

Hepatocellular Carcinoma in South America: Evaluation of Risk Factors, Demographics, and Therapy

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Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; NAFLD, Non-alcoholic Fatty Liver Disease; AFP, Alpha-fetoprotein; AASLD, American Association for the Study of Liver Diseases; EASL, European Society for the Study of the Liver; OR, Odds ratio; HR, Hazard ratio; CI, Confidence interval; RFA, Radiofrequency ablation; PEI, Percutaneous alcohol injection; TACE, Trans-arterial chemoembolization; NASH, Non-alcoholic steatohepatitis.

Abstract:

Background and Aims: Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death worldwide. Most studies addressing the epidemiology of HCC originate from developed countries. This study reports the preliminary findings of a multinational approach to characterize HCC in South America. **Methods:** We evaluated 1336 HCC patients seen at 14 centers in six South American countries using a retrospective study design with participating centers completing a template chart of patient characteristics. The diagnosis of HCC was made radiographically or histologically for all cases according to institutional standards. Methodology of surveillance for each center was following AASLD or EASL recommendations. **Results:** Sixty-eight percent of individuals were male with a median age of 64 years at time of diagnosis. The most common risk factor for HCC was hepatitis C infection (HCV, 48%), followed by alcoholic cirrhosis (22%), Hepatitis B infection (HBV, 14%), and NAFLD (9%). We found that among individuals with HBV-related HCC, 38% were diagnosed before age 50. The most commonly provided therapy was Trans-arterial chemoembolization (35% of HCCs) with few individuals being considered for liver transplant (<20%). Only 47% of HCCs were diagnosed during surveillance and there was no difference in age of diagnosis between those diagnosed incidentally versus by surveillance. Nonetheless, being diagnosed during surveillance was associated with improved overall survival ($p=0.01$). **Conclusions:** Our study represents the largest cohort to date reporting characteristics, and outcomes of HCC across South America. We found an important number of HCCs diagnosed outside of surveillance programs, with associated increased mortality in those patients.

Abstract Keywords: Hepatocellular Carcinoma; South America; Risk Factors; Demographics

Key Points Box

- Our manuscript provides the most comprehensive study on liver cancer in South America. We found most common risk factor for liver cancer to be hepatitis C virus infection.
- A significant number of patients with hepatitis B virus infection had liver cancers diagnosed earlier than the recommended screening age.
- Over half of patients were diagnosed with liver cancer outside of surveillance programs highlighting deficiencies in surveillance.

□ The majority of individuals received TACE.

Introduction

Hepatocellular carcinoma (HCC) is the most common cancer originating from the liver and it is universally associated with chronic liver disease and cirrhosis (1). HCC is the fifth most common cancer in men and the second overall cause of cancer death accounting for 746,000 deaths worldwide (2). Moreover, a recent study showed that in the United States, during the last 10 years, liver cancer diagnosis increased at a higher rate than any other cancer (3). Risk factors for HCC vary by geographic region (4, 5). For instance, hepatitis B (HBV) and exposure to dietary aflatoxins have been identified as major risk factors in sub-Saharan Africa, while hepatitis C (HCV) has been recognized as a major risk factor in North America and Japan (4, 6, 7). Furthermore, alcohol consumption is thought to play a major role in the development of HCC and related mortality in Eastern Europe and Russia (5).

There are also differences in age-based HCC surveillance protocols depending on the geographic origin of a person, with recommendations to screen earlier in patients of African or Asian origin with non-cirrhotic chronic hepatitis B infection (8). The largest burden of HCC

is in the developing world, with most cases occurring in Asia and Africa (2, 9, 10). To date, studies have focused on characterizing patients with HCC in Europe, North America, Asia

and, to a lesser extent, Africa (11, 12). Moreover, most of the information about clinical outcomes from curative or palliative therapy originates from clinical trials, most of which are

conducted in the United States, Europe or Asia (12-14). The largest study to date describing the demographics of HCC around the globe is the BRIDGE study (12). This study showed the average age of HCC to be 61 years, and the most common associated risk factor to be HCV infection in all areas except for China, South Korea and Taiwan, where HBV was more common. However, this study did not include data from the regions of Africa and South

