Prospective Risk Assessment for Hepatocellular Carcinoma Development in Patients with Chronic Hepatitis C by Transient Elastography

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Liver stiffness, noninvasively measured by transient elastography, correlates well with liver fibrosis stage. The aim of this prospective study was to evaluate the liver stiffness measurement (LSM) as a predictor of hepatocellular carcinoma (HCC) development among patients with chronic hepatitis C. Between December 2004 and June 2005, a total of 984 HCV-RNA positive patients, without HCC or a past history of it, visited the University of Tokyo Hospital. LSM was performed successfully in 866 patients, who gave informed consent. During the follow-up period (mean, 3.0 years), HCC developed in 77 patients (2.9% per 1 person-year). The cumulative incidence rates of HCC at 1, 2, and 3 years were 2.4%, 6.0%, and 8.9%, respectively. Adjusting for other significant factors for HCC development, patients with higher LSM were revealed to be at a significantly higher risk, with a hazard ratio, as compared to LSM ≤10 kPa, of 16.7 (95% confidence interval [CI], 3.71-75.2; $P < 0.001$) when LSM 10.1-15 kPa, 20.9 (95% CI, 4.43-98.8; $P < 0.001$) when LSM 15.1-20 kPa, 25.6 (95%CI, 5.21-126.1; $P < 0.001$) when LSM 20.1-25 kPa, and 45.5 (95% CI, 9.75-212.3; $P < 0.001$) when LSM >25 kPa. *Conclusions:* This prospective study has shown the association between LSM and the risk of HCC development in patients with hepatitis C. The utility of LSM is not limited to a surrogate for liver biopsy but can be applied as an indicator of the wide range of the risk of HCC development. (HEPATOLOGY 2009;49:1954-1961.)

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Hepatocellular carcinoma (HCC) is a common malignancy worldwide,[1] currently showing an increasing incidence in the United States and elsewhere.[2-4] HCC usually develops in liver already suffering from chronic liver diseases. In particular, hepatitis C virus (HCV)-related cirrhosis is associated with an extremely high risk of HCC development, with a reported annual incidence ranging between 3% and 8%.[5-7] The prognosis of HCC is deemed poor unless the cancer is detected and treated at an early stage.[8-10] Thus, the assessment of risk for HCC development is essential in the management of patients with chronic liver diseases.

Chronic hepatitis C is an endemic disease affecting millions of individuals globally.[11-14] HCV infection is typically accompanied by no conspicuous symptoms and may result in cirrhosis unnoticed over a couple of decades. The risk factors for hepatic carcinogenesis in patients with chronic hepatitis C have been vigorously studied,[5,6,15,16] and the degree of liver fibrosis is known to be the strongest.[6] Until recently, however, the degree of liver fibrosis could be reliably assessed only with liver biopsy, an invasive procedure with the possibility of life-threatening complications.[17]

Recently, liver stiffness measured noninvasively by transient elastography has been reported to be well correlated with histologically assessed liver fibrosis stage.[18-22] Both routine and specific biomarkers, together with a combination thereof, have been proposed as noninvasive indicators of the degree of liver fibrosis.[23-25] Among them, Fibrotest is accepted as a promising noninvasive marker to

Abbreviations: AFP, alpha fetoprotein; AIC, Akaike information criterion; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CT, computed tomography; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; HR, hazard ratio; LSM, liver stiffness measurement; SVR, sustained virological response.

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assess liver fibrosis stage and also reported as a useful prognostic factor for patients with hepatitis C.[26] A previous cross-sectional study reported that transient elastography surpassed Fibrotest in the diagnosis of cirrhosis.[18] However, the accuracy of transient elastography in assessing the prognosis of patients with hepatitis C has not been validated in prospective studies. We previously reported in a cross-sectional setting that liver stiffness measurement (LSM) was strongly associated with the probability of the presence of HCC among patients with hepatitis C.[27] Besides its noninvasiveness, LSM has a possible advantage over liver biopsy of being less prone to sampling errors and intra- and interobserver variability.[28,29]

Portal hypertension is a direct consequence of the fibrotic transformation of liver and a progressive complication of cirrhosis. Therefore, the management of patients with cirrhosis and portal hypertensive gastrointestinal bleeding depends on the phase of portal hypertension. Measurement of the hepatic venous pressure gradient (HVPG) is currently employed for the evaluation of portal hypertension.[30] Vizzutti et al.[31] reported that LSM was well correlated with HVPG.

