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ORIGINAL ARTICLE

Basic Study

Shear wave elastography results correlate with liver fibrosis histology and liver function reserve

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Abstract

AIM: To evaluate the correlation of shear wave elastography (SWE) results with liver fibrosis histology and quantitative function reserve.

METHODS: Weekly subcutaneous injection of 60% carbon tetrachloride (1.5 mL/kg) was given to 12 canines for 24 wk to induce experimental liver fibrosis, with olive oil given to 2 control canines. At 24 wk, liver condition was evaluated using clinical biochemistry assays, SWE imaging, lidocaine metabolite monoethylglycine-xylidide (MEGX) test, and histologic fibrosis grading. Clinical biochemistry assays were performed at the institutional central laboratory for routine liver function evaluation. Liver stiffness was measured in triplicate from three different intercostal spaces and expressed as mean liver stiffness modulus (LSM). Plasma concentrations of lidocaine and its metabolite MEGX were determined using high-performance liquid chromatography repeated in duplicate. Liver biopsy samples were fixed in 10% formaldehyde, and liver fibrosis was graded using the modified histological activity index Knodell score (F0-F4). Correlations among histologic grading, LSM, and MEGX measures were analyzed with the Pearson linear correlation coefficient.

RESULTS: At 24 wk liver fibrosis histologic grading

was as follows: F0, *n* = 2 (control); F1, *n* = 0; F2, *n* = 3; F3, *n* = 7; and F4, *n* = 2. SWE LSM was positively correlated with histologic grading (*r* = 0.835, *P* < 0.001). Specifically, the F4 group had a significantly higher elastic modulus than the F3, F2, and F0 groups (*P* = 0.002, *P* = 0.003, and *P* = 0.006, respectively), and the F3 group also had a significantly higher modulus than the control F0 group (*P* = 0.039). LSM was negatively associated with plasma MEGX concentrations at 30 min (*r* = -0.642; *P* = 0.013) and 60 min (*r* = -0.651; *P* = 0.012), time to ½ of the maximum concentration (*r* = -0.538; *P* = 0.047), and the area under the curve (*r* = -0.636; *P* = 0.014). Multiple comparisons showed identical differences in these three measures: significantly lower with F4 (*P* = 0.037) and F3 (*P* = 0.032) as compared to F0 and significantly lower with F4 as compared to F2 (*P* = 0.032).

CONCLUSION: SWE LSM shows a good correlation with histologic fibrosis grading and pharmacologic quantitative liver function reserve in experimental severe fibrosis and cirrhosis.

Key words: Liver fibrosis; Histologic grading; Shear wave elastography; Monoethylglycinexylidide test; Experimental study

Core tip: Non-invasive evaluation of liver histology and function reserve is critical for determination of treatment option and prognosis in severe fibrosis and cirrhotic patients. Shear wave elastography (SWE) is a newly emerging elastrographic modality with relatively high resolution and good reproducibility for liver imaging. Lidocaine/monoethylglycinexylidide is also an advanced, laboratory dynamic liver function assay with good diagnostic sensitivity, specificity, and accuracy. This study sheds light on the correlation of SWE imaging results with pharmacologic quantitative liver function for disease severity and function reserve evaluation in patients with severe fibrosis/cirrhosis scheduled for major hepatectomy or liver transplantation.

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INTRODUCTION

Liver fibrosis is a progressive liver disease characterized by replacement of normal liver parenchymal tissue by fibrotic nonparenchymal tissue with or without concomitant abnormal regenerative nodules[1]. The etiologies of liver fibrosis vary among populations worldwide and mainly include viral hepatitis, especially chronic hepatitis B and C in Eastern and Southeastern Asians, alcoholic liver disease in Westerners, and nonalcoholic fatty liver disease[2]. Aside from portal hypertension, reduced or absent liver function reserve is the major pathophysiologic impairment in severely fibrotic and cirrhotic patients. Diagnosis and severity grading of liver fibrosis, especially the evaluation of liver function reserve, are clinically significant for determining the appropriate treatment modality, such as prioritization of liver transplantation and prediction of prognosis in patients with cirrhosis.