America. A recent study by Yang *et al* described the demographics of HCC in Africa (14). This study showed a much earlier age of HCC diagnosis in sub-Saharan Africa, mean of 47 years, with the most common associated risk factor being HBV infection. To date, little is known about the underlying demographic characteristics, risk factors and use of surveillance for HCC in South America. Moreover, there is a paucity of data, from clinical trials or daily clinical practice, about therapeutic options for HCC in this region. In this manuscript we describe for the first time the demographics of HCC in South America in a comprehensive fashion including data from six different countries in the region. This study represents the early results of a multinational effort to characterize HCC in South America.

Patients and Methods

Data collection: We designed a retrospective cohort study aimed at identifying the demographics and risk factors associated with HCC in South America. A concerted effort was made to identify characteristics of HCC at the time of diagnosis. Overall, fourteen

medical centers from six countries in South America participated. Each center was responsible for adhering to their respective institutional review policies, and ethical approval was obtained from participating centers and Hennepin County Medical Center (supplementary data). No informed consent was obtained due to the retrospective nature of the study. Ten participating centers were considered academic (provided information on

1185 patients) and four centers were non-academic (provided information on 151 patients). The primary objective was to assess the epidemiology of HCC in different countries in South America, focusing mainly on risk factors, age and gender and associated clinical outcomes. Secondary objectives included assessment of therapies offered and evaluation of survival based on the presence of multiple variables.

Participating centers completed a standardized, retrospective chart review of patient characteristics at the time of HCC diagnosis, obtained from each center's database. 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. Radiographically diagnosed cases were requested in accordance with AASLD or EASL guidelines, or comparable local guidelines (8, 15, 16). Variables abstracted included age, gender, chronic infection with viral hepatitis C (HCV) or hepatitis B (HBV), presence of alcohol abuse, evidence of nonalcoholic fatty liver disease spectrum or cryptogenic cirrhosis, and evidence of other underlying liver disease including cirrhosis. Select centers also provided additional data on HCC surveillance and alpha-fetoprotein (AFP) levels at the time of diagnosis, and treatment. When more than one treatment was offered, only the first treatment was included, unless the treatment was in combination with liver transplantation, in that case liver transplantation was considered the main treatment. Diagnosis of HCC under surveillance program in each center was defined when a patient was undergoing systematic screening for HCC following either AASLD or EASL guidelines.

Statistical analyses: Continuous variables were summarized as means or as medians (interquartile range-IQR or range) according to their homogeneity. Categorical variables were compared with the χ^2 test or Fisher's exact test when appropriate. Continuous variables were compared with the Mann-Whitney U test or Student T test. For regression models, we included predictors with $P < 0.05$ in the univariate analysis. Analyses of factors

independently associated with cirrhosis at the time of HCC diagnosis and with administration of curative therapy for HCC were performed using logistic regression. An analysis of factors

independently associated with survival after HCC diagnosis was performed using the Cox regression model.

Survival rates after HCC diagnosis were computed from the day of diagnosis until death or the last follow-up visit using the Kaplan–Meier method and compared by using the log-rank test. Survival was corrected for lead-time bias using a similar approach as Cucchetti *et al* and Mourad *et al* (17, 18). Briefly, because there were no tumor size data in our database we considered a lead-time of 7 months according to previous studies (17, 18). Then, a probabilistic analysis (Monte-Carlo simulation) was applied to estimate the lead-time bias. A theoretical cohort of 1000 patients undergoing HCC screening was compared to a theoretical cohort of 1000 patients with a symptomatic diagnosis. Survival rates in relationship with surveillance programs were properly calculated and reported in 10-years

life expectancy before and after adjustment for lead-time bias, subtracting the lead-time from life expectancy.

