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Position Paper

"Hepatocellular carcinoma surveillance: Current challenges in Latin America"

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, predominantly linked with cirrhosis and chronic hepatitis B. In Latin America, disparities in healthcare access complicate HCC management. A recent expert meeting emphasized the importance of identifying at-risk populations for effective screening and surveillance, underlining the need for structured routine programs.

Early detection of HCC improves outcomes and increases survival rates. Surveillance programs are essential, yet access to healthcare and treatment varies significantly across Latin America, making timely diagnosis and intervention challenging. Additionally, recent shifts in disease etiology, notably the rising prevalence of MASLD, further complicate HCC detection.

Effective HCC surveillance relies on cost-efficient diagnostic tools. Ultrasound is the main screening method, though it has moderate sensitivity. In obese patients, achieving adequate visualization is particularly difficult. Combining ultrasound with alpha-fetoprotein (AFP) improves diagnostic accuracy. Biomarkers such as AFP are commonly used to diagnose and monitor HCC, but their predictive value remains limited. Integrating biomarkers with ultrasound or other novel markers may enhance detection; however, further research is necessary to validate these strategies.

In conclusion, HCC surveillance remains a significant challenge in our region. A comprehensive, multifaceted approach is needed to improve early detection and clinical outcomes.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, constituting the sixth most frequent neoplasm, and the third leading cause of cancer-related death worldwide [1]. Cirrhosis and chronic hepatitis B (CHB) are the main associated risk factors with HCC, although metabolic-associated steatosis (MASLD) is increasingly associated with the occurrence of HCC in Western countries [1,2]. Incidence of HCC varies widely across the world mainly due to variations in HCC risk factors, such as viral hepatitis and MASLD leading to development of different international surveillance guidelines.

Management of HCC is a significant health issue in Latin America due to the high prevalence of chronic liver diseases. Latin America is

Abbreviation: AFP, Alpha-fetoprotein; HCC, Hepatocellular carcinoma; MASLD, metabolic-associated steatosis disease; CHB, Chronic Hepatitis B; HCV, Hepatitis C virus; CT, computed tomography; MRI, magnetic resonance imaging; BCLC, Barcelona Clinic Liver Cancer; DCP, Des-Gamma-Carboxy Prothrombin

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a vast region with approximately 650 million inhabitants characterized by wide socio-cultural and economic heterogeneity. The age-standardized incidence rate of HCC in Latin American countries, considering both sex and age, ranges from below 2.9 to over 6.6 cases per 100,000. In Latin America there is a low prevalence of CHB, and most HCC cases originate from chronic hepatitis C or alcohol-related liver disease [10–12]. However, in recent years, there has been a shift in the trends of liver disease etiologies in the region, with a rising incidence of MASLD [3,4,11]. Throughout the region, there is an increasing disparity in access to the healthcare system, even within the same countries [3].

Prevention policies have been implemented in the region, including universal hepatitis B vaccination, improved access to hepatitis C treatment, and various hepatitis C re-engagement programs, all of which have effectively reduced the prevalence of these diseases and the incidence of HCC. However, there is still room for improvement. While effective strategies for HCC prevention and early detection exist, the implementation of surveillance programs and preventive measures in Latin America continues to face significant challenges.

Overcoming these barriers is essential to altering the incidence trend and improving survival rates among HCC patients in the region

On November 30th and December 1st, 2023, an expert meeting was held at the Austral University Hospital in Argentina, with 80 participants from most Latin American countries. This panel discussed the most frequent barriers in the surveillance policies of HCC in Latin America. In this written proposal, we describe the most important points discussed during the meeting.

2. Concept of cancer screening and surveillance: What are the requirements?

Screening tests are important tools to detect early-stage cancer in asymptomatic individuals. They are not intended to diagnose the disease, but to trigger a prompt diagnostic procedure. In contrast, surveillance is defined as the longitudinal repetition of the screening test over a period. For a surveillance program to be effective, certain principles must be considered [4].

2.1. There should be a recognizable and clearly defined population at risk

Most patients with HCC have underlying chronic liver disease. The main challenge is the correct identification of patients at risk who should undergo surveillance and the implementation of routine surveillance programs in the region. A recent multicentric study in Argentina found that at the time of HCC diagnosis, 25% of patients were unaware of their chronic liver disease diagnosis [5]. In another retrospective study from Brazil, 86 % of patients were unaware of their chronic liver disease before HCC diagnosis [6]. Consequently, lack of identifying the risk population is the first point to be considered.

