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Prognostic value of postoperative change in liver stiffness in patients with HBV-related hepatocellular carcinoma

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Abstract

Objective: To investigate the prognostic value of change in liver stiffness following surgery, in patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC).

Methods: Patients with HBV-related HCC were included. Preoperative (baseline) liver stiffness and postoperative dynamic change in liver stiffness was evaluated.

Results: Out of 158 patients in total, postoperative liver stiffness was increased in 98 patients and decreased in 60 patients compared with baseline values. Kaplan-Meier analysis revealed that patients with elevated liver stiffness had significantly worse overall survival outcomes than those with decreased liver stiffness. Similar trends were observed for diseases-free survival and recurrence outcomes. Multivariate analyses showed that Child–Turcotte–Pugh score (hazard ratio [HR] 1.209) and liver stiffness changes (HR 1.891) were independent factors associated with overall survival. Liver stiffness changes (HR 1.521) and α-fetoprotein level (HR 1.210) were found to be independent factors for disease-free survival in patients with HCC.

Conclusion: Increased postoperative liver stiffness may be an independent risk factor of HCC prognosis. Patients with increased liver stiffness following surgery should undergo additional examinations during follow-up.

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Introduction

Due to the prevalence of hepatitis B virus (HBV) and alcohol consumption, hepatocellular carcinoma (HCC) has become one of the most common cancers, with an increasing incidence worldwide, particularly in China.[1,2] Ablation and liver transplantation are effective in treating HCC, however, surgical resection remains the most important therapy, and is conducted in most patients with early stage HCC.[3–5] Despite the effectiveness of these treatments, recurrence and metastasis are still major problems for long-term survival in patients with HCC.[6–8]

Chronic HBV infection is well-known to be associated with the development of cirrhosis and HCC, resulting in hepatic disease-related deaths.[9–11] The incidence of HCC is reported to be 0.5% in patients infected with HBV, and ranges between 2.5% and 6% in patients with cirrhosis.[6,12–14] In Asia, over 60% of patients with HCC have an aetiology of chronic HBV infection.[15–17] Liver stiffness, measured by transient elastography, has proven to be an effective non-invasive procedure for evaluating liver fibrosis and assessing portal vein hypertension.[18–21] Liver stiffness can be measured using a FibroScan™ device (Echosens, Paris, France) that detects the propagation speed of an elastic sheer wave triggered by a transducer, which is then converted to a measurement of liver stiffness.[22] High levels of liver stiffness have been reported to be associated with the risk of HCC occurrence.[23,24]

To the best of the authors' knowledge, there is no published study to date that evaluates the prognostic effectiveness of liver stiffness measurements in patients with HCC, and thus, the prognostic value of liver stiffness in patients with HCC remains a clinical issue that requires exploration. The aim of the present study was to assess the prognostic value of change in liver stiffness from preoperative values, within one year following hepatic resection in patients with HBV-related HCC.

Patients and methods

Study population

This retrospective study included consecutive patients who were diagnosed with HCC and who had received liver surgery at Heze Municipal Hospital (Shandong, China) between February 2011 and May 2015. Anti-virus treatment and postoperative clinical examinations were conducted at Yantai Infectious Disease Hospital and Yantai Yuhuangding Hospital (both in Yantai, Shandong, China). Liver stiffness measurements, using Fibroscan™ (Echosens), were conducted at Jining No.1 People's Hospital (Jining, Shandong, China). Inclusion criteria were: (1) Histologically confirmed HCC with HBV infection; (2) Child–Turcotte–Pugh score $\leq$9; (3) Single lesion located in the liver; and (4) Valid clinical characteristics and laboratory outcomes. Exclusion criteria were: (1) Coinfection with hepatitis C virus and/or human immunodeficiency virus; (2) Alcoholic hepatic diseases; (3) Schistosomiasis; and (4) Invalid clinical characteristics and laboratory outcomes.

This study was conducted under compliance with the Declaration of Helsinki and

was approved by the Human Ethics Committees of Yantai Infectious Disease Hospital, Yantai Yuhuangding hospital and Jining No.1 People's Hospital (Approval No. YIDH-201703-K3). All patients provided written informed consent prior to enrolment into the study.

