JOURNAL OF
EMERGING INVESTIGATORS

Article

A 1D model of ultrasound waves for diagnosing hepatomegaly and cirrhosis

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SUMMARY

The liver is an integral part of the body and liver diseases are a prevalent issue worldwide. Ultrasound is one of the methods used to diagnose them initially. It transmits high-energy waves from one surface to the other and reflections between the surfaces are recorded. In this study, we present the application of ultrasound waves for the diagnosis of hepatomegaly and cirrhosis, under the assumption that the size of these tissues varies majorly in one dimension (thickness) and there are minor or negligible changes in other two dimensions (length and breadth). The model uses the ratio of intensities of the ultrasound waves inside and across the liver and simple one-dimensional (1D) diagram to mathematically analyze a normal, enlarged liver and cirrhotic liver. Since our method was not tested on an actual liver, a 1D model provided better clarity and simplicity for making the mathematical model. We aim to provide a non-invasive way of diagnosing hepatomegaly in adults. We hypothesized that under diseased conditions, the changes in the liver's tissue structure will increase the loss of ultrasound. It will therefore show an inversely proportional graph between the intensity of the ultrasound and thickness of the liver for both hepatomegaly and cirrhosis. Results showed a change in the ratio of reflected intensities in cirrhosis and hepatomegaly vis-à-vis a normal liver. This is promising as non-invasive methods like mathematical models can be used to diagnose liver conditions. However, the current results were not statistically significant and therefore require further testing.

INTRODUCTION

Every year, the world faces two million deaths because of liver problems (1). The liver is an important organ since it controls various processes in the body including deamination, bile and cholesterol production, and storage of glycogen (2). Two common liver complications are cirrhosis and hepatomegaly. Hepatomegaly describes an enlarged liver and is a marker for various underlying conditions including liver diseases, congestive heart failure, and cancer (3). A liver diagnosed with hepatomegaly is swollen beyond its usual size. Such swelling can be caused by cysts, tumors, problems with blood flow, and various other causes (4). The liver presents as enlarged inferiorly and laterally towards the left iliac fossa (LIF), a lower region in the abdomen, close to the small intestine (5). Cirrhosis is an end-stage liver disease that is currently untreatable and has been linked to alcohol liver disease, hepatitis, non-alcoholic fatty liver disease and chronic hepatitis B and C in adults (6, 7). In patients with cirrhosis, scar tissue replaces the normal liver parenchyma, leading to blockage of portal blood flow (8). This is the last stage of many chronic liver diseases and problems; therefore, the liver ceases function as the cirrhosis worsens. In cirrhosis, the vestigial umbilical vein recanalizes because of portal hypertension (9). Since cirrhosis is usually the last stage for diseases like fatty liver or hepatitis, its development starts with fibrosis, followed by nodular regeneration and distortion of liver architecture, and it is therefore expected that the tissue's changed properties will also impact the disease's detection in the ultrasound (9).

Liver ultrasounds provide images to show changes in liver conditions. It is a preferable method in check-ups since ultrasounds can diagnose liver problems without biopsy and are inexpensive, quick, and non-invasive (9). Ultrasounds are sound waves with a frequency greater than 20 KHz. Since the waves are longitudinal, they need a medium to propagate themselves. This provides ultrasound with the ability to penetrate the human body and reflect off the surfaces and is utilized in diagnostic sonography. Ultrasound can be used to scan and image various parts of the body (9). An abdominal ultrasound can provide visuals of organs such as the liver and stomach. The results of abdominal ultrasounds are impacted by the variation in the liver's acoustic impedance, reflectivity, and absorption coefficient. Acoustic impedance is defined as the resistance to the propagation of ultrasound waves through tissues and is found by multiplying the density of the tissue by the speed of sound through it (10). The speed of sound varies based on the medium the sound waves pass through but remains constant when moving through the same medium (medium having the same properties throughout). When the ultrasound beam reaches a tissue_1-tissue_2 boundary, only a fraction of the ultrasound transmits, the rest reflects. The absorption coefficient determines the fraction of ultrasound that passes through the liver and depends on the material of the tissue (11). The amount of ultrasound absorbed increases with the distance it travels (11).

