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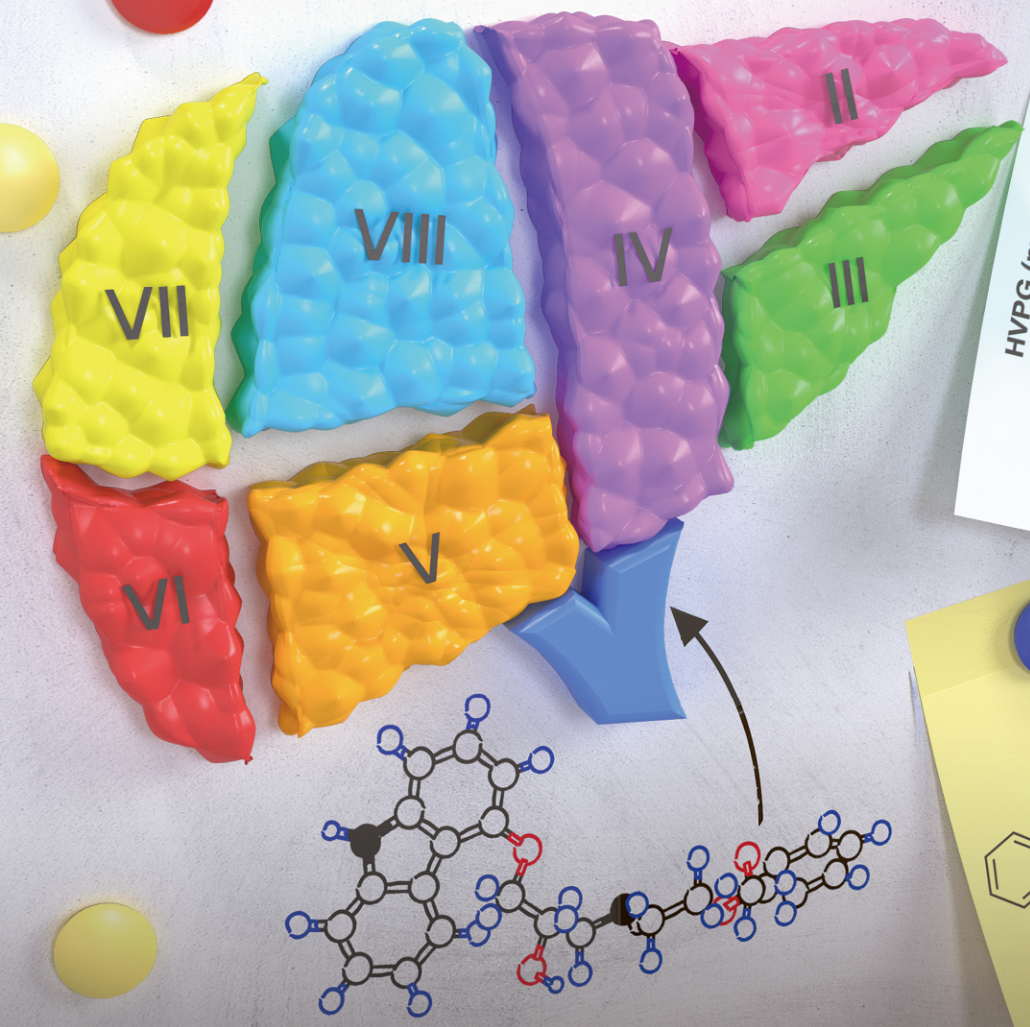

