BMC Gastroenterology

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Dynamic changes in liver stiffness measurement by 2D shear-wave elastography predict hepatocellular carcinoma in patients with chronic hepatitis B and well-controlled viremia: a retrospective study

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Abstract

Background Antiviral treatment reduces, but does not eliminate, the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). Predicting HCC risk in this population remains challenging. This study aimed to use dynamic changes in liver stiffness measurement (LSM) obtained using two-dimensional (2D) shear-wave elastography (SWE) to predict HCC in patients with non-cirrhotic and cirrhotic CHB who had well-controlled viremia.

Methods We retrospectively enrolled 303 patients with CHB (45 patients with cirrhosis) who had well-controlled viremia (hepatitis B virus DNA < 100 IU/mL for ≥ 6 months) during antiviral treatment. Patients were followed up every 3–6 months and had two to twelve reliable LSMs using 2D SWE. Clinical and laboratory variables, single LSM, change between two LSMs, and dynamic LSM changes were analyzed using least absolute shrinkage and selection operator and multivariable Cox regression analysis to identify risk factors for HCC. Dynamic LSM changes were classified into sustained low LSM (all LSMs ≤ 8.1 kPa), unstable LSM (LSM ≤ 8.1 kPa at least once and > 8.1 kPa at least once), and sustained high LSM (all LSMs > 8.1 kPa).

Results Among the 303 patients, 27 developed HCC. In the multivariable analysis, sustained high LSM in dynamic LSM changes (HR = 11.624, 95% CI: 4.241–31.861; $P < 0.001$; compared with sustained low LSM) and older age (HR = 1.046, 95% CI: 1.009–1.084; $P = 0.013$) independently predicted HCC. A novel model combining age and dynamic LSM changes achieved a C-index of 0.845 for internal validation, demonstrating reliable agreement between the

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predicted and observed probabilities of HCC development. The novel model showed better performance in non-cirrhotic patients with a C-index of 0.860, whereas the C-index was only 0.634 in cirrhotic patients.

Conclusions Dynamic LSM changes can predict HCC in patients with CHB who have well-controlled viremia, especially in non-cirrhotic patients.

Keywords Liver stiffness measurement, Dynamic changes, Hepatocellular carcinoma, Chronic hepatitis B, Well-controlled viremia, Two-dimensional shear-wave elastography

Introduction

An estimated 257 million people worldwide are infected with the hepatitis B virus (HBV) [1], which can lead to the development of hepatocellular carcinoma (HCC) [2]. Antiviral treatment is recommended for patients with chronic hepatitis B (CHB) [3–6]. However, even with effective treatment, the risk of HCC is reduced but not eliminated [4, 6], with reported annual HCC incidence ranging from 0.01 to 5.4% [7]. Therefore, it remains important to identify high-risk population of HCC, even after achieving well-controlled viremia through effective antiviral treatment.

Predicting HCC in patients undergoing antiviral treatment with well-controlled viremia is challenging due to their reduced risk. Consequently, only a few studies have focused on this population, and these studies have suggested an association between liver stiffness measurement (LSM) obtained by transient elastography (TE) and HCC development [8–11]. In contrast to TE, two-dimensional shear-wave elastography (2D SWE) is integrated into a traditional ultrasound system. LSM obtained using 2D SWE shows even better performance than TE-derived LSM for predicting HCC [12, 13]; however, the performance of 2D SWE-derived LSM in patients with CHB who had well-controlled viremia is currently unknown.

Most previous studies focused on a single LSM at a specific time point [14]. However, LSM changes may also be useful in predicting HCC development, and this is worth evaluating. Several studies have analyzed the correlation between changes in LSM measured by TE and the risk of HCC [9, 15, 16]. However, the patterns of LSM changes analyzed in these studies differed, leading to controversial results. Moreover, few studies have investigated the predictive value of changes in LSM obtained using 2D SWE for HCC development. Therefore, whether a single LSM or change in LSM value best correlates with HCC development remains to be clarified.

As patients with cirrhosis have a higher risk of HCC, many studies have focused on cirrhotic patients [9, 15–17], whereas few have examined patients without cirrhosis. However, 30–50% of HCC cases in HBV-endemic areas occur in the absence of cirrhosis [2]; therefore, HCC prediction in patients with non-cirrhotic CHB is an important topic that warrants further investigation.

Therefore, this retrospective study aimed to determine the usefulness of changes in 2D SWE-derived LSM values, particularly dynamic changes, during continuous follow-up in predicting HCC development in patients with CHB who had well-controlled viremia. Subgroup analyses were performed for patients without and with cirrhosis.

Methods

Study design

This retrospective study focused on patients with CHB who had undergone antiviral treatment and achieved well-controlled viremia. The main risk factor for HCC development analyzed was the dynamic changes in LSM measured by 2D SWE, which were obtained from at least two LSM values. Ethical approval for the study protocol was obtained from the ethics committee of our hospital (No. [2021]02-387-01). The need for informed consent was waived because this was a retrospective study.

Study population

Among the 609 patients with CHB who underwent 2D SWE for the first time in our hospital between 2016 and 2020, 303 who met the selection criteria were enrolled in this study (Fig. 1). The following inclusion criteria were applied: (a) age ≥ 18 years old, (b) undergoing antiviral treatment, (c) achievement of well-controlled viremia which was defined as HBV DNA < 100 IU/mL for more than 6 months, and (d) with at least 2 reliable LSMs. Patients with HCC before their second 2D SWE or a history of HCC, those who were co-infected with other hepatitis viruses (such as hepatitis C or D virus) or human immunodeficiency virus, and those with autoimmune or alcoholic liver disease were excluded.

