Liver stiffness measurement by transient elastography can predict outcome after hepatic resection for hepatitis C virus-induced hepatocellular carcinoma

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Objective
The aim was to assess the predictive value of liver stiffness (LS) measurement by transient elastography (FibroScan) on the risk of postoperative hepatic decompensation in patients with cirrhosis undergoing hepatectomy for hepatocellular carcinoma (HCC).
Patients and methods
This prospective study was conducted on 40 adult patients with hepatitis C virus (HCV)-related HCC eligible for hepatic resection between 2015 and 2017. LS was prospectively measured for all patients. Preoperative and postoperative variables (patients' demographics, comorbidities, laboratory, and radiological data) were collected.
Results
Hepatic insufficiency occurred in 35% of patients (14 patients). Receiver operating characteristic curve analysis of preoperative LS measurement identified a value equal to or higher than 15.4 KPa as the best cutoff value for predicting postoperative hepatic decompensation, with a sensitivity of 100%, specificity 100%, a positive predictive value of 100%, and a negative predictive value of 100%.
Conclusion
LS measured by transient elastography (FibroScan) is a potentially reliable tool to predict postoperative hepatic decompensation in patients undergoing surgical resection for HCC.

Keywords:
elastography, fibroscan, fibrosis, hepatitis C, hepatocellular carcinoma, liver stiffness, resection

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Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary neoplasm of the liver, the sixth most common malignancy ever, and third cause of cancer-related mortality worldwide [1]. Surgical resection of the tumor is considered a potentially curative treatment for patients with HCC. However, HCC is a complex tumor that often develops on the background of chronic liver disease especially liver cirrhosis [2].

Although the prognosis of patients referred to liver resection has improved substantially in the recent years attributed to advances in perioperative patient evaluation, surgical technique, and intensive care management, life-threatening complications can still develop in some patients who undergo liver resection for HCC, the most dreadful of which is postoperative liver failure (PLF) [2].

Assessment of postoperative outcome is a crucial step in HCC management before surgical resection, and any attempt to assess for the outcome should consider not only tumor-related factors but also the functional hepatic reserve, which determines the feasibility and the expected complication after all known therapeutic options including resection [3]. Several scores and stratification systems such as Barcelona Clinic Liver Cancer (BCLC) staging system and model for end-stage liver disease (MELD) score have been proposed for proper preoperative appraisal of hepatic functional reserve, which is aimed to decrease the risk of postoperative morbidity and mortality [4]. Indocyanine green clearance test is used for quantitative liver function reserve assessment in Asian countries and is increasingly used in other parts of the world. However, it is an expensive and time-consuming test [5].

Liver fibrosis or cirrhosis results in increased liver stiffness (LS). Transient elastography measured by

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FibroScan, an ultrasound-based modality, is considered an easy, rapid, and reproducible method that can be used to quantitatively assesses LS as a surrogate for liver fibrosis [6],but with certain limitations in obese patients and those with ascites and unreliable results in patients with acute hepatitis and elevated serum transaminases level [7]. As LS measured by FibroScan can reflect the degree of liver fibrosis, liver stiffness measurement (LSM) can predict the liver functional reserve [8,9].

The aim of this work was to assess the predictive value of LSM by transient elastography (FibroScan) on the risk of postoperative hepatic decompensation, and consequently the prognosis of patients undergoing hepatectomy for HCC.

Patients and methods

Study group

After approval of the local Institutional Review Board (IRB), 40 adult patients with hepatitis C virus (HCV)-related HCC presented at National Liver Institute, Menoufia University between 2015 and 2017 and eligible for liver resection were recruited. All patients fulfilled the inclusion criteria and signed an informed consent to participate in this study.

Inclusion criteria

The following were the inclusion criteria:

(1) Patients with HCV-related HCC eligible for hepatic resection.
(2) Patients with BCLC stages 0 and A (Child class A cirrhosis).
(3) Selected patients with early Child class B cirrhosis.
(4) Any size of HCC tumors eligible for resection.
(5) Any degree of fibrosis or cirrhosis.

Exclusion criteria

(1) HCC on top of other causes of cirrhosis.
(2) Patients with decompensated cirrhosis (child C).
(3) Those with unresectable tumor and those with recurrent tumors were excluded from this study.

Preoperative workup

Preoperative assessment, including patient demographics, comorbidities, laboratory investigations (complete blood count, liver function tests, renal function tests, serology for hepatitis B virus and HCV viral infections, and serum α-fetoprotein) and radiological findings (abdominal ultrasound and triphasic computed tomography) were performed for all patients. Child-Pugh and the MELD scores were calculated.

