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Practical Steps of Shear Wave Elastography for Nonalcoholic Fatty Liver Disease in an Adult Population

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a growing epidemic worldwide and is widely prevalent in India with a community-based study in South India reporting a prevalence of 49.8%. Imaging modalities are used to screen for NAFLD, identify different stages of the disease from early to advanced stages, and to monitor the progress of the condition and responsiveness to therapy. Computed tomography and magnetic resonance imaging modalities are used to assess NAFLD but have limitations in availability and affordability. B-mode ultrasound provides a viable imaging alternative but only provides a gross assessment and the presence or absence of fibrosis. Shear wave elastography is a newer modality that allows for the measurement of tissue stiffness or elasticity in response to tissue deforming forces generated as shear waves. The changes in elasticity can usually be determined before obvious structural changes and can be used for early diagnosis of disease and to assess the progress of the condition. In this article, we present the practical steps to perform an ultrasound shear wave elastography for the assessment and staging of NAFLD.

Keywords
- elastography
- nonalcoholic fatty liver disease
- quality
- shear wave
- ultrasound

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Introduction

Nonalcoholic fatty liver disease (NAFLD), a leading cause of chronic liver disease worldwide, is a liver disease where fat is deposited in $\geq$ 5% of hepatocytes in the absence of significant alcohol use or secondary causes of hepatosteatosis.[1,2] The spectrum of NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis, advanced fibrosis, cirrhosis, and ultimately hepatocellular carcinoma and liver failure.[1,2] The global prevalence of NAFLD is about 15 to 20% among general population.[1,3,4] In a meta-analysis of 86 studies from 22 countries, the prevalence of NAFLD was 25.24% in the general population with the highest prevalence rates in the Middle East and South America.[4] Studies from Asian countries like China, India, Japan, Korea, and Taiwan have found a high community prevalence ranging from 15 to 49.8%.[3–7] The prevalence of NAFLD was 49.8% in a population-based cohort study done in Trivandrum, a southern district of Kerala, India.[8]

Histopathological examination of specimens obtained by liver biopsy is the diagnostic gold standard for chronic liver diseases. However, liver biopsy is an invasive procedure that can lead to substantial pain and discomfort to the patient and other side effects related to the procedure and offers a study of only a small section of the liver. The need to overcome limitations of liver biopsy led to the deployment of several noninvasive assessments for chronic liver disease. These include several imaging modalities like ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI).[9] CT performs adequately in assessing significant fibrosis and cirrhosis and MRI studies exhibits great accuracy at all stages of chronic liver diseases but is costly.

Ultrasound for NAFLD

B-mode ultrasound is often used as the first-line imaging modality to screen for fatty liver as it is widely available, affordable, and accessible, can be used as a portable test with minimal radiation side effects, and is noninvasive.[10] The echotexture of the liver surface is assessed and compared to the renal cortex. The normal liver has an echotexture similar to or slightly higher than the renal cortex and intracellular fat accumulation in hepatocytes is seen as a raised echotexture of the liver surface. However, a limitation is that the intracellular fat deposits in the hepatocytes may reduce visibility of deeper structures like the portal and hepatic veins and diaphragm.[11] Additional limitations of routine ultrasound for NAFLD include intra- and-interoperator variability and hence dependence on the skill and experience of the sonographer, and difficulty to assess the liver in obese patients.[12–14]

Elastography

Elastography is a technique to assess tissue stiffness and can be performed using various imaging modalities including ultrasound and MR. Elastography allows measurement and display of biomechanical properties associated with the elastic restoring forces in the tissue that act against shear deformation which is generated by a force applied to a single location or broadly across the body surface. Ultrasound is the propagation of a transient density deformation that may be used to measure tissue displacements at precise phases of shear deformation. The measurement of tissue stiffness or elasticity is useful as these changes usually precede structural changes and hence can be used for early diagnosis of disease and to assess progress of the condition.[15,16]

Shear Wave Elastography

Shear wave elastography (SWE) generates shear waves using a dynamic stress. The shear waves are generated in the parallel or the perpendicular directions and the measurements of the shear wave speed provide qualitative and quantitative estimates of tissue elasticity. The speed of the generated shear waves inside the tissue is measured using Young's modulus E in either m/s or kilopascal (kPa) units. The generated shear waves are measured over a grid of points and a real-time image is created from a map of the shear wave arrival time at different focal positions. The image is displayed as a semitranslucent color overlay on the gray-scale image and interpreted.[15,17]

The shear wave techniques have less operator dependence, better depth penetration, and are less susceptible to decay. However, the technique has less spatial resolution compared to strain imaging and can be impacted by tissue heterogeneity, tissue attenuation, and external precompression.

Practical Steps for a SWE Assessment of NAFLD

The practical steps and protocol for a SWE assessment in NAFLD is presented briefly. These recommendations may vary slightly based on vendor-specific recommendations related to the instrumentation used for the assessment.

1. The patient should be fasting for at least 4 hours prior to the SWE study. This is an important step as the liver stiffness values increase after a meal in patients with chronic liver disease and can lead to erroneous staging of NAFLD.[18,19]
2. Use a linear high-resolution probe to assess the liver surface for irregularities and presence or absence of micronodules. A micronodule is considered as a nodule $<$ 2 mm in size (see ►**Fig. 1** for nodularity).
3. Patient position for SWE: Following the recommendations of World Federation for Ultrasound in Medicine and Biology and European Federation of Societies for Ultrasound in Medicine and Biology guidelines, use the intercostal approach with the patient in the left lateral position, at 30 degrees and with the right arm raised above the head to increase the width of the intercostal space to survey the liver in B-mode. The patient may be assessed in the supine position if they cannot maintain the left lateral position or are unable to hold breathing in the left lateral position.

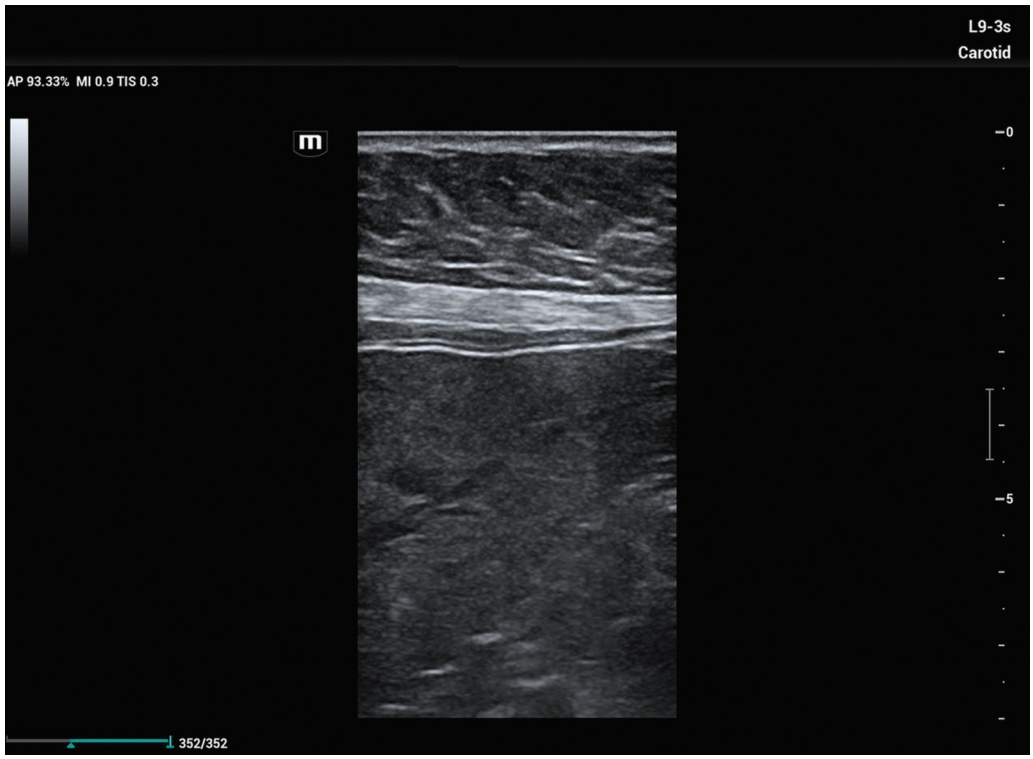

Fig. 1 Nodularity of the liver surface using B-mode ultrasound and a linear high-frequency probe.

