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Original Research

Significantly Increased Liver Stiffness Detected by ElastPQ Ultrasound Shear Wave Elastography in Patients with Chronic Liver Disease of Over 75 Years of Age: A Cross-Sectional Study

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ABSTRACT

Objective: Aging is associated with worsening of disease severity and poor prognosis in patients with non-alcoholic fatty liver disease (NAFLD), chronic hepatitis B/C (HBV/HCV), alcoholic liver disease, and liver transplantation. The aim of this study was to determine the frequency of liver fibrosis (LF) and its related parameters by calculating the liver stiffness (LS) value in patients having NAFLD and HBV/HCV who were over 75 years of age.

Methods: A total of 120 individuals over 75 years of age were included in our study, according to their liver disease status as having normal liver function (NLF), NAFLD, or HBV/HCV. The LS measurement was performed with the elastography point quantification (ElastPQ) technique. If a patient had an LS value of >7.0 kPa, he or she was was accepted as having LF.

Results: The LS values of patients over 75 years of age with NLF, NAFLD, and HBV/HCV were 4.75±2.34 kPa, 6.45±3.12 kPa, and 8.68±2.76 kPa, respectively. LF was found to be 25%, 40%, and 70% in the NLF, NAFLD, and HBV/HCV groups, respectively. Creatinine and AST levels were independently associated with the LS value. Creatinine, AST values, and liver size were independently determined to be associated with LF; creatinine (0.1 increase), AST (1 increase), and liver size (1 cm decrease) levels were found to increase the LF by 18.4%, 14.6%, and 42.9% respectively.

Conclusion: Patients with NAFLD and HBV/HCV who were over 75 years old had their level of LS determined by liver elastography, which was increased as compared to those with NLF. Patients older than 75 years of age with NAFLD and HBV/HCV also showed significant decrease in LF as compared to NLF patients.

Keywords: Aged, chronic hepatitis B and C, non-alcoholic fatty liver disease

INTRODUCTION

Worldwide socioeconomic developments with advancing medical care and increasing life expectancy have become more prevalent in recent years. This is why the elderly population is increasing globally, especially in developed countries (1). Aging is associated with worsening of disease severity and poor prognosis in patients with non-alcoholic fatty liver disease (NAFLD), chronic viral hepatitis B/C (HBV/HCV), alcoholic liver disease, and liver transplantation (2). The treatment of liver disease in elderly patients is difficult and long-lasting, but more so in patients over 75 years of age, with respect to whom there are problems with data incompetence, existing co-morbid diseases, and involvement in the study. NAFLD and HBV/HCV are associated with impaired liver function and increased liver fibrosis (LF) in such patients (3-5).

Elastography is a newly developed ultrasonography (USG) technique that can measure tissue stiffness and fibrosis development noninvasively and quantitatively. Liver stiffness (LS) measurements have also been made using liver elastography (LE) in patients with NAFLD and HBV/HCV and it has been shown that LF was increased in these patients as compared to the control groups (3-6). To our knowledge, there is no information regarding the changes in LS or LF in patients with NAFLD and HBV/HCV who are over 75 years of age in the current literature. In addition, LS normal range is not even known in individuals who are over 75 years of age and who have a normal liver function (NLF).

The aim of this study was to determine the LF frequency using the LS value in patients over 75 years of age with NAFLD and HBV/HCV, and describe the LF-related parameters in the same

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patients. In addition, we aimed to obtain a normal range of LS values in patients with NLF who were over 75 years of age, in addition to the NAFLD and HBV/HCV patients.