Liver stiffness measurement

LSM using Fibroscan was performed for all patients within one week before surgery using Fibroscan 502 (Echosens, Paris, France). Only results with ten valid measurements and a success rate of at least 60% and the interquartile range lower than 30% of the median value were considered reliable. The results were expressed in kilopascals (kPa) [10,11].

Surgical procedure

Selected patients underwent hepatic resection of HCC focal lesions according to the standard protocols of surgery and anesthesia departments. The type of resection, either major resection or segmentectomy, was selected on case-by-case basis.

Postoperative follow-up

For evaluating postoperative complication, development of ascites was considered a sign of hepatic decompensation [12]. PLF was defined as both a prothrombin concentration less than 50% [international normalized ratio (INR) >1.7] and a serum bilirubin concentration greater than 50 mmol/l on postoperative day 5 [13,14].

Statistical analysis

Patient characteristics were expressed as the mean±SD or median (range). Continuous variables were compared using an independent *t*-test, and categorical variables were analyzed using χ^2-test or Fisher's exact test. A two-sided *P* value less than 0.05 was considered significant.

Variables associated with the development of postoperative hepatic insufficiency, which were significant at a *P* less than 0.10 in the univariate analyses, were subjected to multivariate logistic regression analyses to identify independent predictors for the development of postoperative hepatic insufficiency. The diagnostic accuracy of the identified risk factors was evaluated using receiver operating characteristic curve (ROC). A *P* value of less than 0.05 was considered statistically significant. SPSS 21.0 for Windows was used for all statistical analyses (SPSS Inc., Chicago, Illinois, USA) [15].

Results

Patients and tumor characteristics

The baseline characteristics of patients are summarized in Table 1. Forty patients were included in this study, with nine (22.5%) females and 31 (77.5%) males, with a mean age of 52.5 years. Most patients had a Child-Pugh score class A, with 29 (72.5%) patients, and 11

Table 1 Baseline demographics of enrolled patients

Variables	*n* (%), mean±SD, or median (range)
Male/female	31(77.5)/9 (22.5)
Age (years)	52.5±7.445
White blood cell count (10^3/l)	6340.0±2243.0
Hemoglobin (g/dl)	11.703±1.304
Platelet count (10^9/l)	104.825±37.392
Albumin (mg/dl)	3.28 0±0.386
Total bilirubin (mg/dl)	0.973±0.157
ALT (IU/l)	49.300±18.361
AST (IU/l)	56.575±20.529
Na (mg/dl)	134.175±3.137
Serum creatinine (mg/l)	0.913±0.234
Prothrombin time (seconds)	12.950±0.639
Esophageal varices	19 (47.5)
Child A cirrhosis/Child B cirrhosis	29 (72.5)/11 (27.5)
MELD score	8.5±1.84
Transient elastography (kPa)	16.19±5.62
Size of focal lesions (<3 cm/ >3 cm)	21 (52.5) /19 (47.5)
Number of focal lesions	
Single	27 (67.5)
Two focal lesions	12 (30)
Three focal lesions	1 patient (2.5%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MELD, model for end-stage liver disease.

(27.5%) patients were Child-Pugh class B. The preoperative mean MELD score calculated for the patients was 8.5±1.84.

Preoperative laboratory assessment showed that the mean serum albumin was 3.28±0.386 g/dl, mean total serum bilirubin was 0.97±0.157 mg/dl, mean platelets count was 104 825±37 392.504/10^9 l, mean alanine aminotransferase level was 49.3±18.361 IU/l, whereas mean aspartate aminotransferase level was 56.58 ±20.529 IU/l. All patients were subjected to upper gastrointestinal endoscopy before liver resection, and nineteen of them had small esophageal varices (47.5%), 21 had no esophageal varices (52.5%), and none had gastric varices. Preoperative abdominal ultrasonography revealed that none of our patients had ascites.

LSM by transient elastography (fibroscan) was done to all patients with no dropout, and the mean was 16.19 ±5.62 kPa.

Preoperative computed tomography revealed that the size of focal lesions was variable. Twenty-one (52.5%) patients had small focal lesions (<3 cm) whereas 19 (47.5%) patients had larger focal lesions.

Regarding the number of focal lesions, a single focal lesion was found in 27 (67.5%) patients, two focal lesions in 12 patients (30%), and three focal lesions in one patient (2.5%).

Postoperative course and identification of risk factors in predicting postoperative hepatic insufficiency

All patients were followed up and re-evaluated for development of postoperative hepatic insufficiency. Hepatic insufficiency developed in 14 (35%) patients, and on univariate analysis of all preoperative variables that have a potential effect in predicting liver insufficiency (summarized in Table 2), it was found that the patients' sex, the mean age, the number of focal lesions, and presence of esophageal varices were not independent risk factors in predicting liver insufficiency after liver resection. In addition, the preoperative MELD score, serum Na, hemoglobin level, white blood cells, alanine aminotransferase, aspartate aminotransferase, serum creatinine, and INR had no significance in predicting postoperative decompensation.

