ORIGINAL ARTICLE

Prediction of postoperative hepatic insufficiency by liver stiffness measurement (FibroScan®) before curative resection of hepatocellular carcinoma: a pilot study

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Abstract

Background Liver stiffness measurement (LSM) using transient elastography (FibroScan®) reflects the degree of hepatic fibrosis. This prospective study investigated how well LSM predicts the development of hepatic insufficiency after curative liver resection surgery for hepatocellular carcinoma.

Methods The study enrolled 72 consecutive patients who underwent a preoperative LSM to assess the degree of liver fibrosis followed by curative liver resection surgery for hepatocellular carcinoma between July 2006 and December 2007. The primary end point was the development of hepatic insufficiency.

Results The mean age of the patients was 54.9 years. Twenty patients (27.7%) had chronic hepatitis and 52 (72.3%) had cirrhosis (44 and 8 patients showed Child-Pugh class A and B, respectively). The mean LSM was 17.1 kPa. Twelve patients (16.6%) had segmentectomy only, 16 patients (22.2%) had bisegmentectomy, and 44 patients (61.2%) had lobectomy. Nine patients (12.5%) had stage I tumor, 56 (77.7%) had stage II, and 7 (9.8%) had stage III. Univariate and subsequent multivariate analyses revealed that preoperative LSM was the only independent risk factor for predicting the development of postoperative hepatic insufficiency (cutoff, 25.6 kPa; $P = 0.001$; relative risk, 19.14; 95% confidence interval, 2.71–135.36).

Conclusions LSM is potentially useful to predict the development of postoperative hepatic insufficiency in patients with hepatocellular carcinoma undergoing curative liver resection surgery.

Keywords Liver stiffness measurement · Indocyanine green · Hepatic insufficiency · Hepatectomy

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Introduction

With considerable improvements in perioperative intensive care and refinements in surgical technique, the rates of death and complications after major liver resection surgery have decreased significantly [1–4]. Nevertheless, because many patients still have liver cirrhosis or other chronic liver disease, death and complications may follow liver resection surgery. Therefore, it is important to investigate the functional liver reserve before liver resection surgery [5–7]. The Child-Pugh scoring system is widely used to

determine the hepatic functional status, although its ability to predict mortality after liver resection surgery is inconsistent. Consequently, various laboratory and imaging techniques have been used to complement the Child-Pugh scoring system in order to predict the development of postoperative hepatic insufficiency. For example, the serum hyaluronic acid (HA) level, liver volumetry measured using computed tomographic (CT) scan, hepatic uptake ratio of technetium-99m-diethylene triaminepentaacetic acid galactosyl-human serum albumin at 15 min (LHL 15), indocyanine green retention rate at 15 min (ICG R15), and hepatic venous pressure gradient are usually performed [8–10]. These preoperative tests are important because they allow physicians to decide the extent of liver resection [11]. Such careful preoperative evaluation of liver function together with the refined operating techniques has significantly reduced the incidence of postoperative hepatic insufficiency [12–14].

Of these preoperative functional tests, hepatic venous pressure gradient is a widely used preoperative test to estimate the degree of hepatic fibrosis and liver reserve in Western countries, whereas ICG R15 is used in Eastern countries including Korea and Japan. However, ICG R15 remains imperfect because of its dependency on both the hepatic flow and the functional capacity of the liver [15]. Recently, liver stiffness measurement (LSM) using FibroScan® was reported to reflect the degree of hepatic fibrosis, which is an important factor determining the functional liver reserve [16]. Therefore, we hypothesized that LSM can predict the hepatic functional reserve.

This prospective study investigated the usefulness of LSM as a predictor of the liver reserve.

Patients and methods

Patients

In this pilot study, 91 consecutive patients who were eligible for curative liver resection surgery for hepatocellular carcinoma between July 2006 and December 2007 at Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, were enrolled prospectively. Patients who underwent surgery because of causes other than hepatocellular carcinoma or had Child-Pugh class C liver function were excluded.

Among all enrolled patients, 19 patients who underwent liver transplantation were also excluded. Written informed consent was obtained from all patients. This study was approved by the Institutional Review Board of Severance Hospital.

The primary end point was the development of postoperative hepatic insufficiency. *Hepatic insufficiency* was

defined as persistent hyperbilirubinemia (total bilirubin level >5 mg/dl) for more than 5 days after surgery or postoperative death without other causes [17, 18].

