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Spleen Stiffness Differentiates Between Acute and Chronic Liver Damage and Predicts Hepatic Decompensation

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Objectives: Spleen stiffness (SS) correlates with liver stiffness (LS) and hepatic venous pressure gradient. The latter is currently the most accurate predictor of hepatic decompensation. Our study aims to check whether SS has a similar predictive capability, while being an easy-to-perform noninvasive test in a real-life patient cohort.

Methods: Concomitantly, 210 successive patients were examined and received liver and SS measurements and a standard laboratory. Patients were observed for 1 year in terms of clinical signs of decompensation.

Results: One hundred fifty-nine of the initial 210 patients had a valid LS and SS measurement and were evaluable for clinical follow-up. Twelve patients developed a hepatic decompensation; with a SS >39 kPa ($P=0.0005$). Especially in a group with elevated LS, patients with a high risk of decompensation could be identified using SS. Patients with comparable LS who suffered from acute liver damage had significantly lower SS than respective patients with chronic liver damage (30.97 vs. 46.03 kPa; $P=0.04$). Acute liver failure was associated with elevated LS (16.47 kPa) but not with elevated SS (30.97 kPa).

Conclusions: The risk of a hepatic decompensation can easily be assessed using SS measurement. Therefore SS measurement might be a powerful screening tool identifying patients who need closer monitoring. Moreover, SS is able to differentiate between acute and chronic or acute on chronic liver damage.

Key Words: hepatic decompensation, liver disease, spleen stiffness, liver stiffness

(*J Clin Gastroenterol* 2019;53:457–463)

Received for publication February 20, 2017; accepted June 6, 2017.

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Supported by the Wilhelm-Laupitz Foundation to A.C.

P.M., A.C., C.J.: study concept and design. P.M., A.D., M.B., J.K., A.C., C.J.: acquisition of data. P.M., A.D., M.B., J.K., A.C., C.J.: analysis and interpretation of data. P.M., A.C., C.J.: drafting of the manuscript. P.M.: statistical analysis. A.C.: obtained funding. P.M., G.G., A.C., C.J.: administrative, technical, or material support. P.M., A.C., C.J.: study supervision.

The authors declare that they have nothing to disclose.

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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.jcge.com.

DOI: 10.1097/MCG.0000000000001044

Portal hypertension is common sequel of chronic liver disease and cirrhosis. Increasing portal hypertension leads to clinical hepatic decompensation with esophageal and gastric varices, ascites, and hepatorenal syndrome, which may further determine the outcome of the disease.[1] Invasive diagnostic procedures are used to assess portal hypertension such as upper gastrointestinal endoscopy for the presence of esophageal varices or measurement of the hepatic venous pressure gradient (HVPG).[2] Especially HVPG measurement is considered to be the gold standard for predicting clinical decompensation; however, this method is not easy to perform and is only available in specialized centers. Therefore, there is need for reliable and reproducible easy-to-perform noninvasive methods to assess portal hypertension.[3] Recent studies showed that measurement of liver stiffness (LS) by transient elastography may predict portal hypertension and subsequently hepatic decompensation[4,5] However, LS measurement alone cannot differentiate between acute or chronic liver injury and validation is limited in patients with a HVPG above 12 mm Hg.[6] A recent study showed a positive correlation between LS together with spleen stiffness (SS) and the risk of esophageal variceal bleeding.[7]

Furthermore, Colecchia et al[8] and Sharma et al[9] recently stated that SS measurement using transient elastography may be an even more reliable for identifying portal hypertension and presence of esophageal varices. Indeed SS is not limited to a certain degree of portal hypertension and correlates with all HVPG levels. Although the role of the spleen and its' diagnostic role in patients with portal hypertension had been evaluated before[10,11] still long-term data are lacking. Studies using the similar Shear-Wave-Elastography for assessment of SS underline a possible clinical importance of SS measurement.[12,13]

Therefore we checked (I) the applicability and reliability of SS measurement in real-life cohort, (II) the link between SS and disease activity within 1 year in addition to LS, (III) and finally, the predictive capability of SS for esophageal varices and hepatic decompensation.