METHODS

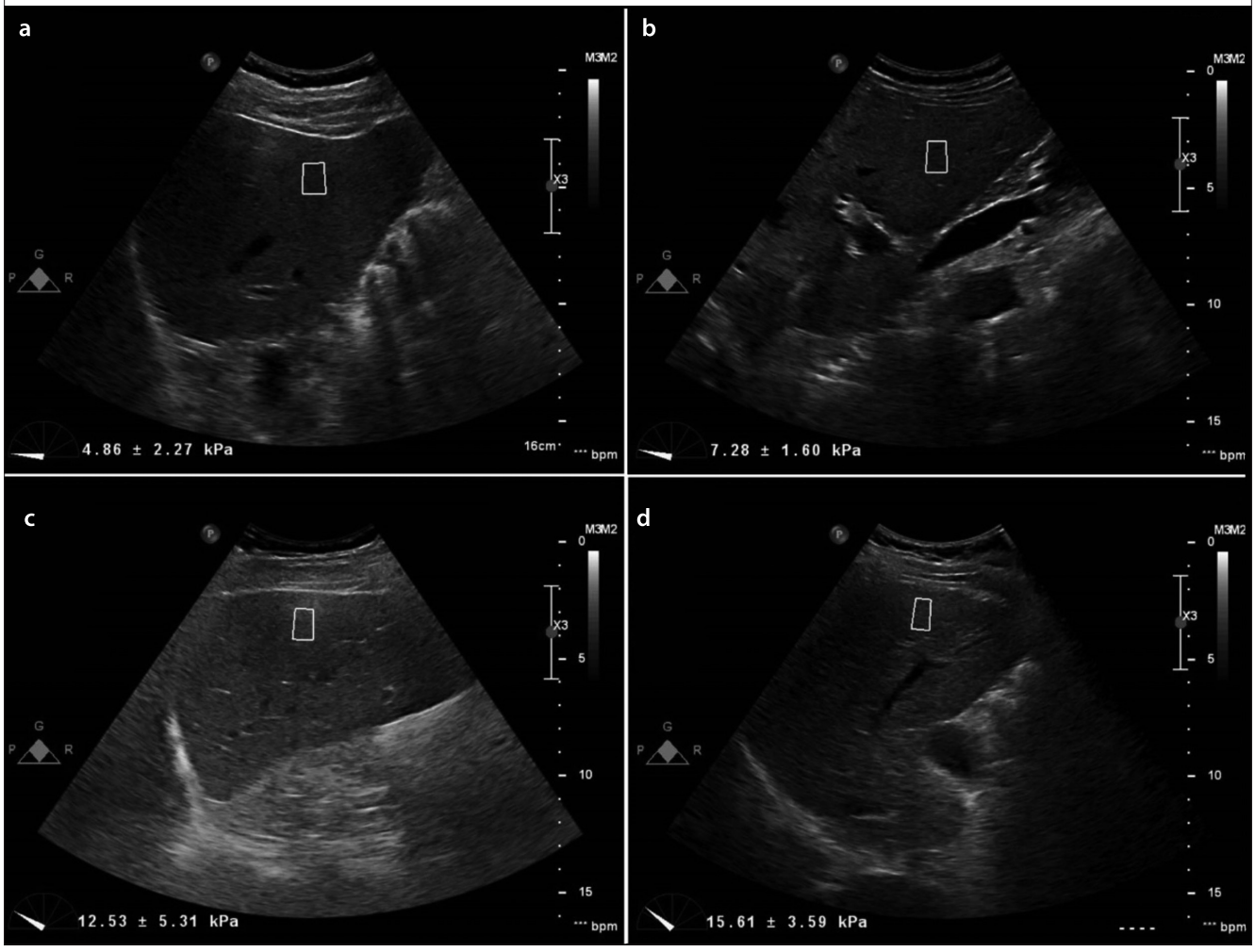
A total of 165 individuals with three different liver disease conditions were screened for this study. Patients were classified and grouped according to the AASLD guidelines for the diagnosis of chronic liver disease (CLD) (7). Patients with known regular alcohol use (>20 gr/day), <18 years of age, hepatocellular carcinoma, cirrhotic status, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≥3 times more than normal, very severe ascites, serious heart valve disease, right or left heart failure, pulmonary or portal hypertension (HT), active thyroid disease, cancer, morbid obesity and/or pregnancy, and HBV or HCV patients who were continuing with their treatment were excluded from the study. Forty-five patients were excluded based on the set criteria and the remaining 120 patients were included in the study. The study included individuals with Group 1: NLF; Group 2: patients with NAFLD, and Group 3: those with a new diagnosis or active HBV/HCV.

