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EDITORIAL

Hepatocellular carcinoma in Latin America: Diagnosis and treatment challenges

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Abstract

Latin America, a region with a population greater than 600000000 individuals, is well known due to its wide geographic, socio-cultural and economic heterogeneity. Access to health care remains as the main barrier that challenges routine screening, early diagnosis and proper treatment of hepatocellular carcinoma (HCC). Therefore, identification of population at risk, implementation of surveillance programs and access to curative treatments has been poorly obtained in the region. Different retrospective cohort studies from the region have shown flaws in the implementation process of routine surveillance and early HCC diagnosis. Furthermore, adherence to clinical practice guidelines recommendations assessed in two studies from Brazil and Argentina demonstrated that there is also room for improvement in this field, similarly than the one observed in Europe and the United States. In summary, Latin America shares difficulties in HCC decision-making processes similar to those from developed countries. However, a transversal limitation in the region is the poor access to health care with the consequent limitation to standard treatments for overall population. Specifically, universal health care access to the different World Health Organization levels is crucial, including improvement in research, education and continuous

medical training in order to expand knowledge and generation of data promoting a continuous improvement in the care of HCC patients.

Key words: Latin America; Liver cancer; Limitations; Challenge

Core tip: Which are the implications in regard to clinical decision making processes related to hepatocellular carcinoma (HCC) in daily practice in Latin America? Should we consider making these decisions taking into account both, local experiences and their feasibility together with the best available evidence in parallel with patient preferences? These decision-making processes must be individualized according to local barriers to health care systems. Primary prevention programs of liver diseases, surveillance for HCC and intervention programs following the best evidence will be possible only if we are aware of local barriers and develop efficient strategies to overcome them.

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INTRODUCTION

Latin American comprises a region of the Americas of Latin origin, in which the most common speaking languages are Spanish and Portuguese. The region accounts for more than twenty million square kilometers of surface area, with more than six hundred million population. Due to its geographic extension, Latin America has a great socio-cultural heterogeneity and an important socio-economic difference among countries. While there are high earners like Chile and Uruguay with a gross domestic product (GDP) per capita over $20000, others like Haiti and Honduras have GDPs per capita lower than $ 5000[1]. At the same time, each country in itself is highly unequal, presenting some of the highest Globalization of Inequality (GINI) scores in the world. Brazil, Chile, Ecuador and Colombia all present GINIs above 0.45 for the year 2016; Argentina and Uruguay having slightly better scores[1]. In comparison, Sweden, Norway, Netherlands and Denmark all have GINI scores less than 0.30[1].

It is in this socio-cultural and economic scenario, where settles a large variety in access to health care systems in the region. These systems are mainly made up of a common payer and provider that is the state. However, in several countries, there are other type of health providers through social security and private insurances and providers. Furthermore, expenditure on access care in many Latin American countries comes from out-of-pocket money among high to middle income people. On the other hand, among low socio-economic classes, expenditure comes purely and exclusively from public services, which in most of the cases provide with low to regular quality of medical care services and shortage of appropriate medical supplies and devices.

WHERE DO WE STAND IN LATIN AMERICA REGARDING HEPATOCELLULAR CARCINOMA?

Hepatocellular carcinoma (HCC) is the second leading cause of cancer related death worldwide and the main cause of cancer in patients with cirrhosis. Incidence of HCC varies according to geographic location, depending on the prevalence of viral hepatitis among the world. The predominant reported causes of HCC in different geographic areas around the world have been related with chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection and alcoholic liver disease[2-5]. Heterogeneous data regarding epidemiology of HCC in Latin America has been reported[6-12]. While HCV and alcoholic liver disease are the most frequent etiologies of HCC in the region, HBV is a leading cause in some countries, mainly in Brazil. More recently, we have observed a changing epidemiological trend of HCC towards an increasing non-alcoholic fatty liver disease, becoming an important public health burden in the region[6,7].

