

# Epidemiology of Liver Cancer in Latin America: Current and Future Trends

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Semin Liver Dis

## Abstract

Over 38,000 cases of hepatocellular carcinoma (HCC) are estimated to occur in Latin America annually. The region is characterized by sociocultural heterogeneity and economic disparities, which impose barriers in addressing this major health issue. A significant proportion of patients are still diagnosed in the later stages of the disease, although efforts to implement effective screening programs have been reported by referral centers. While viral hepatitis remains the predominant etiology of liver disease among HCC cases in Latin America, a high prevalence of fatty liver disease in the region is a matter of concern, reflecting the current scenario in many Western countries. In addition, other risk factors such as alcohol, aflatoxin, and early-onset HCC in hepatitis B virus infection contribute to the burden of HCC in Latin America. Interventions to increase screening coverage, expand healthcare access, and implement continuing medical training are key challenges to be overcome.

## Keywords

- ▶ Latin America
- ▶ demographics
- ▶ hepatocellular carcinoma
- ▶ risk factors

Hepatocellular carcinoma (HCC) accounts for 75 to 85% of all liver cancers, and carries a high burden in terms of incidence and mortality worldwide. Cholangiocarcinoma represents around 15%, and other subtypes of liver cancers are even rarer. Generally, global statistics report data on liver cancer, without discriminating the histologic subtype.<sup>1</sup>

In 2016, there were over 1 million cases of liver cancer worldwide and 800,000 deaths.<sup>1</sup> From 1990 to 2016, the incidence of liver cancer increased by 114% with a standardized incidence ratio of 0.34% per year in this period.<sup>2</sup> In the United States, liver cancer diagnosis increased at a higher rate than any other malignancy in the past decade.<sup>3</sup> The World Health Organization estimates that more than 1 million patients will die of this neoplasia in 2030.<sup>4</sup>

The incidence of liver cancer varies significantly across different regions because of the varying prevalence of underlying risk factors. The highest incidence is observed in East Asia

with an age-standardized incidence rate of 34.1 per 100,000, followed by Asia-Pacific (22.9 per 100,000), South-East Asia (11.8 per 100,000), and Central sub-Saharan Africa (10.3 per 100,000). On the other hand, North America presents an incidence of 7.1 per 100,000 and Western Europe 7.4 per 100,000.<sup>2</sup> Similarly, the age-standardized mortality rates are highest in Eastern Asia (16.0 per 100,000) followed by Northern Africa (13.9 per 100,000) and Eastern Asia (13.2 per 100,000).<sup>5</sup> Incidence and mortality are numerically close across different regions, which reflects the high lethality of this neoplasia. Indeed, this is explained by the significant proportion of patients with HCC who are diagnosed at advanced stage or will develop disease recurrence after locoregional treatments.

The most frequent etiologies are chronic infection by hepatitis B (HBV) or C viruses (HCV) and alcohol intake. Notably, an increasing trend in the prevalence of nonalcoholic fatty liver disease (NAFLD) associated with an increasing prevalence of

obesity, diabetes mellitus, and metabolic syndrome is leading to changes in the geographic distribution of HCC, mainly in Western countries.<sup>6</sup> This explains why a more pronounced increase in incidence is being observed in countries with favorable sociodemographic indicators. On the contrary, chronic infection by HBV is the main cause of HCC in high-prevalence countries such as China, while HCV still represents the main cause of HCC in Japan, Europe, and North America.<sup>7</sup>

The implementation of effective antiviral therapy with the direct-acting antiviral (DAA) drugs will potentially impact positively on reducing the global incidence of HCV-related HCC, although some issues regarding the risk of recurrence after local treatments are still being debated.<sup>8</sup> HBV vaccination has also been shown to significantly reduce the incidence of HCC, demonstrating that mortality can be prevented by controlling and eradicating the causative factors.<sup>9</sup> Taken together, these findings support the prediction that HCC epidemiology is shifting from an infectious background to a disease primarily associated with fatty liver disease.

Having briefly contextualized the global landscape, we aim to describe the current scenario and future trends of HCC in Latin America, focusing on the main risk factors, surveillance, and particularities of HCC epidemiology in this region.

### Latin America—Structural Challenges

Latin America is composed of 20 countries, representing almost 13% of the Earth's land surface area with an estimated population of more than 639 million. Latin America presents cultural and demographic heterogeneity and also a remarkable wealth disparity. Some Latin American countries account for the highest indicators of social and economic inequality.<sup>10</sup> There are significant inequities between urban and rural areas, some of which are remote and lack access to healthcare, even in primary needs. Countries that rank lower in human development index,<sup>11</sup> such as Haiti, Honduras, Nicaragua, and Bolivia, suffer from lack of human and technology resources, which explains the paucity of health data from many of them.

