Liver stiffness measurement in the risk assessment of hepatocellular carcinoma for patients with chronic hepatitis

Yuan-Hung Kuo · Sheng-Nan Lu · Chao-Hung Hung · Kwong-Ming Kee · Chien-Hung Chen · Tsung-Hui Hu · Chuan-Mo Lee · Chi-Sin Changchien · Jing-Houng Wang

Received: 22 June 2010 / Accepted: 18 September 2010 / Published online: 8 October 2010
© Asian Pacific Association for the Study of the Liver 2010

Abstract

Background/aims The risk of hepatocellular carcinoma (HCC) increased with progression of hepatic fibrosis as assessed by liver stiffness measurement (LSM). This study used LSM to assess the risk of HCC presence in patients with chronic hepatitis.

Methods The patients with liver tumor or chronic hepatitis indicated for biopsy were prospectively enrolled. LSM was performed on the same day as biopsy. The diagnostic performances of clinical parameters and LSM in predicting HCC presence were compared with the areas under receiver operating characteristics curves (AUROC). The risk of HCC presence was assessed with stratum-specific likelihood ratios (SSLR). The cut-off values and its diagnostic validity were calculated for LSM.

Results A total of 435 patients, including 106 HCC and 329 chronic hepatitis, were enrolled. The AUROC in predicting HCC presence was 0.736, 0.733, 0.594, 0.579 and 0.532 for LSM, alpha-fetoprotein, platelet count, total bilirubin, and aspartate aminotransferase–platelet ratio index, respectively. Multivariate analysis showed liver stiffness was an independent factor for HCC presence (odds ratio 1.07, 95% confidence interval (CI) 1.05–1.09). SSLR for HCC presence by liver stiffness was 0.43 (95% CI 0.32–0.57) in <12 kPa, 1.28 (0.89–1.84) in 12–24 kPa, and 5.94 (3.77–9.35) in >24 kPa. With 12 and 24 kPa as the cut-offs in predicting HCC presence, the sensitivity was

69.8 and 41.5%, respectively. The specificity was 69.6 and 92.7%, respectively.

Conclusions LSM identified the risk group for HCC presence in chronic hepatitis patients and had high specificity in the prediction of HCC with the cut-off of 24 kPa.

Keywords Hepatocellular carcinoma · Transient elastography · Liver stiffness measurement · Stratum-specific likelihood ratios (SSLR)

Introduction

Liver fibrosis is a wound-healing response to chronic liver injury, which may contribute to cirrhosis and hepatocellular carcinoma (HCC) [1]. Chronic infection of hepatitis B virus (HBV) or C virus (HCV) leads to progressive liver fibrosis and is the main cause of chronic liver disease. Hence, the incidence of HCC is particularly high in geographical areas where there is the prevalence of HBV or HCV infection [2]. The degree of liver fibrosis has been reported to be a strong predictor of risk of HCC development [3]. Therefore, the assessment of liver fibrosis is important in identifying patients at high risk of HCC development, for whom surveillance for HCC is necessary. Percutaneous liver biopsy remains the standard method for assessing fibrosis [4]; however, sampling variability and possible serious complications limit its acceptance by patients [5–7].

Transient elastography (TE) is an ultrasound-based technique for measuring liver stiffness by the difference in the velocity of the elastic shear wave propagation across the liver. Liver stiffness measurement (LSM) by TE is a rapid, non-invasive, reproducible and operator-friendly method, which has been reported as accurately representing

Y.-H. Kuo · S.-N. Lu · C.-H. Hung · K.-M. Kee · C.-H. Chen · T.-H. Hu · C.-M. Lee · C.-S. Changchien · J.-H. Wang (✉)
Division of Hepato-Gastroenterology, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, 123 Ta-Pei Rd, Niao-Sung, Kaohsiung 833, Taiwan
e-mail: wajing@adm.cgmh.org.tw

the state of liver fibrosis [8–12]. It was recently proposed to assess the risk of HCC development in patients with chronic HCV infection by TE [13]. The aim of this study was to assess the relationship between liver stiffness and the risk of HCC presence in patients with chronic hepatitis.