The aim of this study was to understand the application of ultrasound for diagnosis of liver cirrhosis and hepatomegaly, through a mathematical model, using know. n quantities like the liver dimensions, attenuation coefficient, and the acoustic impedance. The data used within our mathematical model is from previously published studies. This data has been used as a sample and approximation to be able to input values in the model which can predict the trend rather than the specific values. A previous study from Ito *et al*. generated acoustic impedance measurements from mouse livers that were used within our mathematical model (12). Another previous study

https://doi.org/10.59720/23-147

by Fujii *et al.* measured the attenuation coefficient in the liver using two different types of ultrasounds and was used within our mathematical model (14).

We hypothesized that in a cirrhotic liver, the tissue is scarred and damaged and due to this the attenuation coefficient and the acoustic impedance increase. This increases the loss of ultrasound waves traveling through the liver and hence we expect the reflected intensity ratio of ultrasound from the back and front surface of the liver to decrease. Similarly, in the case of hepatomegaly, the liver is enlarged, which changes the density of the liver medium for ultrasound waves. Thus, upon increasing the acoustic impedance, we expect a non-linear decrease in the ratio of intensity reflected from front and back of liver medium. The study found an exponential decrease in the intensity of reflected ultrasound waves in both cirrhosis and hepatomegaly. The decrease was more in hepatomegaly. However, the results, when tested for significance with two-tailed t-test, were not significant, hence further testing is required.

RESULTS

The independent variable of the study is the thickness of the liver, the dependent variable is the transmitted ultrasound intensity ratio I_6/I_1. The controlled variables include uniform thickness of fat around the liver, ultrasound only across the midclavicular line, uniformity of thickness and density of tissue, and normal angle of incidence of ultrasound.

We gathered the data from secondary sources and used it for mathematical modelling. We found a linear relationship between the intensity of ultrasound ratios from the front and back of liver (log(I6/I1)) and liner thickness (t) (**Table 1**, **Figure 1**). The slope of this graph is value of -2μ which gives the value of attenuation coefficient (μ). The thickness of the liver varied from 0 cm to 15 cm, and we analyzed the variation of intensity ratio with normal liver, cirrhotic liver, and enlarged liver. The variation of intensity ratio and the thickness of liver is shown for both cirrhotic liver and hepatomegaly liver (**Figure 1**).

Figure 1 shows the difference in the ratio of reflected intensity from the ventral and dorsal of the liver for cirrhotic and normal liver. The linearized graph shows three straight lines. The gradient of the cirrhotic liver's line (y = -37.6x - 150) is steeper than the normal liver's line (y = -33.7x - 135), and the y-intercept differs by 15.47 decibels (dB) (**Figure 1**). The graph of cirrhotic liver is consistently lower than the normal liver, showing that a smaller ratio of waves is reflected in the ultrasound recording device (**Figure 1**).

It also shows the logI6/I1 comparison for hepatomegaly and normal liver (**Figure 1**). Here the gradient of the hepatomegaly liver (y = -38.7x – 155) steeper, and the y-intercept differs by 20.42 dB. The graph for the hepatomegaly liver is consistently below the normal liver line showing that a smaller ratio of waves is reflected to the ultrasound recording device.

We conducted a two tailed t-test to compare our hypothesis for normal, enlarged and cirrhotic liver. The t-value and p-value for the relationship between intensity ratio and liver thickness for normal and enlarged is found to be t=0.047 and p=0.963 at a significance level α=0.05. At the same time, a two tailed test to compare our hypothesis of relation between the intensity ratio and thickness of normal and cirrhotic liver gives the t=0.028 and p=0.977. Larger p values than the significance level shows negligible difference between the sample and population mean, suggesting that the sample provides weak evidence about the hypothesis.

