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Decreased liver stiffness by transient elastography indicates lower incidence of hepatocellular carcinoma in patients with chronic hepatitis B

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Abstract

The prognositc value of dynamic liver stiffness (LS) variation on hepatocellular carcinoma (HCC) incidence in patients with chronic hepatitis B (CHB) remains to be explored. We aim to compare HCC incidence in patients with compensated CHB-related cirrhosis with increased and decreased LS after nucleos(t)ide analog (NA) regimens.

A total of 168 patients with CHB-related compensated cirrhosis were divided into groups according to LS variation post to NA treatment. The laboratory results of 2 groups were reviewed and investigated. The probability of HCC development among each group was analyzed and compared.

A total of 168 patients with CHB with compensated cirrhosis received NA treatment and Fibroscan. Child–Pugh score, alanine aminotransferase, total bilirubin level, status of hepatitis B e antigen, and serum hepatitis B virus DNA level were compared between groups. The cumulative probability of HCC development in patients with decreased LS was significantly lower than in patients with increased LS ($P < .05$). Multi-variant analysis indicated that decreased LS was significantly associated with lower probability of HCC development (hazard ratio, 0.65; 95% confidence interval range, 0.33–0.84, $P < .05$).

Decreased LS after NA treatment indicates a lower HCC incidence in patients with CHB with compensated cirrhosis.

Abbreviations: ADV = adefovir, AFP = α-fetoprotein, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHB = chronic hepatits B, CT = computed tomography, CTP = Child–Trucott–Pugh score, ETV = entecavir, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, LAM = lamivudine, LdT = telbivudine, NAs = nucleos(t)ide analogs, TBIL = total bilirubin.

Keywords: chronic hepatits B, cirrhosis, fibroscan, hepatocellular carcinoma, nucleos(t)ide analogs

1. Introduction

Hepatocellular carcinoma (HCC) accounts for ~7% of all cancer and is ranked as the 6th most common cancer worldwide.[1] According to the 2015 China cancer survey, HCC is the 3rd most common cancer causing cancer-related deaths in China.[2] Cirrhosis is one of the main risk factors of HCC in China and over 80% of patients with HCC have the background of cirrhosis.[3,4] Hepatitis B virus infection in patients is the main cause of cirrhosis and chronic hepatitis B progress to cirrhosis at a rate of 2% per year.[5]

Quantification of liver fibrosis and liver cirrhosis is essential for the establishment of prognosis and guidance of surveillance. Liver biopsy is the gold standard for the assessment of both liver fibrosis and cirrhosis. However, with the invasive feature and potential complications, liver biopsy is limited in serial assessment of chronic hepatic diseases.[6,7] The histologic changes are not always distributed across the whole liver parenchyma, which increases sampling error.[8–11]

Recent advances of noninvasive methods to assess chronic hepatic diseases have proved liver stiffness (LS) by transient elastography as a fast, simple, and safe procedure.[12,13] It is efficient and safe to evaluate liver cirrhosis, assessing liver portal vein hypertension and predicting HCC development.[14–20] LS can be measured by FibroScan (Echosens, Paris, France) through detecting the propagation speed of an elastic sheer wave triggered by transducer, which is related to LS.[21] High LS was reported to be associated with the risk of HCC development.[19] But whether patients with CHB with different dynamic changes of LS after the initiation of anti-virus treatment will have different prognosis is not determined. Thus, we reviewed the changes of LS within 1 year after the anti-virus treatment in patients with CHB with cirrhosis and compared the HCC development in patients with increased and decreased LS variations.

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YZ and CW contributed equally to this work.

This study was conducted under compliance with the Declaration of Helsinki and was approved by the Human Ethics Committee of Jining No. 1 People's Hospital and the Human Ethics Committee of Heze Municiple Hospital.

