

## Etiology of hepatocellular carcinoma in Argentina: results of a multicenter retrospective study

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### Summary

Incidence and etiology of hepatocellular carcinoma (HCC) are variable around the world, depending mainly on the prevalence of chronic hepatitis B carriers in each region. No study has been published analyzing epidemiological features of patients with HCC in Argentina. The aim of this retrospective study was to describe demographical and etiological results in a series of 587 consecutive patients with HCC diagnosed in 15 Hepatology and Gastroenterology Units distributed all around our country. Seventy-two per cent of patients were male, the median age was 62 years (interquartile range 55-68 years), and 93% had cirrhosis. Regarding to etiological data (fully available in 551 cases), main etiologies were chronic alcoholism in 229 patients (41.6%) (the sole risk factor in 182, associated to HCV in 35 and to HBV in 12); hepatitis C in 223 patients (40.5%) (the sole risk factor in 181, associated to alcoholism in 35 and to HBV in 7); hepatitis B in 74 patients (13.4%) (the sole risk factor in 55, associated to alcoholism in 12 and to HCV in 7); cryptogenic cirrhosis in 51 patients (9.2%). There were significant differences in percentages of genders

between main groups: males were highly predominant in alcoholic cirrhosis (93%), hepatitis B (87%) and HCV plus alcohol (94%), compared to 63% in cryptogenic cirrhosis and 49% in hepatitis C ( $p < 0.01$ ). There were no differences in age at presentation between the main etiologies. In conclusion, the main causes of HCC in Argentina are alcoholic cirrhosis and hepatitis C (76% of cases). A majority of patients with HCC in our country are cirrhotics, males, and in their 6<sup>th</sup> or-7<sup>th</sup> decades of life.

**Key words:** Hepatocarcinoma, Etiology, Epidemiology, Cirrhosis, Alcoholic cirrhosis Hepatitis C.

### Etiología del hepatocarcinoma en Argentina: resultados de un estudio multicéntrico retrospectivo

#### Resumen

La incidencia y etiología del hepatocarcinoma (HCC) son variables alrededor del mundo. Dependen especialmente de la prevalencia de portadores crónicos del HBV en las diversas regiones. En Argentina, no se ha publicado ningún estudio que analice aspectos epidemiológicos en pacientes con HCC. El objetivo de este estudio retrospectivo fue describir resultados demográficos y etiológicos en una serie de 587 pacientes consecutivos con HCC, diagnosticados en 15 Servicios de

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*Hepatología y Gastroenterología de todo el país. Setenta y dos por ciento de los pacientes fueron varones, con una edad mediana de 62 años (rango intercuartil 55-68 años), 93% tenían cirrosis. Datos sobre etiología fueron completados en 551 casos. Las principales causas fueron: alcoholismo crónico en 229 pacientes (41.6%) (único factor en 182, asociado a HCV en 35 y a HBV en 12); hepatitis C en 223 pacientes (40.5%) (único factor en 181, asociado a alcoholismo en 35 y a HBV en 7); hepatitis B en 74 pacientes (13.4%) (único factor en 55, asociado a alcoholismo en 12 y a HCV en 7); cirrosis criptogénica en 51 pacientes (9.2%). Se observaron diferencias significativas en la relación de sexos entre los principales grupos: predominio de varones en la cirrosis alcohólica (93%), hepatitis B (87%) y en el grupo HCV más alcohol (94%); comparado con 63% en la cirrosis criptogénica y 49% en el grupo de hepatitis C pura ( $p < 0.01$ ). En cambio, no hubo diferencias en la edad de presentación entre los diferentes grupos etiológicos. En conclusión, las principales causas de HCC en Argentina son la cirrosis alcohólica y la hepatitis C, que estuvieron presentes en 76% de los casos. La mayoría de los pacientes con HCC de nuestro país eran cirróticos, de género masculino, en la 6<sup>a</sup>-7<sup>a</sup> décadas de la vida.*

**Palabras claves:** *hepatocarcinoma, etiología, epidemiología, cirrosis, alcoholismo cirrosis, Hepatitis C*

#### Abbreviations:

HCC: hepatocellular carcinoma.

HCV: hepatitis C virus.

HBV: hepatitis B virus.

CLIP: Cancer of the Liver Italian Program.

BCLC: Barcelona Clínic Liver Cancer.