Comparing the graphs for the cirrhotic liver and hepatomegaly liver, the gradient for the cirrhotic liver is -37.573 cm^{-1} while the gradient for the hepatomegaly liver is -38.709 cm^{-1} (**Figure 1**). Therefore, the decrease in intensity of reflected ultrasound waves is greater for an enlarged liver. Since the y-intercept for the enlarged liver is -155.02 whereas, for cirrhotic liver it is -150.47, it shows that the initial loss in intensity is greater for the cirrhotic liver, but its decrease after that is smaller than the decrease for the liver with hepatomegaly.

Moreover, if we compare the slope of cirrhotic liver and that of enlarged liver (**Figure 1**), the difference between their slopes only of approximately 5 units of $\log(I_6/I_1)$ dB which is very small considering that the slope difference between normal and diseased liver was also not large enough. Their y-intercepts also differ by 1 unit of $\log(I_6/I_1)$ dB only. As the slopes were not significantly different between disease states, this model could not predict the health of the liver from ultrasound data.

Thickness (cm)	$log\ \frac{I_6}{I_1}$ (dB) Normal Liver	$log\ \frac{I_6}{I_1}$ (dB) Cirrhosis Liver	$log\ \frac{I_6}{I_1}$ (dB) Hepatomegaly liver
5	-168	-188	-194
6	-202	-226	-232
7	-236	-263	-271
8	-269	-301	-310
9	-303	-338	-349
10	-337	-376	-387
11	-370	-413	-426
12	-404	-451	-465
13	-438	-489	-503
14	-471	-526	-542
15	-505	-564	-581

Table 1. Intensity ratio log [I_6/I_1] (dB) for normal, Cirrhosis, Hepatomegaly liver. The log of the ratio of ultrasound (initial and reflected) for the normal and liver diseases against their thickness in centimeter.

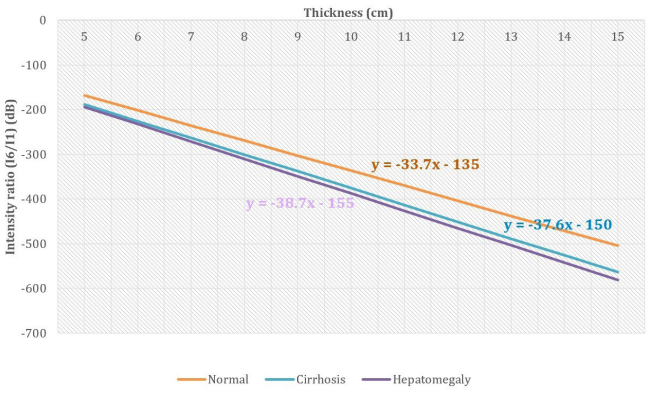

Figure 1. Intensity ratio (I_6/I1) of the ultrasound wave. The ultrasound wave was reflected from the front and back surface of liver against liver tissue thickness of normal (red), cirrhotic (purple), and hepatomegaly (orange).

https://doi.org/10.59720/23-147

DISCUSSION

In this work, we aimed to determine whether our method could detect differences in normal, cirrhotic, and enlarged livers based on ultrasound data. We see variation in the intensities of reflected ultrasound waves from both ends of liver in normal, Cirrhotic, and Hepatomegaly liver through the slope and the y-intercepts (**Figure 1**). The attenuation coefficient of normal and Cirrhotic liver shows a variation of approximately -2 dB, which corresponds to an additional loss of intensity of 37% in Cirrhotic liver compared to normal liver. This loss possibly occurred because the scar tissue, which formed during cirrhosis, increased the obstruction of ultrasound through the liver. Also, the attenuation coefficient of normal liver and hepatomegaly liver shows a variation of approximately -3 dB which shows an additional loss of intensity of approximately 50% in Hepatomegaly liver compared to normal liver.