LSM using 2D SWE

Experienced technicians performed 2D SWE according to the guidelines of the Society of Radiologists in Ultrasound Liver Elastography [18]. And the Aixplorer US system (SuperSonic Imagine) with an SC6-1 convex probe was used. A 4 × 3 cm elasticity box was placed in the parenchymal area without large vessels in the right lobe of the liver. Five measurements were obtained for each patient. A measurement was considered successful if more than two-thirds of the signal was obtained within

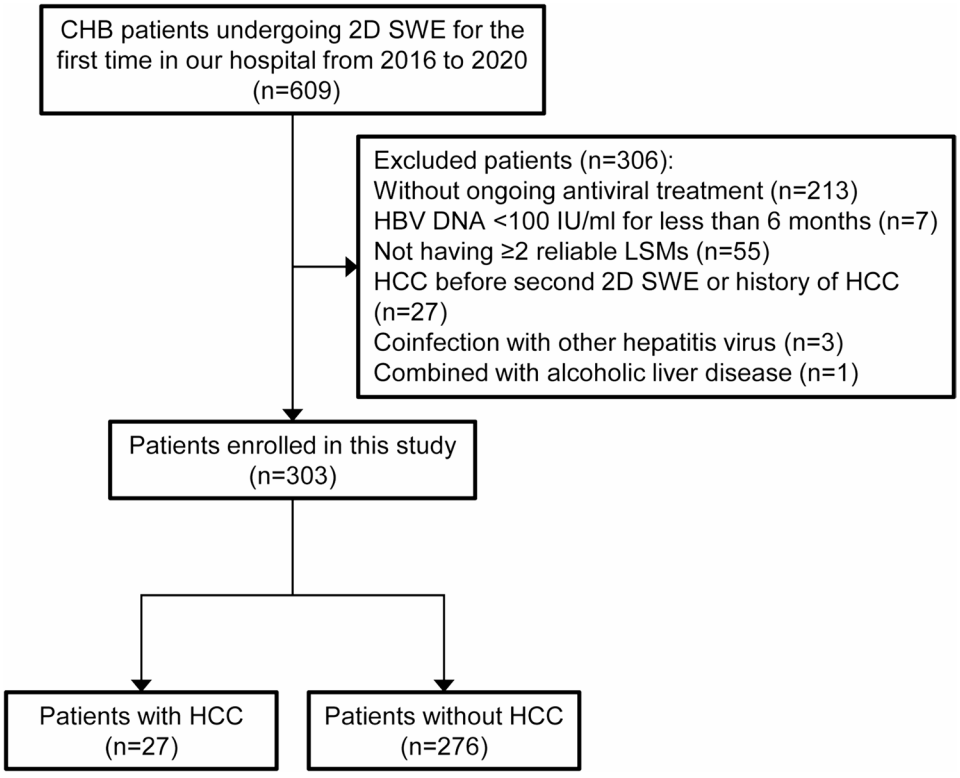

Fig. 1 Flowchart of patient enrollment in this study. CHB: chronic hepatitis B; 2D SWE: two-dimensional shear-wave elastography; LSM: liver stiffness measurement; HBV: hepatitis B virus; HCC: hepatocellular carcinoma

the box. Measurements were considered reliable when the success rate exceeded 60% according to our previous reports [19, 20]. The LSM is expressed as the median value in kilopascals (kPa).

LSM follow-up and LSM changes

LSM follow-up was performed every 3–6 months according to the guideline by the American Association for the Study of Liver Diseases [21]. The last LSM analyzed in this study was the value obtained at the final follow-up before the occurrence of HCC or the value obtained at the last follow-up in patients who did not develop HCC during the study period. For overall 303 patients, LSM values could have been missed during follow-up because of (a) failed 2D SWE measurements ($n=5$), (b) LSM using other machines ($n=8$), and (c) lack of LSM follow-ups at certain time points ($n=252$). Thus, the number of LSMs varied from two to twelve.

Since patients with fibrosis stage F3 are also at significant risk of HCC [22], we chose a cutoff value of 8.1 kPa (for diagnosing fibrosis stage F3 or worse) to classify dynamic LSM changes, based on a multicenter study focused on LSM using SuperSonic Imagine [23]. To classify the dynamic changes, all available LSM values for each patient, from the first to the last measurement, were compared with the cutoff value of 8.1 kPa. Based on this comparison, patients were stratified into the following three groups (Fig. 2): (a) all LSMs ≤ 8.1 kPa (sustained low LSM group), (b) LSM ≤ 8.1 kPa at least once and > 8.1 kPa at least once (unstable LSM group), and (c) all LSMs > 8.1 kPa (sustained high LSM group).

The change between two LSMs (the first and last) was analyzed qualitatively (decrease, no change, or increase) and quantitatively (absolute and relative changes). Cutoff values of 1 kPa and 30% were applied for the absolute and relative changes in LSM values, respectively, in the quantitative analysis, according to previous studies [24, 25].

