

Detection of Fibrous Liver Under Congestion by a Gravity-assisted Evaluation of Liver Stiffness

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Abstract

To evaluate architectural deformities of the liver under congestive conditions, shear wave elastography (SWE) was measured in the supine (Sp) and left decubitus (Ld) positions in 298 subjects. The inferior vena cava (IVC) diameter was significantly reduced at Ld in subjects with higher Ld-SWE than Sp-SWE but not in those with lower Ld-SWE. In 81 subjects, Sp-SWE was increased or decreased in Ld beyond the magnitude of robust coefficient of variation. Among these subjects, all 37 with normal Sp-SWE had higher Ld-SWE than Sp-SWE (NH), whereas in 44 residual subjects with abnormal Sp-SWE Ld-SWE was higher in 27 subjects (HH) and lower in 17 subjects (HS) than Sp-SWE. Sp-SWE was significantly correlated with the difference between Sp-SWE and Ld-SWE only in HS. When HH and HS were examined for each lobe, Fibrosis-4 or platelet counts were significantly higher only for HS versus NH. The paradoxical increase/decrease of liver stiffness/IVC diameter in Ld indicates the pressure threshold between the hepatic veins and IVC. Gravity alters the hepatic architecture during body postural changes, causing outflow blockage in hepatic veins. A rigid liver is resistant to structural deformation. Stiff-liver softening in Ld suggests fibrous liver.

Introduction

The survival of children and adolescents undergoing the Fontan procedure continues to improve as various modifications of this operation have been applied since 1968¹⁻³. In conjunction with a technological advancement in the pathophysiological evaluation of the liver, the frequency of encountering the spectrum of liver disease is increasing in patients with heart diseases. The frequency of nonalcoholic cirrhosis is reported to be greater than 4% among hospital admissions of patients with a single functional ventricle, whereas it is approximately 0.3% of hospitalizations for patients without congenital heart diseases⁴. The pathophysiology is termed congestive hepatopathy, which is not restricted to the postoperative condition of the Fontan procedure but arises from chronically elevated hepatic venous pressures secondary to biventricular or isolated right-sided heart failure. Low cardiac output itself may also accelerate fibrosis pathways by reducing circulating blood flow to the liver. To determine a specific patient's prognosis, screening and management strategies (including candidacy for isolated heart or combined heart-liver transplantation), the detection of fibrous progression in the liver is critical. Unfortunately, there is a growing awareness that fibrosis biomarkers, such as serum tests, fibrosis calculators, and liver stiffness are not reliable in congestive hepatopathy⁵⁻⁷. Even liver biopsy is unlikely to stage fibrosis and predict clinical outcomes accurately because the heterogeneity of fiber deposition is quite large in congestive hepatopathy⁵.

Liver stiffness is a useful surrogate marker in viral hepatitis and alcoholic and nonalcoholic fatty liver diseases to assess the degree of fibrous accumulation in the liver⁸⁻¹¹, which is a good prognostic indicator irrespective of etiologies for chronic liver diseases. Because liver stiffness is directly measured in the liver as a physical property, the value is fundamentally spared from systemic disparity. Based on its noninvasive nature, the value can be repeatedly measured from various sites especially in shear wave

elastography using an acoustic radiation force impulse technology or in magnetic resonance elastography. On the other hand, the clinical feasibility may be limited in magnetic resonance imaging as many patients with congestive hepatopathy have non-magnetic resonance compatible cardiac devices. Furthermore, congestion itself increases liver stiffness measurements and causes overestimation of the amount of fibrosis in transient elastography¹².

This study aims to establish a strategy that enables the evaluation of fibrous accumulation in the liver with respect to architectural rigidity under congestive circumstances by measuring shear wave elastography. After assessing the impacts of interstitial tissue pressure on shear wave elastography, the effects of body postural change on the diameter of inferior vena cava (IVC) and liver stiffness were evaluated. Based on the different reaction of shear wave elastography upon changing body positions, the patients were hypothetically divided into three groups: normal liver, congestive liver, and congestive liver with fiber accumulation. The Fibrosis-4 index (FIB4) and its constituents were compared among groups to endorse the significance of hypothetical classification. The possibility to dissociate congestion from underlying fibrosis using a gravity aid to induce architectural deformity of the liver is discussed.

Results

Liver with normal stiffness in the supine position stiffens in the left decubitus position, whereas stiff livers harden or soften.

