Predicting the risk of postoperative liver failure and overall survival using liver and spleen stiffness measurements in patients with hepatocellular carcinoma

Dongbo Wu, MD, Enqiang Chen, MD, PhD, Tao Liang, MD, Menglan Wang, MD, Bin Chen, MD, PhD, Bai Lang, MD, PhD, Hong Tang, MD, PhD

Abstract

Postoperative liver failure (PLF) is the primary cause of morbidity and mortality after hepatic resection for hepatocellular carcinoma (HCC). In this study, we evaluated the efficacy of liver stiffness (LS) and spleen stiffness (SS), as measured by transient elastography (TE), for predicting the risk of PLF and overall survival (OS) in these patients. This prospective cohort study included 54 patients diagnosed with HCC who underwent hepatic resection between March 2013 and March 2014. Preoperative measurement of LS and SS using TE was performed on all patients underwent. The predictivity of LS and SS for PLF was assessed by receiver operating characteristic curve analysis. OS according to LS and SS was analyzed using the Kaplan–Meier method and compared using the log-rank test.

PLF developed in seven (12.96%) patients. LS was significantly higher in patients with than in those without PLF (P = .03). The area under the curve of LS for predicting PLF was 0.76 (95% confidence interval, 0.62–0.86; P = .02). However, there was no significant difference in SS between patients with and without PLF (P = .36). Moreover, patients with an LS ≥ 16.2 kPa had significantly better OS than those with an LS < 16.2 kPa (P = .028). No significant difference in OS was observed between patients with an SS of < 22.3 and ≥ 22.3 kPa (P = .378).

LS measured by TE can be used to predict the risk of PLF as well as OS in patients with HCC who have undergone hepatic resection. However, SS obtained using TE was not found to be a significant predictor for PLF and OS in our patients.

Abbreviations: γ-GGT = gamma-glutamyl transpeptidase, AFP = α-fetoprotein, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, APRI = aspartate aminotransferase to platelet ratio index, AST = aspartate aminotransferase, AUC = area under the curve, CHB = chronic hepatitis B, CT = computed tomography, CTP = Child–Turcotte–Pugh score, FIB-4 = fibrosis-4, FLR = future liver remnant, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, ICG R15 = indocyanine green retention rate at 15 minutes, INR = international normalized ratio, LS = liver stiffness, MELD = model for end-stage liver disease, MRI = magnetic resonance imaging, OS = overall survival, PLF = postoperative liver failure, PLT = platelet, PT = prothrombin time, RLE = relative liver enhancement, ROC = receiver operating characteristic, sFLR = standardized future liver remnant, SS = spleen stiffness, TBIL = total bilirubin, TE = transient elastography, US = ultrasonography.

Keywords: hepatocellular carcinoma, liver stiffness, postoperative liver failure, spleen stiffness, transient elastography

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, accounting for approximately 7% of all cancer cases.[1] HCC is also the third most common cause of cancer deaths in China according to the 2015 Chinese cancer statistics,[2] thus, it is still a major public health problem in our country. Improvements in imaging modalities such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), as well as the use of tumor biomarkers such as α-fetoprotein (AFP) and protein induced by vitamin K absence, or antagonist-II have recently been achieved.[3] These improvements have enabled an increasing number of patients to be diagnosed as having HCC at an early stage (the Barcelona Clinic Liver Cancer stage 0 or A), and hepatic resection in such patients is associated with a 5-year survival rate of approximately 40% to 70%.[1] However, postoperative liver failure (PLF), the incidence of which ranges from 1.2% to 32.0%, is still the primary cause of morbidity and mortality after hepatic resection.[4,5] Improving the ability to accurately predict PLF might lead to a reduction in the incidence of PLF and the mortality rate among patients who have undergone hepatectomy for the treatment of HCC.

Various clinical parameters and methods have been developed to predict the development of PLF. These techniques include the use of the platelet count,[6] future liver remnant (FLR)/
standardized liver volume ratio (sFLR),
relative liver enhancement (RLE),
in the present study was performed in accordance with the ethical
guidelines of the 1975 Declaration of Helsinki and it was
approved by the Ethics Committee of West China Hospital of
Sichuan University. The procedure and nature of the study were
explained to the patients, and written informed consent was
obtained from each patient.

