Fibrosis Stage as a Predictor of Outcome after Resection for Hepatocellular Carcinoma

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Abstract

Background: As liver stiffness measured by FibroScan® can reflect the degree of liver fibrosis, liver stiffness measurement can predict the liver functional reserve.

Aim of Study: To evaluate the relationship between liver fibrosis stage and the risk of post-operative hepatic decompen-sation in patients with liver cirrhosis undergoing hepatectomy for hepatocellular carcinoma.

Patients and Methods: This prospective study was conducted on forty adult patients with HCV-related HCC eligible for hepatic resection between May 2015 and February 2017. Liver stiffness measurement by Fibroscan® was prospectively done for all enrolled patients. Patients' demographics, comorbidities, laboratory and radiological data were collected.

Results: Hepatic decompensation occurred in 14 patients (35%) after liver resection. Analysis of ROC curve of liver stiffness measurement done before resection revealed a value equal to or higher than 15.4KPa as the best cutoff value for liver fibrosis stage predicting post-operative hepatic decompen-sation with a sensitivity of 100%; specificity 100%, a positive predictive value 100% and negative predictive value of 100%.

Conclusion: Liver stiffness measurement by transient elastography (Fibroscan®) may be a reliable tool to predict hepatic decompensation after liver resection for HCC.

Key Words: Liver Stiffness – Elastography – Fibroscan – Fibrosis – Hepatocellular carcinoma resection – Hepatitis C.

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 a 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 Hepatocellular Carcinoma (HCC), the most dreadful of which is Post-operative Liver Failure (PLF) [2].

Assessment of post-operative 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 determine 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 pre-operative appraisal of hepatic functional reserve which aimed to decrease the risk of post-operative morbidity and mortality [4].

Indocyanine Green (ICG) 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 result in increased Liver Stiffness (LS). Transient Elastography measured by FibroScan®, an ultrasound-based modality,
Fibrosis Stage Affects the Outcome of Hepatocellular Carcinoma

is considered an easy, rapid and reproducible method that can be used to quantitatively assess 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 transaminase levels [7]. As liver stiffness measured by FibroScan® can reflect the degree of liver fibrosis, liver stiffness measurement can predict the liver functional reserve [8,9].

The aim of this work was to assess the predictive value of LS measurement by transient elastography (FibroScan®) on the risk of post-operative 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 HCV-related HCC presented at National Liver Institute (NLI), Menoufiya University between May 2015 and February 2017 were enrolled in this study. All patients met the inclusion criteria of the study and signed an informed consent to participate in this study.

Inclusion criteria:

Patients with HCV-related HCC eligible for hepatic resection.

Exclusion criteria:

- Patients with decompensated cirrhosis (child C), those with unresectable tumors and those with recurrent tumors patients with portal vein thrombosis were excluded from this study.
- Pre-operative assessment, including patient demographics, comorbidities, laboratory investigations (CBC, liver function tests, renal function tests, serology for HBV and HCV viral infections and serum AFP) and radiological findings (abdominal ultrasound and triphasic computed tomography) were performed to all patients. Child-Pugh and the Model for End stage Liver Disease (MELD) scores were calculated.
- Liver stiffness measurement:
  - Liver stiffness measurement using Fibroscan® was performed for all patients within one week before surgery using fibroscan 504® machine, echosens, 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 liver HCC focal lesions according to the standard protocols of Surgery and Anesthesia Departments. Left hepatectomy, right hepatectomy or segmentectomy were selected on case-by-case basis.

According to BCLC, only patients with BCLC stages 0 and A (Child class A cirrhosis) were eligible for surgical resection of HCC, however, this was exceeded in this study which included some patients with early Child class B cirrhosis and small tumors.

Post-operative follow-up: For evaluating post-operative complications, development of ascites was considered the most relevant sign of hepatic decompensation [12]. Post-operative Liver Failure (PLF) was defined as both a prothrombin concentration less than 50% (International Normalised Ratio (INR) > 1.7) and a serum bilirubin concentration greater than 50 mmol/L on fifth post-operative day [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 chi-square test or Fisher's exact test. A two-sided p-value < 0.05 was considered significant.

Variables associated with the development of postoperative hepatic insufficiency which were significant at a p < 0.10 in the univariate analyses were subjected to multivariate logistic regression analyses to identify independent predictors for the development of post-operative hepatic insufficiency. The diagnostic accuracy of the identified risk factors was evaluated using Receiver Operating 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 [15].

Results

Patients and tumor characteristics: The baseline characteristics of patients are summarized in (Table 1). Forty patients were included in this study, nine females (22.5%) and thirty one males (77.5%) with a mean age of 52.5 years. Twenty nine patients were Child-Pugh score class A (72.5%) and 11 patients (27.5%) were Child-Pugh class B. The mean pre-operative MELD score calculated for the patients was (8.5 ± 1.84).