Clinical follow-up and outcomes

We collected the clinical and laboratory data obtained within 3 days of the first LSM, including age, sex, cirrhosis diagnosis, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, alpha-fetoprotein (AFP), creatinine, and hepatitis B e antigen (HBeAg). Cirrhosis was clinically diagnosed in patients who met at least one of the following criteria: (a) ultrasound findings suggestive of cirrhosis, (b) serum albumin < 35 g/L, platelet count (PLT) < 100×10^9/L, international normalized ratio (INR) > 1.3, prolonged prothrombin time, AST-to-PLT ratio index > 2 (meeting two or more of the above criteria), or (c) evidence of portal hypertension [26].

Patients were followed up using ultrasonography, 2D SWE, and laboratory tests every 3–6 months. The primary outcome was the occurrence of HCC, which was

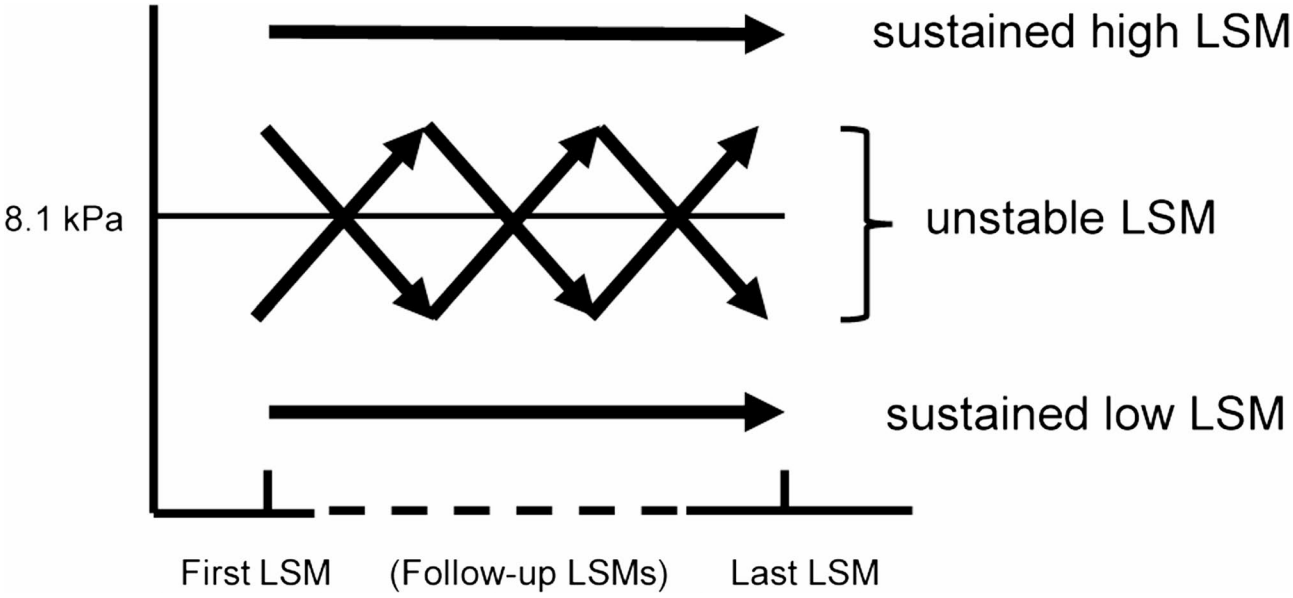

Fig. 2 Classification of dynamic LSM changes. For 20 patients without follow-up LSMs, classification of the dynamic LSM changes was based on the first and last LSM values. LSM: liver stiffness measurement

diagnosed via pathological examination or typical imaging findings using at least one contrast-enhanced imaging methods, including computed tomography, magnetic resonance imaging, or ultrasonography [22].

The follow-up time (analysis time) was defined as the time interval between the initiation of antiviral treatment and the occurrence of HCC or the last follow-up without HCC development. The follow-up was censored at 180 months.

Statistical analysis

All statistical analyses were conducted using the SPSS (v26.0) and R (v4.5) software packages. Data are expressed as medians with interquartile ranges (IQRs) or as numbers with percentages. Comparisons of continuous and categorical variables between different groups were performed using the Mann–Whitney U test and the χ^2 test (or Fisher's exact test), respectively. The cumulative incidence of HCC was calculated using the Kaplan–Meier method and compared using the log-rank test. To mitigate overfitting, least absolute shrinkage and selection operator (Lasso) regression was used to identify potential risk factors for HCC. The optimal regularization parameter (λ) was determined through 10-fold cross-validation using the minimum mean squared error criterion, with variables retained at the selected λ value. Variables screened by Lasso regression were further evaluated in the multivariable Cox regression analysis using the forward stepwise method. Hazard ratios (HRs), 95% confidence intervals (CIs), and P values were reported. The Cox proportional hazards regression model for HCC prediction was derived from multivariable analysis. Discrimination and calibration of the model were assessed using Harrell's C-index and a calibration curve. The C-indices of different models were compared using the R package "compareC". A nomogram was developed based on the final model. Internal verification of the model was performed using the bootstrap method and 5-fold cross-validation method. $P<0.05$ was considered to indicate statistical significance.

Results

The patient characteristics are shown in Table 1. Among the 303 patients, 238 (78.5%) were men, and the median patient age was 41.6 years (IQR, 35.2–50.0 years). Cirrhosis was detected in 45 patients at the time of the first LSM. There were 96 (31.7%) patients who tested positive for HBeAg. The median values of first and last LSMs were 5.9 kPa (IQR, 5.0–7.3 kPa) and 5.8 kPa (IQR, 4.9–7.1 kPa), respectively. The median LSM number per patient was 6 (IQR, 4–8). The number of patients with 2, 3, 4, 5, 6, 7, and ≥8 LSMs was 20 (6.6%), 40 (13.2%), 45 (14.9%), 43 (14.2%), 38 (12.5%), 39 (12.9%), and 78 (25.7%), respectively. The median interval time between the antiviral treatment initiation and the first LSM was 62.0 months (IQR, 34.0–100.0 months), and that between the first and last LSMs was 47.0 months (IQR, 33.0–57.0 months).

