Original Article

Prediction of Liver Fibrosis in Chronic Hepatitis B Patients by Using Score of Routine Laboratory Tests

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ABSTRACT

Background: The prognosis and management of patients with chronic hepatitis B depend on the amount and progression of the liver fibrosis. Liver biopsy is currently the gold standard for staging of fibrosis and histological activity, but it is poor tolerated. Noninvasive methods are now used increasingly to reduce the need for liver biopsy. Our aim is to validate simpler model, consisting of routine laboratory markers for predicting liver fibrosis in chronic hepatitis B patients.

Methods: Sixty patients with chronic hepatitis B virus infection who underwent liver biopsy before anti-viral treatment at Vajira Hospital from June 2012 to January 2014 were recruited. On the day of scheduled liver biopsy, complete laboratory tests were done. Liver histology was evaluated and grading by METARVIR scoring system. S index (S index = 1000*GGT/(Plt*Alb^2) was validated in this cohort and by receiver operating characteristics (ROC) analysis.

Results: For predicting significant fibrosis, S index cut point value ≥ 0.771 had sensitivity 80%, specificity 44.4%, PPV 32.4%, NPV 87%, and the area under the ROC curve (AUROC) of 0.597. For predicting significant histology (significant fibrosis and/or histological activity), the S index cut point value ≥ 0.587 had sensitivity 82.6%, specificity 35.1%, PPV 44.2%, NPV 76.7%, and AUROC 0.609. As in our study, for significant fibrosis and significant histology diagnosis, we can reduce the need for liver biopsy by 33.34% and 27% with missed diagnosis rate of 20% and 17% respectively.

Conclusions: The S index may be used as a screening method for considering liver biopsy in chronic hepatitis B patients, but it had fair accuracy.

Key words : Chronic hepatitis B, liver biopsy, S index

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Introduction

Chronic hepatitis B virus (HBV) infection affects 400 million individuals globally[1]. Chronic HBV infection is the major cause of end stage liver disease, 25% of them will die prematurely with liver cirrhosis or hepatocellular carcinoma[2].

Thirty to forty percent of patients with chronic HBV infection will progress to advanced fibrosis and cirrhosis[3,4]. Accurate staging of liver fibrosis is the most important factor for predicting prognosis and management decision (to follow up or to consider antiviral treatment).

Liver biopsy is currently the gold standard in assessing severity of necro- inflammation activity and fibrosis[5]. Although percutaneous liver biopsy is in general a safe procedure, it is costly and it carries a small risk of complications such as pain, pneumothorax, with the mortality rate of 0.01-0.1%[6-8]. It is also limited by sampling error and poor intra- and inter-observer concordance[9,10]. Hence, there is a need to develop accurate, reliable, and simple noninvasive models to assess the severity of hepatic fibrosis and inflammation in HBV related chronic liver disease.

A new imaging technique, Fibroscan, has been shown to determine the degree of liver fibrosis with high accuracy[11]. However, the equipment is expensive and not achievable for routine testing in most clinical units worldwide.

In recent years, efforts have been made to develop noninvasive predictive models that may correlate with stage of liver fibrosis, however, most such studies have been performed in chronic hepatitis C (CHC) patients[12-16]. The cost and complexity of these algorithms along with the fact that their diagnostic accuracies were not highly and such complex formulas may be more useful for research setting, not for clinical practice.

In chronic hepatitis B (CHB) patients, few studies have been performed to predict significant liver fibrosis. Predictive models designed especially for CHB patients have been proposed by Shanghai Liver Fibrosis Groups (SLFG)[17], Hui *et al*[18], Mohamadnejad *et al*[19], and Zhou *et al*[20]. However, only S index (proposed by Zhou et al) have been validated and implemented in clinical practice.

The aim of this study is to validate S index model, for predicting liver fibrosis in patients with chronic HBV infection in Vajira hospital, Thailand and calculate the best cut point for considering liver biopsy.