2. Materials and methods

2.1. Patients

This study included 65 adult patients diagnosed with HCC, who planned to undergo hepatic resection between March 2013 and March 2014 at the West China Hospital of Sichuan University. The diagnosis of HCC was based on clinical history, laboratory tests, and imaging findings (US, CT, or MRI), according to the American Association for the Study of Liver Diseases guidelines. Exclusion criteria for this study were patients with a history of infectious skin disease, splenectomy, liver transplantation, radiofrequency ablation, or interventional treatment for liver cancer. All patients underwent prospective TE (FibroScan, Echosens, Paris, France) to obtain measurements of LS and SS before hepatic resection. The demographic characteristics, clinical history, laboratory data, and radiological data of each patient were collected for further evaluation. Liver cirrhosis was confirmed through a pathologic examination of resected liver tissue. The specific surgical procedure performed on each patient was chosen by the attending surgeon.

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2.2. Measurements of LS and SS

LS was evaluated with TE in the morning after a ≥2-hour fast. Measurement for the right lobe of the liver was obtained through the intercostal spaces while the patient lay in the dorsal decubitus position with the right arm in maximal abduction. After applying coupling gel, measurements were obtained by placing the probe tip on the intercostal skin over the ninth to eleventh intercostal spaces. SS was measured as previously described. Briefly, SS values were obtained using the TE with the same probe tip used to perform the LS measurement under US guidance. The probe tip was positioned in an intercostal space through which the spleen had been visualized with US.

The measurement was considered valid in a patient if the following criteria were met: ≥10 successful measurements, success rate (ratio of the number of successful measurements to the total number of acquisitions) at ≥60%, and the interquartile range at <30% of the median. All results are expressed in kilopascals (kPa), and the median value was used as a representative measurement of LS and SS. ALL LS and SS were measured by the same experienced observer who had FibroScan certification training and had performed ≥500 time examinations.

2.3. Definition of PLF

In the present study, PLF was defined as prothrombin time (PT) <50% and serum bilirubin level >50 μmol/L postoperatively on day 5. This criterion was proposed by Balzan et al. after analyzing the data from 775 elective liver resections.

2.4. Statistical analysis

Continuous variables are expressed as medians (ranges), and categorical data are expressed as numbers (percentages). For group comparisons, the Mann–Whitney U test was used for continuous variables and the χ² test was used for categorical variables. The clinical values of LS and SS for predicting PLF were assessed with receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), sensitivity, and specificity were calculated. OS curves were created using the Kaplan–Meier method and compared using the log-rank test. A P-value <.05 was considered statistically significant in all analyses. Statistical analysis was performed using SPSS, version 20.0 (IBM Corp., Armonk, NY), and ROC analysis was performed with MedCalc, version 7.2.1.0 (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Baseline characteristics of the study population

Sixty-five patients with HCC were enrolled in this study. However, 11 patients were excluded because of undetectable SS (n = 7), a history of splenectomy (n = 2), a history of splenic embolization (n = 1), and unwillingness to undergo the procedure (n = 1). Baseline characteristics of the remaining 54 patients are summarized in Table 1.

The median age was 48 years (33–71 years), and 49 (90.70%) patients were men. The potential causes of HCC were hepatitis B virus (HBV) in 35 (64.80%) patients, hepatitis C virus (HCV) in 4 (7.40%), alcoholic liver disease in 3 (5.60%), and other reasons in 12 (22.00%). Liver cirrhosis was confirmed in 35 (64.80%) patients based on the pathological and imaging examination findings. Fifty (92.59%) patients had Child–Pugh class A liver diseases, while the remaining 4 (7.41%) had Child–Pugh class B liver disease. The median model for end-stage liver disease (MELD) score of all patients was 6.85 (1.33–13.63). Median scores of the aspartate aminotransferase to platelet ration index (APRI) and fibrosis-4 (FIB-4) score were 0.94 (0.23–13.67) and 3.32 (1.03–20.57), respectively. The median of the maximum tumor size was 4 cm (1–12 cm), AFP was 7.07 ng/mL (1.25–1210 ng/mL), total bilirubin (TBIL) level was 13.45 μmol/L (4.30–39.80 μmol/L), alanine aminotransferase (ALT) level was 36 IU/L (9–261 IU/L), aspartate aminotransferase (AST) level was 36 IU/L (16–257 IU/L), gamma-glutamyl transpeptidase (γ-GGT) level was 53.50 IU/L (10–728 IU/L), alkaline phosphatase (ALP) level was 96.50 IU/L (46–179 IU/L), albumin (ALB) level was 40.05 g/L (31.90–51.50 g/L), creatinine level was 73.40 μmol/L (8.40–127.50 μmol/L), platelet (PLT) count was...
106.50 × 10^9/L (25–297 × 10^9/L), PT was 12.60 s (10–18.90 s), and PT international normalized ratio (INR) was 1.13 (0.89–1.67). The median LS and SS were 12.1 kPa (3.30–54.2 kPa) and 28.50 kPa (11.30–75.50 kPa), respectively.