METHODS

Patient Demographics and Laboratory Parameters

A total of 210 patients with liver injury [115 males, 95 females, age between 20 and 86 y (55.6 ± 13.5 y)] were collected. For 6 consecutive weeks each patient underwent LS and SS measurements using transient elastography at the University Hospital of Essen, Germany. Most patients also routinely received a sonography of the upper abdomen where spleen size and portal vein flow velocity were assessed. Most patients are connected to the hospital's outpatients department and present themselves at least every 6 months. With every visit blood samples were once again

taken and the clinical status has been assessed. Few patients also received upper gastrointestinal endoscopy when showing a risk profile.

Blood values based on individual patients need were measured at the central laboratory unit (Department of Clinical Chemistry and Laboratory Medicine, University Hospital Essen) and are depicted in Tables 1 and 2 and Supplementary Table 1 and 2 (Supplemental Digital Content 1, http://links.lww.com/JCG/A406). For all analyses we used the values measured on admission. The following blood values had been determined at every visit: hemoglobin (g/dL), leukocyte count (1/nL) and platelet count (1/nL), bilirubin (mg/dL), creatinine (mg/dL), and international normalized ratio (INR). For the calculation alone creatinine and bilirubin levels were raised to 1 mg/dL, if in fact below.[14] In addition, aspartate aminotransferases (AST, U/L), alanine aminotransferases (ALT, U/L), gamma-glutamyltransferase (U/L), and albumin level (g/dL) were determined. For further comparison the AST-platelet-ratio-index has been determined as a noninvasive assessment of liver fibrosis although AST-platelet-ratio-index has yet only been evaluated for patients suffering from viral hepatitis.[15] To evaluate the progress of the disease the change in every laboratory parameter between the measurement points has been calculated for each patient. Those changes where then checked for significant differences or correlations. The clinical parameters that were recorded at the regular follow-up examinations in the outpatients department consisted of new signs of hepatic decompensation (eg, ascites, variceal bleeding, or hepatic encephalopathy), presence of esophageal varices (either newly detected or still present ones), and death or liver transplantation. Furthermore, the model for end-stage liver disease (MELD) score was determined as previously described.[16]

TABLE 1. Clinical and Laboratory Parameters of Patients With Liver Injury

Variables	No. Patients (%)	Value
Age (y)	55.6 ± 13.5	
Gender (male/female) [n (%)]	115 (54.8)/95 (45.2)	
LS (kPa)		
LS < 7	75 (35.7)	9.05 ± 15.4
LS 7-14	64 (30.5)	
LS > 14	71 (33.8)	
SS (kPa)		
SS <39	119 (56.7)	28.8 ± 21.9
SS > 39	63 (30.0)	
No valid SS	28 (13.3)	
Etiology		
Viral hepatitis	58 (27.6)	
Fatty liver disease	36 (17.7)	
Autoimmune liver disease	34 (16.2)	
Vascular or genetic liver disease	34 (16.2)	
Liver transplant recipients	48 (22.9)	
Clinical		
Esophageal varices	31 (14.8)	
Hepatic decompensation	12 (5.7)	
Death or liver transplant	9 (4.3)	
Laboratory parameters	Reference range	
Hemoglobin (g/dL)†	Male: 13.8-17.2 Female: 12.1-15.1	13.1 ± 2.12
Leukocytes (1/nL)†	3.6-9.2	7.15 ± 10.4
Platelets (1/nL)†	150-450	198.1 ± 104.6
Creatinine (mg/dL)‡	0.9-1.3	1.20 ± 0.40
Bilirubin (mg/dL)‡	0.3-1.2	2.08 ± 3.66
INR§	—	1.07 ± 0.16
AST (U/L)†	Male: <50; Female: <35	66.0 ± 144.7
ALT (U/L)†	Male: <50; Female: <35	81.0 ± 253.8
GGT (U/L)†	< 55	115.5 ± 189.9
Albumin (g/dL)¶	3.5-5.5	4.14 ± 0.53
APRI	—	3.87 ± 37.3
MELD*‖	—	8 (6-37)