Liver stiffness measurement

On the same day that the ICG R15 test was performed, liver stiffness in the right lobe of the liver was measured, using FibroScan®, through the intercostal spaces with the patient lying in the dorsal decubitus position and with the right arm in maximal abduction. The tip of the transducer probe was covered with coupling gel and placed on the skin between the ribs at the level of the right lobe of the liver. Before performing FibroScan® in all patients, sonographic evaluation was used to target nontumor liver parenchyma. The operator, assisted by real time ultrasound, located a liver portion that was at least 6-cm thick and free of large vascular structures, and then pressed the probe button to commence the measurements. Ten validated measurements were performed on each patient. The success rate was calculated as the number of validated measurements divided by the total number of measurements. The results were expressed in kilopascals (kPa). The median value was considered as representative of the elastic modulus of the liver. Only procedures with ten validated measurements and a success rate of at least 60% were considered reliable.

ICG R15 evaluation

After an overnight fast, 0.5 mg/kg of ICG was administered intravenously. Blood samples were drawn at 5, 10, and 15 min and the plasma ICG concentration was measured spectrophotometrically (710 nm). The plasma retention rate at 15 min (ICG R15, %) and the plasma disappearance rate (ICG-k, min^{-1}) were calculated.

Liver resection surgery

All the patients were examined to confirm the number, size, location, and extent of the tumor and the existence of distant metastases by abdominal ultrasonography, CT scan, magnetic resonance imaging, hepatic angiography, and positron emission tomography. In addition to preoperative routine laboratory examinations and physical examination for determining Child-Pugh classification, ICG R15 was performed to determine the optimal treatment strategy. Anatomical resection was performed according to tumor size, location, and liver reserve function. Indications for hepatic resection and the types of operative procedures were mainly determined on the basis of the criteria of Makuuchi, i.e., the presence or absence of ascites, the serum total bilirubin level, and ICG R15 [19]. All liver resection surgeries were performed by two surgeons

(J.S. Choi and K.S. Kim) and followed the anatomic definitions of segments and lobes of Couinaud [20]. Patients routinely underwent intraoperative ultrasonography to determine tumor localization and extent and to exclude the presence of additional lesions in the residual liver.

Statistical analysis

Patient characteristics are given as the mean $\pm$ SD or median (range). Continuous variables were compared using an independent t-test and categorical variables were compared using χ^2-test. A two-sided P-value < 0.05 was considered significant.

Variables associated with the development of postoperative hepatic insufficiency were first assessed using a univariate analysis. Then, the variables that were significant ($P < 0.1$) were subjected to multivariate logistic regression analysis to identify the independent predictors for the development of postoperative hepatic insufficiency.

The optimal cutoff value for liver stiffness was set as the value maximizing the sum of sensitivity and specificity. The predictive ability of LSM and ICG R15 was assessed by the receiver operating characteristic (ROC) curve and corresponding area under the ROC (AUROC) curve for each. All statistical analyses were performed with SPSS 12.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

The baseline characteristics of the patients are summarized in Table 1. The mean age of the 72 patients (56 men and 16 women) was 54.9 years. The surgical specimens of the 72 hepatocellular carcinomas revealed a background of chronic hepatitis in 20 cases (27.7%) and cirrhosis in 52 cases (72.3%). Forty-four patients had Child-Pugh class A and eight had class B. The mean liver stiffness value was 17.1 kPa and the mean ICG R15 was 11.8%. There were no dropouts due to LSM failure.

Operation and tumor characteristics

Twelve patients (16.6%) had segmentectomy only, 16 patients (22.2%) had bisegmentectomy, and 44 patients (61.2%) had lobectomy. According to the Tumor-Node-Metastasis stage of the modified Union Internationale Contre le Cancer (UICC) staging system, 9 patients (12.5%) had stage I tumor, 56 patients (77.7%) had stage II tumor, and 7 patients (9.8%) had stage III tumor (Table 2).