4. Optimize the B-mode image: A SWE study of good quality depends on the quality of the B-mode image. An important prerequisite for a reliable liver stiffness measurement is the quality of the ultrasound image, which should show the liver capsule as a white line without rib's or lung's shadowing in the liver parenchyma.
5. Probe: Position the probe searching for the best acoustic window with the transducer held at 90 degrees perpendicular to the liver capsule.
6. To avoid reverberation artifacts always position the upper edge of the sampling box (region of interest [ROI]) at least 1 to 2 cm below the liver capsule and avoid including any large vessels, and small vessels as well whenever it is possible.
7. Even if the size of the ROI could be very large, it is recommended to choose a size that reduces the possibility of including artifacts, which may degrade the quality of the sampling. An ROI of 2 to 3 cm in size is a good compromise to qualitatively assess the stiffness of the targeted liver parenchyma area possibly without artifacts.
8. Place the ROI box in the middle center of the B-mode image in a homogeneous area of the liver parenchyma, avoiding ligaments, vessels, or bile ducts.
9. Holding the probe steady in place, ask the patient to hold the breath for a few seconds at mid expiration while placing the targeted segment at the center of the image.
10. Observe both B-mode and SWE display, coded with colors, side by side when the patient stops breathing or at neutral breath. Establish the presence of a good acoustic window. The elastography mode is activated by the examiner after the elastogram is stable for five consecutive frames.
11. Wait for the system to generate consecutive frames and capture sequential images in a cine loop.
12. Best possible frame of SWE image is indicated by the reliability indices of each vendor-specific machine. These may include the five green stars motion stability (M-STB) index and reliability (RLB) map with full green color as good shear wave quality, color-coded confidence maps, signal-to-noise ratio, and stability index. The measurement must never be performed on elastogram of poor quality or poor reliability.
13. Use the measurement key to place the "circle" 15-mm diameter size within the ROI box in a homogenous color area. For better accuracy, it is recommended to perform only one measurement for each acquisition either in m/s (speed of the shear waves) or kPa (stiffness value derived from the speed of the shear wave by using the Young module). The size of the "circle" can be reduced to 10 mm in case of artifacts within the ROI.
14. It is important to note that the colors captured in the ROI are related to the E scale, which goes from dark blue to dark red. As a rule, for routine assessment it is better to always use the same scale. With the default scale, that is, up to 30 kPa, it is easier to differentiate the quality of the elastogram and the shades of colors for the different ranges of liver stiffness.
15. We recommend obtaining a minimum of five acquisitions of images of high quality and to use the median value of them as representative of the stiffness. The accuracy is not lost with five acquisitions of high quality with an

Table 1 Categories of liver stiffness values for NAFLD using Shear Wave Elastography

Category	Liver stiffness values	Clinical interpretation
1	< 5 kPa (1.3 m/s)	High probability of being normal
2	< 9 kPa (1.7 m/s)	In absence of other known clinical signs, rule out cACLD. May need further tests for confirmation if there are known clinical signs
3	9–13 kPa (1.7–2.3 m/s)	Suggestive of cACLD and needs further evaluation
4	> 13 kPa (2.1 m/s)	Rules in cACLD
5	> 17kPa (2.4 m/s)	Suggestive of CSPH

Abbreviations: cACLD, compensated advanced chronic liver disease; CPSH, clinically significant portal hypertension.

interquartile range-to-median ratio (IQR/M) ≤ 30% when the median value is given in kPa and ≤ 15% when the median value is given in m/s.[2].,[20,21] If quality assessments are not possible, it is generally recommended to obtain 10 acquisitions.[2]

16. It is recommended to use the IQR/M as a quality factor to assess the variability between consecutive liver stiffness measures. The IQR/M should be ≤ 30% when the median value is given in kPa and ≤ 15% when the median value is given in m/s.[20,21]
17. The liver can be staged or grouped into five categories for clinical interpretation and radiological follow-up.[2] ►**Table 1** presents the narrative description and ►**Figs. 2–11** present the images of the different stages of NAFLD identified with SWE. This categorization is a vendor-neutral rule that can be applied to measures obtained by any SWE machine based on the acoustic radiation force impulse (ARFI) techniques for NAFLD.[2]
18. Activate the report box on the touch screen to autotransfer the measurement data to the table report page.
19. Assess the liver attenuation based on the vendor-specific recommendations (check if your machine allows you to measure this). Generally, lower values indicate a healthy liver and higher values indicate an unhealthy liver. The