Transient elastography

All patients underwent liver stiffness measurements by transient elastography on at least two occasions: one prior to surgery (baseline) and the other within 1 year following liver resection surgery. Transient elastography was conducted by Fibroscan™ (Echosens) as previously described.[25] Results were expressed as kPa and the median value of 10 successful measurements in each patient was used as the liver stiffness value.

Diagnosis and anti-virus treatment

Fibrosis and HCC were diagnosed by histopathology of tissue specimens acquired during liver surgery. The maximum tumour diameter was calculated with images obtained during preoperative contrast-enhanced computed tomography (CT) using a GE LightSpeed VCT system (GE Healthcare, Tokyo, Japan). HBV infection was diagnosed with a positive serum viral marker and/or elevated serum HBV-DNA level (>1000 copies/ml during two consecutive detections). Briefly, serum HBV DNA was detected using a Daan test (Daan Gene Co., Ltd., Guangdong, China) according to the manufacturer's instructions. DNA was extracted from 100 µl of serum and detected by real-time polymerase chain reaction (PCR) with HBV-DNA specific fluorescence probing, using a Roche LightCycler 480 system (Roche Diagnostics Ltd., Rotkreuz, Switzerland). HCC recurrence during follow-up was screened by contrast-enhanced CT and ultrasonography (GE Volusion™ E10 ultrasound system; GE Healthcare, Shanghai, China). Blood laboratory parameters were obtained for each patient, and Child–Turcotte–Pugh score classification was applied for consideration of prognosis, as previously described.[25,26] All patients received anti-HBV regimens (entecavir) for at least 6 months prior to surgery and after surgery, as previously described.[27,28]

Study outcomes

The primary outcome of this study was change in liver stiffness following hepatic resection, from preoperative (baseline) value, as a prognostic marker in patients with HBV-related HCC. Secondary outcomes included independent factors associated with prognosis following hepatic resection among patients with HBV-related HCC.

Statistical analyses

Data are presented as n (%) prevalence, median (range) or mean ± SD. Student's t-test and Wilcoxon signed–rank test was used to analyse continuous variables with or without normal distribution, respectively. Categorical variables were analysed using χ^2-test and Fisher's exact test. Survival was assessed using Kaplan-Meier estimator and Log-rank test, as appropriate. Multivariate analysis was performed using Cox proportional hazards model. All statistical analyses were conducted using SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA) and a P value < 0.05 was regarded as statistically significant.

Results

Baseline patient characteristics

Out of 186 patients initially enrolled, a total of 158 patients were included in the final analyses (Figure 1; Table 1). Male patients were predominant ($n = 123$ [77.85%]), and median age was 50 years (range, 22–74 years).

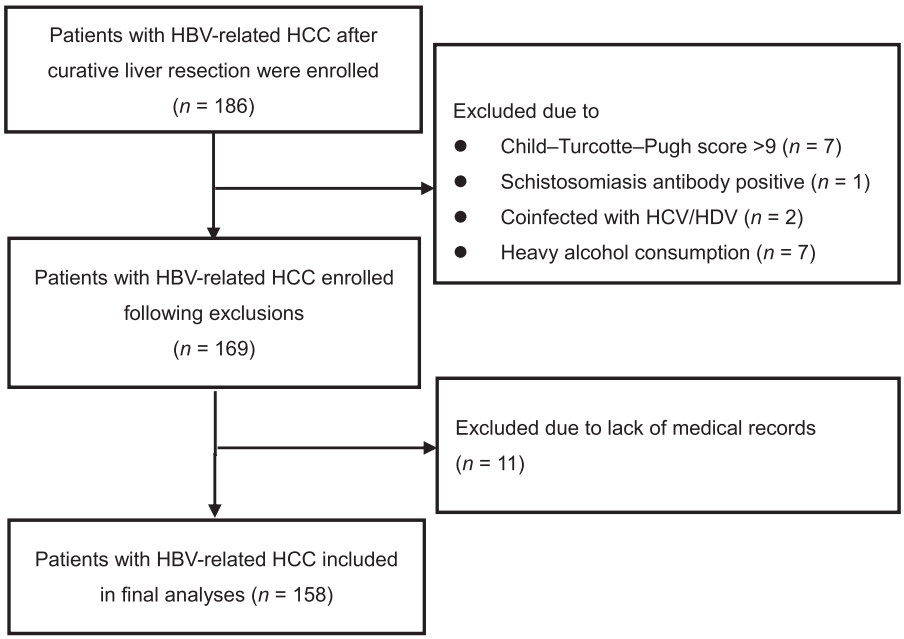

Figure 1. Flow chart showing selection of the study population. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus.