Table 1 Patient baseline characteristics ($n = 72$)

Variables	n (%), mean $\pm$ SD, or median (range)
Male	56 (72.2%)
Age (years)	54.9 $\pm$ 10.6
Background liver disease[a]	
CHB/child A cirrhosis/child B cirrhosis	20 (27.7%)/44 (61.1%)/8 (11.2%)
Body mass index (kg/m^2)	24.0 $\pm$ 2.8
White blood cell count (10^3/μl)	5,740 (2,420–26,930)
Hemoglobin (g/dl)	14.1 $\pm$ 1.5
Platelet count (10^9/l)	154.2 $\pm$ 72.8
Total protein (mg/dl)	7.0 $\pm$ 1.1
Albumin (mg/dl)	4.1 $\pm$ 0.7
Total bilirubin (mg/dl)	1.2 $\pm$ 0.6
AST (IU/l)	48.5 $\pm$ 49.3
ALT (IU/l)	49.3 $\pm$ 40.9
Cholesterol (mg/dl)	150.2 $\pm$ 32.2
Gamma glutamyltranspeptidase (IU/l)	63.4 $\pm$ 70.5
Alkaline phosphatase (IU/l)	95.6 $\pm$ 45.2
Prothrombin time (%)	90.0 $\pm$ 9.5
Alpha-feto protein (ng/ml)	15.5 (2.6–39,879.7)
<20	41 (56.9%)
<400 and $\geq$20	17 (23.6%)
$\geq$400	14 (19.5%)
Spleen size (cm)	10.8 $\pm$ 2.29
ICG R15 (%)	11.8 $\pm$ 7.1
Liver stiffness/IQR (kPa)/SR	17.1 $\pm$ 11.2/ 1.7 $\pm$ 0.8/88.8%

CHB, chronic hepatitis B; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ICG R15, indocyanine green retention at 15 min; IQR, interquartile range; SR, success rate

[a] Background liver disease was defined after surgery

Comparison between patients with and without postoperative hepatic insufficiency

Seven patients had hepatic insufficiency postoperatively, and there was no mortality associated with liver resection surgery. Surgical specimens of those with postoperative hepatic insufficiency revealed that all of them had liver cirrhosis. The seven patients who developed postoperative hepatic insufficiency after curative liver resection surgery had a significantly higher mean LSM before surgery (26.8 $\pm$ 9.5 kPa) than those without postoperative hepatic insufficiency (15.1 $\pm$ 10.5, $P = 0.010$). The other tested variables affecting liver function did not differ statistically between the groups (Table 3).

All patients who developed hepatic insufficiency postoperatively decompensated with ascites.

Table 2 Operation and tumor characteristics ($n = 72$)

Variables	n (%), mean ± SD, or median (range)
Etiology	
HBV/HCV/non-B and non-C	60 (83.3%)/9 (12.5%)/3 (4.2%)
Operation method	
Segmentectomy	12 (16.6%)
Bisegmentectomy	16 (22.2%)
Trisegmentectomy	0 (0.0%)
Lobectomy	44 (61.2%)
Right/left/central	28/12/4
Blood loss (cc)	800 (10–8,100)
Operation time (min)	341.4 ± 147.9
Tumor size (cm)	3.32 ± 1.82
Tumor number	
One	65 (90.2%)
Two	7 (9.8%)
Tumor site	
Right	37 (51.4%)
Left	33 (45.8%)
Both	2 (2.8%)
Tumor stage[a]	
Stage I	9 (12.5%)
Stage II	56 (77.7%)
Stage III	7 (9.8%)

HBV, hepatitis B-virus; HCV, hepatitis C-virus

[a] Tumor stage is expressed according to the modified UICC staging system

Prediction accuracy of LSM and ICG R15

In order to compare the predictive value of LSM and ICG R15, we first analyzed ROC curve of LSM and R15 (Fig. 1). Corresponding AUROC curve was 0.824 (95% confidence interval, 0.682–0.967; $P = 0.007$) for LSM and 0.620 (95% confidence interval, 0.422–0.819; $P = 0.319$) for the ICG R15, respectively. The cutoff of LSM was set at 25.6 kPa, which gave the best statistical accuracy (sensitivity, 71.4%; specificity, 88.6%; positive predictive value, 55.6%; and negative predictive value, 93.9%).

Analyses for identifying the risk factors predicting development of postoperative hepatic insufficiency

Table 4 lists the results of the univariate and subsequent multivariate logistic regression analyses for identifying the various clinicopathologic factors associated with postoperative hepatic insufficiency.

Multivariate analysis identified LSM as the only significant predictor of postoperative hepatic insufficiency (cutoff 25.6 kPa, $P = 0.001$; relative risk, 19.14; 95% confidence interval, 2.71–135.36).