PBC: primary biliary cirrhosis; AIH, autoimmune hepatitis.

Hepatocellular carcinoma (HCC) is a malignant tumor that usually appears in cirrhotic patients, and is most commonly associated to hepatitis B, hepatitis C and chronic alcoholism. It is the fifth most common solid tumor around the world and causes approximately 500.000 deaths each year.<sup>1</sup> HCC incidence varies largely across the world, depending on the relative predominance of the underlying liver diseases at each region<sup>1,2</sup> and especially on the prevalence of chronic carriers of hepatitis B virus (HBV). Thus, incidence is very high in Asian (China, Mongolia, Korea) and African countries (Gambia, Guinea, Congo) with high endemicity of hepatitis B.<sup>1,2</sup> In contrast, in areas with a rate of chronic carriers of HBsAg lower than 2%, like Australia,

European countries and North America, the incidence of HCC is consistently lower and the main underlying diseases are hepatitis C and alcoholic cirrhosis.<sup>3-8</sup> In southern European countries, such as Spain and Italy, hepatitis C is clearly the most frequent etiology.<sup>4,6</sup> In Australia, chronic alcoholism seems to be the first risk factor.<sup>3</sup> In United States of North America, two recently published single-center studies have shown differing results, with predominance of alcoholic cirrhosis in one<sup>7</sup> and hepatitis C in the other.<sup>8</sup>

In Argentina, no study has been published as a full paper reporting the etiology of cirrhosis in patients with HCC. In 1998, Findor et al analysed a series of 216 cases studied at 9 Liver Units (median age 63 years, 77% males).<sup>9</sup> They found hepatitis C in 39% of patients (associated to chronic alcoholism in 20% of them); hepatitis B in 20% (associated to alcoholism in 7% of them); chronic alcoholism as the only risk factor in 16%; cryptogenic cirrhosis in 12% and minor percentages of hemochromatosis, autoimmune hepatitis and primary biliary cirrhosis.<sup>9</sup> This study was the only one previously performed in our country aimed to evaluate HCC etiology. However, as a retrospective survey of data collected in 9 tertiary centers, the results might have some bias. First, our country has low endemicity of HBV. Therefore, it was unexpected that hepatitis B was found to be the second most frequent risk factor. Second, we think that alcoholic cirrhosis might have been underestimated because only referral centers participated in the survey.

Prospective studies on the etiology of HCC are still lacking in our country and the rest of Latin America. Recently, authorities of the Latin American Association for the Study of the Liver began an international, multicenter, prospective study, that is still ongoing in all Latin American countries. In the present report, we show the results of a larger and more recent retrospective survey with the aim to know epidemiological aspects of HCC in Argentina.

#### Patients and methods

In September 2005, a questionnaire and an Excel file was sent to 30 different centers (including Liver Units and general Gastroenterology Services) distributed all around our country (10 in Buenos Aires city, 7 in different sites of Buenos Aires province, 3 in Córdoba province, 3 in Mendoza province, 2 in Santa Fe province, 2 in Tucumán province, and 1

each in Neuquén, Corrientes and Entre Ríos provinces). Each site members were asked about whether they had a database containing results on consecutive HCC patients. In the affirmative cases, they were requested to answer specific questions, including gender, age at the diagnosis of HCC, presence of cirrhosis, etiology of cirrhosis, number and diameter of nodules and staging [using Okuda,<sup>10</sup> CLIP<sup>11</sup> and BCLC<sup>12</sup> classifications]. In addition, the questionnaire asked whether the HCC diagnosis had been made through a surveillance program and whether patients had received a specific therapy. Colleagues from 15 centers [7 in Buenos Aires city, 5 in Buenos Aires province (one in greater Buenos Aires, 2 in La Plata, 1 in Mar del Plata, 1 in Bahía Blanca cities), one each in Tucumán, Neuquén and Mendoza provinces] completed the questionnaire. This publication is based on data of 587 patients with HCC, and only demographical and etiological data are presented.