Not only the presence of cirrhosis but also the degree of fibrosis in noncirrhotic liver, as expressed in fibrosis stages, is known to be correlated with the risk of HCC. The correlation can be more rigorously analyzed by using LSM, which is expressed in kPa as a continuous variable. Moreover, LSM has a wide dynamic range within the cirrhotic stage, from the cutoff level from noncirrhosis (15-17 kPa) to the upper measurement limit of the present device (75 kPa). It is of interest to know whether the risk of HCC can be differentiated further among cirrhotic patients according to their LSM.

We conducted the present study to prospectively evaluate the efficacy of LSM by transient elastography as a predictor of HCC development among a cohort of patients with hepatitis C with various degrees of liver fibrosis.

Patients and Methods

Patients. Between December 2004 and June 2005, a total of 984 HCV-RNA positive patients, excluding those with HCC or a past history of it, visited the liver clinic of Department of Gastroenterology, the University of Tokyo Hospital. LSM was performed on those patients who gave informed consent. All patients were positive for serum HCV-RNA and showed at least a transiently elevated serum alanine aminotransferase (ALT) level. We excluded from this study patients with concomitant hepatitis B virus surface antigen positivity, patients with uncontrollable ascites, patients on interferon (IFN) therapy, and patients who visited only for consultation purposes. We also examined the history of IFN therapies and responses during the follow-up period. A sustained virological response (SVR) was defined as undetectable HCV-RNA at least 24 weeks after the end of therapy. Diagnosis of cirrhosis was based on the presence of clinical and laboratory features of portal hypertension (the presence of esophageal varices and/or collateral circulation at endoscopy and ultrasonography). The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by the Institutional Review Board. All blood tests were performed at the time of LSM.

Patient Follow-up and Diagnosis of HCC. Each patient was screened for HCC with ultrasonography at or immediately after the first visit and those in whom HCC was detected were not included in this study. Afterwards, patients were followed up at the outpatient clinic with blood tests including tumor markers and ultrasonography every 3 to 6 months. Contrast-enhanced computed tomography (CT) was performed when serum alpha fetoprotein (AFP) levels showed an abnormal rise and/or tumors were detected as possible HCC on ultrasonography.[32] HCC was diagnosed by dynamic CT, considering hyperattenuation in the arterial phase with washout in the late phase as the definite sign of HCC.[33,34] When the diagnosis of HCC was not clear, ultrasound-guided tumor biopsy was performed and pathological diagnosis was made based on Edmondson-Steiner criteria.[35] The last observation analyzed in this study was May 31, 2008.

Transient Elastography. LSM was performed using Fibroscan (Echosens, Paris, France), a new medical device based on elastometry.[21] The investigators had undergone a previous training period in which each had performed at least 50 measurements. The procedure is totally noninvasive and performed on the right lobe of the liver through the intercostal space. LSM was performed within 1 week after laboratory tests were obtained. Only LSM obtained in at least eight successful acquisitions with a success rate of at least 60% were considered valid.

Statistical Analysis. Data are expressed as the mean $\pm$ standard deviation (SD) and range in parentheses unless otherwise indicated. The categorical variables were compared by chi-square tests, whereas continuous variables were compared with unpaired Student's t test (parametric) or Mann-Whitney U test (nonparametric). A P-value < 0.05 on two-tailed test was considered significant. Annual incidence of hepatocarcinogenesis was assessed with the person-year method. Patients were censored at the time of death without HCC development, the last visit when lost to follow-up, or the end of the study period. Cumulative incidence of HCC was estimated using the Kaplan-Meier method. In the analysis of

risk factors for hepatocarcinogenesis, we tested the following variables obtained at the time of entry in univariate and multivariate Cox proportional hazard regression analysis: age, gender, body mass index (BMI), heavy alcohol drinking, liver stiffness, clinical cirrhosis, serum albumin concentration, total bilirubin concentration, ALT levels, aspartate aminotransferase (AST) levels prothrombin activity, platelet counts, and AFP concentration. Stepwise variable selection with Akaike information criterion (AIC) was used to find the best model in multivariate analysis. Multichotomous categorical variables were represented by corresponding binary dummy variables. Subgroup analyses using a Cox proportional hazard model was applied to estimate the hazard ratios (HRs) of higher LSM (>15 kPa) versus lower LSM (≤15 kPa), with their two-tailed *P*-values, for explanatory variables. The explanatory variables used for HR estimation were: age, gender, serum albumin concentration, BMI, AST level, ALT level, platelet counts, AFP concentration, clinical cirrhosis, and IFN therapy (with or without history of therapies and SVR or non-SVR during the follow-up period). The median value was chosen as each cutoff level. Processing and analysis were performed using S-PLUS 2000 (MathSoft, Seattle, WA).