Associations are reported as odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals (CI). A 2-sided probability value < 0.05 was considered to be significant. Statistical analysis was performed using the SPSS v 24.0 statistical package (IBM Corp., Armonk, NY).

Results

Fourteen centers from six countries across South America contributed data for an aggregate 1,336 patients. Brazil accounted for 40% ($n=540$) of patients, Argentina 19% ($n=251$), Colombia 18% ($n=239$), Peru 16% ($n=220$), Ecuador 5% ($n=65$) and Uruguay 2% ($n=21$) (Figure 1A). Each center provided information on HCC from a period between 5 and 10 years (depending on the center) retrospectively, with the earliest report being from April 2005 and the latest from May 2015. 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 (Table 1). The most common risk factor for HCC was HCV infection (48%), followed by alcoholic cirrhosis (22%), HBV infection (14%), NAFLD (9%) and other causes (8%) (Figure 1B). Twenty-nine percent of HCV and 18% of HBV patients also had alcohol consumption as a second risk factor. Comprising the “other causes” risk factor group were 44 patients with cryptogenic cirrhosis, 17 patients with hemochromatosis, 12 patients with autoimmune related liver disease, 12 patients with HBV/HCV co-infection, 4 patients with primary biliary cirrhosis, 4 patients with schistosomiasis, 2 patients with drug related liver injury and 2 with reported vascular complications. The distribution of risk factors was relatively homogeneous through out the countries, with HCV and Alcohol use being the two most common risk factors for HCC in all countries except Peru (Figure 2). Interestingly, in this country HBV infection was the most important risk factor for HCC accounting for 34% of cases. Of those patients infected with HCV, 64% were males compared to 74% males in those infected with HBV, 89% of individuals with alcohol related liver disease, and 56% of those with NAFLD associated HCC. Age at time of diagnosis differed by independent risk factor as shown in Figure 2. When evaluating all new cases of HCC in individuals infected with HBV, we found that 38% ($n=48$) of HCCs 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 (percentage of cases per age group described in Figure 3). Even larger differences were observed when HBV-induced HCC was compared with NAFLD, median age at diagnosis 67 years ($p<0.001$) and alcohol-induced HCC, median age at diagnosis 68 years ($p<0.001$).

Extended data was provided by eight centers from the six countries (Figure 4). Descriptive statistics were calculated to determine the proportion of HCC diagnoses that were made during regular surveillance for HCC, as well as to evaluate AFP levels at the time of diagnosis. Of 732 patients for whom screening information was available, we found that only 343 (47%) were diagnosed with HCC during surveillance as defined by institutional standards. The median ages of those diagnosed during surveillance vs. incidental or symptom-based diagnosis were not significantly different, both being 64 years ($p=0.967$). Median time of follow-up was 49 months (IQR: 27-65 months). Using logistic regression models we found that HCV (OR 3.25, 95% CI 1.63-7.08, $p=0.001$) and alcoholic liver disease (OR 3.82, 95% CI 1.46-13.17, $p=0.005$) were significantly associated with the presence of cirrhosis at the time of HCC diagnosis, while other risk factors were not. We also examined the risk factors associated with a higher likelihood of receiving curative therapy, defined as resection, transplantation, radiofrequency ablation (RFA) or percutaneous ethanol ablation (PEA). We found significant associations of cirrhosis (OR 3.96, 95% CI 2.09-7.44, $p < 0.001$), having been diagnosed during surveillance (OR 2.22, 95% CI 1.43-3.48, $p < 0.001$) and AFP $>200\text{ng/ml}$ (OR 2.29, 95% CI 1.25-4.24, $p=0.007$) with receipt of curative therapy. A proportional hazards model was then used evaluate survival. Having underlying HCV (HR: 0.74, 95% CI 0.56-0.98, $p=0.042$), and being diagnosed under surveillance (HR: 0.62 (95% CI 0.48-0.78, $p < 0.001$) were both significantly associated with decreased mortality (Table 2). Survival rates after HCC diagnosis were higher in patients that underwent screening after lead-time correction (log rank $P = 0.001$). The median life expectancy in the screening group before and after lead-time correction was 47.3 months (IQR 34.3-66.1 months) and 40.4 months (IQR 27.3-59.1 months) respectively (Table 3). In the symptomatic diagnosis group the median life expectancy was 24.6 months (IQR 14.4-45.9 months).

