

A simple algorithm for non-invasive diagnosis of significant liver histological changes in patients with CHB and normal or mildly elevated alanine transaminase levels

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Abstract

Significant liver histological changes (SLHC) were defined as moderate to severe liver inflammation (A2 or higher) and/or fibrosis (F2 or higher) using the METAVIR scoring system. This study aimed to develop an algorithm for the non-invasive detection of SLHC in patients with chronic hepatitis B (CHB) and normal or mildly elevated alanine transaminase (ALT) levels.

Using liver histology as gold standard, we developed a simple algorithm for the diagnosis of SLHC in a training set (504 patients), and then validated the diagnostic accuracy in a validation set (166 patients).

A new algorithm (AAG) attributed to age, ALT, and gamma-glutamyl transpeptidase (GGT) was developed. In the training set, the area under ROC curve (AUROC) of AAG was significantly higher than that of ALT, aspartate transaminase (AST), GPR, and APRI for the diagnosis of SLHC (0.74, 0.68, 0.65, 0.56, and 0.53, respectively; all $P < .05$). In the validation set, the AUROC of AAG was also higher than that of ALT, AST, GPR, and APRI (0.73, 0.65, 0.62, 0.62, and 0.61, respectively; all $P < .05$). Using $AAG \geq 2$, the sensitivity and negative predictive value was 84% to 98% and 75% to 94%, respectively, for the diagnosis of SLHC. Using $AAG \geq 6$, the specificity and positive predictive value was 93% to 97% and 67% to 79%, respectively, for the diagnosis of SLHC.

The AAG algorithm represents a novel noninvasive method for the diagnosis of SLHC in CHB patients with normal or mildly elevated ALT levels.

Abbreviations: AASLD = American Association for the Study of Liver Diseases, ALT = alanine transaminase, APRI = aspartate transaminase to platelet ratio index, AST = aspartate transaminase, AUROC = area under the receiver operating characteristic curve, CHB = chronic hepatitis B, CI = confidence interval, EASL = European Association for the Study of Liver Diseases, GGT = gamma-glutamyl-transpeptidase, GPR = gamma-glutamyl-transpeptidase to platelet ratio, HBsAg = HBV surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, LSM = liver stiffness measurement, NPV = negative predictive value, PPV = positive predictive value, ROC curve = receiver operating characteristic curve, SLHC = significant liver histological changes, ULN = upper limit of normal.

Keywords: chronic hepatitis B, liver fibrosis, liver inflammation, non-invasive tests, significant liver histological changes

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QL, CH, and WX contributed equally in this study.

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1. Introduction

Infection with hepatitis B virus (HBV) remains a global public health problem. Approximately 240 million people are HBV surface antigen (HBsAg) carriers.^[1] Chronic HBV infection can lead to a progressive accumulation of liver histological injury which progressively evolves to cirrhosis, hepatocellular carcinoma (HCC), or liver failure.^[2] The number of HBV related deaths increased between 1990 and 2013 by 33%, relating to 686,000 cases in 2013 worldwide.^[3,4]

The main goal of treatment for patients with chronic hepatitis B (CHB) is to improve survival and quality of life by preventing disease progression, and consequently HCC development.^[4] Achieving the goal depends on the prompt and timely antiviral therapy. According to the guideline for treatment of CHB, patients with significant liver histological changes (SLHC) defined as moderate to severe inflammation (METAVIR A2 or higher) and/or fibrosis (METAVIR F2 or higher) should be considered for antiviral therapy.^[5] Therefore, the diagnosis of SLHC is important for physicians to decide treatment initiation for CHB patients.

Liver biopsy is the reference procedure for liver inflammation and fibrosis evaluation, but its invasive nature makes it unsuitable as first-line procedure.^[6] The alanine transaminase (ALT) has been used to assess liver inflammation, but has no diagnostic value for

liver fibrosis.^[7] Blood fibrosis tests and liver stiffness measurement (LSM) by FibroScan have been used for evaluation of liver fibrosis, but have no diagnostic value for liver inflammation.^[8] Liver inflammation and fibrosis should be taken into account simultaneously for the treatment decisions of CHB patients. Therefore, the noninvasive method for the diagnosis of SLHC is urgently needed.