Liver ultrasonography is an non-invasive imaging modality most frequently used for routine liver fibrosis screening but suffers from a low sensitivity and specificity, especially for early liver disease or that complicated by another non-fibrotic disease[3]. A variety of elastrographic techniques, including quasistatic elastrography, transient elastography, acoustic radiation force impulse imaging, shear wave elastography (SWE), and magnetic resonance elastography, have been applied or investigated for quantitative evaluation of liver fibrosis[4]. SWE, also called supersonic shear imaging, is a newly emerging elastrographic modality[5] that has been shown to be clinically beneficial for breast[6], thyroid gland, prostate, musculoskeletal, and liver[7] imaging with relatively high resolution and good reproducibility.

Routine liver function biochemistry assays cannot detect compensated liver insufficiency, and thus, liver-based metabolism tests are normally performed for this purpose. The indocyanine green elimination test is a dynamic, liver metabolism-based function assay mainly used for preoperative bedside evaluation of a patient scheduled for liver resection[8] or transplantation[9]. Lidocaine/monoethylglycinexylidide (MEGX) is also an advanced, laboratory dynamic liver function assay based on the metabolization of lidocaine into MEGX by abundant cytochrome P450 in hepatocytes, with good diagnostic sensitivity, specificity, and accuracy, especially for critically ill patients[10].

The primary objective of this study was to assess the correlation of SWE imaging results and liver histology and MEGX liver function test results in an experimental canine model of liver fibrosis. Specifically, the investigation into the correlation of SWE imaging results with pharmacologic quantitative liver function might aid in the evaluation of the liver function reserve in patients with severe fibrosis/cirrhosis scheduled for major hepatectomy or liver transplantation using a bedside, noninvasive modality rather than an invasive laboratory diagnostic modality.

MATERIALS AND METHODS

Laboratory animals

The study protocol was approved by the Animal Research Committee of Beijing Friendship Hospital, Capital Medical University, in accordance with the

National Institute of Health Guidelines for Laboratory Animal Care and Use. Fourteen healthy laboratory Beagles (Rixin Technology Co., Ltd., Beijing; license No. SCXK[BJ]2011-0007) weighing 6-8 kg, including 6 males and 8 females, were bred at the Center of Laboratory Large Animal in Jilin Sino-Japan Friendship Hospital and housed in individual cages with free access to high-lipid canine feed and tap water containing 1:10 (v/v) ethanol. Under general anesthesia by subcutaneous injection of 3% phenobarbital (1 mg/kg), 12 animals were given a subcutaneous injection of 60% carbon tetrachloride (1.5 mL/kg; Shanghai Chemical Co., Ltd, China) diluted in commercially available olive oil, at a weekly interval for 24 consecutive weeks after the initial injection to induce experimental liver fibrosis[11]. Two animals were given 1.5 mL/kg olive oil alone using the same protocol as controls.

Liver SWE imaging

At 24 wk, the animals were anesthetized and positioned supine with the anterior abdominal wall shaved on the operating table. An Aixplorer color Doppler ultrasound system (SuperSonic Imagine, Aix-en-Provence, France), equipped with a 4-15 MHz probe, was operated by an independent ultrasound technician for SWE imaging. An appropriate right-side intercostal space was located for identifying the optimal liver parenchymal window with gray scale ultrasound imaging. The SWE module was subsequently switched on for elastography of the right lobe parenchyma approximately 1 cm below the liver capsule. Liver stiffness was measured in triplicate from three different intercostal spaces and expressed as the mean elastic modulus (kPa)[12].

Clinical biochemistry assays and MEGX liver function tests

Clinical biochemistry assays were performed at the institutional central laboratory for routine liver function evaluation, including serum total protein, albumin, alanine aminotransferase, asparate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, and bilirubin (total, unconjugated, conjugated). After blood sampling for clinical biochemistry assays, lidocaine hydrochloride (1 mg/kg) was injected through the cephalic vein into the anesthetized animals. The femoral vein was punctured for venous blood sampling (2 mL) at 0, 5, 10, 15, 20, 30, 40, 50, and 60 min after lidocaine injection. Plasma concentrations of lidocaine and its metabolite MEGX were determined using high-performance liquid chromatography repeated in duplicate[13]. A plasma MEGX concentration curve was plotted against time.