As previously proposed by the World Health Organization the structural challenge in the region is the uneven access to health care. To our knowledge there is not even one country with an integrated program to assist on the prevention of chronic liver diseases and early identification of the population at risk for developing HCC. Consequently, the common challenge for scientific societies is to induce regional policy makers to develop interventions and strategies able to identify the population at risk, implement surveillance programs, and improve access to curative and palliative treatments. Once we have assured access to adequate care we should move into next step which is the correct adherence to recommendations from clinical practice guidelines[2-5].

A clinical case scenario as an example of where do we fail in Latin America

The following clinical case demonstrates the regional shortcomings related to HCC diagnosis at late stages and its therapeutic consequences. A 60-year-old male patient with compensated cirrhosis and clinically significant portal hypertension due to chronic HCV infection, who started antiviral treatment with direct-acting antiviral agents, began an erratic path of ultrasound (US) screening for HCC. Surveillance was performed by non-liver expert

Table 1 Surveillance for hepatocellular carcinoma in Latin America

Study	Population	Design	Results
Fassio *et al*[8]	*n* = 240 HCC Brazil, Arg, Colombia, Chile, Uruguay, Venezuela	Prospective cohort (Surveillance retrospectively analyzed)	54% under surveillance; BCLC A 70% *vs* 39% not under surveillance; No survival analysis
Paranaguá-Vezozzo *et al*[9]	*n* = 884 Cirrhosis Child A-B Brazil, Sao Paulo	Retrospective cohort US ± AFP annual	HCC annual incidence 2.9%; 75% under annual surveillance; 80% within Milan, better survival
Piñero *et al*[10]	*n* = 643 Cirrhosis, waiting list for liver transplantation. Argentina	Retrospective cohort Surveillance Failure = incidental HCC in the explant	US accuracy: S 33% and E 99%
Campos Appel-da-Silva *et al*[11]	*n* = 453 Child A-C Cirrhosis Brazil, Porto Alegre	Retrospective cohort US ± AFP every 6 mo	50.7% under surveillance; More BCLC 0-A *vs* no screening; Better survival within Milan criteria
Debes *et al*[12]	*n* = 1336 HCC Brazil, Argentina, Colombia, Peru, Uruguay, Ecuador	Retrospective cohort	47% under surveillance; Better survival *vs* symptomatic diagnosis (adjusted for lead-time bias)

BCLC: Barcelona Clinic Liver Cancer; HCC: Hepatocellular carcinoma; US: Ultrasound.

sonographers due to insurance's related lack of access to academic sites. Initially a 24-mm nodule was visualized and he was recommended to stay on a follow-up visit with no further imaging evaluation. Twelve months later, another US was performed; this time the nodule grew to 38 mm. He performed an abdominal computed tomography (CT) scan with oral contrast only, and the finding of an "uncharacteristic" nodule leaded to a CT-guided biopsy. The pathologic report was "nodules of hepatocellular regeneration separated by broad fibrous septa, cirrhosis". Result: No cancer. His physician suggested him to continue life normally and the patient happily went home.

A year later, a liver specialist suggested him to perform an abdominal CT scan with intravenous contrast. A heterogeneous 80-mm diameter lesion in the right hepatic lobe with "non-characteristic findings" was observed. Not satisfied, the patient looked for a second opinion. A second hepatologist performed a three-phase dynamic abdominal magnetic resonance imaging (MRI). Result: One lesion with arterial enhancement and wash out during portal and late phases: HCC of 83 mm, without vascular invasion. Serum alpha-fetoprotein value was 1200 ng/mL.

In the end, the patient consulted at least 4 medical doctors during a 2-year period, with extended and inadmissible delay in HCC diagnosis that at this point will probably exclude him from potentially curative treatments. Where did we fail?

Early diagnosis of HCC: Challenges and areas of improvement

This case, clearly illustrates some of the reasons for failure in routine surveillance and HCC diagnosis at early stages in Latin America, and as a consequence, failure in the appropriate staging and selection of therapies.

Screening failure entails three important points to be considered. First, absence of early identification of the population at risk, such as chronic HBV or HCV. Second, ineffective application of routine surveillance (semi-annual ultrasound performed by expert operators) and third, errors in interpretation of a positive or negative screening tests, misinterpreting its sensitivity and specificity.