When 2dSWE was measured for both supine and left decubitus positions, the values revealed a significant positive correlation as shown in Fig. 1a ($p < 0.0001$, $r = 0.68$). Because 12 values of 2dSWE in each liver were dispersed on a case-by-case basis, it is reasonable to assume that SWE is substantially affected by changing body positions only when the difference between SpSWE and LdSWE ($\Delta 2dSWE$, $SpSWE - LdSWE$) is greater than the dispersion of SpSWE. Among 298 cases, LdSWE increased or decreased from SpSWE over the magnitude of CVR in 81 cases (27.2%). These 81 cases can be classified into four groups based on SpSWE normality and positive/negative $\Delta 2dSWE$ values. For 37 cases in which SpSWE was slower than the upper normal limit of 1.41 m/sec (see Methods), $\Delta 2dSWE$ was negative as shown in Fig. 1b in all the cases (NH). On the other hand, in 44 cases with stiff livers in the supine position, $\Delta 2dSWE$ was negative (HH) or positive (HS) in 27 and 17 cases, respectively. To assess the possibility that $\Delta 2dSWE$ is determined by cardiac function, the cardio-thorax ratio was compared between cases with negative and positive $\Delta 2dSWE$. As shown in Fig. 1c, the cardio-thorax ratio was not significantly different between the two groups ($p = 0.51$).

IVC shrinks in the left decubitus position as the liver hardens but not as the liver softens.

Next, the effects of the body positions on IVC diameter were evaluated irrespective of whether the $\Delta 2dSWE$ scale was beyond or within CVR. In the results, the diameter of IVC in the left decubitus position was significantly reduced compared with the supine position in the cases with SpSWE slower than 1.41 m/sec as shown in the left panel of Fig. 2a ($p = 0.013$). Consistently, the diameter also shortens in cases

with SpSWE of 1.41 m/sec or faster and negative Δ 2dSWE values (Fig. 2a middle panel, $p = 0.0070$). On the other hand, IVC diameters in the supine and left decubitus positions were not significantly different in cases with SpSWE of 1.41 m/sec or faster and positive Δ 2dSWE (Fig. 2a right panel, $p = 0.32$).

Liver stiffness is tightly associated with body postural change in cases in which a stiff liver softens in the left decubitus position, especially in the right lobe.

To understand the implications of the pressure connection between the liver and IVC, the correlation between SpSWE and Δ 2dSWE was evaluated. As shown in Fig. 2b, a significant correlation was not observed in cases with SpSWE slower than 1.41 m/sec ($p = 0.56$) or a SpSWE value of 1.41 m/sec or faster and negative Δ 2dSWE ($p = 0.88$). In contrast, SpSWE and Δ 2dSWE revealed a significant positive correlation in cases with SpSWE of 1.41 m/sec or faster and positive Δ 2dSWE ($p < 0.0001$, $r = 0.38$). When the same relation was separately evaluated in the right or left lobe, as shown in Fig. 2c the correlation was clearly tighter in the right lobe ($p < 0.0001$, $r = 0.48$) compared with the left lobe ($p < 0.0001$, $r = 0.31$).

Gravity unevenly impacts liver architecture between the right and left lobes.

The paradoxical increment/shrinkage of LdSWE/IVC on the left decubitus position indicates that pressure thresholds exist between the hepatic veins and IVC, where outflow blocks would be built under architectural deformation of the liver during postural changes. Given that postural change may not evenly impact liver architecture, Δ 2dSWE was separately evaluated in right and left lobes. As shown in Fig. 3, large differences in Δ 2dSWE are noted between the right and left lobes in both cases with positive or negative Δ 2dSWE in the entire liver. When Δ 2dSWE is positive or negative in the entire liver, Δ 2dSWE in a single lobe is reciprocally negative or positive, respectively, suggesting that the impact of postural change on liver architecture would be detected much easier in a single lobe compared with the entire liver.

Softening of the stiff liver on left decubitus position suggests fibrous progression of the liver.

To infer the relationship between pathological differences of the liver and Δ 2dSWE, FIB4 and its constituents, including platelet count, age, and alanine aminotransferase, were compared among NH, HH, and HS cases. As shown in Fig. 4, FIB4 and platelet counts are significantly increased and decreased, respectively, in HS against NH, especially when HH and HS were not evaluated in the entire liver but in a single lobe of the right or left (judged in the entire liver, right lobe, left lobe; (FIB4) $p = 0.04$, $p = 0.006$, $p = 0.01$; (platelet counts) $p = 0.29$, $p = 0.05$, $p = 0.05$, respectively). In terms of age and alanine aminotransferase, no significant differences are noted between NH and HS even when HH and HS were judged in each lobe (Fig. 5). In addition, no significant differences in factors are noted between NH and HH.

Discussion

IVC diameter and area decreased significantly from the right lateral to the supine position and further to the left lateral position¹⁶. The height of IVC relative to the right ventricle, compression of IVC between the liver and spine, different venous return and/or splanchnic blood pooling are thought to cause postural differences in IVC size^{16,17}. Consistently, IVC diameter was significantly reduced in cases with normal liver stiffness when the body positions were changed from supine to left decubitus in our cohort. Liver stiffness is clearly correlated with IVC pressure/diameter in the supine position as shown in Supplemental Figs. 1a and 1b. Thus, if the pressure is equilibrated between the IVC and hepatic veins during body position changes, liver stiffness should be reduced in the left decubitus position. However, IVC diameter and liver stiffness exhibited paradoxical changes in this study. The liver hardened, whereas IVC was reduced. These findings suggest that a pressure threshold exists between the IVC and hepatic veins at the left decubitus position in livers with normal stiffness. Given that intra-abdominal organs relocate along with the postural change¹⁸, it is reasonable to assume that the hepatic veins are vented and twisted against the IVC in the left decubitus position, establishing an outflow block. Furthermore, it is anticipated that the rigid liver is less deformed after body position change. A minimal outflow block keeps the efflux from the liver to IVC and obviates the shrinkage of IVC. Therefore, we hypothesized that a stiff liver in the supine will soften in the left decubitus position if substantial fiber accumulation is present. Otherwise, the liver will further harden (Supplemental Fig. 2).

