Liver Stiffness and Fibrosis Used as Early Diagnosis of Patients with Chronic Liver Disease in A Retrospective Cross-Sectional Study

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Abstract

Background: Chronic liver disease (CLD) is a significant health concern globally, often linked to lifestyle factors such as alcohol consumption and obesity. Early identification and intervention are crucial for preventing disease progression. Liver stiffness measurement (LSM) using transient elastography (FibroScan) is a non-invasive method for assessing liver fibrosis, but factors influencing its accuracy need further exploration. This study aims to investigate predictors of liver stiffness and fibrosis in patients with CLD. Methods: A retrospective cross-sectional study was conducted at the Kurdistan Center for Gastroenterology and Hepatology (KCGH) in Iraq from June to December 2019. Medical records of 609 CLD patients who underwent LSM by FibroScan were analyzed. Sociodemographic data, liver function tests, liver size, and fibrosis stage were collected. Multivariate linear regression analysis was performed to identify predictors of LSM. Results: Hepatitis B (47.3%) and non-alcoholic fatty liver disease (NAFLD) (17.9%) were prevalent diagnoses. Liver stiffness ranged from 2.7 to 71.6 kPa, with a mean of 8.8 kPa. Fibrosis staging revealed 38.3% at F0, 23.5% at F1, and 9.2% at F4. Significant associations were found between liver enzyme abnormality, liver size, controlled attenuation parameter (CAP), and fibrosis. Multivariate regression identified fibrosis grade (OR: 4.431), liver disease type (OR: 0.338), and liver size (OR: 3.025) as predictive of FibroScan liver stiffness values ($p<0.001$). Advanced fibrosis (F4) correlated with elevated alanine aminotransferase (ALT) levels and hepatomegaly. Conclusion: Liver stiffness, fibrosis stage, liver enzyme abnormalities, and liver size are important predictors of fibrosis in patients with CLD. Early detection and intervention are crucial in managing CLD patients, especially those with hepatitis B and NAFLD. Further research is needed to explore additional predictors and refine diagnostic algorithms for better risk stratification and treatment guidance in CLD.

Keywords: Chronic Liver Disease, FibroScan, Liver Stiffness Measurement, Predictors of Fibrosis, Non-Invasive Assessment

Significance | Early diagnosis of chronic liver disease is vital for intervention. Transient elastography aids in predicting fibrosis, guiding treatment decisions effectively.

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Introduction

Chronic liver disease is increasingly prevalent in developed countries, largely due to lifestyle factors such as excessive alcohol consumption and obesity. Early identification and diagnosis of chronic liver disease are paramount as they enable timely

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intervention and treatment, potentially slowing or even reversing disease progression. This is particularly critical for individuals with significant liver fibrosis, as it can advance to cirrhosis and other severe complications if untreated. Liver fibrosis assessment is a crucial component of managing chronic liver disease (Lai and Afdhal, 2019; Vivarelli et al., 2013).

Traditionally, liver biopsy has been the gold standard for diagnosing liver fibrosis. However, it is an invasive procedure with associated risks and is not practical for repeated use. Consequently, non-invasive and cost-effective methods, such as transient elastography (TE), also known as FibroScan, have been developed. TE measures liver stiffness (LSM) using ultrasound waves, though its accuracy can be influenced by various factors (A et al., 2022). Additionally, serum biomarkers, imaging techniques, and other biopsy substitutes are used to evaluate liver fibrosis and guide treatment decisions.

Liver stiffness measurements (LSM) are indicative of fibrosis or scar tissue in the liver. The FibroScan device offers a safe, painless procedure that can be performed in an outpatient setting (Li et al., 2018; Vivarelli et al., 2018). LSM is essential for predicting the risk of complications such as cirrhosis or liver failure (Zhang et al., 2015; Hashimoto et al., 2006). Regular LSM and other appropriate tests are recommended for patients with chronic liver disease to monitor their condition and ensure timely treatment (Abou Zaghla et al., 2021).