More than half of the patients were confirmed by pathology to have fibrosis (67.72%). Most patients were Child–Turcotte–Pugh class A ($n = 147$ [93.04%]), and all patients received anti-virus therapy prior to hepatic resection. The median serum HBV DNA level was 4.1 log copies/ml. A total of 102 patients (64.56%) had serum HBV DNA level <3 log copies/ml (the lower limit of detection) prior to surgery, and 56 patients (35.44%) were serum HBV DNA positive. The median maximum tumour diameter was 4.1 (range, 3.0–5.3) cm, and median liver stiffness was 6.7 (range, 4.3–12.5) kPa (Table 1).

Demographic and clinical characteristics in patients with increased or decreased postoperative liver stiffness

All patients received liver stiffness assessments on at least two occasions. Mean baseline liver stiffness was 8.53 ± 2.41 Kpa and was 9.26 ± 2.29 Kpa after surgery. Compared with baseline values prior to surgery, 98 patients (62.03%) experienced increased liver stiffness (mean change, 3.8 ± 1.3 kPa) and 60 patients (37.97%) had decreased liver stiffness (mean change, 2.4 ± 1.1 kPa) within 12 months following surgery (dynamic changes are shown in Figure 2). In patients categorised according to postoperative increase or decrease in liver stiffness, there was a statistically significant between-group difference in platelet count only ($P = 0.04$; Table 2).

Prognostic performance of liver stiffness changes in patients with HCC

Patient outcomes were analysed using Kaplan–Meier estimator in patients categorised according to postoperative increase

Table 1. Baseline characteristics of patients with hepatitis B virus-related hepatocellular carcinoma.

Variable	Study population, $n = 158$
Sex, male	123 (77.85)
Age, years	50 (22–74)
Fibrosis	107 (67.72)
Cirrhosis	81 (51.27)
CTP class	
A	147 (93.04)
B	11 (6.96)
C	0 (0)
Tumour maximum size, cm	3.6 (1–8)
HBV DNA, log copies/ml	4.1 (3.0–5.3)
HBeAg positive	96 (60.76)
AFP, ng/ml	347.82 (1.19–1210)
TBIL, mmol/l	6.87 (2.60–24.70)
ALT, IU/l	24 (11–46)
AST, IU/l	21 (17–58)
ALP, IU/l	69 (45–203)
ALB, g/l	4.2 (2.8–6.1)
Platelet count, $\times 10^9$/l	193.67 (89–267)
Prothrombin time, s	12.7 (11.0–15.6)
INR	0.97 (0.78–1.54)
Liver stiffness, kPa	6.7 (4.3–12.5)

Data presented as *n* (%) prevalence or median (range). AFP, α-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP, Child–Turcotte–Pugh score; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; INR, international normalized ratio; TBIL, total bilirubin.

or decrease in liver stiffness, in order to investigate the potential difference in prognosis between the two groups. Patients with increased postoperative liver stiffness were revealed to have significantly worse overall survival outcomes than those with decreased postoperative liver stiffness ($P = 0.042$). Similar trends were observed for diseases-free survival and recurrence outcomes, which showed that patients with increase postoperative liver stiffness had significantly worse outcomes than those with decreased liver stiffness ($P = 0.045$ for disease-free survival and $P = 0.041$ for recurrence outcomes; Figure 3).