Because IVC pressure strikingly affects liver stiffness¹² as shown in Supplemental Figs. 1a and 1b, the correlation of liver stiffness before and after changing IVC pressure strongly indicates a direct connection between IVC and hepatic veins (Supplemental Fig. 1c). Along with the body position changes from the supine to left decubitus position, a significant correlation between SpSWE and Δ 2dSWE was only observed in cases with a liver that softened in the left decubitus position. These results strongly support the notion that pressure thresholds generally exist between IVC and hepatic veins in the left decubitus position, but fewer pressure differences are noted between IVC and hepatic veins in cases with a stiff liver that softens in the left decubitus position. Furthermore, the correlation coefficients were substantially different between the lobes. In addition, Δ 2dSWE revealed large differences between the right and left lobes. These values are reciprocally negative and positive, suggesting that poor venous drainage in the left decubitus position heterogeneously occurs in the liver and is compensated through the area where gravity generates less impact. It is well known that if the flow volume is reduced from the portal vein, the arterial flow instantly compensates, and vice versa¹⁹. In a similar way, if venous drainage is hindered in a certain area, congestion is avoided by opening latent vascular connections toward the outside of burden area, as noted in the case of Budd-Chiari syndrome²⁰.

The different anatomical connections between IVC and hepatic veins is one reason for the uneven impacts of gravity on the lobes among cases²¹. Given that liver stiffness is measured in two different body positions, it is assumed that a separate evaluation of each lobe should have a higher probability to detect the different architectural rigidity. In fact, higher probabilities are calculated when the groups for the comparison of FIB4 were assessed in each lobe. Although the significance of our hypothesis was supported by FIB4 and platelet counts of surrogates for liver fibrosis, these findings should be

histologically reconfirmed in a future study. The efficacy as a prognostic indicator of liver stiffness measurements in supine and left decubitus postures also has to be validated in a cohort of congestive heart diseases for guiding decisions with respect to the burden of liver diseases.

Conclusion

In this report, a strategy was proposed to measure shear wave elastography that enables evaluation of architectural deformity under congestive circumstances. With the help of gravity, the impacts on architectural rigidity and interstitial tissue pressure are dissociated when measuring liver stiffness. The basic data presented in this report provide insights not only for the clinical application of liver stiffness in patients with congestive heart diseases but also for the physiological components and mechanisms defining liver stiffness.

Methods

Patients

Two-dimensional shear wave elastography (2dSWE) was measured in both supine and left decubitus positions in 298 cases with various diseases including nonalcoholic fatty liver diseases (NAFLD). The patients' characteristics are summarized in Table 1. All studies were conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008. Routine blood biochemistry was measured in the clinical laboratories of our hospital, where a quality control of each test is regularly performed every day. NAFLD was diagnosed based on the criteria proposed by the Asia-Pacific Working Party on NAFLD¹³. Fatty liver was diagnosed by abdominal US as defined by an increased echogenicity of the liver along with the presence of any two of the following three findings: liver-kidney contrast, vascular blurring, and deep-attenuation of echo-beam¹⁴.

Table 1
Patients' characteristics

Background			
Sex (F:M)		142:156	
Age	62.3	years old	49.6–71.4*
BMI	22.9	kg/m ²	20.8–25.5*
Liver diseases			
Alcoholic liver disease	28		
HBV	38		
HCV	40		
Nonalcoholic fatty liver diseases	56		
Hepatocellular carcinoma	12		
Other chronic liver dysfunction	69		
Miscellaneous	55	Total	298
Shear wave speed			
2dSWE (supine)	1.52	m/sec	1.43–1.67*
2dSWE (left decubitus)	1.57	m/sec	1.46–1.74*
<i>Wilcoxon matched-pairs signed rank test</i>	p < 0.0001		
%CVRsup \leq Δ2dSWE%	81 (27.2%)		

*, inter quartile range; F, female; M, male; BMI, body mass index; 2dSWE, two-dimensional shear wave elastography; %CVRsup, robust coefficient-of-variation on supine position in percentage against the median value; Δ2dSWE%, the difference of 2dSWEs between supine and left decubitus positions in percentage against the median value

To define the cut-off value of 2dSWE suggesting least fiber accumulation in the liver, 2dSWE was measured in a different cohort of 480 voluntary annual medical checkup visitors who were diagnosed with NAFLD one year ago. Because median 2dSWE values in the 480 visitors fit well on a Gaussian distribution represented by an average of 1.324 m/sec with a standard deviation of 0.0847 m/sec ($r^2 = 0.98$), a cut-off value to distinguish the liver with fiber accumulation was statistically defined as the average plus standard deviation of 1.41 m/sec¹⁵ and was employed in this study.