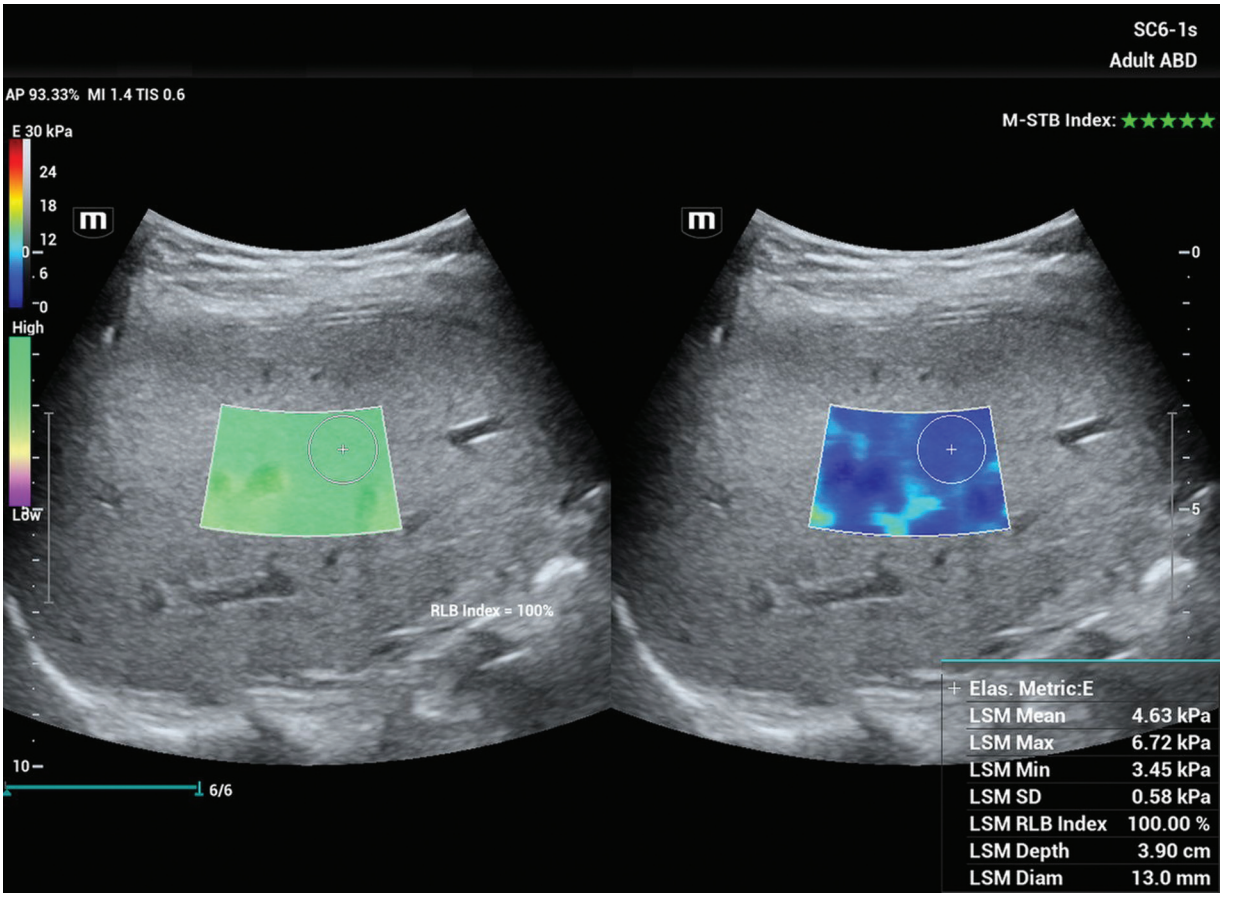

Fig. 2 Shear wave elastography assessment of the liver stiffness using the Resona i9 machine (Mindray, Shenzhen, China). The mean liver stiffness is 4.63 kPa and suggests a high probability of being normal. The image also shows the quality indicators—motion stability (M-STB) index and reliability (RLB) index. The five green stars of the M-STB and the RLB index of 100% are suggestive of a high-quality acquisition.

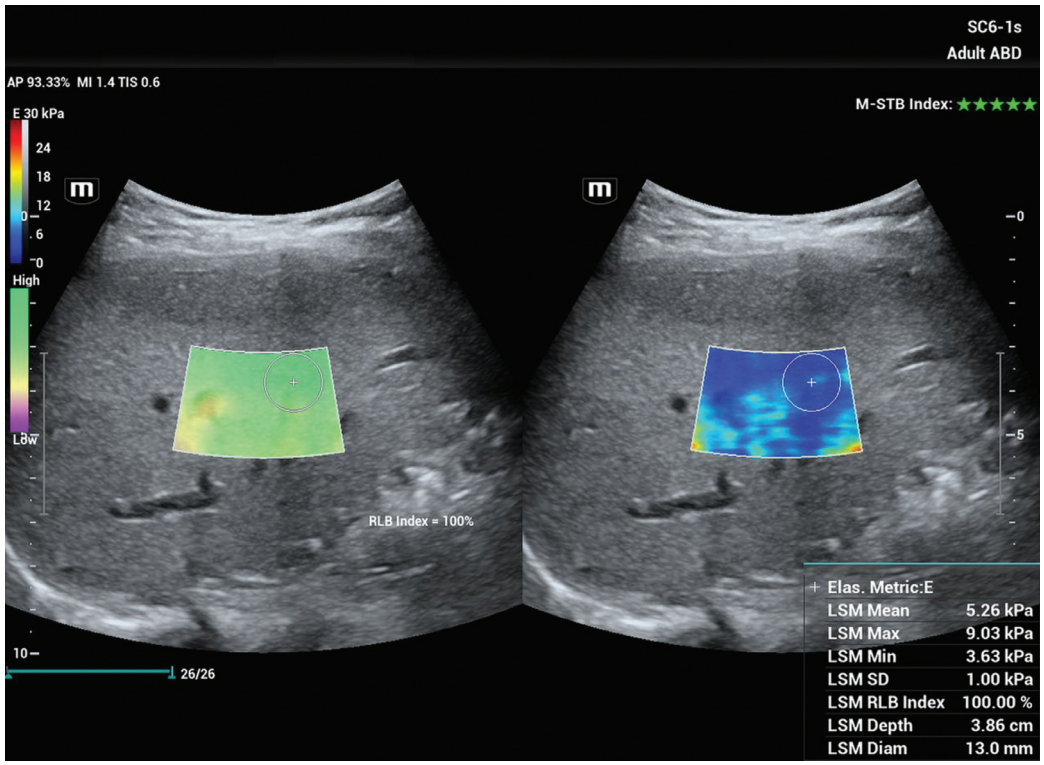

Fig. 3 Shear wave elastography assessment of the liver stiffness using the Resona i9 machine (Mindray, Shenzhen, China). The mean liver stiffness is 5.26 kPa and rules out compensated advanced chronic liver disease (cACLD) in the absence of clinical signs. Further confirmatory tests are needed if known clinical signs are present. The image also shows the quality indicators—motion stability (M-STB) index and reliability (RLB) index. The five green stars of the M-STB and the RLB index of 100% are suggestive of a high-quality acquisition.

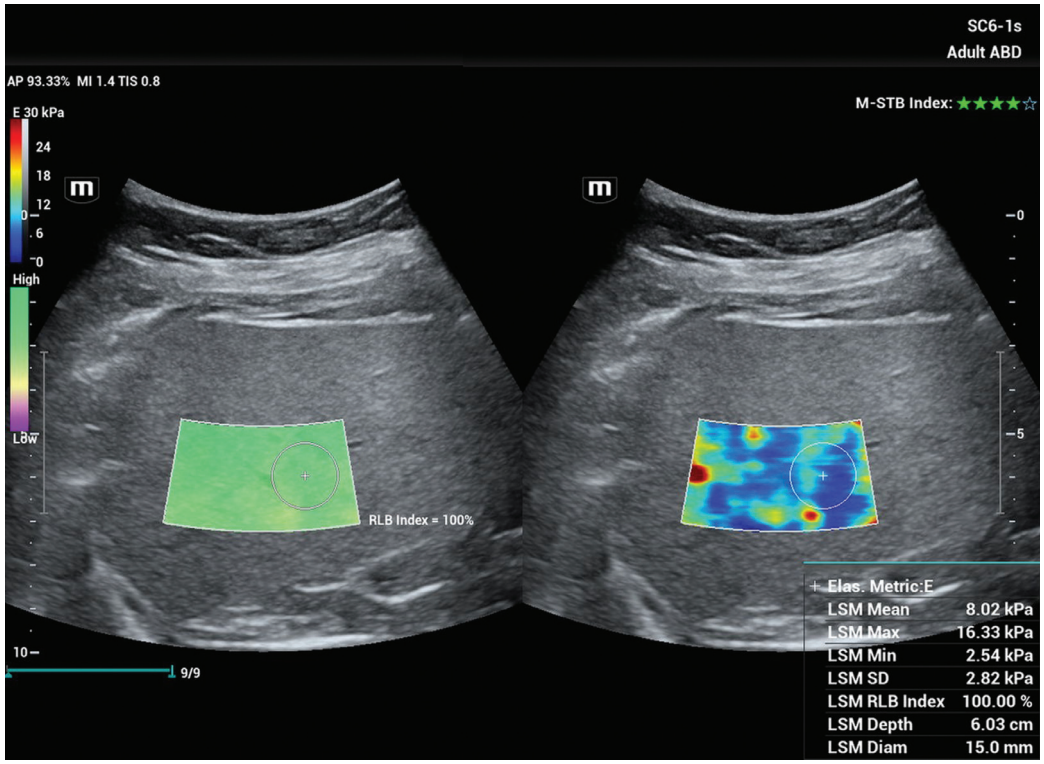

Fig. 4 Shear wave elastography assessment of the liver stiffness using the Resona i9 machine (Mindray, Shenzhen, China). The mean liver stiffness is 8.02 kPa and rules out compensated advanced chronic liver disease (cACLD) in the absence of clinical signs. Further confirmatory tests are needed if known clinical signs are present. The image also shows the quality indicators—motion stability (M-STB) index and reliability (RLB) index. The five green stars of the M-STB and the RLB index of 100% are suggestive of a high-quality acquisition.