Several factors may predict liver stiffness and fibrosis, including age, gender, body mass index (BMI), alcohol consumption, disease severity and duration, and comorbidities such as diabetes and hypertension (Hart et al., 2010). Additional predictors include viral hepatitis, specific medications, and genetic factors. False results in LSM can occur due to severe hepatic necroinflammation, extrahepatic cholestasis, and hepatic congestion, all of which can increase liver stiffness (Zhang et al., 2019).

In obese patients, subcutaneous and prehepatic fat thickness can interfere with the transmission of shear and ultrasound waves through the liver parenchyma (Geng et al., 2016; Fernandez et al., 2015). Geng et al. (2016) demonstrated that FibroScan's diagnostic accuracy for advanced fibrosis and cirrhosis surpasses that of other non-invasive methods such as FibroTest, APRI, Forns' test, and FIB-4. Zhang et al. (2019) found that TE could effectively predict hepatic fibrosis and exclude cirrhosis in patients with chronic hepatitis B (CHB) and non-alcoholic fatty liver disease (NAFLD). A study by Salkic et al. (2014) suggested that a diagnostic algorithm incorporating TE was effective in identifying patients with chronic liver disease who traditional methods might miss.

Notably, a high percentage of individuals with normal liver enzymes but elevated liver stiffness may still be at risk for chronic liver disease, warranting further evaluation and monitoring. Incorporating transient elastography into a diagnostic algorithm in a community setting could effectively identify at-risk patients who might otherwise go undetected (Harman et al., 2015; Shi et al., 2013). Overall, TE has proven to be a valuable diagnostic tool for detecting fibrosis and cirrhosis in patients with liver disease (Geng et al., 2016; Elzawawy et al., 2018).

The aim of this study is to utilize FibroScan to measure liver tissue stiffness and identify factors associated with liver stiffness or fibrosis.

Material and methods

Study Design

This retrospective cross-sectional study was conducted from June 1, 2019, to December 1, 2019, at the Kurdistan Center for Gastroenterology and Hepatology (KCGH) in Sulaymaniyah province, northern Iraq. KCGH, the largest specialized center in the region, receives referrals from various areas, particularly northern Iraq.

Inclusion and Exclusion Criteria

A comprehensive review was performed on the medical records of liver disease patients treated at KCGH during the study period. The inclusion criteria encompassed all chronic liver disease patients aged 18 years and above, regardless of gender, who underwent liver stiffness measurement (LSM) via transient elastography (TE) at KCGH. Exclusion criteria included patients with incomplete medical charts, those who had experienced hepatic complications prior to undergoing FibroScan, pregnant individuals, and those with invalid LSMs after ten attempts (Figure 1).

Data Collection Procedures

Experienced doctors retrospectively collected data on socio-demographic characteristics, baseline liver disease, liver function tests, liver size, liver stiffness, and fibrosis from the patients' medical records.

Liver Stiffness Measurements (LSMs)

Medical reports of TE (FibroScan examinations) performed at KCGH between June and December 2019 were meticulously reviewed. Under sonographic image control, patients were examined in a dorsal decubitus position. Over an average duration of five minutes, the tip of the M probe or the XL probe (for obese patients) was placed on the patient's skin and moved over the right lobe of the liver. A segment of liver tissue with a thickness of six cm or more, free of major vessels, was selected to perform at least ten successful attempts to obtain valid LSMs.

The number of successful measurements was divided by the total number of attempts to determine the success rate. The median of ten values (in kilopascals, kPa) was calculated. The ratio of the interquartile range (IQR) of liver stiffness to the median (IQR/M) was reported. An LSM was considered valid if there were ten or more successful measurements, the success rate was sixty percent or above, and the IQR/median ratio was less than 30%. If any of

these criteria were not met, the LSM was deemed invalid. The results were reported in kilopascals (kPa) (Jung et al., 2018).