Guidelines recommend performing an abdominal ultrasound every 6 months, with or without serum alpha-fetoprotein (AFP), in patients with compensated cirrhosis—regardless of the underlying etiology (e.g., Child-Pugh A and B)—as well as in those with decompensated cirrhosis awaiting liver transplantation, where the annual incidence of HCC is approximately 1–8 %. Surveillance is also recommended for individuals with chronic hepatitis B (CHB) who have an intermediate or high estimated risk (e.g., PAGE-B score >9 points) In patients with intermediate o high-risk the 5-year cumulative probability of HCC is 3 % and 17 %, respectively [7–9].

The annual HCC incidence rate proposed as the clinical threshold for incorporating patients into surveillance programs is 1.5–3.0 % [1]. This estimated annual risk has been shown to be cost-effective. Cirrhosis and CHB with a PAGE score >9 points have an estimated incidence rate above this threshold and are therefore target populations to be screened. These clinical settings have strong recommendations, with low to moderate quality of evidence in most international and regional clinical guidelines, due to the lack of global and reproducible randomized controlled trials [13–16]. However, there is considerable uncertainty regarding effectiveness of HCC surveillance below this threshold in other clinical settings. First, except for CHB, in chronic liver diseases without advanced fibrosis, there is no evidence to support population-based surveillance implementation. This is the case of MASLD in which robust evidence for HCC surveillance is still lacking [17]. Secondly, a group of interest includes patients with grade 3 liver fibrosis, who may have an increased risk of developing HCC, particularly in some etiologies. Lastly, the eradication of viral or other chronic etiologic insult in the liver may promote fibrosis regression, even in patients with cirrhosis. However, there is some uncertainty about whether cirrhosis regression significantly reduces the risk of HCC. Therefore, stopping HCC surveillance is rather controversial or uncertain. Particularly, there is a risk reduction of HCC development after HCV eradication, but this risk is not completely suppressed [18].

2.2. There should be a cost-effective diagnostic tool for screening

Other individual determinants to be considered for HCC surveillance include comorbidities, age, and performance status. Safety, cost, applicability, and expertise are also relevant points when performing a screening test. Moreover, the availability of effective treatments for the specific population under screening is part of a well-structured surveillance program.

It is important to highlight that the efficacy of a diagnostic test is its ability to diagnose the disease, in other words, the performance of the test. The ability of the test to correctly identify those with the disease is known as sensitivity. When the result of a sensitive test is positive, a confirmatory test is required next (a specific test, therefore). As a result, a highly sensitive test is more clinically useful for ruling out the disease rather than confirming it.

For more than 20 years, ultrasound has been the current cost-effective HCC screening method, showing high specificity when conducted in the population at risk. However, it has low to moderate sensitivity for early-stage diagnosis of HCC (95 % CI: 35–70 %), which improves to 63 % when combined with AFP [19]. Moreover, it is operator-dependent. In Latin America and other regions, the operator's skill and the quality of the equipment can vary across centers, expertise and health infrastructure [20]. Additionally, obesity and heterogeneity of the cirrhotic liver may impair the technical quality of the method [21].

With this evidence available, the latest guidelines from the American Association for the Study of Liver Diseases (AASLD), recommend the combination of ultrasound and AFP for HCC screening [22]. Other guidelines still recommend ultrasound with AFP only when ultrasound quality is deficient [23,24].

Other screening methods have been proposed. Low-dose two-phase computed tomography (CT) may have greater sensitivity (83 % vs. 29 %) and specificity than ultrasound combined with AFP [22,25]. However, it is not recommended in most guidelines probably due to inherent risks of excessive radiation exposure [26].

Abbreviated nuclear magnetic resonance imaging (MRI) reduces screening times and costs compared to conventional MRI, without losing sensitivity (80–90 %) or specificity. However, studies evaluating CT and MRI screening performance were conducted on small Asian cohorts, mainly CHB, making external validation necessary.

These alternative screening methods, which appear to be more sensitive but rather unspecific, may be useful where ultrasound is expected to perform poorly to exclude HCC diagnosis (e.g. overweight people). It is important to take into consideration other limitations, particularly in our region, such as accessibility and higher costs [3,20].

Over the past years, multiple studies have compared different surveillance strategies with shorter or longer ultrasound intervals. A 3-month ultrasound interval has shown no superior benefit in HCC detection rates compared with a 6-month period, the latter showing increased sensitivity [27]. However, a short-term ultrasound repetition is recommended when nodules less than 1 cm in diameter are observed. In this scenario, consensus agreement recommends repeating ultrasound at a 3-month interval. If after 18-24 months the nodule has not grown, HCC probability may be low, and surveillance should restart using 6-month intervals. When an ultrasound nodule surpasses 1cm diameter, a contrast-enhanced CT or MRI is mandatory to confirm or exclude HCC diagnosis [19,22,23].

