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Editorial Board Member of *World Journal of Hepatology*, Igor Skrypnyk, MD, MDS, PhD, Professor, Internal Medicine #1, Poltava State Medical University, Poltava 36011, Ukraine. inskrypnyk@gmail.com

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ORIGINAL ARTICLE

Retrospective Study

Liver stiffness in hepatocellular carcinoma and chronic hepatitis patients: Hepatitis B virus infection and transaminases should be considered

Jia-Yao Huang, Jian-Yun Peng, Hai-Yi Long, Xian Zhong, Yu-Hua Xie, Lu Yao, Xiao-Yan Xie, Man-Xia Lin

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Jia-Yao Huang, Jian-Yun Peng, Hai-Yi Long, Xian Zhong, Yu-Hua Xie, Lu Yao, Xiao-Yan Xie, Man-Xia Lin, Department of Medical Ultrasonics, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, Guangdong Province, China

Corresponding author: Man-Xia Lin, PhD, Doctor, Professor, Department of Medical Ultrasonics, The First Affiliated Hospital, Sun Yat-sen University, No. 58 Zhongshan Road II, Yuexiu District, Guangzhou 510080, Guangdong Province, China. linmxia@mail.sysu.edu.cn

Abstract

BACKGROUND

Liver condition is a crucial prognostic factor for patients with hepatocellular carcinoma (HCC), but a convenient and comprehensive method to assess liver condition is lacking. Liver stiffness (LS) measured by two-dimensional shear wave elastography may help in assessing liver fibrosis and liver condition. Chronic hepatitis B (CHB) is an important risk factor for HCC progression, but LS was found to be less reliable in assessing liver fibrosis following hepatitis viral eradication. We hypothesize that the status of hepatitis virus infection would affect the accuracy of LS in assessing the liver condition.

AIM

To test the feasibility and impact factors of using LS to assess liver condition in patients with HCC and CHB.

METHODS

A total of 284 patients were retrospectively recruited and classified into two groups on the basis of serum CHB virus hepatitis B virus (HBV)-DNA levels [HBV-DNA ≥ 100.00 IU/mL as Pos group (n = 200) and < 100.00 IU/mL as Neg group (n = 84)]. Correlation analyses and receiver operating characteristic analyses were conducted to evaluate the relationship between LS and liver condition.

RESULTS

A significant correlation was found between LS and most of the parameters considered to have the ability to evaluate liver condition (P < 0.05). When alanine aminotransferase (ALT) concentrations were normal (≤ 40 U/L), LS was correlated with liver condition indices (P < 0.05), but the optimal cutoff of LS to

identify a Child-Pugh score of 5 was higher in the Neg group (9.30 kPa) than the Pos group (7.40 kPa). When ALT levels were elevated (> 40 U/L), the correlations between LS and liver condition indices were not significant (P > 0.05).

CONCLUSION
LS was significantly correlated with most liver condition indices in patients with CHB and HCC. However, these correlations varied according to differences in HBV-DNA and transaminase concentrations.

Key Words: Liver function; Liver stiffness; Elastography; Chronic hepatitis B; Hepatocellular carcinoma

Core Tip: Liver stiffness measurement by two-dimensional shear wave elastography was significantly correlated with most liver condition indices in patients with chronic hepatitis B and hepatocellular carcinoma, but these correlations varied according to differences in hepatitis virus DNA and transaminase concentrations.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major type of liver cancer with high morbidity and mortality rates. It is the sixth most common cancer and causes approximately 830000 deaths annually[1,2]. Liver condition is a crucial prognostic factor in the current tumor stratification for HCC patients[3,4]. A thorough and precise assessment of the liver condition is essential for tailoring the treatment strategy[5]. Traditionally, the Child-Pugh (CP) classification was widely used to evaluate liver conditions. However, it was found to be inadequate at accurately assessing liver condition and was omitted from the latest version of the Barcelona Clinic Liver Cancer (BCLC) guidelines[3]. Thus, many new methods have been developed over recent years to evaluate liver conditions[5,6]. However, a convenient and comprehensive method for assessing liver condition remains lacking.

Two-dimensional shear wave elastography (2D-SWE) is a new ultrasound (US) elastic technique that is used to evaluate the fibrosis stage in chronic hepatitis B (CHB)[7,8]. Studies have demonstrated that an elevated level of liver stiffness (LS), as determined using 2D-SWE, is also associated with the occurrence of surgical complications, including post-hepatectomy liver failure (PHLF)[9-14]. A preoperative model based on LS data exhibited discrimination abilities with a C-index of 0.824 of PHLF[12]. Because of the relevance of liver fibrosis and overall liver condition[15] and the prognostic value of preoperative liver condition in predicting postoperative complications[16], there is growing interest in using LS data to assess preoperative liver condition.

Although LS measurements are highly valuable for staging liver fibrosis, studies have shown that LS is affected by inflammation associated with active hepatitis, complicating the assessment of liver fibrosis[17-20]. In Asia, hepatitis B virus (HBV) infection is highly prevalent, the leading cause of cirrhosis, and an important risk factor for HCC development[21]. However, LS was found to be less reliable in assessing liver fibrosis following viral eradication[22]. Thus, we hypothesize that the stages of hepatitis virus infection affect the accuracy of LS in assessing liver condition. However, to the best of our knowledge, studies on this topic are limited.