Many Latin American zones have experienced an intense urbanization process over the last 50 years. Today, approximately 80% of the region's population lives in cities. However, urbanization is high concentrated. Only Mexico and Brazil have more than a dozen cities with over a million inhabitants, while Uruguay and Paraguay do not have more than two cities with a population of more than a million. Despite the rates of urbanization, ineffective urban planning models prevent the implementation of a comprehensive health access in many urban centers. Even within urbanized areas, center-periphery disparities are notable.<sup>12</sup>

Overall, Latin American countries have improved the amount of investments in healthcare in the past two decades (7.3% of the gross domestic product in 2014 vs. 6.3% in 1995), but still below the average of the Organization for Economic Co-operation and Development (12.3%).<sup>12</sup> Also, different systems of health coverage coexist in many countries, ranging from private to public models. As a consequence, healthcare access, development, and incorporation of new technologies

are heterogeneous between different countries and also across different regions in the same country. The epidemiology of HCC in Latin America mirrors important aspects of the healthcare organization and may be an indicator of defective points such as screening coverage, early identification of at-risk populations, primary prevention, early diagnosis, and expansion of access to proper treatment.

### HCC Incidence and Mortality in Latin America

In 2018, there were around 840,000 cases of liver cancer, of which 4.6% (representing around 38,400 cases) occurred in Latin America. Data from GLOBOCAN 2018 point out an age-standardized incidence rate in different Latin American countries (considering both sex and age) that ranges from less than 2.9 to more than 6.6 cases per 100,000. According to region and sex, in Central America the male/female incidence is 6.7/6.0 per 100,000; in South America, it is 5.8/3.5 per 100,000; and North America (Mexico) presents 10.1/3.4 per 100,000.<sup>5</sup>

In terms of global mortality, there were an estimated 762,000 deaths due to liver cancer in 2018. The proportion of cases in Latin America is 4.7% (representing around 36,000 cases). The mortality in different countries ranges from less than 2.8 to more than 6.3 per 100,000 (►Fig. 1).<sup>5</sup> In accordance with what is observed in other parts of the world, the ratio between incidence and mortality is close to 1, confirming the high lethality of liver cancer in the region (►Table 1).

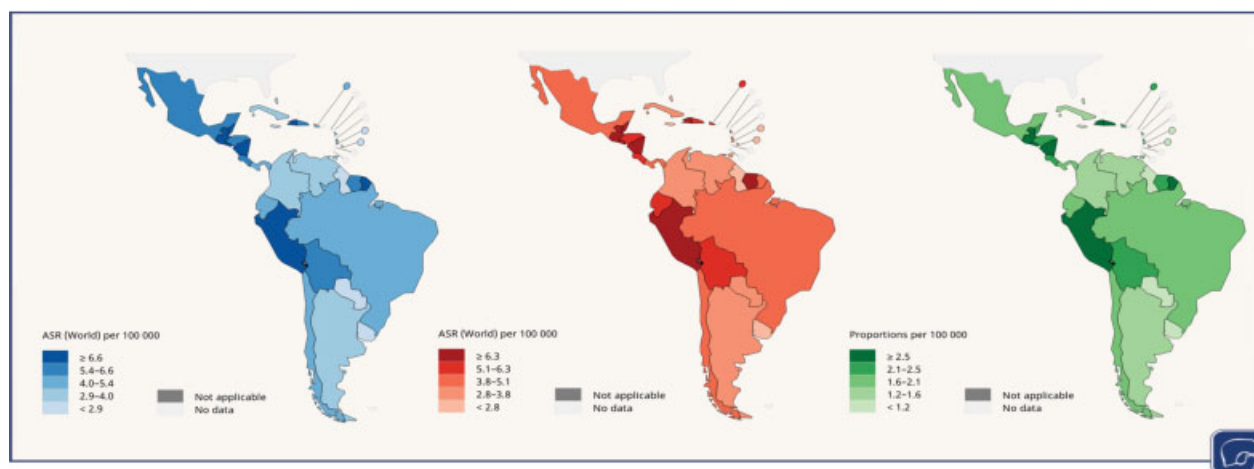
There is a paucity of data regarding HCC survival and long-term follow-up in Latin America. However, reports are consistent with a high proportion of advanced stage at diagnosis (20–41%), a significant rate of symptomatic disease at first presentation (around 50%), and a better survival in patients under screening treated with curative intent (around 30% at 5 years).<sup>13–15</sup>

### Burden of Risk Factors for HCC in Latin America

Cirrhosis is the main risk factor for HCC regardless of the underlying etiology. It is estimated that one-third of patients with cirrhosis will develop HCC during their lifetime.<sup>16</sup>

The BRIDGE study, which was a multiregional longitudinal study that aimed to report the real-life management of more than 18,000 HCC patients, showed that the most common risk factor in all areas is HCV infection, except in China, South Korea, and Taiwan where HBV was the predominant etiology.<sup>17</sup> This study did not report data from Latin America. Indeed, there is a paucity of comprehensive information regarding demographic characteristics and occurrence of risk factors in this region.