Biomarkers are routinely used in identifying individuals at high risk of developing HCC and monitoring disease progression or response to locoregional or systemic therapies. Although there is a clear prognostic association with increasing AFP levels across all Barcelona Clinic Liver Cancer (BCLC) stages [28], its predictive value for treatment selection has been shown in resection, liver transplantation, and within second-line systemic treatment with ramucirumab. In other settings, AFP thresholds are widely unspecific without predictive discrimination.

AFP values or thresholds for HCC diagnosis and screening are still controversial. Most of the patients diagnosed at very early or early BCLC stages (the aim of surveillance), present with low to very low levels of this biomarker. On the other hand, evidence supporting AFP for HCC surveillance comes from case-control or uncontrolled observational studies. Therefore, increasing sensitivity with decreasing specificity threshold has been proposed [29,30] It is important to underline that the aim of HCC screening is to detect HCC at very early stage, in which the best survival benefit can be obtained.

Nevertheless, several authors have advocated for incorporating AFP to improve HCC detection regardless of BCLC stage, despite the variation in AFP cut-off values and the significant heterogeneity across studies. In a recent meta-analysis, the use of AFP has shown increasing sensitivity but decreasing specificity [19]. Among patients with early-stage HCC, ultrasound sensitivity alone was 45 % (CI 30 −62 %), which is significantly lower when compared to the 63 % (CI 48−75 %) sensitivity reported for US combined with AFP. On the contrary, the use of AFP plus ultrasound significantly reduced specificity for HCC diagnosis at early stage from 92 % (CI 85−96 %) to 84 % (CI 77-89 %) [19].

Combining AFP with other biomarkers, such as AFP-L3 %, Des-Gamma-Carboxy Prothrombin (DCP or PIVKA II), not only increases HCC discrimination for early-stage HCC, but also significantly outperforms AFP alone [24,31] However, these studies were conducted in case-control or nested case-control studies with low quality level of evidence. Logistic regression models were proposed to address HCC probabilities. The GALAD score combines age, gender, AFP, AFP-L3 %, and DCP, showing increased accuracy of HCC detection compared to individual biomarkers alone (area under the receiving characteristic curve −AUROC- 0.96 for GALAD, 0.84 for AFP- L3, 0.88 for AFP and 0.90 for DCP [32]. Some authors have suggested that the contribution of AFP-L3 % in the GALAD algorithm may be negligible and proposed the GAAD score (gender, age, AFP, DCP) [33,34]. A recent study evaluates the performance of the GALAD score in Latin America showing that discriminant function was adequate for HCC detection, but lower for early HCC stages. Therefore, confirming that on the one hand, there is still a need for a sensitive and specific biomarker for HCC surveillance and on the other hand, that GAAD performance is similar than GALAD score [34].

The HCC early detection screening (HES) algorithm incorporates the rate of AFP change within the last year, age, ALT, platelets, HCC etiology, and interaction terms (AFP and ALT, AFP and platelets) [35]. In a phase 3 biomarker study, the sensitivity within 6 months before early-stage HCC diagnosis was comparable between the HES algorithm (39−42 %) and the GALAD score (31−74 %) at a specificity of 90 % [31]. However, the comparison of performance between the HES algorithm, the GALAD score, AFP, AFP-L3 %, and DCP remains controversial.

In summary, HCC biomarkers and scoring models still need to be validated in larger phase 4 biomarker studies to improve detection of HCC at early or very early stages and therefore confirm a survival benefit. High quality based studies are still necessary.

2.3. Early detection leads to better outcomes using curative treatments

As aforementioned, the main goal of surveillance programs is to reduce cancer-related mortality. A recent metanalysis of observational studies confirmed that HCC surveillance was associated with increased odds of early HCC detection (OR 1.86; CI 1.73−4.98), access to curative therapies (OR 1.83; CI 1.69−1.97), and better survival (hazard ratio 0.67; CI 0.61−0.72) [36].

Nevertheless, surveillance of HCC remains controversial regarding survival benefit due to the lack of high-quality randomized controlled trials (RCTs). To date, the only RCT published in 2004 showed that biannual ultrasound screening was associated with a 37 % reduction in relative risk mortality [37]. In patients with cirrhosis, observational studies support the strong recommendation for HCC surveillance [22,25,38]. While methodologically needed, designing a RCT including cirrhotic patients with and without surveillance as treatment and control arms is currently challenging, unfeasible and unethical.

3. Challenges and opportunities for Latin America

The Latin American health system faces difficulties in ensuring proper patient care dynamics throughout different stages, especially for patients with chronic liver diseases and HCC [39].

The referral and counter-referral systems are fragmented, and there is a lack of adherence to guidelines due to limited access to treatment options. Access to medications varies across the region. Furthermore, countries such as Nicaragua, Honduras, Guatemala or Venezuela do not have liver transplant programs, nor access to interventional radiologic procedures.