The present study examined the feasibility of using LS, measured by 2D-SWE, to assess liver condition in patients with HCC and CHB, considering various stages of hepatitis virus infection and different levels of HBV-DNA.

MATERIALS AND METHODS

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The protocol of this single-center retrospective study was in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board (Approval No. [2019]046), and the need for written informed consent was waived for the retrospective analysis.

Patient selection

From August 2018 to May 2021, 284 treatment-naive patients with HCC and CHB were consecutively enrolled in this

retrospective study. The inclusion criteria were as follows: (1) Age ≥ 18 years, male or female; (2) A diagnosis of CHB; (3) HCC diagnosed at stages 0 to B in accordance with the BCLC guidelines; and (4) Completion of the 2D-SWE examination of the liver parenchyma and HBV-DNA testing before any HCC treatment. The exclusion criteria were as follows: (1) A history of liver resection for any reason; (2) Coinfection with hepatitis C virus (HCV); (3) Alcohol abuse; (4) Prior liver transplantation; (5) Pregnancy or lactation; (6) Severe complications of heart, lung, kidney, brain, or hematological diseases or other important systemic diseases, including acquired immune deficiency syndrome; or (7) An unsuccessful 2D-SWE examination.

CHB was diagnosed in accordance with the guidelines for managing CHB[23], which include being seropositive for hepatitis B surface antigen and/or HBV-DNA positive for 6 months or longer, and exhibiting hepatic necroinflammatory features caused by persistent HBV infection, such as persistently or repeatedly elevated alanine aminotransferase (ALT) levels or hepatitis identified through biopsy. HCC was diagnosed either pathologically or noninvasively in accordance with the American Association for the Study of Liver Diseases clinical practice guidelines for HCC (2018 Edition)[4]. HCC was classified using the BCLC staging system[3]. Alcohol abuse was defined as the recurrence of clinically significant impairments within 12 months, including failure to fulfil major role obligations, use in hazardous situations, alcohol-related legal problems, or social or interpersonal problems caused or exacerbated by alcohol[24].

The recruited patients were divided into two groups based on HBV-DNA levels. Using the local minimum testing threshold of 100.00 IU/mL, we classified those with HBV-DNA levels of ≥ 100.00 IU/mL into the HBV-DNA positive group (Pos group) and those with levels below this threshold into the HBV-DNA negative group (Neg group). The recruitment flowchart is shown in Figure 1.

Data collection

Forty baseline items were collected, including clinical characteristics (demographics, blood chemistry, and virological analyses), radiological traits, and histopathologic data. Histopathologic data was collected after liver biopsy or surgery of HCC. Clinical characteristics and radiological traits were obtained within 1 week before HCC treatment, and for those data, there were not any treatments or important changes in the dominating diseases during the interval between the LS measurement and the other data acquisition.

Splenomegaly was defined as craniocaudal length exceeding 12 cm, as measured through computed tomography or magnetic resonance imaging. Composite indices, including CP score, albumin-bilirubin (ALBI) score, Model for End-Stage Liver Disease (MELD) score, and fibrosis-4 score, were calculated according to specific formulae (Supplementary Table 1). Pathological cirrhosis was diagnosed as stage F4 using the METAVIR classification system in patients with available histological data. For patients without histological data, records of cirrhosis were not included.

LS

Liver 2D-SWE examinations were conducted based on the needs of clinical doctors and patients and the data were retrospectively collected. The 2D-SWE examinations of LS were conducted after a fasting period of more than eight hours and a complete abdominal US examination. Measurements were performed using the Aixplorer US system (SuperSonic Imagine, Aix-en-Provence, France) with a convex broadband probe (SC6-1, 1-6 MHz) by one of three experienced radiologists. Each radiologist had more than 10 years of experience in US and had performed more than 100 2D-SWE examinations. The radiologists were blinded to the clinical and biochemical data of the patients. The patients were placed in the supine position and asked to hold their breath momentarily during the examination. The test site was selected as the liver parenchyma away from large vascular structures and ducts (diameter ≥ 3 mm) and at least 5 cm from the tumor in the liver, preferentially in the right lobe if accessible. Upon switching to the elasticity imaging mode, the probe was positioned over a sampling frame measuring 4.0 cm × 3.0 cm, located 1.5-2.0 cm beneath the liver capsule. The region of interest was set at 1.5 cm × 2.0 cm, and the scale was adjusted to 40 kilopascals (kPa). Five independent measurements were obtained for each patient once the elastography performance became stable and the color filling in the sampling frame exceeded 75%. The measurements (in kPa) were considered successful only when the interquartile range was < 30% of the median value[20]. The median of the five mean values of LS (Emean) was then used as the representative measurements.

Statistical analysis

Data are presented as the mean ± SD, median (range), or frequency (percentage) as appropriate. Continuous variables were compared using the student *t*-test or Mann-Whitney *U* test, whereas categorical variables were compared using the chi-square test or Fisher's exact test as needed. The correlation between LS and parameters related to liver condition was analyzed using Pearson's or Spearman's correlation coefficients (*r*). Receiver operating characteristic (ROC) curves were used to identify the optimal cutoffs for LS and to assess the discrimination ability of LS based on the area under the ROC curves. The cutoff value of the ROC curve was calculated according to the Youden Index (sensitivity + specificity-1), where the index reached its maximum value corresponded to the optimal cutoff value of the ROC curve. Box plots, scatter diagrams, and regression lines were used to illustrate the correlations between the indices as appropriate. A two-sided *P*-value < 0.05 was considered statistically significant. All analyses were conducted using SPSS version 25.0 software (IBM Corporation, Armonk, NY, United States) and MedCalc version 20.1 software (MedCalc, Mariakerke, Belgium).