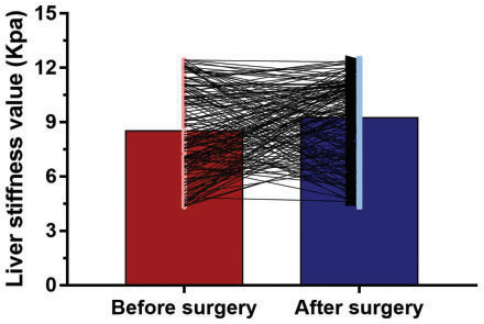

Figure 2. Dynamic changes in liver stiffness values from baseline (before surgery) to within 1 year after surgery in 158 patients with hepatitis B virus-related hepatocellular carcinoma. Mean ± SD liver stiffness was 8.53 ± 2.41 Kpa at baseline and 9.26 ± 2.29 Kpa post-surgery; 98 patients (62.03%) experienced increased liver stiffness (mean change, 3.8 ± 1.3 kPa) and 60 patients (37.97%) had decreased liver stiffness (mean change, 2.4 ± 1.1 kPa) following surgery.

Univariate and multivariate analyses of prognostic variables in patients with HCC

The potential correlations between clinical parameters and overall survival, disease-free survival and recurrence were analysed using Cox proportional hazards model in patients with HCC. Univariate analyses showed that age, Child–Turcotte–Pugh score and postoperative change in liver stiffness were all prognostic variables for overall survival. Multivariate analysis revealed that only Child–Turcotte–Pugh score (hazard ratio [HR] 1.209, $P = 0.039$) and liver stiffness changes (HR 1.891, $P = 0.042$) were independent prognostic variables that were associated with overall survival (Table 3).

To evaluate whether postoperative change in liver stiffness was an independent risk factor for disease-free survival and recurrence outcomes, both univariate and multivariate analyses were conducted (Table 4 and Table 5). Multivariate analyses showed that α-fetoprotein (AFP) level

Table 2. Comparison of baseline variables in 158 patients with increased or decreased liver stiffness following surgery.

Variable	Study subgroup		Statistical significance
	Increased LS	Decreased LS	
Patients	98 (62.03)	60 (37.97)	
Sex, male	71 (72.45)	52 (86.67)	NS
Age, years	48 (27–73)	50 (22–74)	NS
Fibrosis	68 (69.39)	39 (65.00)	NS
CTP class			NS
A	89 (90.82)	58 (96.67)	
B	9 (9.18)	2 (3.33)	
C	0	0	
Tumour maximum size, cm	4.7 (2.4–8)	3.3 (1–8)	NS
HBV DNA, log copies/ml	3.7 (3.0–4.7)	3.9 (3.0–5.3)	NS
HBeAg positive	61 (62.24)	31 (58.33)	NS
AFP, ng/ml	379.42 (2.56–1210)	319.87 (1.19–1210)	NS
TBIL, mmol/l	4.78 (2.60–24.70)	7.41 (3.90–21.60)	NS
ALT, IU/l	21 (11–38)	27 (19–46)	NS
AST, IU/l	28 (17–46)	18 (17–58)	NS
ALP, IU/l	71 (47–203)	58 (45–102)	NS
ALB, g/l	4.7 (2.8–5.7)	3.9 (2.8–6.1)	NS
Platelet count, $\times 10^9$/l	189.77 (103–267)	213.52 (89–241)	$P = 0.04$
Prothrombin time, s	13.2 (11.0–14.7)	12.6 (11.0–15.6)	NS
Differentiation			NS
Well–moderate	48 (49.0)	31 (51.7)	
Poor–undifferentiated	50 (51.0)	29 (48.3)	
Vascular invasion			NS
Yes	22 (22.4)	16 (26.7)	
No	76 (77.6)	44 (73.3)	
INR	1.01 (0.87–1.54)	0.88 (0.78–1.21)	NS

Data presented as *n* (%) prevalence or median (range).
AFP, α-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP, Child–Turcotte–Pugh score; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; INR, international normalized ratio; LS, liver stiffness; TBIL, total bilirubin.
NS, no statistically significant between-group difference ($P > 0.05$).

(HR 1.210, $P = 0.029$) and change in liver stiffness (HR 1.521, $P = 0.040$) were independent prognostic variables for HCC disease-free survival (Table 4) while serum HBV DNA viral load (HR 1.011, $P = 0.040$), AFP level (HR 1.929, $P = 0.035$) and change in liver stiffness (HR 1.052, $P = 0.032$) were independent prognostic variables for HCC recurrence (Table 5).

