S-index and APRI Score to Predict Liver Fibrosis Chronic in Hepatitis B and C Patients

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ABSTRACT

Background: *A great interest has been dedicated to the development of non invasive predictive models in recent years to substitute liver biopsy for fibrosis assessment and follow-up. The aim of this study was to compare the accuracy between S-index and aspartate aminotransferase to platelet ratio index (APRI) to FibroScan for predicting liver fibrosis in chronic hepatitis B and C patients.*

Method: *A cross-sectional study was conducted in 40 patients with chronic hepatitis B and C between January 2010 - May 2011 at Division of Gastroentero-hepatology, Department of Internal Medicine, Adam Malik Hospital, Medan. Patients underwent laboratory examination and FibroScan, then used predictive values to assess the accuracy of S-index scores and APRI compared to FibroScan. The analysis was performed using SPSS 15.0.*

Results: *S-index identified significant fibrosis in 87.5% patients with sensitivity (Se) 87.5% and specificity (Sp) 100%. About 67.5% of 40 patients could be identified correctly. S-index also could accurately predict the absence or presence of cirrhosis in 87.5% of the total 40 patients, with NPV 91.7% and PPV 81.25%, respectively. APRI for significant fibrosis has Se 85.7%, Sp 88%, PPV 88.8%, NPV 69.2%; while Se 53%, Sp 88%, PPV 72.7%, NPV 75.8% for liver cirrhosis. AUROC value for S-index was higher than APRI in predicting significant fibrosis and cirrhosis, i.e. 0.938 vs. 0.917 and 0.873 and 0.707, respectively.*

Conclusion: *The S-index has a higher accuracy than APRI in predicting significant fibrosis and cirrhosis in patients with chronic hepatitis B virus and hepatitis C virus infection.*

Keywords*: S-index, APRI score, FibroScan, chronic hepatitis B and C*

ABSTRAK

Latar belakang: *Minat yang besar didedikasikan untuk pengembangan model prediksi non invasif dalam beberapa tahun terakhir untuk menggantikan biopsi hati dalam penilaian fibrosis beserta tindak lanjutnya. Tujuan penelitian ini adalah untuk membandingkan akurasi antara S-indeks dan aspartate aminotransferase to platelet index (APRI) dengan FibroScan untuk memprediksi fibrosis hati pada pasien hepatitis B dan C kronis.*

Metode: *Dilakukan penelitian potong lintang pada 40 pasien hepatitis B dan C kronik sejak Januari 2010 sampai Mei 2011 di Divisi Gastroentero-hepatologi Departemen Ilmu Penyakit Dalam, Rumah Sakit Adam Malik Medan. Terhadap pasien dilakukan pemeriksaan laboratoriun dan FibroScan serta dibandingkan derajat akurasi skor S-indeks dan APRI. Analisis data dilakukan dengan menggunakan SPSS 15.0.*

Hasil: *S-indeks mengindentifikasi fibrosis signifikan pada 87,5% pasien dengan sensitifitas (Se) 87,5% dan spesifitas (Sp) 100%. Sejumlah 67,5% dari 40 pasien dapat diidentifikasi dengan baik. S-indeks juga dapat secara akurat memprediksi ada tidaknya sirosis pada 87,5% dari 40 pasien dengan NPV 91,7% dan PPV 81,25%. APRI memprediksi fibrosis signifikan dengan Se 85,7%, Sp 88%, PPV 88,8%, NPV 69,2%; dimana pada pasien sirosis hati didapat Se 53%, Sp 88%, PPV 72,7% dan NPV 75,8%. Nilai AUROC lebih tinggi pada S-indeks dibandingkan pada APRI dalam memprediksi baik fibrosis signifikan maupun sirosis yaitu masing-masing 0,938 vs. 0,917 serta 0,873 dan 0,707.*

Simpulan: *S-indeks memiliki akurasi yang lebih tinggi dibandingkan APRI dalam memprediksi fibrosis signifikan dan sirosis pada pasien dengan infeksi hepatitis B dan C kronik.*