The diagnoses of HCC was made following international guidelines.<sup>13</sup> Regarding to cirrhosis etiology, responders selected etiology for the following categories: HCV; HBV; alcohol; HCV plus alcohol; HCV plus HBV; HBV plus alcohol; HCV plus HBV plus alcohol; cryptogenic; hereditary hemochromatosis; primary biliary cirrhosis (PBC); autoimmune hepatitis (AIH). These etiological diagnoses were made according to standard international recommendations.<sup>14-17</sup>

A comparison was made between the etiological results found in centers that perform or do not perform liver transplantation. The proportions of the different etiologies in both groups were compared using Chi square test. Proportions of genders in the main etiological groups were also compared by Chi square test. A *p* value < 0.05 was considered as statistically significant.

## Results

The study population included 587 patients: 421 males (71.7%) and 166 females (28.3%). The median age was 62 years old (range 16 to 93 years). The interquartile range was 55 to 68 years. Cirrhosis was present in 546 cases (93%), absent in only 41 (7%).

Table 1 shows the etiological results in the 551 cases whose data were fully completed, including 531 with cirrhosis and 20 without cirrhosis. In the other 36 cases of HCC, a whole investigation of etiological factors was not performed. Chronic alcoholism

**Table 1.** Etiology of chronic liver disease in 551 cases with diagnosis of HCC.

Etiology	n	Percentage
Alcohol	182	33.0
HCV	181	32.8
HBV	55	10.0
Cryptogenic	51	9.2
HCV + alcohol	35	6.3
Hemochromatosis	15	2.7
HBV + alcohol	12	2.2
PBC	12	2.2
HCV + HBV	7	1.3
AIH	1	0.2

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis.

was present in 229 of patients (41.6%): as the sole risk factor in 182, associated to HCV in 35 and to HBV in 12. Hepatitis C was present in 223 patients (40.5%): as the sole risk factor in 181, associated to alcoholism in 35 and to HBV in 7. Hepatitis B was present in 74 patients (13.4%): as the sole risk factor in 55, associated to chronic alcoholism in 12 and to HCV in 7. In 51 patients (9.2%), the etiology of the chronic liver disease was considered as cryptogenic. Other less frequently found causes of cirrhosis were hemochromatosis (n 15), PBC (n 12) and autoimmune hepatitis (n 1).

Tables 2 and 3 show demographical data in the main etiological groups. Percentages of male and female gender were significantly different between groups (*p* < 0.01). An important male predominance was observed in alcoholic cirrhosis (93%), hepatitis B (87%) and HCV plus alcohol (94%). In contrast, in patients with only hepatitis C, male/female ratio was approximately one; and 63% of patients were men in cryptogenic group (Table 2). The median age at diagnosis was similar and not significantly different between the main groups, ranging from 59 to 64 years old (Table 3).

Table 4 shows the main etiologies of liver chronic disease in patients with HCC separated in two groups: 145 and 404 patients corresponding to series of centers that perform or do not perform liver

**Table 2.** Percentages of male and female genders in the main etiological groups in patients with HCC.<sup>a</sup>

Etiology	n	Male gender n (%)	Female gender n (%)
Alcohol*	182	169 (92.9)	13 (7.1)
HCV*	181	89 (49.2)	92 (50.8)
HBV*	55	48 (87.3)	7 (12.7)
Cryptogenic	51	32 (62.7)	19 (37.3)
HCV + alcohol	35	33 (94.3)	2 (5.7)

<sup>a</sup> Percentages are significantly different ( $\chi^2$  106.45,  $p < 0.01$ ).

\* As the only risk factor present.

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus.

**Table 3.** Age at diagnosis in the main etiological groups of patients with HCC (in years).<sup>a</sup>

Etiology	Median	Interquartile range
Alcohol* (n 182)	62	57-68
HCV* (n 181)	63	57-68
HBV* (n 55)	60	51-67.5
Cryptogenic (n 51)	64	57.5-72
HCV + alcohol (n 35)	59	50-64.5

<sup>a</sup> Ages were not significantly different between main etiological groups.

\* As the only risk factor present.

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus.

transplantation, respectively. Results show significant differences between them: in liver transplant centers, HCV was the more frequent etiology (51%), followed by HBV (19%) and alcohol (14%). In contrast, in non liver transplant centers, alcohol was the main etiology (40%), followed by HCV (26%). In both groups, cryptogenic cirrhosis was found in similar percentages (9.6 and 9.2%, respectively).