Discussion

The present study demonstrated that increased postoperative liver stiffness may be a potential risk factor for poor HCC outcomes in patients with HBV-related HCC. The study showed that patients with decreased postoperative liver stiffness values had better survival outcomes than patients with elevated liver stiffness values. In addition, Child–Turcotte–Pugh score

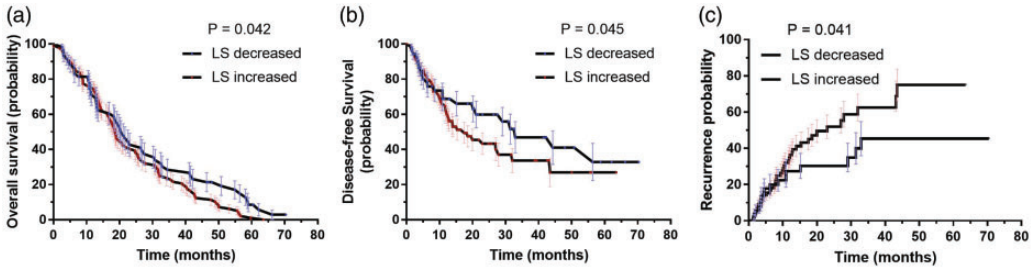

Figure 3. Kaplan-Meier estimator curves in 158 patients with hepatitis B virus-related hepatocellular carcinoma, categorised according to increased or decreased postoperative liver stiffness (LS), showing: (a) significantly worse overall survival outcomes in patients with increased LS versus those with decreased LS ($P = 0.042$); (b) significantly worse diseases-free survival in patients with increased LS versus those with decreased LS ($P = 0.045$); and (c) significantly worse recurrence outcomes in patients with increased LS versus those with decreased LS ($P = 0.041$).

Table 3. Univariate and multivariate analyses of prognostic variables for overall survival in patients with hepatitis B virus-related hepatocellular carcinoma.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	Statistical significance	HR	95% CI	Statistical significance
Age	0.935	0.165, 0.974	$P = 0.004$			
Sex	0.805	0.236, 2.110	NS			
CTP score	1.235	1.156, 2.502	$P = 0.011$	1.209	1.010, 1.742	$P = 0.039$
HBV DNA	0.905	0.818, 1.290	NS			
HBeAg status	1.606	0.270, 1.962	NS			
AFP level	1.604	0.516, 2.021	NS			
Platelet count	1.363	0.296, 2.366	NS			
Total bilirubin	2.129	0.724, 2.363	NS			
LS changes	2.112	1.839, 2.326	$P = 0.003$	1.891	1.441, 2.620	$P = 0.042$

AFP, α-fetoprotein; CTP, Child–Turcotte–Pugh score; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LS, liver stiffness; HR, hazard ratio; CI, confidence interval.
NS, no statistically significant correlation ($P > 0.05$; Cox proportional hazards).

and liver stiffness changes were found to be independent variables associated with overall survival. AFP level and liver stiffness changes were found to be independent variables associated with HCC disease-free survival while serum HBV DNA viral load, AFP level and liver stiffness changes were independent variables associated with HCC recurrence. As such, these factors may have prognostic value in patients with HBV-related HCC.

Although liver histology is useful regarding diagnosis of hepatic diseases, such as cirrhosis, the invasive nature of the procedure limits its wider use in clinical practice.[29,30] FibroScan™ (Echosens) has been routinely applied for liver diseases detection worldwide, and allows clinicians to quantitatively evaluate the status of the liver.[31] As a non-invasive procedure, FibroScan™ is also suitable for patients following liver resections. Previous advances have

Table 4. Univariate and multivariate analyses of prognostic variables for disease-free survival in patients with hepatitis B virus-related hepatocellular carcinoma.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	Statistical significance	HR	95% CI	Statistical significance
Age	1.001	0.991, 1.012	NS			
Sex	0.972	0.670, 1.594	NS			
CTP score	0.662	0.221, 0.976	$P = 0.037$			
HBV DNA	0.495	0.330, 1.109	NS			
HBeAg status	1.230	1.065, 1.692	$P = 0.021$			
AFP level	1.291	1.061, 2.182	$P = 0.015$	1.210	1.115, 1.692	$P = 0.029$
Platelet count	1.211	1.067, 1.877	$P = 0.027$			
Total bilirubin	1.159	0.698, 1.912	NS			
LS changes	1.530	1.051, 2.248	$P = 0.035$	1.521	1.074, 2.081	$P = 0.040$

AFP, α-fetoprotein; CTP, Child–Turcotte–Pugh score; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LS, liver stiffness; HR, hazard ratio; CI, confidence interval.
NS, no statistically significant correlation ($P > 0.05$; Cox proportional hazards).

