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Targeting Liver Biopsies For Optimal Biopsy Site In Diffused Liver Disease Using Real-Time Shear Wave Elastography: A Prospective, Single Center Study

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Abstract

Objective: The study aimed to pinpoint the precise site for liver biopsy using ultrasound and elastography guidance and to assess and compare the diagnostic accuracy of shear wave elastography (SWE) and transient elastography (TE) through histopathological correlation.

Methods: In this prospective single-centre study, the researchers divided the participants into two groups. One group (Group A) had their biopsy guided by ultrasound, which is a standard imaging technique. The other group (Group B) had their biopsy guided by a newer technique called elastography. For the group with elastography-guided biopsy, the researchers used this technique to find the stiffest part of the liver before taking the biopsy sample.

Results: The study investigated how stiffness throughout the liver (mean liver stiffness) compared to stiffness measured in the biopsy samples (biopsy segment velocities). Even though the overall stiffness didn't differ much between different sections of the liver, the stiffness measured in the biopsy samples itself did vary. The traditional technique (TE) worked well for identifying moderate and severe stages of scarring (F2, F3, and F4). The new sound wave technique (SWE) was good at identifying moderate fibrosis (F2) but less accurate for mild stages (F1). However, it performed similarly to the traditional technique for moderate to severe stages (F2 and F3). The new technique (SWE) could distinguish between mild or no scarring and moderate/severe scarring with good accuracy (over 95%) if the stiffness measured by the sound waves was at least 1.92 meters per second (m/s).

Conclusions: The findings suggest that the new technique is just as accurate as the traditional one for diagnosing moderate and severe scarring stages. Importantly, the study also found that scarring may not be evenly distributed throughout the liver. This is why the new sound wave technique, done at the time of biopsy, may be helpful.

Keywords: Elastography, Cirrhosis, Hepatitis C, Liver biopsy, Ultrasound.

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1. Introduction

Many diffuse liver diseases can cause scarring (fibrosis) in the liver. This scarring can lead to serious problems like cirrhosis, high blood pressure in the liver's veins (portal hypertension), and even liver cancer.[1] These liver diseases are a major health concern worldwide, affecting people in both developed and developing countries. They can be caused by things like infections (hepatitis viruses), the immune system attacking the liver (autoimmune disorders), toxins, and problems with how the body processes substances (metabolic disorders).[2,3]

The earlier we catch this scarring, the better the chances of treating or even curing the underlying liver disease. Unfortunately, the current best test, a liver biopsy, only takes a small sample of the liver, and scarring can be patchy throughout the organ. This means the test results might not be entirely accurate. Plus, biopsies are uncomfortable and invasive! Doctors need a better way to check for scarring, something that's easier on the patient and gives a more complete picture of the liver's health.[4-6]

Right now, the best way to check for scarring in the liver (hepatic fibrosis) is with a liver biopsy. But this isn't ideal. It involves taking a small piece of tissue with a needle, which can be uncomfortable for the patient. Doctors are looking for better ways to do this.[7]

There are already some non-invasive tests, like real-time shear wave elastography (SWE) and transient elastography (FibroScan).[8] These use sound waves to measure how stiff the liver is, which can be a sign of scarring.

Ideally, the best test would be easy, painless, affordable, and accurate. Ultrasound elastography, especially with the newer SWE technology, seems very promising. This technology is already being used to check for problems in other parts of the body, and it seems like it could be a great option for the liver too!

Liver scarring (fibrosis) can cause high blood pressure in the liver's veins (portal hypertension) in people with chronic liver disease.[9] Two tests, SWE and TE, use sound waves to measure liver stiffness, which can be a sign of scarring. These tests are less invasive than a traditional liver biopsy, but they might not always give the whole picture because scarring can be patchy throughout the liver.

Previous research suggests SWE might be just as good or even better than TE at finding portal hypertension.[10,11] However, no one has figured out the best place to take a biopsy sample based on these sound wave tests. Since scarring can vary throughout the liver, this study used ultrasound and sound wave tests (SWE and TE) before a biopsy to see if they could pinpoint the best spot for an accurate sample.