Patients and methods

Between July 2006 and October 2007, consecutive patients with liver tumor suspicious of HCC or with chronic hepatitis indicated for biopsy were enrolled. There was no HCC in those patients with chronic hepatitis. LSM was performed on the same day before liver biopsy. Chronic hepatitis C or chronic hepatitis B was defined as a detectable serum antibody for HCV (anti-HCV) or HBV surface antigen (HBsAg) longer than 6 months. Biochemical and clinical parameters were obtained from the patients on the day of LSM. The variables recorded included the patient's age, gender, etiology of liver disease, body-mass index (BMI), serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) level, total bilirubin concentration, platelet cell count and alpha-fetoprotein (AFP) level. The AST–platelet ratio index (APRI) was calculated according to the formula: $[\text{AST (upper limit of normal)/platelet count (10}^9/\text{l)}] \times 100$. Exclusion criteria were patients that failed the liver stiffness measurement or with liver tumor other than HCC by pathology. The study protocol was approved by the Institution Review Board of Chang Gung Memorial Hospital. Patients were enrolled after giving their written informed consents.

Liver stiffness measurement

LSM was performed with a FibroScan[®] (Echosens, Paris, France) system, a device based on one-dimensional transient elastography technique. The details of the technical background and examination procedure have been previously defined [12]. The result was considered reliable only when 10 validated measurements had been obtained with a success rate greater than 60%.

Statistical analysis

LSM results were expressed as a median value with an interquartile range (IQR) in kilopascal (kPa). The Student *t* test or the chi-square test was used to compare the continuous or discrete variables, respectively. The logistic regression model was used in the multivariate analysis. The diagnostic performances of LSM and serum biomarkers in predicting HCC presence were evaluated by receiver

operating characteristic (ROC) curves. The area under the ROC curves (AUROC) and its 95% confidence interval (CI) were used to assess the diagnostic accuracy and compared with the Hanley and McNeil method [14, 15]. The cut-off value was determined on the basis of the level of validity required. The stratum-specific likelihood ratio (SSLR) is the probability of a test result within a given range or stratum when the disease is present, divided by the probability of the same test result when the disease is absent [16, 17]. We determined these risk ratios by means of the formula $\text{SSLR} = (x_1/n_1)/(x_0/n_0)$, where x_1 is the number of patients in the stratum with HCC, n_1 is the total number with HCC, x_0 is the number of patients in the stratum without HCC, and n_0 is the total number of patients without HCC. The 95% confidence interval (CI) of each SSLR was calculated following the principle proposed by Peirce et al. [16]. Statistical analyses were performed with the Statistical Package for the Social Sciences 15.0 (SPSS Inc, Chicago, Ill). All *p* values were derived from 2-tailed tests, and a level of <0.05 was accepted as statistically significant.

Results

Patients

Four hundred and thirty-five patients were enrolled in the study, including 106 newly diagnosed HCC patients and 329 chronic hepatitis patients. The demographics and clinical characteristics of all patients are summarized in Table 1. The patients with HCC were significantly older. In chronic hepatitis patients, HCV infection accounted for the main etiology; however, chronic HBV infection was more than HCV infection in HCC patients. The proportion of liver cirrhosis was higher in HCC patients than in chronic hepatitis patients (75.5 vs. 22.5%, $p < 0.001$). HCC was single nodule in 39 (36.8%) patients, 2 nodules in 25 (23.6%) patients, and 3 or more than 3 nodules in 42 (39.6%) patients. The tumor size ranged from 1.0 to 13.0 cm (mean $\pm$ SD, 2.2 ± 1.9 cm). Twenty-three (21.7%) HCC patients and 13 (4%) chronic hepatitis patients had an AFP level of more than 200 ng/ml. The serum ALT level was lower in patients with HCC than in chronic hepatitis patients; on the contrary, APRI was higher in HCC patients. Liver stiffness ranged from 3.9 to 75.0 kPa (mean $\pm$ SD, 28.2 ± 23.4 kPa) in HCC patients and from 2.3 to 67.9 kPa (mean $\pm$ SD, 11.1 ± 8.7 kPa) in chronic hepatitis patients. HCC patients had significantly higher liver stiffness than chronic hepatitis patients. There were no significant differences in BMI, platelet count, AST and bilirubin level in both groups.