Clinical Outcomes

A total of 27 patients were diagnosed with HCC based on pathological examination (7 patients) or imaging findings (20 patients) during the follow-up period. The median follow-up time was 9.4 years (IQR, 6.8–12.6 years).

Table 1 Patient characteristics

Variable	All patients (*n* = 303)	Patients with HCC (*n* = 27)	Patients without HCC (*n* = 276)	*P*
Age (y)*	41.6 (35.2–50.0)	52.4 (47.8–62.1)	40.7 (33.8–49.2)	< 0.001
Sex*				0.379
Male	238 (78.5%)	23 (85.2%)	215 (77.9%)	
Female	65 (21.5%)	4 (14.8%)	61 (22.1%)	
Cirrhosis*	45 (14.9%)	13 (48.1%)	32 (11.6%)	< 0.001
AST (U/L) *	24.0 (20.0–29.0)	32.0 (26.0–36.0)	23.0 (20.0–28.0)	< 0.001
ALT (U/L) *	25.0 (19.0–33.0)	33.0 (26.0–47.0)	24.0 (19.0–31.0)	< 0.001
Albumin (g/L) *	48.0 (46.3–49.7)	46.7 (45.2–48.3)	48.1 (46.5–49.8)	0.005
Total bilirubin (μmol/L) *	13.1 (10.3–17.2)	13.4 (11.3–19.9)	13.0 (10.0–17.0)	0.335
Creatinine (μmol/L) *	80.0 (69.0–92.0)	86.0 (70.0–98.0)	80.0 (69.0–91.0)	0.188
HBeAg status*				0.268
Positive	96 (31.7%)	6 (22.2%)	90 (32.6%)	
Negative	207 (68.3%)	21 (77.8%)	186 (67.4%)	
AFP (ng/mL) *	2.3 (1.5–3.4)	2.9 (1.7–4.4)	2.2 (1.4–3.3)	0.041
LSM follow-up				
First LSM (kPa)	5.9 (5.0–7.3)	9.5 (7.1–16.8)	5.8 (5.0–7.0)	< 0.001
Last LSM (kPa)	5.8 (4.9–7.1)	9.1 (7.0–15.1)	5.6 (4.9–6.8)	< 0.001
Change between first and last LSMs				0.874
No change	10 (3.3%)	0 (0.0%)	10 (3.6%)	
Decrease	168 (55.4%)	15 (55.6%)	153 (55.4%)	
Increase	125 (41.3%)	12 (44.4%)	113 (40.9%)	
Change between first and last LSMs (1 kPa)				0.018
−1 kPa to 1 kPa	166 (54.8%)	8 (29.6%)	158 (57.2%)	
< −1 kPa	83 (27.4%)	11 (40.7%)	72 (26.1%)	
> 1 kPa	54 (17.8%)	8 (29.6%)	46 (16.7%)	
Change between first and last LSMs (30%)				0.385
−30–30%	248 (81.8%)	20 (74.1%)	228 (82.6%)	
< −30%	27 (8.9%)	3 (11.1%)	24 (8.7%)	
> 30%	28 (9.2%)	4 (14.8%)	24 (8.7%)	
Dynamic LSM changes				< 0.001
Sustained low LSM	197 (65.0%)	6 (22.2%)	191 (69.2%)	
Unstable LSM	76 (25.1%)	7 (25.9%)	69 (25.0%)	
Sustained high LSM	30 (9.9%)	14 (51.9%)	16 (5.8%)	

Data shown are expressed as medians (interquartile ranges) or numbers (percentages)

HCC Hepatocellular carcinoma, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *HBeAg* Hepatitis B e antigen, *AFP* alpha-fetoprotein, *LSM* Liver stiffness measurement

*Data were collected at the time of the first LSM

In the overall cohort, the cumulative incidence rates of HCC were 3.4%, 7.1%, 10.8%, and 17.9% at 6, 9, 12, and 15 years, respectively (Fig. 3A), with an annual incidence rate of 0.6%. The cumulative incidence rates of HCC at 6, 9, 12, and 15 years in patients without cirrhosis were 1.2%, 4.1%, 6.7%, and 13.0%, respectively (Fig. 3B), with an annual incidence of 0.4%, whereas those in patients with cirrhosis were 15.9%, 24.1%, 33.1%, and 46.5%, respectively (Fig. 3B), with an annual incidence of 2.2%. The cumulative incidence rate of HCC in patients with cirrhosis was significantly higher than that in patients without cirrhosis ($P < 0.001$; Fig. 3B).