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Committee of Iraqi Board of Medical Specialization (Ref. No. 11, 5th October 2016). Authorization to access patient medical records was granted by the Kurdistan Center for Gastroenterology and Hepatology (KCGH) in Sulaymaniyah (Ref. No. 9192, 9th October 2016).

Statistical Analysis

The data were analyzed using SPSS software version 20. Descriptive analysis, including frequency and percentages, was conducted. For bivariate analysis, ANOVA was utilized to compare means of continuous variables, while the Chi-square test examined associations between categorical variables. Multivariate linear regression, using stepwise backward elimination and including only statistically significant variables, was employed to identify predictors of liver stiffness. Statistical significance was set at a p-value of less than 0.05 for all variables.

Results

Sociodemographic Characteristics

A total of 609 patients were included in the study. The mean age (±SD) of patients was 45.7 (± 8.2) years, with an age range of 21 to 65 years. Over half of the patients (54.4%) were male, and the majority (58.6%) were aged 45 years or less (Table 1).

Baseline Liver Disease Diagnosis

The most common diagnoses among the patients were Hepatitis B (47.3%) and non-alcoholic fatty liver disease (NAFLD) (17.9%) (Table 2).

Hepatomegaly and Alanine Aminotransferase (ALT) Levels

Routine physical examinations and radiological tests confirmed hepatomegaly in 117 patients (19.2%), while 6 patients (1.0%) presented with a shrunken liver. The mean (±SD) serum ALT level was 47.1 (±22.5) IU/dL, with values ranging from 20 to 120 IU/dL. Elevated ALT levels were observed in 283 patients (46.5%).

Liver Stiffness and Fibrosis

The mean liver stiffness (±SD) was 8.8 (±9.2) kPa, with a range from 2.7 to 71.6 kPa. The distribution of patients across fibrosis stages was as follows: 233 patients (38.3%) in the F0 category, 143 patients (23.5%) in the F1 category, and the smallest group, 56 patients (9.2%), in the F4 category. One-way ANOVA revealed a statistically significant difference in liver stiffness among the different fibrosis groups ($F(4, 604) = 358.3$, $P < 0.001$) (Table 3).

Association of Fibrosis with Liver Enzyme Abnormality, Liver Size, and Controlled Attenuation Parameter (CAP) Measurement

Among patients with F4 fibrosis, 64.3% (n=36) had abnormal ALT levels, 55.5% (n=31) had hepatomegaly, and 10.7% (n=6) had a shrunken liver. The Chi-square test showed a statistically significant association between fibrosis and liver enzyme abnormality ($P=0.001$) as well as liver size ($P<0.001$). The average CAP measurement was 251.0 ± 42.9 dB/m, with a range from 180 to 400 dB/m. One-way ANOVA indicated a statistically significant difference in CAP measurement among the fibrosis groups ($F (4, 604) = 2.69$, $P=0.03$) (Table 3).

CAP Measurement, Fibrosis Score, and Disease Type

There was a statistically significant association between fibrosis score and the type of liver disease ($\chi2=56.85$, $P<0.001$). Specifically, 11 Hepatitis B and 13 NAFLD patients were in the F4 fibrosis category (Table 4).

Predictors of Liver Stiffness

Multivariate analysis using stepwise backward elimination included variables that were statistically significant at $P=0.049$. The analysis identified fibrosis grade (odds ratio [OR]: 4.431; 95% confidence interval [CI]: 4.012-4.923; $P<0.001$), type of liver disease (OR: 0.338; 95% CI: 0.101-0.615; $P=0.019$), and liver size (OR: 3.025; 95% CI: 1.707-4.336; $P<0.001$) as significant predictors of liver stiffness as measured by FibroScan (Table 5).