However, the preoperative serum albumin, platelets count, and serum bilirubin had low significance in predicting postoperative decompensation, and the tumor size, Child-Turcotte-Pugh (CTP) score, and preoperative liver transient elastography measurement were highly correlated with postoperative liver insufficiency development.

Patients with CTP class B were more liable to develop postoperative decompensation, with sensitivity of 71.43, specificity of 96.9%, positive predictive value of 91%, and (negative predictive value of 90.91%, with accuracy of 87.50%.

Relationship between postoperative hepatic insufficiency and liver stiffness

The mean FibroScan value for patients who developed postoperative hepatic insufficiency was 22.321 ±8.033 kPa, which was significantly higher than that of patients who did not (13.977±1.049 kPa, $P<0.001$).

ROC curve analysis of preoperative LSM identified an LS value equal to or higher than 15.4 kPa has the best cutoff value for predicting postoperative hepatic insufficiency. This cutoff value gave the best statistical accuracy [sensitivity 100%; specificity 100% (Fig. 1), with a positive predictive value 100%; and negative predictive value of 100%].

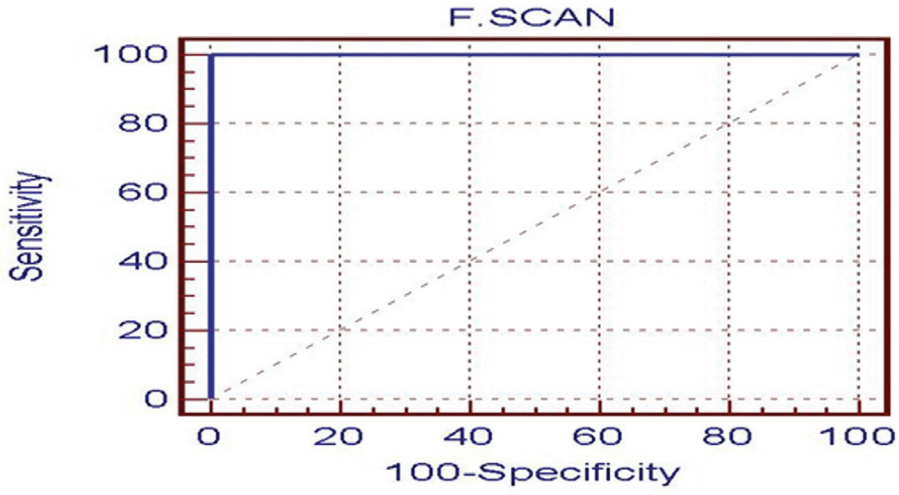
Patients with high LS (>15.4 kPa) had lower postoperative serum albumin levels (<3 g/dl), higher serum bilirubin (≥2 mg/dl), lower platelet count, and higher probability of developing postoperative ascites.

Table 2 Comparison between patients without and with postoperative hepatic insufficiency

Variables	Patients without postoperative hepatic insufficiency (*n*=26) (mean±SD)	Patients with hepatic insufficiency (*n*=14) (mean±SD)	*P* value
Male/female [*n* (%)]	21 (80.77)/5 (19.23)	10 (71.43)/4 (28.57)	0.505
Age (years)	52.577±7.700	52.429±7.229	0.285
White blood cell count (10^3/l)	6365.0±2112.428	6292.857±2553.268	0.924
Hemoglobin (g/dl)	11.850±0.883	11.429±1.864	0.336
Platelet count (10^9/l)	112.005±42.377	90.571±20.110	0.077
Albumin (mg/dl)	3.369±0.390	3.114±0.332	0.045
Total bilirubin (mg/dl)	0.938±0.142	1.036±0.169	0.06
ALT (IU/l)	51.962±15.074	44.357±23.107	0.216
AST (IU/l)	60.192±20.008	49.857±20.486	0.131
Na (mg/dl)	134.000±3.274	134.500±2.955	0.637
Serum creatinine (mg/l)	0.923±0.203	0.893±0.292	0.703
Prothrombin time (s)	12.923±0.628	13.000±0.679	0.721
Esophageal varices [*n* (%)]	10 (38.46)	9 (64.29)	0.117
MELD score	8.269±1.663	8.929±2.129	0.285
Size of focal lesions [*n* (%)]			
Small	19 (73.08)	2 (14.29)	<0.001
Large	7 (26.92)	12 (85.71)	
Preoperative CTP score [*n* (%)]			
CTP A	25 (96.15)	4 (28.57)	<0.001
CTP B	1 (3.85)	10 (71.43)	
Transient elastography (kPa)	13.977±1.049	20.321±8.033	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MELD, model for end-stage liver disease.