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2. Materials and methods

2.1. Patients and study design

All patients with CHB were diagnosed with compensated liver cirrhosis and received anti-hepatitis B virus (anti-HBV) treatment in Jining No 1 People's Hospital and Heze Municiple Hospital (Shandong, China) from May 2012 to October 2014. Inclusion criteria were: diagnosed as HBV infection with compensated liver cirrhosis; Child–Pugh scoring ≤ 9; valid clinical characteristics and laboratory outcome in electronic medical record. The exclusion criteria were: HCC; HCV coinfection; alcoholic hepatic diseases; schistosomiasis; invalid clinical characteristics and laboratory outcomes; HCC during the 1st year after anti-virus treatment; serum viral load remains over 1000 copies/mL at the 6th month after anti-virus treatment. About 298 patients were recruited into this retrospective study and 94 patients were excluded due to HCV coinfection (n = 9), alcoholic hepatic diseases (n = 2), and invalid data (n = 27). About 28 patients were excluded during follow-up for HCC recurrence within 1 year. Serum viral load of 34 patients were over 1000 copies/mL at the 6th month and 30 patients were lost to follow-up. A total of 168 patients were included in this study.

This study was conducted under compliance with the Declaration of Helsinki and was approved by the Human Ethics Committee of Jining No 1 People's Hospital and the Human Ethics Committee of Heze Municiple Hospital.

2.2. Diagnosis and anti-virus treatment

All patients were histologically confirmed with cirrhosis through liver biopsy or contrast-enhanced computed tomography (CT). HBV infection was diagnosed with positive serum viral marker and elevated serum HBV-DNA level (>1000 copies/mL during 2 consecutive detection). Contrast-enhanced CT, ultrasonography, or liver biopsy was conducted to screen HCC recurrence during follow-up. Child–Trucott–Pugh (CTP) scoring was applied for consideration of prognosis as previously reported.[22] All patients received nucleos(t)ide analogs (NAs) as anti-virus treatment.

2.3. Transient elastography

All scans were conducted in outpatient setting. The procedure was conducted as previously described.[23] All patients underwent at least twice LS measurements: 1 prior to anti-HBV treatment and the other after 1-year NA treatment. About 21 patients were excluded for insufficient measurement and regarded as invalid data.

2.4. Statistics

Continuous variables were expressed as mean ± standard deviation with normal distribution and median (range) without normal distribution. The comparison of continuous variables with or without normal distribution was analyzed with Student *t* test and Wilcoxon rank test, respectively. Chi-squared and Fisher test were applicated for analysis of categorical variables. $P < .05$ was regarded as statistically significant. The univariate analysis was conducted through Kaplan–Meier statistics and Log-rank test. Multivariate analysis was assessed with Cox regression test. Variables with $P < .05$ were employed into the Cox regression model. $P < .05$ was considered as statistically significant. Statistics analysis was conducted with SPSS (version 16.0; SPSS Inc, Chicago, IL) software package. Figures were made with GraphPad Prism 5 software.

Table 1

Baseline characteristics.

Variable	Value
Patients, n	168
Male sex, n (%)	114 (67.86)
Age, M (range)	50 (22–74)
CTP class A/B/C, n (%)	147/11/0 (93.04/6.96/0)
Tumor maximum size, cm, M (range)	3.6 (1–8)
HBV DNA, log copies/mL	4.1 (3.0–5.3)
HBeAg postive, n (%)	96 (60.76)
AFP, ng/mL, M (range)	5.88 (1.19–21)
TBIL, mmol/L, M (range)	6.87 (2.60–24.70)
ALT, IU/L, M (range)	31 (11–46)
AST, IU/L, M (range)	27 (17–58)
ALP, IU/L, M (range)	57 (45–203)
ALB, g/L, M (range)	4.1 (2.8–6.1)
PLT, 10^9/L, M (range)	193.67 (89–267)
PT, s, M (range)	11.7 (11.0–15.6)
INR, M (range)	0.99 (0.78–1.54)
Liver stiffness, kPa, M (range)	8.9 (6.9–12.5)

AFP = α-fetoprotein, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTP = Child–Trucott–Pugh score, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus, INR = international normalized ratio, PLT = platelet, PT = prothrombin time, TBIL = total bilirubin.

3. Results

3.1. Baseline characteristics

The baseline characteristics of whole patients in our study are presented in Table 1. A total of 168 patients were included in our study. Male patients were predominant (n = 114, 67.86%). The median age was 50 years old ranging from 22 to 74. The majority of patients were Child–Pugh A (n = 147, 93.04%). The median serum HBV DNA level was 4.1 log copies/mL and 96 patients (60.76%) were serum HBV DNA positive. The median maximum diameter of tumor was 3.6 (1–8) centimeter and the median α-fetoprotein (AFP) was 5.88 ng/mL. Median total bilirubin was 6.87 mmol/L and average alanine aminotransferase (ALT) level was 31 IU/L. The median LS was 8.9 (6.9–12.5) kPa.

