Spleen Stiffness Measurement as a Predictor of Advanced Liver Fibrosis in Chronic Hepatitis B Patients

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ABSTRACT

Background: *Chronic hepatitis B is a viral infection that may progress to liver fibrosis. Progressive fibrosis increases portal pressure, leading to elevated spleen stiffness. Although inflammatory reactions and mechanical cholestasis affect liver stiffness, the effect is comparatively limited. Therefore, this study aims to analyze spleen stiffness as a noninvasive marker of liver fibrosis and evaluate the correlation between spleen and liver stiffness.*

Methods: *A retrospective cross-sectional study was performed on chronic hepatitis B patients. Fibroscan was used to measure liver and spleen stiffness. Liver fibrosis was categorized as nonsignificant (F0–F1), significant (F2–F3), and advanced (F4). Correlations between spleen stiffness and liver fibrosis stages were assessed using Spearman's test, with $p < 0.05$ considered statistically significant.*

Results: *The results showed that 127 patients were eligible for analysis, predominantly male (71.7%), with a mean age of 46.4 ± 9.8 years. The median spleen and liver stiffness were 25.5 kPa (range 5.6–100) and 9.4 kPa (range 2.4–75), respectively. Moreover, spleen stiffness had a positive correlation with liver stiffness (Spearman $r = 0.503$; $p < 0.001$) and liver fibrosis stages (Spearman $r = 0.479$; $p < 0.001$). The optimal cutoff for spleen stiffness in predicting advanced fibrosis was 28 kPa, with an area under the receiver operating characteristic curve(AUROC) of 0.816, sensitivity of 0.739, and specificity of 0.753.*

Conclusion: *Spleen stiffness is significantly correlated with liver fibrosis severity. A cutoff of 28 kPa was identified for advanced fibrosis, suggesting spleen stiffness measurement serves as a promising alternative to biopsy.*

Keywords: *Chronic Hepatitis B, Fibroscan, Liver Fibrosis, Liver Stiffness, Spleen Stiffness*

ABSTRAK

Latar Belakang: *Hepatitis B kronis merupakan infeksi virus yang dapat menyebabkan fibrosis hati, dimana jika berkelanjutan akan meningkatkan tekanan porta. Kemudian, dapat mengakibatkan peningkatan pada kekakuan limpa. Kekakuan hati dipengaruhi oleh reaksi inflamasi dan kolestasis mekanis, sedangkan proses tersebut lebih sedikit pengaruhnya pada kekakuan limpa. Penelitian ini bertujuan untuk menganalisis kekakuan limpa untuk pemeriksaan fibrosis hati dan korelasi antara kekakuan limpa dan kekakuan hati.*

Metode: *Penelitian desain retrospective cross-sectional dilakukan pada pasien hepatitis B kronis. Kekakuan hati dan limpa subjek penelitian diukur menggunakan Fibroscan. Derajat fibrosis hati dikelompokkan menjadi fibrosis nonsignifikan (F0-F1), fibrosis signifikan (F2-F3), dan fibrosis tingkat lanjut (F4). Data dianalisis dengan uji korelasi Spearman yang signifikan jika p < 0,05 antara kekakuan limpa dan derajat fibrosis hati.*

Hasil: *127 pasien terlibat dalam penelitian ini didominasi oleh laki-laki (71,7%) dengan rerata usia 46,39 ± 9,791 tahun. Median kekakuan limpa sebesar 25,5 (5,6 – 100) kPa. Median kekakuan hati sebesar 9,4 (2,4 – 75) kPa. Kekakuan limpa berkorelasi positif dengan kekakuan hati (Spearman r = 0,503; p < 0,001). Korelasi antara kekakuan limpa dan derajat fibrosis hati juga signifikan (Spearman r = 0,479; p < 0,001). Batas kekakuan limpa untuk fibrosis hati tingkat lanjut sebesar 28 kPa (AUROC 0.816, sensitivitas 0.739, dan spesifisitas 0.753).*