Material and Methods

Patients

All CHB patients who underwent a liver biopsy at Vajira Hospital since June 1, 2012 to January 31, 2014 were enrolled into the study. The inclusion criteria included age over 18 years old, following indication to liver biopsy according to Thailand practical guideline for management of hepatitis B and C 2012, and informed consents taken. The exclusion criteria included pregnancy, co-infection with HCV and/or HIV, contraindication for liver biopsy, currently treated with any antiviral agents, alcohol use greater than 20 gm/day, other liver diseases, and malignancy. The following parameters were collected: sex, age, body weight, height, history of alcoholic consumption, medical co-morbidity, and current medical drug use.

Biochemical measurement

Blood sample was taken for complete blood count (CBC), liver tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, globulin, total bilirubin, direct bilirubin, indirect bilirubin, gamma-glutamyl transpeptidase (GGT), BUN, Cr, prothrombin time (PT), partial thrombin time (PTT), INR, on the enrollment day or within 1 week and HBV DNA viral load (Tagman®) within 3 months before liver biopsy.

S-index was determined by using the following equation:

$$\text{S-index} = 1000 \times \text{GGT}/(\text{Platelets} \times \text{Albumin}^2)$$

Unit: GGT, IU/L; Platelets,10^9/L; Albumin, g/L

Liver histopathology

Standard liver biopsy was performed under ultrasound guidance. Liver histology was evaluated by one experienced gastrointestinal pathologist who was blinded for their clinical and biochemical data. Biopsy specimens were fixed in 10% neutralized formaldehyde, embedded in paraffin and section was stained with hematoxylin-eosin and Masson's trichrome.

The degree of necroinflammatory activity and fi-

brosis were scored by Metavir scoring system as A0 (no inflammation) to A3 (severe inflammation) and F0 (no fibrosis) to F4 (cirrhosis), respectively. Significant inflammation was determined by activity score of A2-3 and significant fibrosis was determined by fibrosis score of F2-4.

Statistical analysis

Baseline descriptive data were expressed as means and standard deviations for continuous variables, and as percentages and frequencies for categorical variables. Differences between groups were assessed by Student *t*-test for continuous data, and by Chi-square test for proportional data. Univariate analysis and multivariate analysis were carried out to identify variables that were significantly different between patients in each group. The ROC curve is a plot of sensitivity versus 1-specitivity for cut off values. The most commonly used index of accuracy is area under the ROC curve (AUROC). Values closed to 1.0 indicate high diagnostic accuracy. Statistical analysis was performed using the SPSS software version 15.0 where a *p* value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 60 patients were enrolled in the study. There were 32 male (53.3%) and 28 female (46.7%) with a mean age of 47.83±12.45 years old and a mean BMI of 24.99±4.86 kg/m^2. Majority were HBeAg negative CHB (73.3%). The mean HBV DNA was 5.82±1.67 log. Physical examination revealed signs of chronic liver disease in 5 patients (8.3%) and ascites in 2 patients (3.3%). Pre-procedure serum biochemistries including coagulogram were within normal range except liver function tests and GGT. Histological results showed significant fibrosis (F2-4) in 15 patients (25%) and significant activity or necroinflammation (A2-3) in 20 patients (33.3%). All variables were shown in Table 1.

Liver biopsy

The patients were divided into 2 groups according to liver histology; group 1, significant fibrosis (F2-4), n = 15 and group 2, significant histology (F2-4 and/or A2-3), n = 23. We studied to find the characteristic which could predict the significant fibrosis/histology and to validate S index score from previous study. We also determined the best cut point value of S index in our study to predict the significant fibrosis or necroinflammation (Table 1).

Associated factors with histology (univariate and multivariate analysis)

Significant fibrosis (F2-4 vs. F0-1)

When we compared the patients with significant fibrosis to patients without significant fibrosis, the patients with significant fibrosis had higher mean age (55.60±10.67 vs. 45.24±12.00, *p*=0.004), higher mean BMI (28.84±6.08 vs. 23.71±3.63, *p*<0.001), more prevalence of obesity; BMI > 25 (10 (66.7%) vs. 13 (28.9%), *p*=0.009), lower mean Hb (12.31 ± 1.73 vs. 14.09 ± 1.43, *p*=<0.001), higher mean serum globulin level (3.76 ± 0.52 vs. 3.35 ± 0.4, *p*=0.002), more patients with proportion of AST/ALT >1 (10 (66.7%) vs. 13 (28.9%), *p*=0.009), but no significant different of underlying disease (Table 1).