Data presented as the number of patients in groups or (mean ± SD).
*Data given as median (interquartile range).
Frequencies are calculated out of:
†n = 204.
‡n = 203.
§n = 187.
‖n = 186.
¶n = 126.
ALT indicates alanine aminotransferase; APRI, AST-platelet-ratio-index; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; INR, international normalized ratio; LS, liver stiffness; MELD, model for end-stage liver disease; SS, spleen stiffness.

The study protocol was approved by the local ethics committee at the University Hospital Essen (Duisburg-Essen-University, Essen, Germany, Institutional Review Board reference number 15-6337-BO) and conducted in accordance with the Declaration of Helsinki and the guidelines of the International Conference for Harmonization for Good Clinical Practice. Written informed consent was obtained from the patient according to the ethical guidelines of the 2000 Declaration of Helsinki as well as the 2008 Declaration of Istanbul. All authors had access to the study data and had reviewed and approved the final manuscript.

Stiffness Measurement and Patient Classification

The measurements of both LS and SS were performed using the Fibroscan touch device (Echosens, France). All LS and SS were carried out by the same experienced examiner. Patients are lying on their back with their respective arm elevated, while the examiner places the transient elastography probe with a drop of ultrasound gel in the intercostal space right above either liver or spleen. Especially when scanning the spleen the exact position for the probe had to be acquired by using ultrasound first. The final result, displayed in kPa, was the median of 10 successful single measurements. Sonography was used to assess the portal vein flow (m/s) and to estimate the spleen size by planimetric measurement at the level of the hilus of the spleen, where the artery and splenic vein entered the organ displayed in cm^2.

For the first step of analysis patients were grouped in 3 groups according to a low LS (< 7 kPa), intermediate LS (7 to 14 kPa), or high LS (> 14 kPa) approximately representing patients with no significant fibrosis, significant fibrosis, and cirrhosis. These groups were formed on the basis of present clinical standard at Universitätsklinikum Essen in accordance with current literature.[17] The low LS (< 7 kPa) group consisted of 75, the intermediate LS (7 to 17 kPa) group of 64, and high LS (> 14 kPa) group of 71 patients (35.7%, 30.5%, and 33.8%, respectively). These groups then have been correlated to the respective SS, spleen size, and the according initial blood values.

Empirically we determined the lowest SS, which patients displayed a decompensation in the follow-up and evaluated this cutoff further regarding its predictive capabilities. Although, 210 patients were enrolled in this study, 28 patients (13.3%) were excluded because of not valid SS measurement (Table 1). This was mostly due to anatomic reasons like larger amounts of dermal fat, interposition of gas-filled intestines, or

TABLE 2. Relevant Differences and Pearson Correlation With SS (Product-Moment Correlation) of Mean Blood Parameters at Study Baseline Total

	Total			At Study Baseline			Change		
Parameter	**SS <39 kPa**	**SS >39 kPa**	***P***	**Pearson *r***	***P***	**Parameter**	**SS <39 kPa**	**SS >39 kPa**	***P***
Hemoglobin (g/dL)	13.3 ± 1.96	12.86 ± 2.45	0.2	−0.155	0.04	AST (U/L)	−39.93 ± 197.61	−6.43 ± 32.30	0.109
Platelets (1/nL)	201.9 ± 84.4	166.5 ± 108.1	0.03	−0.227	0.002	ALT (U/L)	−73.42 ± 364.32	−8.21 ± 33.81	0.089
INR	1.06 ± 0.14	1.12 ± 0.22	0.04	0.290	<0.001	GGT (U/L)	−50.42 ± 174.49	1.03 ± 65.66	0.011
Albumin (g/dL)	4.25 ± 0.48	3.94 ± 0.63	0.01	−0.301	0.001				
MELD*	8 (6-22)	9 (6-37)	0.04	0.238	0.002				

Data presented as the number of patients in groups or (mean ± SD).
Change of liver enzymes until follow-up sorted by spleen stiffness group.
*Data given as median (interquartile range).
ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; SS, spleen stiffness.

undersized spleen, which was not viable for transient elastography examination. Twenty-three patients (10.9%) were not included because of loss to follow-up. All etiologies of liver diseases were included (Table 1).