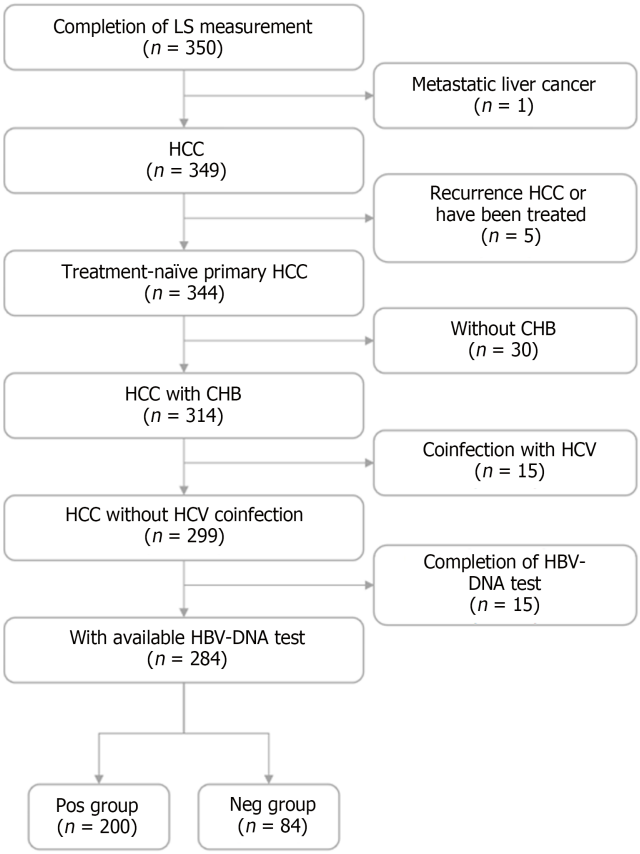

Figure 1 Flow chart of recruitment of patients. LS: Liver stiffness; HCC: Hepatocellular carcinoma; CHB: Chronic hepatitis B; HCV: Hepatitis C virus; HBV: Hepatitis B virus; Pos group: HBV-DNA positive group; Neg group: HBV-DNA negative group.

RESULTS

Patient characteristics

Among the 284 patients, 200 (70.4%) were classified in the Pos group and 84 (29.6%) in the Neg group. The study population consisted of 259 (91.2%) males and 25 (8.8%) females. The mean age of the patients was 53.26 ± 11.40 (range 25 to 83) years. The baseline concentrations of inflammatory markers, including ALT and aspartate aminotransferase (AST), were significantly higher in the Pos group than in the Neg group (all $P < 0.05$). Most of the patients were classified as having CP grade A [257 (90.5%) patients] and ALBI grade 2 [179 (63.0%) patients]. No significant differences in CP scores were observed between the groups ($P = 0.200$), but a significant difference in ALBI scores was noted between the groups ($P = 0.036$). The size of the HCC lesion was significantly larger in the Pos group [6.25 (0.70-21.60) cm] than in the Neg group [4.00 (1.10-18.00) cm, $P < 0.001$]. However, the number of lesions did not significantly differ between the two groups ($P = 0.125$), and most of the included patients had a single HCC lesion (73.6%). Moreover, no significant difference in BCLC stage was observed between the groups ($P = 0.082$), and most of the patients were at BCLC stage A (71.5%). Although all the patients had CHB, only 97 (34.2%) underwent antiviral treatment before recruitment. The median Emean was 9.60 kPa (9.65 kPa in the Pos group *vs* 9.15 kPa in the Neg group), and no significant difference in LS was observed between the groups ($P = 0.453$). Details of these baseline characteristics are listed in Table 1.

Correlation between LS and liver condition

In both the Pos and Neg groups, a significant correlation was found between LS and most of the parameters considered to have the ability to evaluate liver condition ($P < 0.05$; Table 2, Figure 2). A weak correlation was found between Emean and CP score ($r = 0.25$ and $P < 0.001$ in the Pos group and $r = 0.24$ and $P = 0.026$ in the Neg group). Furthermore, a weak correlation was noted between Emean and ALBI scores ($r = 0.35$ and $P < 0.001$ in the Pos group and $r = 0.27$ and $P = 0.012$ in the Neg group). In addition, we observed a significant correlation between Emean and ALBI grade ($r = 0.24$ and $P < 0.001$ in the Pos group and $r = 0.28$ and $P = 0.011$ in the Neg group). No difference was observed between the two groups in the ability of Emean to assess the CP and ALBI systems (all $P > 0.05$). Moreover, the Emean was significantly correlated with total bilirubin (TBIL) concentration, prothrombin time, and albumin (ALB) concentration in both groups (all $P < 0.05$).

We identified factors that influenced the different correlations between LS and liver condition, particularly within the most commonly used CP and ALBI systems, in the two groups.