In 2017, Debes et al<sup>15</sup> reported a multinational cohort study involving 14 medical centers of six different countries from South America, which aimed to identify the demographic features and risk factors associated with HCC. This study included 1,336 patients between 2005 and 2015. Brazil accounted for 40% of the cohort ( $n = 540$ ), followed by Argentina (19%;  $n = 251$ ), Colombia (18%;  $n = 239$ ), Peru (16%;  $n = 220$ ),



**Fig. 1** Epidemiology of liver cancer in Latin America. Data are from the International Agency for Research on Cancer (<https://gco.iarc.fr/today/home>, accessed August 15, 2019). (A) Estimated age-standardized incidence rates in 2018; (B) estimated age-standardized mortality rates in 2018; (c) estimated number of prevalent cases (1 year) as a proportion in 2018. (ASR: age-standardized rate per 100,000 population).

**Table 1** Estimated number of new cases and deaths due to liver cancer in 2018 (both sexes and all ages)

Regions	New cases	ASR (world)	Deaths	ASR (world)
Latin America and the Caribbean	38,400	5.0	36,436	4.7
Asia	609,596	11.4	566,269	10.5
Europe	82,466	5.1	77,375	4.4
Africa	69,779	8.4	63,562	8.3
North America	41,851	6.6	34,339	4.8
Oceania	3,988	6.9	3,650	5.8

Abbreviation: ASR, age-standardized rates per 100,000.

Note: Data are from the International Agency for Research on Cancer (accessed August 14, 2019).

Ecuador (5%,  $n = 65$ ), and Uruguay (2%,  $n = 21$ ). The majority of patients were male (68%) and the median age was 64 years. HCV infection was the most frequent risk factor, representing 48% of the cases. Alcoholic cirrhosis was the second leading cause with 22%, followed by HBV infection in 14%, NAFLD in 9%, and other causes in 8% (cryptogenic cirrhosis, hemochromatosis, autoimmune liver disease, HBV/HCV coinfection, schistosomiasis, and primary biliary cirrhosis). Besides, alcohol intake was associated with 29% of HCV and with 18% of HBV-related cases.

In all countries, HCV and alcohol abuse were the main common risk factors. The only exception was Peru. In this country, HBV was the leading cause, comprising 34% of cases. In fact, the majority of the HCC cases related to HBV infection in Latin America are reported from Peru and Brazil (34 and 38%, respectively), followed by Argentina (16%), Colombia (7%), Ecuador (7%), and Uruguay (2%). Almost half of HBV-associated cases in Peru were from the Amazonian region,<sup>18</sup> which comprehends a large area of Northwest Brazil, Peru, Venezuela, Colombia, and Ecuador. HBV genotype F is the most prevalent in Amerindian population<sup>19</sup> and also in countries from Central<sup>20</sup> and South America<sup>21</sup> that cover

the Amazonian region. This genotype is reported to be associated with early onset of HCC in Alaska natives.<sup>21</sup> Notably, 38% of the HCC patients with HBV in Latin America were diagnosed before the age of 50 years with a median age of 58 years. In patients with HCV, 94% were diagnosed after age 50 years, with a median age of 63 years. NAFLD patients were diagnosed with a median age of 67 years, and among patients with alcoholic cirrhosis, the median age at diagnosis was 68 years.<sup>15</sup>

In a national Brazilian survey including 29 centers and 1,405 patients between 2004 and 2009, HCV infection was the main etiology (54%). HBV was found in 16% and alcohol in 14%. Among HBV cases, 14.5% were associated with HCV coinfection and 3.4% with hepatitis delta virus. Distinct prevalences of HCC were observed across different Brazilian regions, probably due to differing prevalence of HBV (higher in Amazonian region).<sup>22</sup> In 1997, another survey had showed that HBV was the most common cause of liver disease in patients with HCC at that time in Brazil.<sup>23</sup> This suggests temporal changes in the distribution of risk factors over the past two decades. Similar changes are also observed in global data: the proportion of HCV increased from 37.1 to 40.1% between 1990 and 2016 in Western Europe, while alcohol consumption decreased from 39.3 to 34.5% during the same period.<sup>2</sup>