The increase in the attenuation coefficient in hepatomegaly liver may be caused by tumors and cysts, which result in liver enlargement, thereby increasing the density of liver. The increase in density corresponds to an increase in the attenuation coefficient of liver. The attenuation coefficient in enlarged liver decreases the reflection intensity ratio I_6/I_1. At a liver thickness of 12cm, we can see the intensity ratio decreases from enlarged liver to normal liver. There is also a significant variation in acoustic impedance in Cirrhotic and Hepatomegaly liver in comparison to normal liver.

It is important to note, however, that the results use secondary data, and this has not been tried over a sample of people and their individual acoustic impedance or attenuation coefficient to know whether the difference between normal livers and either of the diseased liver types persists mathematically. Therefore, the difference in the graphs' slopes between the two diseased livers is negligible with the current data and cannot be used to differentiate between the kind of diseased liver. The difference in slopes implies that at any thickness of liver, the model cannot predict the ultrasound intensity variation. More intensity values for different thicknesses and data samples need to be found to determine the effect of a disease on the liver's ultrasound.

The difference was seen majorly due to the difference in thickness of the two livers and the difference in the mean acoustic impedance of the enlarged liver and the cirrhotic liver. The data we used was based on secondary experimental data and therefore, our method can't perfectly diagnose the liver, but it can show us the ultrasound symptoms or trends of a Cirrhotic liver and Hepatomegaly liver. It is also important to note that the data used involves both human and rat data sets and their livers vary physiologically. However, due to the limitations in available data sets and omitting primary data collection, these data sets were used. We want to extend this work by performing the experiment using commercially available animal liver and an ultrasound source. We want to see to what extent does the results of our theoretical study and the experimental results match.

MATERIALS AND METHODS

Mathematical Modeling

Reference values for acoustic impedance and attenuation coefficient for normal liver, fat, and tissues are shown in **Table 2**. Since there was a lack of sufficient numerical data available for human beings (since most of the data is available in the form of images) and there is sufficient data available on rats we have used these values for rats (12-15).

Layer	Acoustic Impedance (z) ($10^6 kgm^{-2} s^{-1}$)	Attenuation coefficient (μ) (dB/cm/MHz)	Thickness (t) (mm)
Fat-A (z_1)	1.34	0.60	24.31
Liver Normal (z_2)	1.80	0.52	60-120
Hepatomegaly	1.62-1.71	0.37-0.66	150
Cirrhosis	1.75-1.80	0.62±0.09	60-120
Fat-B (z_3)	1.34	0.60	24.31

Table 2. Acoustic impedance, attenuation coefficient and thickness of Fat-A layer and Liver in human body [12-15]. Values given for normal liver, Hepatomegaly (enlarge liver), Cirrhotic liver. The acoustic impedance and attenuation were found using ultrasound imaging [12]. The attenuation coefficient was found using spectral shift central frequency method [13,14]. Thickness was found using abdominopelvic CT [15].

The acoustic impedance is the resistance to the propagation of ultrasound (10). The intensity of the reflected ultrasound at the boundary of an organ depends on the acoustic impedance of all the tissues (16). The acoustic impedance depends on the density ρ and the speed of sound c in the material. It is defined by (16):

$$Z = \rho c \qquad \text{[Eqn 1]}$$

The greater the difference in acoustic impedances, the greater the reflected fraction of the ultrasound waves. When an ultrasound wave is reflected at the interface of medium 1 and 2, then the reflected intensity can be calculated by the ratio, given by:

$$I_r = I_0 \left[\frac{z_2 - z_1}{z_2 + z_1}\right]^2 \qquad \text{[Eqn 2]}$$

Where Z_1 and Z_2 are the acoustic impedance of medium 1 and 2. I_0 is the incident intensity and I_r is the reflected intensity from the interface of medium 1 and 2.