Results

Patients' Profile. Between December 2004 and June 2005, a total of 876 patients underwent LSM. Ten patients were excluded because of unsuccessful measurements, mostly due to obesity (four patients had less than eight valid measurements and six had a success rate lower than 60%). Thus, 866 patients were included in the current analysis. Their characteristics at the time of LSM are summarized in Table 1. There were 398 men and 468 women, with a mean age of 62.2 ± 11.4 years. Heavy alcohol consumption was noted in 33 (3.8%). There were 109 patients whose AFP level exceeded 20 ng/mL.

Incidence of HCC. The mean follow-up period was 3.0 years, constituting 2,627 person-years overall. During the follow-up period a total of 35 (4.0%) patients had been lost to follow-up and censored at the time of last visit. Six patients died without HCC and they were censored at the time of death. The remaining patients were censored at the end of the study observation period (May 31, 2008). By the end of the follow-up, HCC developed in 77 patients (2.9% per 1 person-year). The cumulative incidence rates of HCC at 1, 2, and 3 years estimated by the Kaplan-Meier method were 2.4%, 6.0%, and 8.9%, respectively. The baseline characteristics of patients who developed HCC and those who did not are shown in Table 2.

Table 1. Baseline Characteristics of Patients (n = 866)

Variables	n = 866
Age (years) *	62.2 ± 11.3 (17–89)
Male, n (%)	398 (46.0)
Alcohol consumption > 80 g/day, n (%)	33 (3.8)
BMI (kg/m^2)*	22.5 ± 3.1 (14.4–36.9)
Serum albumin (g/dL)*	4.0 ± 0.4 (2.5–5.0)
Total bilirubin (mg/dL)*	0.8 ± 0.4 (0.3–4.6)
AST (IU/L)*	51 ± 34.2 (9–286)
ALT (IU/L)*	54 ± 46.9 (2–503)
Prothrombin time activity (%)*	84.9 ± 14.9 (38.9–100)
Platelet count (10^9/L)*	160 ± 67 (21–436)
AFP (ng/mL)*	14.9 ± 44.6 (0.8–591.8)
Liver stiffness (kPa)*	11.9 ± 9.7 (2.5–75)
IQR	2.4 ± 1.9 (0.5–12.0)
Success rate	78.5 ± 12.5 (60–100)
Patients who received IFN, n (%)	173 (20.0)
Patients who achieved SVR, n (%)	83 (9.6)

*Expressed as mean ± SD (range).

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; IQR, interquartile range; IFN, interferon; LSM, liver stiffness measurement; SVR, sustained virologic response.

Cause of Death. Two patients died of HCC. Two patients died of liver failure without HCC development. Four patients died of liver-unrelated causes. None received liver transplantation.

Incidence of HCC Stratified by LSM. Cumulative incidence rates at 1, 2, and 3 years in each group were 0.4%, 0.4%, and 0.4% (0.11% per 1 person year) in the patients with LSM ≤10 kPa; 1.4%, 5.5%, and 11.7% (2.9% per 1 person-year) in the patients with LSM 10.1-15 kPa; 3.8%, 12.0%, and 19.2% (5.0% per 1 person-year) in the patients with LSM 15.1-20 kPa; and 8.7%, 15.7%, and 25.2% (8.3% per 1 person-year) in the patients with LSM 20.1-25 kPa, 11.5%, 30.4%, and 38.5% (14.4% per 1 person-year) in the patients with LSM >25 kPa, respectively (Fig. 1). The incidence rates differed significantly among the five groups ($P < 0.001$ by the log-rank test), increasing in accordance with liver stiffness.

The number of patients who developed HCC and those who did not in each rank of LSM is shown in Table 3, together with a summary of some baseline characteristics. Patients who developed HCC tended to be older and have a higher AFP level at the time of entry than those in the same rank of LSM who did not develop cancer.

Risk Analyses. Univariate analyses showed that the risk of HCC increased in accordance with LSM (Table 4). Other significant risk factors for HCC included older age, male gender, clinical cirrhosis, heavy alcohol intake, lower serum albumin level, higher total bilirubin level, higher ALT and AST levels, lower prothrombin time activity, lower platelet counts, higher BMI level, AFP over 10 ng/mL, no treatment of IFN, and without SVR.