Kesimpulan: *Terdapat hubungan signifikan antara kekakuan limpa dan fibrosis hati. Batas kekakuan limpa untuk fibrosis hati tingkat lanjut sebesar 28 kPa. Hal ini menunjukkan bahwa kekakuan limpa dapat menjadi alternatif yang menjanjikan untuk biopsi.*

Kata kunci: *Hepatitis B Kronis, Fibroscan, Fibrosis Hati, Kekakuan Hati, Kekakuan Limpa*

INTRODUCTION

Chronic hepatitis B is one of the significant public health concerns in Indonesia due to the ability to progress into advanced liver fibrosis and cirrhosis. Universally, approximately 30% of cirrhosis cases and 50% of hepatocellular carcinoma are attributed to chronic hepatitis B infection.[1] In 2019, the World Health Organization (WHO) estimated that around 296 million individuals worldwide were diagnosed with chronic hepatitis B. Moreover, approximately 1.5 million new cases occur each year, with an estimated 820,000 deaths, mainly due to cirrhosis and hepatocellular carcinoma.[2] In Indonesia, the average prevalence is 2.1%, categorized as an intermediate prevalence level, underscoring the need for improved monitoring and management of the disease.[3]

Liver fibrosis is characterized by excessive deposition of scar tissue in response to chronic liver injury. Over time, progressive fibrosis increases liver stiffness and leads to portal hypertension, which is one of the several complications. When left untreated, portal hypertension may further advance to cirrhosis or liver failure.[4] In general, the gold standard for assessing liver fibrosis is an invasive procedure, namely, biopsy.[5] However, due to the limitations, noninvasive methods such as transient elastography (TE) have become more popular as an alternative. TE is used for liver stiffness measurement (LSM), which is a marker of fibrosis progression.[6] Despite the benefits, TE has limitations, including limited patients accessibility and reduced accuracy in conditions such as obesity, ascites, or pregnancy.[7]

In recent years, spleen stiffness measurement (SSM) has been considered a promising noninvasive marker for assessing liver disease progression. This approach is supported by the close anatomical connection between the spleen and the liver through the portal system, as a congested and fibrotic spleen is often found in portal hypertension.[8] Although LSM is a representation of liver fibrosis and inflammation, SSM directly reflects the extent of portal hypertension. LSM is also largely modulated by inflammatory activity, antiviral therapy, and mechanical cholestasis, in contrast to spleen stiffness, which is less affected by these processes.[9, 10] In cases where LSM is compromised, measuring spleen stiffness may serve as an alternative to predict advanced liver fibrosis in chronic hepatitis B patients.

Despite the potential, studies on spleen stiffness as a liver fibrosis marker are limited, specifically in Indonesia. Therefore, this study aims to investigate the correlation between spleen stiffness and advanced liver fibrosisand the ability to predict advanced liver fibrosis in chronic hepatitis B patients enrolled in Dr Soetomo Regional Hospital, Surabaya. The results will also contribute to developing a noninvasive diagnostic approach to assess liver fibrosis and improve patients outcomes. SSM was evaluated as a predictor of advanced liver fibrosis without clinical decompensation.

METHODS

Patients

The study was conducted in the Division of Gastroenterology and Hepatology, Dr. Soetomo Regional Hospital, Surabaya, from January 2023 to December 2023. A total of 229 patients were enrolled, as shown in Figure 1.

The inclusion criteria include patients (1) between the ages of 20 and 60 years old, (2) both men and women, (3) diagnosed with chronic hepatitis B based on the *Perhimpunan Peneliti Hati Indonesia* (PPHI) 2017, and (4) had received the Fibroscan procedure. Meanwhile, exclusion criteria include

(1) being infected with other hepatitis viruses, (2) acute hepatitis, (3) hepatocellular carcinoma, (4) autoimmune liver diseases, (5) decompensated liver cirrhosis, (6) alcoholic liver disease, (7) non-alcoholic liver disease, (8) systemic lupus erythematosus (SLE), (9) rheumatoid arthritis (RA), (10) scleroderma, (11) polycythemia vera, (12) chronic myeloid leukaemia, (13) schistosomiasis, (14) myelofibrosis with myeloid metaplasia, (15) obesity, (16) ascites, and (17) pregnancy. All patients had serum-positive HBsAg for at least 6 months.