Lasso regression and multivariable Cox regression analyses of risk factors for HCC

All 16 variables in Table 1 were included in the Lasso regression. Since four of 16 variables were three-category variables, which required dummy encoding (two variables per category), Lasso regression evaluated 20 variables in total. Figure 4A shows that as the regularization parameter λ increases, the coefficients of some weak variables shrink progressively toward zero, and the strongest variables remain in the model. Four significant variables including age, AST, last LSM, and sustained high LSM in dynamic LSM changes were selected using the minimum criterion (left dashed vertical line in Fig. 4B). In the multivariable Cox regression analysis, older age (HR = 1.046, 95% CI: 1.009–1.084; $P = 0.013$), and sustained high LSM values (HR = 11.624, 95% CI: 4.241–31.861; $P < 0.001$; compared with sustained low LSM values) in dynamic LSM changes were identified as independent risk factors for HCC development (Table 2).

Nomogram and performance of the novel model for HCC prediction

Based on the multivariable Cox regression analysis, we constructed a novel model incorporating age and dynamic LSM changes. A nomogram using the novel model is shown in Fig. 5: for instance, a 40-year-old patient (contributing 31 points) with sustained high LSM values (contributing 85 points) would have a total score of 116 points and estimated HCC-free survival probabilities of approximately 89%, 79%, 70%, and 51% at 6, 9, 12, and 15 years, respectively. Through the internal validation, the novel model achieved a C-index of 0.845 with bootstrap method and 0.843 with 5-fold cross-validation. The calibration curve demonstrated good agreement between the predicted and observed probabilities of HCC development (Fig. 6).

Comparison of the performance of the novel model and previous models

We compared the discrimination performance of our novel model with that of three other models for HCC

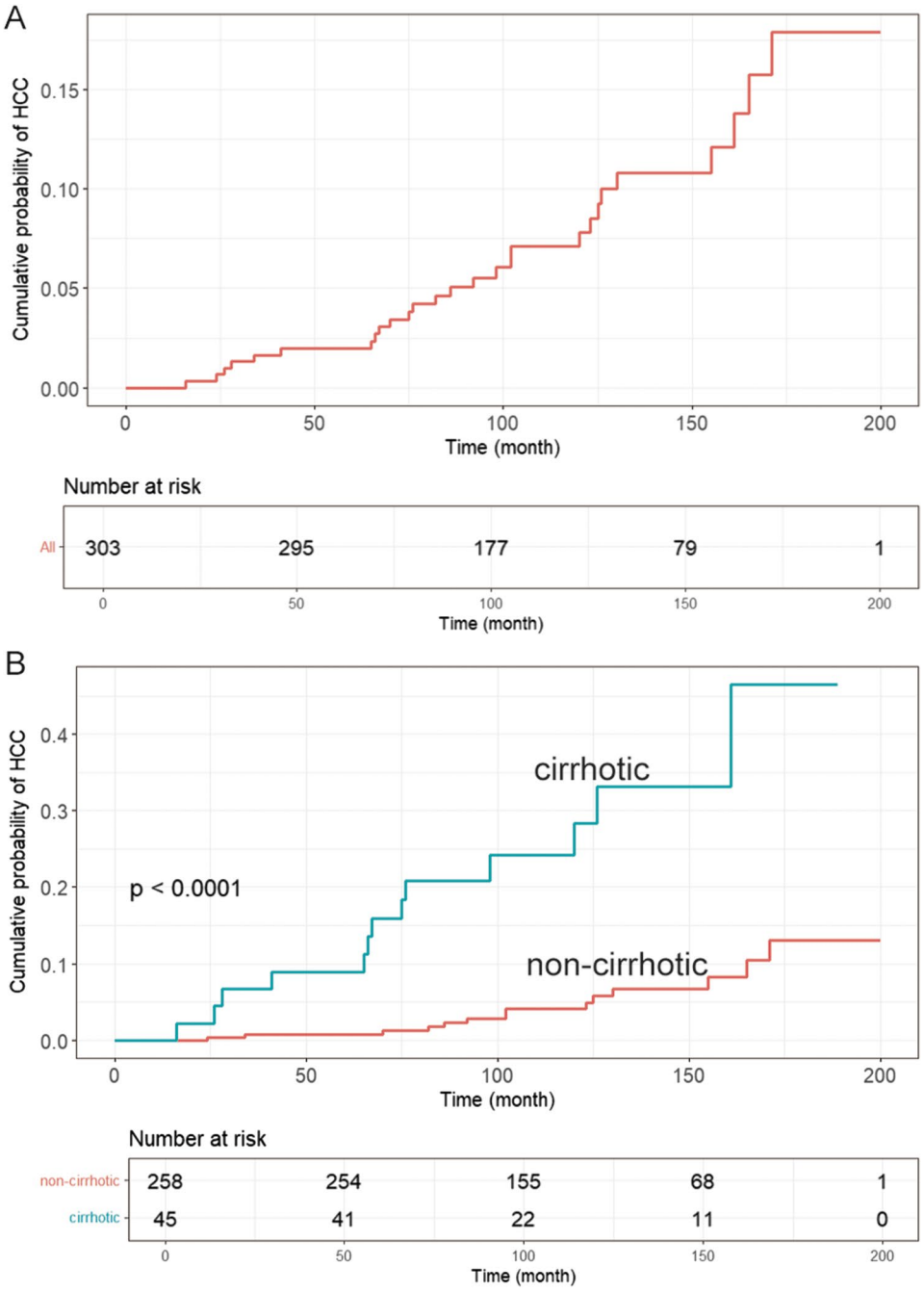

Fig. 3 Cumulative incidence of HCC in (**A**) overall patients and (**B**) cirrhotic and non-cirrhotic patients. HCC: hepatocellular carcinoma

development, including the SAGE-B (comprising LSM and age) [27], HCC-RESCUE (comprising age, sex, and cirrhosis) [28], and REACH-B II model (comprising age, sex, ALT, HBeAg, and LSM) [8]. The novel model performed better than the SAGE-B model (0.758, $P = 0.042$). The C-index of the novel model was slightly, but not significantly, higher than that of the HCC-RESCUE (0.814, $P = 0.430$) and REACH-B II model (0.822, $P = 0.480$).