Discussion

This study identified Hepatitis B and non-alcoholic fatty liver disease (NAFLD) as the predominant causes of chronic liver disease (CLD) in the Kurdish population of Iraq, consistent with findings by Bondini and Younossi (2006). The etiology of CLD can vary significantly depending on the region and population studied, as demonstrated by Jadoo et al. (2021). In contrast, NAFLD is the leading cause of CLD in the United States across all ethnic groups, followed by alcoholic liver disease, as reported by Mokdad et al. (2014) and Vaz et al. (2020). In other Western countries, there is a rising prevalence of alcoholic liver disease, NAFLD, and Hepatitis C as causes of CLD (Setiawan et al., 2016).

The relatively low prevalence of Hepatitis C and alcoholic steatohepatitis (ASH) in the Kurdish population may be attributed to cultural and religious norms that discourage alcohol consumption and the use of injected drugs. Our study found that less than half (46.5%) of the cases had abnormal ALT levels, with only a small percentage showing hepatomegaly or a shrunken liver. Elevated ALT levels are typically indicative of liver damage or disease; however, studies have shown that ALT levels can fluctuate in patients with CLD or cirrhosis (Kaplan, 2002).

Lai et al. (2007) highlighted that ALT levels might remain normal in some individuals with liver disease or mild liver damage. These findings imply that ALT levels alone may not be sufficient for accurately diagnosing and monitoring liver disease. Other signs, symptoms, and liver function tests should be considered to confirm or rule out liver disease, even in the absence of abnormal ALT levels (Kaplan et al., 2000; Liu et al., 2014; Lai et al., 2007; Salman et al., 2022).

Table 1. demographic characteristics of patients with liver disease

Demographic characteristic	Categories	N (%)
Age	≤ 45 years	357 (58.6)
	> 45 years	252 (41.4)
Sex	Male	331 (54.4)
	Female	278 (45.6)
Residency	Urban	358(58.8)
	Rural	251(41.2)

Table 2. the baseline liver disease diagnosis of patients (n=609)

NO.	Liver disease	N	%
1	Hepatitis B	288	47.3
2	NAFLD	109	17.9
3	Hepatitis C	84	13.8
4	Chronic cholestasis	34	5.6
5	Alcoholic steatohepatitis (ASH)	12	2.0
6	Others	82	13.4

Table 3. Liver stiffness and fibrosis score in one-way ANOVA test (n=609)

Fibrosis score	Frequency (%)	LSM kPa	F-statistics
		Mean ±SD (range)	
F0	233 (38.3)	4.4±0.7 (2.7-7.1)	F (4,604) =358.3, P<0.001
F1	143 (23.5)	6.1±0.5 (5-7.6)	
F2	116 (19.1)	8.2±1.2 (7.0-11.7)	
F3	61 (10.0)	12.0±2.9 (8.0-19.6)	
F4	56 (9.2)	31.9±16.2(11.0-71.6)	

Table 4. CAP measurement, liver enzyme abnormality and liver size by fibrosis

Fibrosis	Liver enzyme (ALT), n (%)		Liver size, n (%)			CAP measurement, dB/m
	Normal N(%)	Abnormal N(%)	Normal N(%)	Hepatomegaly N(%)	Shrunken N(%)	Mean ±SD
Observation	326(53.5)	283(46.5)	486(79.8)	117(19.2)	6(1.0)	
F0(n=233)	138(59.2)	95(40.8)	218(93.6)	15(6.4)	0	244.3±39.5
F1(n=143)	80(55.9)	63(44.1)	124(86.7)	19(13.3)	0	254.5±46.4
F2(n=116)	66(56.9)	50(43.1)	99(85.3)	17(14.7)	0	252.1±41.0
F3(n=61)	22(36.1)	39(63.9)	26(42.6)	35(57.4)	0	258.5±45.3
F4(n=56)	20(35.7)	36(64.3)	19(33.9)	31(55.4)	6(10.7)	259.2±45.6
P-Value	0.001		P<0.001**			F (4,604) =2.69 P=0.03