Table 2. Baseline Characteristics of Patients According to HCC Development

Variables	HCC Development (+), n = 77	HCC Development (−), n = 789	*P* Value
Age (years) *	68.2 ± 8.0 (50–89)	61.6 ± 11.5 (17–88)	<0.001
Male, n (%)	41 (53.2)	357 (45.2)	0.19
Alcohol consumption > 80 g/day, n (%)	7 (9.1)	26 (3.2)	0.02
BMI (kg/m^2)*	23.3 ± 3.1 (16.8–29.7)	22.4 ± 3.1 (14.4–36.9)	0.02
Serum albumin (g/dL)*	3.6 ± 0.4 (2.7–4.5)	4.0 ± 0.4 (2.5–5.0)	<0.001
Total bilirubin (mg/dL)*	1.1 ± 0.6 (0.4–3.3)	0.9 ± 0.4 (0.3–4.6)	<0.001
AST (IU/L)*	70 ± 33 (29–217)	49 ± 34 (9–286)	<0.001
ALT (IU/L)*	66 ± 42 (19–231)	53 ± 47 (2–503)	0.019
Prothrombin time activity (%)*	73.6 ± 10.9 (50–100)	86.1 ± 14.8 (38.9–100)	<0.001
Platelet count ($10^9/L$)*	104 ± 44 (36–246)	166 ± 66 (21–436)	<0.001
AFP (ng/mL)*	53.4 ± 111 (2.0–591.8)	11.1 ± 28.8 (0.8–339.4)	<0.001
Liver stiffness (kPa)*	26.0 ± 13.8 (8.9–69.1)	10.5 ± 8.0 (2.5–75)	<0.001
Clinical cirrhosis, n (%)	57 (74.0)	139 (17.6)	<0.001

*Expressed as mean ± SD (range).

Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index.

Stepwise variable selection with AIC was used to find the best model in multivariate analysis (Table 5). Patients with higher LSM were revealed to be at a significantly higher risk, with an HR of 16.7 (95% confidential interval [CI], 3.71-75.2; $P < 0.001$) with LSM 10.1-15 kPa, 20.9 (95% CI, 4.43-98.8; $P < 0.001$) with 15.1-20 kPa, 25.6 (95%CI, 5.21-126.1; $P < 0.001$) with 20.1-25 kPa, and 45.5 (95% CI, 9.75-212.3; $P < 0.001$) with >25 kPa, as compared to LSM ≤10 kPa. The presence of clinical cirrhosis is also found to be a significant risk factor for HCC development. LSM is thought to represent the degree of live fibrosis, whereas clinical cirrhosis is based not directly on fibrosis but on the degree of liver dysfunction and portal hypertension. Thus, these two factors are mutually related but not identical, and may be complementary in evaluating the risk of HCC. The other risk factors considered significant are older age, male gender, and serum albumin level.

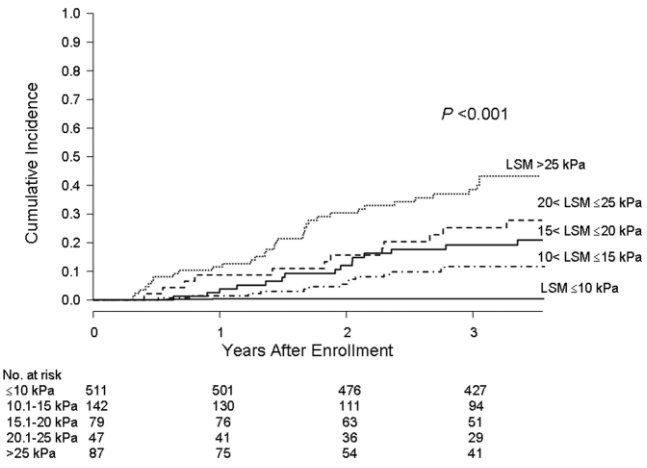

Fig. 1. Cumulative incidence of HCC development stratified based on LSM (N = 866). LSM, liver stiffness measurement.

The effects of LSM on the risk of HCC development were also evaluated in subgroup analyses to check whether higher LSM was a significant risk factor over strata (Fig. 2). Indeed, higher LSM was found to be a significant risk factor for HCC development in almost every subgroup. Interestingly, the HR attributed to higher LSM (>15 kPa) was greater in the subgroups unlikely to develop HCC, such as those with higher platelet count, absence of clinical cirrhosis, or lower AFP, than in the alternative subgroups. Higher LSM was a significant risk factor in both IFN-treated and IFN-untreated patients. Higher LSM may indicate a risk of HCC also among IFN-treated patients who achieved SVR, although statistical significance was not reached because of the small number of events among the subgroup (n = 2).