In multivariate analysis, only the mean age of >50 was independent associated factor for predicting significant fibrosis (OR=11.28 (1.23, 103.16), *p*=0.032) (Table 2).

Significant histology (F2-4 and/or A2-3)

We compared patients with significant histology to patients without significant histology. Patients who had significant histology have higher mean age (53.17 ± 9.86 vs. 44.51 ± 12.85, *p*=0.005), higher mean BMI (27.51 ± 5.51 vs. 23.44 ± 3.7, *p*= 0.001), more prevalence of DM and HT (8 (34.8%) vs. 2 (5.4%), *p*=0.005), more prevalence of obesity (10 (66.7%) vs. 13 (28.9%), *p*=0.011), lower mean Hb (12.77 ± 1.63 vs. 14.18 ± 1.5, *p*=0.001), and higher mean globulin (3.61 ± 0.5 vs. 3.35 ± 0.42, *p*=0.036) (Table 1). But all these factors were not independent associated factors for predicting significant histology (*p*>0.05 by regression analysis) (Table 3).

S index value for the diagnosis of significant fibrosis

The S index was calculated using the formulas from the original publication, the appropriate cut point value was ≥ 0.771, sensitivity 80%, specificity 44.4%, PPV 32.4%, NPV 87% to predict significant fibrosis (Table 4). The AUROC of the S index for predicting significant fibrosis is 0.5970, as shown in Figure 1.

S index value for the diagnosis of significant histology (F2-4 and/or A2-3)

For significant histology indicating the need of

Table 1. Characteristics of patients.

Variable	Total patients	Group I Significant Fibrosis (F2-4)			Group II Significant histology (F2-4 and/orA2-3)		
	(n = 60)	No (n=45)	Yes (n=15)	*p*-value	No (n=37)	Yes (n=23)	*p*-value
Age	47.83 ± 12.45	45.24 ± 12.00	55.60 ± 10.67	0.004*	44.51 ± 12.85	53.17 ± 9.86	0.005*
- Age >50 yr.	34 (56.7%)	22 (48.9%)	12 (80%)	0.035*	17 (45.9%)	17 (73.9%)	0.031*
Female	28 (46.7%)	17 (37.8%)	11 (73.3%)	0.017*	13 (35.1%)	15 (65.2%)	0.023*
BMI	24.99 ± 4.86	23.71 ± 3.63	28.84 ± 6.08	<0.001*	23.44 ± 3.7	27.51 ± 5.51	0.001*
- BMI ≥ 25 kg/m^2	23 (38.3%)	13 (28.9%)	10 (66.7%)	0.009*	13 (28.9%)	10 (66.7%)	0.011*
DM	10 (16.7%)	6 (13.3%)	4 (26.7%)	0.25	2 (5.4%)	8 (34.8%)	0.005*
HT	10 (16.7%)	5 (11.1%)	5 (33.3%)	0.102	2 (5.4%)	8 (34.8%)	0.005*
DLP	15 (25%)	9 (20%)	6 (40%)	0.169	7 (18.9%)	8 (34.8%)	0.168
HBeAg							
- Positive	16 (26.7%)	15 (33.3%)	1 (6.7%)	0.05	14 (37.8%)	2 (8.7%)	0.013*
- Negative	44 (73.3%)	30 (66.7%)	14 (93.3%)	23 (62.2%)	21 (91.3%)		
Sign chronic liver¶	5 (8.3%)	2 (4.4%)	3 (20%)	0.094	0 (0%)	5 (21.7%)	0.006*
Ascites	2 (3.3%)	0 (0%)	2 (13.3%)	0.059	0 (0%)	2 (8.7%)	0.143
Hb(g/dL)	13.64 ± 1.68	14.09 ± 1.43	12.31 ± 1.73	<0.001*	14.18 ± 1.5	12.77 ± 1.63	0.001*
- Hb ≤ 11.5 (g/dL)	6 (10%)	2 (4.4%)	4 (26.7%)	0.030*	2 (5.4%)	4 (17.4%)	0.191
WBC(*10^3cell/mm^3)	7.93 ± 9.60	7.85 ± 10.00	8.18 ± 8.61	0.911	8.02 ± 11.04	7.80 ± 6.90	0.932
Plt (10^9/L)	204.07 ± 62.4	204.07 ± 51.3	204.07 ± 90.22	1	205.32 ± 52.22	202.04 ± 77.28	0.858
AST	45.73 ± 32.6	43.89 ± 31.27	51.27 ± 36.92	0.453	42.7 ± 33.78	50.61 ± 30.7	0.366
ALT	52.48 ± 47.28	54.31 ± 52.34	47 ± 27.75	0.608	52.14 ± 56.27	53.04 ± 28.53	0.943
AST/ALT ratio	1 ± 0.5	1 ± 0.5	1.1 ± 0.4	0.313	1.03 ± 0.53	1.02 ± 0.34	0.958
- AST/ALT ratio >1	23 (38.3%)	13 (28.9%)	10 (66.7%)	0.009*	13 (35.1%)	10 (43.5%)	0.518