2. Materials & Methods

This study got approval from the Islamabad Diagnostic Centre's ethics committee and was conducted at IDC from July 2023 to December 2023. It involved only adults who weren't already diagnosed with cirrhosis and weren't younger than 18. Everyone involved signed a consent form and was then put into one of two groups:

Group A: This group had a regular ultrasound-guided liver biopsy.

Group B: This group had a special ultrasound with sound wave technology (elastography) to find the stiffest part of their liver before the biopsy.

The flowchart shows how the biopsies were done.

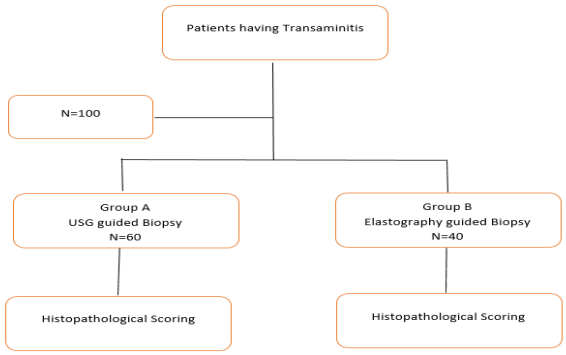

Figure 1: Flow Chart of the Study

The researchers compared the results of both biopsy techniques with two other measures of scarring:

FibroScan score: This is a non-invasive test that uses sound waves to measure liver stiffness.

METAVIR score: This is a scoring system based on looking at the liver tissue under a microscope.

Examination through TE

For the TE (transient elastography) part of the study, patients lay on their backs with their arms raised above their heads. The doctor used a special ultrasound setting on the FibroScan machine to find the best spot on the right side of the ribcage to see the liver. Then, they gently pressed a probe with gel on that spot to send sound waves through the liver. The machine measured how stiff the liver was in kilopascals (kPa) and took multiple measurements to get the most accurate result. To make sure the results were reliable, the researchers only used measurements where the variation wasn't too big. They also looked at other liver health measures along with the stiffness.

Examination through SWE

The SWE (shear wave elastography) test used a special machine to measure how stiff the liver was. This machine sent tiny waves through the liver and measured how fast they travelled. The faster the waves travelled, the stiffer the liver. The results were shown as a coloured map on a regular ultrasound image. Two radiologists performed the test in the radiology department.

Patients needed to fast for a few hours before the test and hold their breath for a short moment while the doctor scanned their liver with an ultrasound. The doctor carefully positioned the scan to avoid major blood vessels and get the best picture of the liver. They took multiple measurements from different parts of the right lobe of the liver.

The results were recorded in meters per second (m/s), but the researchers converted them to kilopascals (kPa) to match the results of the other test. They then compared these stiffness measurements to the METAVIR score, which is a system for grading liver scarring based on a biopsy sample.

Liver Biopsy

The researchers used ultrasound to guide a needle biopsy of the liver in the radiology department of IDC. After getting the patient's consent, they numbed the area around the liver capsule with a local anaesthetic. A thin needle was used to take a sample of tissue, measuring between 1.8 and 2 centimetres, from the right lobe of the liver. This site was chosen because breathing and heartbeat can make it harder to get an accurate sample from the left lobe. To see how severe the liver disease was, the doctors used a scoring system called METAVIR. This system looks at two main things: scarring (fibrosis) and inflammation.

Histologic Examination

To see how severe, the liver disease was, the researchers used a scoring system called METAVIR.
Scarring (Fibrosis): This is scored on a scale from 0 to 4.
0 means no scarring.
4 means cirrhosis, the most severe stage of scarring.
In between, there are scores for different levels of scarring severity.
Inflammation: This is scored by looking at two areas of the liver tissue and combining those scores. The total score can range from 0 to 3.
0 means no inflammation.
3 means severe inflammation.
The researchers also looked at how much fat was in the liver cells (steatosis) using a separate scoring system (S0 to S4). Statistical analysis was done to compare these scores between the different groups in the study.
The researchers used a computer program to analyze the data they collected. Here's what they looked at:

- SWE velocity: They compared the average speed of the shear waves in the different liver sites between the two groups (USG and elastography).
- Correlation between tests: They checked how well the SWE measurements matched the results of the other tests (TE and liver biopsy).
- Best liver site for SWE: The researchers compared the SWE measurements from different parts of the liver to see which spot gave the most consistent results.
- Accuracy of SWE: The researchers looked at how good SWE was at identifying different stages of scarring (fibrosis) by comparing it to the liver biopsy results.
- Best cut-off values for SWE and TE: The researchers determined the results (SWE velocity and TE score) that most accurately separated healthy livers from livers with different stages of scarring.