Table 1 Patient characteristics, *n* (%)

Characteristics	Total, 284 patients	Pos group, 200 patients	Neg group, 84 patients	*P* value
Age, year	53.26 ± 11.40	52.59 ± 11.17	55.35 ± 11.88	0.054
Male	259 (91.2)	180 (90.0)	79 (94.0)	0.272
BMI, kg/m²	22.64 ± 2.93	22.51 ± 2.96	22.95 ± 2.87	0.289
Diabetes	22 (7.7)	16 (8.0)	6 (7.1)	0.805
Hypertension	48 (16.8)	33 (16.5)	15 (17.9)	0.781
PLT, $\times 10^9$/L	185.00 (32.00-454.00)	197.00 (40.00-427.00)	155.50 (32.00-454.00)	< 0.001[b]
PT, s	12.05 (9.60-16.10)	12.00 (9.60-14.90)	12.15 (10.20-16.10)	0.808
INR	1.03 (0.82-1.40)	1.03 (0.82-1.29)	1.04 (0.88-1.40)	0.861
ALB, g/L	37.80 (25.10-65.50)	37.40 (27.2-47.9)	39.45 (25.10-65.50)	0.026[a]
TBIL, mol/L	13.60 (5.10-83.30)	13.40 (5.10-83.30)	13.95 (5.10-42.70)	0.559
ALT, U/L	33.00 (7.00-468.00)	35.00 (7.00-468.00)	26.00 (8.00-155.00)	< 0.001[b]
AST, U/L	37.00 (12.90-438.00)	39.50 (18.00-438.00)	30.50 (12.90-209.00)	< 0.001[b]
GGT, U/L	59.00 (12.00-951.00)	66.00 (12.00-951.00)	47.00 (13.00-705.00)	0.008[b]
CHE, U/L	6180.00 (1141.00-20174.00)	6030.00 (1141.00-20174.00)	6682.00 (2024.00-10368.00)	0.496
CREA, μmol/L	80.00 (3.00-371.00)	78.00 (3.00-280.00)	85.00 (46.00-371.00)	< 0.001[b]
AFP, μg/L	45.26 (0.00-1.14 × 10^6)	53.92 (0.00-1.14 × 10^6)	22.91 (0.00-927002.45)	0.008[b]
[1]HBV-DNA, IU/mL	3360.00 (0.00-3.53 × 10^7)	46300.00 (101.00-3.53 × 10^7)	0.00 (0.00-88.80)	< 0.001[b]
CP score of 5/6/7/8	205/52/21/6 (72.2/18.3/7.4/2.1)	145/39/14/2 (72.5/19.5/7.0/1.0)	60/13/7/4 (71.4/15.5/8.3/4.8)	0.200
CP grade A (*vs* B)	257 (90.5)	184 (92.0)	73 (86.9)	0.182
ALBI score	-2.48 [(-4.77)-(-1.14)]	-2.45 [(-3.33)-(-1.61)]	-2.55 [(-4.77)-(-1.14)]	0.036[a]
ALBI grade 1/2/3	104/179/1 (36.6/63.0/0.4)	66/134/0 (33.0/67.0/0.0)	38/45/1 (45.2/53.6/1.2)	0.039[a]
MELD score	4.87 [(-26.65)-18.60]	4.55 [(-26.65)-18.60]	5.85 [(-2.87)-17.80]	0.001[b]
FIB-4	0.70 (0.12-9.29)	0.62 (0.12-4.23)	0.87 (0.17-9.29)	0.001[b]
Antiviral treatment	97 (34.2)	43 (21.5)	54 (64.3)	< 0.001[b]
Pathological cirrhosis yes/no/censored	85/168/31 (29.9/59.2/10.9)	53/62.5/11.0 (26.5/62.5/11.0)	32/43/9 (38.1/51.2/10.7)	0.047[a]
Single/multiple HCC lesion(s)	209/75 (73.6/26.4)	142/58 (71.0/29.0)	67/17 (79.8/20.2)	0.125
Diameter of HCC lesion, cm	5.75 (0.70-21.60)	6.25 (0.70-21.60)	4.00 (1.10-18.00)	< 0.001[b]
Splenomegaly	67 (23.6)	44 (22.0)	23 (27.4)	0.330
Absent/slight/moderate or abundant ascites	264/18/2 (93.0/6.3/0.7)	187/12/1 (93.5/6.0/0.5)	77/6/1 (91.7/7.1/1.2)	0.762
Esophagogastric varices	30 (10.6)	14 (7.0)	16 (19.0)	0.003[b]
BCLC stage 0/A/B	11/203/70 (3.9/71.5/24.6)	6/138/56 (3.0/69.0/28.0)	5/65/14 (6.0/77.4/16.7)	0.082
[2]Emin, kPa	7.90 (1.00-28.30)	8.00 (1.00-25.10)	7.50 (4.00-33.90)	0.809
[2]Emean, kPa	9.65 (1.00-33.90)	9.70 (1.00-31.50)	9.15 (4.00-33.90)	0.453
[2]Emax, kPa	12.00 (1.00-46.70)	12.10 (1.00-38.00)	11.45 (5.50-46.70)	0.536

[1]Patients' HBV-DNA was recorded as 0 when it was < 100.00 IU/mL.