Subgroup analyses in non-cirrhotic and cirrhotic patients

During follow-up, 14 and 13 patients developed HCC in the non-cirrhotic ($n = 258$) and cirrhotic subgroups ($n = 45$), respectively. We evaluated the performances of our novel model (comprising age and dynamic LSM changes) in both subgroups. In the non-cirrhotic subgroup, the novel model showed good performance with a C-index of 0.860. However, the C-index of the novel model in the cirrhotic subgroup was only 0.634.

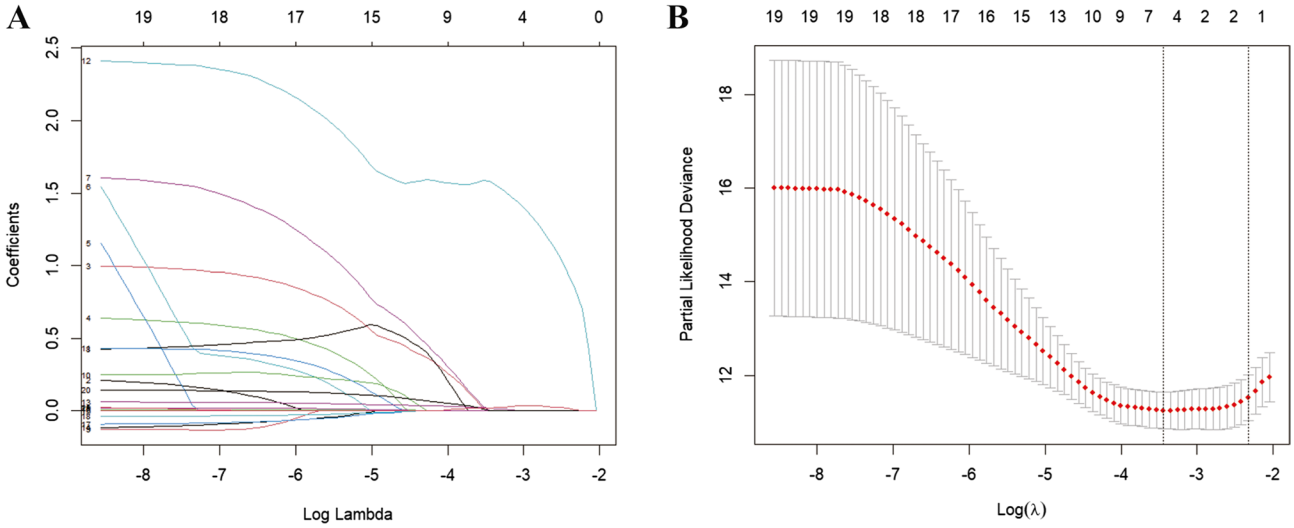

Fig. 4 Risk factors selection using the least absolute shrinkage and selection operator (LASSO) regression. (**A**) The plot shows coefficient distributions of 20 variables across different levels of regularization parameter (lambda). Originally, 16 variables were included into analysis, but four of these were three-category variables, which required dummy encoding (two variables per category). Thus, Lasso regression evaluated 20 variables in total. (**B**) Ten-fold cross-validation for regularization parameter (λ) selection in the LASSO model. Dashed vertical lines indicate the optimal λ values chosen by the minimum criterion (left line) and the 1-standard-error criterion (right line)

Table 2 Multivariable Cox regression analysis of risk factors for HCC development in overall patients

Characteristics	HR	95% CI	*P*
Age (y)	1.046	1.009, 1.084	0.013
AST (U/L)			0.171
Last LSM (kPa)			0.869
Dynamic LSM changes			
Sustained low LSM	Reference		
Unstable LSM	2.225	0.712, 6.950	0.169
Sustained high LSM	11.624	4.241, 31.861	< 0.001

HCC Hepatocellular carcinoma, *HR* Hazard ratio, *CI* Confidence interval, *AST* Aspartate aminotransferase, *LSM* Liver stiffness measurement

Discussion

In the present study, individual LSM values obtained using 2D SWE (that is, the first and last measurements), different patterns of change between the first and last LSMs, and dynamic LSM changes were entered into the analysis for HCC prediction. Only sustained high LSM (all LSMs > 8.1 kPa) in dynamic LSM changes independently predicted HCC occurrence in patients with CHB who received antiviral treatment and had well-controlled viremia. The predictive value of dynamic LSM changes was also demonstrated in non-cirrhotic patients.

This study focused on patients with CHB who had well-controlled viremia and a reduced risk of HCC. In our cohort, the annual HCC incidence rates were 0.4% and 2.2% in non-cirrhotic and cirrhotic patients, respectively, which are consistent with previously reported rates (0.01–1.4% in non-cirrhotic patients and 0.9–5.4% in cirrhotic patients). Considering that HCC surveillance is considered cost-effective when the annual risk for HCC exceeds 0.2% [6], identifying risk factors can help to pinpoint high-risk populations and improve follow-up strategies for these patients. Four studies focusing on this population have found that LSM is an independent risk factor for HCC [8–11]. However, LSM values can vary during treatment; therefore, the usefulness of LSM changes in predicting HCC warrants investigation. Specifically, it is necessary to determine whether a single or multiple LSMs should be used for HCC prediction.

