio.