

Etiology of hepatocellular carcinoma in Latin America: a prospective, multicenter, international study

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ABSTRACT

Background/aims. No prospective study has been published investigating etiology of HCC in Latin America. The primary aim of this prospective study was to analyze the etiology of liver disease in patients with HCC from our area. Secondary aims were to evaluate staging using Okuda and BCLC classifications; and percentage of patients receiving treatment. **Methods.** The Governing Board of the Latin American Association for the Study of the Liver designed the protocol. During a 18 month period, all members were invited to load their incident HCC cases on line. **Results.** 240 cases from 9 countries were uploaded, 174 were male (72.5%), median age was 64 years, interquartile range 57-72. In 85.4% of cases, patients had underlying cirrhosis. Main etiological factors were: HCV in 74 patients (30.8%), alcohol in 49 (20.4%), cryptogenic cirrhosis in 35 (14.6%), HBV in 26 (10.8%), HCV plus alcohol in 14 (5.8%). Considering the combinations, hepatitis C was shown in 91 patients (38%); chronic alcoholism in 68 patients (28%); and hepatitis B in 33 patients (14%). There were no significant differences between the groups in the age at diagnosis. Percentage of male gender was higher in groups of alcohol (94%), HCV plus alcohol (93%) and HBV (85%) than in cryptogenic cirrhosis (60%) and HCV (59%) ($p < 0.001$). **Conclusions.** Our prospective study showed that hepatitis C is the more frequent etiology of HCC in Latin America, followed by alcoholic cirrhosis. Demographical results showed a male predominance (male:female ratio 2.6) with an important proportion of patients being diagnosed at their sixties.

Key words. Hepatitis C. Alcoholic cirrhosis. Cryptogenic cirrhosis. Hepatitis B. BCLC staging system.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a malignant tumor that usually emerges in cirrhotic patients, mostly associated with hepatitis B, hepatitis C and chronic alcohol intake. The incidence of HCC is highly variable across the world, depending on the relative presence of the underlying liver diseases at each

region.^{1,2} It especially depends on the prevalence of chronic carriers of hepatitis B virus (HBV). Therefore, annual incidence is very high (greater than 30/100.000 individuals) in some Asian (China, Mongolia, Korea) and African countries (Gambia, Guinea, Congo) with high endemicity of hepatitis B.^{1,2} In contrast, in areas where the rate of chronic carriers of HBsAg is low, like Australia, European countries and North America, the annual incidence of HCC is much lower (consistently under 10/100.000 individuals) and main underlying diseases are hepatitis C and alcoholic cirrhosis.³⁻⁸ In 1989, with the introduction of the first-generation enzyme-immunoassay, it was found that most of patients with HCC studied in tertiary centers from Spain and Italy had

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antibodies to HCV.^{4,5} More recent studies performed in Italian tertiary centers also showed that hepatitis C was the leading cause of HCC in that setting.⁶ However, Donato et al, in Brescia, North of Italy, found that heavy alcohol intake accounted for 45% of cases of HCC, chronic HCV infection for 36%, and chronic HBV infection for another 22%.⁷ In Australia, chronic alcoholism seems to be the leading risk factor.³ In the United States of North America, two recently published single-center studies have shown differing results, with predominance of alcoholic cirrhosis in one⁸ and hepatitis C in the other.⁹ Furthermore, there may be synergistic effects between alcohol and hepatitis C in the development of HCC,^{7,10} between alcohol and hepatitis B,⁷ and also between alcohol and diabetes.⁸

In Latin America, no prospective study has been performed analyzing epidemiological aspects of HCC patients. In the medical literature, there is no publication on the incidence or the ranking of HCC as a cause of death in Latin American countries. A few retrospective studies performed in our countries have been published, approaching the aspect of the relative contribution of different etiologies. In Brazil, a large retrospective study included 287 patients followed in 19 sites from 8 different States.¹¹ Complete medical history and serological information about the 3 main causes of HCC was available in only 132 out of 287 cases. Among them, chronic alcoholism was present in 36%, chronic hepatitis B in 35% and hepatitis C in 25% (as the sole risk factors or in different combinations).¹¹ In Mexico, a single-center retrospective study analyzed epidemiological features of 127 patients.¹² However, the full serological results on HBV and HCV were completed in only 71 out of 127 cases. Among them, HCV was shown in 73% (alone in 45%, associated with alcohol in 15% and with HBV in 13%).¹² In contrast, two studies from Peru have found that HBV was the more frequent etiology in patients with HCC in that country (present in 44% and in 63% of cases, respectively).^{13,14} Another small study was performed in Chile, showing predominance of hepatitis C, present in 48% of 50 cases of HCC.¹⁵ A multicenter, retrospective study including 551 patients with HCC completed in Argentina during 2005 evidenced that alcoholic cirrhosis and hepatitis C (present in 76% of cases) were the more frequent etiologies in the series.¹⁶ All of these studies have been retrospective and most of them share the problem of etiological results not being completely assessed. Less frequent diseases such as hereditary hemochromatosis have not been investigated in many cases. As a consequence, the prevalence of cryptogenic cirrhosis

as a cause of HCC is also unknown in our countries. Another possible bias in some of these studies is that they were performed in tertiary referral centers and percentages of alcoholic cirrhosis as a cause of HCC might have been underestimated in those settings, because alcoholic patients with HCC are many times diagnosed in general hospitals and they are not usually referred for specific therapies like liver transplantation.

In order to increase the knowledge of the disease in this area of the world, the Governing Board of the Asociación Latinoamericana para el Estudio del Hígado (ALEH) [in English, Latin American Association for the Study of the Liver (LAASL)] decided to organize and support a prospective study aimed in knowing epidemiological aspects of HCC. The primary aim of this prospective, multicenter, international and observational study was to analyze the etiology of the underlying chronic liver disease in patients with HCC from Latin America. Secondary aims were to evaluate: a. Staging of HCC by using two systems: the historical Okuda classification¹⁷ and the BCLC system,¹⁸ recommended by the AASLD Guidelines for the management of HCC; b. Percentage of patients receiving specific treatment for HCC and types of therapy.

PATIENTS AND METHODS

All members of ALEH received an e-mail inviting them to participate in this prospective study. During the period of patient inclusion, they were sent reminder e-mails. A database was constructed and a specific link was placed at the web page of ALEH. Through this link, members and non-members of ALEH could firstly register, read the text of the protocol, revise the Okuda and BCLC classifications, and upload the patient data. Enrollment of cases could be performed in two or more times: in the first time, the main results concerning the primary objective of the study (gender, dates of birth and diagnosis of HCC, countries of birth and diagnosis, etiology of chronic liver disease, presence or absence of cirrhosis, number and diameter of nodules, diagnosis performed through a surveillance program or not) were loaded. In the following times, data about the staging systems (Okuda and BCLC classifications)^{17,18} and type of treatment that patients received could be completed. However, if only demographical and etiological data were loaded and results about staging and type of treatment were lacking, the case was still included because our main objective was to know the etiology of HCC in Latin America.

Inclusion of patients was allowed during a period of 18 months, from September 01, 2006 to March 31, 2008. Participants were asked to include in the study only incident cases (new and consecutive diagnoses of HCC during the 18 month period) or cases with a diagnosis previous to the starting date but with an active follow-up or treatment during the study period. The definition of case of HCC was according to the EASL and AASLD guidelines.^{19,20} In completing the "etiology" field, participants could choose among the following fixed categories: alcohol; HCV; HBV; HCV plus alcohol; HBV plus alcohol; HCV plus HBV; HCV plus HBV plus alcohol; hemochromatosis; primary biliary cirrhosis; autoimmune hepatitis; nonalcoholic steatohepatitis; cryptogenic cirrhosis; other. The etiology of the chronic liver disease was defined according to conventional and international criteria.²¹⁻²⁵ Alcohol was considered as the etiological factor when there was a history of ethanol intake greater than 80 g/day for more than 10 years.¹⁰ Anti-HCV antibodies were assessed by using third-generation enzyme-immunoassay and anti-HBc and HBsAg were also analyzed using enzyme-immunoassay. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

During the study period, 120 colleagues from 14 Latin American countries completed their registration at the web site: 34 from Brazil, 28 from Argentina, 24 from Venezuela, 10 from Peru, 5 from Chile, 4 from Colombia, 3 from Uruguay, 3 from Dominican Republic, 2 from Mexico, 2 from Ecuador, 2 from Paraguay, 1 each from Bolivia, Costa Rica and Cuba. Among them, 27 participants from 9 different countries uploaded all the cases of HCC included in this report.

Statistical analysis: Mean $\pm$ standard deviation, median, interquartile range, minimal and maximal values were used to describe quantitative variables; frequencies and proportions were used to describe categorical variables. In the comparison of quantitative variables, test t Student and ANOVA were used, whereas Chi square test was used to compare qualitative variables. A p value < 0.05 was considered as statistically significant.