[2]Emin, Emean, and Emax were recorded as the median values of the minimum, mean, and maximum in the five liver stiffness measurements.

[a]$P < 0.05$.

[b]$P < 0.01$. AFP: Alpha-fetoprotein; ALB: Albumin; ALBI: Albumin-bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BCLC: Barcelona clinic liver cancer; BMI: Body mass index; CHE: Choline esterase; CP: Child-Pugh; CREA: Serum creatinine; Emax: Maximum of liver stiffness; Emean: Mean of liver stiffness; Emin: Minimum of liver stiffness; FIB-4: Fibrosis-4 score; GGT: Gamma-glutamyl transpeptidase; HBV: Hepatitis B virus;

HCC: Hepatocellular carcinoma; INR: International normalized ratio; MELD: Model for end-stage liver disease; Neg group: HBV-DNA negative group; PLT: Platelet; Pos group: HBV-DNA positive group; PT: Prothrombin time; TBIL: Total bilirubin.

Table 2 Correlation between Emean with liver condition related index and liver enzymes

Parameter	Total		Pos group		Neg group	
	r	*P* value	*r*	*P* value	*r*	*P* value
CP score	0.25	< 0.001[b]	0.25	< 0.001[b]	0.24	0.026[a]
CP grade	0.21	< 0.001[b]	0.23	0.001[b]	0.18	0.106
ALBI score	0.31	< 0.001[b]	0.35	< 0.001[b]	0.27	0.012[a]
ALBI grade	0.26	< 0.001[b]	0.24	< 0.001[b]	0.28	0.011[a]
MELD	< 0.01	0.955	-0.06	0.432	0.11	0.308
TBIL	0.18	0.002[b]	0.17	0.016[a]	0.23	0.038[a]
ALB	-0.25	< 0.001[b]	-0.27	< 0.001[b]	-0.23	0.038[a]
PT	0.33	<0.001[b]	0.39	< 0.001[b]	0.23	0.033[a]
ALT	0.12	0.042[a]	0.16	0.023[a]	0.08	0.447
AST	0.19	0.002[b]	0.24	0.001[b]	0.14	0.205
ALP	0.26	< 0.001[b]	0.36	< 0.001[b]	0.08	0.447

[a]$P < 0.05$.

[b]$P < 0.01$. ALB: Albumin; ALBI: Albumin-bilirubin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CP: Child-Pugh; MELD: Model for end-stage liver disease; Neg group: HBV-DNA negative group; Pos group: HBV-DNA positive group; PT: Prothrombin time; TBIL: Total bilirubin.

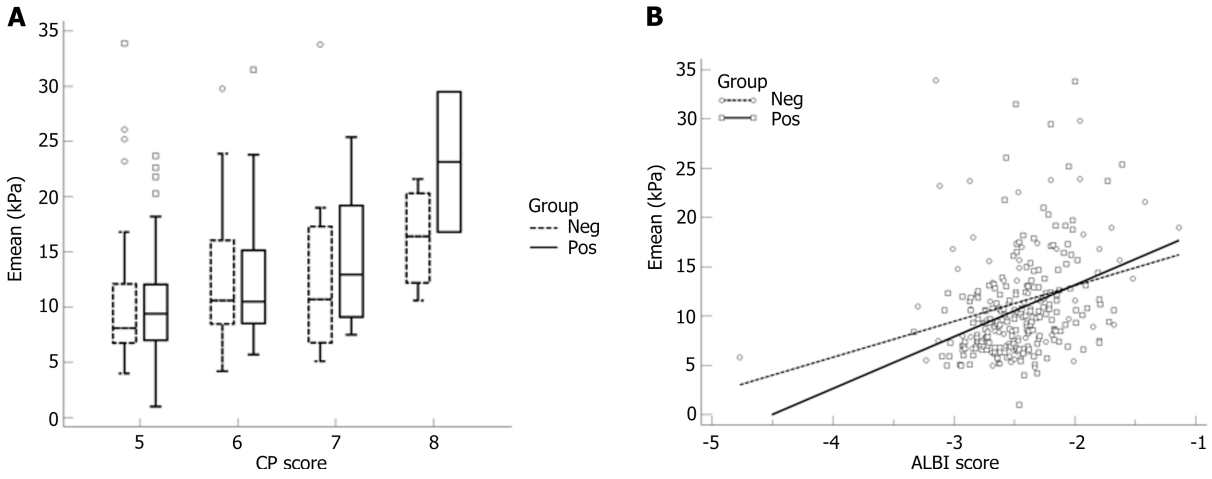

Figure 2 Correlation between Emean and liver condition. A: Box plot of the correlation between Emean and Child-Pugh score; B: Line graph of the correlation between Emean and albumin-bilirubin score. HBV: Hepatitis B virus; Pos group: HBV-DNA positive group; Neg group: HBV-DNA negative group; CP: Child-Pugh; ALBI: Albumin-bilirubin.

ALT

In the Neg group, significant correlations were observed between Emean and the CP score, ALBI score, TBIL, and ALB when ALT concentrations were normal (≤ 40 U/L; all $P < 0.05$). However, when ALT levels were elevated (> 40 U/L), the correlations between Emean and these four indices were not significant (all $P > 0.05$).

