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Determination of Normal Liver Stiffness Range among Healthy Adults in Pakistan Using Shear Wave Elastography

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ABSTRACT

Objective: To determine the reference values of liver stiffness in Pakistan using Shear Wave Elastography in subjects without liver disease, with a range of ages and BMI for both genders and to assess the influence of Hepatic Steatosis on liver stiffness values.

Study Design: Cross-sectional study.

Place and Duration of Study: Armed Forces Institute of Radiology and Imaging, Rawalpindi Pakistan Aug 2018 to Sep 2019.

Methodology: One hundred twenty-three subjects who underwent Shear Wave Elastography were enrolled. Measurements were taken from the right hepatic lobe, and the median kilopascal value of 10 measurements was taken as the representative value. The reference range of liver stiffness was calculated using upper and lower limits at 97.5 and 2.5 percentiles. The influence of hepatic steatosis age, body mass index, and gender on liver stiffness was also recorded.

Results: The mean age of the subjects was 39.7±12.7 years with a male-to-female ratio of 1.4:1. The Mean liver stiffness value in healthy subjects was 4.90±0.64 kPa. No statistically significant difference was found in the values among various age groups (p=0.013) or the groups based on body mass index, except for the Obese-Group, whose values were considerably higher (p<0.001). Shear Wave Elastography values were significantly influenced by male gender and hepatic steatosis (p<0.001).

Conclusion: Real-time Shear Wave Elastography can be used to estimate liver stiffness reliably. Male gender, obesity, and hepatic steatosis are significant factors affecting liver stiffness in otherwise healthy adults.

Keywords: Elastography, Hepatic steatosis, Liver stiffness, non-invasive diagnosis, Shear Wave Elastography (SWE).

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INTRODUCTION

All chronic liver diseases, including chronic viral hepatitis and alcoholic liver disease, eventually progress to liver fibrosis.[1,2] Chronic viral hepatitis is a significant public health problem in Pakistan. Approximately 10 million cases across the country are reported to have hepatitis C.[3] About 75% of these cases across the country are reported at risk of progression to chronic liver disease and eventually hepatic fibrosis. A lower-income, developing country like Pakistan is more at a disadvantage due to the significant morbidity and mortality attributed to this disease.[4]

In clinical practice, the prognosis can significantly improve with successful detection and accurate staging of liver fibrosis at an early stage.[2] Histopathological analysis is still considered the reference standard for diagnosing and assessing hepatic disease; however, being an invasive procedure, biopsy carries the risk of bleeding and infection.[5] Histological analysis has also been found to have variability in intra- and inter-observer agreement: a difference of at least one grade may be reported in as many as 25% of the cases.[6] Thus, minimally invasive/non-invasive methods to assess disease processes, including hepatic fibrosis, are of great clinical interest.

Elastography is a non-invasive technique that measures changes in tissue elasticity caused by disease processes like fibrosis and tumors. Magnetic resonance and ultrasound elastography can be used to measure tissue elasticity.[7] Ultrasound elastography techniques include real-time Shear Wave Elastography (SWE), which has been used to estimate liver stiffness with reliable results.[5] Several studies have investigated the nexus between human health and the normal range of liver stiffness in healthy subjects in varying geographical locations. The mean liver stiffness value in healthy subjects reported with SWE in the literature

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ranges from 4.4 kPa to 5.6 kPa.[8-10] However, local studies on the subject are scarce. Our study aims to determine the reference values of liver stiffness using SWE in healthy subjects with a range of ages and BMI for both genders. It also aims to assess the influence of Hepatic Steatosis on SWE value.

METHODOLOGY

The cross-sectional study was conducted at the Armed Forces Institute of Radiology and Imaging Rawalpindi, Pakistan from August 2018 to September 2019. The study was approved by the Institutional Ethical Review Board (ERC Number: 53). The sample size was calculated using a WHO sample size calculator, taking a a 98% success rate.[11]

Inclusion Criteria: Healthy adults above the age of 18 years with no history of hepatic disease, normal liver function tests and absent viral markers (Hep B virus, Hep C virus) were included.

Exclusion Criteria: Patients with history of liver disease, systemic disease, alcohol or drug abuse were excluded.