All patient groups were then correlated to the change of their blood values and the appearances of clinical events such as hepatic decompensation in course of 1 year.

Eventually patient groups proving to show distinct characteristics were selected and examined further regarding the collected parameters. For comparison the baseline values and latest follow-up examination were used.

Statistical Analysis

For statistical comparison, a 2-sided *t* test was performed. Statistical significance was assumed with a *P*-value <0.05. Furthermore the product-moment correlation (Pearson coefficient) has been determined to evaluate the linear correlation between the different results. The diagnostic viability of SS and LS has been assessed using sensitivity, specificity, positive predictive value, and negative predictive value. Receivers operating characteristic (ROC) calculations were performed to evaluate the empirically determined cut-off point. Calculations and graphics were performed using GraphPad Prism-SoftwareVersion 6 Oc and Microsoft Excel 2013.

RESULTS

Patient Characteristics

The baseline characteristics and clinical data of study patients are summarized at Table 1.

Fifty-eight patients (27.6%) suffered from viral hepatitis, 34 patients (16.2%) suffered from autoimmune liver disease (including primary biliary cirrhosis and primary sclerosing cholangitis) and 36 patients (17,1%) had alcoholic or not alcoholic fatty liver disease, and 34 patients (16.2%) suffered from vascular or genetic or other rare liver diseases. Forty-eight patients (22.9%) were liver transplant recipients (Table 1).

SS Correlates With LS and Spleen Size

LS (210 patients) and SS (182 patients) were 9.05 ± 15.4 and 28.8 ± 21.9 kPa, respectively for all patients involved to the study (Table 1). SS of patients showed a significant linear correlation to LS ($r = 0.4754$; $P < 0.0001$; Fig. 1B). SS differs between low (<7 kPa), intermediate (7 to 14 kPa), and high (>14 kPa) LS groups (mean SS values, 25.7 ± 18.1, 32.5 ± 17.9, and 47.8 ± 23.3 kPa, respectively; Fig. 1A) and these differences were statistically significant ($P = 0.04$, low vs. intermediate; $P = 0.0000001$, low vs. high; $P = 0.0001$, intermediate vs. high; Fig. 1A). The ratio between LS and SS increased from 0.33 to 0.44 and to 1.15 between the 3 groups ($P = 0.1$, low vs. intermediate; $P = 0.02$, low vs. high; $P = 0.04$, intermediate vs. high). Furthermore, spleen size differs significantly between low, intermediate, and high LS groups (38.27 vs. 61.40 vs. 87.90 cm^2, respectively; $P < 0.001$, low vs. intermediate; $P < 0.001$, low vs. high; $P < 0.001$, intermediate vs. high) and there were significant correlation between SS and spleen size ($r = 0.4957$; $P \leq 0.0001$; Fig. 1C) as well as between LS and spleen size ($r = 0.435$; $P \leq 0.0001$; Fig. 1D). The group of liver transplant patients showed no significant correlation between LS and SS and was, respectively, not considered in this and further analysis.

Baseline Laboratory Values Correlate With Liver and SS

The most blood parameters were significantly different between low, intermediate, and high LS groups and show correlation with LS at the study baseline, but only hemoglobin and platelets show correlation with LS at the study follow-up ($r = -0.155$ and $P = 0.046$ for hemoglobin; $r = 0.188$ and $P = 0.015$ for platelets; Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JCG/A406). As expected, LS groups were correlated significantly with MELD score ($r = 0.379$, $P < 0.001$; Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JCG/A406).

