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Applicability of liver stiffness measurement based nomograms to the assessments of hepatitis B related significant fibrosis and cirrhosis

Si-Si Ji, Hai-Dan Jiang, Jia-Chun Jiang, Jia Li, Shu-Ting Lin, Bin Chen*, Shi-Hao Xu*

Department of Ultrasonography, the First Affiliated Hospital of Wenzhou Medical University, China

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ABSTRACT

Background: We evaluated liver fibrosis in patients with chronic hepatitis B (CHB) and mildly raised alanine transaminase (ALT) activities between 1–2 times the upper limit of normal (ULN) which was near the threshold for initiating treatment.

Methods: Nomogram-Fibrosis and Nomogram-Cirrhosis were elaborated with variables independently associated with significant fibrosis and cirrhosis determined by multivariate logistic regression. Calibration, receiver operator characteristic (ROC) and decision curves were applied to comparing nomograms with aspartate aminotransferase (AST) to platelet count (PLT) ratio index (APRI), age-AST-PLT-ALT index (FIB-4) and liver stiffness measurement (LSM).

Results: The Nomogram-Fibrosis was constructed with LSM, PLT, and gamma-glutamyl transpeptidase (GGT). Nomogram-Cirrhosis contained one more variable of age other than Nomogram-Fibrosis. The calibration demonstrated that the assessments of significant fibrosis or cirrhosis by nomograms were in line with liver biopsy. The AUROC of Nomogram-Fibrosis was 0.788, lager than APRI (0.586), FIB-4 (0.656) and LSM (0.735). The AUROC of Nomogram-Cirrhosis was 0.889, larger than APRI (0.642), FIB-4 (0.725) and LSM (0.837). Furthermore, the decision curve analysis suggested the most net benefits were provided by the nomograms.

Conclusions: Nomogram-Fibrosis and Nomogram-Cirrhosis could be promising tools for recognizing significant fibrosis and cirrhosis for CHB patients with mild raised ALT activities.

1. Introduction

It is estimated that about 6% of the world's population are chronically infected with hepatitis B virus (HBV) [1] which caused approximately one-third of cirrhosis worldwide [2]. Treatment for chronic HBV infected (CHB) patients are recommended on the basis of three criteria: serum alanine aminotransferase (ALT) activities, serum HBV DNA and severity of liver disease [2,3]. For patients with minimaly raised ALT but < 2 times the upper limit of normal (ULN), it is unanimously agreed that antivirus therapy should be initiated where there is significant fibrosis in aimed at inhibiting the progression of fibrosis and development of other complications [2,3]. Therefore, the assessment of the extent of hepatic fibrosis is essential for making clinical decision and predicting prognosis for patients with this frequent condition.

Liver biopsy is traditionally recognized as a “gold standard” for staging liver fibrosis [4]. However, liver biopsy has several disadvantages including sampling errors, high costs, subjectivity in reporting and discomfort and risk for recipients [5,6]. More importantly, this invasive measurement is inappropriate for long-term dynamic fibrosis monitoring. For these reasons, some non-invasive algorithms for assessment of liver fibrosis stage have been developed as promising alternative methods to liver biopsy recently [7,8].

Scoring systems based on clinical parameters like aspartate aminotransferase (AST) to platelet (PLT) ratio index (APRI) and age-AST-PLT-ALT index (FIB-4) have been applied to hepatic fibrosis evaluation for patients with CHB [9,10]. Due to the characteristics of safety, inexpensive and accessibility, APRI and FIB-4 have been recommended to rule out advanced liver fibrosis for CHB in resource-limited countries by the World Health Organization (WHO) guidelines [11]. Whereas, their accuracy for assessing the severity of CHB related hepatic fibrosis remains controversial in previous studies [12,13].

Recently, liver stiffness measurement (LSM) by transient elastography (TE) has emerged as a favorable non-invasive examination for numerical fibrosis test [14,15]. It has been widely reported as a reproducible and potential measurement for assessing the degree of fibrosis in various liver diseases [8,16]. However, LSM has been

* Corresponding authors at: Department of Ultrasonography, the First Affiliated Hospital of Wenzhou Medical University, Nanbaixiang, Ouhai District, Wenzhou 325000, China.