We assessed treatment data on 727 patients from the six countries (all centers that provided such information). Specific treatment modalities for each country varied widely per country and are described in Figure 5. Trans-arterial chemoembolization (TACE) was the most commonly used method as first therapeutic approach (269 patients) regardless of whether tumors were found incidentally or during screening (37% and 35% of HCCs, respectively). Palliative treatment (aside from TACE) was the second most often used modality (218 patients), with an overall of 30% of patients being offered such approach. Only 50 patients (7%) underwent radiofrequency ablation (RFA) as first approach, although it should be noted that 78% of those tumors treated by RFA were found during screening.

Only eight participating centers performed liver transplantation, and 120 patients underwent a liver transplant as a therapeutic option for HCC. The great majority of tumors (95%) that were treated with liver transplantation were found during screening, but across the board, with the exception of Colombia (43%), the option of liver transplantation was available to less than 20% of the patients, and as low as 4% in some cases as Brazil, likely reflecting the advanced stage of presentation.

Discussion:

This study provides the first comprehensive description of risk factors, demographics, data on surveillance, and therapy offered for HCC in the continental region of South America.

When comparing our data from South America to results from the BRIDGE Study by Park *et al*, the overall demographics and age at the time of diagnosis in our South American cohort were similar to the results from North America, Europe and Japan (7). However, we found that 38% of HCCs in HBV-infected individuals occurred before age 50. This finding is concerning and questions whether current guidelines are appropriate for the region. Moreover, our results suggest the presence of unknown environmental factors in the region that could predispose to HCC. The early-age diagnosis of HBV-related HCC has usually been reported from Africa and in association to aflatoxin exposure (19). Exposure to aflatoxins affects the TP53 gene and this is thought to lead to a rapid occurrence of HBV-induced HCC (19, 20). Aflatoxins have not been thought to represent a major risk factor in South America, although aflatoxin-associated p53 mutations have been found in HBV-related HCCs in a small Brazilian study (21).

Similar to other populations, we found that HCV and alcoholic liver disease were associated with the presence of cirrhosis at the time of HCC diagnosis (22, 23). This reflects the observation that both HBV and NASH induced HCC have a higher propensity to develop in individuals without cirrhosis. Interestingly, the presence of NALFD was not a major single risk factor associated to HCC. This was a rather surprising finding since the NAFLD prevalence is higher in South America than in other regions of the world (24). Although we did not specifically address the presence of NAFLD within other risk factors, such as HCV or HBV infection, it is probable that the underlying presence of fatty liver contributed to HCC when combined with other risk factors (25, 26). Nonetheless, it is possible that the clinical presentation of NAFLD in the region differs from that of other parts of the world with a lower propensity to HCC (25). More research in this area will be needed with studies addressing biopsy-proven NAFLD or NASH as well as detailed risk factor exposure, in order to address this question. We found that the presence of cirrhosis, a diagnosis of HCC during surveillance, or an AFP >200ng/dl were associated with receiving curative therapies. AFP levels varied quite significantly between countries, with Argentina and Peru showing higher medians of AFP on HCC diagnosis (>50 ng/ml) and Ecuador showing a lower median AFP of 4 ng/ml. This finding is similar to that of the BRIDGE study, which found large differences between regions (25 ng/ml in Europe and 219 ng/ml in China) (12). It is unclear whether these differences represent lack of standardization of AFP testing or variable clinical behavior of the tumors. We did not find, however a significant correlation with AFP levels and survival. The presence of cirrhosis in our cohort correlated with receipt of curative therapy, but did not correlate positively with survival. Edenvik *et al* in Europe did not study the association between cirrhosis and survival. However, the authors found a significant association between cirrhosis and missed surveillance, which did indeed correlate with higher mortality (27).