Different statistical tests for each of these analyses were done including Mann-Whitney, t-test, Spearman's correlation, etc. The researchers checked how well the new SWE test worked compared to other methods.

3. Results

The study involved 100 patients, with a mix of men and women (70 men and 30 women). Their ages ranged from 18 to 65, with an average age of around 38. The researchers split them into two groups based on how the doctors took their liver samples:

Group A (US): This group had 60 patients and the researchers used ultrasound only to guide the needle.
Group B (Elastography): This group had 40 patients and the researchers used both ultrasound and a special wave test (elastography) to guide the needle.
The ages between the two groups were more or less similar, averaging around 38 years old. Overall, the two groups seemed to have similar health backgrounds in terms of like, the cause of their liver problems (NASH, Hepatitis B, etc.), fat content in the liver, liver stiffness, scarring, inflammation, and standard liver function tests. The demographics of the study participants and other details are mentioned in Table 1.

Table 1: Demographics of the Study Population

Variables	Category	Group A (US) N=60	Group B (Elastography) N=40	P value
Mean age (years) 38	Male: 70 Female: 30	41.60 ± 8.10	41.98 ± 10.22	0.18
LFT	ALT	108.46 ± 132.68	74.10 ± 54.220	0.208
	AST	104.20 ± 112.24	60.21 ± 44.101	0.164
	Albumin	4.662 ± 0.446	4.532 ± 0.116	0.322
	Bilirubin	2.181 ± 2.462	1.124 ± 1.324	0.420
	GGT	72.22 ± 64.226	64.10 ± 82.220	0.116
	AKP	112.80 ± 76.662	88.24 ± 64.426	0.119

The average liver stiffness measurement using the FibroScan test (TE) was 8.4 kPa, with a range of values from 3.0 kPa to 40 kPa. The average CAP score was 258.8 kPa, with a range of values from 178 kPa to 390 kPa. (CAP and TE scores are technical measures not important to understand the overall message).
Similarly, the breakdown of the causes of liver disease in the study is shown in Figure 2.

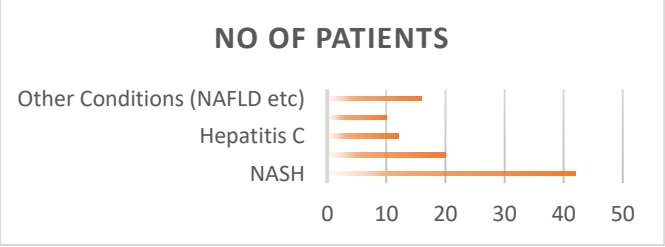

Figure 2: Causes of liver disease in the study groups

Out of the 100 patients who participated in the study, 44 had no detectable scarring (fibrosis) in their liver biopsies. The other participants had varying degrees of scarring, with some having mild scarring (18 patients), moderate scarring (16 patients), severe scarring (16

patients), and even cirrhosis (6 patients). The results are mentioned in the figure 3.

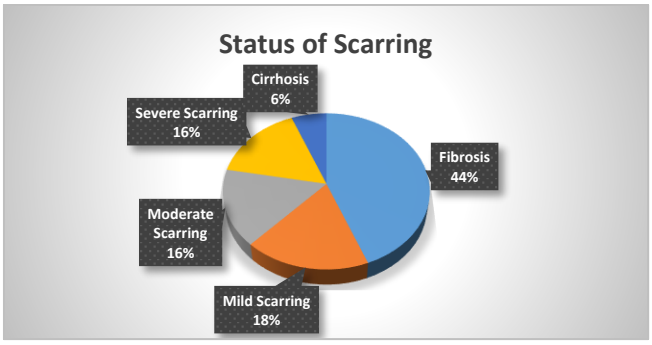

Figure 3: Status of Scarring in the study groups

The amount of fat in the liver cells (steatosis) also varied among participants. About 24% had no detectable fat. The researchers also looked at inflammation in the liver tissue.