## Discussion

In this report, we are presenting results of the largest series of HCC patients ever studied in Argentina. We tried to collect data of patients with HCC diagnosed all around the country, including not only tertiary or liver transplant centers but also ge-

neral Gastroenterology services. Thirty centers of 9 different provinces were invited to participate and, although only 15 of them (of 5 different provinces) finally did so, we think that the spectrum of patients diagnosed in our country is rather well represented. Twelve out of 15 participating centers correspond to public hospitals, and 3 out of 15 to private hospitals, including 2 that perform liver transplantation.

Regarding to demographical aspects of the 587 patients with HCC included in this series, results are very similar to those found in the previous retrospective survey, presented by Findor et al.<sup>9</sup> The median age at diagnosis was 62 years old in our study and 63 years old in the previous study. Most of the patients were male: 72% in our study and 77% in Findor study. However, some differences were found between both studies in the etiological aspects. In the present series, alcoholic cirrhosis and chronic hepatitis C showed the same importance as causes of HCC: chronic alcoholism was present in 42% of patients while chronic HCV infection was found in 40% of them (as the only risk factors or in different associations). These two factors were present in 417 (75.7%) of the 551 patients who had all the etiological studies. The findings that are presented in Table 4 (comparing etiological data among liver transplant and non transplant centers) might explain the lower percentage of patients with alcoholic cirrhosis in the previous study: when the survey is limited to tertiary or very specialized centers, that etiology may be underestimated, because

**Table 4.** Main etiologies of liver chronic disease in 549 cases of HCC according to procedence of the series: liver transplant center (n 145) versus non liver transplant center (n 404).

Etiology	Liver transplant center n (%)	Non liver transplant center n (%)	p
HCV	74 (51.0)	107 (26.5)	<0.01
Alcohol	20 (13.8)	162 (40.1)	<0.01
HBV	28 (19.3)	27 (6.7)	<0.01
Cryptogenic	14 (9.6)	37 (9.2)	NS
HCV plus alcohol	3 (2.1)	32 (7.9)	0.01

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus.

many of the alcoholic patients are diagnosed in general hospitals and are not usually referred for liver transplantation or even for follow-up and management by hepatologists. Another discrepancy between present and previous studies was the role of HBV. In our study, chronic HBV infection was present in 13% of patients, being the third cause of HCC but in a much lower percentage than the two main etiologies. This finding could be anticipated in a country with low endemicity of chronic carriers of HBsAg.<sup>18,19</sup> Studies in general population have not been performed in our country, but recent percentages of HBsAg positivity in blood donors are consistently below 1%, according to the annual reports of Sentinel Units of Viral Hepatitis. Furthermore, the median age at presentation of our patients with hepatitis B and HCC (60 years old) is older than that observed in patients from Africa and Asia and this difference might be due to the predominant route of transmission in each region: vertical (mother-to-child) in Orient (involving newborns and infants) and sexual in Occident (involving young people and adults). In fact, in our country, data from Sentinel Units of Viral Hepatitis have shown that the median age of patients with acute hepatitis B is in the thirty's, being sexual transmission the more frequent risk factor.

Approximately 9% of 551 patients with HCC fully studied in this survey were considered as having cryptogenic cirrhosis. This figure is very similar to that described in a large HCC series from Italy;<sup>6</sup> and, in some studies from United States of America (USA), this etiology is ranking now as the second more frequent.<sup>8</sup> At present, insulin resistance syndrome manifesting as obesity and diabetes is emerging as a risk factor for HCC in USA.<sup>20,21</sup> It has been postulated that this feature might be secondary to the existence of a nonalcoholic fatty liver disease (considered as the hepatic component of the metabolic syndrome). In fact, some recent studies affirm that a proportion of patients with cryptogenic cirrhosis may actually have a "burned out" nonalcoholic steatohepatitis,<sup>22,23</sup> because they have a greater rate of obesity and/or diabetes than other etiologies of cirrhosis. Considering the retrospective nature of our study, we were not able to speculate about the origin of these cases of cryptogenic cirrhosis.

In the near future, very interesting knowledge on HCC etiology in our countries will be obtained from the ongoing prospective study supported by

the Latin American Association for the Study of the Liver. In the meantime, we may propose some conclusions derived from our retrospective but large survey: 1. HCC in Argentina is observed almost exclusively in cirrhotic patients; 2. The main etiologies are alcoholic cirrhosis and chronic HCV infection, that were present in 76% of cases; 3. In all etiological groups, the disease affects people in their 6th or 7th decade of life and is more common in men.

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