Discussion

Liver fibrosis is the strongest prognostic indicator of chronic hepatitis, which is currently best evaluated by liver biopsy.[6,17,36,37] However, liver biopsy has several disadvantages, including poor patient compliance, sampling errors, limited usefulness for dynamic follow-up, and a risk of complications. LSM has been confirmed to be well correlated with histological fibrosis stage in the literature.[18-22] We have previously shown the relationship between LSM and hepatocarcinogenesis in a cross-sectional study.[27] However, the results remained to be confirmed prospectively.

Various risk factors have been reported for HCC development among patients with HCV: older age,[6] male sex,[6] heavy alcohol intake,[38] high BMI,[39] cirrhosis,[6,16] lower platelet count, high serum AFP level,[40] low serum albumin level,[38] and high serum ALT level.[40] Our results were consistent with these findings. In the present cohort

Table 3. Characteristics of Patients in Each Rank of LSM

	Patients Who Developed HCC (n = 77)	Patients Who Did Not Develop HCC (n = 789)	*P* Value
LSM ≤ 10 kPa, n (%)	2 (0.4)	509 (99.6)	
Gender, male/female	0/2	231/278	0.50
Age, years*	74.5 ± 0.1	60.0 ± 11.8	0.08
AFP (ng/mL)*	11.2 ± 8.7	4.3 ± 4.8	0.07
Platelet count (per 10^9/L)*	141 ± 60	191 ± 60	0.24
LSM 10.1-15, n (%)	14 (10.0)	128 (90.0)	
Gender, male/female	11/3	68/60	0.12
Age, years*	68.7 ± 8.8	63.7 ± 11.0	0.10
AFP (ng/mL)*	12.3 ± 9.2	12.5 ± 9.2	0.06
Platelet count (per 10^9/L)*	114 ± 57	138 ± 54	0.13
LSM 15.1-20, n (%)	15 (19.0)	64 (81.0)	
Gender, male/female	9/6	25/39	0.23
Age, years*	69.3 ± 7.2	65.7 ± 9.5	0.17
AFP (ng/mL)*	31.8 ± 57.7	19.0 ± 25.3	0.59
Platelet count (per 10^9/L)*	117 ± 40	114 ± 48	0.84
LSM 20.4-25, n (%)	12 (25.5)	35 (74.5)	
Gender, male/female	7/5	8/27	0.05
Age, years*	70.0 ± 8.3	67.9 ± 9.0	0.46
AFP (ng/mL)*	17.2 ± 22.7	47.8 ± 79.0	0.14
Platelet count (per 10^9/L)*	119 ± 31	102 ± 38	0.18
LSM >25, n (%)	34 (39.1)	53 (61.9)	
Gender, male/female	14/20	25/28	0.74
Age, years*	66.4 ± 8.1	63.0 ± 9.9	0.09
AFP (ng/mL)*	95.1 ± 153.5	39.6 ± 60.5	0.005
Platelet count (per 10^9/L)*	87 ± 39	103 ± 55	0.15

*Expressed as mean ± SD.

study we have shown that LSM is also a significant risk factor of HCC development independent of these factors. Transient elastography can be considered as a surrogate marker for liver fibrosis. Although it is not clear whether liver fibrosis plays a direct role in hepatocarcinogenesis, the degree of fibrosis may be a surrogate for the accumulated DNA damage as a consequence of long-term necroinflammation and regeneration. A distinct advantage of LSM over liver biopsy is the wider dynamic range in the evaluation of liver cirrhosis. In the METAVIR[41] and Desmet et al.[42] scoring systems, cirrhosis is represented by a single category, F4. However, the degree of fibrosis may vary widely among patients in this category, and the risk of HCC may not be uniform. In the Ishak scoring system, incomplete cirrhosis scores 5 and complete cirrhosis scores 6 in fibrosis staging. Complete cirrhosis is not further divided. These histopathologic scoring systems are