Improved survival was seen in patients with HCV and in those who were diagnosed while under regular surveillance. Survival rates for those on HCC surveillance were significant at 1 and 3 years on the lead-time analysis, but were not significant at 5 years. However our follow up period was shorter than in other studies likely leading to a non-significant difference at 5 years. Interestingly, the receipt of curative therapy was not associated with a survival benefit, however, one could postulate that this is due to selection bias as patients who are still living at the time of the study were unlikely to have a date of death included in the data set and were thus excluded from the analysis. It is concerning that over half of the individuals in our study had HCCs diagnosed outside of surveillance programs. However, a low rate of HCC diagnosis through surveillance programs represents a well-known deficiency around the world (28, 29). In this regard, Edenvik *et al* reported a 30% HCC diagnosis through surveillance in Sweden and Singal *et al* reported

24% surveillance screening, which improved to 47% after outreach (27, 30). Although our data is preliminary, we found a survival advantage for those diagnosed during surveillance and therefore more emphasis on adherence to surveillance programs should be encouraged in the region. Edenvik *et al* had similar findings in a European cohort. Interestingly, in that study although the rate of curative treatment was similar in HCCs diagnosed through surveillance or not, those diagnosed under surveillance programs had a significant survival benefit (27).

In those patients from whom we had treatment information, the majority was offered either curative therapy or disease modifying approach with only 30% being offered a palliative option. TACE was the most frequently first used therapeutic modality with liver transplantation being the less used modality and this remained constant throughout the different countries. These findings are similar to those the United States, China, Japan and Europe and likely reflect diagnosis of HCC at late stages (12). The use of resection,

RFA/PEI, liver transplantation and sorafenib did vary among the countries, and likely reflects regional differences in clinical practice due to access and cost. Despite liver transplantation being the most efficacious treatment, very few patients received this therapy. In South

America, this is likely related to an inadequate availability of donors, but also possibly affected by a less efficient system to identify suitable candidates. A high percentage of

individuals (30%) were offered palliative approach, only, as therapy. This is concerning, and likely related to a high percentage of patients diagnosed with HCC by symptom presentation

and not during surveillance. Much improvement is needed in health-related infrastructure and organization, to detect HCCs earlier in order for a possible referral to a transplant center and a curative approach being possible. Interestingly, 116 patients (16%) underwent treatment with sorafenib. The frequency of use and success rate of the multi-kinase inhibitor has been evaluated in multiple regions, but only one study has addressed its efficacy in Hispanic individuals within the context of a larger cohort of patients (31).

The limitations of this study include its retrospective nature and the absence of validated information on the standards used for determining NAFLD spectrum or alcohol misuse disorders. There was also selection bias as site participation was voluntary and some countries were only represented by one center. However, it is likely that the large sample size partially overcomes such confounding. On the other hand, due to the size of the studied population and difference in centers, some interactions between variables are difficult to account for and therefore results should be interpreted with some caution. Moreover, due to a large proportion of data collected through paper charts we did not properly address Barcelona Clinic Liver Cancer Stage in all patients. As our research network develops a prospective assessment of HCC in South America we expect to address these variables.

In summary, our study represents the largest cohort to date addressing HCC in South America. Similar to North America, Europe and Japan, HCC in South America is most often diagnosed in older males, with HCV being the predominant risk factor. We also highlight a large number of patients with HBV in South America diagnosed at an early age. The most commonly used treatment modality was TACE with liver transplantation being the less frequently used. As in many other countries and continents around the globe, HCC surveillance is under-utilized in South America.