Discussion

Liver transplantation, liver resection, and local ablation therapy are curative treatments for hepatocellular carcinoma. Among them, liver transplantation is the best option because it is the only treatment that offers a chance of cure for hepatocellular carcinoma and the underlying cirrhosis by complete extirpation of both. However, the limitation of organ supply remains unresolved. Therefore, liver resection surgery for curative goal is widely performed instead of liver transplantation regardless of restriction of its application to a liver with limited functional reserve and high chance of recurrence in the liver remnant [21].
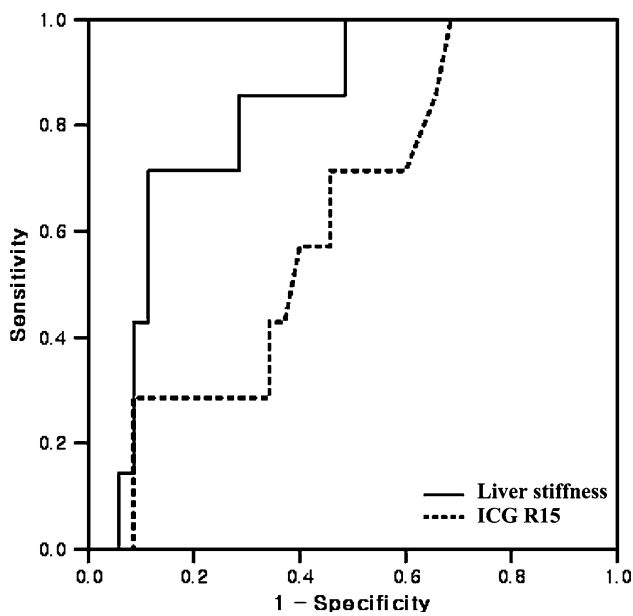
Table 3 Comparison between patients without and with postoperative hepatic insufficiency

Variables	Patients without hepatic insufficiency ($n = 65$)	Patients with hepatic insufficiency ($n = 7$)	P-value
Age (years)	55.3 ± 10.3	52.9 ± 12.6	0.580
Liver stiffness (kPa)	15.1 ± 10.5	26.8 ± 9.5	0.010
AST (IU/l)	51.1 ± 53.6	35.4 ± 10.5	0.448
ALT (IU/l)	51.9 ± 44.0	36.1 ± 15.6	0.358
Albumin (mg/dl)	4.15 ± 0.68	4.13 ± 0.90	0.229
Total bilirubin (mg/dl)	1.19 ± 0.59	1.34 ± 0.98	0.292
Prothrombin time (%)	90.1 ± 9.7	89.4 ± 9.2	0.858
Platelet (10^9/L)	159.4 ± 66.1	128.6 ± 102.7	0.313
ICG R15 (%)	11.3 ± 7.0	14.2 ± 7.5	0.317
Blood loss (cc)	1,222.1 ± 1,418.3	2,028.6 ± 2,751.2	0.258
Operation time (min)	322.6 ± 125.2	435.7 ± 219.5	0.229
Tumor size (cm)	3.42 ± 1.86	2.84 ± 1.63	0.453
Tumor stage I/II/III (n)	8/51/6	1/5/1	0.170
<lobectomy vs. ≥lobectomy (n)	27/38	1/6	0.010

ALT, alanine aminotransferase; ICG R15, indocyanine green retention at 15 min

[a] 25.6 kPa of liver stiffness and 12.0% of ICG R15 are the cutoff of best accuracy

Fig. 1 The ROC curves of LSM and ICG R15 for predicting postoperative hepatic insufficiency (0.824 and 0.620, respectively)

Because surgery removes parts of the functioning liver, the volume of the remnant liver determines the risk of postoperative hepatic insufficiency, which is the major cause of mortality and morbidity after liver resection surgery, especially in the cirrhotic liver.

The lack of well-designed, randomized, controlled trials, the use of different staging systems, and the different definitions of postoperative hepatic insufficiency have led to the confusion in the analysis of postoperative outcomes for liver resection surgery [22]. Careful preoperative evaluation of the functional liver reserve is necessary to minimize the postoperative morbidity and mortality in cirrhotic and noncirrhotic patients [12, 13]. Several preoperative tests are available for such purposes, including the serum HA assay, liver volumetry using CT scan, LHL 15, ICG R15, and hepatic venous pressure gradient [8–10]. Of these, the ICG R15 is the most reliable and widely available test to determine the extent of liver resection and liver reserve function in Eastern countries [12]. Although, the ICG R15 has some limitations because it depends on both the hepatic flow and the functional capacity of the liver, there is general agreement concerning the retention value [15].