In the Pos group, significant correlations were observed between Emean and the CP score, ALBI system, and ALB regardless of ALT concentrations (all $P < 0.05$). However, the correlation between Emean and TBIL concentration was not significant under both normal and abnormal ALT (both $P > 0.05$; Table 3, Figure 3).

According to the ROC analysis, the optimal cutoff of Emean to identify a CP score of 5 when ALT concentration was ≤ 40 U/L was 7.40 kPa in the Pos group ($P = 0.017$) and 9.30 kPa in the Neg group ($P = 0.013$). When ALT concentration was > 40 U/L, the cutoff was 13.00 kPa in the Pos group; however, the discrimination ability of Emean was not significant ($P =$

Table 3 Correlation between Emean and liver condition with different alanine aminotransferase

Parameter	Pos group				Neg group			
	ALT ≤ 40 U/L, *n* = 122		ALT > 40 U/L, *n* = 78		ALT ≤ 40 U/L, *n* = 71		ALT > 40 U/L, *n* = 13	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
CP score	0.22	0.016[a]	0.23	0.044[a]	0.31	0.009[b]	0.23	0.447
CP grade	0.2	0.030[a]	0.21	0.065	0.2	0.102	0.23	0.447
ALBI score	0.29	0.001[b]	0.36	0.001[b]	0.35	0.003[b]	0.06	0.855
ALBI grade	0.21	0.018[a]	0.27	0.018[a]	0.23	0.054	0.39	0.182
MELD	-0.06	0.508	-0.08	0.48	0.18	0.125	0.02	0.945
TBIL	0.14	0.127	0.13	0.264	0.25	0.036[a]	0.09	0.779
ALB	-0.24	0.007[b]	-0.29	0.009[b]	-0.29	0.015[a]	-0.1	0.817
PT	0.43	< 0.001[b]	0.33	0.004[b]	0.28	0.018[a]	0.07	0.811

[a]*P* < 0.05.

[b]*P* < 0.01. ALB: Albumin; ALBI: Albumin-bilirubin; MELD: Model for end-stage liver disease; ALT: Alanine aminotransferase; CP: Child-Pugh; HBV: Hepatitis B virus; Neg group: HBV-DNA negative group; Pos group: HBV-DNA positive group; PT: Prothrombin time; TBIL: Total bilirubin.