Table 1. Characteristics of patients.

Variable	Total patient	Group I Significant Fibrosis (F2-4)			Group II Significant histology (F2-4 and/orA2-3)		
	(n = 60)	No (n=45)	Yes (n=15)	*p*-value	No (n=37)	Yes (n=23)	*p*-value
ALP	82.73 ± 59.22	79.13 ± 62.16	93.53 ± 49.67	0.419	71.59 ± 28.02	100.65 ± 87.04	0.133
Albumin (g/dL)	4.93 ± 5.41	5.25 ± 6.22	3.96 ± 0.53	0.43	5.53 ± 6.85	3.95 ± 0.46	0.276
Globulin (g/dL)	3.45 ± 0.47	3.35 ± 0.4	3.76 ± 0.52	0.002*	3.35 ± 0.42	3.61 ± 0.5	0.036*
- Globulin ≥ 3.6	26 (43.3%)	15 (33.3%)	11(73.3%)	0.007*	13 (35.1%)	13 (56.5%)	0.104
GGT	51.53 ± 47.44	49.09 ± 41.48	58.87 ± 63.24	0.494	49.19 ± 43.81	55.3 ± 53.59	0.631
DB	0.32 ± 0.74	0.37 ± 0.84	0.16 ± 0.15	0.343	0.41 ± 0.93	0.16 ± 0.13	0.201
IDB	0.66 ± 0.46	0.68 ± 0.48	0.6 ± 0.39	0.547	0.68 ± 0.52	0.62 ± 0.35	0.618
HBV DNA							
Viral Load	23,008,320.75 ±	20,484,147.67 ±	30,580,840 ±	0.51	19,389,333.65 ±	28,830,169.57 ±	0.489
(IU/mL)	50,840,155.13	49,472,339.14	55,844,910.96		48,035,079.33	55,665,041.6	
Log	5.82 ± 1.67	5.72 ± 1.72	6.12 ± 1.53	0.431	5.58 ± 1.81	6.21 ± 1.38	0.154
Fibrosis							
- F0-F1	45 (75%)	45 (100%)	0 (0%)	<0.001*	37 (100%)	8 (34.8%)	<0.001*
- F2-F4	15 (25%)	0 (0%)	15 (100%)	0 (0%)	15 (65.2%)		
Histologic activity							
- A0-A1	40 (66.7%)	37 (82.2%)	3 (20%)	<0.001*	37 (100%)	3 (13%)	<0.001*
- A2-A3	20 (33.3%)	8 (17.8%)	12 (80%)	0 (0%)	20 (87%)		
S index	2.10 ± 4.52	1.46 ± 1.48	4.04 ± 8.59	0.267	1.38 ± 1.52	3.26 ± 6.98	0.216
Median (p25, p75)	9.65 (5.61,18.30)	8.32 (5.59,16.59)	11.21 (7.72,30.57)	0.263	8.32 (5.38,15.32)	11.21 (6.15,30.57)	0.155

Value presented as mean ± SD or n (%). *p*-value corresponds to *t*-test and chi-square test. (M) Mann-Whitney Test

¶ consist of palmar erythema, spider nevi, parotid gland enlargement, gynecomastia and testicular atrophy

*$p < 0.05$

Table 2. In dependent factors associated with significant fibrosis (multivariate analysis).