The incidence of HCV-related HCC is expected to decrease due to the incorporation of DAAs.<sup>24</sup> In Latin America, a prospective multinational cohort that followed 1,400 patients treated with DAA reported an incidence of de novo HCC of 2% at 12 months and 4% at 24 months. In this cohort, most of the patients presented F3 or F4 fibrosis and around 28% had clinically significant portal hypertension. Achieving sustained virologic response resulted in a relative HCC risk reduction of 73%, while failure to achieve it was independently associated with de novo HCC. However, patients with F4 fibrosis showed a cumulative incidence of 3 and 6% at 12 and 24 months, which suggests that advanced liver disease demands continuous surveillance even in cases with sustained virologic response.<sup>25</sup>

Conflicting information regarding the impact of DAA regimens on the occurrence of de novo HCC are being published in other parts of the world.<sup>8,26</sup> In this regards, Latin American initiatives, as mentioned earlier, are crucial in gathering evidence to future research on this topic.

In sum, the available evidence supports that the current scenario in Latin America is similar to what is observed in the United States, Western Europe, and Japan regarding the predominance of HCV and alcohol intake as the main etiologies. However, some regional peculiarities are remarkable, as exemplified by the occurrence of HBV-related HCC in Peru.

## NAFLD/NASH: Current Trends Worldwide and in Latin America

Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH) are recognized as important causes of liver disease and HCC. In the United States, around 6 million people have NASH and it represents a leading indication for liver transplantation.<sup>27</sup> About 10 to 30% of NAFLD cases may progress to cirrhosis, and HCC might appear even in the absence of significant liver fibrosis in these patients.<sup>28</sup> Another relevant issue in this context is the likely overlap with alcohol, and there is a need to better clarify the coexistence of alcohol and fatty liver disease in some settings.

Patients with NASH seem to present a lower risk of HCC than patients with HCV-related liver disease. In a large cohort study with NASH patients in the United States, the incidence of HCC was 1.06 per 100 person-years.<sup>29</sup> NAFLD probably carries a lower risk of liver cancer than patients with NASH cirrhosis, but because NAFLD affects a huge number of people around the world, this condition is a relevant factor. Patients with non-cirrhotic NAFLD have an incidence of HCC of 0.008 per 100 person-years.<sup>29</sup>

The impact of NAFLD/NASH on HCC epidemiology is likely to be underestimated due to heterogeneous definitions, differing proportions of patients with metabolic syndrome, and referral bias.<sup>30</sup> Other adjuvant features of metabolic syndrome, such as diabetes and obesity, are also considered emergent risk factors for HCC.

In Latin America, obesity and overweight have become major challenges. Around 57% of the adult population (54% of men and 70% of women) is overweight and 19% (14.6% of men and 24% of women) is obese. The highest prevalence of obesity is found in El Salvador (33.0%) and Paraguay (30.1%) for women, and Uruguay (23.3%) and Chile (22.0%) for men.<sup>31</sup> Additionally, NAFLD is highly prevalent in South America (31%), comparing to an estimation of 25% in the adult population globally.<sup>32</sup>

In 2016, a Brazilian study aimed to evaluate clinical characteristics of patients with HCC and NASH included 110 patients. In this cohort, obesity was observed in 52.7% of cases, diabetes in 73.6%, dyslipidemia in 41.0%, and metabolic syndrome in 57.2%. Fifty-two (47.2%) patients had histological diagnosis of HCC. Among those 52 patients, NASH with cirrhosis was found in 32 (61.5%), NASH with fibrosis grades 1 to 3 in 14 (27%), and NASH without fibrosis in 2 (3.8%) patients. In four (7.7%) patients, HCC was the only histological diagnosis, with a clinical diagnosis of NAFLD.<sup>33</sup>

A longitudinal cohort from Argentina included 708 HCC patients diagnosed between 2009 and 2015 and showed that NAFLD was the third cause of HCC, representing 11.4% of the cases (the first was HCV in 37%, followed by alcoholic liver disease in 20.8%). During the study period, there was a sixfold increase in the incidence of NAFLD-related HCC, with 4.3% of NAFLD-related HCC in 2009 and 25.6% in 2015.<sup>34</sup>

In the same sense, a study involving two hospitals from Chile with 288 patients with HCC reported an increase in NAFLD and a decrease in alcoholic liver disease. Notably, the leading cause of liver disease in this cohort was NAFLD (38.8%), followed by HCV (25.2%).<sup>35</sup>

Unpublished data from Brazilian registries of 508 liver transplantations in Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo reported an increase in the proportion of NASH as the etiology of liver disease in patients submitted to liver transplantation. Between 2007 and 2009, 4 (0.5%) were attributed to NASH and between 2016 and 2018, there were 25 cases (3.2%). However, surgical series may overestimate the occurrence of HCC in noncirrhotic NASH liver, as these patients are more likely to be considered for resection than patients with the same tumor burden but with poor liver function. Besides, NASH requires histological confirmation. This is an important consideration when analyzing epidemiological data on this topic.