Liver biopsy

Percutaneous liver biopsy was performed using an 18-gauge needle by an independent, board-certified interventional ultrasound physician under B-mode ultrasound guidance. Liver biopsy samples were fixed in 10% formaldehyde, and liver fibrosis was graded using the modified histological activity index, *i.e.*, Knodell score (F0-F4), with a higher score indicating more serious liver fibrosis[14].

Statistical analysis

The statistical software package SPSS 11.0 (SPSS Inc., Chicago, IL, United States) was used for statistical analyses. All continuous data are expressed as median ± interquartile range (IQR), and the medians were compared using the Wilcoxon rank-sum test. Multiple comparisons were performed using the Fisher least significance difference test at an adjusted significance level. Correlations among histologic grading, LSM, and MEGX measures were analyzed with the Pearson linear correlation coefficient. A two-sided P value < 0.05 was considered statistically significant.

RESULTS

Correlation of clinical biochemistry with liver histology

All 14 animals survived at 24 wk, and liver fibrosis histologic grading was as follows: F0, n = 2 (control); F1, n = 0; F2, n = 3; F3, n = 7; and F4, n = 2. The liver biochemistry assay results are shown in Table 1. All biochemical measures remained similar among the four histologic groups (P > 0.05); however, the serum albumin level was significantly lower in the F4 group than in the F2 and F0 groups (P = 0.003 and P = 0.021, respectively) but not statistically different among the F3, F2, and F0 groups and between F4 and F3 groups (P > 0.05).

Correlation of SWE with liver histology

Representative SWE images for F0 and F2-F4 are shown in Figure 1A-D. SWE liver stiffness modulus data are shown in Table 2 and exhibited a significant positive correlation with histologic grading (r = 0.835, P < 0.001) (Figure 1E). Specifically, the F4 group had a significantly higher elastic modulus than the F3, F2, and F0 groups (P = 0.002, P = 0.003, and P = 0.006, respectively), and the F3 group also had a significantly higher modulus than the control F0 group (P = 0.039). However, the elastic modulus was similar between the F3 and F2 groups and the F2 and F0 groups (P > 0.05).

Correlation of plasma MEGX pharmacokinetics with liver histology

A plasma MEGX concentration *vs* time plot is shown in Figure 2, and the pharmacokinetics of plasma MEGX are described in Table 3. The four fibrosis grading groups showed no significant differences in all of the pharmacokinetic measures, although a declining trend was observed from F0 to F4, which was statistically significant for plasma MEGX concentrations at 30 min (P = 0.033) and 60 min (P = 0.020) as well as with respect to the area under the curve (P = 0.016).

Table 1 Liver biochemistry assays (median ± IQR) by fibrosis grade (*n* = 14)

Variable	F0 control (*n* = 2)	F2 (*n* = 3)	F3 (*n* = 7)	F4 (*n* = 2)	*P* value
Albumin (g/Dl)	3.9 ± 1.8[1]	3.1 ± 0.5[1]	2.6 ± 0.9[1,2]	1.8 ± 0.5[2]	0.021
Total protein (g/dL)	6.5 ± 1.1	7.0 ± 1.7	6.1 ± 1.2	6.2 ± 1.8	0.639
AST (IU/L)	28 ± 14	21 ± 12	28 ± 15	60 ± 76	0.711
ALT (IU/L)	44 ± 17	43 ± 22	31 ± 28	58 ± 27	0.669
GGT (IU/L)	5.2 ± 2.1	5 ± 1.3	5.2 ± 2.6	6.3 ± 6.2	0.938
ALP (IU/L)	44 ± 25	49 ± 8	61 ± 19	74 ± 31	0.140
TBil (mg/dL)	0.27 ± 0.08	0.24 ± 0.07	0.25 ± 0.11	0.33 ± 0.21	0.865
UBil (mg/dL)	0.13 ± 0.05	0.13 ± 0.06	0.16 ± 0.10	0.17 ± 0.12	0.825
CBil (mg/dL)	0.15 ± 0.03	0.09 ± 0.05	0.10 ± 0.07	0.16 ± 0.09	0.318

[1,2]The two groups with no common letter have a statistically significant difference. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Asparate aminotransferase; CBil: Conjugated bilirubin; GGT: Gamma-glutamyl transpeptadase; IQR: Interquartile range; TBil: Total bilirubin; UBil: Unconjugated bilirubin.