E-mail addresses: doctorchbe@126.com (B. Chen), dcxshvip@wmu.edu.cn (S.-H. Xu).

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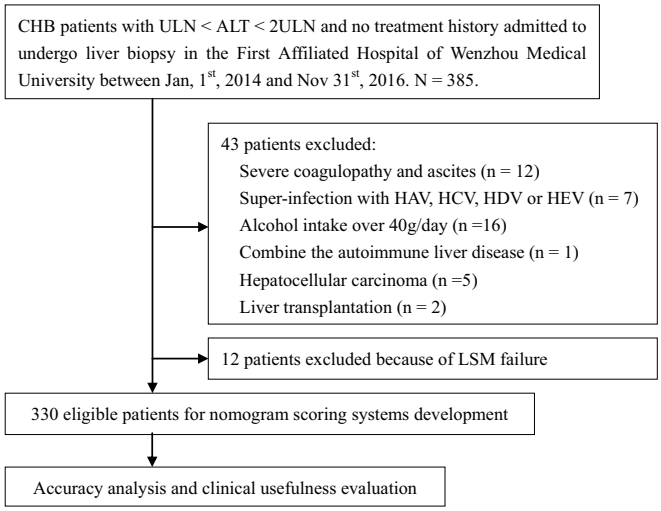

Fig. 1. Flowchart for participants inclusion. CHB, chronic hepatitis B.

Table 1
Clinical characteristics of patients.

Variables	Mean ± SE/proportion
Age (y)	40.32 ± 9.06
Male gender[a] (%)	213 (61%)
ALT (U/l)	68.74 ± 12.41
AST (U/l)	64.42 ± 19.76
ALP (U/l)	79.61 ± 25.41
GGT (U/l)	27.83 ± 20.19
TBil (mg/dl)	11.99 ± 5.39
Albumin (g/l)	41.79 ± 3.70
Total protein (g/l)	71.06 ± 5.79
PLT (g/l)	177.02 ± 49.22
Leukocyte ($\times 10^9$/l)	5.91 ± 1.62
HBV DNA (log10 IU/ml)	5.62 ± 2.17
HBeAg[a] (positivity rate, %)	185 (53.6%)
LSM (kPa)	9.00 ± 3.92
APRI	1.15 ± 0.69
FIB-4	2.00 ± 1.37
Ishak fibrosis score (0-1-2/3-4/5-6)	105/185/40

[a] Dichotomous values. ALP, alkaline phosphatase; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis 4 score; G LSM, liver stiffness measurement.

hampered to replace liver biopsy by the different cutoff values from different studies [17–20]. One reason is that the accuracy of LSM value could be confounded by severe inflammatory infiltration, hepatocyte swelling and tissue edema associated with increased ALT activities [21,22].

Nomogram is a graphic calculating tool helping clinicians quickly evaluate patients with specific models in a visual way, which does not require complex interpretation by computer software. It has been applied to various diseases and shown superior to conventional methods in clinical practice for severity evaluation, prognostic prediction and therapy selection [23]. To improve the non-invasive assessment of significant fibrosis and cirrhosis for CHB patients with minimally raised ALT activities, we constructed nomogram scoring systems based on optimized combination of LSM and accessible clinical parameters and evaluated the diagnostic ability of the nomograms in comparison with APRI, FIB-4 and LSM alone.