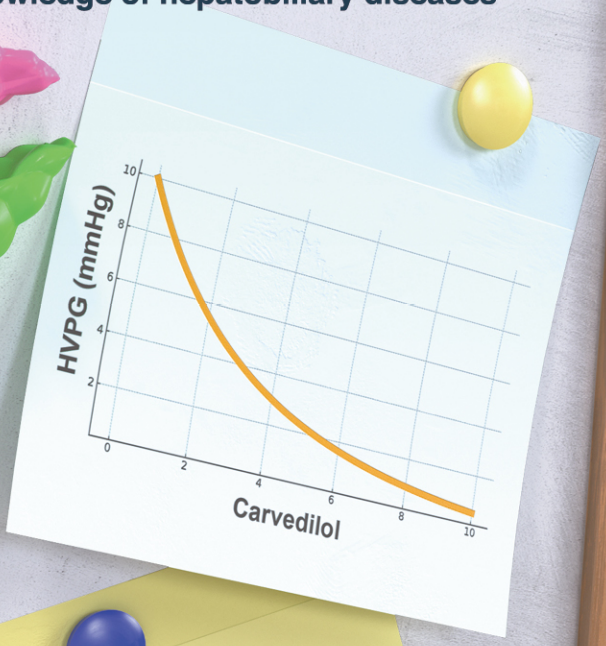

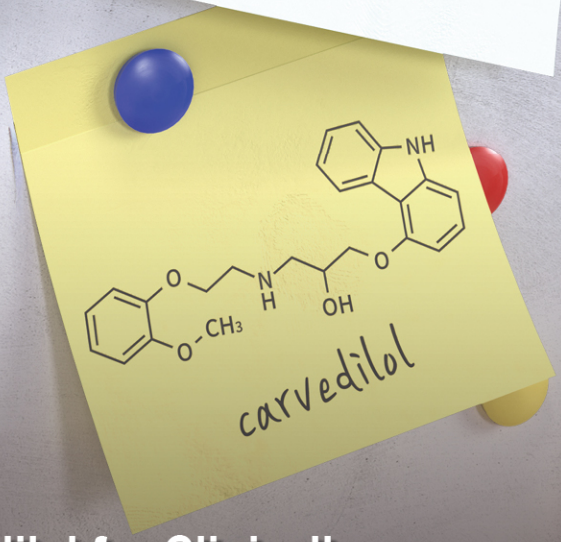

Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

Intrapatient variability of tacrolimus on CKD in LT
HCV self-testing and disease burden reduction
MASLD and microbiota
Bariatric surgery for metabolic cirrhosis

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Editorial

The use of transient elastography for predicting hepatocellular carcinoma in chronic hepatitis B patients: Editorial on "Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using vibration-controlled transient elastography: Systematic review and meta-analysis"

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Keywords: Transient elastography; Fibroscan; Non invasive test; Hepatocellular carcinoma; Chronic hepatitis B

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Chronic hepatitis B (CHB) virus infection continues to pose a significant global public health challenge, influenced by evolving epidemiological patterns due to several factors, such as vaccination policies and migration. The diagnosis of hepatitis B is established by the presence of hepatitis B surface antigen (HBsAg), and chronic hepatitis B infection is confirmed when HBsAg persists in the bloodstream for at least 6 months.[1-4] The global prevalence of HBsAg varies greatly across different countries.[5] Almost 296 million people worldwide have CHB, with the highest rates observed in Africa and Asia.[1] Such patients require lifelong monitoring and potentially antiviral treatment. In 2022, hepatitis B virus (HBV)-related complications resulted in approximately 1.1 million deaths, and these numbers are expected to increase in the coming years unless effective interventions are implemented.[1] In particular, predicting the risk of developing hepatocellular carcinoma (HCC) in patients with CHB is still a challenge nowadays, as this might develop even in patients who do not have cirrhosis or in patients who are responding to antiviral treatment.

Given this, it becomes crucial to identify those patients who are at a higher risk of developing HCC, to ensure they receive timely and effective care. Effective risk stratification can play a pivotal role in this regard, allowing for HCC surveillance and potentially improving outcomes. In this context, a meta-analysis by Jin et al.[6] has provided interesting insights on the efficacy of transient elastography (TE) as a non-invasive test (NIT) for predicting HCC development in this patient population.

TE performed using the Fibroscan is a well validated NIT for assessing liver fibrosis in CHB[7] and is recommended in

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various guidelines.[3,8] TE measures liver stiffness in kPa, providing a quantitative evaluation of the extent of the liver fibrosis.

In their systematic review and meta-analysis, Jin and colleagues identified 10 studies (including a total of 18,150 patients) that assessed the risk of HCC development and used TE for stratifying liver fibrosis in CHB patients. Seven of these studies were retrospective and three were prospective. Antiviral treatment was received by all patients in four studies and by some in the remaining six. There were no data on HBeAg status and viral load and/or viral suppression. Remarkably, all studies were performed in Asia, and nine of them were performed in South Korea. According to the results of the meta-analysis, the authors found that a liver stiffness measurement (LSM) of ≥11 kPa was associated with a hazard ratio (HR) of 3.3 for the development of HCC, thus providing a practical cut-off for identifying high-risk patients.[6] This finding is potentially important for refining surveillance strategies and improving CHB patient outcomes.