Kata kunci: *S-indeks, skor APRI, FibroScan, hepatitis B dan C kronik*

INTRODUCTION

Chronic liver disease is a global issue today as it often leads to liver cirrhosis and hepatocellular carcinoma, which is initially characterized by fibrosis in the liver.[1,2,3] Liver fibrosis occurs due to chronic damage to the liver, which is associated with excessive accumulation of extracellular matrix protein.[1,2,3,4,5] The main etiologies of liver fibrosis include chronic infection of hepatitis B and C virus, alcohol drinks, and non-alcoholic steato hepatitis (NASH).[1,6,7,8] The accumulation of extracellular matrix protein will distort liver architectures by forming fibrous connective tissue and resulting in the development of nodules. When the nodules have been developed, the condition is defined as cirrhosis.[1,2,9,10,11,12]

Liver biopsy, an invasive method, is still regarded as the gold standard for determining the stage of fibrosis. As there are so many obstacles, complication and expensive cost of the invasive method, numerous studies have proposed a diagnostic method for fibrosis staging using non-invasive methods.[4,7,9] Liver fibrosis can be measured by FibroScan significantly, in consistent with or equal to the liver staging made by liver biopsy. The diagnostic accuracy of FibroScan is higher compared to biomarkers to evaluate the stage of liver fibrosis.[13,14] FibroScan offers some advantages compared to liver biopsy since it is a rapid and painless test with less interpretation error.[13,14]

Evaluation of liver fibrosis using non-invasive method may also be done by APRI score and S-index. By comparing some of simple laboratory markers, the methods can predict patients with chronic liver disease. The aim of this study was to compare the accuracy of predictive value between S-index and aspartate aminotransferase to platelet ratio index (APRI) to FibroScan for predicting liver fibrosis in patients with chronic hepatitis B and C.

METHOD

A cross-sectional study was conducted in 40 patients, who had been diagnosed with chronic hepatitis B and C and underwent FibroScan test at Division of Gastroentero-hepatology, Department of Internal Medicine, Adam Malik Hospital Medan. The serum of patients was collected between January 2010 and May 2011.

The following markers were analyzed, including aspartate transaminase (AST), g-glutamyltransferase (GGT), platelets (PLT) and albumin (ALB) level, as well as S index score and APRI. The stage of liver fibrosis was determined and scored based on a scale of F0 to F4 using FibroScan. Predictive values were subsequently determined to assess the accuracy of S-index scores and APRI. The formula to calculate the score was:

$$\text{S-index} = 1{,}000 \times GGT/(PLT \times ALB^2)$$

Table 1. Cut off points of S-index

Stages	Absence	Presence
Significant fibrosis (F2-4)	< 0.1	≥ 0.5
Advanced fibrosis (F3-4)	< 0.2	≥ 0.6
Cirrhosis	< 0.3	≥ 1.5

Units of measurement in the formula: GGT (IU/L); PLT (10^9/L); ALB (g/L)

$$\text{APRI} = \frac{\text{AST level (U/L)} / \text{upper normal limit of AST (U/L)} \times 100}{\text{Platelets } (10^9/\text{L})}$$

Cut-off points of APRI: score < 0.5 = non fibrosis; 0.5–1.5 = mild fibrosis; score > 1.5 = cirrhosis. Cut-off point of FibroScan were determined according to Ledingen V, i.e.: F0-1 = 0–7.1 kPa; F2 ≥ 7.1–9.3 kPa; F3 ≥ 9.3–14.5 kPa; F4 ≥ 14.5 kPa.[15]

Inclusion criteria of this study were patients with chronic liver disease caused by hepatitis B and C viruses with positive viral marker result, male and female patients aged 18 years or over and willing to participate in the study; while the exclusion criteria were co-infection with HIV, alcohol drinks of > 30 g/day, other causes of chronic liver disease and patients with renal failure.