In clinical practice, physicians encounter challenges in the evaluation of the severity of liver disease in CHB patients with normal or mildly elevated ALT levels. Therefore, in this study, we aimed to develop an algorithm that can be easily used by physicians to detect SLHC in CHB patients with normal or mildly elevated ALT levels.

2. Patients and methods

2.1. Patients

A total of 1327 consecutive CHB patients who underwent liver biopsies in Shanghai Public Health Clinical Center, China,

between January 2010 and January 2017, were retrospectively recruited. Exclusive criteria:

1. alcohol consumption > 20g/d (n=103),
2. with non-alcoholic fatty liver disease (n=128),
3. hepatitis C virus, hepatitis D virus, or HIV co-infection (n=87),
4. with autoimmune liver disease (n=40),
5. antiviral therapy before liver biopsy (n=147), and
6. ALT \geq 2 times upper limit of normal (ULN) (n=152) (ULN is 40IU/ml^[4,9,10]).

Finally, 670 treatment-naïve CHB patients with ALT \leq 2 ULN were included. The 504 patients between January 2010 and January 2015 constituted the training set, and 166 patients between February 2015 and January 2017 constituted the validation set. Figure 1 is the flow diagram of the study population.

The study protocol conformed to the ethical guidelines of the *Declaration of Helsinki*, and was permitted by the ethics