Although the results are important, there are also limitations that need to be taken into account. The fact that all included studies came from Asia, raises questions about the generalizability of these findings to other populations. A critical aspect not considered in the analysis was the duration of antiviral treatment, which is inversely correlated with the risk of HCC. Prolonged antiviral therapy has been shown to reduce HCC risk in CHB patients,[9] and also the specific antiviral molecule used in therapy can have a role,[10] consequently these variables could significantly influence the study outcomes. Additionally, the meta-analysis did not consider the HBeAg status, which is a known risk factor for HCC,[1,3] which further complicates the interpretation of the results. Thus, it is difficult to interpret the finding that the HR for HCC development was higher in the studies where all patients received antiviral treatment compared to the studies where only a subset of patients were receiving treatment. Finally, the lack of randomized controlled trials (RCTs) and the presence of potential confounders in retrospective studies are also factors that suggest caution in interpreting these results. For instance, the attributable risk conferred by alcohol misuse or the presence of metabolic risk factors could not be quantified.

Regarding the use of TE as a predictive tool, the sensitivity and specificity (61% and 78%) of the 11 kPa cut-offs were rather moderate which means that it cannot be used as a standalone test but needs to be complemented by other prognostic methods or incorporated in existing HCC prediction scores (Fig. 1). Combining TE with other established HCC prediction factors for CHB patients, such as age, gender, platelets count, diabetic status, HBV DNA levels, could enhance the accuracy of predicting which CHB patients are at risk of developing HCC and would benefit most from surveillance. Therefore, in terms of future directions, a reasonable next step would be to integrate TE into existing HCC risk prediction models for HBV. Several models have been developed, including GAG-HCC and HCC-CU scores (from Hong-Kong cohorts),[11,12] REACH-B score (in Asian CHB populations without cirrhosis),[13] THRI (from a Toronto cohort of cirrhotic patients),[14] PAGE-B score (in Caucasian CHB populations on entecavir/tenofovir),[15,16] mPAGE-B score (in Asian CHB patients on antiviral therapy),[17] PLAN-B prediction model (developed using artificial intelligence, in South Korean CHB patients on antiviral teraphy),[18] and the recently proposed PAGED-B score (from South Korean CHB patients treated with entecavir/tenofovir) (summarised in Table 1).[19] However, further work is needed to incorporate LSMs into these or new models, particularly by including populations from other continents to enhance the generalizability and applicability across diverse populations.

Increasingly, the use of concordant independent NITs (such as TE and other NITs for liver fibrosis, such as serum-based scores like fibrosis-4, aminotransferase to platelet ratio index, and ELF) is recommended to increase the confidence of a positive diagnosis of cirrhosis.[20] This would further increase the ability to stratify risk and customize surveillance strategies for CHB patients. While TE focuses on liver stiffness, serum-based tests offer additional "layers" of risk assessment, contributing to a more complete approach to managing CHB patients. Combining these NITs with imaging techniques can improve the accu-

Abbreviations:

CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; LSM, liver stiffness measurement; NIT, non-invasive test; RCT, randomized controlled trial; TE, transient elastography