To clarify the relationship between liver stiffness and interstitial tissue pressure, virtual touch quantification of point shear wave elastography (pSWE) was measured before and after cardiac surgery in a different cohort consisting of 41 cases with disorders, including 10 valvular and 31 congenital heart

diseases. Physical properties with respect to cardiac function were evaluated using ultrasound (US), chest X-ray, and cardiac catheterization. The data is shown in supplementary digital content Fig. 1 and referenced in the discussion section.

The review boards of Uonuma Institute of Community Medicine and Niigata University Medical and Dental Hospital approved the study measuring liver stiffness in our main cohort consisting of 298 cases with various diseases in two body positions and another cohort of 41 patients undergone cardiac surgery, respectively. These studies did not require informed consent because it was a retrospective study using only medical records or noninvasive imaging examinations. The study to define the cut-off value of 2dSWE suggesting least fiber accumulation in the liver was approved by the institutional review boards of Uonuma Institute of Community Medicine and our affiliated institution of Joetsu Medical Checkup Center. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000018715). A written informed consent was obtained from each medical checkup visitor.

Shear Wave Elastography Measurements

SWE evoked by acoustic radiation force impulse was measured as pSWE using an ACUSON S2000 ultrasound system (Siemens Healthcare, Erlangen, Germany) or as 2dSWE using an Aprio 500 (Canon Medical System Corporation, Ohtawara, Japan). SWE was measured thrice in each segment (posterior, anterior, medial, and lateral) while the patient was in the supine position. When 2dSWE was measured on two body positions, the measurements were performed again in the liver at 12 sites on the left decubitus position.

Statistical analyses

A robust counterpart to the standard deviation was calculated as follows. First, the median absolute deviation was calculated as the median of the difference in the absolute values between each SWE and the median of 12 measurements; thereafter, a constant factor of 1.4826 was multiplied. Finally, the robust coefficient of variation (CVR) was calculated by dividing the robust standard deviation with the median and is expressed as a percentage. Numerical data from independent cases were compared using the Mann-Whitney U or Kruskal-Wallis test followed by Dunn's post hoc multiple comparisons between two groups or among three groups, respectively. IVC diameters on different body positions in each case were compared using Wilcoxon matched pairs signed rank test. A correlation of 2dSWE between different body positions was evaluated by calculating Spearman correlation coefficients. All statistical analyses were conducted with GraphPad Prism version 7.0 (GraphPad Software Inc., La Jolla, CA, USA), and two-sided P-values less than 0.05 were considered statistically significant.

Declarations

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especially in laborious manner with two body positions. This study was supported for data collection and statistical analyses by a grant from the Niigata University Medical and Dental Hospital (Clinical research support project/2013) to Takeshi Suda.

Author contributions

Each author is a main contributor to the following points. TS, study concept, study design, analysis and interpretation of data, and writing the manuscript; AS, TK, and TY, analysis and interpretation of the data; TH, SA, SM, KK, AT, MT, acquisition of the data; KY, study supervision; MT, critical revision of the manuscript for important intellectual content; AA, material support, statistical analysis, and critical revision of the manuscript for important intellectual content; ST, administrative supervision.

Competing interests

Takeshi Suda, Ai Sugimoto, Atsushi Abe, Tsutomu Kanefuji, Takahiro Hoshi, Satoshi Abe, Shinichi Morita, Takeshi Yokoo, Kenya Kamimura, Atsunori Tsuchiya, Masaaki Takamura, Kazuyoshi Yagi, Masashi Takahashi, and Shuji Terai declare that they have no conflict of interest. There is no relationship that should be disclosed in association with this study. The authors have nothing to disclose in relation with this manuscript.