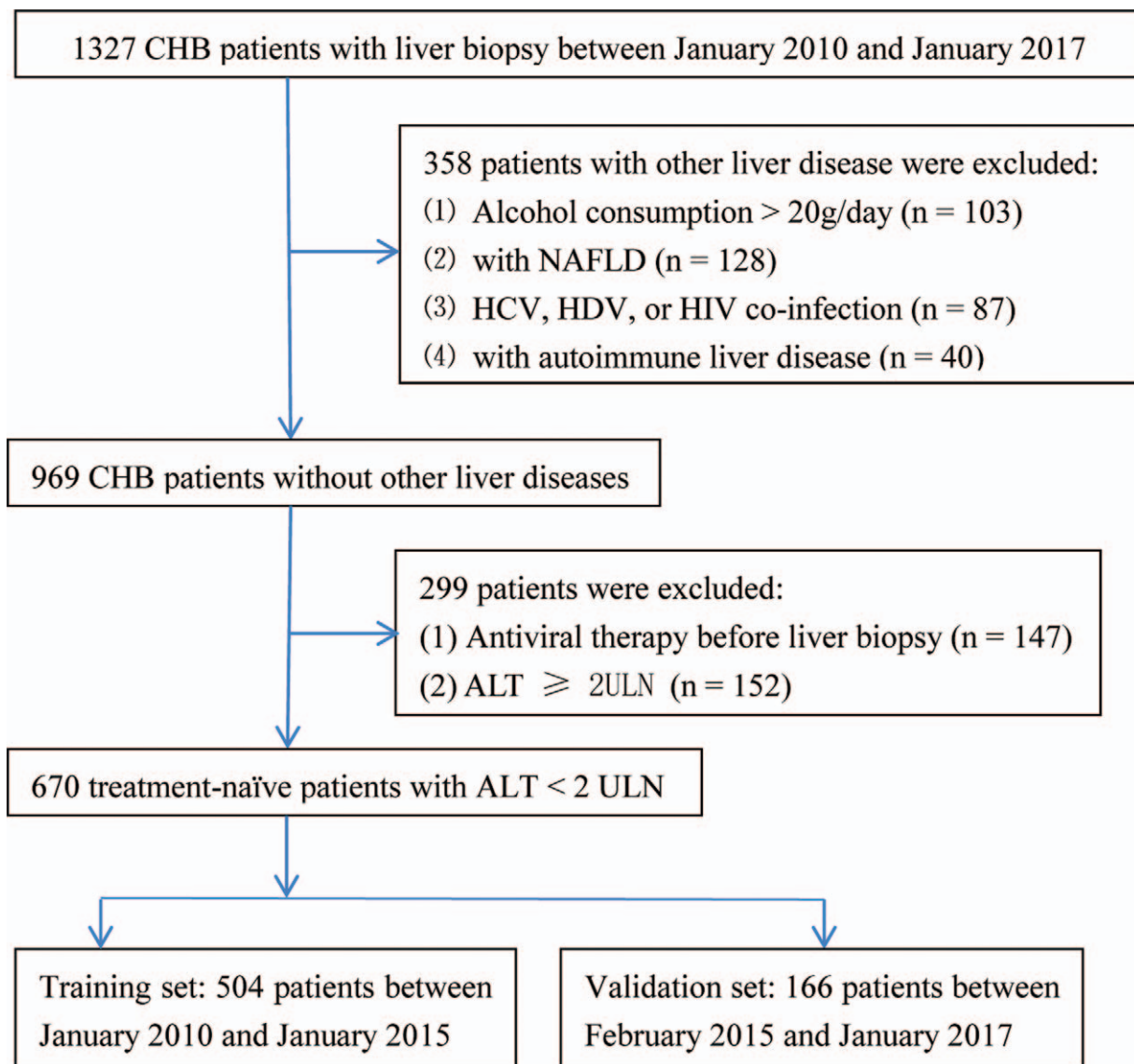


Figure 1. Flow diagram of the study population. ALT=alanine transaminase, CHB=chronic hepatitis B, HCV=hepatitis C virus, HDV=hepatitis D virus, HIV=human immunodeficiency virus, NAFLD=non-alcoholic fatty liver disease, ULN=upper limit of normal.

committee of Shanghai Public Health Clinical Center. All patients signed the informed consent before liver biopsy, and all experiments were performed in accordance with relevant guidelines and regulations.^[9,11]

2.2. Liver biopsy

All patients had a liver biopsy taken and used as the reference for liver inflammation and fibrosis evaluation. A minimum of 15 mm of liver tissue with at least 6 portal tracts were considered suitable for liver histological scoring.^[11] Liver pathological examinations were performed by 2 pathologists specialized in hepatology and blinded for patient data. In case of discrepancies, slides were reviewed by a third senior pathologist. Liver inflammation and fibrosis scoring refers to the METAVIR staging system.^[12]

2.3. Blood tests

Fasting blood samples were taken. The biochemical parameters including ALT, aspartate transaminase (AST), and gamma-glutamyl transpeptidase (GGT) were measured using a biochemistry analyzer (7600 Series; Hitachi, Tokyo, Japan). The platelet count test was conducted with a hematology analyzer (XT-2000i, Sysmex, Kobe, Japan). The HBV DNA levels were quantified using real-time PCR (ABI 7500; Applied Biosystems, Foster City, CA) with the lowest detection limit of 500 copies/mL. According to published formulas, the calculation of blood fibrosis tests are aspartate transaminase to platelet ratio index (APRI)^[13] and gamma-glutamyl transpeptidase to platelet ratio (GPR).^[14]

2.4. Statistics

In order to identify predictors of SLHC, univariable logistic regression was computed for the following variables: age, sex, HBeAg, HBV DNA, ALT, AST, alkaline phosphatase, GGT, total bilirubin, albumin, globulin, and platelet count. Multiple logistic regression models were then fitted by including all the factors associated with SLHC in the univariable logistic regression ($P < .05$). The independent predictors of SLHC were transformed into ordinal variables according to the thresholds corresponding to 33% and 66% prevalence for SLHC. The ALT and GGT were capped at four points, to keep ALT and GGT from weighing too heavily in the AAG algorithm. The β coefficients of the multivariate analysis were used to determine the AAG algorithm. The diagnostic accuracies of noninvasive tests were expressed as the area under ROC curve (AUROC) and compared using the DeLong test.^[15] Two sets of cut-offs were calculated: (1) obtaining a sensitivity of at least 90%, or (2) obtaining a specificity of at least 90%. All significance tests were two-tailed, and $P < .05$ was considered statistically significant. Statistical analyses were performed using SPSS version 18.0 software (IBM, Armonk, NY) and MedCalc Statistical Software version 16.1 (MedCalc Software bvba, Ostend, Belgium).

3. Results

3.1. Patient characteristics

Patient characteristics were detailed in Table 1. In the training set, 59.5% of patients were male, 65.7% were HBeAg positive, and median age of patients was 35 years. The prevalence of SLHC was 40.7% in the training set, and 44.6% in the validation set.