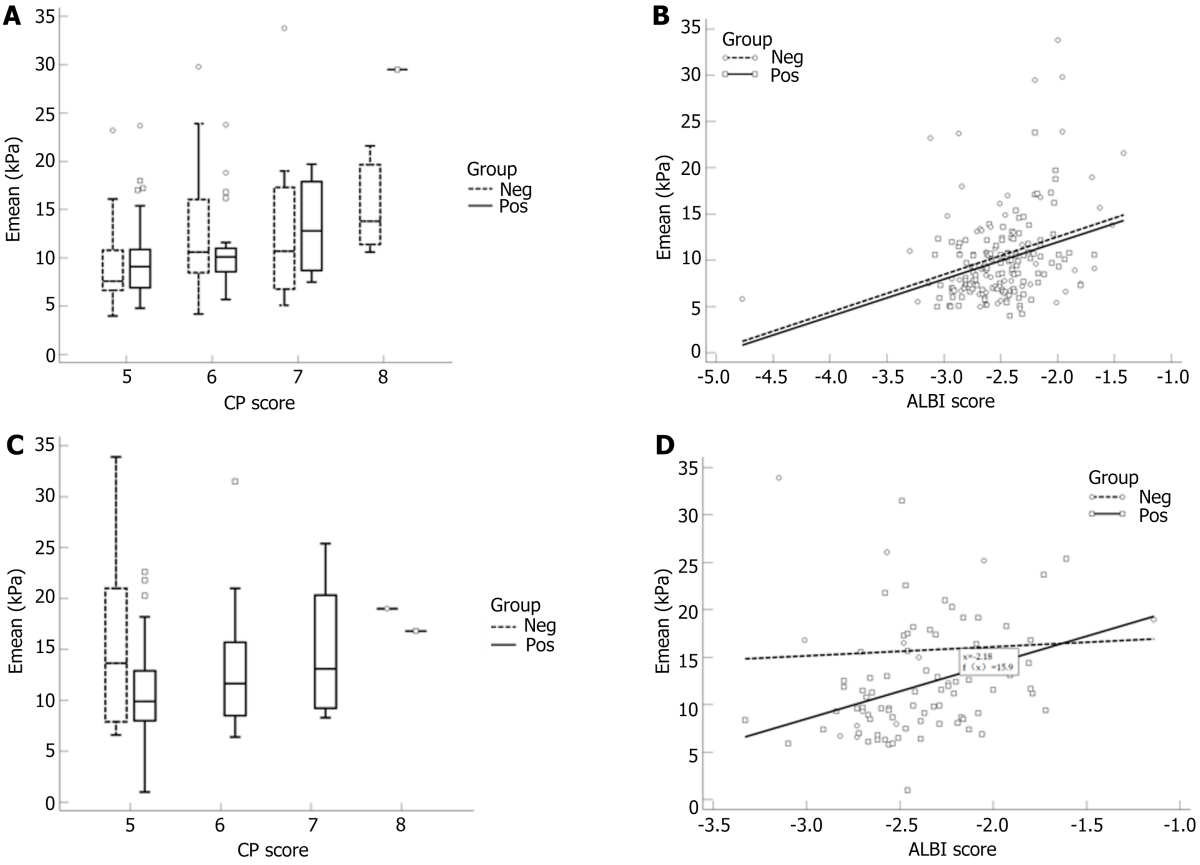

Figure 3 Correlation between Emean and liver condition in patients with different levels of alanine aminotransferase. A: Box plot of the correlation between Emean and Child-Pugh score in patients with normal alanine aminotransferase (ALT); B: Line graph of the correlation between Emean and albumin-bilirubin (ALBI) score in patients with normal ALT; C: Box plot of the correlation between Emean and Child-Pugh score in patients with increased ALT; D: Line graph of the correlation between Emean and ALBI score in patients with increased ALT. HBV: Hepatitis B virus; Pos group: HBV-DNA positive group; Neg group: HBV-DNA negative group; CP: Child-Pugh; ALBI: Albumin-bilirubin.

0.067). An effective ROC curve could not be established in the Neg group when ALT concentration was > 40 U/L because of the small sample size. When using ALBI grade 1 as the demarcation point, the ROC analysis results of each subgroup were similar to those mentioned above. However, when using CP score 6 as the demarcation point, for the Pos group, when ALT was normal, LS could distinguish different CP levels (P = 0.034); but when ALT was elevated, LS did not significantly distinguish between different CP levels (P = 0.064). For the Neg group, when ALT was normal, LS did not significantly distinguish between different CP levels (P = 0.133), and the subgroup with elevated ALT was difficult to conduct ROC analysis on due to a small number of cases. When using CP score 7 as the demarcation point, among patients in the Neg group with normal ALT, LS significantly distinguished between different CP levels (P = 0.001), while other subgroups have too few cases for analysis (Supplementary Table 2).

AST

In the Neg group, no significant correlation was observed between Emean and any of the liver condition indices analyzed, regardless of the AST concentration (all P > 0.05).

In the Pos group, significant correlations were observed between Emean and both the CP and ALBI systems (all P < 0.05) when AST concentrations were elevated (> 37 U/L). However, these correlations were not significant (all P > 0.05) when AST was within the normal range (≤ 37 U/L; Table 4, Supplementary Figure 1).

According to the ROC analysis, the discrimination ability of Emean for identifying a CP score of 5 was significant only in the Pos group when the AST concentration was > 37 U/L (P = 0.003), with an optimal Emean cutoff of 13.60 kPa. When AST concentration was ≤ 37 U/L, the optimal cutoff of Emean for identifying a CP score of 5 was 7.00 kPa in the Pos group (P = 0.571) and 10.20 kPa in the Neg group (P = 0.293). When AST concentration was > 37 U/L in the Neg group, the cutoff was 9.30 kPa (P = 0.150); however, none of these values reached a significant threshold. When CP score 6 and ALBI grade 1 were used as the demarcation point, the ROC analysis results of each subgroup were similar to those of CP score 5. When CP score 7 was used as the demarcation point, the ability to distinguish different CP levels was significant in both the Pos and Neg groups for AST > 37 U/L (P < 0.050), while the subgroups with AST ≤ 37 was difficult to conduct ROC analysis on due to the small sample size (Supplementary Table 3).

DISCUSSION

LS is commonly used to noninvasively evaluate liver fibrosis. However, the accuracy of measuring liver fibrosis can be compromised by inflammation, especially when ALT concentrations are increased[25]. In the present study, we found that liver condition, which is affected by both liver fibrosis and inflammation, was positively correlated with LS; this finding is consistent with those of previous studies[5,26]. However, the correlation between LS and various liver condition indices varied when we classified patients according to their HBV-DNA and transaminase concentrations. Our findings suggested that although LS can be useful in assessing liver condition in patients with CHB and HCC, its effectiveness varies depending on the concentrations of HBV-DNA and ALT.

A previous study on patients with CHB found that significant inflammatory activity, indicated by HBV-DNA concentrations of 4.5 ± 1.4 (log10 IU/mL), led to incorrect staging of liver fibrosis using LS measurements[19]. However, most previous studies have included all patients with CHB based solely on a 6-month history of elevated HBV-DNA concentration, without considering their HBV-DNA concentrations at the time of enrollment. In the present study, we integrated HBV-DNA concentrations with the concentrations of inflammation-related factors to categorize patients into different subgroups. We found that the relationship between LS and liver condition varied across these subgroups. Specifically, subgroups with different ALT concentrations demonstrated varying correlations between LS and liver condition and cutoff for LS. When ALT concentration was ≤ 40 U/L, LS was correlated with liver condition; however, the LS cutoff for distinguishing the same level of CP score was higher in the Neg group than in the Pos group. Conversely, when ALT concentration was > 40 U/L, LS did not accurately differentiate between liver condition scores. These results support our initial hypothesis.