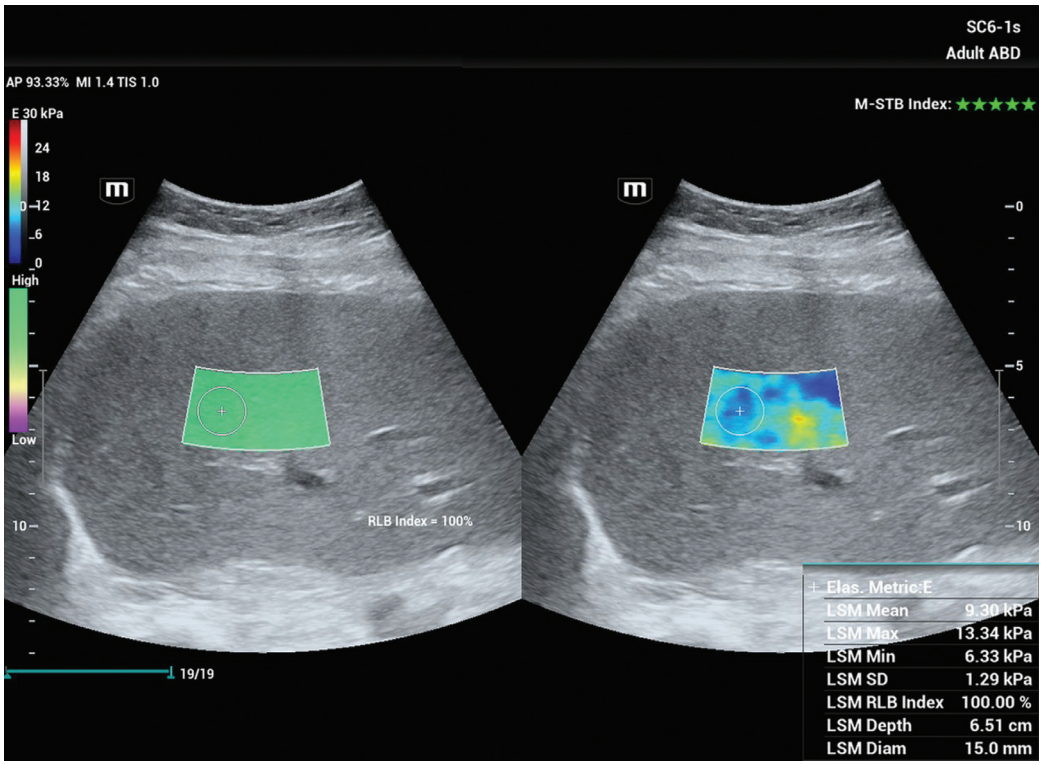

Fig. 5 Shear wave elastography assessment of the liver stiffness using the Resona i9 machine (Mindray, Shenzhen, China). The mean liver stiffness is 9.30 kPa and is suggestive of compensated advanced chronic liver disease (cACLD) and needs further investigation. The image also shows the quality indicators—motion stability (M-STB) index and reliability (RLB) index. The five green stars of the M-STB and the RLB index of 100% are suggestive of a high-quality acquisition.

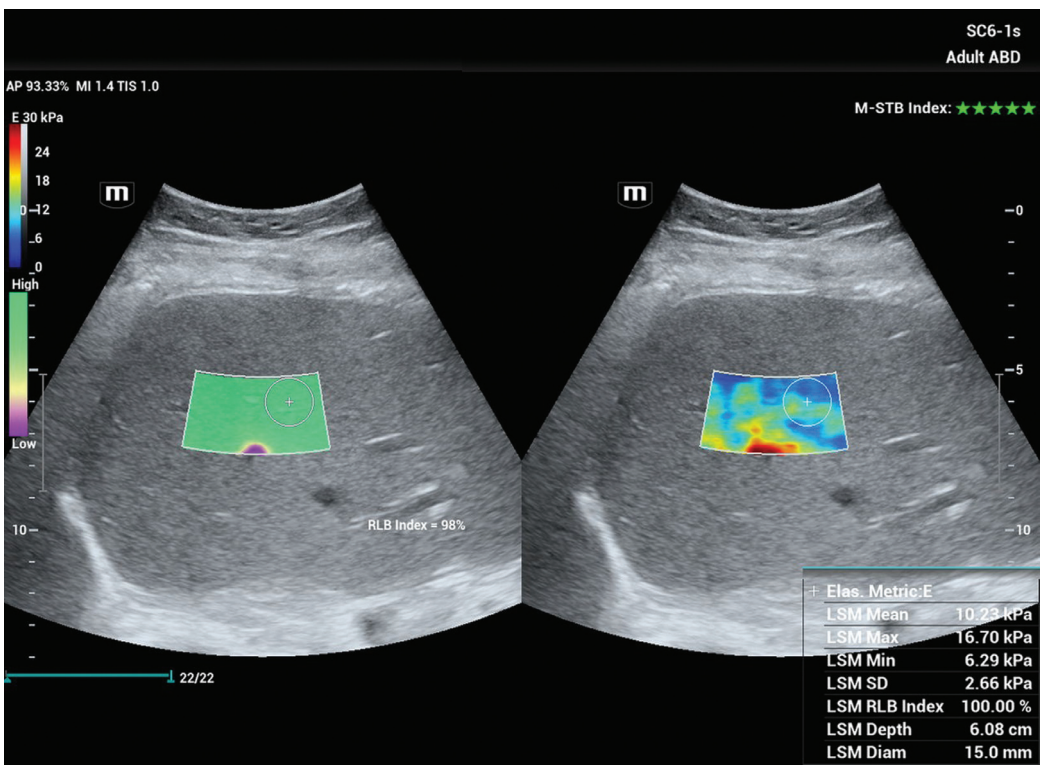

Fig. 6 Shear wave elastography assessment of the liver stiffness using the Resona i9 machine (Mindray, Shenzhen, China). The mean liver stiffness is 10.23 kPa and is suggestive of compensated advanced chronic liver disease (cACLD) and needs further investigation. The image also shows the quality indicators—motion stability (M-STB) index and reliability (RLB) index. The five green stars of the M-STB and the RLB index of 98% are suggestive of a high-quality acquisition.