**The chi-square test was done only for normal and hepatomegaly liver sizes

Table 5. Fibrosis score by disease

Diagnosis	Fibrosis score N (%)					Total N (%)
	F0	F1	F2	F3	F4	
Hepatitis B	140(23.0)	62(9.9)	58(9.5)	17(2.8)	11(1.8)	288 (47.3)
NAFLD	34(5.6)	26(4.3)	20(3.3)	16(2.6)	13(2.1)	109(17.9)
Hepatitis C	33(5.4)	18(3.0)	15(2.5)	11(1.8)	7(1.1)	84(13.8)
Chronic cholestasis	2(0.3)	5(0.8)	10(1.6)	8(1.3)	9(1.5)	34(5.6)
ASH	5(0.8)	4(0.7)	1(0.2)	0(0)	2(0.3)	12(2.0)
Others	19(3.1)	28(4.6)	12(2.0)	9(1.5)	14(2.3)	82(13.4)
$\chi 2$=76.5, P<0.001						

Table 6. Factors affecting liver stiffness measurements determined by transient elastography (fibroscan) (n=609)

Predictor variable	Coefficient	Standard error	t	P-value	95% CI
Fibrosis grade	4.431	0.221	19.430	P<0.001	4.012-4.923
Type of Liver diseases	0.338	0.204	2.351	0.019	0.101-0.615
Liver size	3.025	0.742	4.405	P<0.001	1.707-4.336

Moreover, ALT levels are less useful for diagnosing and prognosing Hepatitis C virus (HCV) infections compared to Hepatitis B virus (HBV) infections. HCV infections often cause less liver inflammation and damage, resulting in less elevated ALT levels. Many individuals with HCV infection are asymptomatic and may have normal or mildly elevated ALT levels, even when hepatic histologic lesions are present on liver biopsy (Yan et al., 2019; Liaw and Chu, 2009). This underscores the need for additional diagnostic tests, such as HCV RNA levels, to monitor HCV infection effectively.

NAFLD and non-alcoholic steatohepatitis (NASH) can also present with normal ALT levels. Both conditions can progress to more severe liver diseases, such as cirrhosis or liver cancer, if untreated. The histologic severity of these conditions does not always correlate with ALT levels, necessitating liver biopsy or imaging studies for accurate diagnosis and monitoring (Liu et al., 2014; Burke et al., 2004).

Our investigation revealed that liver stiffness, liver enzyme abnormality, liver size, and the various causes of liver disease were significantly associated with the degree of liver fibrosis. The mean liver stiffness (8.8 kPa) showed significant variation across different fibrosis levels, with the majority of chronic cholestasis cases progressing to advanced fibrosis (F4). The mean Controlled Attenuation Parameter (CAP) measurement also varied significantly among fibrosis levels. These findings suggest that liver stiffness, assessed by CAP, along with liver enzyme abnormality, liver size, and the variety of liver disease causes, can serve as valuable predictors for assessing liver fibrosis severity (Jiang et al., 2022; Ramírez-Vélez et al., 2022).

Graupera & Lammert (2018) reported a liver stiffness measurement of 6.9 kPa among 780 Australian chronic hepatitis C (CHC) patients, noting that 16.5% were at risk of advanced fibrosis (≥12.5 kPa), despite 8.5% lacking laboratory signs of advanced liver disease. This discrepancy may result from differences in patient populations. Our study included a mix of liver diseases, potentially leading to higher proportions of advanced liver fibrosis and elevated liver stiffness measurements. Variations in measurement methods and patient characteristics might also account for these differences (Lee et al., 2021).