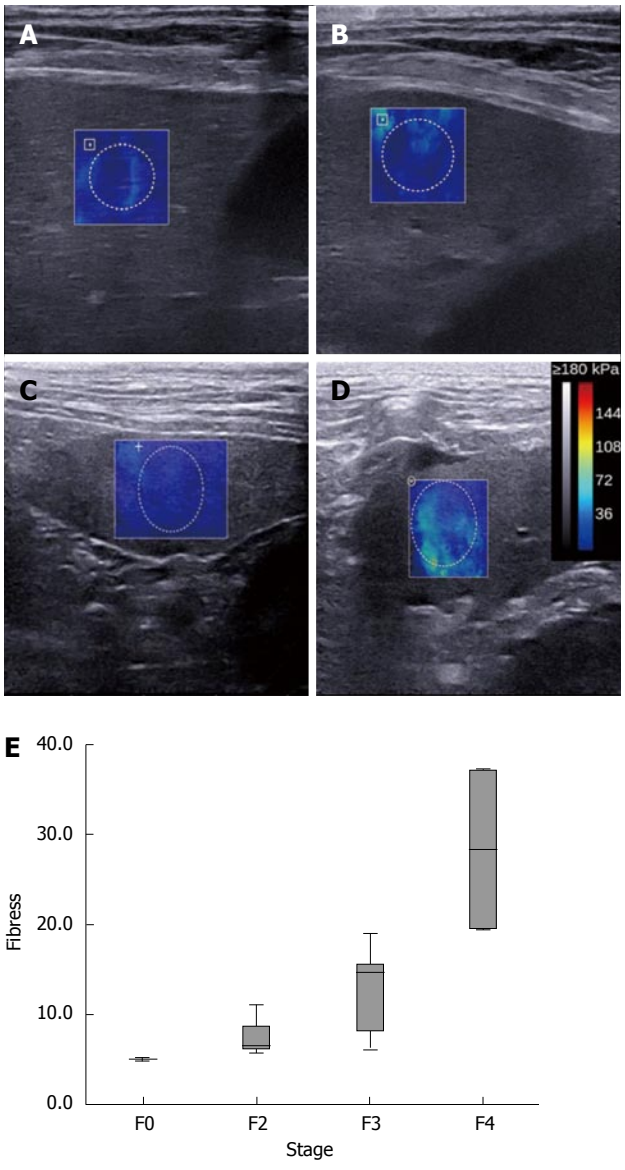

Figure 1 Correlation of shear wave elastography with fibrosis grading. A-D: Representative shear wave elastography images for F0, F2, F3, and F4, respectively; E: Box plot of the elastic modulus (kPa) expressed as median ± IQR against fibrosis grading. IQR: Interquartile range.

Table 2 Shear wave elastography elastic modulus (kPa, median ± IQR) by fibrosis grade (*n* = 14)

Variable	F0 control (*n* = 2)	F2 (*n* = 3)	F3 (*n* = 7)	F4 (*n* = 2)	*P* value
LSM	5.0 ± 0.4[1]	6.5 ± 5.4[1,2]	14.6 ± 9.4[2,3]	28.3 ± 17.8[4]	0.004

[1,2,3,4]The two groups with no common letter have a statistically significant difference. IQR: Interquartile range; LSM: Liver stiffness modulus.

Multiple comparisons showed identical differences in these three measures: significantly lower with F4 (*P* = 0.037) and F3 (*P* = 0.032) as compared to F0 and significantly lower with F4 as compared to F2 (*P* = 0.032), but similar between F3 and F2 and between F2 and F0 (both *P* values > 0.05). LSM was negatively associated with plasma MEGX concentrations at 30 min (*r* = -0.642, *P* = 0.013) and 60 min (*r* = -0.651, *P* = 0.012), time to ½ of the maximum concentration (*r* = -0.538, *P* = 0.047), and the area under the curve (*r* = -0.636, *P* = 0.014).