Availability of materials and data

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figures

Figure 1

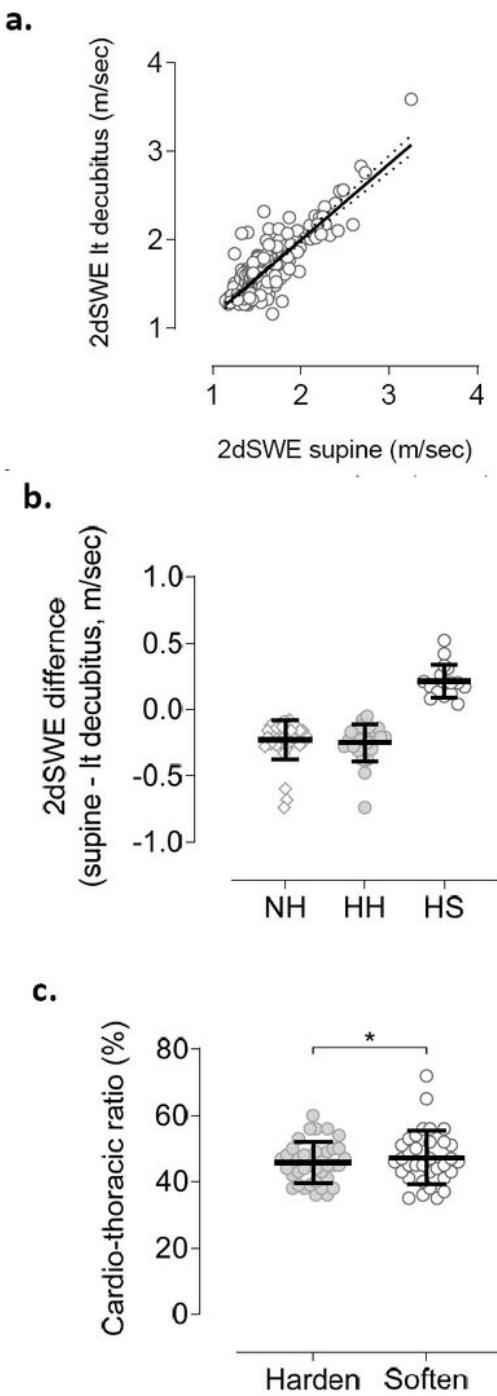


Figure 1

Body position effects on liver stiffness a) Two-dimensional shear wave elastography values (2dSWE) that were measured in the supine and left decubitus positions revealed a significant positive correlation ($p < 0.0001$, $r = 0.68$). The black continuous and dotted lines reveal the best fit and 95% confidence band in the equation of least squares. b) The cases in which 2dSWE increased or decreased in association with changing body positions beyond the magnitude of robust coefficient of variation can be classified into 3

groups: normal 2dSWE (NH) or abnormal 2dSWE that increased (HH) or decreased (HS) on the left decubitus position. c) The cardiothoracic ratio was not significantly different between the patients with abnormal 2dSWE in the supine position, which further hardened or softened in the left decubitus position (*, p=0.51). The horizontal bars in b) and c) indicate average (bold) and standard deviation.