2. Materials and methods

2.1. Patients

From 2014 to 2016, patients (N = 330) with CHB but no treatment history who were admitted for liver biopsy were prospectively recruited from the First Affiliated Hospital of Wenzhou Medical University. The participants enrolled in this study had to meet the condition of ALT over ULN (the ULN was defined as 50 IU/l) and less than 2ULN. All the patients were > 18 y and signed informed consent forms before participating in this study. Chronic HBV infection was confirmed by positive hepatitis B surface antigen (HBsAg) for at least 6 months and detectable serum HBV DNA. Patients would be excluded if one of the following conditions was true: previously diagnosed with significant fibrosis or cirrhosis; severe coagulopathy and ascites; alcohol intake over 40 g/day; clinical evidences of other causes of liver disease; co-infection with other hepatitis virus or human immunodeficiency virus; combination of hepatocellular carcinoma or other malignancies; prior liver transplant therapy. The protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. All the laboratory tests were done no > 12 h before liver biopsy was performed.

2.2. Liver stiffness measurement

Liver stiffness measurements were performed using Fibroscan 502 (Echosens) according to the manufacturer instructions (in kilopascals). FibroScan examinations consisted of > 10 validated measurements with a success rate of > 60% and an interquartile range < 30% of the median ratio was considered to be reliable.

2.3. Liver biopsy

After signing a written informed consent, every patient underwent a liver biopsy. Liver samples were obtained from the right lobe of liver using 16G Temno needle under ultrasound guidance. Liver specimens were fixed in formalin, embedded in paraffin and independently and triply analyzed by three experienced pathologists with information of only random code. The degree of liver fibrosis was determined according to the Ishak scoring system [24,25]. Significant fibrosis was defined as Ishak ≥3. Cirrhosis was defined as Ishak grade 5 and 6 [2,26].

2.4. Formulas

APRI and FIB-4 scores were calculated using clinical and laboratory data based on the formulas illustrated as follows (ULN for AST was defined as 40 U/l for men and 35 U/l for women):

$$\text{APRI [27]} = (\text{AST} / \text{ULN}) / \text{PLT} \times 100.$$
$$\text{FIB-4 [28]} = (\text{Age} \times \text{AST}) / (\text{PLT} \times \sqrt{\text{ALT}}).$$

2.5. Statistics

Continuous variables were expressed as mean and standard derivation and compared using an independent-samples *t*-test. Categorical variables were expressed as proportions and compared using the χ^2 test and Mann-Whitney *U* test. Variables showed significant influences ($P < .05$) in univariate logistic regression analysis were further tested on a multivariate stepwise forward logistic regression with P value thresholds of 0.05 and 0.1 for stepwise entry and removal, respectively. The nomogram scoring systems for significant fibrosis (Nomogram-Fibrosis) and cirrhosis (Nomogram-Cirrhosis) for the evaluation of significant fibrosis and cirrhosis were developed using the rms package

Table 2
Univariate and multivariate logistic regression analysis for significant fibrosis and cirrhosis assessment for patients with CHB in training cohort.

	Univariate analysis			Multivariate analysis		
	OR	95%CI	P-value	OR	95%CI	P-value
Significant fibrosis						
Clinical parameters						
Age (y)	1.064	1.034–1.094	0.000			
Male gender[a]	1.711	0.897–2.317	NS			
Laboratory parameters						
ALT (IU/l)	1.008	0.989–1.027	NS			
AST (IU/l)	0.996	0.984–1.007	NS			
ALP (IU/l)	1.007	0.997–1.017	NS			
GGT (IU/l)	1.048	1.027–1.070	0.000	1.026	1.006–1.047	0.010
TBil (mg/dl)	1.027	0.982–1.074	NS			
Albumin (g/l)	0.974	0.914–1.037	NS			
Total protein (g/l)	0.999	0.960–1.040	NS			
PLT (g/l)	0.986	0.981–0.991	0.000	0.989	0.984–0.995	0.000
Leukocyte ($\times 10^9$/l)	0.950	0.824–1.094	NS			
HBV DNA (Log10 IU/ml)	0.952	0.855–1.059	NS			
HBeAg[a] (positivity rate, %)	0.926	0.582–1.475	NS			
LSM (kPa)	1.351	1.217–1.499	0.000	1.273	1.140–1.421	0.000
Cirrhosis						
Clinical parameters						
Age (y)	1.111	1.065–1.158	0.000	1.063	1.007–1.121	0.027
Male gender[a]	2.199	1.009–4.791	0.047			
Laboratory parameters						
ALT (IU/l)	1.012	0.986–1.039	NS			
AST (IU/l)	1.008	0.992–1.024	NS			
ALP (IU/l)	1.020	1.009–1.032	0.001			
GGT (IU/l)	1.031	1.016–1.046	0.000	1.023	1.007–1.121	0.005
TBil (mg/dl)	1.073	1.018–1.131	0.009			
Albumin (g/l)	0.935	0.854–1.023	NS			
Total protein (g/l)	0.964	0.909–1.022	NS			
PLT (g/l)	0.979	0.971–0.988	0.000	0.987	0.977–0.998	0.015
Leukocyte ($\times 10^9$/l)	0.986	0.802–1.212	NS			
HBV DNA (Log10 IU/ml)	0.883	0.756–1.030	NS			
HBeAg[a] (positivity rate, %)	0.527	0.269–1.033	NS			
LSM (kPa)	1.432	1.293–1.586	0.000	1.358	1.208–1.526	0.000