RESULTS

During the study period, 240 patients with HCC were uploaded in the database: 174 were male (72.5%), 66 were female (27.5%). Median age was 64 years old, interquartile range 57-72, minimal 19, maximal 92 years old. In 205 out of 240 (85.4%) cases, patients had underlying cirrhosis. The number

Table 1. Etiology of chronic liver disease in 240 patients with diagnosis of HCC.

Etiology	n	Percentage
HCV	74	30.8
Alcohol	49	20.4
Cryptogenic	35	14.6
HBV	26	10.8
HCV + alcohol	14	5.8
Other	14	5.8
NASH	11	4.6
HBV + alcohol	4	1.7
AIH	4	1.7
Hemochromatosis	4	1.7
HCV + HBV	2	0.8
PBC	2	0.8
HCV + HBV + alcohol	1	0.4

HCC: Hepatocellular carcinoma. **HCV:** Hepatitis C virus. **HBV:** Hepatitis B virus. **NASH:** Nonalcoholic steatohepatitis. **AIH:** Autoimmune hepatitis. **PBC:** Primary biliary cirrhosis.

Table 2. Age at diagnosis time in the main etiological groups of patients with HCC (in years).*

Etiology	Mean	SD
HCV** (n 74)	64.1	9.9
Alcohol** (n 49)	64.4	8.8
Cryptogenic (n 35)	62.2	16.9
HBV** (n 26)	62.0	11.8
HCV + alcohol (n 14)	60.1	11.5

* There were no significant differences. ** As the only risk factor present.

HCC: Hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus.

of cases diagnosed by country was: 90 in Argentina, 44 in Brazil, 43 in Venezuela, 32 in Colombia, 10 in Chile, 8 in Uruguay, 6 in Mexico, 4 in Antigua and Barbuda (treated and uploaded in Argentina), 3 in Ecuador.

Table 1 shows the etiology of chronic liver disease in the 240 patients with HCC. The main etiological groups were: HCV in 74 patients (30.8%), alcohol in 49 (20.4%), cryptogenic cirrhosis in 35 (14.6%), HBV in 26 (10.8%), HCV plus alcohol in 14 (5.8%).

Table 2 shows mean $\pm$ SD age at diagnosis time in the main etiological groups. There were no significant differences between the groups. Table 3 shows that percentages of male and female gender in the main etiological groups were significantly different (p < 0.001). Although the majority of patients were male in all categories, percentages were higher in groups of alcohol (93.9%), HCV plus alcohol (92.9%) and HBV (84.6%) than in cryptogenic cirrhosis (60%) and HCV (59.5%).

Table 3. Percentages of male and female genders in the main etiological groups in patients with HCC.*

Etiology	n	Male gender (%)	Female gender (%)
HCV**	74	59.5	40.5
Alcohol**	49	93.9	6.1
Cryptogenic	35	60.0	40.0
HBV**	26	84.6	15.4
HCV + alcohol	14	92.9	7.1

* Differences are significantly different ($p < 0.001$). ** As the only risk factor present. **HCC**: Hepatocellular carcinoma. **HCV**: Hepatitis C virus. **HBV**: Hepatitis B virus.

Table 4. Staging of HCC patients by BCLC classification according to diagnosis with or without a surveillance program.^a

BCLC stages	Surveillance program (n 102)		No surveillance program (n 86)	
	n	%	n	%
A	71	69.6	34	39.5
B	18	17.6	36	41.9
C	8	7.8	11	12.8
D	5	4.9	5	5.8

^a Differences are statistically significant among both groups ($p < 0.01$). **HCC**: Hepatocellular carcinoma. **BCLC**: Barcelona Clinic Liver Cancer.

Considering the different combinations, chronic hepatitis C was shown in 91 patients (37.9%): as the sole risk factor in 74, associated with chronic alcoholism in 14, associated with hepatitis B in 2, and with hepatitis B and alcoholism in 1; history of chronic alcoholism was present in 68 patients (28.3%): as the sole risk factor in 49, associated with HCV in 14, associated with HBV in 4, and with HCV plus HBV in 1; chronic hepatitis B was shown in 33 patients (13.8%): as the sole risk factor in 26, associated with chronic alcoholism in 4, associated with HCV in 2, and with HCV plus alcohol in 1.

Regarding tumor extension, in 152 cases (63.3%), only one nodule was detected; in 30 (12.5%) and in 16 (6.7%) patients, two and three lesions, respectively, were shown. In 32 cases (13.3%), more than 3 nodules were detected. Finally, in 10 patients (4.2%), a massive pattern of growth was described. The mean $\pm$ SD diameter of the major (or the only) nodule was 48.9 ± 31 mm (interquartile range 25-69 mm). Among the 240 patients with HCC, 124 (51.7%) were diagnosed being involved in a surveillance program. There was a significant difference in

the tumor diameter between HCC cases diagnosed through a surveillance program and those who were not involved in an early detection program (43.5 ± 28.9 versus 54.8 ± 32.3 mm, respectively) ($p = 0.004$).