Figure 2

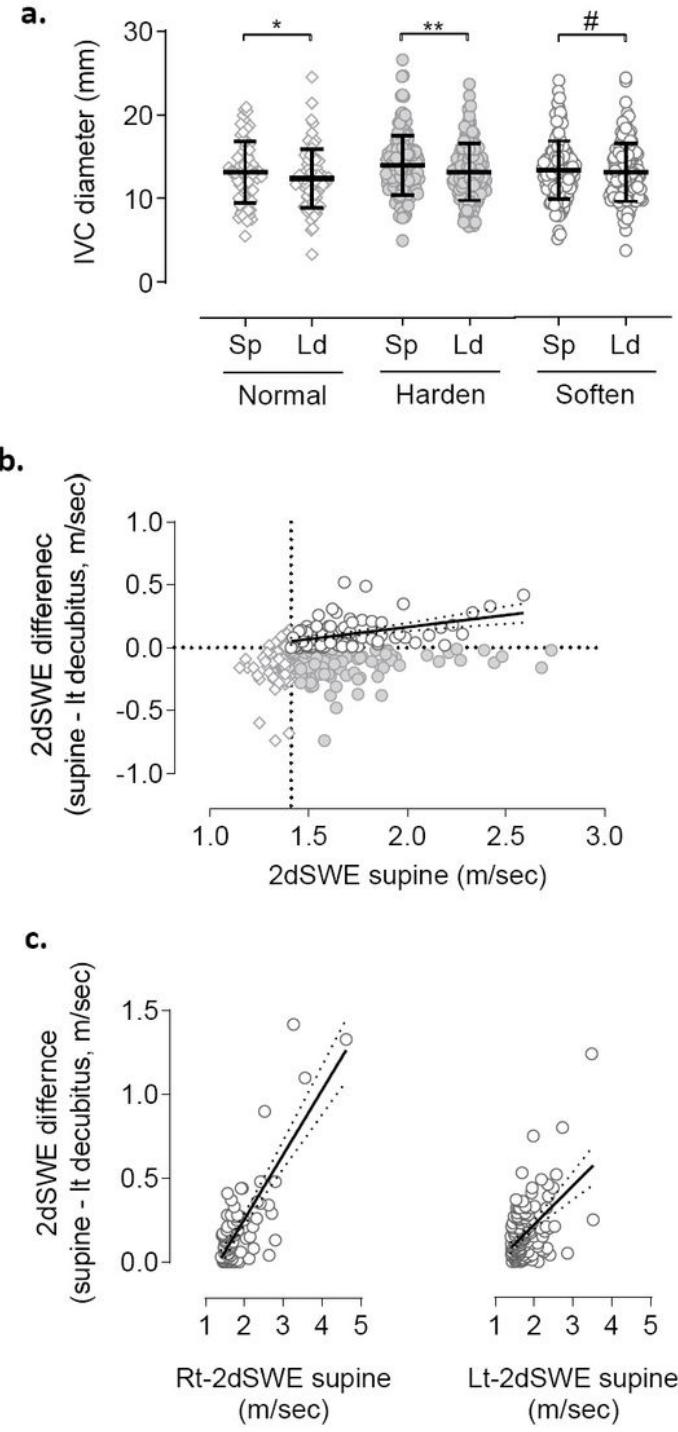


Figure 2

Alteration of inferior vena cava (IVC) diameter and liver stiffness after changing body positions a) IVC diameter was significantly reduced in patients with normal two-dimensional shear wave elastography values (2dSWE) in the supine position (Normal, *, p=0.013) or patients with abnormal 2dSWE in the supine position, which further hardened in the left decubitus position (Harden, **, p=0.0070). However, the diameter was not reduced in patients with abnormal 2dSWE in the supine position, which softened in the left decubitus position (Soften, #, p=0.32). The horizontal bars in each plot indicate average (bold) and standard deviation. Sp and Ld indicate supine and left decubitus positions, respectively. b) 2dSWE in the supine position revealed a significant positive correlation with the difference of 2dSWE between two body positions only in the Soften group (black open circle) ($p<0.0001$, $r=0.38$) but not in the Normal (grey open circle) and Harden (grey closed circle) groups. c) In the Soften group, 2dSWE in the supine position was plotted against the difference in 2dSWE between the supine and left decubitus positions in right or left lobe. A Spearman's correlation coefficient of 0.48 in the right lobe was increased compared with 0.31 in the left lobe. The black continuous and dotted lines reveal the best fit and 95% confidence band in the equation of least squares between 2dSWE in the supine position and the difference in 2dSWE for two body positions in b) and c).