Informed consent was obtained after providing the participants with a complete description of the study. A total of 136 subjects were employed by non-probability consecutive sampling, including patients, potential liver donors, college students, and hospital staff. Thirteen participants were excluded from the analysis because of evidence of hepatic disease on ultrasound or failed measurement (inadequate breath holding). Liver stiffness was evaluated in 123 healthy subjects, and the influence of gender, age, and body mass index on liver stiffness values was assessed. Liver stiffness of subjects who underwent biopsy revealing no fibrosis (F0), with or without steatosis, was also evaluated and compared. The subjects were divided into five age groups: older than 60 years, 50-59 years, 40-49 years, 30-39 years, and 18-29 years. According to the body mass index (BMI), they were segregated into four groups: underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9), and obese (BMI >30). The subjects were also grouped into two categories based on the presence or absence of hepatic steatosis.

The SWE examination was performed after conventional B-mode liver ultrasound by experienced radiologists. Each scan was conducted with an Aplio 500 ultrasound system with a broadband convex array probe (1-6MHz). The subjects had fasted for more than 04 hours before the scanning. The patient was asked to lie supine with the right arm maximally abducted. An intercostal window was used to measure liver stiffness from the right lobe of the liver while the participant held his breath for 3-5 seconds after exhalation. An SWE color box was positioned and frozen on the liver parenchyma, at least 2 cm below the hepatic capsule, carefully avoiding large vessels. The round Q-box (region of interest – ROI) was then positioned in the SWE color box in an area of relatively uniform elasticity. The diameter of ROI was kept at 20 mm. The mean value of hepatic elastic modulus (in units of kPa) was calculated within the ROI. Ten measurements were performed during separate breath holds, and the median value, taken in kPa, was recorded as the representative value for statistical analysis.[12]

Statistical Package for Social Sciences (SPSS) version 22.0 was used for the data analysis. Frequencies and percentages were calculated for qualitative variables. Mean and standard deviation were calculated for liver stiffness measurements (LSMs). Results were recorded and analyzed for any statistical differences. An independent samples t-test and one-way ANOVA were applied to evaluate the mean difference. The p-value of ≤0.05 was considered statistically significant.

RESULTS

Measurements were successfully recorded in 100% of the subjects. Mean age of the subjects was 39.7±12.7 years with a male to female ratio of 1.4:1. The mean liver elasticity value of 123 healthy adults was 4.90±0.64 kPa, which, with 95% confidence interval, was 4.79–5.02 kPa (range: 3.6–6.4 kPa). Table-I gives the characteristics of hepatic elastic modulus for healthy subjects in different age groups. No significant association could be determined between the LSM values and the subjects' age.

The mean values of liver elasticity in males and females are given in Table-II. The mean LSM for men was significantly higher than for women (5.08±0.61 kPa vs. 4.68±0.60 kPa, respectively).

The evaluation of the relationship between the groups based on BMI and mean SWE values (Table-III) revealed significantly higher values in the obese group with a BMI of more than 30 kg/m^2. The liver stiffness measurements among underweight, normal BMI, and overweight groups were comparable. Table-IV shows the characteristics of SWE values with and without fatty infiltration of the liver. A statistically significant difference was observed in the SWE values among the two groups.

Five patients with normal parameters on clinical and sonographic evaluation and SWE values of 4.5 kPa, 3.9 kPa, 4.4 kPa, 4.1 kPa, and 5.6 kPa underwent liver biopsy. The histopathological evaluation confirmed no evidence of fibrosis.

not reveal any significant difference between men and women.

Our subjects' BMI-based evaluation revealed that while there was no notable difference in the SWE measurements between under-weight, normal, and

Table-I: Liver Stiffness Measurements Using Shear Wave Elastography (kPa) Among Different Age Groups (n=123)

Shear Wave Elastography Value (kPa) (Mean±SD)	Age Groups (Years)					*p*-value
	18–29 yrs n=29	30–39 yrs n=36	40–49 yrs n=31	50–59 yrs n=15	>60 yrs n=12	
	4.72±0.54	4.93±0.69	4.90±0.75	4.95±0.51	5.26±0.35	0.187

Table-II: Shear Wave Elastography Values (kPa) Among Male and Female Study Participants (n=123)

Shear Wave Elastography Value (kPa) (Mean±SD)	Gender Ditribution		*p*-value
	Male Study Participants (n=71)	Female Study Participants (n=52)	
	5.08±0.61	4.68±0.60	0.001

Table-III: Shear Wave Elastography Values (kPa) in Underweight, Normal Body Mass Index and Overweight Groups (n=123)