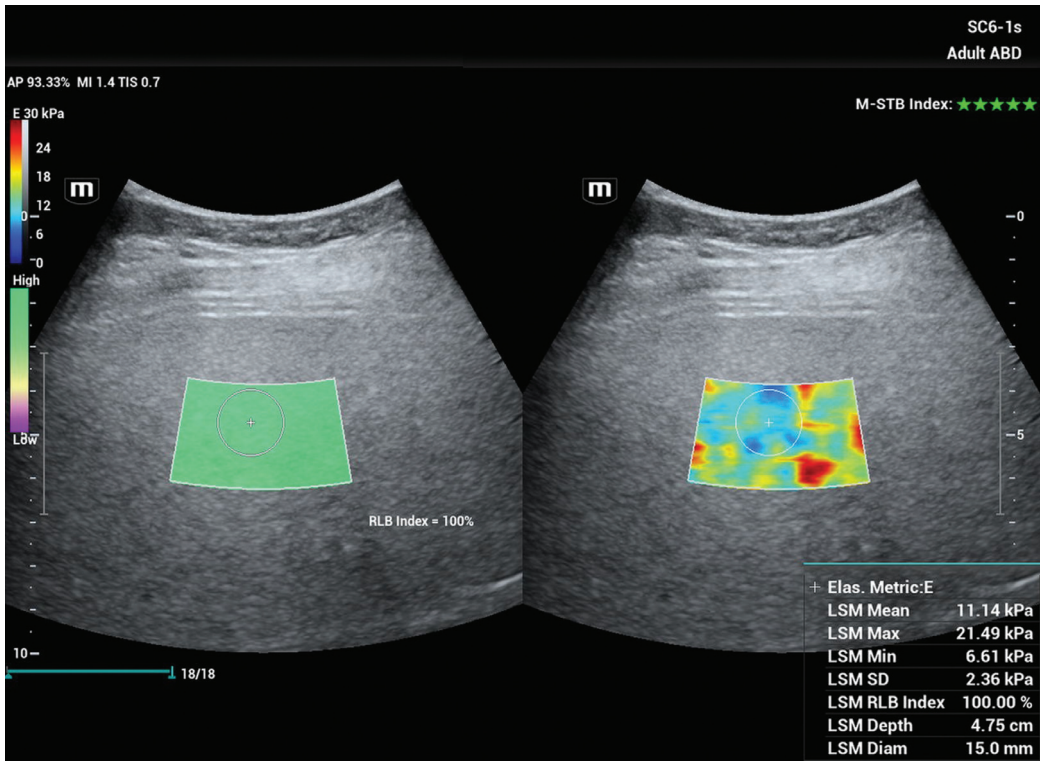

Fig. 7 Shear wave elastography assessment of the liver stiffness using the Resona i9 machine (Mindray, Shenzhen, China). The mean liver stiffness is 11.14 kPa and is suggestive of compensated advanced chronic liver disease (cACLD) and needs further investigation. The image also shows the quality indicators—motion stability (M-STB) index and reliability (RLB) index. The five green stars of the M-STB and the RLB index of 100% are suggestive of a high-quality acquisition.

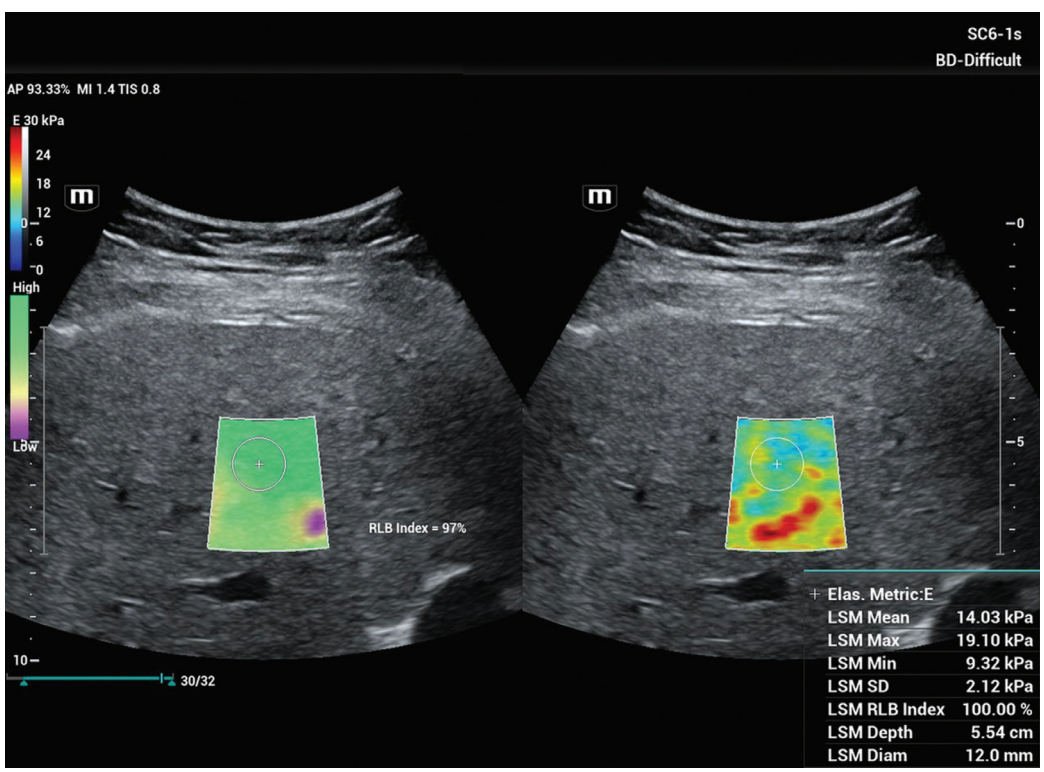

Fig. 8 Shear wave elastography assessment of the liver stiffness using the Resona i9 machine (Mindray, Shenzhen, China). The mean liver stiffness is 14.03 kPa and rules in compensated advanced chronic liver disease (cACLD). The image also shows the quality indicators—motion stability (M-STB) index and reliability (RLB) index. The five green stars of the M-STB and the RLB index of 97% are suggestive of a high-quality acquisition.

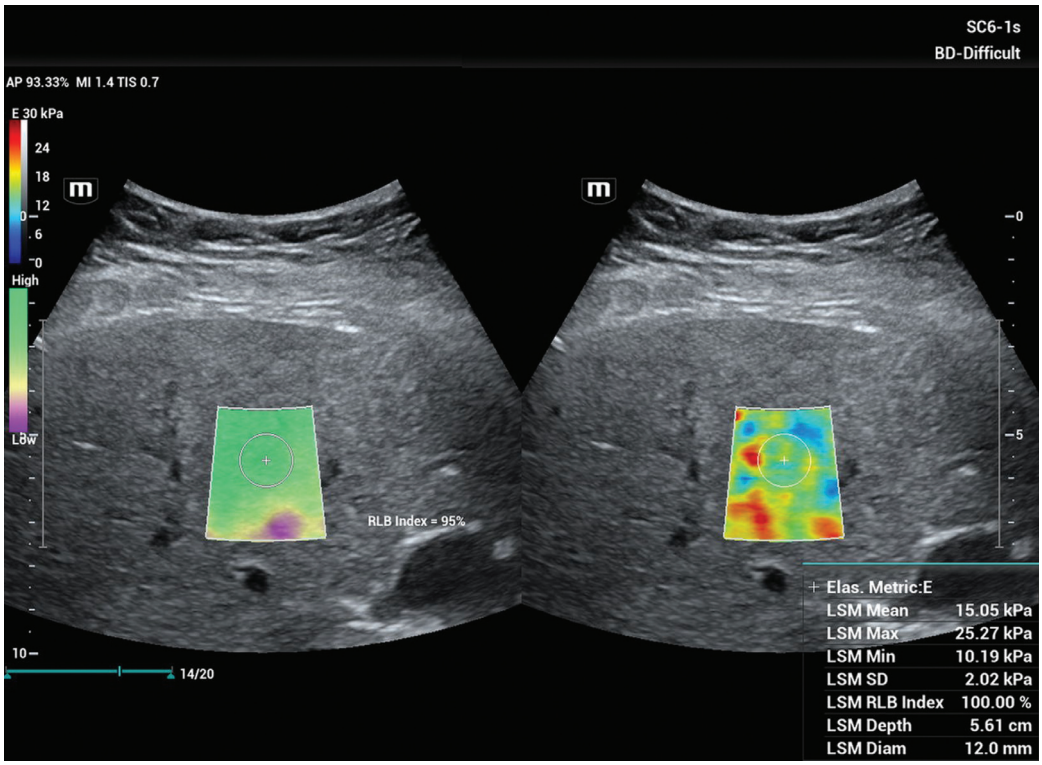

Fig. 9 Shear wave elastography assessment of the liver stiffness using the Resona i9 machine (Mindray, Shenzhen, China). The mean liver stiffness is 15.05 kPa and rules in compensated advanced chronic liver disease (cACLD).