Platelets, INR, albumin counts were significantly different between SS groups (<39 and >39 kPa) ($P = 0.03$, 0.04, 0.01, respectively; Table 2). And significant correlations were observed for hemoglobin (Pearson coefficient, −0.155; $P = 0.04$), platelets ($r = -0.23$; $P = 0.002$), INR (Pearson coefficient, 0.29; $P \leq 0.001$), and albumin ($r = -0.3$; $P = 0.001$) at study baseline (Table 2). Furthermore, the MELD scores between SS groups showed significant differences ($P = 0.04$) and correlation with SS ($r = 0.24$; $P = 0.002$). However, no correlations were observed between SS values and blood parameters at the study follow-up Table 2 and Supplementary Table 2 (Supplemental Digital Content 1, http://links.lww.com/JCG/A406).

Liver Enzymes Change is Different Between Low and High SS

Concerning the change of blood parameters in course of the study especially the change of liver enzymes attracts

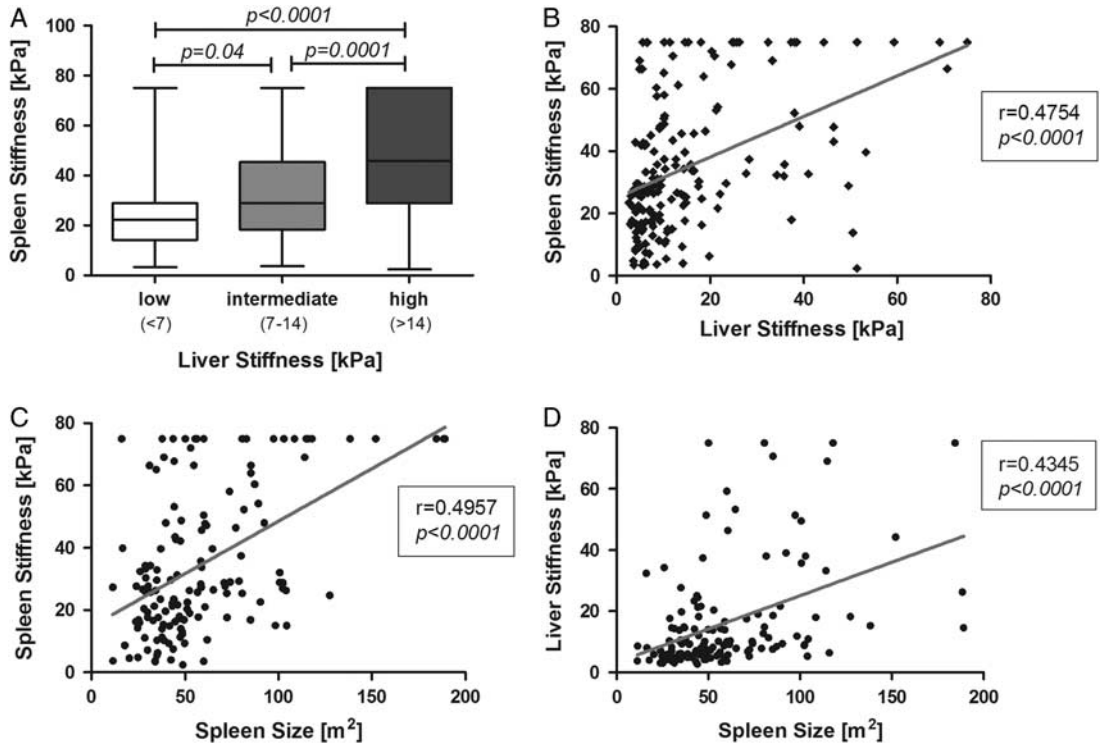

FIGURE 1. A, Liver fibrosis groups according to transient elastography in correlation to their respective spleen stiffness values. B, Transient elastography of liver and spleen are in correlation with according linear trend line. Transient elastography of the spleen (C) and liver (D) in correlation to spleen size with according linear trend line.

attention. Patients with a SS below 39 kPa rather drop with their enzymes in average in difference to patients with an elevated SS. The differences between the group with either low or high SS in the change of AST (−39.94 vs. −6.43; $P = 0.1$) and ALT (−73.43 vs. −8.22; $P = 0.08$) did not reach statistical significance in contrast to the change of gamma-glutamyltransferase (−50.43 vs. 1.04; $P = 0.01$).