Several studies have analyzed the correlation between changes in LSM and HCC development. One study showed that an increase in LSM values between the first and second measurements correlated with HCC development [15]. Another study reported that the absolute change between two LSMs was smaller in patients who progressed to HCC [16]. However, another study by Wang et al. [9] found that neither the absolute nor the relative change between the first and last LSMs was associated with HCC development, which aligns with our results. The study by Wang et al. also analyzed the difference in HCC incidence among four groups based on dynamic LSM changes, and found that patients with persistent LSM ≥ 21.5 kPa had a higher incidence rate of HCC than those with persistent LSM < 21.5 kPa, but the difference was not statistically significant [9]. In our study, dynamic LSM changes were classified into three patterns using a cut-off value of 8.1 kPa: sustained low LSM, unstable LSM, and sustained high LSM. We found that sustained high LSM values were significantly associated with HCC development. The difference between our finding and the result reported by Wang et al. may be attributed to the following reasons. First, LSM was

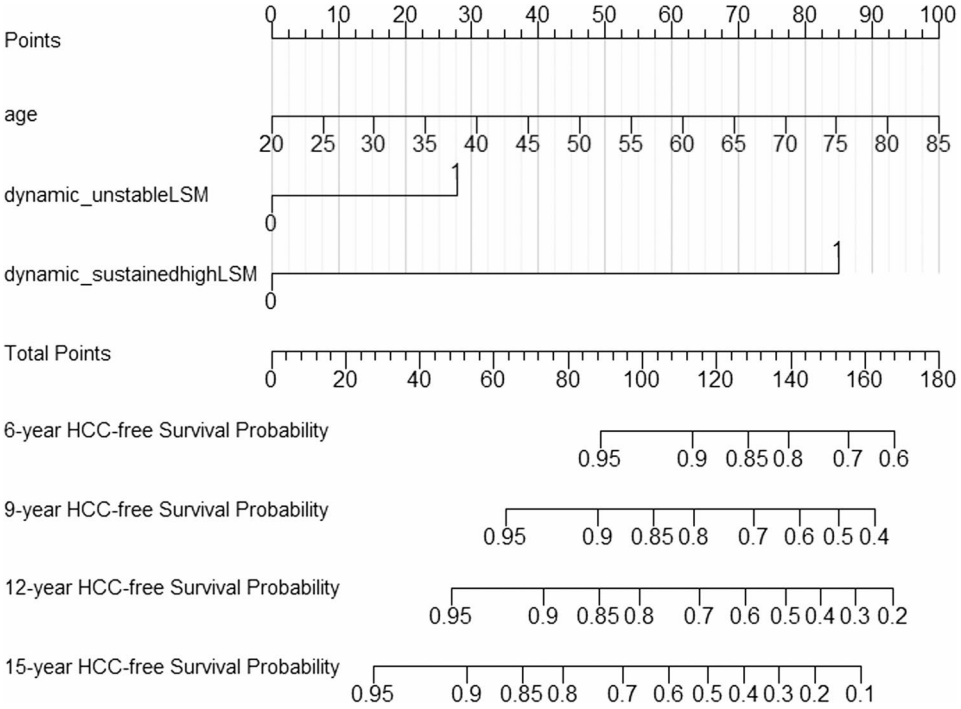

Fig. 5 Nomogram using our novel model to predict the HCC-free survival probability for patients with well-controlled viremia. For instance, a 40-year-old patient (contributing 31 points) with sustained high LSM values (contributing 85 points) would have a total score of 116 points and estimated HCC-free survival probabilities of approximately 89%, 79%, 70%, and 51% at 6, 9, 12, and 15 years, respectively. CHB: chronic hepatitis B; LSM: liver stiffness measurement; HCC: hepatocellular carcinoma

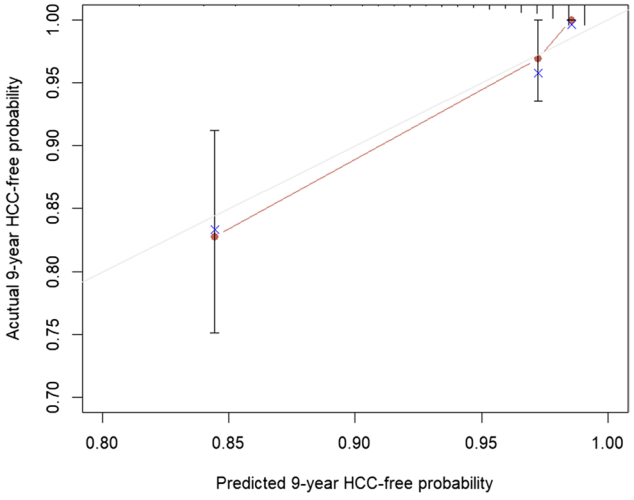

Fig. 6 Calibration curve of our model (comprising age and dynamic LSM changes) on internal validation. LSM: liver stiffness measurement

performed using 2D SWE rather than TE in our study. Studies have shown that LSM using 2D SWE outperforms TE-based LSM for liver fibrosis staging and HCC prediction [13]. Second, our patient cohort consisted mainly of patients without cirrhosis (85.1%), whereas only patients with cirrhosis were enrolled in the study by Wang et al. [9]. Patients without cirrhosis usually have a low stage of liver fibrosis and low LSM values. In non-cirrhotic patients, sustained high LSM values may indicate advanced liver fibrosis, which is associated with HCC development.