3.2. Variation of LS after NA treatment

All the patients received at least twice transient elastography: 1 before anti-virus treatment and the other at the 12th month after anti-virus therapy. Of 168 patients, 85 patients (50.60%) had elevated LS (median change = 4.1 ± 1.1 kPa) and 83 patients (49.6%) experienced decreased LS (median change = 3.7 ± 1.4 kPa) compared to their baseline value. In patients with increased LS, 64 patients (75.29%) received entecavir (ETV), 12 patients (14.12%) received lamivudine (LAM), and 9 patients (10.59%) received tenofovir (TDF). For patients with decreased LS, 54 patients (65.06%) received ETV, 21 patients (25.30%) received LAM, and 8 patients (9.64%) received TDF. The clinical parameters of each group were presented in Table 2. Except from blood platelet count (PLT) ($P < .05$) and hepatitis B e antigen (HBeAg) rate ($P < .05$), all the other parameters were comparable, include AFP, TBIL, ALT, alkaline phosphatase (ALP), and LS.

To investigate the potential difference of prognosis in 2 groups, we compared the HCC incidence 1 year after NA treatment. We used Kaplan–Meier survival analysis to conduct the cumulative probability of HCC development in 2 groups, the results showed that patients with decreased LS had a lower HCC incidence compared to patients with elevated LS ($P < .05$) (Fig. 1).

Table 2

comparison of baseline variables in patients with LS increased and decreased.

Variable	LS increased	LS decreased	*P*
Patients, n (%)	85 (50.60)	83 (49.40)	
Male sex, n (%)	65 (76.47)	49 (59.04)	.53
Age, M (range)	48 (27–73)	50 (22–74)	.11
CTP class A/B/C, n (%)			.56
A	73 (85.88)	67 (80.72)	
B	12 (14.12)	16 (19.28)	
C	0	0	
HBV DNA, log copies/mL	5.3 (3.0–7.7)	4.9 (3.0–6.8)	.13
HBeAg postive, n (%)	61 (62.24)	35 (42.17)	.03
AFP, ng/mL, M (range)	6.77 (2.56–18)	5.21 (1.19–21)	.72
TBIL, mmol/L, M (range)	4.78 (2.60–24.70)	7.41 (3.90–21.60)	.08
ALT, IU/L, M (range)	21 (11–38)	27 (19–46)	.11
AST, IU/L, M (range)	28 (17–46)	18 (17–58)	.41
ALP, IU/L, M (range)	71 (47–203)	58 (45–102)	.09
ALB, g/L, M (range)	4.7 (2.8–5.7)	3.9 (2.8–6.1)	.64
PLT, 10^9/L, M (range)	189.77 (103–267)	213.52 (89–241)	.04
PT, s, M (range)	13.2 (11.0–14.7)	12.6 (11.0–15.6)	.77
INR, M (range)	1.01 (0.87–1.54)	0.88 (0.78–1.21)	.49
Liver stiffness, kPa, M (range)	8.1 (6.9–12.4)	9.2 (7.4–12.5)	.16

AFP = α-fetoprotein, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTP = Child–Trucott–Pugh score, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus, INR = international normalized ratio, PLT = platelet, PT = prothrombin time, TBIL = total bilirubin.

3.3. Risk factors of HCC development

During the follow-up period, 82 patients (48.81%) developed HCC. In patients with increased LS, 49 patients (57.65%) experienced HCC development and 35 patients (42.17%) HBeAg seroconversion. Thirty-three patients (39.76%) in decreased LS group developed HCC and 40 patients (47.06%) had HBeAg seroconversion. The univariant analysis indicated HBV DNA ≤4 log copies/mL, positive HBeAg, and decreased LS were related to HCC development ($P < .05$). Multivariate stepwise COX regression analysis showed that decreased LS was independently associated with lower HCC cumulated probability (hazard ratio, 0.65; 95% confidence interval range, 0.33–0.84, $P < .05$) (Table 3).