[a] Dichotomous values. LSM, liver stiffness measurement.

in R. The performances of established nomograms, APRI, FIB-4 and LSM alone were evaluated with the receiver operating characteristics curve (ROC) and calibration curve analysises. Decision curves were also plotted to describe the net benefit given by the nomograms, APRI, FIB-4, LSM and treat all/treat none strategies. Bootstrap resampling was used to address model overfit. All statistical tests were two-sided. Statistical significance was taken as $P < .05$. Statistical analysis was performed using SPSS ver. 22.0 and R 3.3.2 (http://www.r-project.org/).

3. Results

3.1. Patient characteristics

In total, 330 eligible patients were prospectively recruited (Fig. 1). The clinical features of the enrolled population are listed in Table 1.

3.2. Prognostic factors in cohort

Multivariate logistic analysis revealed that LSM (P = .000), PLT (P = .000), and GGT (P = .010) were independent risk factors associated with HBV related significant fibrosis, meanwhile, LSM (P = .000), age (P = .027), GGT (P = .005) and PLT (P = .015) were associated with cirrhosis (Table 2). When patients were stratified by observed liver fibrosis stage by liver biopsy examination, it was interesting to note that there were significant differences between subgroups of significant fibrosis and non-significant fibrosis for variables of age (P = .000, Table 3), GGT (P = .000), PLT (P = .000) and LSM (P = .000). Besides, variables of age (P = .000), gender (P = .043), ALP (P = .020), GGT (P = .000), TBil (P = .045), PLT (P = .000) and LSM (P = .000) were found to be statistically different between cirrhosis and non-cirrhosis subgroups.

3.3. Prognostic nomogram establishment and calibration

Prognostic nomograms for significant fibrosis (Nomogram-Fibrosis) and cirrhosis (Nomogram-Cirrhosis) assessments were established incorporated independent predictors (Fig. 2). A total score could be calculated as the sum of scores of associated predictors, and referred to the probability of significant fibrosis or cirrhosis in the bottom axis. For more accurate calculation of established probability of significant fibrosis and cirrhosis, the nomogram scoring systems (Table 4) could be utilized. For example, the total point of 65 in Nomogram-Fibrosis suggests that the probability of significant fibrosis is 95%, and the total point of 104 in Nomogram-Cirrhosis predicts a 95% probability of cirrhosis in CHB patients.

The calibration plots (Fig. 2C, D) for the probability of significant fibrosis and cirrhosis showed good agreement between the prediction by the nomograms and actual observation in liver biopsy.

Table 3
Characteristics of patients, stratified by fibrosis stage determined by liver biopsy.