To sum up, there is a global concern regarding a potential increasing in the number of patients with NAFLD- and NASH-related HCC. This is particularly important in Latin America, given that NAFLD is highly prevalent in this region. Up till now, there is no strong data from the region supporting that NAFLD/NASH is a leading cause of HCC. However, the initial reports mentioned in this section warrant continued exploration and data collection, with detailed risk factor exposure and histological evaluation. Importantly, alcohol intake in studied populations should be registered to rule out a biased conclusion.

## Regional Particularities: Early Onset of HBV-Related HCC and Molecular Profile of Aflatoxin-Related HCC

Despite the fact that the general context of HCC in Latin America shares similarities with many Western countries, some groups have described patterns of HCC occurrence with specific characteristics in different Latin American regions.

This is the case for an unusual form of HCC affecting children, adolescents, and young adults described in a retrospective series of 232 HCC patients submitted to surgical resection in Peru between 1990 and 2006. The median age of this cohort was 36 years, and 44.2% were associated with chronic HBV infection (not including those with resolved infection: HBsAg negative and anti-HBc positive). Only 16.3% of them had cirrhosis and the median AFP level was 5,467 ng/mL.<sup>36</sup> This lower incidence of cirrhosis, when comparing to data from other Western regions,<sup>37</sup> probably relies on the early onset and the etiologic background, with a predominance of HBV and only 5% related to HCV infection.<sup>36</sup> Another study in the Peruvian population with 1,541 patients described a bimodal



incidence of HCC, with a first peak of incidence around the age of 25 years and a second one at the age of 64 years.<sup>38</sup>

The retrospective nature of the data prevents any definitive conclusion and selection bias may affect interpretation. However, this result suggests a particular behavior in terms of clinical course and an unusual HCC population, mirroring data from sub-Saharan Africa and Taiwan with HBV infection during birth or immediately after.<sup>39</sup>

To analyze whether genetic variations exist between younger and older HCC patients, Marchio et al<sup>40</sup> performed a study involving 80 Peruvian patients, 41 diagnosed under 40 years old, and 39 diagnosed over 40 years old. Mutations in the *Wnt* pathway were more frequent among younger patients compared with patients older than 40 years and *AXIN1* mutations were more frequent in women than in men. The authors also described a predominance of genetic alterations represented by insertions/deletion.

In a subsequent analysis, another molecular study including 65 Peruvian patients was conducted. The authors found HBV DNA in the tumor and/or matched nontumor tissue in 81.5%, predominantly among younger patients. Besides, a low viral HBV DNA burden among younger patients was also found, which challenges the hypothesis that associates high HBV DNA load with earlier tumor development.<sup>41</sup>

Although these findings were not validated in other Latin American cohorts, they suggest that key aspects in the hepatocarcinogenesis might be different to that observed in other parts of the world. In this regard, additional studies are required to support the implementation of strategies on prevention (mainly expanding HBV vaccination in Amazonian region), diagnosis, and treatment for HCC patients who share these molecular features.<sup>41</sup>

Latin America compromises 3% of the global burden of aflatoxin-related HCC.<sup>42</sup> Aflatoxins are produced by the fungi *Aspergillus parasiticus* and *Aspergillus flavus*, which colonize food commodities such as groundnuts and tree nuts in tropical regions of the world. Aflatoxin exposure in food is a well-documented risk factor for HCC, presenting most often in individuals with chronic HBV infection, with up to 30 times greater risk than aflatoxin exposure without HBV.<sup>43,44</sup> Aflatoxin exposure predominantly affects rural populations more than urbanized populations.<sup>45</sup>

Liu et al<sup>42</sup> conducted a quantitative cancer risk assessment that approached aflatoxin exposure and HBV prevalence to estimate the global burden of aflatoxin-related HCC. The estimation in Latin America is 6.0 to 15.0 and 0.20 to 0.50 aflatoxin-induced HCC cases per year per 100,000 people in HBsAg-positive and HBsAg-negative patients, respectively. This estimation was based only on data from Brazil, Mexico, and Argentina; therefore, it is not fully representative of the entire Latin America. This indicates a higher incidence compared with North America (0.08–0.3 and 0.003–0.01 per 100,000) and Europe (0–1.2 and 0–0.04 per 100,000), but with a better general outlook compared with Africa (3.0–54.0 and 0.1–1.8 per 100,000) and Southeast Asia (9.0–30.0 and 0.30–1.00 per 100,000).