Kardashian e*t al*[22] conducted a study on patients infected with HCV and suggested that the clinical application of LS may vary depending on virologic response. Previously, expert consensus has also indicated that the cutoffs for assessing liver fibrosis using LS might differ between patients who have successfully undergone antiviral therapy and those who have not, likely due to differences in inflammation levels[27]. However, studies on the application of LS in assessing liver condition are limited, and most previous studies have focused on whether LS can evaluate liver condition, rather than specifying the conditions under which LS is effective. The findings of the present study revealed that the correlation between LS and liver condition varied among patients with different HBV-DNA and transaminase concentrations, and the optimal LS cutoff values for distinguishing the same level of liver condition were also different. A previous study indicated that more than 90% of patients with CHB can achieve a reduction in serum HBV-DNA concentration after antiviral therapy, often to concentrations that are undetectable through conventional testing methods[28]. This finding suggests that with the use of antiviral therapy, the majority of patients will become negative for HBV-DNA, necessitating adjustments in the use of LS for assessing liver conditions.

Although subgroup classification based on AST concentrations revealed differences in correlation analysis, the results of the ROC analysis did not align with our initial hypothesis. However, the potential impact of AST concentration on the relationship between LS and liver condition cannot be ruled out because of the small sample size of these subgroups. Moreover, we did not find any significant correlation between Emean and MELD score (all P > 0.05). This finding might be because MELD score was primarily designed to predict survival in patients with advanced liver disease[29], whereas the majority of patients in the present study had persevered liver conditions.

Table 4 Correlation between Emean and liver condition with different aspartate aminotransferase

Parameter	Pos group				Neg group			
	AST ≤ 37 U/L, *n* = 92		AST > 37 U/L, *n* = 108		AST ≤ 37 U/L, *n* = 61		AST > 37 U/L, *n* = 23	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
CP score	0.06	0.575	0.29	0.002[b]	0.15	0.252	0.3	0.161
CP grade	0.08	0.445	0.24	0.013[a]	0.07	0.612	0.22	0.321
ALBI score	0.18	0.087	0.33	< 0.001[b]	0.19	0.135	0.28	0.200
ALBI grade	0.09	0.401	0.23	0.018[a]	0.18	0.177	0.41	0.055
MELD	0.08	0.428	-0.1	0.321	0.04	0.783	0.25	0.244
TBIL	0.07	0.51	0.08	0.442	0.15	0.247	0.15	0.485
ALB	-0.13	0.207	-0.31	0.001[b]	-0.16	0.211	-0.26	0.228
PT	0.27	0.009[b]	0.35	< 0.001[b]	0.17	0.186	0.19	0.380

[a]$P < 0.05$.

[b]$P < 0.01$. ALB: Albumin; ALBI: Albumin-bilirubin; ALT: Alanine aminotransferase; CP: Child-Pugh; HBV: Hepatitis B virus; Pos group: HBV-DNA positive group; MELD: Model for end-stage liver disease; Neg group: HBV-DNA negative group; PT: Prothrombin time; TBIL: Total bilirubin.

Although various methods are available for assessing liver condition, including the widely recognized CP and ALBI systems, they typically require blood tests or more invasive procedures for assessment. The results of this study indicate that LS has the potential to quickly and conveniently assess liver conditions without causing any harm to patients. However, the effectiveness of LS may vary depending on HBV infection status, which could be influenced by factors such as inflammation. Nevertheless, because of the retrospective nature of the present study, we could not exclude patients with mild metabolic or autoimmune diseases based on their existing medical records, and these diseases may affect the liver condition and HCC development[30-33]. In addition, although this study indicates that LS can be used to assess liver condition, the correlations between LS and liver condition indicators were weak ($r < 0.50$). Thus, further studies involving large samples, multicenter collaboration, prospective designs, and multivariate analyses are necessary to confirm our findings.

Nevertheless, there were still some other limitations of this study. First, we included only patients for whom 2D-SWE measurements were successfully obtained. However, a previous study indicated that the rate of failure to obtain reliable measurements is approximately 2.1%[34]. Second, the Pos and Neg groups were categorized based solely on the lower detection limit of the HBV-DNA test used at our institution, with the cutoff value of 100.00 IU/mL. This threshold has not been validated as the optimal point for distinguishing the different correlations between Emean and liver condition. Moreover, serum HBV-DNA concentrations may rapidly change in patients who have recently started antiviral therapy [35], potentially affecting our results, particularly for those whose corresponding values were close to the cutoff value of our subgrouping. Third, this study only included patients with active CHB, but previous hepatitis B infection may also affect HCC development and liver conditions[36]. Thus, further research involving a broader population is needed to address these issues.

CONCLUSION

In conclusion, LS was significantly correlated with most liver condition indices in patients with CHB and HCC. However, these correlations varied according to differences in HBV-DNA and transaminase concentrations. When LS is used to assess liver condition, both ALT and HBV-DNA concentrations should be considered.

FOOTNOTES

Author contributions: Huang JY and Lin MX designed the research study; Huang JY, Peng JY, Long HY, Zhong X, Xie YH, Yao L, Xie XY and Lin MX collected the cases in the study; Huang JY, Peng JY, Long HY, Zhong X, Xie YH, Yao L, Xie XY and Lin MX performed the research; Huang JY and Lin MX analyzed the data; Huang JY and Lin MX wrote the manuscript; All authors have read and approved the final manuscript.

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Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: The data that support the findings of this study are available from the corresponding author (linmxia@mail.sysu.edu.cn) upon reasonable request.

Country of origin: China

ORCID number: Jia-Yao Huang 0000-0002-7884-5906; Hai-Yi Long 0000-0001-5158-5879; Man-Xia Lin 0000-0002-2969-0020.

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