SS and LS Predict Esophageal Varices

To evaluate the prospective capabilities of SS and LS we included 159 patients who showed up for a second clinical examination. Among them, 31 patients (14.8% of all patients) were diagnosed with esophageal varices (Table 1). Their mean transient elastography values of both liver and spleen were elevated compared with the patients without varices 33.25 ± 24.4 versus 11.96 ± 10.1 kPa ($P = 0.00001$) and 54.53 ± 23.1 versus 31.85 ± 19.9 kPa ($P = 0.00001$), respectively (Fig. 2A). When using LS above 14 kPa as diagnostic cut-off value 22/31 patients with varices were covered with this measure. Thirty-eight percent of all patients in the high LS group had varices, whereas only 7% in the intermediate LS group and 9% in low LS group had varices ($P < 0.001$ for low vs. high and intermediate vs. high).

LS of 14 kPa as cut-off value results in a sensitivity of 71%, a specificity of 68%, a positive predictive value of 35%, and a negative predictive value of 91%. SS of 39 kPa as cut-off value results in a sensitivity of 81%, a specificity of 74%, a positive predictive value of 43%, and a negative predictive value of 94%. A SS cutoff of 39 kPa results in an inclusion of 25/31 patients with varices. Seven percent of patients with an SS below 39 kPa and 39% of all patients with an elevated SS above 39 kPa had detectable varices ($P = 0.0002$). When further evaluating a risk group of patients having a LS above 10 kPa only 2 patients with an SS below 39 kPa had detectable varices (5% of all patients with LS > 10 kPa and SS <39 kPa). Accordingly 20 patients (41% of this group) with both LS and SS above the cut-off value had varices. These differences were statistically significant ($P = 0.000004$).

SS and LS Predict Hepatic Decompensation

Twelve patients developed hepatic decompensation in course of 1 year. In these patients' LS and SS values were significantly elevated compared with the other patients. LS was elevated from 13.23 ± 12.3 to 46.01 ± 23.1 kPa ($P = 0.0002$), whereas SS showed a difference of 33.1 ± 20.6 versus 69.02 ± 11.2 kPa ($P = 0.0000001$) (Fig. 2B).

ROC curve analysis was performed using SS and hepatic decompensation events. With an LS cutoff of 14 kPa 11/12 patients were included. All 12 patients with a hepatic decompensation were covered by an SS cutoff of 39 kPa and sensitivity and negative predictive value were 100% (Fig. 2C). Accordingly in patients with a LS above 10 kPa all patients who actually suffered from a decompensation event were included by the SS cutoff and no patient with elevated LS and below cutoff developed a decompensation ($P = 0.0005$). Furthermore 26% of all patients with both SS and LS above the respective cut-off values developed a hepatic decompensation in course of 1 year (Fig. 2B).

LS of 14 kPa as cut-off value results in a sensitivity of 91%, a specificity of 58%, a positive predictive value of 17%,