Poon et al. [23] assessed the patient suitability for liver resection surgery by evaluating the Child-Pugh score combined with ICG R15 measurements; in their study, the occurrence of hepatic failure was 1%. Torzilli et al. [4] reported a preoperative evaluation pattern for liver resection surgery, which included the presence of ascites, serum bilirubin levels, and estimation of the ICG R15, and reported no mortality after liver resection in 107 patients.

Table 4 Logistic regression analysis of risk factors associated with postoperative hepatic insufficiency after hepatectomy

Variables	*P*-value		Odds ratio
	Univariate	Multivariate	
Gender			
Male vs. female	0.247	–	
Age (years)			
<55 vs. ≥55	0.885	–	
Background liver disease			
Noncirrhosis vs. cirrhosis	0.099	0.922	1.214
Body mass index (kg/m^2)			
<30 vs. ≥30	0.308	–	
Child-Pugh class			
A vs. B	0.434	–	
Total bilirubin (mg/dl)			
<1.2 vs. ≥1.2	0.337	–	
Albumin (mg/dl)			
<4.0 vs. ≥4.0	1.000	–	
ALT (IU/l)			
<50 vs. ≥50	0.308	–	
Cholesterol (mg/dl)			
<150 vs. ≥150	0.415	–	
Prothrombin time (%)			
<90 vs. ≥90	0.836	–	
Tumor stage			
Stage I vs. stages II and III	0.836	–	
Stage I and II vs. stage III	0.434	–	
Type of resection			
<Lobectomy vs. ≥lobectomy	0.142	–	
Operative bleeding (ml)			
<1,350 vs. ≥1,350	0.604	–	
Operative time (min)			
<340 vs. ≥340	0.783	–	
Blood transfusion			
Yes vs. no	0.675	–	
Liver stiffness (kPa)			
<25.6 vs. ≥25.6[a]	<0.001	0.001	19.140
ICG R15 (%)			
<10.0 vs. ≥10.0	0.415	–	
<12.0 vs. ≥12.0[a]	0.675	–	
<15.0 vs. ≥15.0	0.753	–	

Recently, LSM has been shown to reflect the degree of hepatic fibrosis, which is an important determinant of the development of postoperative hepatic insufficiency [16]. Therefore, we postulated that LSM could be used to predict postoperative hepatic insufficiency before liver resection surgery. In order to test this hypothesis, we compared the abilities of LSM and ICG R15 in predicting the

development of hepatic insufficiency after curative liver resection surgery. Although several studies have already reported the correlation between intraoperative liver consistency using specific probes and postoperative outcome [24–26], to the best of our knowledge, no other study has investigated LSM as a preoperative evaluation for predicting the development of postoperative hepatic insufficiency after liver resection surgery, compared with the relationship for ICG R15.

In this study, the cutoff liver stiffness value was set at 25.6 kPa, which gave the best accuracy. Multivariate logistic regression analysis revealed that LSM was the only independent predictor of the development of postoperative hepatic insufficiency. In terms of the AUROC for predicting hepatic insufficiency, the value for LSM was greater than that for the ICG R15. Therefore, in our study population, LSM was better than the ICG R15 in predicting the development of postoperative hepatic insufficiency.

We are aware of several limitations of our study. First, the multivariate logistic regression analysis did not include other variables that can affect the outcome of surgery, such as the serum HA level, which is closely correlated with the functional liver reserve and is a useful predictor of liver regeneration [27], or the total or resected liver volume measured using CT scan. Second, there were some factors differently represented between who showed hepatic insufficiency and who did not, such as total bilirubin level, bleeding amount, operation time, and the portion of undergoing lobectomy, although there were no statistical differences between the two groups. These points might influence the final results. Finally, because all enrolled patients showed chronic liver disease status, the results of this study are not applicable to patients without chronic liver disease. In order to overcome these limitations, a well-designed, well-controlled, randomized study of a large population is required.

In conclusion, our study showed that preoperative LSM was significantly higher in patients who developed postoperative hepatic insufficiency than in those patients who did not. Therefore, our results suggest that the preoperative liver stiffness is a potentially useful predictor of the development of postoperative hepatic insufficiency in patients with hepatocellular carcinoma undergoing liver resection surgery.

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