Our study subjects were included based on the recommendations of the Biennial Research Helsinki Declaration of Human Subjects and the protocol was approved by the ethics committee of Çukurova University (date: 06.07.2018; no: 2018–79-59). Voluntary consent forms were explained in detail and the patients were included in the study only after the written consent was obtained.

Detailed anamnesis and physical examination were performed and the presence of hypertension (HT), diabetes mellitus, active smoking, hyperlipidemia was assessed, followed by age- and gender-related questioning in all the groups. The systolic blood pressure and diastolic blood pressure were recorded. The body mass index (BMI) was calculated by measuring the patients'weight and height. Fasting blood glucose, blood urea nitrogen, creatinine, AST, ALT, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglyceride levels were measured (Abbott, Aeroset, USA and commercial kits).

Figure 1. a-d. In NLF subjects: normal LS in 4.86±2.27 kPa (a); In NAFLD patients: increased LS in 7.28±1.60 kPa (b); In HBV patients: severely increased LS in 12.53±5.31 kPa (c); In HCV patients: severely increased LS in 15.61±3.59 kPa (d)

NLF: normal liver function; LS: liver stiffness; NAFLD: non-alcoholic fatty liver disease; HBV: hepatitis B virüs; HCV: hepatitis C virüs



All patients underwent liver USG screening using a high-resolution USG device (Philips EPIQ 7, Philips Health Care, Bothell, WA, USA) with a 1–5 MHz high-resolution convex probe (Philips Health Care, Bothell, WA, USA). The liver ultrasound (US) was performed after a minimum initial fasting period of 8 hours with B-mode US on gray-scale, which was used to assess the liver dimensions. LS measurements were performed using the elastography point quantification (ElastPQ) technique, which is a point shear wave elastography (SWE) assessment, with the patient being in the lateral decubitus position. During the procedure, the subjects were asked to pause breathing for a few seconds to minimize the hepatic movement occurring with respiration. All measurements were made at the end of the inspiration period. After traditional hepatic US images were obtained, the target area was determined and the measurements were performed after positioning the range of imaging (ROI) on the target (Figure 1a-d). The ROI was positioned perpendicular to an area containing no vascular structures or space-occupying lesions. The maximum ROI target distance was 8 cm in our study, with a constant ROI box dimension of 0.5–1 cm. The compression during the imaging was maintained as low as possible to avoid mechanical pressure on the liver. In each subject, 10 valid measurements from different hepatic parenchymal segments were obtained and their average was calculated and the results were expressed in terms of kilopascal (kPa). When the reliability of the measurement was low, the image had a kPa value of 0.00. Based on the value of LS, the subjects were stratified into two groups; as those with or without LF. Using the cut-off values reported in two important recent studies, the LS threshold for the presence of LF was adopted as ≥7 kPa (3, 5). Subjects were evaluated by a single well-experienced radiology specialist for conventional, Doppler, and SWE examinations. The specialist had more than 5 years of experience in SWE studies and had performed at least 500 SWE procedures in a year.