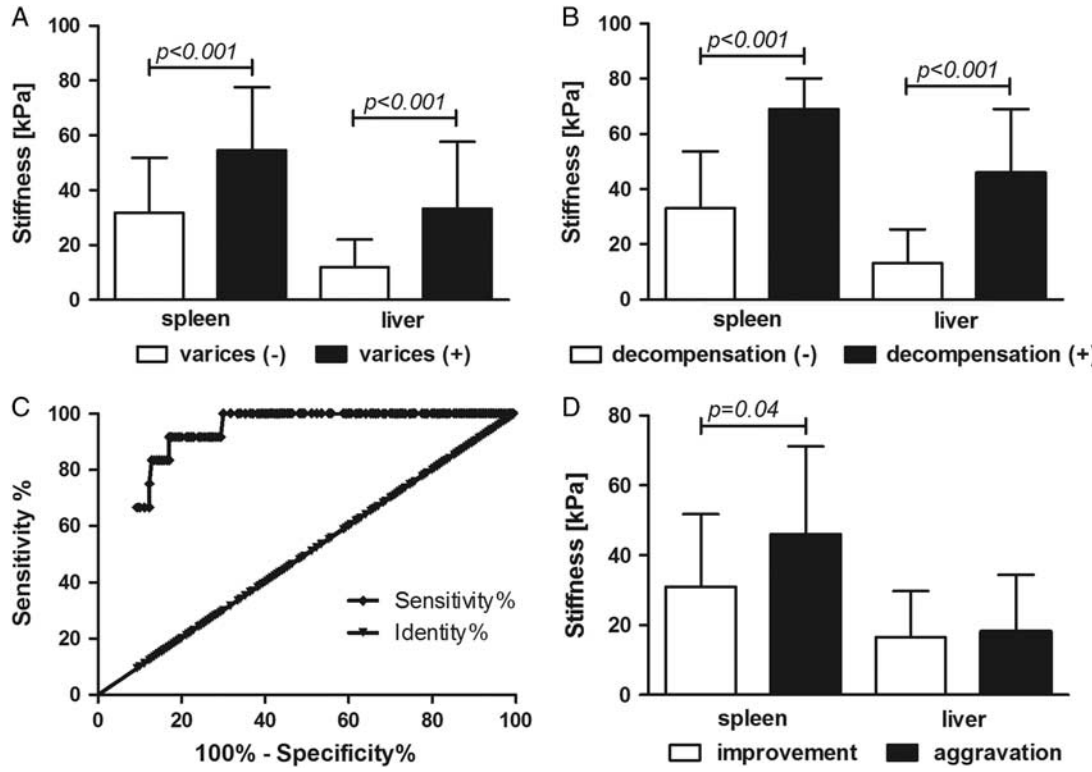

FIGURE 2. Transient elastography values of liver and spleen show significant increases according to presence of varices (A), hepatic decompensation (B), and improvement or aggravation of previously elevated liver enzymes (D). Receivers operating characteristic (ROC) curve for the empirically determined spleen stiffness cut-off value of 39 kPa and decompensation events. C, the area under the ROC curve is 0.9088.

and a negative predictive value of 85%. SS of 39 kPa as cut-off value results in a sensitivity of 100%, a specificity of 69%, a positive predictive value of 21%, and a negative predictive value of 100%. The area under curve of the ROC curve as quality test shows a value of ROC-area under curve = 0.9088 with a 95% confidence interval of 0.8544-0.9632 ($P < 0.0001$).

Nine patients died or received liver transplantation in course of 1 year. All of these patients had an LS above 14 kPa, but no statistically significant differences in SS. Only 2 patients with an SS below 39 kPa died or were transplanted, whereas 7% of patients with an SS above 39 kPa shared their fate.

SS Differentiate Between Acute and Chronic/Acute on Chronic Liver Damage

We identified 59 patients with ongoing liver damage, defined as ALT and AST above 50 U/L in male patients and, respectively, above 35 U/L in female patients. Liver transplant recipients were not considered. Of those patients 38 showed an improvement or normalization of liver enzymes due to treatment accordable with an acute course of the liver damage. The remaining 21 patients aggravated or showed a chronic elevation of liver enzymes, suggesting a chronic course of the disease. Interestingly, SS values in patients with an acute liver damage were significantly lower than patients with a chronic liver damage (30.97 vs. 46.03 kPa; $P = 0.04$) groups showed a significant difference in their SS, whereas their LS was comparable (acute: 16.47 kPa vs. chronic: 18.19 kPa; NS).