Table 4. Risk Factors for HCC Development: Univariate Analysis

Variables	Hazard Ratio (95%CI)	*P* Value
Age (per 1 year old)	1.06 (1.04–1.09)	<0.001
Male	1.36 (0.87–2.01)	0.17
BMI (per 1 kg/m^2)	1.08 (1.01–1.16)	0.02
Alcohol consumption > 80g/day	1.81 (1.04–3.34)	0.03
Clinical cirrhosis	12.3 (7.3–20.6)	<0.001
LSM (kPa)		
≤10	1.00	
10.1-15	28.8 (6.55–126.8)	<0.001
15.1-20	54.7 (12.5–239.1)	<0.001
20.1-25	76.3 (17.1–340.7)	<0.001
>25	135.6 (32.6–564.8)	<0.001
Serum albumin (per 1.0 g/dL)	0.11 (0.07–0.17)	<0.001
Total bilirubin (per 1.0 mg/dL)	2.04 (1.53–2.70)	0.005
AST (per 1 IU/L)	1.01 (1.01–1.01)	<0.001
ALT (per 1 IU/L)	1.00 (1.00–1.01)	<0.001
Prothrombin time activity (per 1%)	0.94 (0.94–0.95)	<0.001
Platelet count (per 10^9/L)	0.84 (0.80–0.88)	<0.001
Patients treated by IFN	0.46 (0.22–0.95)	0.036
Patients with SVR	0.24 (0.059–0.97)	0.0045
AFP > 10 ng/mL	2.58 (2.05–3.25)	<0.001

Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; LSM, liver stiffness measurement.

Table 5. Risk Factors for HCC Development: Multivariate Analysis

Variables	Hazard Ratio (95%CI)	*P* Value
Age (per 1 year old)	1.04 (1.01–1.07)	<0.001
Male	1.62 (1.03–2.56)	<0.001
Clinical cirrhosis	2.11 (1.15–3.89)	<0.001
LSM (kPa)		
≤10	1.00	
10.1-15	16.7 (3.71–75.2)	<0.001
15.1-20	20.9 (4.43–98.8)	<0.001
20.1-25	25.6 (5.21–126.1)	<0.001
>25	45.5 (9.75–212.3)	<0.001
Serum albumin (per 1.0 g/dL)	0.52 (0.28–0.96)	<0.001

LSM, liver stiffness measurement.

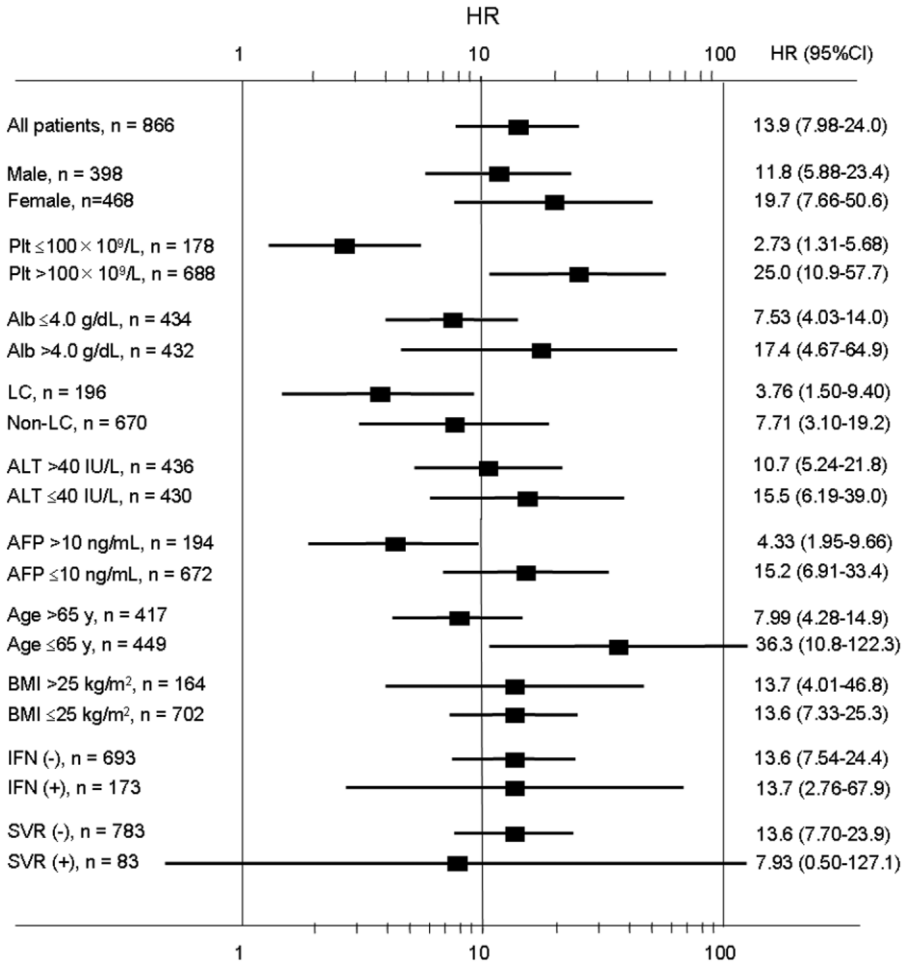

Fig. 2. Sensitivity analyses divided by risk factors. The risk of HCC development was evaluated in subgroups to check whether higher LSM was a significant risk factor over strata, which was confirmed in most subgroups. The HR attributed to higher LSM (>15 kPa) was greater in the subgroups less likely to develop HCC, such as those with higher platelet count, absence of clinical cirrhosis, or lower AFP, than in the alternative subgroups. HR, hazard ratio; LC, liver cirrhosis; ALT, alanine aminotransferase; AFP, alpha fetoprotein; BMI, body mass index; IFN, interferon; SVR, sustained virological response.

defined by qualitative characters, and thus do not constitute an interval scale.