Shear Wave Elastography Value (kPa) (Mean±SD)	Body Mass Index (kg/m²)				*p*-value
	Underweight (<18.5) (n=29)	Normal (18.5–24.9) (n = 50)	Overweight (25–29.9) (n=35)	Obese (>30) (n=09)	
	4.82±0.52	4.87±0.60	4.75±0.58	6.01±0.25	<0.001

Table-IV: Shear Wave Elastography Values (kPa) in Presence or Absence of Hepatic Steatosis (n=123)

Shear Wave Elastography Value (kPa) (Mean±SD)	Hepatic Steatosis		*p*-value
	Yes (n = 32)	No (n = 91)	
	5.30±0.65	4.77±0.57	<0.001

DISCUSSION

Our study demonstrated that male gender, obesity, and hepatic steatosis are significant factors affecting liver stiffness in otherwise healthy adults. The mean liver stiffness value of normal livers in our study was 4.90±0.64 kPa, which was consistent with previously reported ranges of values.[8-10,13] The mean normal SWE value reported by a study conducted in China was 5.1 kPa,[14] in Norway was 4.5 kPa,[15] and in Albania was 5.1 kPa.[16]

Our work explored the influence of relevant factors like age, gender, BMI, and hepatic steatosis on the SWE. We did not find any significant impact of age on the liver stiffness measurement

which was consistent with previous studies of Mulabecirovic *et al.*,[15] Huang *et al.*,[11] Suh *et al.*,[8] and Arda *et al.*,[17] which revealed no significant effect of age on liver stiffness.

In this study, the mean SWE values in male subjects were found to be higher than in the female population, with a statistically significant difference between the two groups. This difference is similar to the outcome of studies in Norway,[15] and China.[14] Other studies conducted in India,[17] and Egypt,[18] did

overweight subjects, SWE values in obese cases were significantly higher than the rest. The influence of BMI on liver stiffness is controversial in the literature. Previous studies by Mulabecirovic *et al.*,[15] and Huang *et al.*,[11] reveal no significant influence of BMI on liver stiffness; however, these studies only compared the values between under-weight, normal, and over-weight groups. Obese subjects having a BMI greater than 30kg/m² were not included in these studies. Hence, the results are similar to our findings. A study on Egyptian population 18 showed significantly raised LSM values with BMI ≥ 26 kg/m². On the contrary, a study on the Albanian population reported comparable mean LSM values between subjects with BMI ≥ 30 kg/m² and those with BMI < 30 kg/m² with no statistically significant difference.[16]

Our analysis showed a notable influence of hepatic steatosis on the subjects' SWE values. A study by Suh *et al.*, revealed no statistical significance in the mean values for liver elasticity between steatotic and non-steatotic groups.[8] This divergent finding may be because 65 out of 71 subjects in the study by Suh *et al.*, had only a low degree of steatosis (Grade-1).

Only five patients in our study had normal clinical and sonographic evaluation parameters and

underwent liver biopsy. The histopathological evaluation confirmed there was no evidence of fibrosis. These subjects were potential donors for liver transplant surgery. In our settings, the relative paucity of healthy adults undergoing invasive biopsy procedures made it difficult to use histopathological confirmation to rule out hepatic fibrosis.

Liver elastography has been utilized for quite some time to evaluate liver stiffness and may emerge as a reliable alternative to liver biopsy and histopathological analysis. There are published studies delineating the normal ranges in healthy subjects. To our knowledge, this study is the first one focusing on healthy Pakistani subjects, providing an initial detection criterion for the regional population as well as a reference value for future local studies.

LIMITATIONS OF STUDY

There were certain constraints in our study. Firstly, subjects were declared healthy and without liver disease solely based on clinical information and laboratory data; histopathological confirmation was not available in most patients. However, this was the most feasible approach since a biopsy in a healthy individual is not justified. Secondly, although the sample size was relatively small, the current study was performed at a single tertiary care center that draws patients from all regions across Pakistan.

CONCLUSION

Real-time SWE can reliably measure liver stiffness. Male gender, obesity, and hepatic steatosis are significant factors affecting LSM in otherwise healthy adults, while age and BMI less than 30 kg/m2 did not influence the results.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AI & AURS: Conception, study design, drafting the manuscript, approval of the final version to be published.

SS & AAA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

NS & WA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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