Patients age was limited to 20–60 years old, considering the age-related variability in liver and spleen stiffness as well as age-associated comorbidities.

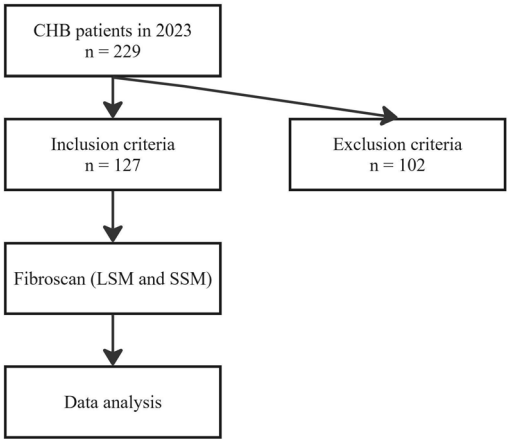

Figure 1. Flow chart

Study design

This retrospective cross-sectional study, conducted at Dr Soetomo Regional Hospital, Surabaya, between January and December 2023, assessed spleen stiffness as a predictor of advanced liver fibrosis in chronic hepatitis B patients.

Data collection

Data were collected through the medical records and Fibroscan results. The Fibroscan assesses the liver and spleen stiffness in kilopascals (kPa) and follows established protocols to ensure accurate and consistent measurement.

Fibroscan Procedure

TE was performed using Fibroscan. Measurement was taken at the seventh to ninth intercostal spaces on the right side for liver stiffness and at the ninth to eleventh intercostal spaces on the left side for spleen stiffness. The individual patient was subjected to a minimum of ten valid measurement for each organ, and the median value was recorded as the final stiffness score. Liver stiffness cut-off values were based on thresholds for different fibrosis stages, namely nonsignificant (F0 and F1), significant (F2 and F3), and advanced (F4). Both liver and spleen stiffness were expressed in kilopascals (kPa). The probe was placed vertically on the skin surface, ensuring that any large blood vessel structures did not hinder the liver and spleen area. Based on the manufacturer recommendations, ten valid measurement were performed on each patient, and the median value was accepted as the representative.[11]

Statistical Analysis

Data were analyzed using descriptive and inferential statistical methods. Descriptive statistics showed the demography and clinical characteristics, which include age, gender, BMI, haemoglobin, leukocytes, thrombocytes, bilirubin, liver function tests (ALT, AST), fibrosis stages, and the therapy received. ANOVA one-way, Kruskal-Wallis, and Chi-square test were used to assess the correlation between gender, age, BMI, AST, ALT, haemoglobin, leukocyte, thrombocyte, direct bilirubin, total bilirubin, and liver fibrosis stages. A significance level of $p < 0.05$ was set for the previously mentioned tests. Spearman correlation analysis assessed the correlation between spleen and liver stiffness, with a significance level of $p < 0.001$. A post-hoc analysis was also conducted between spleen stiffness and liver fibrosis stages with a significance level of $p < 0.05$. Finally, a diagnostic value test was conducted to acquire the AUROC, cut-off, sensitivity, and specificity of spleen stiffness to predict liver stiffness. All analyses were performed using the Statistical Package for the Social Sciences (SPSS).

Ethical Considerations

The Dr. Soetomo Regional Hospital Ethics Committee approved this study (2506/119/3/X/2023). Confidentiality of patients was strictly maintained, and all data were anonymized and used solely for this study.