Out of 100 patients, almost 56% showed no inflammation activity. The results are shown in Figure 4. The researchers mostly took liver samples from the lower part of the right lobe of the liver. Interestingly, even though stiffness varied slightly between different sections of the liver, the average stiffness measurement seemed to be a good overall indicator of the scarring severity found in the biopsy.

However, when the researchers looked at the speed of the shear waves (Vmean) in different sections compared to the biopsy results, they saw a more interesting pattern. This speed seemed to be more closely linked to the scarring level in the specific section where the sample was taken, especially in the lower sections. This suggests that scarring might be patchy throughout the liver, and the best measure might be the one closest to where the sample is taken.

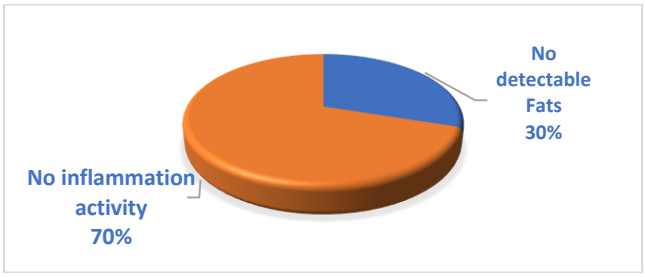

Figure 4: Steatosis Classification among the study groups

The study also looked at how stiffness varied within different sections of the right lobe of the liver, using a system called Couinaud's classification. Here's what the researchers found:

The stiffness measured by the sound wave test (Vmean and Vbiopsy) correlated well with all sections of the right lobe (front/back and top/bottom). However, the correlation was strongest with the lower sections (segments 5 and 6).

This suggests that the lower part of the right lobe might be the most consistent area for taking liver biopsy samples using the sound wave test.

The study found a link between how stiff the liver was and the severity of scarring (fibrosis). Patients with more severe scarring (higher fibrosis stages) had a higher average speed of the sound waves (mean velocity) travelling through their liver. Here's a breakdown of the results:

- Stage F4 fibrosis (severe): Average speed of sound waves - 2.62 meters per second (m/s)
- Stage F3 fibrosis (severe): Average speed of sound waves - 2.68 m/s
- Stage F2 fibrosis (moderate): Average speed of sound waves - 2.02 m/s
- Stage F1 fibrosis (mild): Average speed of sound waves - 1.92 m/s

Overall, the stiffer the liver (the higher the speed of sound waves), the more severe the scarring was likely to be.

4. Discussion

Knowing how much scarring there is in the liver (fibrosis) is very important for doctors treating chronic liver disease. Traditionally, doctors take a small piece of liver tissue (biopsy) to measure this scarring, but this can be uncomfortable for patients.[12] In our study, we investigated a new test that uses sound waves to measure liver stiffness (elastography). We wanted to see if this test could be used to:

Find the best place to take a biopsy sample

Measure scarring more accurately

The results were promising! The stiffness measured by the sound wave test (elastography) lined up well with how severe the scarring was according to the traditional biopsy samples (correlation: 0.86). Also, the sound wave test was very good at detecting both moderate and severe scarring stages. This suggests that sound wave elastography could be a valuable tool for doctors treating chronic liver disease.[13] It might be a more comfortable way to assess scarring in the liver and help doctors target biopsy samples more effectively.

We focused on the right lobe of the liver for two reasons:

1. Easier access: The right lobe is easier to reach with biopsy needles compared to the left lobe.
2. Similar stiffness: Previous research (by Friedrich-Rust et al.) showed that stiffness measurements weren't significantly different between the two lobes.

Interestingly, the stiffness within the right lobe itself wasn't uniform. The sound wave test (elastography) showed variations in stiffness across different sections. This suggests that scarring may not be evenly distributed throughout the liver.