In general, liver stiffness measurements above 12.5 kPa indicate a risk of "advanced fibrosis." Graupera & Lammert's (2018) finding that 8.5% of patients had no laboratory indicators of advanced liver disease despite elevated liver stiffness measurements warrants further investigation (Pang et al., 2014). Kumar et al. (2013) identified cut-off values for liver stiffness measurements to distinguish between fibrosis stages, which may differ from other studies or clinical practices. Ferraioli et al. (2013) also found significant differences in liver stiffness measurements among fibrosis stages in chronic hepatitis patients, identifying optimal cut-off values for predicting advanced fibrosis and cirrhosis.

In our study, the distribution of liver stiffness measurements was 23.5% for fibrosis stage 1, 19.1% for stage 2, 10.0% for stage 3, and 9.2% for stage 4. These values are lower than those reported by Raizner et al. (2017), who found that 33.7% of children and young adults undergoing liver stiffness measurements had fibrosis stages 3 and 4. Differences in patient populations and comorbidities may explain the variation in advanced fibrosis prevalence.

Lallukka et al. (2017) found that baseline liver fat was an independent predictor of increased liver stiffness in Finnish subjects with NAFLD, indicating that higher liver fat levels might be associated with increased liver stiffness. However, the relationship between liver fat, liver stiffness, and fibrosis stage can vary depending on the patient population and other factors such as disease etiology and comorbidities (Xi et al., 2021).

In our study, multivariate analysis identified fibrosis stage, type of liver disease, and liver size as significant predictors of liver stiffness. This aligns with Kumar et al. (2013), who found a significant correlation between liver stiffness measurement and fibrosis stage in NAFLD cases. Similarly, Sporea et al. (2010) reported a direct correlation between liver stiffness measurements and fibrosis in HCV patients.

Seppelt et al. (2022) demonstrated that measuring liver diameter in the anterior-posterior direction had a high correlation in distinguishing healthy from pathological liver changes, with statistically significant results. Mena et al. (2022) found that individuals with HBV had a higher likelihood of developing fibrosis, suggesting the need for antiviral management. Independent predictors of elevated liver stiffness included at-risk alcohol consumption, older age, high BMI, and elevated ALT levels (Graupera and Lammert, 2018; Wong et al., 2021).

This study has limitations, such as being a single-center study, which may limit the generalizability of the results to the broader population. However, the relatively large sample size enhances the robustness of the findings. Further research involving multiple centers and a more diverse patient population is needed to validate these findings and provide a more comprehensive understanding of CLD in different populations.

Conclusion

This study provides valuable insights into the epidemiology and clinical characteristics of chronic liver disease (CLD) in the Kurdish population of Iraq, with chronic hepatitis B and non-alcoholic fatty liver disease (NAFLD) identified as the most prevalent causes. The findings underscore the utility of liver stiffness measurements (LSM) using FibroScan, which revealed an average LSM of 8.8 kPa among the patients. There was a significant association between liver stiffness and both liver enzyme abnormalities (ALT) and liver

size, emphasizing the importance of these parameters in the clinical assessment of liver disease. The stage of fibrosis, type of liver disease, and liver size emerged as independent predictors of liver fibrosis, underscoring the need for comprehensive evaluation of these factors in managing patients with CLD. Regular evaluation using non-invasive methods like FibroScan is recommended for early detection and intervention, which can potentially slow disease progression and improve patient outcomes. Further research is essential to identify additional predictors of liver stiffness and fibrosis, enhancing the understanding of disease mechanisms and leading to more effective treatment strategies. This study highlights the critical role of FibroScan in the non-invasive assessment of liver stiffness in patients with CLD, advocating for its regular use and the importance of timely and effective care based on comprehensive diagnostic evaluations.

Author contributions

A.S.M. led the study's conceptualization, design, data analysis, and manuscript preparation. H.A.H. handled data collection, patient recruitment, and findings interpretation. S.A.A.J. assisted with data analysis and manuscript writing. M.H.A. ensured clinical relevance. L.F.H. oversaw study protocol and ethical considerations. M.R.H. managed data extraction and quality assurance.

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Competing financial interests

The authors have no conflict of interest.

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