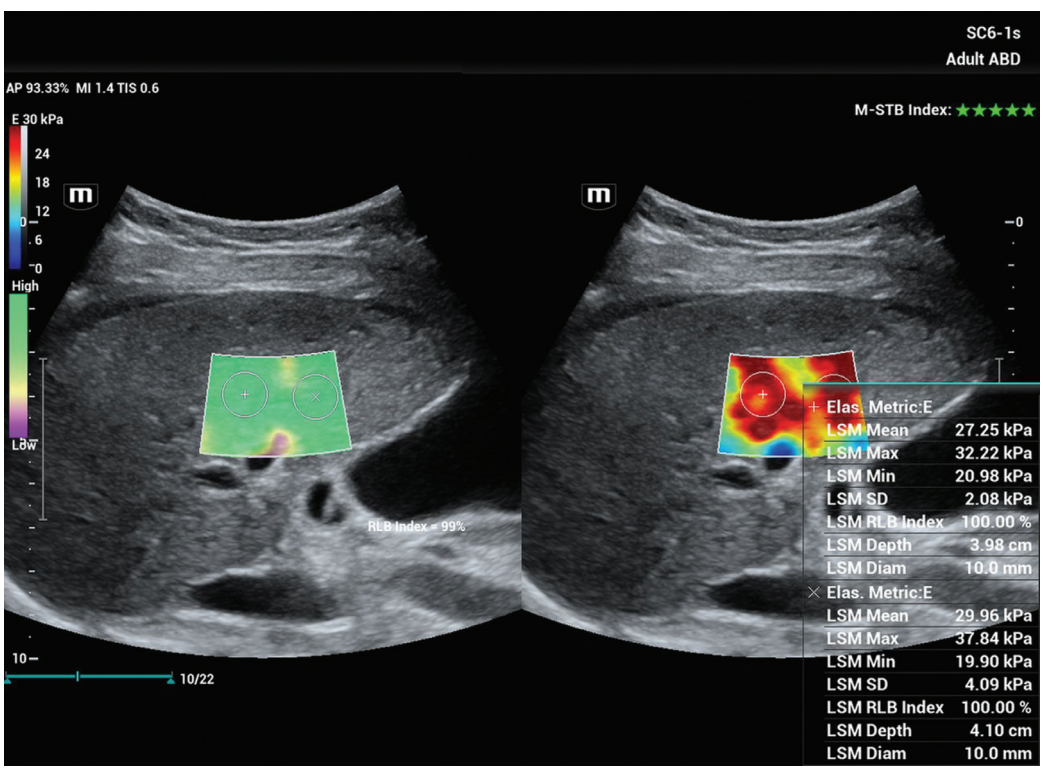

Fig. 10 Shear wave elastography assessment of the liver stiffness using the Resona i9 machine (Mindray, Shenzhen, China). The mean liver stiffness is > 17 kPa and is suggestive of clinically significant portal hypertension (CSPH). The image also shows the quality indicators—motion stability (M-STB) index and reliability (RLB) index. The five green stars of the M-STB and the RLB index of 100% are suggestive of a high-quality acquisition.

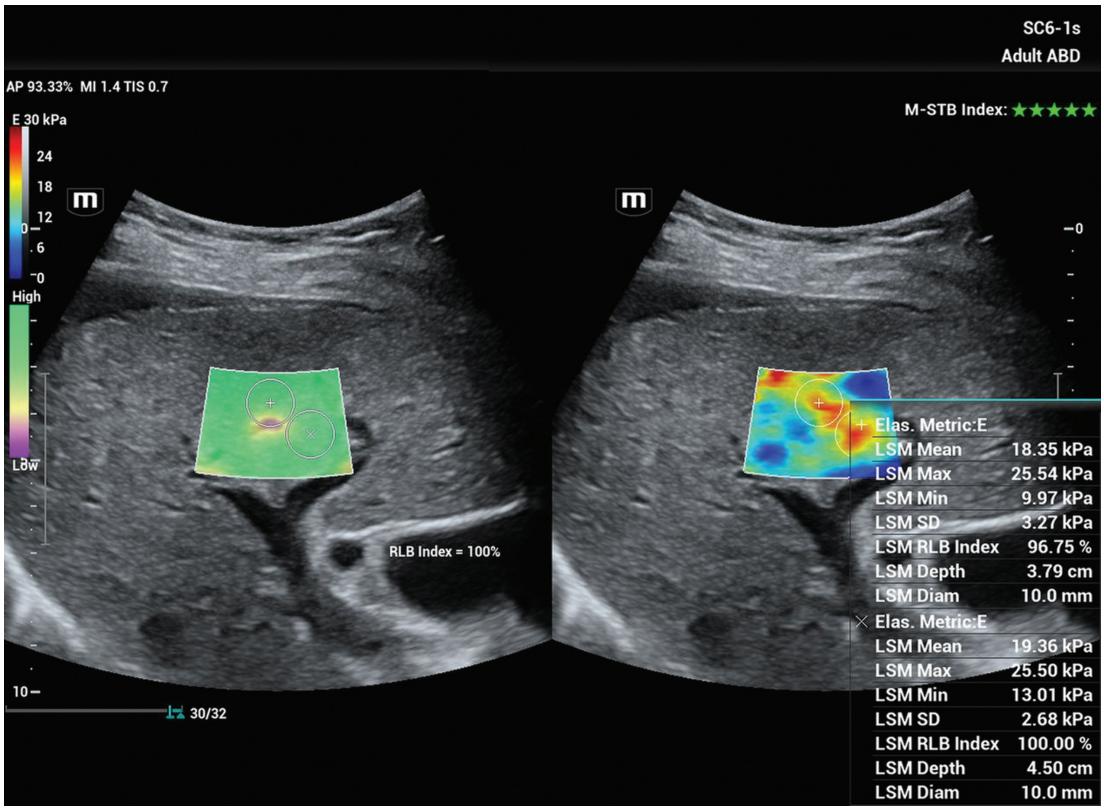

Fig. 11 Shear wave elastography assessment of the liver stiffness using the Resona i9 machine (Mindray, Shenzhen, China). The mean liver stiffness is > 17 kPa and is suggestive of clinically significant portal hypertension (CSPH). The image also shows the quality indicators—motion stability (M-STB) index and reliability (RLB) index. The five green stars of the M-STB and the RLB index of 99% are suggestive of a high-quality acquisition.

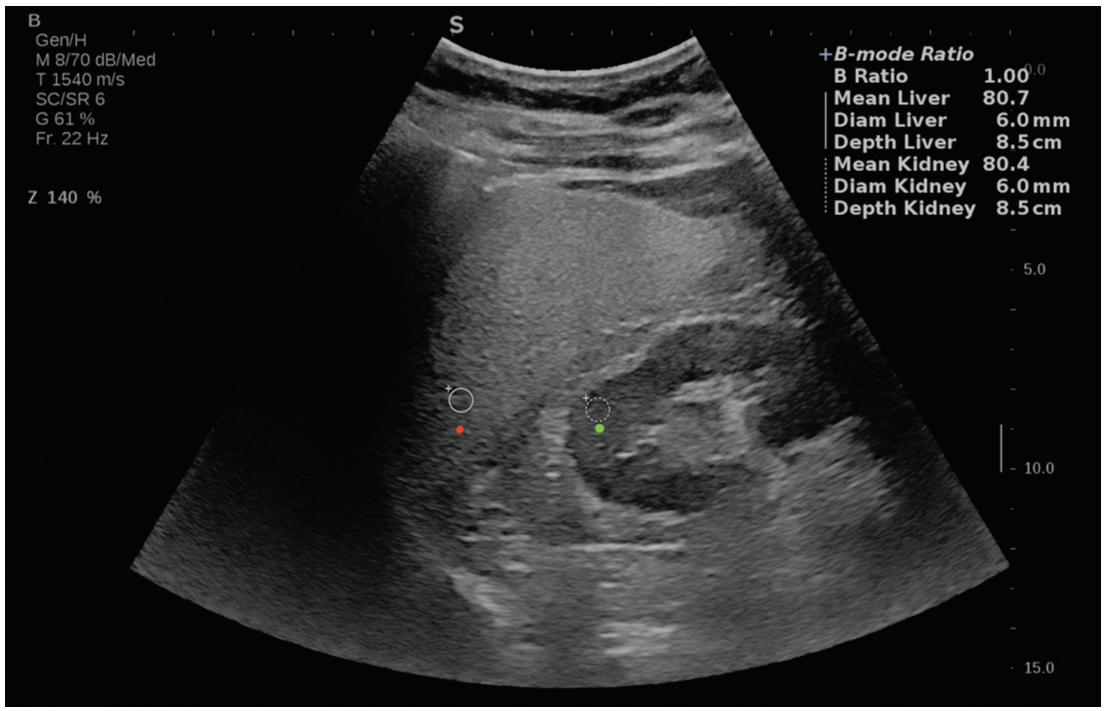

Fig. 12 Assessment of the hepatorenal index using a Supersonic (Aix-en-Provence, France) machine showing a normal hepatorenal index with similar echogenicity from the liver and renal cortex. The red dot indicates the liver acquisition area, and the green dot indicates the acquisition from the renal cortex. The acquisitions from the liver and the renal cortex are at the same depth.

liver attenuation assessment needs further validation and standardization in our population before clinical application on a larger scale.