Table 1 The demographics and clinical characteristics of enrolled patients ($n = 435$)

	Patients without HCC ($n = 329$)	Patients with HCC ($n = 106$)	p value
Age (years, mean $\pm$ SD)	51.0 $\pm$ 11.8	61.8 $\pm$ 11.8	<0.001
Gender (%)			<0.001
Male	203 (61.7)	84 (79.2)	
Female	126 (38.3)	22 (20.8)	
Etiology (%)			<0.001
HBV	87 (26.4)	44 (41.5)	
HCV	213 (64.7)	35 (33)	
HBV + HCV	19 (5.8)	9 (8.5)	
Non-B/non-C	10 (3.0)	18 (17)	
Liver cirrhosis (%)	74 (22) ^a	80 (75.5) ^b	<0.001
BMI (kg/m ²)	24.2 $\pm$ 3.4	23.6 $\pm$ 3.5	0.110
AST (u/l)	87.5 $\pm$ 67.8	86.9 $\pm$ 67.6	0.944
ALT (u/l)	123.2 $\pm$ 111.8	76.2 $\pm$ 75.9	<0.001
Platelet ($\times 10^3/\text{mm}^3$)	180.6 $\pm$ 65.0	172.7 $\pm$ 111.4	0.371
APRI	1.6 $\pm$ 1.5	2.0 $\pm$ 2.4	0.028
Bilirubin (mg/dl)	1.02 $\pm$ 0.88	1.63 $\pm$ 4.39	0.018
AFP (ng/ml, %)			<0.001
<200	316 (96)	83 (78.3)	
≥ 200	13 (4)	23 (21.7)	
Stiffness (kPa)	11.2 $\pm$ 8.9	26.7 $\pm$ 22.5	<0.001
Log stiffness (kPa)	0.96 $\pm$ 0.26	1.27 $\pm$ 0.38	<0.001

HBV hepatitis B virus,
HCC hepatocellular carcinoma,
HCV hepatitis C virus,
Non-B/Non-C etiology outside
from HBV or HCV,
BMI body-mass index,
AST aspartate aminotransferase,
ALT alanine aminotransferase,
APRI AST–platelet ratio index,
AFP alpha-fetoprotein

^a Confirmed by pathology

^b Diagnosis with images
including ultrasonography
and/or computed tomography

The diagnostic performance of LSM and serum markers

Figure 1 showed box plots of liver stiffness in patients with chronic hepatitis and HCC, who were stratified as total, HBV and HCV patients. The median levels of the liver stiffness between patients with and without HCC were 17.6 and 8.4 kPa for all patients; 16.0 and 7.4 kPa for HBV patients; and 18.2 and 8.1 kPa for HCV patients, respectively (all $p < 0.001$). Liver stiffness was significantly higher in HCC patients than chronic hepatitis patients, irrespective of etiology. Figure 2 shows the ROC curves of liver stiffness and serum markers in predicting HCC presence. The performances, as assessed by AUROC, were 0.736 (95% CI 0.691–0.778), 0.733 (0.688–0.776), 0.594 (0.545–0.642), 0.579 (0.530–0.628) and 0.532 (0.482–0.581) for liver stiffness, AFP level, platelet count, total bilirubin level and APRI, respectively. The diagnostic accuracy of liver stiffness for HCC presence was superior to platelet count, bilirubin level and APRI ($p < 0.001$). However, there is no significant difference between liver stiffness and AFP ($p = 0.930$).

Associated factors of HCC presence

Multivariate analysis showed that high liver stiffness, old age, male gender and elevated AFP level were independent factors for HCC presence. The odds ratio related to HCC

presence was 1.07 (95% CI 1.05–1.09) for liver stiffness, 1.09 (1.06–1.12) for age, 2.66 (1.37–5.19) for male and 16.29 (2.54–104.41) for AFP level more than 200 ng/ml (Table 2).

SSLR for HCC presence

To estimate the likelihood ratios of HCC presence, we ranked the values of liver stiffness into 3 strata. For all patients, the SSLR for HCC presence was 0.43 (95% CI 0.32–0.57), 1.28 (0.89–1.84), and 5.94 (3.77–9.35) for liver stiffness <12, 12–24 and >24 kPa, respectively (Table 3). Stratified according to virus etiology; for HBV patients, SSLR was 0.42 (95% CI 0.26–0.68), 1.32 (0.74–2.33) and 6.72 (2.77–17.02) for liver stiffness <10, 10.1–24, and >24 kPa, respectively. For HCV patients, SSLR was 0.49 (95% CI 0.31–0.78), 1.04 (0.54–2.00) and 5.71 (3.11–10.47) for liver stiffness <12, 12–24 and >24 kPa, respectively. Irrespective of virus etiology, the relative risk of HCC presence increased with the progression of liver stiffness.