RESULTS

The 127 patients included were diagnosed with chronic hepatitis B and subjected to Fibroscan assessment without liver cirrhosis. Among the 127 patients, 30 had nonsignificant fibrosis, 51 had significant fibrosis, and 46 had advanced fibrosis. Furthermore, 67 had received treatment, and 60 were naïve patients. From the 67 patients who have received

treatment, 59 were given tenofovir, 8 were given entecavir, and the mean for the treatment duration was 9,07 ± 3,7 months. Several patients were found to have comorbidities, including 45 with fatty liver, 10 with type 2 diabetes mellitus, 6 with hypertension, and 2 with dyslipidemia. The patients clinical characteristics are shown in **Table 1.**

Data are presented as n (%), mean ± standard deviation, or median (range). BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, haemoglobin; WBC, white blood cell; D-BIL, direct bilirubin; T-BIL, total bilirubin.

Correlation between patients characteristics and liver fibrosis

The patients were then grouped into fibrosis stages, and **Table 2** shows each group characteristics as well as the correlation value between each variable and liver stiffness. Variables with significant p-values include sex, age, AST, ALT, and thrombocyte (p<0,05). These variables were then analyzed in a multivariate analysis, as shown in **Table 2.**

Table 1. Characteristics of the 127 patients

Characteristic	Value
Male, n (%)	91 (71,7)
Age, y	49,5 (20–60)
BMI, kg/m^2	22,389 ± 2,718
AST, U/L	30 (6–696)
ALT, U/L	29 (10–777)
Hb, g/dL	13,398 ± 2,423
WBC, 10^3/µL	6,57 (2,15–24,43)
Thrombocyte, 10^3/µL	223,5 (5,05–802)
D-BIL, mg/dL	0,3 (0,07–14,43)
T-BIL, mg/dL	0,705 (0,2–21)
Liver stiffness, kPa	9,4 (2,4–75)
Spleen stiffness, kPa	25,5 (5,6–100)
Therapy status, n (%)	
Treatment-naive	60 (47,2)
Received antiviral therapy	67 (52,8)
Entecavir	8 (6,3)
Tenofovir	59 (93,7)
Antiviral Therapy Duration (months)	9,07 ± 3,7
Comorbidities, n (%)	
Type 2 diabetes mellitus	10 (7,9)
Hypertension	6 (4,7)
Dyslipidemia	2 (1,6)
Fatty liver	45 (35,4)

Data are presented as n (%), mean ± standard deviation, or median (range). BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, haemoglobin; WBC, white blood cell; D-BIL, direct bilirubin; T-BIL, total bilirubin.

Table 2. Characteristics Based on Fibrosis Stage

Variable	Fibrosis Stage			p-value
	Nonsignificant	Significant	Advanced	
Sex (M)[c]	16 (53,3%)	37 (72,5%)	30 (88,2%)	0,021*
Sex (F)	14 (46,7%)	14 (27,5%)	4 (11,8%)	
Age (y)[b]	41,73 ± 11,65	46,67 ± 8,618	49,13 ± 8,73	0,015*
BMI (kg/m^2)[a]	21,894 ± 2,385	23,212 ± 2,7	21,8 ± 2,762	0,066
AST (U/L)[b]	23 (16–77)	29,5 (17 - 282)	43 (6 - 696)	0,000*
ALT (U/L)[b]	22,5 (12 - 94)	28 (11 - 561)	38 (10 - 777)	0,005*
Hb (g/dL)[b]	13,7 ± 2,071	13,702 ± 2,027	12,884 ± 2,93	0,186
WBC (10^3/µL)[b]	7 (4,42 - 10.73)	6,29 (2,7 - 24,43)	6,48 (2,15 - 13,26)	0,290
Thrombocyte (10^3/µL)[b]	271,481 ± 70,934	220,74 ± 120,853	170,96 ± 95,677	0,000*
D-BIL (mg/dL)[b]	0,3 (0,7 - 2,6)	0,3 (0,1 - 2,09)	0,4 (0,07 - 14,43)	0,288
T-BIL (mg/dL)[b]	0,87 (0,36 - 3,7)	0,66 (0,22 - 4,31)	0,8 (0,2 - 21)	0,184

[a]ANOVA *one-way test,* [b]*Kruskal-Wallis test*, [c]*Chi-square test*, *significant if p<0,05
Correlation between spleen stiffness and liver stiffness