Table 1

Baseline characteristics of the study population.

Characteristics	Training set (n=504)	Validation set (n=166)	P
Age (years)	35 (28–42)	34 (27–39)	.132
Male gender, n (%)	300 (59.5%)	104 (62.7%)	.475
HBeAg positive, n (%)	331 (65.7%)	110 (66.3%)	.889
HBV DNA (log ₁₀ copies/mL)	5.8 (4.0–7.5)	6.2 (5.0–8.0)	<.001
ALT (IU/L)	35 (26–52)	36 (28–53)	.103
AST (IU/L)	29 (23–36)	28 (22–38)	.687
Alkaline phosphatase (IU/L)	71 (58–86)	70 (58–83)	.625
GGT (IU/L)	21 (14–34)	20 (13–32)	.185
Total bilirubin (μmol/L)	13 (10–17)	12 (10–16)	.273
Albumin (g/L)	44 (41–47)	45 (41–47)	.111
Globulin (g/L)	29 (27–32)	30 (27–32)	.832
Platelet count (10 ⁹ /L)	170 ± 55	172 ± 53	.774
SLHC, n (%)	205 (40.7%)	74 (44.6%)	.376
Liver Inflammation stage			
A0	93 (18.5%)	27 (16.3%)	.524
A1	240 (47.6%)	73 (44.0%)	.415
A2	121 (24.0%)	49 (29.5%)	.157
A3	50 (9.9%)	17 (10.2%)	.905
Liver fibrosis stage			
F0	61 (12.1%)	19 (11.4%)	.821
F1	299 (59.3%)	100 (60.2%)	.835
F2	71 (14.1%)	25 (15.1%)	.756
F3	32 (6.3%)	9 (5.4%)	.665
F4	41 (8.1%)	13 (7.8%)	.901

ALT = alanine transaminase, AST = aspartate transaminase, GGT = gamma-glutamyl transpeptidase, SLHC = significant liver histological changes.

No significant differences were found between the training and validation sets, except HBV DNA which was higher in the validation set (6.2 vs 5.8 log₁₀ copies/ml, $P < .001$). Although 6.2 and 5.8 log₁₀ copies/ml was statistically different, clinically these were not really distinguishable. Therefore, the training set was comparable with the validation set in the baseline characteristics.

3.2. Develop a simple noninvasive diagnostic model for SLHC

By univariate and multivariate regression analysis, age (OR = 1.024, 95% CI, 1.000–1.049, $P = .049$), ALT (OR = 1.028, 95% CI, 1.012–1.044, $P < .001$), and GGT (OR = 1.028, 95% CI, 1.017–1.040, $P < .001$) were identified as the independent predictors of SLHC (Table 2). The β coefficients of the multivariate analysis were used to determine a new algorithm for SLHC: the AAG algorithm (Table 3).

3.3. Compare the AAG algorithm and commonly used noninvasive tests.

The diagnostic performance of the AAG algorithm for SLHC was evaluated in the training set and validation set, respectively, versus commonly used noninvasive tests (Table 4). In the training set, the AUROC of AAG was significantly higher than that of ALT, AST, GPR, and APRI (0.74, 0.68, 0.65, 0.56, and 0.53, respectively; all $P < .05$). In the validation set, the AUROC of AAG was also higher than that of ALT, AST, GPR, and APRI (0.73, 0.65, 0.62, 0.62, and 0.61, respectively; all $P < .05$). The ROC curves were shown in Figure 2.

Table 2
The independent predictors of SLHC.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	1.028 (1.007–1.049)	.008	1.024 (1.000–1.049)	.049
Male	2.086 (1.434–3.034)	<.001	1.145 (0.714–1.834)	.574
HBeAg positive	1.414 (0.967–2.068)	.074		
HBV DNA (copies/ml)	1.117 (1.011–1.235)	.030	1.048 (0.996–1.105)	.092
ALT (IU/L)	1.038 (1.026–1.049)	<.001	1.028 (1.012–1.044)	<.001
AST (IU/L)	1.040 (1.023–1.056)	<.001	1.006 (0.988–1.024)	.536
Alkaline phosphatase (IU/L)	1.013 (1.006–1.021)	<.001	1.001 (0.992–1.010)	.860
GGT (IU/L)	1.035 (1.024–1.046)	<.001	1.028 (1.017–1.040)	<.001
Total bilirubin (μ mol/L)	1.036 (1.012–1.061)	.003	1.028 (0.995–1.061)	.094
Albumin (g/L)	0.963 (0.924–1.003)	.072		
Globulin (g/L)	1.018 (0.979–1.058)	.364		
Platelet count ($10^9/L$)	0.995 (0.992–0.998)	.003	0.999 (0.995–1.003)	.574