Table 5. Univariate and multivariate analyses of prognostic variables for recurrence in patients with hepatitis B virus-related hepatocellular carcinoma.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	Statistical significance	HR	95% CI	Statistical significance
Age	0.172	0.129, 1.284	NS			
Sex	1.201	0.882, 1.729	NS			
CTP score	1.209	1.019, 1.812	$P = 0.025$			
HBV DNA	1.029	1.008, 1.892	$P = 0.037$	1.011	1.002, 1.928	$P = 0.040$
HBeAg status	0.662	0.197, 1.236	NS			
AFP level	1.861	1.081, 2.162	$P = 0.029$	1.929	1.028, 2.788	$P = 0.035$
Platelet count	1.191	0.772, 1.962	NS			
Total bilirubin	1.099	0.294, 1.621	NS			
LS changes	1.012	1.008, 1.425	$P = 0.012$	1.052	1.005, 1.752	$P = 0.032$

AFP, α-fetoprotein; CTP, Child–Turcotte–Pugh score; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LS, liver stiffness; HR, hazard ratio; CI, confidence interval.
NS, no statistically significant correlation ($P > 0.05$; Cox proportional hazards).

indicated that elevated liver stiffness is associated with HCC, but the mechanisms for liver regeneration after surgery are complicated in patients with underlying HBV infection.[32] Postoperative screening with transient elastography provides a reproducible method of quantification to assess the alteration of liver regeneration, as well as potential impact on the prognosis of patients with HCC.[33] The present study found a correlation between dynamic changes of liver stiffness and prognosis in patients with HBV-related HCC, which may be utilized as a dynamic approach to

monitor HCC or evaluate the recovery of patients.

Several markers have been identified as effective in evaluating prognosis in patients with HCC.[34–36] For example, AFP has been widely reported as a prognostic marker in patients with HCC,[37–39] and is a serum HCC marker that is used to diagnosis and monitor HCC progression. However, AFP levels are not only elevated in HCC. Other diseases, such as those involving tumours of the female reproductive system, may also manifest with elevated AFP levels.[40,41] Although high postoperative AFP levels are associated with poorer HCC prognosis, there is a certain proportion of patients with HCC who are AFP negative.[42] For those AFP-negative patients with HCC, AFP is not suitable as a prognostic marker. According to the present study, patients with HCC with abnormal or normal AFP levels may instead be effectively stratified using liver stiffness measured by transient elastography.

The present study results may be limited by several factors. The relatively small sample size may limit the generalizability of the results, and the retrospective study design may have biased the results. In the present study, the antiviral treatment was determined by clinical experts at Yantai Infectious Diseases Hospital, liver stiffness was measured at Jining No.1 People's Hospital, and HCC diagnosis and surgery were performed at Heze Municipal Hospital. In addition, patients included in the present study received various different treatments following surgery, for example, some received no further treatment following radical resection, while some were treated with sorafenib, and these factors were not included in the present analyses. All of these additional variables may have affected the present results, and whether or not postoperative treatment may further improve the prognosis of patients with HCC remains unclear. Data were collected and analysed at a single centre. Larger multicentre prospective studies are required to validate the present results and further investigate the value of liver stiffness as a prognostic marker in patients with HCC.