Foucher et al.[19] reported that the LSM in cirrhotic patients ranged from 17.6 to 75 kPa (maximum measurable value) and correlated well with clinical parameters indicating severity of cirrhosis. They established the cutoff values for complications of cirrhosis with a negative predictive value of greater than 90%. The cutoff was 27.5 kPa for the presence of esophageal varices stage 2/3, 37.5 kPa for liver function Child B or C, 49.1 kPa for a past history of ascites, 53.7 kPa for HCC, and 62.7 kPa for esophageal variceal bleeding. In other words, cirrhosis can be further stratified with clinical relevance based on LSM. In the current study the risk of HCC development increased in accordance with LSM, even within the range of cirrhosis, reemphasizing the importance of further stratification of cirrhosis.

In clinical practice, surveillance is intensively performed on patients at high risk of development of HCC. Our data suggested that LSM may sometimes be high even in patients without other risk factors for HCC such as low platelet count, low albumin level, or high bilirubin level. Such patients are nevertheless at a high risk of HCC, which indicates that transient elastography complements other laboratory tests in identifying high-risk patients. Indeed, among 77 patients who developed HCC, 19 patients were diagnosed as noncirrhosis by clinical parameters. However, LSM was higher than 15 kPa in eight of these 19 patients (data not shown). Subgroup analyses also suggest that even in those patients who are unlikely to develop HCC, i.e., female, young, with high platelet count, low BMI, low transaminase level, and low AFP level, a high LSM indicates a significant risk of HCC development.

One of the limitations of the present study is that this cohort was constructed based on a split-sample technique. Although validation in an independent study population will be of greater value, the number of patients is currently not large enough for that. Another limitation is the fact that about 20% of the patients underwent IFN therapy after enrollment, possibly affecting disease progression and hepatocarcinogenesis. Among those who underwent IFN therapy, 83 patients achieved SVR and two among them developed HCC during the follow-up period. LSM

was 12 kPa and 21.8 kPa, respectively, in these two patients. This result suggests that patients with a high LSM need attention for the development of HCC even after achieving SVR by IFN therapy. The changes in LSM after IFN therapy, especially after achieving SVR, together with the changes in the risk of HCC development, is to be elucidated in future studies.

In the present study, HCC rarely developed in patients with LSM ≤10 kPa. The two patients who did develop HCC in spite of low LSM had F3 liver fibrosis at the time of HCC development and one of them had esophageal varices on endoscopy. Moreover, those patients who developed HCC in spite of lower LSM tended to be of older age and had higher baseline AFP levels and lower platelet counts than those patients in the same range of LSM who did not develop cancer. Thus, patients with clinical cirrhosis or other risk factors need proper attention for HCC development even if the LSM is low.

