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

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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]. Hetero-
geogeneous 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
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
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 led 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

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**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: 83% 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.
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 led 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\textsuperscript{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\textsuperscript{18-26}, including that from the Latin American Association for the Study of the Liver (ALEH)\textsuperscript{18}. 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\textsuperscript{18}. In addition, there are different guidelines and recommendations, including those from Asia (APASL)\textsuperscript{19}, 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{26} (Table 2).

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

| Study             | Population          | Design                  | Results                                                                 |
|-------------------|---------------------|-------------------------|-------------------------------------------------------------------------|
| Leoni et al\textsuperscript{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\textsuperscript{20} | $n = 137$ HCV 62% | Retrospective cohort (2009-2010) One center | Adherence to BCLC 62%; Better overall survival; Heterogeneous causes of non-adherence |
| Kim et al\textsuperscript{20} | $n = 3515$ 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\textsuperscript{20} | $n = 292$ 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\textsuperscript{20} | $n = 1008$ 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\textsuperscript{20} | $n = 364$ 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\textsuperscript{20} | $n = 708$ 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.

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**PERSPECTIVE**

Consequently, we shall make decisions considering local education, expertise and feasibility together with...
Hepatocellular carcinoma
"challenges en LATAM"

Screening failure: What can we improve?
- Earlier identification of the population at risk for HCC

Surveillance programs: US local and experts

Diagnostic failure
- Correct imaging method indication
- Correct and precise imaging evaluation
- Re-evaluation if unclear diagnosis

Failure in therapeutic decisions
- Correct treatment individualization
- Evidence-based-medicine approach
- Scientific rational: Adherence to clinical practice guidelines

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[30].

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