### 3.2. Comparison of clinical parameters in patients with and without PLF

Based on the 50-50 criterion, PLF developed in 7 (12.96%) of 54 patients with HCC. The clinical parameters of the patients with and without PLF are compared in Table 2. There were significant differences in the LS and SS between patients with and without PLF (P < .05 and .04, respectively). The following variables were generally comparable between the 2 groups: sex, age, Child–Turcotte–Pugh (CTP) score, MELD score, APRI score, FIB-4 index, maximum tumor size, AFP, ALT, AST, γ-GGT, ALP, PLT count, PT, and INR between patients with and without PLF (P > .05).

### 3.3. Predictive effectiveness of LS and SS in patients with and without PLF

Among all patients who had undergone hepatic resection for the treatment of HCC but did not develop PLF, the median LS and SS were 11.9 kPa (3.30–49.6 kPa) and 26.3 kPa (11.3–75.5 kPa), respectively. The median LS and SS in patients with PLF were 19.1 kPa (10.5–54.2 kPa) and 48 kPa (14.3–75 kPa), respectively. There was a significant difference in LS (P = .03) but no significant difference in SS (P = .36) was found between patients with and without PLF (Fig. 1A).

We performed ROC analysis to evaluate the efficacy of LS and SS for predicting PLF. As demonstrated in Fig. 1B, the AUC of LS for predicting PLF was 0.76 (95% confidence interval [CI], 0.62–0.86; P = .02), and the cut-off value of LS for diagnosing PLF was 16.2 kPa (sensitivity, 71.43%; specificity, 85.11%). However, the AUC of SS for the prediction of PLF was 0.61 (95% CI, 0.47–0.74; P = .34), and the cut-off value of SS for diagnosing PLF was 22.3 kPa (sensitivity, 85.7%; specificity, 44.7%). These findings suggested that LS might be suitable for predicting PLF in our patients who have undergone hepatic resection for the treatment of HCC.

### 3.4. OS analysis according to LS and SS

Since the cut-off value of LS for predicting PLF was 16.2 kPa, we chose this value to divide our patients into 2 groups: group A (LS < 16.2 kPa) and group B (LS ≥ 16.2 kPa). The median OS for all patients with HCC was 33.5 months (4–42 months), that for patients in group A (LS < 16.2 kPa) was 30.4 months (4–42 months), and that for patients in group B (LS ≥ 16.2 kPa) was 33.5 months (4–42 months).
was 29.0 months (4–42 months). OS was better in group A than in group B, according to Kaplan–Meier survival analysis (log-rank, 4.814; \( P = .028 \)) (Fig. 2A). However, the survival analysis according to the SS value (cut-off value of 22.3 kPa) showed no significant differences between patients with an SS < 22.3 kPa and those with an SS ≥ 22.3 kPa (log-rank, 0.779; \( P = .378 \)) (Fig. 2B). Thus, LS may have clinical value for evaluating the prognosis of patients who have undergone hepatic resection for the treatment of HCC.

4. Discussion

TE is one of the most promising tools used for the clinical evaluation of the severity and prognosis of liver diseases, such as liver fibrosis and cirrhosis.\(^\text{16}\) In the present study, we found a significant difference in LS between HCC patients with and without PLF and we observed that LS may predict the risk of PLF in patients with HCC after hepatic resection. Furthermore, HCC patients with an LS < 16.2 kPa had a better prognosis than did patients with an LS ≥ 16.2 kPa by Kaplan–Meier survival analysis. These findings are generally consistent with previous reports in patients with HCC.\(^\text{20–22}\)

PLF is a serious complication leading to morbidity and mortality after hepatic resection in clinical practice.\(^\text{16}\) Many studies have been performed to explore the predictive factors for the risk of PLF. The sFLR as well as the ratio of the sFLR to the ICG R15 may be acceptable predictors of PLF after hepatectomy.\(^\text{19}\) Tomimaru et al.\(^\text{7}\) reported that the PLT count could be used to assess the risk of PLF, and found it to be more useful than the ICG R15 for predicting the development of PLF in patients with HCC. A study showed that the RLE, as measured with gadoxetic acid-enhanced MRI preoperatively, was lower in patients with PLF than those without PLF, and RLE was also useful for predicting the development of PLF.\(^\text{6}\) However, some of these technologies such as MRI may require specific facilities, injections, or established quality criteria, and some may currently be too costly and time-consuming for routine clinical practice. A fast, simple and safe technology with which to accurately predict PLF is needed.