Variables	OR (95%CI)	*p*-value
Age ≥ 50 yr	11.28 (1.23, 103.16)	0.032*
Female	4.02 (0.69, 23.49)	0.123
BMI ≥ 25 kg/m^2	0.61 (0.06, 6.17)	0.679
Hb ≤11.5 g/dL	10.34 (0.82, 129.97)	0.070
AST/ALT ratio	2.65 (0.52, 13.49)	0.240
Globulin ≥3.6 g/dL	7.49 (0.81, 69.66)	0.077

Table 3. Independent factors associated with significant fibrosis/activity (mutivariate analysis).

Variables	OR (95%CI)	*p*-value
Age >50 yr	1.56 (0.308, 7.88)	0.591
Female	1.82 (0.36, 9.09)	0.467
BMI >25 (kg/m^2)	2.55 (0.609, 10.73)	0.200
DM	3.49 (0.37, 32.57)	0.274
HT	3.52 (0.28, 43.59)	0.327
HBeAg negative	3.28 (0.47, 22.84)	0.231
Hb (g/dL)	0.67 (0.15, 3)	0.596
BUN (mg/dL)	0.84 (0.69, 1.02)	0.071
Globulin (g/dL)	1.55 (0.18, 13.39)	0.688

antiviral treatment, the appropriate cut point value is ≥0.587, sensitivity 82.6%, specificity 35.1%, PPV 44.2%, NPV 76.5% (Table 5). The AUROC of the S index for predicting significant fibrosis and/or histological activity was shown in Figure 2.

Discussion

Many studies on noninvasive diagnostic models of liver fibrosis in chronic liver diseases have been published in the past years. Most of them were conducted in CHC and few data are available on CHB patients. The need of complex tests requiring a logarithmic calculator for calculation and the extra cost in calculation obviously reduce their practical utility.

Only S index that proposed by Zhou *et al.* is easily calculated by a simple formulation consisting of three routine markers (GGT, platelet and albumin), so that allows it to be determined in the clinical practice or bedside use.

In original publication, the S index cut point value of ≥ 0.5 predicted significant fibrosis and the cut point value of ≤ 0.1 predicted no significant fibrosis with the accuracy for predicting significant fibrosis of 42.5% (sensitivity 36.53%, specificity 86.23%, PPV 77.67,

Table 4. Predictive values of the S index for the diagnosis of significant fibrosis (F2-4).

Cut point S index	Sensitivity	Specificity	PPV	NPV
0.771	80.0%	44.4%	32.4%	87.0%

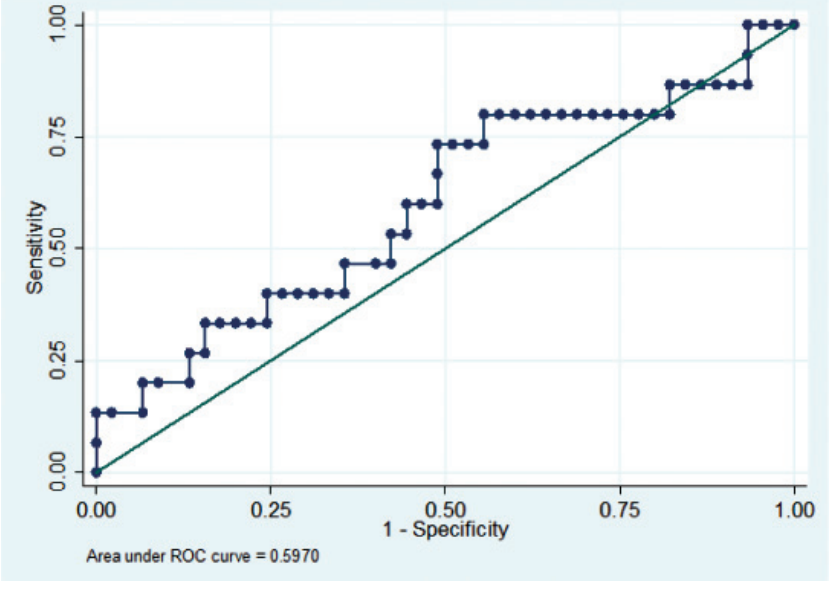

Figure 1. Receiver operating characteristic (ROC) curve in the prediction of significant fibrosis (group 1).