To determine diagnostic value of S-index panel marker, an evaluation was performed based on receiver operating characteristic (ROC) curve analysis as well as evaluate the sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy (DA), positive likelihood

ratios (LR+) and negative likelihood ratios (LR-), which were calculated based on cut-off points mentioned in its original publication and journals. Statistical analysis was performed using SPSS version 15.0

RESULTS

Table 2. Baseline data of patients

Variable	n (%)
Sex	
Male	23 (57.5)
Female	17 (42.5)
Age (year)*	48.5 (SD ± 12.70)
Platelets (10^9/L)*	153.0 (SD ± 84.6)
Albumin**	3.75 (2.0 – 3.90)
Gamma GT**	55 (12 – 371)
S index**	57 (1.97 – 330.47)
APRI score**	0.91 (0.17 – 13.41)
FibroScan**	12.5 (4.30 – 69.2)

Based on normality test of Kolmogorov – Smirnov; *data of age and platelets have normal distribution (mean, SD); **abnormal distribution (median, min – max); APRI: aspartate aminotransferase to platelet ratio index

Table 3. Staging of liver fibrosis based on S-index and APRI

Degree of fibrosis	S-index n (%)	APRI index n (%)
Non significant fibrosis	19 (47.5%)	13 (32.5%)
Significant fibrosis	5 (12.5%)	16 (40%)
Advanced fibrosis	13 (32.5%)	0 (0%)
Cirrhosis	3 (7.5%)	11 (27.5%)
Total	40 (100%)	40 (100%)

APRI: aspartate aminotransferase to platelet ratio index

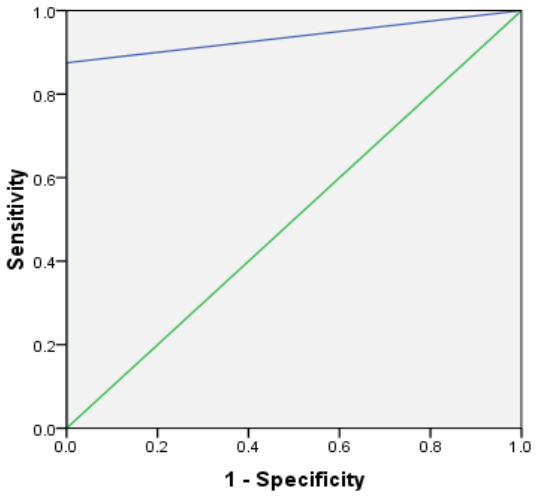

Figure 1. ROC curve of S-index to predict significant fibrosis with sensitivity 87.5%, specificity 100%, positive predictive value 100%, negative predictive value 66.7% and AUROC 0.938

Table 4. Staging of liver fibrosis based on FibroScan in accordance with sex

Sex	FibroScan				Total n (%)
	Non Sig Fib	Sig Fib	Adv Fib	Cirrhosis	
Male	6 (50%)	2 (50%)	5 (56.6%)	10 (66.7%)	23 (57.5%)
Female	6 (50%)	2 (50%)	4 (44.4%)	5 (33.3%)	17 (42.5%)
Total	12 (100%)	4 (100%)	9 (100%)	15 (100%)	40 (100%)

Sig: significant; Fib: fibrosis; Adv: advance

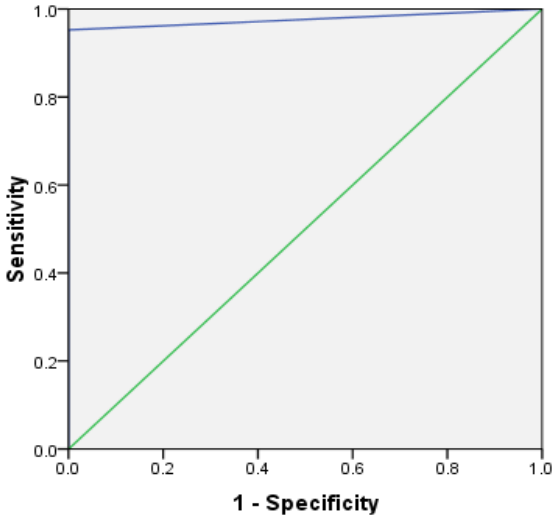

Figure 2. ROC curve of S-index to predict significant fibrosis with sensitivity 95%, specificity 100%, positive predictive value 100%, negative predictive value 93.7% and AUROC 0.976