Information on staging systems was answered in 188 out of 240 HCC cases. In respect to Okuda classification, 117 cases corresponded to stage I, 59 to stage II, and 12 to stage III. In the BCLC system, 105, 54, 19 and 10 cases were classified in stages A, B, C and D, respectively. Among the 188 cases of HCC with data fully completed on staging, 102 had been diagnosed through a surveillance program and 86 had not. Table 4 shows that there were significant differences in the proportions of patients being diagnosed in stages A, B, C and D among both groups ($p < 0.01$). Patients diagnosed through a screening strategy were in stages A and B in 69.6 and 17.6%, respectively; compared to 39.5 and 41.9% in patients diagnosed without a screening program.

Specific treatments for HCC were indicated in 164 out of 240 (68.3%) patients: surgical resection in 21, liver transplantation in 21, percutaneous ethanol injection in 23, radiofrequency ablation in 19, transarterial chemoembolization in 87, sorafenib in 5, other systemic therapies in 2. Eleven more patients were allocated to the local waiting list for liver transplants. Among patients with diagnosis through a surveillance program, 77% received specific therapies, compared to 59% in patients without diagnosis by that strategy ($p = 0.002$).

DISCUSSION

This report shows the results of the first prospective study performed in Latin America analyzing epidemiological features of 240 patients with HCC. Regarding demographical aspects, we found that our population was similar to that described in occidental countries, with a male predominance (72.5% of cases), a male:female ratio of 2.6 and a median age of 64 years old at diagnosis time. Another finding that resembles results from European countries was that HCC had emerged on underlying cirrhosis in 205 out of 240 (85.4%) cases. In respect to the etiology, we found that hepatitis C was the more frequent cause of HCC, shown in 91 patients (37.9%), either as the sole risk factor (in 74 cases) or in different combinations. Following to HCV, the second risk factor was chronic alcoholism, present in 68 patients (28.3%) (as the only risk factor in 49, and with different combinations in other 19). The third

more frequent etiology was the cryptogenic cirrhosis, diagnosed in 35 cases (14.6%).

As shown in table 2, we did not find significant differences between the main groups in the age of presentation and the interquartile range observed (57-71 years old) suggests that most of the patients were in their sixties. In contrast, we found some differences in the gender relationship between etiological groups. The male:female ratio was 1.5 in pure hepatitis C and cryptogenic cirrhosis whereas it was 15.3 in alcoholic cirrhosis and 5.5 in pure hepatitis B. Interestingly, the group of patients with HCV plus alcohol was in this aspect very similar to that with only chronic alcoholism (with 93% of males and a male:female ratio of 13). It has been shown in case-control studies that the intake of alcohol greater than 80 gr/day for more than 10 years increases the risk for HCC.^{8,10,26} In patients with alcoholic cirrhosis, the risk for HCC is approximately 1% per year.²⁷ Furthermore, case-control studies have shown that among patients with chronic hepatitis C, there is an approximately 2-fold increased risk for HCC in those who drink heavily alcohol as compared to nondrinkers,^{28,29} and longitudinal studies performed in Japan have found that lifetime alcohol use was independently associated with risk for HCC in patients with hepatitis C.^{30,31} It has been suggested that hepatitis C and chronic alcoholism have not only an additive but a synergistic effect in increasing risk for HCC.^{7,10}

Cryptogenic cirrhosis has increasingly been recognized as a risk factor for HCC in recent studies. In a large series from Italy, including 641 cases of HCC, the etiology of cirrhosis was considered as cryptogenic in 6.9%.⁶ A similar percentage (9.2%) was found in the retrospective series of 551 patients studied in Argentina.¹⁶ In a recent single-center study from USA, cryptogenic cirrhosis was the second most frequent etiology among patients with HCC, accounting for 29% of cases.⁹ Patients with cryptogenic cirrhosis described in these HCC series usually have features of the so-called metabolic syndrome: obesity has been observed in 41-58% of cases,^{6,9,32,33} and diabetes, in 47 to 88%.^{6,9,32,33} In USA, insulin resistance syndrome manifesting as obesity and diabetes is now emerging as a risk factor for HCC.³⁴ In fact, both obesity and diabetes are recognized as independent risk factors for HCC.^{35,36} In a recent study from USA, the relative risk of dying from liver cancer was 4.52 times higher for men with a body mass index ≥ 35 kg/m² compared with the reference groups (body mass index from 18.5 to 24.9).³⁷ In another large study, 173,643 pa-