Table 3. Spearman correlation analysis between spleen stiffness and liver stiffness

		Liver stiffness
Spleen stiffness	**p**	Correlation coefficient (r**)**
	0,00**0**	0,50**3**

Table 3 shows the result of the statistical analysis (Spearman test), indicating a correlation between spleen and liver stiffness (p<0,001, r = 0,503). The higher the SSM, the greater the liver stiffness. The results were then re-analyzed by testing the difference between the three groups, namely nonsignificant, significant, and advanced fibrosis, using the *Kruskal-Wallis* test. The test proceeded with the post-hoc sub-analysis when p<0,05 as shown in **Table 4.**

Table 4 shows a significant difference between spleen stiffness in the three groups of liver fibrosis degree (p = 0.000). Therefore, post-hoc analysis was continued using the Mann-Whitney test. The results showed that spleen stiffness was significantly different in the nonsignificant fibrosis group compared to the advanced (p = 0.000) and between the significant group compared to advanced fibrosis (p = 0.000). The nonsignificant and significant fibrosis groups were also significantly different compared to advanced fibrosis (p = 0.000). On the other hand, the nonsignificant and significant fibrosis groups did not show a significant difference (p>0.05).

Multivariate Analysis between Significant Variables and Liver Stiffness

Variables significant to the degree of liver fibrosis were further analyzed by multivariate logistic regression test, where the degree of liver fibrosis was divided into two groups, namely advanced and non-advanced fibrosis (nonsignificant and significant). The multivariate test results in **Table 5** show that spleen stiffness significantly influenced the degree of liver fibrosis (p<0.05, OR 1.036). Therefore, each 1 kPa rise in SSM increases the risk of advanced fibrosis by 3.6%.

Diagnostic Value of Spleen Stiffness to Predict Advanced Liver Fibrosis

Diagnostic tests (AUROC, cutoff, sensitivity, and specificity) were performed to determine the ability of spleen stiffness to predict liver fibrosis. For the diagnostic test, the degree of liver fibrosis was divided into two groups, namely, the advanced and non-advanced (nonsignificant and significant), as shown in **Table 6.**

Table 4. Post-Hoc Sub-Analysis Between Spleen Stiffness And Liver Fibrosis Stages

Variable	P value[a]	Liver Fibrosis Stage			
		Nonsignificant vs Significant[b]	Nonsignificant vs Advanced[b]	Significant vs Advanced[b]	Nonsignificant, Significant vs Advanced[b]
Spleen stiffness	0,000*	0,732	0,000	0,000	0,000

[a]*Kruskal-Wallis test*, [b]*Mann-Whitney test*. *Significant if p<0,05

Table 5. Multivariate analysis of variables that impact liver fibrosis

Variable	P value	Odds Ratio
Sex	0,382	1,652
Age	0,345	1,025
AST	0,132	1,007
ALT	0,911	1,000
Thrombocyte	0,060	0,996
Spleen stiffness	0,002	1,036

Table 6. Diagnostic Value of Spleen Stiffness to Predict Advanced Liver Fibrosis by the AUROC

Parameter	Advanced vs Nonsignificant–Significant
AUROC	0,816
95% CI	0,740 – 0,893
Cutoff, kPa	28
Sensitivity	0,739
Specificity	0,753

Based on **Table 6,** the AUROC of spleen stiffness to predict the degree of advanced liver fibrosis was 0.816. The optimal cutoff of spleen stiffness for advanced liver fibrosis was 28 kPa. In addition, the sensitivity and specificity of spleen stiffness were 0.739 and 0.753, respectively.