Nogueira et al<sup>46</sup> assessed the frequency of TP53 249Ser mutation in 74 HCC patients submitted to resection or

transplantation in a Brazilian cohort. This mutation is a molecular evidence of aflatoxin-related carcinogenesis and there is a strong correlation between this mutation and dietary exposure of aflatoxin. In this study, the 249-Ser mutation was found in 28% of cases, suggesting that aflatoxin is a potential risk factor in the studied population. Moreover, this mutation was correlated with larger tumors and poorly differentiated histology.

## Screening for HCC in Latin America

Screening is widely applied, although evidence of positive impact on reducing mortality is scarce. A randomized controlled trial that supports screening for HCC was performed in China with more than 18,000 patients and demonstrated a 37% reduction in risk of death in screened patients with abdominal ultrasound and  $\alpha$ -fetoprotein (AFP) test performed every 6 months.<sup>47</sup> However, this study included only the HBV-infected population, study adherence was poor, and the trial is limited by the use of randomization by clusters.

A validation trial in other parts of the world, such as the United States, Europe, or Latin America is unfeasible, and its implementation would be ethically questionable. Therefore, ultrasonography every 6 months is a part of the routine evaluation of patients with chronic liver disease and high risk of HCC, and this practice is endorsed by the current clinical guidelines.<sup>48</sup> The role of AFP as a surveillance tool is not well defined, mainly because varying levels of AFP levels might reflect activity of the underlying liver disease<sup>49</sup> and also because only a small proportion of early-stage tumors show elevated AFP levels.<sup>50</sup> Abdominal ultrasound has several advantages including low cost, easy availability, and safety. These features enable ultrasound to be applicable in regions with different socioeconomic contexts.

The implementation of surveillance programs with a significant rate of early detection was reported in a prospective Brazilian study with 884 cirrhotic patients. Paranaguá-Vezozzo et al<sup>51</sup> characterized a long-term follow-up of patients who were submitted to at least one annual liver ultrasonography and a serum AFP measurement. During the study period (1998–2008), 72 (8.1%) patients developed HCC with an annual incidence of 2.9%. Of these 72 patients, around 80% were diagnosed with early stage, which allowed curative-intended treatments in the majority of the cases.

In a Latin American multinational retrospective study of incident HCC cases, there were significant differences in the proportion of patients diagnosed in each of the Barcelona Clinic Liver Cancer (BCLC) stages between patients who were enrolled in screening programs ( $n=102$ ) and those with incidental diagnosis ( $n=86$ ). In the former, 69.6% were diagnosed with BCLC-A stage, while in the latter, only 39.5% were BCLC-A. Consequently, more patients had BCLC-C and -D in the nonscreened group (18.6 vs. 8.0%).<sup>52</sup> Another cohort corroborated that individuals who attended ultrasound surveillance with a frequency of at least every 6 months had a higher probability of being diagnosed with early-stage tumors.<sup>53</sup>

**Table 2** Studies from Latin America approaching risk factors and/or screening coverage

	Population	Period	Risk factors	Methodology	Diagnosis under screening
Debes et al <sup>15</sup>	N = 1,336 Brazil, Argentina, Colombia, Ecuador, Peru, and Uruguay	2005–2015	HCV: 48% HBV: 22% Alcohol: 14% NAFLD/NASH: 9%	Retrospective multicentric study	47% diagnosed during screening
Bertani et al <sup>38</sup>	N = 1,541 Peru	1997–2010	HCV: 4.7% HBV: 50.1% HCV + HBV: 1.4%	Retrospective multicentric study	Not reported
Carrilho et al <sup>22</sup>	N = 1,405 Brazil	2004–2009	HCV: 54% HBV: 16% Alcohol: 14% NASH/NAFLD: 3%	Retrospective multicentric study	Not reported
Fassio et al <sup>52</sup>	N = 240 Brazil, Argentina, Colombia, Chile, Uruguay, and Venezuela	2007–2009	HCV: 30.8% Alcohol: 20.4% HBV: 10.8% HCV + alcohol: 5.8%	Prospective multicentric study	54% diagnosed during surveillance
Kikuchi et al <sup>13</sup>	N = 364 Brazil	2010–2012	HCV: 55% HBV: 13% Alcohol: 16% NASH: 9%	Retrospective multicentric study	65% diagnosed during screening
Piñero et al <sup>14</sup>	N = 708 Argentina	2009–2016	HCV: 37% Alcohol: 20.8% NASH/NAFLD: 11.4% HBV: 5.4%	Multicentric study	58.1% diagnosed during screening