Table 1. Study findings according to liver disease groups

	NLF (n=40)	NAFLD (n=40)	HBV/HCV (n=40)	p
Age (year)	79.1±3.8	78.9±3.2	78.5±3.5	0.732
Sex (male/female)	19/21	12/28	15/25	0.362
Hypertension, n (%)	30 (75%)	24 (0%)	25 (63%)	0.242
Diabetes mellitus, n (%)	10 (25%)	17 (43%)	15 (38%)	0.245
Current smoker, n (%)	4 (10%)	5 (13%)	13 (32%)	0.010
Hyperlipidemia, n (%)	12 (21%)	13 (24%)	17 (31%)	0.277
Systolic blood pressure (mmHg)	130±17	131±17	131±10	0.904
Diastolic blood pressure (mmHg)	77±12	77±8.4	78±5.8	0.854
Body mass index (kg/m^2)	27.6±2.5	27.5±3.5	25.9±3.3	0.030
Fasting plasma glucose (mg/dL)	125±34	142±63	145±48	0.178
Total cholesterol (mg/dL)	184±53	207±60	202±63	0.169
LDL cholesterol (mg/dL)	118±39 β	143±48	133±50	0.041
HDL cholesterol (mg/dL)	47±19	46±13	44±11	0.590
Triglycerides (mg/dL)	141±42	176±90	161±82	0.125
Aspartate aminotransferase (u/L)	22.3±5.8 α, β	26.9±8.4*	33.6±10.6	<0.001
Alanine aminotransferase (u/L)	19.8±5.1 α, β	23.2±7.9*	28.8±9.7	<0.001
Blood urea nitrogen (mg/dL)	40.4±19.7	36.5±15.6	40.8±14.9	0.254
Creatinine (mg/dL)	0.89±0.30	0.98±0.39	0.88±0.30	0.352
Liver size (cm)	13.8±2.1	14.3±1.1*	13.2±1.6	0.013
Liver stiffness (mean±SD) (kPa)	4.75±2.34 α, β	6.45±3.12*	8.68±2.76	
Liver stiffness (median, min– max) (kPa)	5.02 (1.25–9.75)	6.22 (2.20–11.78)	8.39 (4.06–15.62)	<0.001
Liver stiffness >7kPa, n (%)	10 (25%)	16 (40%)	28 (70%)	<0.001

NLF: normal liver function; NAFLD: non-alcoholic fatty liver disease; LDL: low density lipoprotein; HDL: high density lipoprotein; hs-CRP: high sensitive C reactive protein; ACR: albumin creatinine ratio; HBV: hepatitis B virus; HCV: hepatitis C virus

α: the significant association between the NLF group and HBV/HCV group (p<0.05)

β: the significant association between the NLF group and NAFLD group (p<0.05)

*: the significant association between the NAFLD group and HBV/HCV group (p<0.05)

Statistical Analysis

For all analyses, the Statistical Package for the Social Sciences 20.0 statistical software pack (SPSS IBM Corp.; Armonk, NY, USA) was used. The variables were divided into groups: categorical and continuous. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as numbers and percentages. Continuous variables that showed normal distribution were compared using the Student's t-test and the ANOVA, whereas the Mann-Whitney U test and the Kruskal-Wallis test were used for samples without normal distribution. For the comparison of categorical variables, the Chi-square test was used. In univariate analyses, a logistic regression analysis was performed to determine the differences between the independent markers among patients with LF. Parameters associated with LS were determined with univariate Pearson's and Spearman's correlation analyses. Statistically significant parameters were included in a linear regression analysis, and the parameters having the closest association with the LS were identified. A p-level of < 0.05 was considered statistically significant.

RESULTS

LS was successfully measured in 96% of all patients over 75 years of age who were screened for LS measurement in the study, out of the total 120 individuals who were evaluated. The study data were compared among 3 groups, classified according to liver function status as NLF, NAFLD, and HBV/HCV.