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Table 1. Demographic and clinical characteristics of HCC per country

Country	Age *	% Males	% Cirrhotics **	AFP#	%AFP >20#	% Curative treatment#
Argentina	65	74	86	76	60	23
Brazil	61	74	92	51	58	27
Colombia	67	64	95	20	46	49
Ecuador	56	48	72	4	27	32
Peru	67	59	85	90	63	4
Uruguay	65	86	100	11	50	32

*Age: Median age in years

**Number of patients with data about cirrhosis: Argentina: 112, Brazil: 380, Colombia: 125, Uruguay: 21, Peru: 220, Ecuador: 65

#Median ng/ml , number of patients with AFP data: Argentina: 112, Brazil: 370, Colombia: 115, Uruguay: 18, Peru: 130, Ecuador: 65

###Number of patients with data on treatment: Argentina: 110, Brazil: 379, Colombia: 125, Uruguay: 20, Peru: 137, Ecuador: 65

Table 2. Analysis of survival of HCC patients within different variables

Variable	Mean Survival (months)	Standard Deviation	p=	RR
HBV	7.3	7.4	0.063	1.43 (95% CI 0.98-2.07)
HCV	13.6	12	0.042*	0.74 (95% CI 0.56-0.98)
Alcohol	11.3	9	0.169	0.79 (95% CI 0.56-1.10)
NAFLD	10	9.2	0.383	1.21 (95% CI 0.78-1.83)
Cirrhosis	11	10.1	0.128	1.44 (95% CI 0.90-2.42)
Screening	14.4	11	<0.001*	0.62 (95% CI 0.48-0.78)
AFP >20mg/ml	10.1	9.8	0.466	1.12 (95% CI 0.82-1.54)
AFP >200ng/ml	9.5	10.2	0.501	1.10 (95% CI 0.83-1.49)
Curative therapy	17.3	10.1	0.222	0.79 (95% CI 0.53-1.15)

*Denotes statistically significant value. CI: Confidence interval. RR: Risk ratio.

AFP: Alpha-fetoprotein. HBV: Hepatitis B virus. HCV: Hepatitis C virus. NAFLD: Non-alcoholic steatohepatitis.

Table 3. Overall survival according to surveillance (N: 739)

Follow-up	Surveillance	Symptomatic diagnosis	P value
1-year, % (CI 95%)	78.7 (74.5-82.9)	59.8 (54.8-64.9)	<0.001
3-year, % (CI 95%)	52.2 (46.6-57.7)	36.3 (30.8-41.8)	<0.001
5-year, % (CI 95%)	30.6 (24.7-36.4)	25.7 (20.3-31.4)	0.22

Figure Legends

Figure 1. Distribution of hepatocellular carcinoma in South America. *A)* Number of cases of hepatocellular carcinoma (HCC) by contributing countries. *B)* HCC risk factor distribution by country (HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic liver disease; alcohol, current alcohol consumption). Percentage reflects the percentage within the entire cohort.

Figure 2. Distribution of risk factors for hepatocellular carcinoma within each country. Y-axis represents percentage of the cases per each country (1 represents 100%); X-axis represents each country. Filling of bar correlates with description of each risk factor, corresponding to percentage of risk factor within the total of each country. NAFLD, non-alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus.

Figure 3. Percentage of cases hepatocellular carcinoma per age group and associated risk factor. Y-axis represents precedence of HCCs per risk factor, X-axis represents age in 5-year intervals. NAFLD, non-alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus.

Figure 4. Flow chart of patients with specific data based on collection from all centers.

Figure 5. Treatment for HCC distribution within each country. Symbol in the figure correlates with specific treatment on the side legend. Information about transplantation as treatment was included only in those centers that perform liver transplantation. Upper limit of 0.5 in the Y-axis represents 50% of the total number of cases treated in each country. X-axis represents each country. When more than one treatment was offered per patient, only the first treatment was included, unless the treatment was in combination with liver transplantation in which the later one was used.