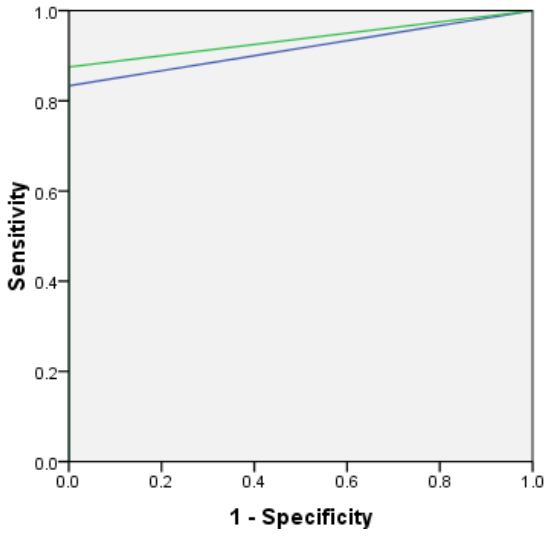

Figure 3. ROC curve of S-index and APRI to predict significant fibrosis of 0.938 and 0.917, respectively with sensitivity 86.67%, specificity 88%, positive predictive value 81.25%, negative predictive value 91.7%, and AUROC = 0.873

Table 5 demonstrates sensitivity 85.7%, specificity 88%, PPV 88.8% and NPV 69.2%.

Table 5. APRI predictive value for significant diagnosis of fibrosis

APRI		FibroScan significant		Total
		Non Sig Fib	Sig Fib	
Sig Fib APRI	Non Sig APRI	9	4	13
	Sig Fib APRI	3	24	27
Total		12	28	40

APRI: aspartate aminotransferase to platelet ratio index; Sig: significant; Fib: fibrosis

Table 6 demonstrates sensitivity 53%, specificity 88%, PPV 72.7%, and NPV 75.8%.

Table 6. APRI predictive value for diagnosis of cirrhosis

Cirrhosis APRI	FibroScan significant		Total
	Non Sig Fib	Sig Fib	
Non cirrhosis APRI	22	7	29
Cirrhosis APRI	3	8	11
Total	25	15	40

APRI: aspartate aminotransferase to platelet ratio index; Sig: significant; Fib: fibrosis

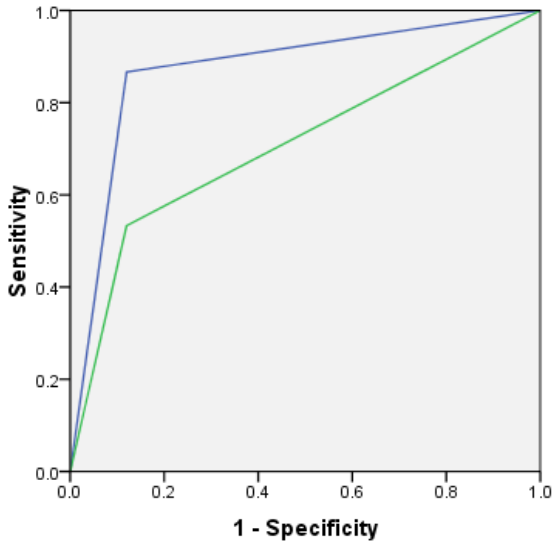

Figure 4. ROC curve of S-Index and APRI to predict cirrhosis of 0.873 and 0.707, respectively

Overall, the APRI in this study could predict significant fibrosis with sensitivity 85.7%, specificity 88%, PPV 88.8% and NPV 69.2%. In patients with cirrhosis, the APRI had sensitivity 53%, specificity 88%, PPV 72.7% and NPV 75.8%. AUROC value for S-index was higher compared to APRI in predicting significant fibrosis and cirrhosis, i.e. 0.938 vs. 0.917, 0.873 and 0.707, respectively.