DISCUSSION

Liver biopsy, usually through the percutaneous approach, is the gold standard diagnostic modality for liver fibrosis/cirrhosis, but this procedure cannot be used and repeated as routine in general clinical practice due to low procedure-associated morbidities, such as bleeding, perforation, and infection[15]. Moreover, histologic grading of fibrosis does not necessarily correlate well with the underlying liver function reserve, but instead may over- or underestimate the disease severity due to the use of a limited liver tissue sample. As an alternative non-invasive diagnostic modality to liver biopsy, liver elastography is an advanced ultrasound or magnetic resonance imaging technique that quantifies liver stiffness by measuring liver tissue distortion (shear wave) and wave transition velocity upon mechanical vibration[16]. Among the elastographic techniques currently available, the

Table 3 Pharmacokinetics (median ± IQR) of plasma monoethylglycinexylidide (n = 14)

Variable	F0 control (n = 2)	F2 (n = 3)	F3 (n = 7)	F4 (n = 2)	P value
$C_{10\ min}$ (ng/mL)	252 ± 31	197 ± 381	99 ± 105	72 ± 38	0.280
$C_{30\ min}$ (ng/mL)	327 ± 56[1]	268 ± 375[1,2]	120 ± 31[2,3]	73 ± 20[3,4]	0.033
$C_{60\ min}$ (ng/mL)	274 ± 71[1]	258 ± 336[1,2]	93 ± 26[2,3]	51 ± 37[3,4]	0.020
C_{max} (ng/mL)	327 ± 56	282 ± 332	143 ± 106	82 ± 22	0.069
t_{max} (min)	30.0 ± 0.0	40.0 ± 20.0	30.0 ± 20.0	17.5 ± 5.0	0.120
$t_{½max}$ (min)	141.3 ± 110.1	151.1 ± 188.3	46.9 ± 50.2	74.9 ± 75.9	0.545
AUC (ng/mL·min)	16644 ± 3139[1]	14421 ± 2515[1,2]	6100 ± 2286[2,3]	3970 ± 1670[3,4]	0.016
K_{max} (ng/mL/min)	43.7 ± 7.2	38.1 ± 83.8	17.7 ± 22.8	6.6 ± 1.5	0.358

[1,2,3,4]The two groups with no common letter have a statistically significant difference. $C_{10\ min}$, $C_{30\ min}$ and $C_{60\ min}$: Concentrations at 10, 30, and 60 min, respectively; C_{max}: The maximum concentration; IQR: Interquartile range; K_{max}: The maximum concentration increase per unit time; t_{max} and $t_{½max}$: Times to the maximum and ½ of the maximum concentration; AUC: Area under the curve.

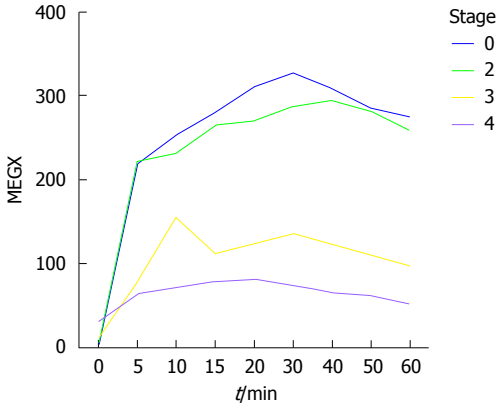

Figure 2 Plasma monoethylglycinexylidide concentration *vs* time plots by fibrosis grade. MEGX: Monoethylglycinexylidide.

FibroScan using transient elastography has been well validated for fibrosis grading in liver fibrosis patients and the results show a good histologic correlation with liver biopsy findings; however, FibroScan measures liver stiffness on a one-dimensional ultrasonograph and also requires an additional designated probe for patients with a narrow rib cage or with complicating fatty liver disease[17]. In contrast, SWE offers a quantitative, real-time, two-dimensional elastography by incorporating an advanced ultrafast imaging technique[5] with a high correlation of histologic fibrosis staging comparable to transient elastography[18]. Our study results add new knowledge to current literature showing that the liver SWE elastic modulus also was well correlated with liver-based drug metabolism in addition to histologic grading. To the best of our knowledge, the present work is the first report regarding correlation of SWE results with fibrosis grading and cytochrome P450-based liver function reserve in experimental liver fibrosis.