All patients were subjected to upper GI endoscopy before liver resection, nineteen of them had small esophageal varices (47.5%) and twenty one had no esophageal varices (52.5%), while none
had gastric varices. Pre-operative abdominal ultrasoundography revealed that none of these patients had ascites.

Liver stiffness measurement by transient elastography (fibroscan®) was done to all patients with no dropouts. The mean level of liver elasticity measured was 16.19±5.62 kPa.

The size of liver HCC focal lesions were variable on pre-operative Computed Tomography (CT). Twenty one patients (52.5%) had small focal lesions (<3cm) while nineteen patients (47.5%) patients had a larger focal lesions. As regards the number of focal lesions, 27 patients (67.5%) had single focal lesion, 12 patients (30%) had two focal lesions and one patient (2.5%) had 3 focal lesions.

On analysis of patients' pre-operative data, the pre-operative MELD score, Hemoglobin level, WBCs, ALT, AST, Serum Creatinine and INR had no significance in predicting post-operative decompen-sation. While the pre-operative serum Albumin, Platelets count and serum Bilirubin had a low significance in predicting post-operative decompen-sation, CTP score and pre-operative liver Transient Elastography measurement were highly correlated with post-operative liver insufficiency development.

Post-operative course and identification of risk factors in predicting post-operative hepatic insufficiency:

All patients were followed-up daily during hospital stay and re-evaluation for development of post-operative hepatic insufficiency was done weekly for one month after resection. Twenty six patients didn't develop any sign of liver decompensation after resection (group I), while evident Hepatic insufficiency developed in 14 patients (35% of the studied patients), (group II), (Table 2).

Table (1): Pre-operative demographic data of enrolled patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%), mean ± SD, or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>31 (77.5%) / 9 (22.5%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.5±7.445</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.703±1.304</td>
</tr>
<tr>
<td>White blood cell count (10^3/l)</td>
<td>6340±2423.0</td>
</tr>
<tr>
<td>Platelet count (10^9/l)</td>
<td>104.825±37.392</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>3.28±0.386</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.973±0.157</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>49.300±18.361</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>56.575±20.529</td>
</tr>
<tr>
<td>Serum creatinine (mg/l)</td>
<td>0.913±0.234</td>
</tr>
<tr>
<td>Prothrombin time (seconds)</td>
<td>12.950±0.639</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>19 (47.5%)</td>
</tr>
<tr>
<td>CTP class A/CTP class B</td>
<td>29 (72.5) / 11 (27.5)</td>
</tr>
<tr>
<td>MELD score</td>
<td>8.5±1.84</td>
</tr>
<tr>
<td>Transient Elastography (kPa)</td>
<td>16.19±±.62</td>
</tr>
<tr>
<td>Size of focal lesions (&lt;3cm/3cm)</td>
<td>21 (52.5) / 19 (47.5)</td>
</tr>
</tbody>
</table>

Number of focal lesions:
- Single                  27 (67.5%)
- Two focal lesions          12 (30%)
- Three focal lesions        1 (2.5%)

Table (2): Post-operative data of enrolled patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n=26)</th>
<th>Group II (n=14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>21 (80.77%) / 5 (19.23%)</td>
<td>10 (71.43%) / 4 (28.57%)</td>
<td>0.505</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.57±7.700</td>
<td>52.42±7.229</td>
<td>0.285</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.850±0.883</td>
<td>11.429±1.864</td>
<td>0.336</td>
</tr>
<tr>
<td>White blood cell count (10^3/l)</td>
<td>6365.0±2112.428</td>
<td>6292.8±2553.268</td>
<td>0.924</td>
</tr>
<tr>
<td>Platelet count (10^9/l)</td>
<td>112.00±54.377</td>
<td>90.57±20.110</td>
<td>0.077</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>3.369±0.390</td>
<td>3.114±0.332</td>
<td>0.045</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.93±0.142</td>
<td>1.036±0.169</td>
<td>0.06</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>51.96±15.074</td>
<td>44.357±23.107</td>
<td>0.216</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>60.19±20.008</td>
<td>49.857±20.486</td>
<td>0.131</td>
</tr>
<tr>
<td>Serum creatinine (mg/l)</td>
<td>0.923±0.203</td>
<td>0.893±0.292</td>
<td>0.703</td>
</tr>
<tr>
<td>Prothrombin time/ sec</td>
<td>12.93±0.678</td>
<td>13.00±0.679</td>
<td>0.721</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>10 (38.46%)</td>
<td>9 (64.29%)</td>
<td>0.117</td>
</tr>
<tr>
<td>MELD score</td>
<td>8.209±1.663</td>
<td>8.929±2.129</td>
<td>0.285</td>
</tr>
</tbody>
</table>

Pre-operative CTP score:
- CTP A                  25 (96.15%)   4 (28.57%)           <0.001
- CTP B                  1 (3.85%)      10 (71.43%)         

Size of focal lesions:
- Small                  19 (73.08%)   2 (14.29%)           <0.001
- Large                  7 (26.92%)     12 (85.71%)         

Transient Elastography/kPa 13.977±1.049 20.321±8.033 <0.001
The mean FibroScan value for patients who developed post-operative 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 pre-operative LSM identified a LS value equal to or higher than 15.4 Kpa has the best cutoff value for predicting post-operative 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 (more than 15.4 Kpa) had lower post-operative serum albumin levels (<3 gm/dl); higher serum bilirubin (≥2 mg/dl), lower platelet count, and higher probability of developing post-operative ascites.