Table 2. Independent parameters for occurrence of liver fibrosis

	Odds Ratio	95% Confidence Interval	p
Aspartate aminotransferase (each–1 u/L)	1.146	1.079–1.216	<0.001
Liver size (each–1 cm)	0.571	0.404–0.808	0.002
Creatinine (each–0.1 mg/dL)	1.184	1.009–1.389	0.039

Table 3. The parameters associated with liver stiffness measurements

	Univariate analysis		Multivariate analysis	
	p	r	p	β
Blood urea nitrogen (mg/dL)	0.010	0.235	0.619	0.046
Creatinine (mg/dL)	<0.001	0.365	0.003	0.187
Aspartate aminotransferase (u/L)	<0.001	0.743	<0.001	0.695
Alanine aminotransferase (u/L)	<0.001	0.625	0.444	0.071
Liver size (cm)	0.022	–0.257	0.459	–0.069

$R^2_{Adjusted}$ = 0.571 in multivariate analysis

Table 4. Normal limiting values in studies with different measurement methods and evaluation of liver stiffness according to age and sex

	Our study	Ling et al. (10)	Huang et al. (12)	Sırlı et al. (14)	Popescu et al. (15)	Kim et al. (16)
Total number of subjects (n)	40	175	502	82	76	69
Mean age	79.1±3.8	35±10.5	37.9±15.5	26 (18–76)	34.5±14.3	38.9±11.9
Maximum age groups	≥75 years	>50 years	≥60 years	≥60 years	≥71 years	≥50 years
Patents in older (n)	40	16	62	5	5	16
LS value (mean or median)	4.75±2.34 kPa	3.60±0.5 kPa	5.10±1.02 kPa	6.0±1.3 kPa	1.15±0.21 m/s	4.6±0.5 kPa
LS value in older patient	4.75±2.34 kPa	4.3±1.3 kPa	5.35±0.89 kPa	–	1.21±0.21 m/s	4.8±0.7 kPa
LS value in men	5.0±2.37 kPa	3.8±0.7 kPa	5.45±1.02 kPaα	6.6±1.5 kPaα	1.16±0.21 m/s	4.6±0.5 kPa
LS value in women	4.15±2.24 kPa	3.5±0.4 kPa	4.89±0.96 kPa	5.7±1.3 kPa	1.14±0.22 m/s	4.5±0.5 kPa
LE technique	ElastPQ	ElastPQ	SWE	ARFI	ARFI	TE
Failed measurement rate	4%	0%	1.4%	10.9%	7.4%	2.7%
Study time (year)	2018	2013	2014	2013	2011	2009

LS: liver stiffness; LE: liver elastography; SWE: shear wave elastography; ARFI: acoustic radiation force impulse; TE: transient elastography
α: a significant association between the men and women group (p<0.05)

The HBV/HCV group had a higher smoking rate and a lower BMI value than the other 2 groups (Table 1). The LDL cholesterol level was the highest in the NAFLD group and was significantly different between this group and the NLF group. Serum levels of AST and ALT were different among the 3 groups, and it was found that the lowest level was in the NLF group and the highest in the HBV/HCV group. It was found that there was a statistically significant difference between all the groups (Table 1). LS values were 4.75±2.34 kPa, 6.45±3.12 kPa, and 8.68±2.76 kPa in the NLF, NAFLD, and HBV/HCV groups, respectively (Table 1, Figure 2). Median and IQR values of NLF were 4.75±2.34 kPa and 5.02 kPa (1.25–9.75 kPa), respectively. In the NLF, NAFLD and HBV/HCV groups included in the study, LF was found to be 25%, 40% and 70%, respectively (LS ≥7 kPa) (Table 1). LS value was found to be the highest and lowest in the HBV/HCV groups and NFL, and statistically significant between only these two groups (Table 1).

Figure 2. Liver stiffness values of the study groups according to liver disease status.