tients with diabetes and without a concomitant liver disease and 650,620 control individuals without diabetes were followed-up.³⁶ The risk of developing HCC was approximately 2 times higher among diabetics compared to nondiabetics (the highest risk was among patients with a longer than 10 year follow-up).³⁶ Most of the experts suggest that the link between metabolic syndrome and HCC is through the sequence insulin resistance syndrome $\rightarrow$ NAFLD $\rightarrow$ cirrhosis $\rightarrow$ HCC. In a prospective study, Sanyal, *et al.* have shown that patients with cirrhosis due to nonalcoholic steatohepatitis do develop HCC although their risk is significantly lower compared with patients with cirrhosis due to hepatitis C.³⁸ However, recent reports have also suggested that HCC may even emerge in patients with metabolic syndrome and fatty liver in the absence of cirrhosis³⁹ or significant liver fibrosis.⁴⁰ In our study, 35 patients (14.6% of the studied population) were defined as having a cryptogenic cirrhosis. Unfortunately, participants were not asked to load data about metabolic syndrome features. Therefore, we cannot infer any conclusion on the possible origin of the cryptogenic cirrhosis in our patients. Besides, the etiology of cirrhosis in 11 patients with HCC (4.6%) of our series was defined as NASH, because there was a previous histological diagnosis of this disease.

Regarding the secondary objectives of the study, we observed that the majority of patients in this HCC series had only one nodule (63%), were in early or intermediate stages in the BCLC classification (85%) and were given a specific treatment (68%). These figures are rather satisfactory and much better than those described in a general population-based study from USA, performed among Medicare recipients.⁴¹ There is an explanation for this discrepancy: although all the members of ALEH were invited to participate in the study, most of whom finally did so are hepatologists working in tertiary centers and as a consequence, our study is not a population-based one. However, treatments considered as curative (surgical resection, liver transplant or percutaneous ablation) were applied in only 84 patients (35%) and many patients (n 87, 36.2%) received transarterial chemoembolization, a palliative therapy, probably reflecting some difficulties in performing liver transplants or resections in our Latin American countries.

An interesting percentage of patients (52%) was diagnosed as having a HCC while they were involved in a surveillance program to detect tumors at early stages, as usually recommended in clinical Guidelines.^{19,20} Compared with those who were not

involved in a surveillance program, these patients presented a significantly lower tumor diameter and a significantly higher percentage of them were at early stage of BCLC classification (70 vs. 39%, respectively) and were given a specific treatment for HCC (77 versus 59%, respectively).

One of the main limitations of the study is the possible selection bias. Trying to avoid this bias, the Governing Board of ALEH decided not to restrict the enrollment of patients to a few Latin American well-recognized experts but to invite all their members to participate. In fact, many of the participants in the survey are young investigators. However, most of them deal with Hepatology and work in tertiary centers. Thus, although they uploaded in the database all the consecutive cases of HCC diagnosed in their hospitals during the period study, some selection bias cannot be discarded. Another weakness is that 87% of cases were enrolled by participants from 4 countries (Argentina, Brazil, Venezuela and Colombia) and only a few patients were included from other ones. Therefore, some caution is warranted when interpreting our results and further larger and more extended studies will be necessary to expand the knowledge on epidemiology of HCC in Latin America.

In conclusion, this first prospective study analyzing epidemiological features of HCC in Latin American countries showed that chronic hepatitis C is also the more frequent etiology in our area, followed by alcoholic cirrhosis. Demographical results were very similar to that described in occidental countries, with a male predominance (male:female ratio 2.6) and an important proportion of patients being diagnosed at their sixties.

ABBREVIATIONS

- **HCC:** Hepatocellular carcinoma.
- **HBV:** Hepatitis B virus.
- **HBsAg:** Hepatitis B surface antigen.
- **HCV:** Hepatitis C virus.
- **ALEH:** Asociación Latinoamericana para el Estudio del Hígado.
- **LAASL:** Latin American Association for the Study of the Liver.
- **BCLC:** Barcelona Clínic Liver Cancer.
- **AASLD:** American Association for the Study of Liver Diseases.
- **EASL:** European Association for the Study of the Liver.
- **USA:** United States of America.
- **NAFLD:** Nonalcoholic fatty liver disease.
- **NASH:** Nonalcoholic steatohepatitis.

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Authors have nothing to declare.

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