Figure 1



Receiver operating characteristic curve of preoperative liver stiffness measurement as a predictor of postoperative hepatic insufficiency.

Discussion

Regardless of their etiology, all chronic liver diseases eventually lead to liver fibrosis and cirrhosis, which can be complicated by HCC. The underlying molecular mechanisms of cirrhosis are still poorly recognized. Mueller [16] introduced the sinusoidal pressure (SP) hypothesis, which identifies an elevated SP as the cause of fibrosis.

According to the sinusoidal pressure hypothesis, however, an elevated SP is the major upstream event that initiates fibrosis via biomechanic signaling by stretching of perisinusoidal cells such as hepatic stellate cells or fibroblasts. Fibrosis progression is determined by the degree and time of elevated SP. Liver cirrhosis is the result of excessive accumulation of extracellular matrix with increased LS. LS also increases in response to pressure changes like

congestion, and rapid changes of LS after ligation of esophageal varices as well as transjugular intrahepatic portosystemic shunt implantation in patients with established cirrhosis were noticed [17].

Development of HCC is a major health problem, and selecting the best treatment option for each patient at different tumor stage depends not only on the tumor stage but also on the functional hepatic reserve and performance of the patient (which are taken into consideration in BCLC staging system).

Potentially curative treatment modalities for HCC include liver transplantation, liver resection, and locoregional ablative therapy. Transplantation offers treatment of both HCC and the underlying liver cirrhosis. However, with the limitation and shortage of available donors, only a minority of patients are finally referred to transplantation. Therefore, surgical hepatic resection for curative purpose can be widely applied to a larger set of patients with HCC. However, it carries the risk of postoperative hepatic decompensation owing to inadequate functional reserve of the remnant liver [18].

Careful preoperative assessment of the functional hepatic reserve remains a major challenge to minimize the perioperative and postoperative morbidity and mortality [19,20]. Several methods are available for this purpose including serum hyaluronic acid assay, volumetric assessment of the remnant liver, and indocyanine green clearance test, which is the most commonly used method for quantitative liver function reserve assessment in Asian countries. However, it is expensive and time consuming [5].

Previous reports suggested the use of noninvasive methods for assessing the LS by transient elastography (Fibroscan) as a rapid, easily performed and accessible method for the diagnosis of liver fibrosis, cirrhosis, and portal hypertension [16–18,21,22].

A cutoff value of 14 kPa was suggested by Sanchez-Conde *et al*. [21] for prediction of portal hypertension in HIV/HCV-co-infected patients. Moreover, Li *et al*. [23] reported a cutoff value of 15.6 kPa to predict postoperative ascites after liver resection for hepatitis B virus-related HCC.

In our study, LS measured by FibroScan was the best predictor of hepatic insufficiency in patients undergoing liver resection for HCC, with an effect significantly higher than any other studied variable, and subsequent ROC curve analysis of preoperative LSM identified an LS value equal to or higher than 15.4 kPa as the best cutoff value for predicting postoperative hepatic insufficiency in our patients. Similarly, Cescon *et al*. [24] also indicated that preoperative LSM by fibroscan contributed to PLF with a cutoff value of 15.7 kPa.

However, Kim *et al*. [8] concluded 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).In a study by Kim *et al*. [25] who tried to identify predictors of mortality from irreversible posthepatectomy liver failure (PHLF), they assumed that patients with chronic liver disease who will undergo liver resection, the combination of PT less than 65% and bilirubin greater than or equal to 38 μmol/l may be a more sensitive predictor of mortality from PHLF.

Our study showed that preoperative serum bilirubin had low statistical significance. However, INR did not have any significance in predicting PLF.

In our study, preoperative Child-Pugh classification was highly significant in predicting PLF with sensitivity of 71.43, specificity of 96.9%, positive predictive value of 91%, and negative predictive value of 90.91%.

Nonetheless, the presence of esophageal varices had no statistical significance as a predictor of postoperative decompensation.

A study by Chen X *et al*., 2012, demonstrated that patients with Child-Pugh class A cirrhosis and clinical evidence of portal hypertension are likely to develop PHLF. This study explored the effect of portal venous pressure on PHLF and the possibility of stratifying patients with Child-Pugh grade A cirrhosis for risk of PHLF using clinical data alone [26].

Conclusion

In conclusion, our results suggest that LS measured by FibroScan is a potentially reliable tool to predict postoperative hepatic decompensation in patients undergoing surgical resection for HCC and at a certain cutoff value can identify patients who have a higher probability of postoperative morbidity and mortality and should be considered as an important part of preoperative evaluation of those patients.

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Conflicts of interest
There are no conflicts of interest.

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