Surveillance for HCC in Latin America demands a continuous improvement. Different retrospective cohort studies have shown flaws in the implementation process of routine surveillance, the consequent failure in the diagnosis in early stages and finally a notorious negative impact upon patient survival[8-12] (Table 1).

Overall, surveillance programs reported to be applied in less than 50% of the patients in Latin America. This number perhaps does not show the "real" regional situation, since most of this data came from academic rather than general hospitals. Consequently, screening failure for HCC in this region might be even greater, demanding strategies to improve its implementation such as application of US done by experts, correct interpretation of imaging tests and finally, adequacy of therapeutic decisions according to the best evidence-based-medicine. Consequently, early HCC diagnosis should be the aim of these strategies.

As exemplified in the clinical case, the misuse of diagnostic tools delays the correct diagnosis. HCC diagnosis implies an appropriate oncologic imaging paradigm, not requiring histological confirmation for diagnosis in most of the cases. However, discordance between images and histology may occur. This situation has been reported up to 10% in Argentina when comparing imaging reports and explanted liver data from liver transplanted patients[13,14]. In a multicenter Latin American cohort study, false positives cases were less than 3%[15]. Two different situations need to be further clarified when discussing imaging accuracy against histological confirmation of HCC. On one hand, when false positives are considered, it should be important to address if complete necrotic nodules were included as false positive cases resulting in a biased report. On the other hand, discrepancy between images

Table 2 Adherence to clinical practice guidelines around the world and in Latin America

Study	Population	Design	Results
Leoni *et al*[20]	*n* = 227 HCV 58% Child A 54%	Retrospective cohort (2005-2010) One center	At HCC diagnosis: BCLC 0-A 55%; Adherence to BCLC 60%; Higher adherence among BCLC A 86%
Gashin *et al*[21]	*n* = 137 HCV 62%	Retrospective cohort (2009-2010) One center	Adherence to BCLC 62%; Better overall survival; Heterogeneous causes of non-adherence
Kim *et al*[22]	*n* = 3515 HBV 77% Child A 82%	Retrospective cohort (2005-2009) One center	At HCC diagnosis: BCLC A 59%; Adherence to BCLC 49%; Better survival for adherence, except BCLC-D (BCLC D who were transplanted were considered "non-adherence")
Wallace *et al*[23]	*n* = 292 OH-HCV 65%	Retrospective cohort (2006-2014) One center	At HCC diagnosis: BCLC 0-A 64%; Adherence to BCLC 48% *vs* HKLC 56% (P.001); No better survival among BCLC adherence *vs* no-adherence but better survival among HKLC (TACE before transplant was considered "no-adherence")
Guarino *et al*[24]	*n* = 1008 HCV Child A 73%	Retrospective cohort (2013-2015) Multicenter study	At HCC diagnosis: BCLC 0-A 59%; Adherence BCLC 71%, lower in BCLC B 36% and C 46%; No better survival (TACE before transplant was considered "no-adherence")
Kikuchi *et al*[25]	*n* = 364 HBV 53% Child A 53%	Retrospective cohort (2010-2012) One center	At HCC diagnosis: BCLC A 36%; Adherence BCLC 52%; Lower adherence in BCLC C-D; No better survival, except in BCLC A (BCLC D who were transplanted were considered "non-adherence")
Piñero *et al*[26]	*n* = 708 HCV 58% Child A 54%	Dual cohort (2009-2016) Multicenter study	At HCC diagnosis: BCLC 0-A 47%; Adherence BCLC 53% initial, 63% subsequently; Adherence to BCLC: better survival HR 0.67 (CI: 0.52-0.87)

BCLC: Barcelona Clinic Liver Cancer; HKLC: Hong Kong Liver Cancer algorithm; HCV: Hepatitis C virus; HBV: Hepatitis B virus; TACE: Transarterial chemoembolization.

and explanted liver should be considered taking into account potential tumor progression, and locoregional response to treatments during the waiting list period.