Attenuation is the loss of energy as it passes through a medium due to which the intensity and amplitude of ultrasound decreases (10). It is a result of absorption and scattering, as well as diffraction, refraction, and reflection of the acoustic waves at the tissue boundaries. Attenuation depends on the type of tissue— its density (16). Attenuation in a medium is represented by the attenuation coefficient where the transmitted intensity of the wave in any medium is given by:

$$I_T = I_0 e^{-\mu t} \qquad \text{[Eqn 3]}$$

Where Io is the intensity of the incident, t is the thickness of the medium and I_T is the intensity of transmitted wave through the medium (16).

We considered a one-dimensional model (**Figure 2**) where the liver is sandwiched between two fat layers A and B, the acoustic impedance of liver was considered as z_2 and that of the A and B fat layers were considered as z_1 and z_3, respectively. The thickness of liver was taken as t. The numerical data was taken from papers on ultrasound imaging (12-15).

As demonstrated in the two-dimensional simplified diagram of liver (**Figure 2**), ultrasound waves from the source were incident on the liver region and I0 was the intensity of wave falling on the fat layer A-liver interface. The reflected

https://doi.org/10.59720/23-147

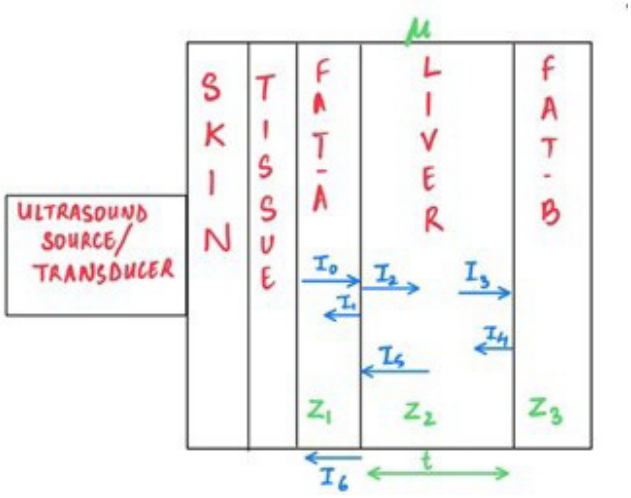

Figure 2. Layers from the skin to the liver in the human body. Intensity of ultrasound waves transmitted and reflected from various layers is shown: I_0 is the intensity of incident ultrasound wave at the interface of Fat A -Liver, I_1 is the intensity of reflected ultrasound wave at the same interface, I_2 is the transmitted intensity of ultrasound waves from the Fat-A -Liver interface, I_3 is the transmitted intensity of these waves attenuated by the Liver medium and incident on the Liver -Fat B interface, I_4 is the reflected wave intensity from the Liver-Fat B interface, I_5 is the transmitted back intensity of ultrasound waves attenuated by the liver medium, I_6 is the transmitted waves from the Liver-Fat A interface. t represents the thickness of the liver, and z_1, z_2 and z_3 represent the acoustic impedance of Fat A, Liver, Fat B layers respectively. μ is the attenuation coefficient of the liver.

wave intensity from this interface was I_1, whose intensity depended on the acoustic impedance z_1 and z_2, as shown in **equation 4** (16):

$$I_1 = I_0 \left[\frac{Z_2 - Z_1}{Z_2 + Z_1}\right]^2 \qquad \text{[Eqn 4]}$$

The transmitted wave intensity from this interface was taken as I_2, which was calculated from incident intensity from **equation 5**:

$$I_2 = I_0 - I_1 \qquad \text{[Eqn 5]}$$

$$I_2 = I_0 - \left[\left(\frac{Z_2 - Z_1}{Z_2 + Z_1}\right)^2 \times I_0\right]$$

The intensity of transmitted wave I_3 through the liver and striking the liver-fat layer B is dependent on the attenuation coefficient μ and thickness of liver (16):

$$I_3 = I_2 e^{-\mu t} \qquad \text{[Eqn 6]}$$

Then, using **equations 4 and 5** we derived:

$$I_3 = \left[1 - \left[\frac{Z_2 - Z_1}{Z_2 + Z_1}\right]^2\right] \times I_0 e^{-\mu t} \qquad \text{[Eqn 7]}$$