Our previous study by Zhang et al. [13] reported that baseline LSM using 2D SWE was associated with HCC development. In this study, we focused on dynamic changes in LSM obtained using 2D SWE, and found that sustained high LSM in dynamic LSM changes, rather than a single LSM, was significantly associated with HCC in the multivariable analysis. This suggests that repeated LSM might be necessary, and that patients with sustained high LSM values require close follow-up.

In our study, the model combining dynamic changes in LSM on 2D SWE with age demonstrated good predictive performance for HCC, with a C-index of 0.845, and reliable agreement between the predicted and observed probabilities in the calibration curve. Several HCC risk prediction models have been developed for patients undergoing antiviral treatment, including the PAGE-B (comprising age, sex, and PLT) [29], modified PAGE^{LS}-B (comprising age, sex, PLT, and LSM) [30], CAGE-B (comprising cirrhosis, LSM, and age) [27], CAMPAS (comprising cirrhosis, age, sex, PLT, albumin, and LSM) [10], and ACCESS-HCC (comprising age, cirrhosis, consumption of ethanol, LSM, and ALT) [31]. Our model, which incorporates age and sustained high LSM, shows similar discrimination (C-index, 0.845) to the range reported by

these models (0.76–0.88). Furthermore, we compared the performance of our model with that of several previous models using our data. The results showed that our model outperformed the SAGE-B model in predicting HCC (C-index, 0.845 vs. 0.758, $P = 0.042$), and the C-index of our model was slightly better than those of the HCC-RESCUE and REACH-B II model (0.845 vs. 0.814 vs. 0.822, $P > 0.05$).

In the subgroup analysis, we found that our model also had good performance in non-cirrhotic patients with a C-index of 0.860. However, the performance of our model in cirrhotic patients was not satisfactory, with a C-index of 0.634, which is probably attributed to the limited sample size ($n = 45$). The sustained low LSM group in the cirrhotic subgroup had especially few cases, with only two patients with HCC and zero patients without HCC. Therefore, the predictive value of our model in cirrhotic patients requires further exploration in future studies with larger sample sizes.

Our study has some limitations. First, this was a retrospective study, and the timing of LSMs was not exactly the same for each patient. Therefore, the appropriate number and duration for LSM follow-up could not be precisely determined, and a prospective study is needed to explore this topic. Second, the number of patients who developed HCC was small ($n = 27$), which may be attributed to a reduced risk of HCC in the enrolled patients with well-controlled viremia. Future studies should extend the follow-up period and enroll larger cohorts to validate the model's accuracy. Third, the appropriate cutoff value when using other elastography equipment may be different. Whether the cutoff value of 8.1 kPa can be applied for other equipment needs to be further explored. In addition, our predictive model was developed from a single dataset. External validation and calibration in independent cohorts are necessary before clinical implementation. In the future, a multicenter prospective study with large sample size is needed to validate our findings. Forth, in the unstable group, patients may have different LSM change trends (e.g. increasing vs. decreasing), and the increasing trend might be associated with HCC development. However, the varying number of measurements prevented reliable stratification of these trends. This limits our ability to assess how direction changes affect HCC risk. Future studies should address this by implementing standardized measurement protocols and applying mixed-effects models. Finally, the enrolled patients did not undergo liver biopsy and cirrhosis was diagnosed only clinically. In the non-cirrhotic subgroup, some patients might have had significant fibrosis. The performance of our model in non-cirrhotic and cirrhotic patients should be validated in a cohort where liver biopsy is used as the diagnostic standard.

In conclusion, dynamic changes in LSM obtained using 2D SWE, rather than a single LSM value or a change between the 2 LSMs, were strongly associated with the risk of HCC development in patients with CHB who had well-controlled viremia. Our novel model, which incorporates dynamic LSM changes and age, can predict HCC development in patients with non-cirrhotic CHB who had well-controlled viremia and help identify high-risk patients who may require enhanced HCC surveillance.

Abbreviations

HBV	Hepatitis B virus
CHB	Chronic hepatitis B
HCC	Hepatocellular carcinoma
LSM	Liver stiffness measurement
2D SWE	Two-dimensional shear-wave elastography
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
HBeAg	Hepatitis B e antigen
AFP	Alpha-fetoprotein
HR	Hazard ratio
CI	Confidence interval

Acknowledgements
We would like to thank Mrs. Ling Jin for her assistance in the data analysis.

Authors' contributions
NW, YW, YC, and LW contributed to the study conception and design. Material preparation and data collection were performed by NW, YW, MX, YJ, JW, MW, JC, LS, ZS, YC, and LW. Data analysis was performed by NW. The first draft of the manuscript was written by NW and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding
This work was supported by 5010 Clinical Research Project of Sun Yat-sen University (No. 2016009), Science and Technology Program of Guangzhou (No. 2023A03J0728), and National Natural Science Foundation of China (No. 82202191).

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committee of Third Affiliated Hospital of Sun Yat-Sen University (No. [2021]02-387-01) and performed in accordance with the Declaration of Helsinki. Because this was a retrospective study, ethics committee of Third Affiliated Hospital of Sun Yat-Sen University waived the need for informed consent to participate.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 12 February 2025 / Accepted: 24 July 2025
Published online: 11 August 2025

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