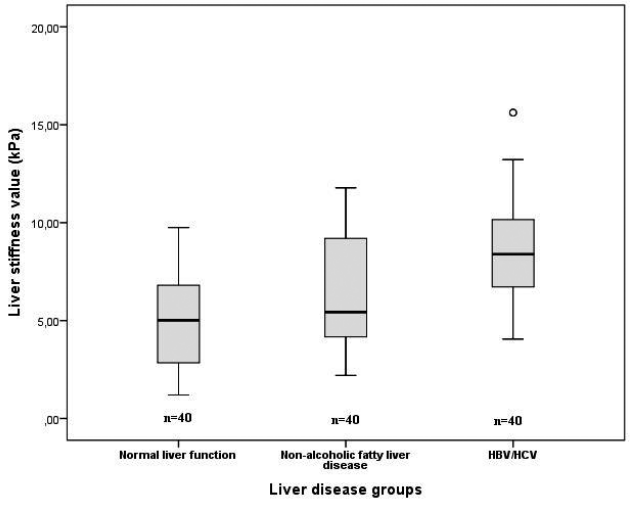
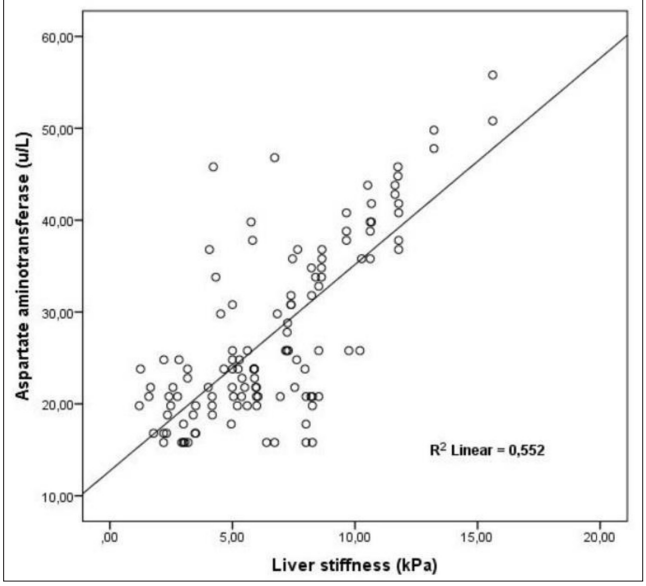


Figure 3. There is a significant correlation between liver stiffness and AST levels.

AST: Aspartate aminotransferase



The 3 parameters associated with LF in univariate analysis were evaluated by multivariate logistic regression analysis. Creatinine, AST, and liver size values were independently determined to be indicative for LF (Table 2). According to this analysis, it was found that creatinine (0.1 increase), AST (1 increase), and liver size (1 cm decrease) increased LF by 18.4%, 14.6%, and 42.9%, respectively (Table 2).

The laboratory and USG parameters associated with LS in the univariate analysis are summarized in Table 3. Linear regression analysis was performed with these LS-related parameters (Table 3). Creatinine and AST levels were found to be independently associated with LS (Table 3, Figure 3).

DISCUSSION

The main finding of this study is that the LS value obtained with the ElastPQ technique was significantly higher in patients with CLD (≥75 years old) with NAFLD and HBV/HCV than in those with NLF. We found that LS values and incidence of LF were increased in patients over 75 years of age as compared to patients under 75 years of age. In patients over 75 years of age, LE was performed using ElastPQ technique, and successful LS measurement was performed in 96% of all patients. Another important finding was that the development of LF increased the serum creatinine, whereas the AST levels and decreased liver size values are independently associated in patients over 75 years of age.

While aging reduces the blood flow to the liver, volume of the liver, and albumin production, it increases the levels of LDL, HDL, and total cholesterol (2). The aging process also decreases the mitochondrial function at the cellular level and increases oxidative stress and inflammation, all of which enhance the susceptibility of hepatocyte injuries (8). In older people with CLD, LF is higher and age is an important risk factor for fibrosis in elderly patients with HCV (9). However, this issue is still a matter of research, and there is no clear and objective data present as yet about LS and LF in patients over 75 years of age. In our study, we tried to find the answer to this question. We objectively found an increase in LS and associated LF in patients over 75 years of age who had CLD, but did not perform invasive and cellular evaluation.