The researchers are exploring why stiffness might vary within the liver.[14-16] They suspect it might be linked to how much oxygen reaches different areas.

The study suggests that the lower part (inferior segments) of the right lobe might be the best place to take liver biopsy samples. Here's why:

The speed of the sound waves (Vbiopsy) in the biopsy samples themselves showed the strongest link (correlation) to the overall scarring severity in the liver. This correlation was even stronger than the average stiffness measurement of the entire right lobe. This aligns with other research (Ling et al.) showing that the lower segment (segment 5) has the least variation in stiffness measurements.

It's important to note that some previous studies (Samir et al.) suggested the upper right lobe might be better. However, this study did not find a significant difference between the lower segments (segments 5 and 6) and the segments closer to the top (segments 7 and 8).

Overall, the lower part of the right lobe seems like a promising area for liver biopsy based on the results of this study. This could help doctors target biopsy samples more effectively and potentially improve the accuracy of the test.

Shear Wave Elastography

The study showed that the sound wave test (SWE) was very accurate at detecting different stages of liver scarring (fibrosis). Here's how they measured accuracy:

AUROC: This is a statistical measure of how good a test is at distinguishing between healthy and diseased patients. In this study, the AUROC was over 90% for all stages of fibrosis, which is very good. There was also an improvement in accuracy as the scarring got worse.[13]

Sensitivity and Specificity: These terms describe how good a test is at correctly identifying people with and without a condition. The SWE test was very good at identifying people with moderate, severe, and cirrhotic stages of fibrosis (sensitivity over 89%). It was also good at identifying people without these conditions (specificity over 72%).[17-20]

Liver Stiffness: The stiffness measured by SWE increased as the scarring got worse. This suggests that SWE can be used to predict how advanced the scarring is. This aligns with other research that showed a link between stiffness and scarring severity. Overall, this study suggests that SWE is a promising tool for diagnosing liver fibrosis. It seems to be accurate, especially for detecting moderate and severe stages of scarring.[21,22]

SWE versus TE

The study compared the new sound wave test (SWE) to existing methods for diagnosing liver disease. The study found that SWE measurements were very consistent, regardless of who performed the test (intra-observer agreement). This is similar to existing tests (TE). Other studies (Leung et al., Zheng et al.)[23,26] reported that SWE is very good at identifying different stages of scarring (fibrosis) and cirrhosis, similar to the results of this study. SWE seems to be as good as the existing TE test for measuring liver stiffness, according to research by Tada et al.[24] and Deffieux et al.[25] Both tests showed similar accuracy in diagnosing different fibrosis stages.

The study also confirmed previous findings that liver fat content (steatosis) and inflammation don't seem to affect the SWE results. Overall, this section suggests that SWE is a promising new tool that is as accurate as existing tests and may be more convenient to perform.

The study identified a few areas for improvement with the SWE test:

Standardization: There isn't a universal standard for SWE measurements across different ultrasound machines from different manufacturers. This can lead to slightly different results depending on the machine used.

Sample size: The study involved a relatively small group of people. Larger studies would be helpful to confirm the findings.

Patient diversity: The study included people with various causes of liver disease. Future studies focusing on specific causes might provide more specific information.

Comparison with other methods: The study only focused on SWE. Future studies could compare SWE to other non-invasive tests like MR elastography or blood tests for liver fibrosis.

The slight difference in accuracy compared to some previous studies might be due to these factors. Overall, this section acknowledges that the SWE test is promising

but highlights areas for further research to refine and validate its use in diagnosing liver disease.

5. Conclusion

The study identified a few areas where the SWE test could be improved: There's no single standard for SWE measurements across different ultrasound machines. This means results may vary slightly depending on the specific machine used. The study involved a relatively small group of people. Larger studies would be helpful to confirm the findings with more certainty. The study included people with different causes of liver disease. Future studies focusing on specific causes might provide more specific information about how SWE performs in different situations.

The study only focused on SWE. Future studies could compare SWE to other non-invasive tests like MR elastography or blood tests for liver fibrosis, giving doctors a wider range of options. These factors might explain the slight difference in accuracy observed when compared to some previous studies.

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All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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