Table 5. Predictive values of the S index for the diagnosis of significant fibrosis.

Cut point S index	Sensitivity	Specificity	PPV	NPV
0.587	82.6%	35.1%	44.2%	76.5%

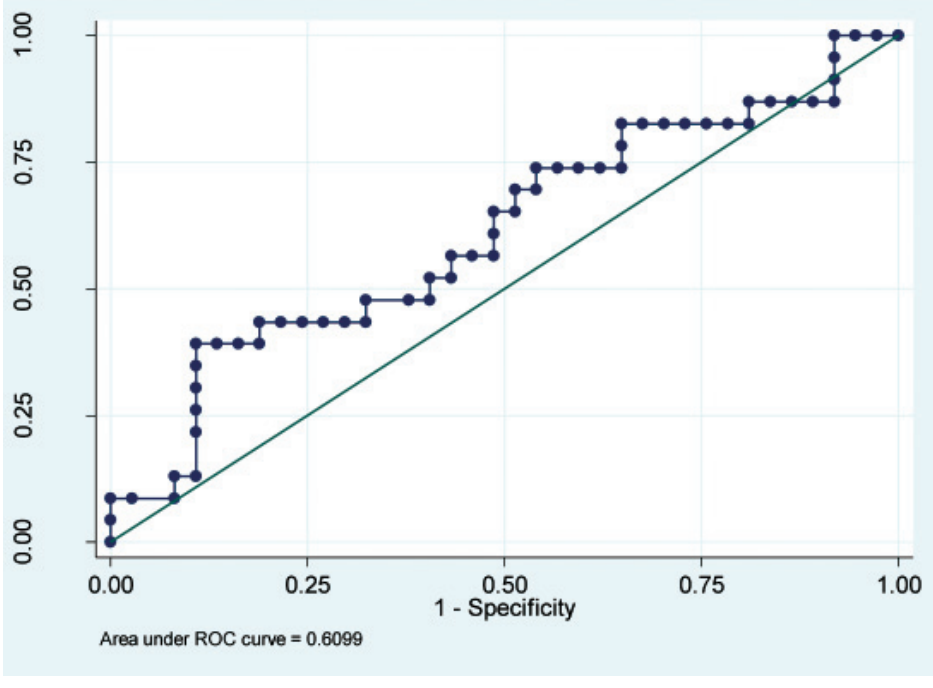

Figure 2. Receiver operating characteristic curve in the prediction of significant histology (group 2).

NPV 50.88%, AUR0C 0.812). Liver biopsy was not necessary in all patients, except for the patients with the S index value between 0.1-0.5. Therefore liver biopsy was needed in 47.9% of patients and missed classified fibrosis was found in 5.5%. However this value (S index ≤0.1 and ≥0.5) could not predict significant fibrosis in our study population. The reason might be that there was no significant difference of the variables including GGT, albumin, and platelet count (the variables in S index formula) between groups in our study, whereas in the original publication, they were significantly different. So the S index cut point value in our study was different from the original publication. The other hypothesis is the S index formula is not proper to predict fibrosis in Thai population.

In our study, the appropriate S index cut point value for predicting significant fibrosis (group 1) was ≥0.771 (sensitivity 80%, specificity 44.4%, PPV 32.4%, NPV 87%, AUROC 0.597).

The indication for treatment of chronic hepatitis B is significant histological inflammation (A2-3) and/or significant fibrosis. Most guidelines recommend the use of significant fibrosis or necroinflammation to guide the therapy. We analyzed for the appropriate S index cut point value to predict this significant histology (group 2).The best score was ≥0.587 which had sensitivity 82.6%, specificity 35.1%, PPV 42.2%, NPV 76.5%, AUROC 0.609.