In conclusion, the present study demonstrated an association between dynamic change in liver stiffness and prognosis in patients with HCC. Liver stiffness measurement with transient elastography may allow the evaluation of outcomes in patients with HCC, and thus, may be used to guide routine follow-up for these patients. In particular, patients with HCC with increased liver stiffness following surgery should undergo more frequent follow-up examinations, even if the most recent exam following liver resection indicates no cause for concern.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018; 69: 182–236.
2. Bertuccio P, Turati F, Carioli G, et al. Global trends and predictions in hepatocellular carcinoma mortality. *J Hepatol* 2017; 67: 302–309.
3. Chaudhari VA, Khobragade K, Bhandare M, et al. Management of fibrolamellar

hepatocellular carcinoma. *Chin Clin Oncol* 2018; 7: 51.
4. Kulik L and El-Serag HB. Epidemiology and management of hepatocellular carcinoma. *Gastroenterology* 2019; 156: 477–491.e1.
5. Mitin T, Degnin C, Chen Y, et al. Radiotherapy for hepatocellular carcinoma in Russia: a survey-based analysis of current practice and the impact of an educational workshop on clinical expertise. *J Cancer Educ* 2020; 35: 105–111.
6. Yu MW, Chang HC, Chen PJ, et al. Increased risk for hepatitis B-related liver cirrhosis in relatives of patients with hepatocellular carcinoma in northern Taiwan. *Int J Epidemiol* 2002; 31: 1008–1015.
7. Cai SH, Lu SX, Liu LL, et al. Increased expression of hepatocyte nuclear factor 4 alpha transcribed by promoter 2 indicates a poor prognosis in hepatocellular carcinoma. *Therap Adv Gastroenterol* 2017; 10: 761–771.
8. Cai SH, Lv FF, Zhang YH, et al. Dynamic comparison between Daan real-time PCR and Cobas TaqMan for quantification of HBV DNA levels in patients with CHB. *BMC Infect Dis* 2014; 14: 85.
9. Cai S, Cao J, Yu T, et al. Effectiveness of entecavir or telbivudine therapy in patients with chronic hepatitis B virus infection pretreated with interferon compared with de novo therapy with entecavir and telbivudine. *Medicine (Baltimore)* 2017; 96: e7021.
10. Ou H, Cai S, Liu Y, et al. A noninvasive diagnostic model to assess nonalcoholic hepatic steatosis in patients with chronic hepatitis B. *Therap Adv Gastroenterol* 2017; 10: 207–217.
11. Wu X, Cai S, Li Z, et al. Potential effects of telbivudine and entecavir on renal function: a systematic review and meta-analysis. *Virol J* 2016; 13: 64.
12. Chu CM and Liaw YF. Hepatitis B virus-related cirrhosis: natural history and treatment. *Semin Liver Dis* 2006; 26: 142–152.
13. Chen YC, Chu CM, Yeh CT, et al. Natural course following the onset of cirrhosis in patients with chronic hepatitis B: a long-term follow-up study. *Hepatol Int* 2007; 1: 267–273.
14. Cai S, Li Z, Yu T, et al. Serum hepatitis B core antibody levels predict HBeAg seroconversion in chronic hepatitis B patients with high viral load treated with nucleos(t)ide analogs. *Infect Drug Resist* 2018; 11: 469–477.
15. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2095–2128.
16. Wang FS, Fan JG, Zhang Z, et al. The global burden of liver disease: the major impact of China. *Hepatology* 2014; 60: 2099–2108.
17. Cai S, Ou Z, Liu D, et al. Risk factors associated with liver steatosis and fibrosis in chronic hepatitis B patient with component of metabolic syndrome. *United European Gastroenterol J* 2018; 6: 558–566.
18. Lemoine M, Shimakawa Y, Njie R, et al. Food intake increases liver stiffness measurements and hampers reliable values in patients with chronic hepatitis B and healthy controls: the PROLIFICA experience in The Gambia. *Aliment Pharmacol Ther* 2014; 39: 188–196.
19. Arena U, Vizzutti F, Corti G, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. *Hepatology* 2008; 47: 380–384.
20. Xue X and Cai S. Comment on "Assessment of liver stiffness in pediatric Fontan patients using transient elastography". *Can J Gastroenterol Hepatol* 2016; 2016: 9343960.
21. Zeng J, Cai S, Liu J, et al. Dynamic changes in liver stiffness measured by transient elastography predict clinical outcomes among patients with chronic hepatitis B. *J Ultrasound Med* 2017; 36: 261–268.
22. Adler M, Larocca L, Trovato FM, et al. Evaluating the risk of hepatocellular carcinoma in patients with prominently elevated liver stiffness measurements by FibroScan: a multicentre study. *HPB (Oxford)* 2016; 18: 678–683.
23. Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 2006; 55: 403–408.
24. Masuzaki R, Tateishi R, Yoshida H, et al. Prospective risk assessment for

hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. *Hepatology* 2009; 49: 1954–1961.
25. Wu D, Chen E, Liang T, et al. Predicting the risk of postoperative liver failure and overall survival using liver and spleen stiffness measurements in patients with hepatocellular carcinoma. *Medicine (Baltimore)* 2017; 96: e7864.
26. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60: 646–649.
27. Wang ZY, Tao QF, Wang ZH, et al. Antiviral therapy improves post-operative survival outcomes in patients with HBV-related hepatocellular carcinoma of less than 3cm - A retrospective cohort study. *Am J Surg* Epub ahead of print 13 June 2019. DOI: 10.1016/j.amjsurg.2019.05.016.
28. Huang G, Lau WY, Wang ZG, et al. Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: a randomized controlled trial. *Ann Surg* 2015; 261: 56–66.
29. Garcia-Tsao G, Friedman S, Iredale J, et al. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. *Hepatology* 2010; 51: 1445–1449.
30. Hytiroglou P, Snover DC, Alves V, et al. Beyond "cirrhosis": a proposal from the International Liver Pathology Study Group. *Am J Clin Pathol* 2012; 137: 5–9.
31. Feier D, Lupsor Platon M, Stefanescu H, et al. Transient elastography for the detection of hepatocellular carcinoma in viral C liver cirrhosis. Is there something else than increased liver stiffness? *J Gastrointestin Liver Dis* 2013; 22: 283–289.
32. Wong GL, Chan HL, Wong CK, et al. Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B. *J Hepatol* 2014; 60: 339–345.
33. Jung KS, Kim SU, Choi GH, et al. Prediction of recurrence after curative resection of hepatocellular carcinoma using liver stiffness measurement (FibroScan®). *Ann Surg Oncol* 2012; 19: 4278–4286.
34. Li D and Satomura S. Biomarkers for hepatocellular carcinoma (HCC): an update. *Adv Exp Med Biol* 2015; 867: 179–193.
35. Cai S, Yu T, Jiang Y, et al. Comparison of entecavir monotherapy and de novo lamivudine and adefovir combination therapy in HBeAg-positive chronic hepatitis B with high viral load: 48-week result. *Clin Exp Med* 2016; 16: 429–436.
36. Xiao YB, Cai SH, Liu LL, et al. Decreased expression of peroxisome proliferator-activated receptor alpha indicates unfavorable outcomes in hepatocellular carcinoma. *Cancer Manag Res* 2018; 10: 1781–1789.
37. Komorowski AL, Hsu CC, Julka KD, et al. AFP role in predicting recurrence of hepatocellular carcinoma after living donor liver transplantation in HCV patients. *Neoplasma* 2018; 65: 455–460.
38. Lim TS, Kim DY, Han KH, et al. Combined use of AFP, PIVKA-II, and AFP-L3 as tumor markers enhances diagnostic accuracy for hepatocellular carcinoma in cirrhotic patients. *Scand J Gastroenterol* 2016; 51: 344–353.
39. Notarpaolo A, Layese R, Magistri P, et al. Validation of the AFP model as a predictor of HCC recurrence in patients with viral hepatitis-related cirrhosis who had received a liver transplant for HCC. *J Hepatol* 2017; 66: 552–559.
40. Isonishi S, Ogura A, Kiyokawa T, et al. Alpha-fetoprotein (AFP)-producing ovarian tumor in an elderly woman. *Int J Clin Oncol* 2009; 14: 70–73.
41. Lu JB, Cai SH, Pan YH, et al. Altered epidermal fatty acid-binding protein expression in hepatocellular carcinoma predicts unfavorable outcomes. *Cancer Manag Res* 2018; 10: 6275–6284.
42. Shu H, Li W, Shang S, et al. Diagnosis of AFP-negative early-stage hepatocellular carcinoma using Fuc-PON1. *Discov Med* 2017; 23: 163–168.