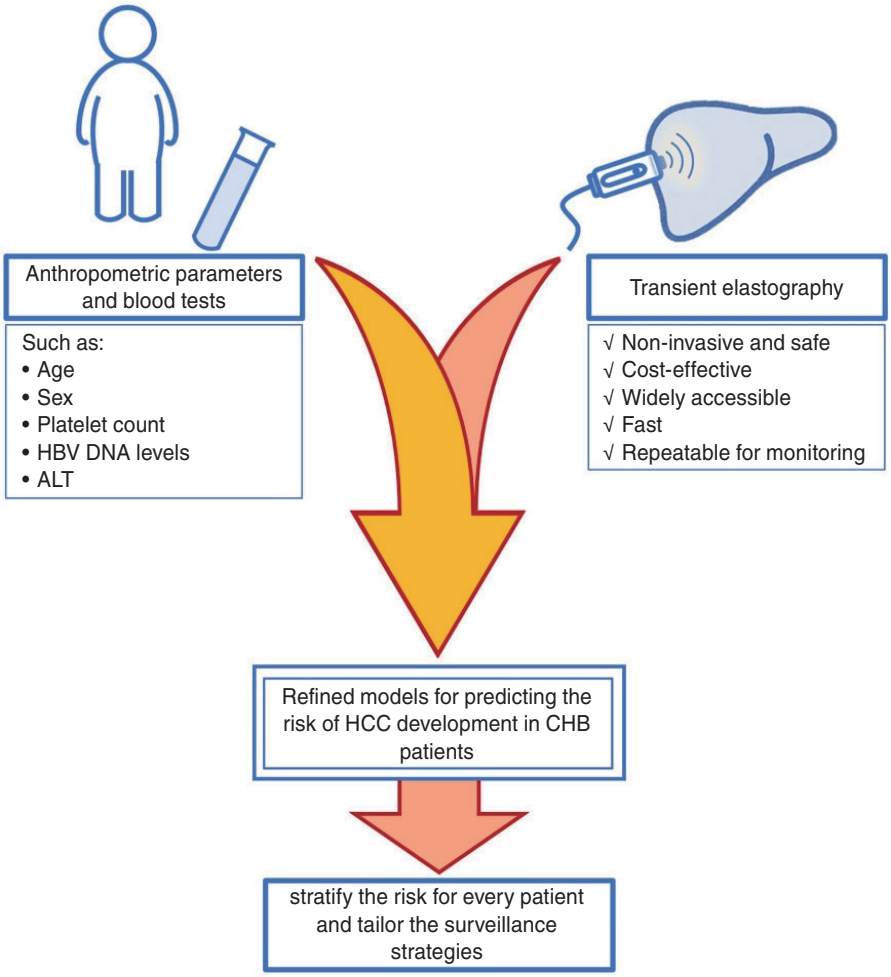

Figure 1. Rationale for combining the transient elastography with anthropometric parameters and blood tests. HBV, hepatitis B virus; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; CHB, chronic hepatitis B.

racy of risk prediction and facilitate more personalized patient management.[1,21-23]

While RCTs could offer a wider perspective, they may not be essential. Instead, future research should focus on the development of robust prediction models with comprehensive derivation and external validation, across different, heterogeneous populations, evaluating TE and other established risk factors. Such models would allow for more accurate risk stratification and tailored surveillance strategies, ultimately improving patient outcomes. Future research should also consider the overall effects of antiviral therapy on TE results and the overall risk of HCC development, and the engagement and adherence of the patients to surveillance protocols. Public health initiatives which aim at increasing awareness and access to TE and NITs could contribute to better management of CHB and reduce the global burden of HBV-related liver cancer.

In conclusion, while TE has demonstrated to be a valuable tool for assessing the risk of HCC development in patients with, its integration within existing risk scores will be pivotal in advancing patient care.

Authors' contribution

Both authors contributed equally to the preparation of this editorial. MZ conceived the idea and wrote the first draft. ET contributed to the content refinement and critical revision. Both authors approved the final version of the manuscript and agree to be accountable for its content.

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Table 1. Comparison of HCC risk of different prediction models available for CHB patients

Model name	Development population	Key parameters used	Target population	Notes
GAG-HCC score	Hong Kong cohort	Age, sex, HBV DNA levels, core promoter mutations, presence of cirrhosis	CHB patients, with/without cirrhosis Exclusion criteria: any form of established treatment for CHB (before or at the moment of enrolment); HCC on presentation, or other concomitant diseases including HCV or HDV infection, autoimmune hepatitis, Wilson's disease, primary biliary cirrhosis, alcoholic liver disease and fatty liver	Developed in Asian populations Proposed score cut-off: 101 Accuracies in 10-years prediction for the total study population: Se, 88.0%; Sp, 78.7%
HCC-CU score	Hong Kong cohort	Age, albumin, bilirubin, HBV DNA levels, presence of cirrhosis	CHB patients, with/without cirrhosis Exclusion criteria: antiviral therapy before enrolment; HCC on presentation or in medical history, Child-Pugh class C cirrhosis	Developed in Asian populations Proposed cut-offs: ≥20 to identify high risk of HCC development; ≤5 to exclude future HCC (NPV: 97.3 and 97.8% in the validation and training cohorts, respectively)
REACH-B	Asian CHB patients without cirrhosis (Hong Kong + South Korea cohorts)	Age, sex, ALT, HBeAg status, HBV DNA levels	CHB patients, between 30 and 65 years, without cirrhosis Exclusion criteria: age <30 or >65 years; HCV positivity; presence of cirrhosis; antiviral treatment during the study	Limited to non-cirrhotic patients; developed in Asian population 17-point risk score, for 3-, 5-, and 10-years risk of HCC development
THRI	Toronto cohorts (data on ethnic groups not available)	Age, sex, aetiology of cirrhosis, platelet count	Patients with biopsy-proven cirrhosis with multiple aetiologies Exclusion criteria: no confirmatory features at liver biopsy; HCC diagnosed within 6 months of referral; patients with Primary Sclerosing Cholangitis and cholangiocarcinoma	The study is performed on multiple aetiologies of cirrhosis, and not specifically for CHB patients Ethnic background of enrolled patients is not available Point-risk score for the 10-year cumulative HCC incidence: 3% (low-risk, <120 points); 10% (medium-risk, 120–240 points); 32% (high risk, >240 points) Recorded incidence per 1000 CHB patients-years: 26.2
PAGE-B risk score	Caucasian CHB patients under antiviral therapy	Age, sex, platelet count	CHB patients, with/without cirrhosis, who had received treatment with entecavir or tenofovir for at least 6 months Exclusion criteria: age<16 years, HCC diagnosed before the onset of antiviral therapy, coinfection with hepatitis D, hepatitis C or human immunodeficiency virus	Developed and validated in Caucasian populations; primarily for prediction of the 5-year HCC risk in Caucasian CHB under entecavir/tenofovir Proposed cut-off (for highest NPV): 10 points (Se, 100%; Sp, 19.6–41.2%; NPV, 100%) Cut-off for maximized sensitivity and specificity: 17 points (Se, 76.0%; Sp, 77.3%)