The intensity of the wave reflected at this interface from liver to fat layer B was I_4, which is related to the acoustic impedance of liver and fat layer B:

$$I_4 = \left(\frac{Z_3 - Z_2}{Z_3 + Z_2}\right)^2 \times I_3 \qquad \text{[Eqn 8]}$$

Using **equations 6 and 8** we derived:

$$I_4 = \left(\frac{Z_3 - Z_2}{Z_3 + Z_2}\right)^2 \left[1 - \left[\frac{Z_2 - Z_1}{Z_2 + Z_1}\right]^2\right] \times I_0 e^{-\mu t} \qquad \text{[Eqn 9]}$$

Then, the intensity of attenuated ultrasound wave again through the liver was given by **equation 10**:

$$I_5 = I_4 e^{-\mu t} \qquad \text{[Eqn 10]}$$

Using **equations 9 and 10** we derived:

$$I_5 = \left(\frac{Z_3 - Z_2}{Z_3 + Z_2}\right)^2 \left[1 - \left[\frac{Z_2 - Z_1}{Z_2 + Z_1}\right]^2\right] \times I_0 e^{-2\mu t} \qquad \text{[Eqn 11]}$$

The transmitted intensity through the liver–fat layer A interface was then given by **equation 12**:

$$I_6 = \left[1 - \left(\frac{Z_1 - Z_2}{Z_2 + Z_1}\right)^2\right] \left(\frac{Z_3 - Z_2}{Z_3 + Z_2}\right)^2 \left[1 - \left(\frac{Z_2 - Z_1}{Z_2 + Z_1}\right)^2\right] e^{-2\mu t} I_0 \qquad \text{[Eqn 12]}$$

Equation 12 was simplified as:

$$I_6 = \frac{16 Z_1^2 Z_2^2 \left[\frac{Z_3 - Z_2}{Z_3 + Z_2}\right]^2 I_0 e^{-2\mu t}}{(Z_1 + Z_2)^4} \qquad \text{[Eqn 13]}$$

If we take the ratios of intensities from the front and back side of the liver, the other multiplication factors coming from attenuation and reflection form other layers between the source and the liver will cancel out and will not interfere in this calculation. The ratio of reflected intensities from the liver was written using **equations 4 and 13**:

$$\frac{I_6}{I_1} = \frac{16 Z_1^2 Z_2^2 (Z_3 - Z_2)^2 e^{-2\mu t}}{(Z_1 + Z_2)^2 (Z_2 - Z_1)^2 (Z_3 + Z_2)^2} \qquad \text{[Eqn 14]}$$

We calculated the intensity ratio I6/I1 for reflected ultrasound waves from both ends of liver by using the data from **Table 2**. **Equation 14** was rearranged as:

$$\frac{I_6}{I_1} = Z\, e^{-2\mu t} \qquad \text{[Eqn 15]}$$

Where $Z = \frac{16 Z_1^2 Z_2^2 (Z_3 - Z_2)^2}{(Z_1 + Z_2)^2 (Z_2 - Z_1)^2 (Z_3 + Z_2)^2}$

The exponential relationship mentioned in **equation 15** was linearized to analyze the data. By taking the logarithm on both sides of **equation 15** we get:

$$\log \frac{I_6}{I_1} = \log (Z) - 2\,\mu\, t \qquad \text{[Eqn 16]}$$

Statistical testing

To test the statistical significance of the results, we used a two-tailed t-test, in which the values found from equation 16 for normal, cirrhotic, and hepatomegaly liver were compared. The greater the t-value, the more significant the difference in the two data sets is. The test also gives a p-value which we took smaller than 0.05 as statistically significant. The test was run on excel.

Received: April 26, 2023
Accepted: May 28, 2024
Published: July 06, 2025

https://doi.org/10.59720/23-147

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