The cut-off and its diagnostic validity of LSM

The cut-off of liver stiffness in diagnosing presence of HCC, as determined with the maximal sum of sensitivity and specificity, was 12 kPa. The sensitivity and specificity was 69.8 and 69.6% for all patients, 70.5 and 75.9% for HBV patients, 65.7 and 69.5% for HCV patients, respectively.

Fig. 1 Box plots of liver stiffness for hepatocellular carcinoma (HCC) presence in the total of 435 patients, 131 chronic hepatitis B (HBV) and 248 chronic hepatitis C (HCV) patients. The top and bottom of the boxes are the first and third quartiles, respectively. The length of the box thus represents the interquartile range (IQR) within which 50% of the values were located. The lines through the middle

of the boxes represent the median. The error bars are the minimum and maximum values. The median levels of liver stiffness between patients with and without HCC were 17.6 and 8.4 kPa for all patients; 16.0 and 7.4 kPa for HBV patients; and 18.2 and 8.1 kPa for HCV patients, respectively. (all $p < 0.001$)

Fig. 2 Receiver operating characteristic (ROC) curves for liver stiffness, alpha-fetoprotein (AFP), platelet count, bilirubin level, and aspartate aminotransferase-platelet ratio index (APRI). The areas under the ROC curves (AUROC) for HCC presence are 0.736, 0.733, 0.594, 0.579 and 0.532, respectively. The difference between liver stiffness and AFP is not statistically significant ($p = 0.930$). But the AUROC of liver stiffness is superior to platelet count, bilirubin level or APRI ($p < 0.001$)

The cut-off, as determined with specificity more than 90%, was 24 kPa. The sensitivity and specificity was 41.5 and 92.7% for all patients, 38.6 and 93.1% for HBV patients, 42.9 and 92.5% for HCV patients, respectively.

Table 2 Multivariate analysis for risk factors of hepatocellular carcinoma presence

Variables	Odds ratio (95% CI)	p value
Stiffness (kPa)	1.07 (1.05–1.09)	<0.001
Age (year)	1.09 (1.06–1.12)	<0.001
Gender		
Female	1	0.004
Male	2.66 (1.37–5.19)	
AFP (ng/ml)		
<200	1	0.003
≥200	16.29 (2.54–104.41)	

AFP alpha-fetoprotein, CI confidence interval

Discussion

Liver biopsy is the best standard for the assessment of liver fibrosis [4], although wound pain and possible severe complications restrict its clinical practice [5–7]. Using non-invasive LSM by TE to assess the stage of liver fibrosis has been proposed in several cohort studies [8–12]. A recent meta-analysis [18] showed that the mean AUROC for the diagnosis of cirrhosis by TE was high, at 0.94 (95% CI 0.93–0.95). The sensitivity was 87% (95% CI 84–90%), specificity 91% (95% CI 89–92), positive likelihood ratio 11.7 (95% CI 7.9–17.1), and negative likelihood ratio 0.14 (95% CI 0.10–0.20). For the detection of cirrhosis, TE is currently the most accurate non-invasive tool and allowed the saving of the liver biopsy in 90% of cases [19]. In this study, we further demonstrated that LSM was an

Table 3 The likelihood ratio of presence of hepatocellular carcinoma (HCC) stratified according to all patients, patients with hepatitis B virus (HBV), or C virus infection (HCV) analyzed with stratum-specific likelihood ratio (SSLR) of liver stiffness

Strata (kPa)	Patients without HCC	Patients with HCC	SSLR (95% CI)
All patients (<i>n</i> = 435)			
<12	233	32	0.43 (0.32–0.57)
12–24	73	30	1.28 (0.89–1.84)
>24	23	44	5.94 (3.77–9.35)
HBV patients (<i>n</i> = 131)			
<10	61	13	0.42 (0.26–0.68)
10–24	21	14	1.32 (0.74–2.33)
>24	5	17	6.72 (2.66–17.02)
HCV patients (<i>n</i> = 248)			
<12	150	12	0.49 (0.31–0.78)
12–24	47	8	1.04 (0.54–2.00)
>24	16	15	5.71 (3.11–10.47)

independent factor in the prediction of HCC presence. And the risk of HCC presence increased with advancement of cirrhosis. With liver stiffness ≥ 24 kPa, the likelihood ratio of HCC presence was 5.9 for chronic hepatitis patients. The sensitivity and specificity in the prediction of HCC presence was 41.5 and 92.7%, respectively.

