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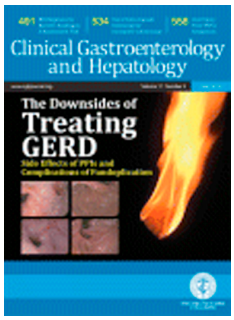

Early-age hepatocellular carcinoma associated with hepatitis B infection in South America

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Early-age hepatocellular carcinoma associated with hepatitis B infection in South America

Short title: Hepatocellular carcinoma in South America

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Introduction:

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and is almost universally associated with chronic liver disease and cirrhosis. Risk factors for HCC generally vary by geographic region. To date, studies have focused on characterizing patients with HCC in Europe, North America, Asia and, to a lesser extent, Africa [1, 2]. However, little is known about the underlying demographic characteristics and risk factors for HCC in South America, particularly the association between viral hepatitis and HCC. In this study we describe the early results of a multinational effort to characterize HBV-related HCC in South America.

Methods:

We designed a retrospective cohort study aimed at identifying the demographics and risk factors associated with HCC in South America. Overall, fourteen medical centers from six countries in South America participated. Each center was responsible for adhering to their respective institutional review policies. Participating centers completed a standardized, retrospective chart review of patient characteristics at the time of HCC diagnosis. Data was then de-identified and placed into a composite database. Diagnosis of HCC was made radiographically or histologically for all cases as defined by institutional standards. Continuous variables were summarized as means or as medians (IQR) according to their homogeneity. Statistical analysis was performed using the SPSS v 22.0 statistical package.

Results:

Fourteen centers from six countries across South America contributed data for an aggregate 1,336 patients. Brazil accounted for 540 patients, Argentina 251, Colombia

239, Peru 220, Ecuador 65 and Uruguay 21. Of the 1,336 patients 68% were male and the overall median age of both males and females was 64 years. A total of 1,153 (86%) patients had complete data on risk factors for HCC. HBV infection represented the main risk factor for HCC in 131 subjects (11% of the those with complete data), of which 74% were males. Centers from Peru and Brazil contributed for the majority of HBV patients (34 and 38% respectively), followed by Argentina (16%), Colombia (7%), Ecuador (3%) and Uruguay (2%). The median Alpha-fetoprotein level on diagnosis was 161 ng/ml and 86% of HBV-infected individuals had evidence of cirrhosis (in those the provided that information, N=81). When evaluating HCC in individuals infected with HBV, we found that 38% (*n*=48) of cases occurred before age 50, with a median age at diagnosis of 58 years, while in those infected with HCV, only 6% (*n*=24) were diagnosed with HCC before age 50 ($p<0.001$) and the median age of diagnosis was 63 years (Figure 1). Even larger differences were observed when HBV-induced HCC were compared with NAFLD (median age at diagnosis 67 years, $p<0.001$) and alcohol-induced HCC (median age at diagnosis 68 years, $p<0.001$). We did analyze inter-country variability for HBV-related HCC and age of incidence and found a larger number of HCC diagnosed below age 50 from Peru (43%) compared to other countries (25%) but the difference was not significant (p=0.09).

Discussion:

Our study unexpectedly found that nearly 40% of HCCs in HBV-infected individuals occurred before age 50. This finding raises the question of whether surveillance at earlier ages should be considered in this group. We did not obtain information about cirrhosis in all HBV-infected patients with HCC before age 50, but less than half of those

with such information had cirrhosis (15/34). Peru contained the highest rate of HBV-related HCC (35%), making it the most common risk factor for HCC in the country. Of those individuals from Peru with specific information about area of origin (N=24), 45% were from the Amazonian region which has a higher prevalence of HBV [3]. Mode of transmission could also play a role in early HCC, but this was not assessed in our study. Interestingly, the most frequent HBV genotype in South America is F and a significant association between HBV genotype F and early HCC occurrence has been found in Alaska natives [3, 4]. It is possible that the viral genotype had a role in early HBV-associated HCC in our cohort. However, our centers did not perform HBV genotype and sequence-specific studies should be performed addressing this question.

The diagnosis of HCC at an early age in individuals infected with HBV in Africa has been attributed to a synergy between HBV and dietary aflatoxins, which is thought to induce mutations in the TP53 gene. However, aflatoxins have not been thought to play a role in South America, although one study found aflatoxin-associated p53 mutations in HBV-related HCCs [5]. Other factors such as insertional mutagenesis or family history could play a role in early HCC [6]. However, we could not assess for these variables in our study. A larger, comprehensive study is needed to further understand the clinical implications of HBV infection in HCC development in South America.

Figure 1. Cumulative percent of HCC per independent risk factors based on age. There was a significant difference between age of diagnosis for HBV-related HCC versus others ($p<0.001$).

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