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

In terms of ultrasonography accuracy for HCC detection, a study performed in Argentina included 643 cirrhotic patients on liver transplantation waiting-list. In this study, the sensitivity was 33% and specificity was 99%.<sup>54</sup> These results are in line with a recent meta-analysis that showed a sensitivity of 45% for detection of early HCC with a specificity of 84%.<sup>55</sup>

There is no large study analyzing the coverage of ultrasound screening for early detection of HCC, mainly in remote areas of Latin America. The proportion of patients diagnosed with an incidental HCC outside a structured surveillance program is over 50%<sup>15</sup> and it is probably higher in unreported areas. Most of the data available come from academic institutions, in which patient care and adherence tend to be broader (→ **Table 2**). As a consequence, there is likely to be an insufficient coverage and a significant rate of under-reported advanced stage at initial presentation.

### Adherence to Clinical Practice Guidelines in Latin America: from Diagnosis to Treatment

Adherence to guidelines is hampered by the heterogeneity in available resources, the unequal structure of healthcare systems, and imbalances in the geographical distribution of reference centers with expertise in HCC. The reality in these centers is further discussed in this section, but this may not be representative of the whole picture of Latin America.

Regarding diagnostic procedures, noninvasive imaging diagnosis of HCC in patients with cirrhosis and typical radio-

logical hallmarks are accepted since 2001<sup>56</sup> and endorsed by clinical practice guidelines.<sup>48,57</sup> Both computed tomography and magnetic resonance have a good accuracy in detecting HCC according to the noninvasive diagnostic criteria,<sup>48,57</sup> although false-positive findings are described. A multinational Latin American study with 422 HCC patients submitted to liver transplantation reported that only 18 patients did not have confirmed HCC in the explanted liver, showing a low rate of disparity between radiologic and histologic findings.<sup>58</sup>

Improvement in diagnostic accuracy, especially in the detection of small and potentially curable lesions, is under active debate worldwide.<sup>59</sup> The use of Li-RADS criteria integrates features not related to tumor enhancement, such as capsule and growth over time. This adds more complexity in clinical decision making, particularly in intermediate categories (Li-RADS 3 and 4), which can represent a potential source of misinterpretation of the system and low adherence to treatment algorithms worldwide.

Several staging systems have been designed to provide prognostic information and help clinical decision. The BCLC staging system<sup>6</sup> is endorsed by practical guidelines, including the Latin America Association for the Study of the Liver.<sup>60</sup> This classification has been externally validated in different clinical settings and is frequently updated to incorporate the ongoing novelties and concepts.<sup>61,62</sup>

The BRIDGE study<sup>17</sup> documented marked heterogeneity of treatment approaches across different regions and countries. Accordingly, regional differences, access, and costs may lead to

a similar context in Latin America. Transarterial chemoembolization was the most frequent used and transplantation was the less used modality in a multicenter South American cohort, while ablation, resection, and systemic therapy varied among countries.

The adherence to the BCLC system varies from 49 to 71% in different publications.<sup>63,64</sup> A multicenter study performed by Piñero et al<sup>14</sup> in Argentina, involving 14 hospitals and 708 patients, evaluated the adherence to the BCLC system. The overall adherence was 53% and the lowest adherence was reported in BCLC-C patients (29.8%).

Accordingly, a Brazilian retrospective study also reported an adherence to the BCLC staging system of 52% in 364 patients between 2010 and 2012. The rate of adherence varied in different stages: BCLC-0, 33%; BCLC-A, 45%; BCLC-B, 78%; BCLC-C, 35%; and BCLC-D, 67%. In early and very early stages, adherence impacted positively on overall survival and no differences were observed between adherent and non-adherent patients in BCLC-B and C stages.<sup>13</sup>

The selection of patients for liver transplantation is key to improve outcomes in the subset of patients with liver-only disease. Unfortunately, lack of access and disparities in health coverage are barriers in the development of liver transplantation programs in Latin America. While some countries, such as Argentina, Brazil, Colombia, Peru, Mexico, and Chile, dispose of consolidated programs, lower middle-income countries, such as Honduras, Nicaragua, and Guatemala, are not able to maintain liver transplantation programs.<sup>65</sup> Even the countries with a large number of liver transplantations face difficulties regarding intraregional disparity and geographic distances. The need for a more structure health system and international cooperation are crucial in Latin America, together with initiatives to educate the population and increase awareness of organ donation in the regions with well-established transplantation activity.