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

Recent reports suggested the use of non-invasive methods for assessing the liver stiffness by transient elastography (Fibroscan®) as a rapid, easily performed and accessible method for the diagnosis of liver fibrosis, cirrhosis and portal hypertension [18-23].

In our study, liver stiffness measured by FibroScan® was the best predictor of hepatic insufficiency in patients undergoing liver resection for HCC, with an impact significantly higher than any other studied variable and subsequent ROC curve analysis of pre-operative Liver Stiffness Measurement (LSM) identified an LS value equal to or higher than 15.4 Kpa as the best cut-off value for predicting post-operative hepatic insufficiency in this patients cohort. Similarly, Cescon et al., also indicated that pre-operative liver stiffness measurement by Fibroscan, contributed to post-operative liver failure with a the cut-off value of 15.7 Kpa [23] and, Kim SU et al., concluded that, that pre-operative LSM was the only independent risk factor for predicting the development of post-operative hepatic insufficiency (cut-off, 25.6kPa; p=0.001; relative risk, 19.14; 95% confidence interval, 2.71-135.36) [8].

In a study by Kim SH et al., 2013 who tried to identify predictors of mortality from irreversible PHLF, he assumed that patients with chronic liver 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 patient with HCC. However it carries the risk of post-operative hepatic decompensation due to inadequate functional reserve of the remnant liver [16].

Careful pre-operative assessment of the functional hepatic reserve remains a major challenge to minimize the peri-and post-operative morbidity and mortality [17,18]. Several methods are available for this purpose including serum Hyaluronic acid assay, volumetric assessment of the remnant liver and ICG clearance test, which is the most commonly used method for quantitative liver function reserve assessment in Asian countries. However, they are expensive and time consuming [5].

Previous reports suggested the use of non-invasive methods for assessing the liver stiffness by transient elastography (Fibroscan®) as a rapid, easily performed and accessible method for the diagnosis of liver fibrosis, cirrhosis and portal hypertension [18-23].

A cut-off value of 14Kpa was suggested by Sanchez-Conde and his colleagues, for prediction of portal hypertension in HIV/HCV-co-infected patients [19]. Moreover, Chuan et al., reported a cut-off value of 15.6Kpa to predict post-operative ascites after liver resection for hepatitis B virus-related HCC [22].

In our study, liver stiffness measured by FibroScan® was the best predictor of hepatic insufficiency in patients undergoing liver resection for HCC, with an impact significantly higher than any other studied variable and subsequent ROC curve analysis of pre-operative Liver Stiffness Measurement (LSM) identified an LS value equal to or higher than 15.4 Kpa as the best cut-off value for predicting post-operative hepatic insufficiency in this patients cohort. Similarly, Cescon et al., also indicated that pre-operative liver stiffness measurement by Fibroscan, contributed to post-operative liver failure with a the cut-off value of 15.7 Kpa [23] and, Kim SU et al., concluded that, that pre-operative LSM was the only independent risk factor for predicting the development of post-operative hepatic insufficiency (cut-off, 25.6kPa; p=0.001; relative risk, 19.14; 95% confidence interval, 2.71-135.36) [8].

In a study by Kim SH et al., 2013 who tried to identify predictors of mortality from irreversible PHLF, he assumed that patients with chronic liver
disease who will undergo liver resection the combination of PT <65% and bilirubin >38 gmol/L may be a more sensitive predictor of mortality from PHLF [24].

Our study showed that pre-operative serum bilirubin had low statistical significance. However, INR didn’t have any significance in predicting post-operative liver failure.

In our study, pre-operative Child-Pugh classification was highly significant in predicting post-operative liver failure with sensitivity (71.43%), specificity (96.9%) and (91%) positive predictive value and (90.91%) negative predictive values.

Nonetheless, the presence of esophageal varices had no statistical significance as a predictor of post-operative decompensation. No correlation was doe between the presence of varices with elastography.

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 Post-Hepatectomy Liver Failure (PHLF). This study explored the impact of Portal Venous Pressure (PVP) on PHLF and the possibility of stratifying patients with Child-Pugh grade A cirrhosis for risk of PHLF using clinical data alone [25].

Conclusion:

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

References