SSLR was the statistical method used to evaluate the risk of disease by a fixed optimal cut-off point [16]. For continuous scores like liver stiffness, SSLRs provide sufficient information for the possibility of disease occurrence by stratifying the population with a given range. Because, with too many strata, the likelihood ratios become unstable and degenerate, we obtained three strata following the principle reported by Peirce and Cornell [16]. Our previous study indicated 12, 12 and 10 kPa as the cut-offs for cirrhosis in all patients, chronic HCV and HBV patients [12], the levels of liver stiffness were used as the cut-off between the lower and medium strata. We used 24 kPa as the cut-off between the medium and higher strata due to the point having a significant difference from the two strata. In the current study, it seems that the possibility of HCC presence was smaller in “non-cirrhotic” patients detected by TE. Even in so-called “cirrhotic” patients, the possibility of HCC presence was elevated slightly when the liver stiffness was less than 24 kPa. However, once the stiffness exceeded 24 kPa, this possibility rose steeply, which was comparable with the report on patients with HCV by Masuzaki et al. [13]. He pointed out that the possibility of HCC presence in HCV-related cirrhosis patients increases from 1.3- to 5-fold when the liver stiffness is higher than 25 kPa. In our study, the risk of HCC presence increased greatly when liver stiffness exceeds 24 kPa, not only for patients with HCV but also for patients with HBV. Hence, the stiffer the liver, the higher risk of HCC the cirrhosis patient might experience.

The likelihood ratio for HCC presence in HCV patients between >24 and <12 kPa was 11.7, whereas in HBV

patients between >24 and <10 kPa it was 16. In cirrhotic liver at the same stiffness level, HBV patients seemed to have higher risk of HCC presence than HCV patients. This might be due to the differences between HBV and HCV in the mechanisms of hepatocarcinogenesis [20, 21]. Except for virus protein in the induction of carcinogenesis in both viruses, HBV viral sequences could be directly integrated into the host genome, which increases the genomic instability and induces HCC development. However, integration of the viral sequences into the host genome does not occur in HCV infection. This difference might explain why patients with HBV infection are at higher risk of developing HCC than patients with HCV infection with the same liver stiffness level.

Those patients with chronic hepatitis enrolled in our study had a higher liver stiffness value due to hepatic inflammation. The degree of liver stiffness in these patients might reduce after their recovery from hepatic inflammation [22], whose severity of liver stiffness in the current study might be over-estimated. Therefore, the likelihood ratio of HCC presence for liver stiffness exceeding 24 kPa might be higher than estimated in this study, if the ALT level was comparable between patients both with and without HCC.

Patients with liver cirrhosis are a high-risk group for the development of HCC. However, the risk of HCC development might be different in patients with different degrees of liver cirrhosis. Case-control study showed that Child-Pugh A cirrhotic patients with HCC had higher liver stiffness values than those without HCC [23]. Our study also proved that those cirrhotic patients with HCC had stiffer liver than those without [LSM values (mean $\pm$ SD) 27.9 $\pm$ 22.1 kPa vs. 20.0 $\pm$ 11.9 kPa, $p < 0.001$]. A recent prospective and longitudinal study also demonstrated the association between liver stiffness and HCC development in patients with chronic hepatitis C [24]. LSM had the potential indication of systemic screening of populations at high risk of chronic liver disease [25]. In our study, LSM was

demonstrated useful in stratifying high-risk group of HCC presence in cirrhosis patients. Therefore, it might be a useful tool in screening patients at high risk of HCC.

In clinical practice, regular HCC surveillance with ultrasonography for cirrhosis patients is recommended to detect early stage HCC and improve the patients' survival [26, 27]. To yield better cost-effective results, there might be different screening or surveillance programs for HCC stratified according to liver stiffness values for patients with chronic hepatitis or cirrhosis. However, the ideal cut-off value of liver stiffness in the implementation of HCC surveillance program is still unknown. In a cohort of patients with chronic liver disease, the cut-off was 53.7 kPa for diagnosis of HCC presence with a negative predictive value more than 90% [8]. In our patients population, we determined that 24 kPa is a useful cut-off, with a specificity of more than 90%, to implement screening or surveillance program for HCC in patients with chronic hepatitis. The discrepancy of cut-offs between studies might be explained by differences in the study populations and in etiologies of enrolled patients. Further prospective studies are necessary in determining the ideal cut-off of liver stiffness in the initiation of HCC screening and surveillance programs for patients with chronic hepatitis.