Patients With Acute Liver Failure Have Increased LS but No Increased SS

In synopsis of the aforementioned results we took a more detailed look at the 5 patients in this cohort who suffer from acute liver failure (by definition without previous liver disease). Those patients had a LS mean of 16.4 kPa and a SS mean of 24.9 kPa. They were all above the LS cutoff for cirrhosis and 4/5 was below the determined SS cutoff of 39 kPa. Concluding we compared the SS of those 5 patients with the SS of the remaining patients with a LS above 14 kPa. The patients with acute liver failure showed a mean SS of 24.9 kPa, whereas the remaining patients showed a mean SS of 50.31 kPa ($P = 0.004$).

DISCUSSION

Our study showed that patients with varices or who develop hepatic decompensation showed significantly higher LS and SS values at baseline than patients without. This is in line with previous studies, which linked SS to portal hypertension.[8,9] As described LS and SS both predict the presence of esophageal varices, whereas the capabilities of SS are superior to those of LS. In general the prognostic values in our study lay below those described in the literature, which can easily be explained by our more diversified patient cohort including all kinds and stages of liver disease and not only patients with (HCV-associated) cirrhosis. In addition, even though patients were told to fast before their examination, we did not check for it. Therefore there might be in some patients a deviation of actual LS values.[18] Furthermore, our data showed clearly that patients with an SS

below 39 kPa do not develop clinical decompensation, which supports Colecchia et al[19] and Radu et al.[20] While Colecchia and colleagues propose a cut-off value of 54 kPa, we set our cutoff at 39 kPa to include all patients with decompensation events. Moreover we could also assess the applicability of SS on precirrhotic stages.

Indeed, another important finding of our study was that SS distinguishes between acute and chronic or acute on chronic liver damage. Patients, who normalized their liver enzymes over time had significant lower SS values than patients who did not. One possible explanation for this finding might be that SS is a prognostic factor able to predict the further development of the disease, this seem rather unlikely as we included all stages and kinds of liver disease. A more plausible and intriguing explanation is that SS simply differentiate between acute and chronic liver disease. Studies have described a transient LS increase in cases of acute necroinflammation or flares of chronic hepatitis.[21–24] Possibly SS is not affected by these changes and might augment LS diagnostic by eluding the former limitations in case of acute inflammation. This is supported in patients with acute liver failure without presenting liver disease. They all boast elevated LS, whereas SS appears not to be influenced by their acute disease. Transient elastography might become an easy noninvasive tool in the differentiation between acute and chronic liver disease and between acute and acute on chronic liver failure, which, for example, is important for organ allocation in high urgency liver transplantation.[25]

One of the drawbacks of our study was the relatively small patient cohort in consideration of its variety. The results certainly have to be confirmed in prospective preferable longitudinal study. Furthermore our patients were not obliged to perform a standardized procedure of examinations, for example, HVPG measurement; therefore we could not assess each patient's status as detailed as possible.

The SS measurement itself also offers a couple of drawbacks: First, the examination is harder to perform than the transient elastography of the liver and mostly requires a previous sonographic examination of the spleen to determine the exact position of the probe. Those limitations lead to a failure rate of 13% in all patients who were accessible for LS measurements. Second, the technical limitations of SS measurement using transient elastography have already been extensively discussed, as the device is not optimized for SS measurement.[26] Importantly, the correlation between LS and SS, just as between SS and spleen size underline the interesting, although not fully understood role of the spleen in the emergence of portal hypertension and chronic liver injury. As investigated by Bolognesi et al[10] and Mejias et al[27] the pathophysiological progress must be far more sophisticated than previously assumed. Data of Chin et al[28] can be seen in line describing a delayed resolve and respective limited correlation of SS after liver transplantation, just as our data suggests. In conclusion, our data suggest that SS might be useful in predicting hepatic decompensation and in differentiation between acute and chronic liver damage as an integrated value of time and damage.

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