DISCUSSION

In the last few years, some studies on non-invasive diagnostic method for liver fibrosis in patients with chronic liver disease have been published. Most of the studies were conducted in patients with chronic hepatitis C and only several data available on the application of the non invasive method for patients with chronic hepatitis B. Liver biopsy has some limitations as a diagnostic method as it is an invasive, expensive method that may cause inconvenience for patients as well as intra- and inter observer variations. The use of some non-invasive diagnostic methods for diagnosing fibrosis and liver cirrhosis have been validated since 2001.[16,17]

APRI scoring system and S-index are relatively inexpensive and simple method that can be easily performed by clinicians. S-index alone had successfully identified significant fibrosis in 87.5% patients with sensitivity 87.5% and specificity 100%, PPV 100%, NPV 66.7%, AUROC 0.938. Together with APRI, about 67.5% of the total 40 patients could be identified correctly; only 7.5% were misidentified by S-index and 25% remained uncertain. S-index also could accurately predict the absence or presence of cirrhosis in 87.5% of the total 40 patients, with NPV 91.7% and PPV 81.25%.

The results of this study are almost similar with previous study conducted by Zhou et al in 2010, which demonstrated cut-off point of S-index for significant fibrosis absence < 0.1 with sensitivity 94.12%, specificity 42.31%, PPV 58.72%, NPV 89.19%; while the cut-off point for significant fibrosis presence was > 0.5 with sensitivity 42.65%, specificity 94.87%, PPV 87.88%, NPV 65.49% and AUROC 0.812. Furthermore, the study also showed that the cut-off point for cirrhosis absence was < 0.3 with sensitivity 80%, specificity 72.52%, PPV 25% and NPV 96.94%; while the cut-off point for cirrhosis presence was > 1.5 with sensitivity 53.33%, specificity 98.47%, PPV 80.00%, NPV 94.85% and AUROC 0.890.[4]

The results of this study showed higher sensitivity and specificity compared to previous studies. A meta-analysis conducted on some report of studies indicated that APRI cut-off point of 0.5 had 81% sensitivity and 50% specificity to predict significant fibrosis ($F \geq 2$, Metavir score) and with cut-off point of 1, it had sensitivity 76% and specificity 71% to predict cirrhosis.[6,20,21]

The result of study conducted by Del Castillo et al showed that APRI score could be used to predict significant fibrosis in patients with chronic hepatitis C, the delimited APRI value on AUC was 0.776 (95% CI = 0.704 - 0.847; $p < 0.01$); with limit threshold of 0.6433, they found sensitivity 74.7%, specificity 67.9%, PPV 70.5%, NPV 72.4% with accuracy 71.3%, PLR 2.33 (1.66 - 3.27); for cirrhosis, the APRI score on AUC

was 0.830 (95% CI = 0.765 - 0.895) with a threshold of 0.7532, sensitivity 89.4%, specificity 70.90%, PPV 55.3%, NPV 94.3%, accuracy 76.2% and PLR 3.08 (2.28 - 4.15).[22]

A study conducted by Zhou et al showed that the APRI score for predicting significant fibrosis had cut-off point of ≤ 0.5 to predict the absence with sensitivity 82.35%, specificity 38.46%, PPV 53.85%, NPV 71.45% ; while to predict the presence, the cut-off point was > 1.5 with sensitivity 48.53%, specificity 85.90%, PPV 75%, NPV 66.60% with AUROC 0.717.[4]

A study about APRI conducted by Bota et al indicated sensitivity 67.7%, specificity 70%, PPV 95.5% and NPV 70% with accuracy 67.7% to predict significant fibrosis; while in predicting the cirrhosis, they found 80% sensitivity, 74.1%, specificity, 33.8% PPV, 95.7% NPV and 75% accuracy.[19]

Varied results in this study compared to previous study may be due to differences in cut-off point to determine the stage of fibrosis as well as differences of AUC value and basic characteristic parameter used in our study. The results of this study showed that S-index had high accuracy as a non-invasive method to evaluate fibrosis staging and cirrhosis compared to APRI scoring system.

The study has several limitations since we did not perform liver biopsy as the gold standard for evaluating the stage of liver fibrosis and there was only one operator performing FibroScan; therefore there was greater difficulty to evaluate inter- and intraobserver variation.

CONCLUSION

S-index is a simple mathematical model containing routine laboratory markers, which has a higher accuracy when compared to APRI in predicting significant fibrosis and cirrhosis in patients with chronic HBV and HCV infection with a high degree of accuracy.

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