Significant fibrosis	Yes (N = 225)	No (N = 105)	P
Clinical parameters			
Age (y)	41.82 ± 8.87	37.10 ± 8.66	0.000
Male gender[a]	148(66%)	60(57%)	NS
Laboratory parameters			
ALT (IU/l)	69.12 ± 12.68	67.94 ± 11.84	NS
AST (IU/l)	63.86 ± 19.61	65.61 ± 20.11	NS
ALP (IU/l)	80.93 ± 27.51	76.83 ± 20.15	NS
GGT (IU/l)	31.34 ± 21.94	20.34 ± 13.05	0.000
TBil (mg/dl)	12.22 ± 5.75	11.49 ± 4.50	NS
Albumin (g/l)	41.67 ± 3.85	42.04 ± 3.38	NS
Total protein (g/l)	71.05 ± 5.67	71.09 ± 6.08	NS
PLT (g/l)	166.78 ± 46.45	198.98 ± 47.98	0.000
Leukocyte ($\times 10^9$/l)	5.86 ± 1.67	6.00 ± 1.49	NS
HBV DNA (Log10 IU/ml)	5.55 ± 2.12	5.78 ± 2.30	NS
HBeAg[a] (positivity rate, %)	120 (53%)	58 (55%)	NS
LSM (kPa)	9.86 ± 4.17	7.16 ± 2.49	0.000
Cirrhosis	Yes (N = 40)	No (N = 290)	P
Clinical parameters			
Age (y)	47.40 ± 7.74	39.34 ± 8.81	0.000
Male gender[a]	31 (77%)	177 (61%)	0.043
Laboratory parameters			
ALT (IU/l)	70.41 ± 13.74	68.51 ± 12.23	NS
AST (IU/l)	67.19 ± 23.97	64.04 ± 19.12	NS
ALP (IU/l)	93.82 ± 40.17	77.70 ± 22.15	0.020
GGT (IU/l)	42.65 ± 18.97	25.78 ± 19.52	0.000
TBil (mg/dl)	14.13 ± 7.23	11.69 ± 5.03	0.045
Albumin (g/l)	40.99 ± 4.67	41.90 ± 3.55	NS
Total protein (g/l)	70.01 ± 6.34	71.21 ± 5.71	NS
PLT (g/l)	139.85 ± 49.79	182.15 ± 46.97	0.000
Leukocyte ($\times 10^9$/l)	5.87 ± 1.92	5.91 ± 1.58	NS
HBV DNA (Log10 IU/ml)	5.11 ± 1.84	5.70 ± 2.21	NS
HBeAg[a] (positivity rate, %)	16 (40%)	162 (56%)	NS
LSM (kPa)	14.19 ± 6.04	8.28 ± 2.89	0.000

[a] Dichotomous values. LSM, liver stiffness measurement.

3.4. Comparison of predictive accuracy of nomograms with APRI, FIB-4 scores and LSM

We used ROC to compare the accuracy of nomograms, APRI, FIB-4 and the single factor of LSM for fibrosis staging in CHB patients with ALT activity between 1 and 2 times the ULN in the cohort (Fig. 3A and B). The discrimination abilities of APRI and FIB-4 were unsatisfactory to recognize significant fibrosis (AUROC = 0.586, 95% CI 0.520–0.650 for APRI and AUROC = 0.656, 95% CI 0.593–0.719 for FIB-4). Even the simple index, LSM (AUROC = 0.735, 95% CI 0.677–0.792) performed better than APRI (P = .001) and FIB-4 (P = .046). Among them, the newly constructed Nomogram-Fibrosis (AUROC = 0.788, 95% CI 0.736–0.841) showed best discrimination power for significant fibrosis assessment (P < .000 for APRI or FIB-4, and 0.010 for LSM). Similarly, the AUROC of Nomogram-Cirrhosis for diagnosing cirrhosis (AUROC = 0.889, 95% CI 0.837–0.941) was significantly higher than APRI (AUROC = 0.642, 95% CI 0.532–0.752, P = .000), FIB-4 (AUROC = 0.725, 95% CI 0.629–0.820, P = .000) and LSM (AUROC = 0.837, 95% CI 0.765–0.909, P = .024).