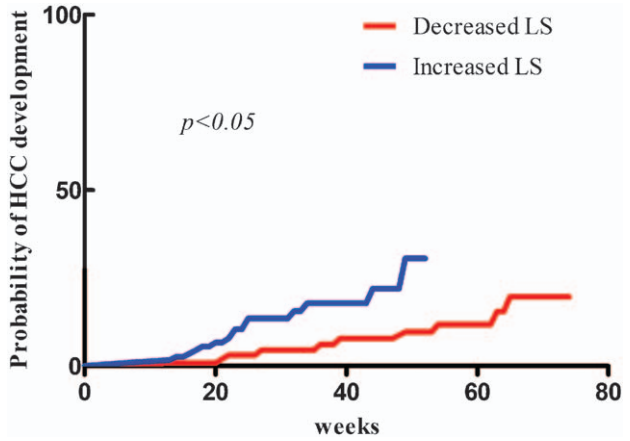

Figure 1. The cumulative probability of hepatocellular carcinoma (HCC) development. The comparison of cumulative HCC development probability between LS increased group (red) and LS decreased group (blue). X-axis represented time (weeks), and Y-axis represented probability of HCC development.

Table 3

Univariate and multivariate analyses of HCC development.

	Univariant analysis HR (95% CI)	*P*-value	Multivariant analysis HR (95% CI)	*P*-value
Gender: male/female	0.87 (0.37–1.59)	NS		
Child–Pugh score: A/B	0.79 (0.31–1.32)	NS		
HBV DNA < 4 (log copies/mL)	0.68 (0.33–0.97)	<.05		
HBeAg: positive/negative	1.23 (1.06–1.69)	<.05	1.43 (1.11–1.78)	<.05
Total bilirubin: <24/≥24, μmol/L	1.15 (0.69–1.91)	NS		
LS decreased/LS increased	0.78 (0.43–0.97)	<.05	0.65 (0.33–0.84)	<.05

AFP = α-fetoprotein, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus, LS = liver stiffness.

4. Discussion

Although NAs have been proved to be effective in anti-HBV treatment as well as delaying HCC development.[24–26] Approximately 10% patients with effective NAs therapy are still at risk of HCC.[27,28] High LS by transient elastography were proved to be associated with HCC development and recurrence, but whether the variation of LS post to anti-virus treatment is associated with HCC development in patients with cirrhosis remains to be explored. Since liver fibrosis and cirrhosis can be quantified by measurement of LS, we supposed that dynamic variation of LS might reflect the progression or alleviation of liver tissue. Our study determined that decreased LS after effective anti-virus therapy was significantly related to lower HCC incidence ($P < .05$). As LS by transient elastography is noninvasive and safe compared to liver biopsy, our study suggested it may be applicable to serially assess the histology in patients with anti-HBV therapy.

As a retrospective study, we also suffered from the common flaws. During our design, to make potential groups comparable, we defined both inclusion and exclusion criteria, which caused a relatively small sample. The heterogeneity of anti-virus regimens confined our study to the general prognosis instead of the potential analysis for comparison between different NAs. The quantification of serum markers for HBV was not available during the time when patients received their treatment, it also limited our further analysis of possible relationships between dynamics of virus and LS. Further studies of prospective design are required to evaluate those issues.

5. Conclusion

Our study determined the significant association between LS variation and HCC development in patients with CHB with compensated cirrhosis. It suggested that LS by transient elastography is an effective serial assessment for hepatic disease progression.

Author contributions

Yinghua Zhang and Chuanfang Wang contribute to patients follow-up, data collection and manuscript preparation.

Hui Li is responsible for patients follow-up.
Yuanyuan Ding is responsible for study design, statistical analysis and patients follow-up.
Data curation: Yinghua Zhang, Chuanfang Wang, Hui Li, Yuanyuan Ding.
Formal analysis: Chuanfang Wang.
Investigation: Yuanyuan Ding.
Project administration: Yinghua Zhang, Chuanfang Wang, Yuanyuan Ding.
Supervision: Yuanyuan Ding.
Validation: Hui Li.
Writing – original draft: Yinghua Zhang, Chuanfang Wang.
Writing – review & editing: Yuanyuan Ding.

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