20. Hepatorenal index (HRI): Take one measurement in the kidney toward the upper pole cortex to avoid the capsule reflection and the second measurement in the liver at the same depth (avoiding the blood vessels and picking a spot that might be suitable for SWE).[22–24] Ensure that there is no shadowing in both areas while doing the measurement. Take up to five measurements (see ►**Figs. 12–14** for images of normal, medium, and high HRI) and compare the echogenicity of the two acquisition areas. The HRI needs further validation and standardization in our population before clinical application on a larger scale.

Quality of the Measures

Appropriate staging of NAFLD using SWE is dependent on the quality of the images obtained. Measurements should be obtained from areas of the liver that are identified as high quality. The quality is determined by a high amplitude of the shear waves, a normal shear-wave propagation, and a linear slope of the time of the peak and distance from ARFI pulse of the displacement curves. Different vendors have machine-specific quality assessment parameters and indicators.

The newer Mindray SWE machines (Resona Series, Shenzen, China) utilize the RLB map and M-STB index to ensure quality of measurements. The M-STB helps to monitor the degree of motion interference and is available in recent machines of certain vendors. A low star number < 4 indicates the presence of high motion interference and a high star number > 4 indicates minimal or no motion interference. The low star and high star numbers are color-coded orange and green, respectively, for easy interpretation. An M-STB index that is green for several consecutive frames indicates a stable SWE. The RLB map is related to the STE shear wave quality and indicates the areas where a reliable measurement is possible with green color, areas that are associated with unreliable measurements are colored purple. STE measures are taken avoiding purple-coded areas and ensuring at least four green stars in the five-star stability index.

The SWE machines of Philips use a color-coded confidence map as a measure of the quality of the signals that are obtained, and the confidence thresholds are set at 60%. A red color indicates that the area is of low quality and a yellow color indicates that the area of acquisition of the signals is not of a high quality. The Supersonic machines (Aix-en-Provence, France) use the signal-to-noise ratio to filter out images of low quality. The stability index is used as an indication of temporal stability and a stability index $> 90\%$ is considered acceptable.

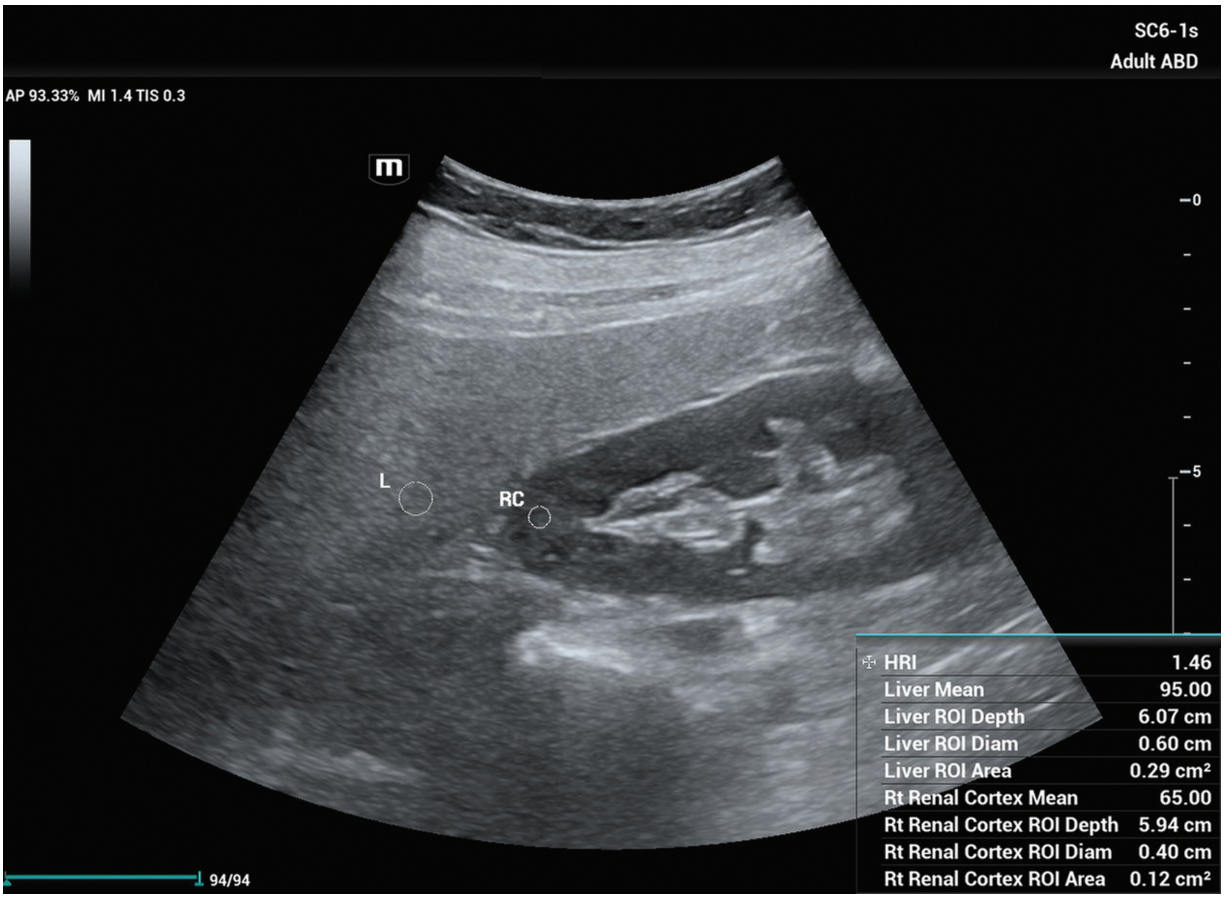

Fig. 13 Assessment of the hepatorenal index using the Resona i9 (Mindray, Shenzhen, China) machine showing a medium hepatorenal index of 1.46 with difference in the echogenicity between the liver and renal cortex. L indicates the liver acquisition area and RC dot indicates the acquisition from the renal cortex. The acquisitions from the liver and the renal cortex are at similar depth.