Figure 3

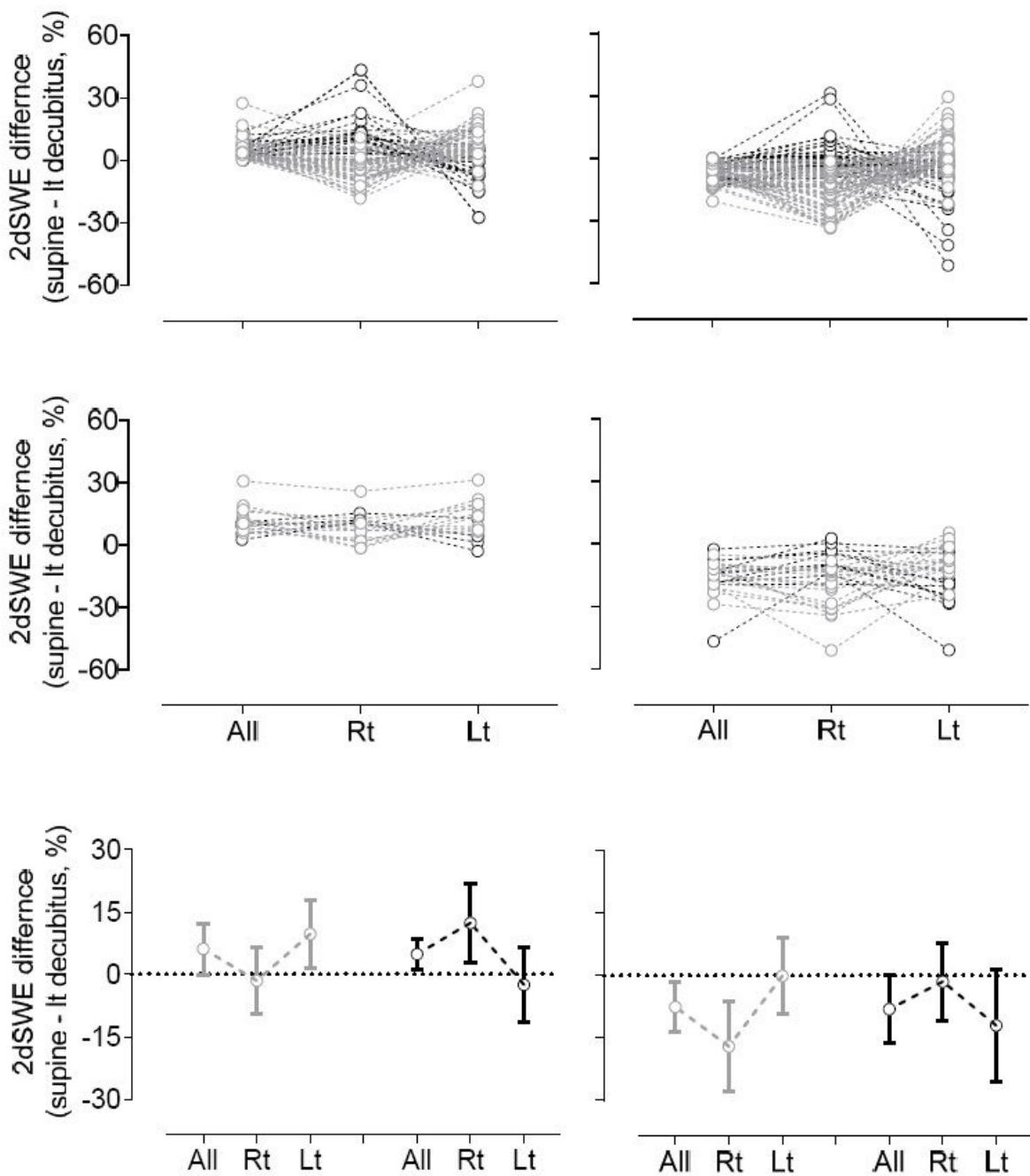


Figure 3

Reciprocal variation of liver stiffness difference between lobes In both cases with positive (left column) or negative (right column) differences of two-dimensional shear wave elastography values (2dSWE) between two body positions in the entire liver (All), the difference varies less or more in the right lobe (Rt) compared with the entire liver (grey or black, respectively) and reciprocally more and less in the left lobe (Lt). The upper and middle panels represent cases where the difference in 2dSWE for the entire liver is

within or beyond the magnitude of robust coefficient of variation, respectively. In the bottom panel, the results in the upper and middle panels are combined. The circle and horizontal bars in each plot indicate average and standard deviation, respectively.

Figure 4

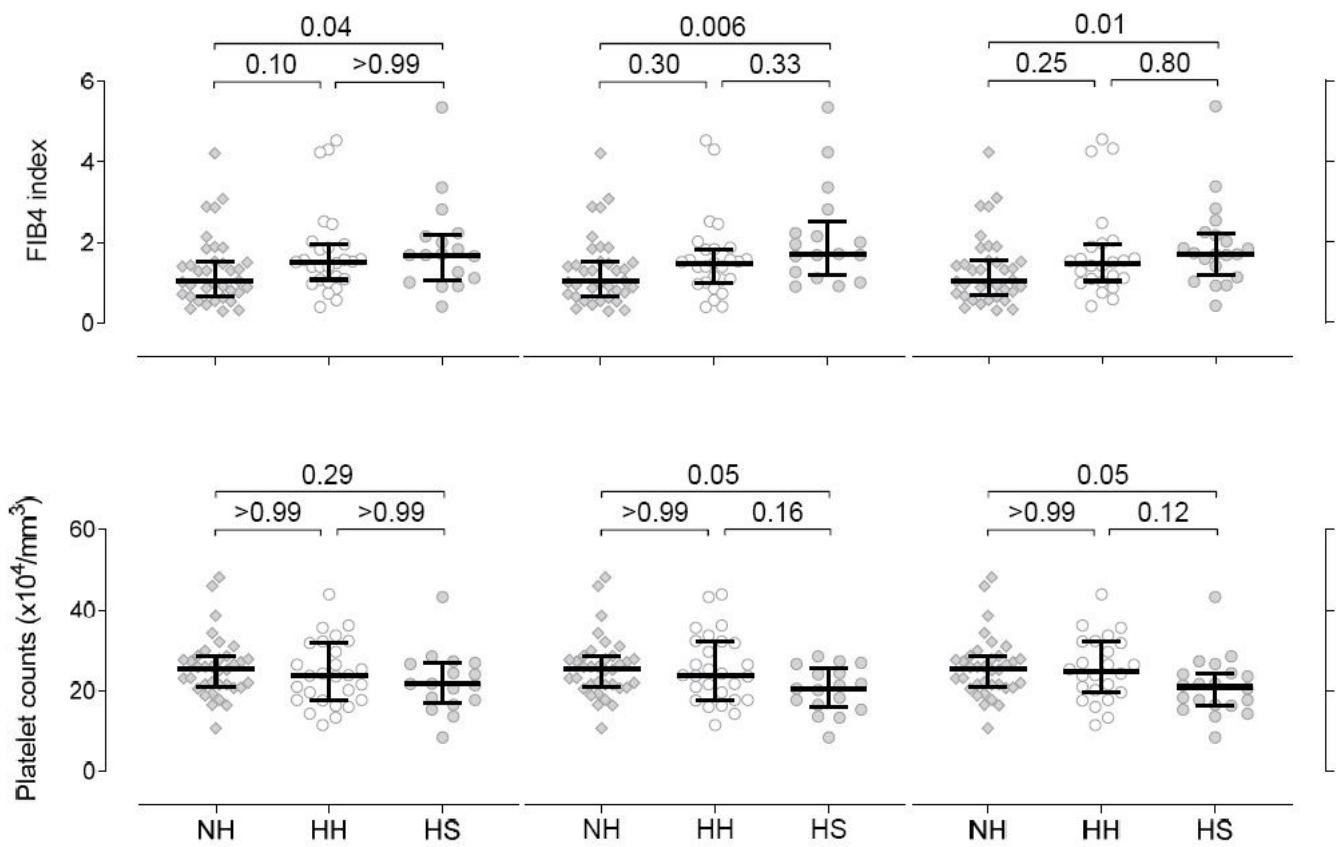


Figure 4

Fibrous progression of the liver was suggested in the Soften group Fibrosis-4 (FIB4, top panel) and its constituent of platelet counts (bottom panel) were compared among 3 groups in which two-dimensional shear wave elastography values (2dSWE) increased or decreased in association with changing body positions beyond the magnitude of robust coefficient of variation and was normal in the supine position (NH) or abnormal and increased (HH) or decreased (HS) in the left decubitus position. The group was classified based on the difference in 2dSWE in the entire liver (left column) or each lobe of right (middle column) or left (right column). A significant difference in FIB4 and platelet counts was observed between NH and HS. The probabilities were higher when the group was determined in each lobe. The horizontal bars in each plot indicate an average (bold) and standard deviation.