LS, as determined using TE, is a widely used noninvasive tool for assessing liver fibrosis and cirrhosis.\(^\text{16}\) It has recently been used to predict PLF in patients with HCC.\(^\text{20–23}\) The first study to evaluate the clinical value of LS for predicting PLF in patients with HCC was reported by Cescon et al.\(^\text{20}\) They found that the incidence of PLF in patients with HCC was 28.9% and patients with an LS value ≥ 15.7 kPa were at a higher risk of PLF, demonstrating that LS measured with TE, could be a valid method for predicting PLF in patients who have undergone hepatic resection for HCC.\(^\text{20}\) A prospective cohort study showed that LS was suitable for predicting high-grade PLF.\(^\text{22}\) LS obtained using Virtual Touch tissue quantification (Mochida Siemens Medical Systems, Tokyo, Japan), an imaging technology

![Figure 1.](image1.png)

**Figure 1.** Clinical values of LS and SS for predicting PLF in patients with hepatocellular carcinoma. (A) LS and SS are compared in patients with and without PLF. (B) The clinical values of LS and SS for predicting PLF are assessed using receiver operating characteristic analysis. LS = liver stiffness, PLF = postoperative liver failure, SS = spleen stiffness; \( P \)-value < .05 indicates statistical significance.

![Figure 2.](image2.png)

**Figure 2.** Overall survival analyses according to LS and SS. (A) Kaplan–Meier survival curves of patients with HCC according to LS. (B) Kaplan–Meier survival curves of patients with HCC according to SS. HCC = hepatocellular carcinoma, LS = liver stiffness, PLF = postoperative liver failure, SS = spleen stiffness; \( P \)-value < .05 indicates statistical significance.
Comparisons between our study and recent studies of the liver stiffness measurement for predicting postoperative liver failure.

| Item/Study       | Cescon et al[20] | Nishio et al[21] | Jin et al[22] | Chong et al[23] | Our study         |
|------------------|-------------------|-------------------|--------------|-----------------|-------------------|
| Age, n, y        | 64 (35–87)        | 69 ± 10           | 58.9 ± 11.1  | 58 ± 9          | 48 (33–71)        |
| Male sex, n (%)  | 77 (85.6)         | 140 (79.1)        | 106 (73.6)   | 218 (85.49)     | 49 (90.7)         |
| HBV, n (%)       | 16 (17.8)         | 53 (18.6)         | 116 (80.5)   | 208 (81.6)      | 35 (64.8)         |
| HCV, n (%)       | 59 (65.6)         | 66 (37.3)         | 16 (11.1)    | 17 (6.7)        | 4 (7.4)           |
| Measurement technology | FibroScan       | VTTQ               | MR elastography | FibroScan      | FibroScan        |
| LS, median (range) | 16.2 (3.8–56.2) kPa | 1.86 ± 0.78 m/s | 3.30 ± 1.02 kPa | 9.5 (3.8–76) kPa | 12.1 (3.3–54.4) kPa |
| LS cut-off value | 15.7 kPa          | 1.61 m/s           | 3.30 kPa     | 11.25 kPa       | 16.2 kPa          |
| Sensitivity of LS | 96.1%             | 90%                | 69.8%        | 59.5%           | 71.43%            |
| Specificity of LS | 68.7%             | 58%                | 72.3%        | 68.6%           | 85.11%            |

AUROC = area under the receiver operating characteristic curve, HBV = hepatitis B virus, HCV = hepatitis C virus, LS = liver stiffness, MR = magnetic resonance, VTTQ = Virtual Touch tissue quantification.

5. Conclusions

In summary, LS measured by TE can be used to predict the risk of PLF as well as OS in patients with HCC who have undergone hepatic resection. However, SS obtained using TE was not found to be a significant predictor for PLF and OS in our patients. To help prevent the development of PLF, LS should be routinely measured in clinical practice before patients with HCC undergo hepatic resection.

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