Given the significant heterogeneity of health care access in Latin America, diagnosing HCC is even more challenging. First, we often fail to identify the population at risk of HCC. Chronic liver diseases should be correctly screened and diagnosed to prevent liver disease progression. In most Latin American countries, healthcare access to primary care services and prevention strategies are limited. These health barriers lead to undiagnosed liver diseases and loss of health opportunities. Even more problematic, undiagnosed liver disease precludes surveillance for HCC. These are the *"foundation stones"* for HCC surveillance improvement and the most important goal for our region.

Over the years, there has been a change in trends in etiologies of liver disease. Based on this, it seems that the best strategy is to prevent liver diseases through hepatitis B vaccination campaigns, raise awareness about alcohol consumption, and promote a healthier lifestyle focusing on diet and exercise. On the other hand, efforts should also focus on implementing routine surveillance programs established by regional guidelines. Moreover, while diagnostic algorithms are published in regional clinical practice guidelines, another challenge is interpretation of the results, access to care and treatments. On certain occasions, fluctuations in AFP values can guide the diagnosis and the need of further contrast studies [15]. Even in patients at risk, it is estimated that less than 50% adhere to these programs, although these numbers are likely to be underestimated. Table 1 [5,40–45]. Ultrasound with or without AFP is available and feasible in most Latin American countries. Adapting new surveillance strategies may be challenging. Efforts should focus on HCC individual risk stratification, adherence to surveillance programs, patient and family education and awareness of health care professionals. The

Table 1
Adherence of surveillance in LATAM.

Study	Population	Design	Results
Fassio *et al Annals of Hepatology 2010.* [41]	*n* = 240 HCC Brazil, Argentina, 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.* [42]	*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 Eu Journal of Gastroenterology and Hepatology 2015*[43]	*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 WJG 2016* [44]	*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
Kikuhi et al. Clinics 2017[45]	*n* = 364 HCC Brazil,	Retrospective Multicentric cohort	Adherence to guidelines 52 % 65 % diagnosed during screening.
Debes *et al Liv. International 2018*[46]	*n* = 1336 HCC Brazil, Argentina, Colombia, Perú, Uruguay, Ecuador	Retrospective cohort	47 % under surveillance; Better survival *vs* symptomatic diagnosis (adjusted for lead-time bias)
Piñero et al Digestive disease and sciences. 2019 [20]	*n* = 533 Cirrhosis, waiting list for liver transplant.	Retrospective cohort	62.4 % were under routine surveillance with a surveillance failure of 38.8 %.
Dirchwolf M, et al. Annals of Hepatology 2020 [5]	*n* = 301 Argentina; 97.6 % cirrhosis, 1.7 % advanced fibrosis	Multi-center cross-sectional study	43 % were under surveillance

Abbreviations: HCC, hepatocellular carcinoma; US, ultrasound; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer staging system; S, sensitivity; E, specificity.

management of patients with HCC should center on early detection in at-risk populations using precise strategies [13].

4. Final considerations and conclusions

Ultrasound every 6 months is effective, simple, and accessible for timely detection of HCC. Still, there is a need to underline the quality of published studies, highlighting potential bias. Lead-time and length-time biases, both related to the natural history of HCC, may overestimate the benefits of surveillance. Moreover, selection bias (when individuals who undergo screening differ systematically from those who do not), particularly the selection of controls in case-control studies, and misclassification bias (when the control group has been exposed to other screening or diagnostic test or time-frame algorithms), are explicit in low quality-based evidence. Finally, socioeconomic bias (when access to healthcare, education, and socioeconomic status can influence participation in cancer screening programs) is a significant problem in the Latin American region [4]. Therefore, the effectiveness of any screening tool must be evaluated not only by its diagnostic accuracy but also by its cost, accessibility, and feasibility in real-world settings [2].

HCC surveillance remains a major challenge across Latin American countries. Enhancing early detection and improving outcomes requires a multifaceted strategy: raising awareness of liver diseases, promoting healthy lifestyles and vaccination; correctly identifying high-risk populations; improving adherence to surveillance programs through reminder systems (like phone calls, emails, or other reminders); and addressing technical limitations in imaging, especially in overweight individuals. The use of combined approaches, such as GAAD scores with ultrasound, may help improve diagnostic performance. Strengthening public health policies that promote equitable healthcare access is crucial for advancing early diagnosis and treatment of HCC in the region. Imaging limitations, especially in overweight individuals, necessitate additional tools like biomarkers and GAAD-ultrasound combinations. Therefore, optimizing HCC surveillance requires a multifaceted approach. Strengthening health policies is crucial to improving access, early diagnosis, and treatment decision-making in Latin America.

Data availability statement

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Declaration of competing interest

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