ALT=alanine transaminase, AST=aspartate transaminase, CI=confidence interval, GGT=gamma-glutamyl-transpeptidase, OR=odds ratios, SLHC=significant liver histological changes.

3.4. Diagnostic thresholds of the AAG algorithm for SLHC

Diagnostic thresholds of the AAG algorithm for SLHC were presented in Table 5. By obtaining a sensitivity of at least 90%, the cut-off value of AAG was 2 (the sensitivity and negative predictive value was 84% to 98% and 75% to 94%, respectively). By obtaining a specificity of at least 90%, the cut-off of AAG was 6 (the specificity and positive predictive value was 93% to 97% and 67% to 79%, respectively).

4. Discussion

Despite the recommendation of early treatment for CHB patients by all guidelines, many patients were treated belatedly when liver-related complications appeared.^[4,5,10] For CHB patients who had ALT > 2 ULN and high HBV DNA levels, guidelines recommended commencement of antiviral therapy and liver histological evaluation may not be necessary.^[4,5,10] For patients who had ALT \leq 2 ULN, liver histological evaluation is necessary for the decision of antiviral therapy. If liver histological evaluation confirmed patients having SLHC, antiviral therapy was recommended.^[5] Therefore, it is important to develop simple and accurate tools able of identifying SLHC in CHB patients with ALT \leq 2 ULN.

The ALT and AST are the most commonly used markers for the noninvasive diagnosis of liver inflammation, but cannot predict the severity of liver fibrosis. The GPR and APRI are simple and commonly available blood fibrosis tests, but cannot evaluate the severity of liver inflammation.^[14,16,17] In this study, we developed a novel noninvasive algorithm, the AAG, to identify patients with SLHC. The AAG algorithm is based on parameters commonly assessed in patients with CHB, which makes AAG easier to use in clinical practice. More importantly, the AAG algorithm can predict SLHC, rather than liver inflammation or fibrosis solely. The purpose of AAG is to be used by physician to identify patients with SLHC who require further evaluation with liver biopsy or should be considered for antiviral therapy.

In this study, AAG \geq 2 was more sensitive (84–98%) and less specific (22–38%) for the diagnosis of SLHC. Therefore, AAG \geq 2 could be used for the screening of SLHC but at the cost of a higher rate of patients requiring a second-line test such as liver biopsy. AAG \geq 6 was more specific (93–97%) and less sensitive (15–22%) for the diagnosis of SLHC. Therefore, AAG \geq 6 could be used for diagnosing SLHC, and avoiding partly liver biopsy. In a word, although the AAG algorithm cannot replace liver biopsy, it can select the candidates for liver biopsy, avoid excessive liver biopsy, and narrow down the group which really needs liver biopsy.

Table 3
The AAG algorithm.

Item	Points	
Age (years)	<30	0
	30–40	1
	\geq 40	3
ALT (IU/L)	<20	0
	20–40	1
	40–60	2
	\geq 60	4
GGT (IU/L)	<20	0
	20–40	1
	40–60	2
	\geq 60	4

The independent predictors of SLHC were transformed into ordinal variables according to the thresholds corresponding to 33% and 66% prevalence for SLHC. The ALT and GGT were capped at four points, to keep ALT and GGT from weighing too heavily in the AAG algorithm. ALT=alanine transaminase, GGT=gamma-glutamyl transpeptidase.

Table 4
Diagnostic performances of the AAG algorithm for SLHC.