To assess the liver fattiness and fibrosis levels, biochemical markers such as AST and ALT or liver USG could be used. Regardless, liver biopsy remains the gold standard for this purpose. However, liver biopsy is an invasive procedure and complications can occur, so it is rarely used. Liver USG is a non-invasive, inexpensive, and easily accessible assay that can be used in detecting fatty liver and fibrosis. For the last 10 years, the LF assessment with LE method has had critical importance and is known to provide clearer and more objective information. LS values detected in LE studies have been shown to be closely related to biopsy-detected fibrosis (4-6). Our study used a high resolution USG device and the ElastPQ technique (one of the point SWE reviews) us-

ing state-of-the-art technology. The most important feature of the ElastPQ technique, along with the different LE measurement methods, is its ease of use, high accuracy of measurement, and high power to predict any liver pathology (6, 10-12).

In a recently published review, it was reported that the most common non-invasive method used in LF evaluation is LS measurement by transient elastography (13). However, non-invasive serum fibrosis markers have also been shown to be associated with LF. It was shown that SWE examination was superior to these studies due to both instantaneous changes in laboratory parameters and technical limitations of transient elastography (13). In the literature, it was not possible to obtain information on the evaluation of the group of patients ≥75 years in these ElastPQ trials that were conducted on a limited number of LF patients. In our study, the LS value obtained with the ElastPQ technique was found to be significantly higher in the elderly (≥75 years) patient group with or without liver disease. LS normal values are known to range from 3.2–5.10 kPa in healthy controls with NLF (10-16). Although these normal values have been shown to increase with age with no statistical significance, there is no information on normal values in patients of ≥75 years. In our study, the LS value obtained with the ElastPQ technique was found to be 4.75±2.34 kPa in patients of ≥75 years of age with NLF for the first time. We were informed about the results obtained from previous studies and the increase in the LS of NLF in patients of over 75 years of age, since these patients have no comparable data for LS in the literature.

In a recent study by Petta et al. (17), NAFLD fibrosis score and Fibrosis-4 (FIB-4) were closely associated with LF in the non-invasive evaluation of LS. LS was reported to be of the highest sensitivity and the highest negative predictive value. In our study, except LS and histological evaluation, other non-invasive fibrosis parameters were not evaluated. The most important reason for this was the fact that LS evaluation was superior to other non-invasive parameters in previous studies.

The age and gender groups and LS values obtained by our study and those obtained with different measurement methods in previous literature are shown in Table 4. Ling et al. (10) used the ElastPQ technique, which is the same method as our study, to investigate the LS change with age and sex in 175 healthy individuals. It was reported that LS value was higher (4.3±1.3 kPa) in the elderly patient group, but this finding was not statistically significant because of the relatively few numbers of patients (only 16 patients were over 50 years of age). Patients with an older age group who were included in the study (≥75 years of age) using the same method showed an LS value that was 0.5 kPa higher than the previous study.