Figure 5

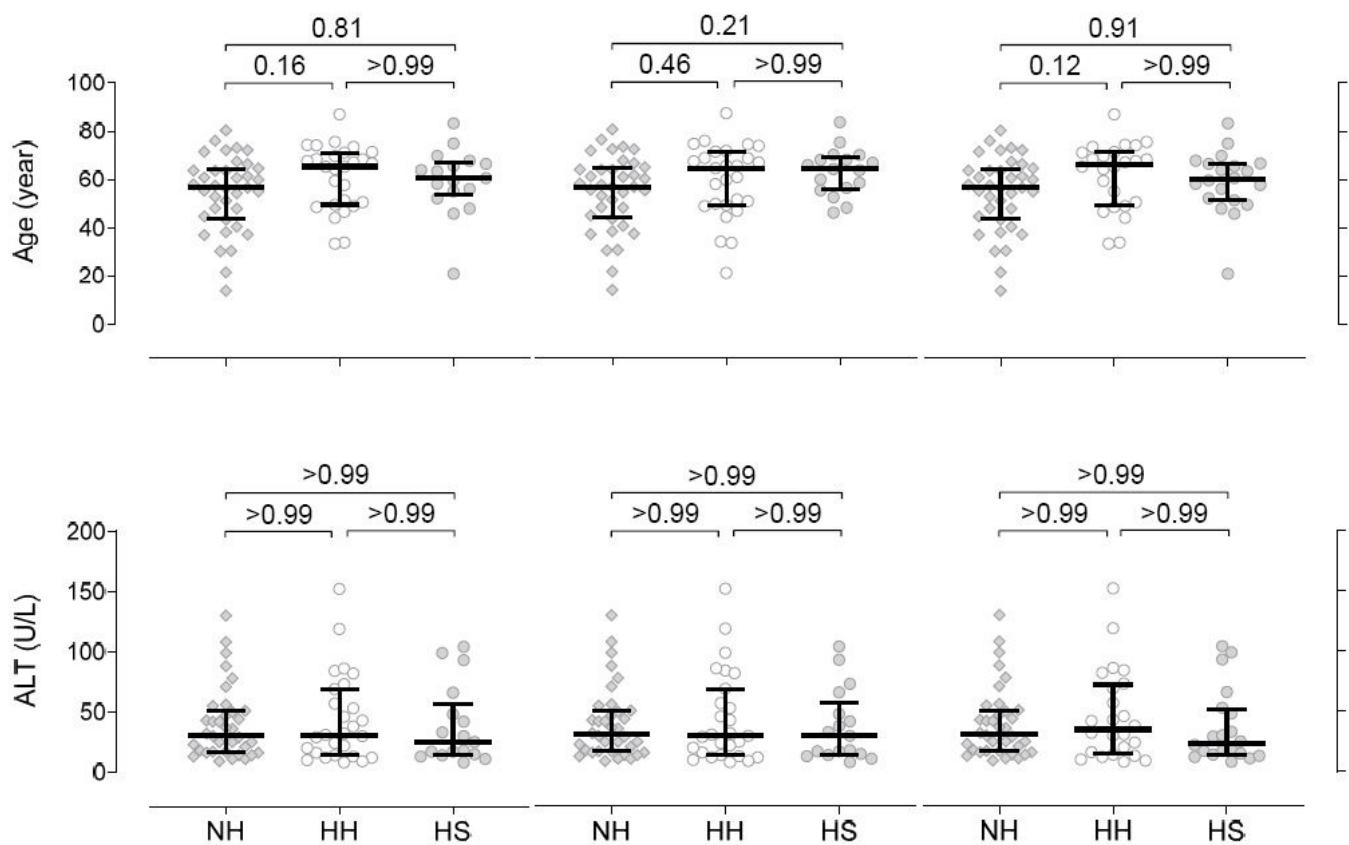


Figure 5

Higher value of fibrosis-4 in Soften is not due to aging or liver cell damage Fibrosis-4 constituents, including age (top panel) and alanine aminotransferase (ALT, bottom panel), were compared among 3 groups in which two-dimensional shear wave elastography values (2dSWE) increased or decreased in association with changing body positions beyond the magnitude of robust coefficient of variation and was normal in the supine position (NH) or abnormal and increased (HH) or decreased (HS) in the left decubitus position. The group was classified based on the difference in 2dSWE for the entire liver (left column) or each lobe of right (middle column) or left (right column). No significant differences in age or ALT were noted between groups. The horizontal bars in each plot indicate an average (bold) and standard deviation.

Supplementary Files

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- [SupFigSciRepSuda02082021.pdf](#)