	Training set		Validation set	
	AUROC	(95% CI)	AUROC	(95% CI)
AAG	0.74	(0.70–0.78)	0.73	(0.65–0.79)
ALT	0.68	(0.64–0.72)	0.65	(0.57–0.72)
AST	0.65	(0.61–0.69)	0.62	(0.54–0.70)
GPR	0.56	(0.51–0.60)	0.62	(0.54–0.69)
APRI	0.53	(0.48–0.57)	0.61	(0.54–0.68)
Comparison of AUROC				
AAG vs ALT	$P=.001$		$P=.012$	
AAG vs AST	$P<.001$		$P=.004$	
AAG vs GPR	$P<.001$		$P=.017$	
AAG vs APRI	$P<.001$		$P=.005$	

AAG=a simple algorithm attributed to age, ALT, and GGT, ALT=alanine transaminase, APRI=aspartate transaminase to platelet ratio index, AST=aspartate transaminase, AUROC=area under the ROC curve, CI=confidence interval, GPR=gamma-glutamyl transpeptidase to platelet ratio, SLHC=significant liver histological changes.

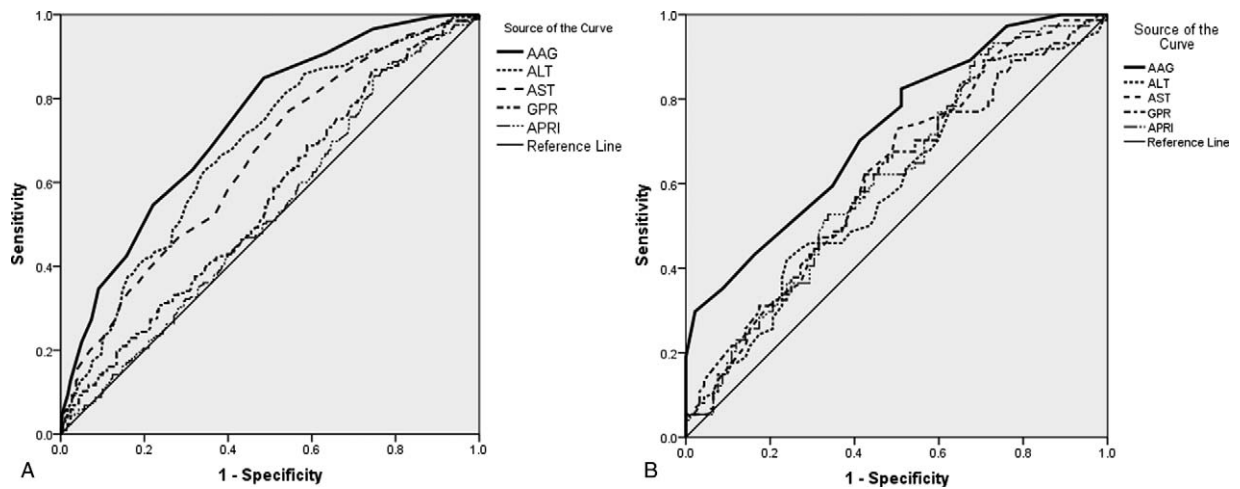


Figure 2. ROC curves of noninvasive tests for SLHC in training (A) and validation set (B). AAG=a new algorithm attributed to age, ALT=and gamma-glutamyl transpeptidase, APRI=aspartate transaminase to platelet ratio, GPR=gamma-glutamyl transpeptidase to platelet ratio, SLHC=significant liver histological changes.

In the training set, the prevalence of SLHC in patients <30 years is 13/138 (9.4%). Because the prevalence of SLHC is less than 10%, thus, the weight of age <30 years is given as 0 point. The prevalence of SLHC is 45/157 (29%) in age 30 to 40 years, and 147/209 (70%) in age ≥ 40 years, respectively. Thus, we weight the points of age 30 to 40 is 1 (the prevalence of SLHC <33%), weight the points of age ≥40 is 3 (the prevalence of SLHC >66%) instead of 2 (the prevalence of SLHC for 33–66%).