NAFLD and HBV/HCV are the most common causes of CLD that are associated with impaired liver function and elevated LF (4-6). NAFLD is the most important cause of liver disease worldwide and NAFLD is present in 1 of 4 patients on average (18). Other important causes of liver disease are HBV and HCV diseases. Chronic viral hepatitis is also affected by increasing age. It has been shown that LF is greater in HCV patients who are ≥40 years of age (9). The most important parameter in the progression of both diseases is the presence and degree of LF, as the case in all liver diseases. Many studies on NAFLD have reported that 7.0 kPa can be used as a limit value in LF evaluation (F stage≥2), although different methods have been used (18). Wong et al. (19) found that ≥7.0, ≥8.7, and ≥10.3 kPa could be used as limiting values for fibrosis grade at the F2 stage, F3 stage, and F4 stage, respectively. Similarly, in HBV/HCV patients, cut-off values of approximately 7.0 kPa have been reported to be associated with LS and LF (5, 6). Only in patients with chronic viral hepatitis, a study with ElastPQ technique reported a lower LS value than the TE, with 5.7 kPa and 6.9 kPa, respectively (11). Very recently, a study by Mare et al. (5) that evaluated HBV/HCV patients with the ElastPQ technique reported that the value of 7.2 kPa independently predicted the presence of LF. The mean value of LS in this study is much higher than our study because cirrhotic patients were also included in the study. For this reason, it cannot be compared with our study. In 2018, Ferraioli et al. (3) used the ElastPQ technique for LS measurement in a study that used a similar patient group as our study; with 664 CLD patients in 4 centers (HBV/HCV patient ratio: 74.6% and NAFLD ratio: 5%). The mean age of the patients in this study was 54.8±13.5 years. The results obtained with the kPa and ElastPQ technique were reported to be 7.53 kPa (5.8–17.8 kPa) for median and IQR values, respectively. In our study, patients had a mean LS value of 7.57±3.16 kPa, 6.45±3.12 kPa and 8.68±2.76 kPa in all patients, in HBV/HCV patients, and NAFLD patients, respectively. In the CLD cases, the median and IQR were found to be 7.58 kPa (2.20–15.62 kPa), respectively. This value is very similar to the previous study. It should be noted that the present study was conducted with an equal number of NAFL and HBV/HCV patients; to avoid obtaining ≥8.0 kPa values, which would have occurred if our study would have been conducted with the patient rates from the study of Ferraioli et al. (3). In another recent study published in 2018, Conti et al. (4) performed LS measurements using the ElastPQ technique, which included a 361 CLD patients (NAFLD and HBV/HCV included). The mean age of the patients in this study was 51±17 years and the obtained values were lower than previous studies. The median LS value obtained with ElastPQ was 5.0 kPa, and the measurement of the failure rate was 1%. Also, for the first time in the present study, the limit value for LF was used as 6.2 kPa, and the LF ratio was reported to be 18.8%.

The most important limitation of our study is that our study data have not been confirmed with liver biopsy because it was an invasive procedure. Further, magnetic resonance imaging was not used in our study because it was expensive. If these tests had been done, we would have obtained more objective results. Our study would have been more meaningful if patients of ≥75 years of age were compared with a different group of patients who were <75 years of age, or if LS measurements were performed within a 5–10-year follow-up period. Recent studies have indicated that patients with pre-diabetes had significantly higher LS as compared to normal glucose metabolism subjects (20). We did not evaluate the presence of pre-diabetes in the patients included in our study. In 2016, 9 noninvasive fibrosis tests including LS values that were obtained with transient elastography were compared (BARD, which was the sum of three variables; BMI

≥28=1 point, AST/ALT ratio≥0.8=2 points, diabetes=1 point; the NAFLD fibrosis score; Fibrometer NAFLD; AST/platelet ratio index (APRI); FIB-4; FibroTest; Hepascore; FibroMeterV2G; and LS) (21). LS was reported to be the most accurate noninvasive fibrosis assessment to detect LF (21). Therefore, we used only LS examination in our study.

CONCLUSION

Our study is the first study to evaluate LS value in patients with and without liver disease over 75 years of age. As in patients aged <75 years, LF is exacerbated with increasing age and LS should be planned following the develpoment of LF in these patients. LE is an inexpensive, noninvasive, reproducible USG, which is measurable in a short amount of time, as less as <5 minutes in most centers. This test can, therefore, be used in the evaluation of LS and associated LF in patients of ≥75 years of age. People with LS of ≥7 kPa should be closely followed-up and treated.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Çukurova University (date: 06.07.2018; no: 2018–79-59).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.D.; Design – D.D.; Supervision – D.D.; Resources – D.D.; Materials – D.D., H.E.S.; Data Collection and/or Processing – D.D., H.E.S.; Analysis and/or Interpretation – D.D., H.E.S.; Literature Search – D.D., H.E.S.; Writing Manuscript – D.D.; Critical Review – D.D.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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