In conclusion, this prospective cohort study has shown the association between LSM and the risk of HCC development in chronic HCV patients. The utility of LSM is not limited to a surrogate for liver biopsy but can be applied as a dynamic indicator of the risk of HCC development.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
2. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. Gastroenterology 2004;127:S27-S34.
3. Colombo M, de Franchis R, Del Ninno E, Sangiovanni A, De Fazio C, Tommasini M, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med 1991;325:675-680.
4. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362:1907-1917.
5. Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993;328:1797-1801.
6. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. Ann Intern Med 1999;131:174-181.
7. Ikeda K, Saitoh S, Koida I, Arase Y, Tsubota A, Chayama K, et al. A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis. HEPATOLOGY 1993;18:47-53.
8. Zoli M, Magalotti D, Bianchi G, Gueli C, Marchesini G, Pisi E. Efficacy of a surveillance program for early detection of hepatocellular carcinoma. Cancer 1996;78:977-985.
9. Cottone M, Turri M, Caltagirone M, Parisi P, Orlando A, Fiorentino G, et al. Screening for hepatocellular carcinoma in patients with Child's A cirrhosis: an 8-year prospective study by ultrasound and alphafetoprotein. J Hepatol 1994;21:1029-1034.
10. Oka H, Kurioka N, Kim K, Kanno T, Kuroki T, Mizoguchi Y, et al. Prospective study of early detection of hepatocellular carcinoma in patients with cirrhosis. HEPATOLOGY 1990;12:680-687.
11. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341:556-562.
12. EASL International Consensus Conference on hepatitis C. Paris, 26-27 February 1999. Consensus statement. J Hepatol 1999;31(Suppl 1):3-8.
13. Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH. Pathogenesis, natural history, treatment, and prevention of hepatitis C. Ann Intern Med 2000; 132:296-305.
14. Kiyosawa K, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Gad A, et al. Hepatocellular carcinoma: recent trends in Japan. Gastroenterology 2004;127:S17-S26.
15. Velazquez RF, Rodriguez M, Navascues CA, Linares A, Perez R, Sotorrios NG, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. HEPATOLOGY 2003;37:520-527.
16. Takano S, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. HEPATOLOGY 1995;21:650-655.
17. Dienstag JL. The role of liver biopsy in chronic hepatitis C. HEPATOLOGY 2002;36:S152-S160.
18. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343-350.
19. Foucher J, Chanteloup E, Vergniol J, Castera L, Le Bail B, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55:403-408.
20. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. HEPATOLOGY 2005;41:48-54.
21. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705-1713.
22. Ganne-Carrie N, Ziol M, de Ledinghen V, Douvin C, Marcellin P, Castera L, et al. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. HEPATOLOGY 2006;44:1511-1517.
23. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. HEPATOLOGY 2003;38:518-526.
24. Le Calvez S, Thabut D, Messous D, Munteanu M, Ratziu V, Imbert-Bismut F, et al. The predictive value of Fibrotest vs. APRI for the diagnosis of fibrosis in chronic hepatitis C. HEPATOLOGY 2004;39:862-863; author reply, 863.
25. Fontana RJ, Lok AS. Noninvasive monitoring of patients with chronic hepatitis C. HEPATOLOGY 2002;36:S57-S64.
26. Ngo Y, Munteanu M, Messous D, Charlotte F, Imbert-Bismut F, Thabut D, et al. A prospective analysis of the prognostic value of biomarkers (FibroTest) in patients with chronic hepatitis C. Clin Chem 2006;52: 1887-1896.
27. Masuzaki R, Tateishi R, Yoshida H, Yoshida H, Sato S, Kato N, et al. Risk assessment of hepatocellular carcinoma in chronic hepatitis C patients by transient elastography. J Clin Gastroenterol 2008;42:839-843.
28. Maharaj B, Maharaj RJ, Leary WP, Cooppan RM, Naran AD, Pirie D, et al. Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver. Lancet 1986;1:523-525.
29. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97: 2614-2618.

30. Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. HEPATOLOGY 2004;39: 280-282.
31. Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. HEPATOLOGY 2007;45:1290-1297.
32. Daniele B, Bencivenga A, Megna AS, Tinessa V. Alpha-fetoprotein and ultrasonography screening for hepatocellular carcinoma. Gastroenterology 2004;127:S108-S112.
33. Torzilli G, Minagawa M, Takayama T, Inoue K, Hui AM, Kubota K, et al. Accurate preoperative evaluation of liver mass lesions without fine-needle biopsy. HEPATOLOGY 1999;30:889-893.
34. Bruix J, Sherman M. Management of hepatocellular carcinoma. HEPATOLOGY 2005;42:1208-1236.
35. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954;7:462-503.
36. Yano M, Kumada H, Kage M, Ikeda K, Shimamatsu K, Inoue O, et al. The long-term pathological evolution of chronic hepatitis C. HEPATOLOGY 1996;23:1334-1340.
37. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. HEPATOLOGY 2004;39:1147-1171.
38. Ikeda K, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Koida I, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. J Hepatol 1998;28:930-938.
39. Ohki T, Tateishi R, Sato T, Masuzaki R, Imamura J, Goto T, et al. Obesity is an independent risk factor for hepatocellular carcinoma development in chronic hepatitis C patients. Clin Gastroenterol Hepatol 2008;6:459-464.
40. Inoue A, Tsukuma H, Oshima A, Yabuuchi T, Nakao M, Matsunaga T, et al. Effectiveness of interferon therapy for reducing the incidence of hepatocellular carcinoma among patients with type C chronic hepatitis. J Epidemiol 2000;10:234-240.
41. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. HEPATOLOGY 1996;24:289-293.
42. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. HEPATOLOGY 1994;19:1513-1520.