Table 1. Continued

Model name	Development population	Key parameters used	Target population	Notes
mPAGE-B risk score	Asian CHB population under antiviral therapy	Age, sex, platelet count, and serum albumin levels	CHB patients, with/without cirrhosis, including both patients naïve to antiviral therapy and patients who had previously received antiviral treatments with NAs other than entecavir and tenofovir Exclusion criteria: HCC diagnosed before the start of antiviral therapy; coinfection with hepatitis C, D or human immunodeficiency virus; active alcoholism, moderate or severe fatty liver at ultrasonography; liver transplant	Modification of PAGE-B for Asian populations under treatment Cut-off value that maximized both sensitivity and specificity for prediction of 5-years HCC development in the derivation cohort: 13 points (Se, 72.4%; Sp, 71.7%; NPV, 97.5%)
PLAN-B	South Korean CHB patients treated with antiviral therapy	Age, platelet count, antiviral agent used (ETV or TDF), sex, ALT, HBV DNA levels, albumin, bilirubin, and HBeAg status at baseline	CHB patients under antiviral therapy with entecavir or tenofovir for more than 6 months Exclusion criteria: development of HCC within 1 year of the initiation of the antiviral therapy; discordance between the indications for NA treatment according to the AASLD criteria and the actual initiation of NA treatment	AI-based model based on a gradient-boosting machine algorithm. Developed in South Korean population and validated in two external cohorts (Korean and Caucasian cohorts) Satisfactory discriminant function (c-index, 0.82)
PAGED-B	South Korean CHB patients treated with entecavir/tenofovir	Age, sex, platelet count, HBV DNA levels, diabetes status	CHB patients without cirrhosis, who started antiviral therapy with ETV/TDF Exclusion criteria: age <18 years; HBV DNA levels <20,000 IU/mL, or active hepatitis before the enrolment; HBeAg-negativity before the enrolment or at treatment starting; presence of cirrhosis; previous use of antiviral agents; other coinfections (HCV, HDV, HIV, or other hepatotropic viruses), or other liver diseases (alcoholism, moderate or severe fatty liver, or autoimmune hepatitis); anamnestic positivity for malignancy or organ transplantation; previous treatment with immunosuppressive agents; follow-up <1 year; HCC or liver transplantation during the first year of follow-up; interval between baseline HBV DNA measurement and antiviral therapy initiation >1 month	Integrates additional parameters to the original PAGE-B score; focused on Asian population 5-year HCC risk prediction in validation cohort: AUROC, 0.85; c-index, 0.87

HCC, hepatocellular carcinoma; CHB, chronic hepatitis B; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; Se, sensitivity; Sp, specificity; NPV, negative predictive value; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; ETV, entecavir; TDF, tenofovir disoproxil fumarate; NA, nucleos(t)ide analog; AASLD, American Association for the Study of Liver Diseases; HIV, human immunodeficiency virus; AUROC, area under the receiver operating characteristic curve.

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Conflicts of Interest

The authors have no conflicts to disclose.

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