Nevertheless this led to changes in diagnostic criteria for HCC in patients enrolled for liver transplantation in Argentina aimed to improve imaging diagnostic accuracy. Although the idea was novel, LIRADS criteria implementation leaded even to a greater uncertainty for those cases where HCC diagnosis is probable or possible (LIRADS 3 or 4). Moreover, imaging expert's agreement on LIRADS in the daily practice has been not assessed at all. Thus, LIRADS system seemed to make the clinical decision making process even more complex in daily practice in that country[16,17].

Challenges regarding staging and adherence to recommended treatment options from clinical practice guidelines

HCC staging considering the Barcelona Clinic Liver Cancer (BCLC) algorithm has been recommended in different clinical practice guidelines[3,4], including that from the Latin American Association for the Study of the Liver (ALEH)[3]. However, strict adherence to these therapeutic recommendations is often not feasible in daily practice. This does not contradict the BCLC algorithm, since its explicitly recommends that the therapeutic choice must be individualized considering feasibility, access and preferences of the patients[18]. In addition, there are different guidelines and recommendations, including those from Asia (APASL)[5], Japan and South Korea. Consequently, there is a wide range of treatment algorithms when considering HCC.

The BRIDGE study demonstrated the great heterogeneity in terms of the treatments performed worldwide at each stage and far from that recommended in the ideal situation[19]. Global and individual context makes therapeutic decisions in HCC heterogeneous in real life. Adherence to clinical practice guidelines recommendations varies between 40%-70% in different retrospective cohort studies[20-26]. Two Latin American studies evaluated adherence to BCLC and its impact on survival. In a study from Brazil, adherence to BCLC did not have a favorable impact on survival[25]. However, there was a selection bias when "non-adherence" was categorized in those patients within BCLC-D stage who were candidates for liver transplantation. Precisely, the BCLC clarifies in its footnote that these patients must be transplanted. In a dual cohort study in Argentina, adherence to BCLC was greater than 50%, being associated with better overall survival[26] (Table 2).

In summary, although Latin America shares some difficulties in HCC decision-making processes similar to those reported in some developed countries, we still have big gaps when compared to them. These gaps are seen in medical education, on early and accurate HCC diagnosis, and in universal access to good diagnostic technology and to curative treatments. Until they are corrected, discrepancy on HCC related survival would remain present.

PERSPECTIVE

Consequently, we shall make decisions considering local education, expertise and feasibility together with

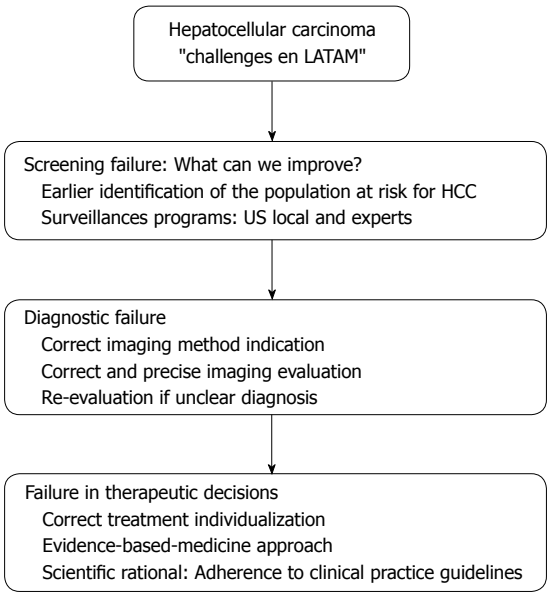

Figure 1 Areas of improvement regarding hepatocellular carcinoma in Latin America. HCC: Hepatocellular carcinoma.

the best available evidence. Ultimately, this decision-making-process must be individualized[27].

Which are the areas for improvement in Latin America? Specifically, universal health care access as per World Health Organization recommendation is crucial. This includes improvement in transmission of information and medical education from academic to primary health care centers, focusing on prevention of development of liver diseases, identification of population at risk for HCC, systematic implementation of routine surveillance programs, improvement in the diagnostic work-up process and finally, promoting overall access to all treatments strategies which have shown improvement in patient's survival (Figure 1). Finally, an important field to promote in the region is the development of research consortia such as the Latin American Liver Research Educational and Awareness Network, through which we can multiply medical education and generation of regional data necessary to develop efficient health interventions for improvement the care of patients with HCC[28].

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