This scenario will probably become more challenging, as new DAA therapy is shown to reduce the indications for liver transplantation due to HCV<sup>66</sup> and less strict criteria (beyond Milan) are being studied to expand the indication in HCC patients.

According to data from Latin American countries with established transplantation programs, HCC accounts for 11 to 17% of the liver transplantations in the region.<sup>67-69</sup> Milan criteria are the most frequent use and around 75 to 90% of the reported cohorts are in these criteria.<sup>67-70</sup> The posttransplantation recurrence rate in a large Brazilian<sup>71</sup> cohort was 8%, similar to what is described in the literature worldwide.<sup>72</sup>

Systemic therapies are recommended for BCLC-C patients or those who progressed on or have contraindications to locoregional modalities. The first agent that improved survival in this group was sorafenib. This drug was incorporated in the clinical practice worldwide in 2008, after the publication of two pivotal trials.<sup>73,74</sup> Although costs are an important issue, sorafenib is currently adopted in many Latin American countries. In a multicenter study with sorafenib-treated patients from Argentina, Brazil, Colombia, Ecuador, and Peru, 80% received sorafenib as the upfront treatment once most of the patients had BCLC-B and C stages.

The median survival of this cohort was 8 months,<sup>75</sup> inferior to what was observed in the SHARP trial.<sup>73</sup> Low survival in patients under systemic treatment with sorafenib was also observed in other Latin American cohorts.<sup>76,77</sup> Socioeconomic differences, delay in starting treatment, administrative and organizational deficiencies, and inclusion of subgroups of patients with no strong evidence (for example, liver dysfunction and BCLC-D stage) are possible reasons for the poor survival.

In 2017, a second-line agent, regorafenib, was approved based on positive results of a phase III trial.<sup>78</sup> This agent received local approval in Latin American countries such as in Brazil, Colombia, Argentina, and Mexico, but is not yet widely included in the daily practice in public health. In the last 2 years, two additional agents (cabozantinib<sup>79</sup> and ramucirumab<sup>80</sup>) also demonstrated survival improvement in phase III studies. However, due to delays in drug approval by local regulatory bodies, most Latin American countries still face difficulties in offering novel drugs to HCC patients. Use of cytotoxic chemotherapy (mainly doxorubicin and fluoropyrimidine combinations) was reported in patients after sorafenib exposure with disappointing overall survival in a Brazilian experience.<sup>81</sup> This scenario highlights that better outcomes with systemic treatment in HCC require integration of financial and organizational factors with the application of clinical criteria grounded on the best evidence available.

## Challenges and Future Perspectives

In this review, we described the available data on HCC epidemiology in Latin America comparing to global trends and the changing landscape in the management of this malignancy. Globally, as well as in Latin America, HCC is a major health problem and one of the leading causes of cancer mortality.

The familiarity with the prevalence of risk factors and how they may change in the coming years should drive new programs directed to improve the rate of early-stage diagnosis. HCV still represents the main etiology associated with HCC. Interferon-free regimens for HCV provided high rates of cure; so, an effort to identify and treat HCV patients will surely impact positively on the incidence of HCC. HBV vaccination is an urgent need in some regions with high incidence. These actions should integrate the general population, medical professionals, academic institutions, and government agencies.

Strategies on how to screen patients with NAFLD/NASH is a matter of intense debate and study worldwide. The current focus is placed on trying to identify which group of patients with NAFLD/NASH without cirrhosis should be screened, and how the screening should be performed.<sup>30</sup> As a region with a clear trend of increasing in NAFLD prevalence, Latin American centers should contribute to generating evidence on this issue.

Research, training, and scientific exchange are a driver for health care improvement, especially in the field of liver cancer. Medical education initiated in reference centers and disseminated to the primary healthcare system is paramount to improve primary prevention, implementation of comprehensive surveillance programs at high-risk patients,

and access to treatment options supported by the best available evidence. Multinational initiatives and dedicated network groups between Latin American countries and integrated with centers in other parts of the world can overcome the inherent socioeconomic difficulties and provide better care to HCC patients.

## Main Concepts and Learning Points

- Hepatocellular carcinoma is a major issue in Latin America. Improvements in health care access, surveillance, and continuing medical training are required.
- Increasing reports of liver cancer associated with fatty liver disease in Latin America mirror a trend observed in many Western countries.
- Viral hepatitis, alcohol, and aflatoxin remain predominant risk factors in Latin America.
- Multinational network efforts integrated with referral groups worldwide are paramount to delivering better care to hepatocellular carcinoma patients.

### Conflicts of Interest

Dr. Leonardo da Fonseca reports personal fees from Bayer.

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