Thrombocytopenia and high APRI were validated markers to identify the risk group for HCC development in cirrhosis patients [28, 29]. However, the diagnostic accuracies of these serum markers, including platelet count, total bilirubin and APRI, in their prediction of HCC presence were low, with an AUROC between 0.5 and 0.6 in this study. Serum AFP was a more accurate predictor for HCC presence in our study. However, none of these serum markers were liver specific and might be affected by other co-morbid disease. Compared with these serum markers, LSM was a liver-specific method and superior or equal to the serum markers in the prediction of HCC presence in the current study.

In conclusion, LSM with FibroScan® identified the risk group for HCC presence in chronic hepatitis patients, irrespective of the virus etiology. With the cut-off of 24 kPa, LSM had high specificity in the prediction of HCC for patients with chronic hepatitis.

Acknowledgement This study was supported by a grant from Chang Gung Memorial Hospital (CMRP G850141) to Sheng-Nan Lu. The authors thank C.Y. Lin for her excellent assistance in statistics and C.L. Li for her secretarial assistance.

References

- Benvegna L, Gios M, Boccato S, et al. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut* 2004;53:744–749
- Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004;127:S35–S50
- Yoshida H, Shiratori Y, Moriyama 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
- Bravo AA, Sheth SG, Chopra S. Liver biopsy. *N Engl J Med* 2001;344:495–500
- Regev A, Berho M, Jeffers LJ, et al. Sampling error and inter-observer variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol* 2002;97:2614–2618
- Bedossa P, Dalgere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003;38:1449–1457
- Piccinino F, Sagnelli E, Pasquale G, et al. Complications following percutaneous liver biopsy: a multicentre retrospective study on 68276 biopsies. *J Hepatol* 1986;2:165–173
- Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 2006;55:403–408
- Fraquelli M, Rigamonti C, Casazza G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. *Gut* 2007;56:968–973
- Ganne-Carrie N, Ziol M, de Ledinghen V, et al. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. *Hepatology* 2006;44:1511–1517
- Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003;29:1705–1713
- Wang JH, Changchien CS, Hung CH, et al. FibroScan and ultrasonography in the prediction of hepatic fibrosis in patients with chronic viral hepatitis. *J Gastroenterol* 2009;44:439–446
- Masuzaki R, Tateishi R, Yoshida H, et al. Risk assessment of hepatocellular carcinoma in chronic hepatitis C patients by transient elastography. *J Clin Gastroenterol* 2008;42:839–843
- Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29–36
- Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839–843
- Peirce JC, Cornell RG. Integrating stratum-specific likelihood ratios with the analysis of ROC curves. *Med Decis Making* 1993;13:141–151
- Furukawa TA, Goldberg DP, Rabe-Hesketh S, et al. Stratum specific likelihood ratios of two versions of the general health questionnaire. *Psychol Med* 2001;31:519–529
- Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. *Gastroenterology* 2008;134:960–974
- Castéra L, Le Bail B, Roudot-Thoraval F, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. *J Hepatol* 2009;50:59–68
- Szabó E, Páska C, Kaposi Novák P, et al. Similarities and differences in hepatitis B and C virus induced hepatocarcinogenesis. *Pathol Oncol Res* 2004;10:5–11
- Gurtsevitch VE. Human oncogenic viruses: hepatitis B and hepatitis C viruses and their role in hepatocarcinogenesis. *Biochemistry (Mosc)*. 2008;73:504–513
- Sagir A, Erhardt A, Schmitt M, et al. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. *Hepatology* 2008;47:592–595

23. Nahon P, Kettaneha A, Lemoine M, et al. Liver stiffness measurement in patients with cirrhosis and hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2009;21:214–219
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. Del Poggio P, Colombo S. Is transient elastography a useful tool for screening liver disease? *World J Gastroenterol* 2009;15:1409–1414
26. Bruix J, Sherman M, Practice guidelines committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208–1236
27. Kudo M, Okanoue T, Japan Society of Hepatology. Management of hepatocellular carcinoma in Japan: consensus-based clinical practice manual proposed by the Japan Society of Hepatology. *Oncology* 2007;72:S2–S15
28. Lu SN, Wang JH, Liu SL, et al. Thrombocytopenia as a surrogate for cirrhosis and a marker for the identification of patients at high-risk for hepatocellular carcinoma. *Cancer* 2006;107:2212–2222
29. Sinn DH, Paik SW, Kang P, et al. Disease progression and the risk factor analysis for chronic hepatitis C. *Liver Int* 2008; 28:1363–1369