DISCUSSION

In this study, a significant positive correlation was found between spleen stiffness and the degree of liver fibrosis in the subjects with moderate strength ($p<0.001$; $r = 0.479$), implying that spleen stiffness can indirectly predict the degree of liver fibrosis. In a similar study conducted in China, a significant positive correlation was established between spleen and liver stiffness in all patients from the group of nonsignificant fibrosis degree to advanced fibrosis degree ($p<0.001$; $r = 0.081$).[12] Another study in China using the TE found that both LSM and SSM were effective in predicting decompensated cirrhosis in viral hepatitis ($p<0.001$), suggesting spleen stiffness can be a predictor of liver fibrosis.[13] Sound touch elastography (STE) examination method also found similar results, showing that spleen stiffness can be one way to assess liver fibrosis.[14] Another study using the magnetic resonance elastography (MRE) method reported a significant correlation between spleen stiffness and the degree of liver fibrosis ($p<0.001$; $r=0.63$).[15] Therefore, the higher the spleen stiffness value, the greater the degree of liver fibrosis.

The strength of the correlation observed in this study was supported by the results of post hoc analysis, which showed a statistically significant difference in the advanced liver fibrosis degree group compared to other groups. However, liver fibrosis is influenced by multiple factors that were not fully assessed in this study, including the effects of chronic hepatitis B therapy, variations in disease stage, and other extracellular matrix components. Therefore, spleen stiffness as a single marker is sufficiently powerful to predict the degree of advanced liver fibrosis in chronic hepatitis B patients.

Multivariate analysis further confirmed spleen stiffness as a significant variable ($p = 0.002$) for the degree of liver fibrosis with an Odds Ratio of 1.036. This result shows that each incremental increase in spleen stiffness is associated with a 1.036-fold higher risk of advanced liver fibrosis. Another study conducted in India found that spleen elastography had higher sensitivity and specificity to predict VE.[16] Three independent factors were found to play a role in identifying liver cirrhosis, namely age, platelet count, and spleen size.[17] In another study, spleen stiffness was identified as the only independent factor affecting clinical decompensation in cirrhotic patients.[18] These results confirm that spleen stiffness as a single marker is sufficiently strong to predict the degree of advanced liver fibrosis in chronic hepatitis B patients.

In this study, the AUROC was 0.816, and the cutoff of spleen stiffness to predict advanced liver fibrosis was 28 kPa. Meanwhile, the sensitivity obtained was 0.739, and the specificity was 0.753. A similar study reported an AUROC of 0.983 at degree F4 compared to degrees F0-F3, and a spleen stiffness cutoff of 34.3 kPa with a sensitivity of 100% and specificity of 94.2%. Statistical analysis showed that the diagnostic value of spleen stiffness was comparable to liver stiffness.[12] In another study using the ARFI elastography method, the AUROC for the F4 degree compared to the F1-F3 degree was 0.932 with a 95% confidence interval of 0.893 - 0.971. Spleen stiffness with ARFI has the potential to be a predictor of liver fibrosis severity.[19] Furthermore, a study conducted using noninvasive marker by combining liver and stiffness measurement, together with spleen length diameter to predict decompensated viral cirrhosis reported that the AUROC of spleen stiffness for grade 4 liver fibrosis was 0.56.[13] Several factors may account for the variability in AUROC reported across studies, including variations in the stage of chronic hepatitis B, the use of antiviral therapy, and other clinical variables.

There are several limitations associated with this study. Liver biopsy was not performed in the study population, the cross-sectional design precluded assessment of causal relationships, and there was heterogeneity in treatment duration and comorbid conditions. In addition, spleen stiffness was not compared with other noninvasive fibrosis assessment methods. However, the sample used was relatively large and represented the Indonesian population.

CONCLUSION

In conclusion, increased SSM in CHB patients correlated with the severity of liver fibrosis. Therefore, spleen stiffness may serve as a predictor of advanced liver fibrosis with a cut-off of 28 kPa, providing an option in place of biopsy. Although these results support the clinical application of SSM, further studies are needed to refine the diagnostic thresholds and validate the use in broader populations.

Conflict of Interest

The authors declare that there is no conflict of interest related to this study.

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Author Contribution

All authors contributed in design and conceptualization. Carisa Irene Hertanto was responsible for data collection and analysis as well as the preparation for the manuscript. Ummi Maimunah, Aryati, Muhammad Miftahussur supervised and provided feedback. All authors discussed the results and contributed to the final manuscript.

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Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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