Although our results were not able to predict significant fibrosis accurately, we could apply using S index as a screening model for considering liver biopsy because its main value is to reduce the need for liver biopsy rather than to substitute liver biopsy.

Figure 3 shows algorithm of S index value in diagnostic yields in our study. For detection of significant fibrosis, the best cut point value was ≥0.771, that needed to perform liver biopsy in 40 patients (66.66%), there were missed diagnosis in 3 patients (20%), the accuracy =53.3%. For detection of significant histology (F2-4, and/or A2-3), the S index cut point value

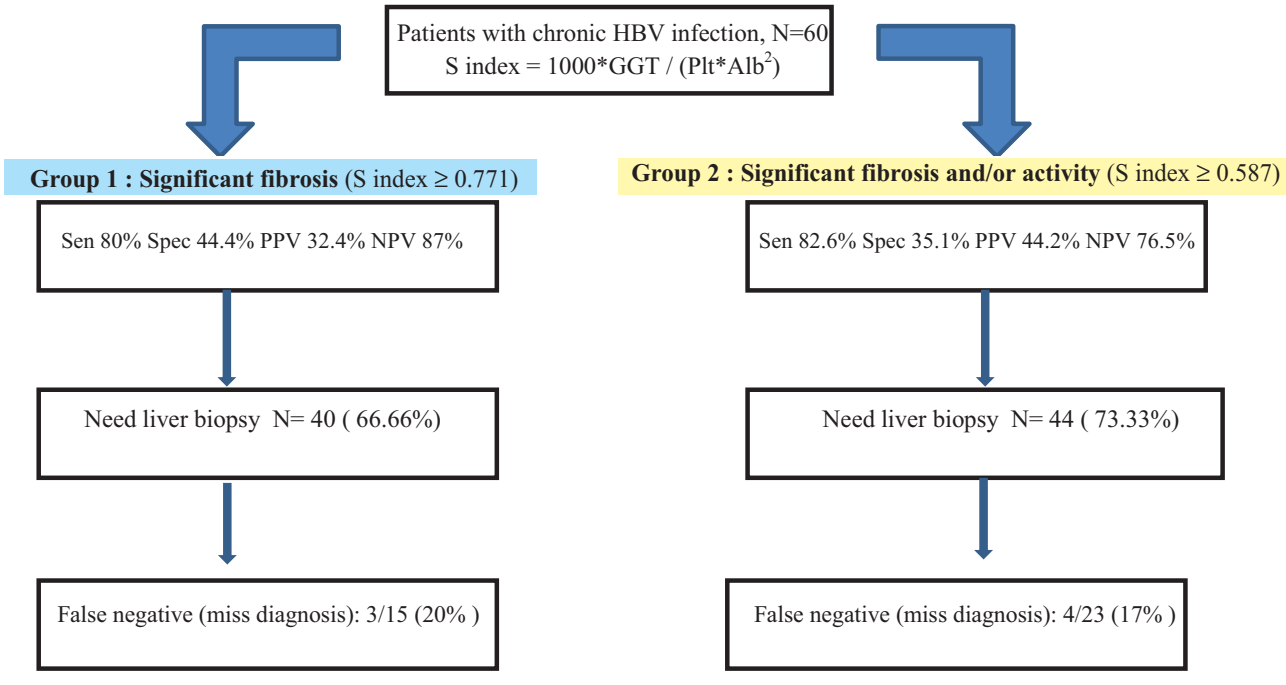

Figure 3. Summary algorithm of S index in diagnostic yield.

was ≥0.587, that needed liver biopsy in 44 patients (73.33%), and missed diagnosis was found in 4 patients (17%), the accuracy =53.3%.

Conclusion

A simple noninvasive predictive model as S index has potential to be used as a screening method for considering liver biopsy because it is easy to calculate requiring only routine laboratory tests, however it has fair accuracy. More controlled population is needed to find out the good cut-point value of S index with high accuracy in the further study.

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