Quantitative evaluation of liver function reserve can improve the predictive accuracy for chronic liver disease progression, including chronic hepatitis to liver fibrosis/cirrhosis[19]. The Child-Pugh score[20] and Model for End-Stage Liver Disease score[21] are most often used and based on clinical manifestations and laboratory biochemistry assays; however, these two scales have a variety of confounding factors and only represent a patient's pre-existing long-term liver function reserve rather than an acute change in liver function. The indocyanine green elimination test is the liver function reserve assay most frequently used in general clinical practice; however, its results may be affected by liver perfusion impairment, biliary obstruction, and complicating hypoalbuminemia[22]. MEGX test is a dynamic, quantitative liver function test that measures cytochrome P450 metabolism of lidocaine in metabolically active hepatocytes and is superior to the indocyanine green elimination test with respect to sensitivity, specificity, accuracy, and reproducibility. The MEGX level has been used for preoperative planning of liver resection[23], prediction of post-hepectomy acute liver failure[24], and survival of decompensated cirrhosis patients on the waiting list for liver transplantation[25]. Moreover, quantitative liver function tests including the MEGX test were reported as independent risk factors for improving the predictability of virologic response and disease progression of chronic hepatitis C virus with antiviral treatment[26]. Our results identified three potential measures, especially the area under the curve of the concentration *vs* time plot a sensitive and specific indicator of cytochrome P450 metabolic functionality, which could differentiate severe fibrosis or cirrhosis from mild disease.

SWE has been widely used for the evaluation of liver fibrosis/cirrhosis of multiple etiologies or with complicating comorbidities, including chronic hepatitis[27], liver cancer[28], steatohepatitis[29], and biliary atresia[30]. This two-dimensional elastographic technique offers better performance for assessing liver fibrosis as compared to conventional transient elastography, especially regarding the correlation of the LSM with histologic grading, with cutoff values of 8.0 kPa and 13.1 kPa for F2 and F4, respectively[31]. Our preliminary results demonstrated that severe fibrosis and especially cirrhosis had a higher LSM than moderate liver disease although no statistically significant difference was observed between F2 and F0

or between F3 and F2. Moreover, our results showed that the LSM on SWE was negatively correlated with MEGX test measures, including plasma concentrations at 30 min and 60 min, the time to ½ of the maximum concentration, and with respect to the area under the curve. Quantification of liver stiffness in patients with severe fibrosis or cirrhosis who are scheduled for major hepatectomy or liver transplantation may help estimate the risk of postoperative liver insufficiency with an advantage over pharmacologic liver function assays due to its non-invasiveness and technical reproducibility[32].

In conclusion, our results demonstrated that SWE results are well correlated with the histologic grading of experimental fibrosis. Moreover, SWE results also correlated well with quantitative liver function reserve measurements obtained by the lidocaine metabolite MEGX test. Therefore, it is beneficial to employ SWE for assessment of liver disease severity and function reserve in patients with severe fibrosis or cirrhosis as this modality is non-invasive and reproducible in the clinical setting.

COMMENTS

Background

Liver ultrasonography is a non-invasive imaging modality most frequently used for routine liver fibrosis screening but suffers from a low sensitivity and specificity, especially for early liver disease or that complicated by another non-fibrotic disease. Routine liver function biochemistry assays cannot detect compensated liver insufficiency, and thus, liver-based metabolism tests are normally performed for this purpose.

Research frontiers

Shear wave elastography (SWE) is a newly emerging elastrographic modality that has been shown to be clinically beneficial for liver imaging with relatively high resolution and good reproducibility. Monoethylglycinexylidide (MEGX) is also an advanced, laboratory dynamic liver function assay based on the metabolization of lidocaine into MEGX by abundant cytochrome P450 in hepatocytes, with good diagnostic sensitivity, specificity, and accuracy, especially for critically ill patients.

Innovations and breakthroughs

SWE results are well correlated with the histologic grading of experimental fibrosis and also with quantitative liver function reserve measurements obtained by the lidocaine metabolite MEGX test.

Applications

SWE is beneficial for assessment of liver disease severity and function reserve in patients with severe fibrosis or cirrhosis as this modality is non-invasive and reproducible in the clinical setting.

Peer-review

Interesting paper and topic. In the present study, the authors evaluated the correlation of shear wave elastrography results with liver fibrosis histology and liver function reserve. In general, the manuscript is well-written and the methodology is acceptable. Although the correlation of SWE in patients with various liver conditions have been extensively handled in the literature, this study throws light for the first time on its correlation with quantitative liver function reserve measurements obtained by the lidocaine metabolite MEGX test.

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