In the training set, the AUROC of AAG (0.74) is higher than ALT (0.68), and their 95% CI is coincident (0.70–0.78 vs 0.64–0.72). In order to show the difference between AAG and ALT in real clinical practice, we showed that how many more SLHC patients were correctly classified when using AAG versus ALT in the training set of 504 patients. By obtaining a sensitivity of at least 90%, the cut-off value was 2 for AAG, and 23 IU/L for ALT, respectively. By obtaining a specificity of at least 90%, the cut-off value was 6 for AAG, and 60 IU/L for ALT, respectively (Table 5). In their low cut-off (AAG ≥ 2, ALT ≥ 23 IU/L) for screening SLHC, 67/71 (94%) and 76/93 (82%) patients were correctly classified by using AAG and ALT, respectively. In their high cut-off (AAG ≥ 6, ALT ≥ 60 IU/L) for making the diagnosis of SLHC, 73/112 (65%) and 46/76 (60%) patients were correctly classified by using AAG and ALT, respectively. These data show that more patients with SLHC were correctly screened using AAG ≥ 2

versus ALT ≥ 23 IU/L, and more SLHC patients were correctly diagnosed when using AAG ≥ 6 versus ALT ≥ 60 IU/L.

A meta-analysis of APRI in 1798 HBV patients found mean AUROC values of 0.79 and 0.75 for significant fibrosis and cirrhosis, respectively.^[18] A retrospective study in China of 1168 patients with chronic HBV infection reported AUROCs of 0.67 and 0.71 for GPR and of 0.68 and 0.66 for APRI, for significant fibrosis and cirrhosis, respectively.^[19] However, in this study, the area under the APRI curve was 0.53, and the GPR was 0.56, which was significantly lower than the previously published data. The possible reasons were as follows. The AAG algorithm represents a novel noninvasive method for the diagnosis of SLHC (significant fibrosis and/or significant inflammation). In order to compare with AAG, we evaluated the AUOROCs of APRI and GPR for the diagnosis of SLHC rather than liver fibrosis solely. Because GPR and APRI have no diagnostic value for liver inflammation, the AUROCs for SLHC (considering inflammation and fibrosis simultaneously) were lower than that for liver fibrosis solely.

In this study, age was identified as an independent predictor of SLHC. This result was consistent with the guidelines, which recommended age as one of the considerations for liver biopsy and treatment decision.^[4,5] The American Association for the Study of Liver Diseases (AASLD) guidelines recommended that liver biopsy should be considered in patients with persistent

Table 5
Diagnostic thresholds of the AAG algorithm for SLHC.

	Cut-off		Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	-LR
AAG	2*	Training set	98	22	46	94	1.26	0.09
		Validation set	84	38	52	75	1.35	0.43
	6**	Training set	22	93	67	63	2.98	0.84
		Validation set	15	97	79	59	4.56	0.88
ALT	23*	Training set	90	27	45	80	1.24	0.36
	60**	Training set	19	90	57	62	1.96	0.90

Cut-off* was established by obtaining a sensitivity of at least 90%; Cut-off** was established by obtaining a specificity of at least 90%; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio.

AAG=a new algorithm attributed to age, ALT, and GGT, SLHC=significant liver histological changes.

borderline normal or slightly elevated ALT, particularly in patients over age 40 years.^[5] The European Association for the Study of Liver Diseases (EASL) guidelines recommended that patients with HBeAg-positive, persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years.^[4]

In this study, we found that GGT was an independent predictor of SLHC. Previous studies have also shown that GGT was a risk factor for the progress of liver disease in CHB patients.^[14,20] Myers et al found that GGT was a predictor of significant liver inflammation in CHB patients.^[20] Lemoine et al found that GGT correlated with significant liver fibrosis in CHB patients ($r=0.48$, $P<.0001$).^[14] Yu et al also found that GGT was an independent predictor of liver inflammation (OR=1.007, $P=.03$) and liver fibrosis (OR=1.009, $P=.003$) in CHB patients.^[21]

This study has some limitations. First, the retrospective design might have caused selective bias. Therefore, prospective studies will be necessary to validate the clinical application of the AAG algorithm. Second, our study was performed in patients from a tertiary centers. Further works are required to validate the diagnostic performance of the AAG algorithm in primary care settings. Third, our study excluded patients with antiviral therapy, other liver diseases, or ALT >2 ULN. Consequently, the diagnostic value of AAG algorithm is unclear in patients with such conditions.

In conclusion, the AAG algorithm is a new, simple, noninvasive method, which can identify patients having SLHC with impaired prognosis and need antiviral therapy. The AAG algorithm defines a pathway help to decide the treatment initiation and timing of liver biopsy.

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