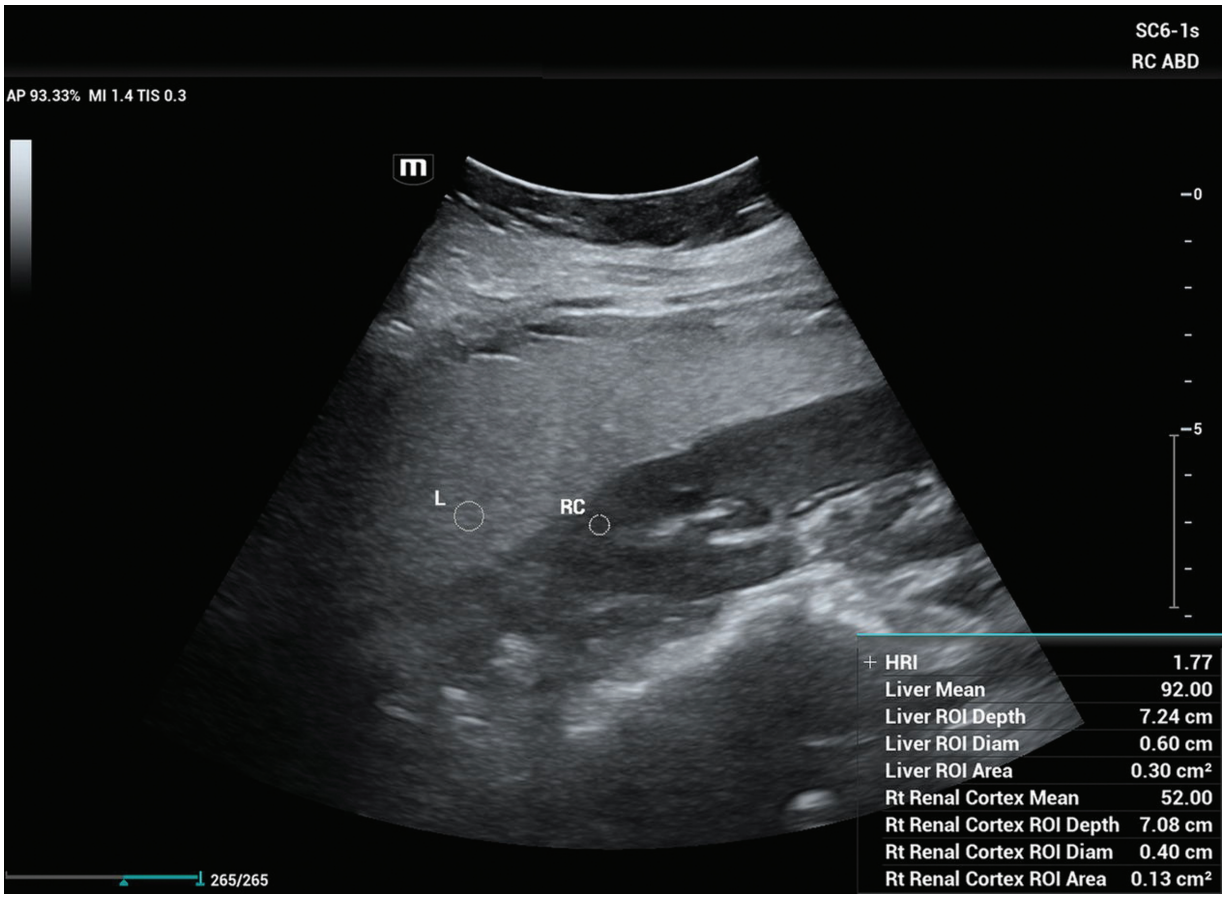

Fig. 14 Assessment of the hepatorenal index using the Resona i9 (Mindray, Shenzhen, China) machine showing a high hepatorenal index of 1.77 with difference in the echogenicity between the liver and renal cortex. L indicates the liver acquisition area and RC dot indicates the acquisition from the renal cortex. The acquisitions from the liver and the renal cortex are at similar depth.

Measures to Eliminate Values from Analysis

The most important criteria for the elimination of measures include the quality of image, image stability, and reliability indices. If these indices are fine, check if the IQR/M is $\leq$ 30% when the median value is given in kPa and $\leq$ 15% when the median value is given in m/s. The images can be retained if the image quality, stability, reliability, and IQR/M are within acceptable limits. For the remaining images, consider extreme values and eliminate them only if they are gross outliers or extreme values.

Confounders and Other Conditions that Impact the Assessment of NAFLD and Fibrosis

Acute inflammation of the liver, extrahepatic cholestasis, congestion of the liver, hepatic infiltrations, and extramedullary hematopoiesis may give imaging results that mimic fibrosis of the liver.[2,25] It is always important to correlate the imaging results with clinical features and other biochemical tests. SWE in a patient without adequate fasting will also produce erroneous results and staging of NAFLD. SWE imaging may also produce erroneous results if the test is performed soon after an intense physical workout or exercise.[2]

Artifacts can also impact the liver stiffness value and artifacts related to blood vessels, liver capsule, and transducer placement are common.[2] Care must be taken to ensure that the transducer is placed parallel to the liver capsule and that the area of acquisition avoids blood vessels. The presence of artifacts will be picked up by the quality indicators.

Staging of the Liver

The recommended cutoff values for the staging of the liver vary by the ultrasound machine used. This variance has implications on the clinical staging as the variance increases with increasing liver stiffness and is largest when the threshold of compensated advanced chronic liver disease (cACLD) is crossed.[26] Efforts to reduce the variance between machines include the use of phantoms that are developed by the Quantitative Image Biomarker Alliance.[27,28] The stiffness value at the mild to moderate spectrum of liver fibrosis show a large overlap although the variance at these categories between vendors is lower than the large liver stiffness value overlap of the METAVIR score.[2] The Society of Radiologists in Ultrasound (SRU) recommends cutoff values taking these differences and overlap into consideration. The SRU recommends a higher cutoff value above which the probability of cACLD is high and a lower cutoff value below which there is a

high probability of no fibrosis or mild fibrosis.[2] The consensus panel of SRU has further divided the liver stiffness values between no or minimal disease and cACLD into two categories (< 9 and 9–13 kPa) and recommend the use of additional tests to confirm and rule in or rule out cACLD.[2] This division is important as liver biopsy and staging by METAVIR scoring will not be feasible for this group. The SRU also proposes an additional cutoff value to rule out clinically significant portal hypertension (CSPH) based on evidence from several studies.[29–32]

A "rule of five" approach is used to stage liver stiffness using vibration-controlled transient elastography using 5, 10, 15, and 20 kPa as the cutoff criteria.[33,34] The consensus panel of SRU has proposed a vendor-neutral "rule of four" (5, 9, 13, 17 kPa) for the ARFI techniques for viral etiologies and NAFLD and an additional category for CSPH.[2] The "rule of four" includes the following: liver stiffness of 5 kPa (1.3 m/s) or less has high probability of being normal; liver stiffness less than 9 kPa (1.7 m/s), which in the absence of other known clinical signs rules out cACLD; liver stiffness values between 9 kPa (1.7 m/s) and 13 kPa (2.1 m/s) are suggestive of cACLD and may need further test for confirmation; and values greater than 13 kPa (2.1 m/s) are highly suggestive of cACLD and liver stiffness values greater than 17 kPa (2.4 m/s) suggest a higher probability of CSPH and may need additional patient. In some patients with NAFLD, the cutoff values for cACLD may be lower and follow-up or additional testing in those with values between 7 and 9 kPa is recommended if there are any clinical signs or symptoms suggestive of cACLD. The consensus panel also reported that most studies that used ARFI (point SWE and two-dimensional SWE) suggest that a liver stiffness value of less than 7 kPa (1.5 m/s) can help rule out significant fibrosis and can be used in clinical practice to rule out significant fibrosis.

Conclusion

SWE is a useful imaging modality to screen for NAFLD in India. SWE offers several advantages over routine B-mode ultrasound, CT, and MR assessments for NAFLD including its availability and affordability. However, several parameters must be validated further for the Indian population including the liver stiffness values, liver attenuation values, and the hepatorenal indices. Even with these limitations, SWE has promise as a first-line imaging filter for NAFLD and suspicious cases can be further explored with MR elastography studies.

Financial Disclosures
None of the authors have any financial interests to disclose with respect to this manuscript.

Conflict of Interest
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