In addition, the decision curve analysis was used to compare the clinical net benefit of the nomograms with LSM alone and the existing models of APRI and FIB-4 (Fig. 4). It was suggested that the Nomogram-Fibrosis provided a higher net benefit than LSM, APRI and FIB-4 at most threshold probabilities in training cohort. Our study revealed that the net benefit gained by Nomogram-Cirrhosis application also surpassed that by LSM, APRI and FIB-4.

4. Discussion

In this study, two nomogram systems were developed to evaluate the extent of liver fibrosis in a non-invasive way for CHB patients with increased ALT activities but < 2ULN. The Nomogram-Fibrosis was constructed to recognize significant fibrosis, consisting of variables of LSM, PLT and GGT. The Nomogram-Cirrhosis for cirrhosis assessment was constructed using another algorithm involving LSM, age, GGT and PLT. The constructed nomogram systems were readily available, helpful and user-friendly in clinical practice. Namely, we provided a new approach in nomogram form to recognize which patient have a more compelling need of liver biopsy for advanced fibrosis recognition and probably appropriate antivirus treatment.

Liver stiffness has been considered significantly associated with fibrosis stage in patients with chronic liver disease of various aetiologies including CHB [19,29–31]. Wong et al. developed an algorithm using LSM and Forns index to improve the discriminate power of LSM alone to predict advanced fibrosis in CHB [32]. It was implied that 50% of liver biopsy could be avoided by using their combined non-invasive algorithm [32]. Gaia et al. recruited 83 subjects with chronic viral hepatitis at the exclusion of acute or severe hepatitis and elaborated a nomogram incorporating LSM, PLT, ALT and ultrasound data for discriminating different fibrosis stages, which was proposed superior to LSM alone [8]. Paradoxically, also suggested by Gaia et al., LSM from mild fibrosis to cirrhosis was irregular and discontinuous in CHB cohort, even though the correlation of LSM with fibrosis stage was statistically significant which is in line with our data [20]. However, the disadvantages of their studies were the inappropriate range of ALT activity and/or the small proportion of the group with CHB on behalf of typical aetiologies in western countries. Our data indicated that LSM was independently associated with significant fibrosis or cirrhosis in 330 individuals with ULN < ALT < 2 ULN, which conformed to our previous studies [17].

The progression of CHB related liver fibrosis results in hypersplenism, which is associated with decreased PLT count [33]. PLT and GGT have been widely accepted as predictors for significant liver fibrosis and cirrhosis in patients with CHB [34–38]. Consistently, PLT and GGT were confirmed to be reliable indicators of significant liver fibrosis and cirrhosis in CHB patients with minimally raised ALT in this study. The Nomogram-Cirrhosis included one more variable of age as an independent indicator other than Nomogram-Fibrosis. Age was taken as an independent factor associated with hepatic extent in most previous researches [39,40]. and a critical factor when considering liver biopsy according to most international guidelines [2,41]. Similarly, there was no doubt that age was closely associated with hepatic fibrosis extent in the univariate analysis, while found to be an independent factor for hepatic cirrhosis but not for advanced hepatic fibrosis in multivariate analysis in this study. Most likely, it is due to the fact that fibrosis slowly progresses with age, and the association is not significant until cirrhosis occurs.

Numerous attempts have been made to develop a reliable biochemical index to evaluate liver fibrosis degree for HBV infected patients. APRI and FIB-4 have been recommended to diagnose significant fibrosis and cirrhosis in the guidelines on management of CHB published by WHO [11]. Ma et al. conducted a retrospective study including a total of 1168 CHB patients with diagnosis of liver fibrosis and concluded that FIB-4 and APRI were suitable for staging fibrosis in CHB [42]. Analogously, Teshale et al. demonstrated that APRI and FIB-4 were strongly associated with fibrosis stage in untreated CHB patients, and were reliable to distinguish advanced fibrosis from none to mild extent [9]. However, a growing number of studies came up with the opposite results. According to data obtained by Kim et al. in two double-blind clinical trials recruiting 575 patients, > 80% of CHB

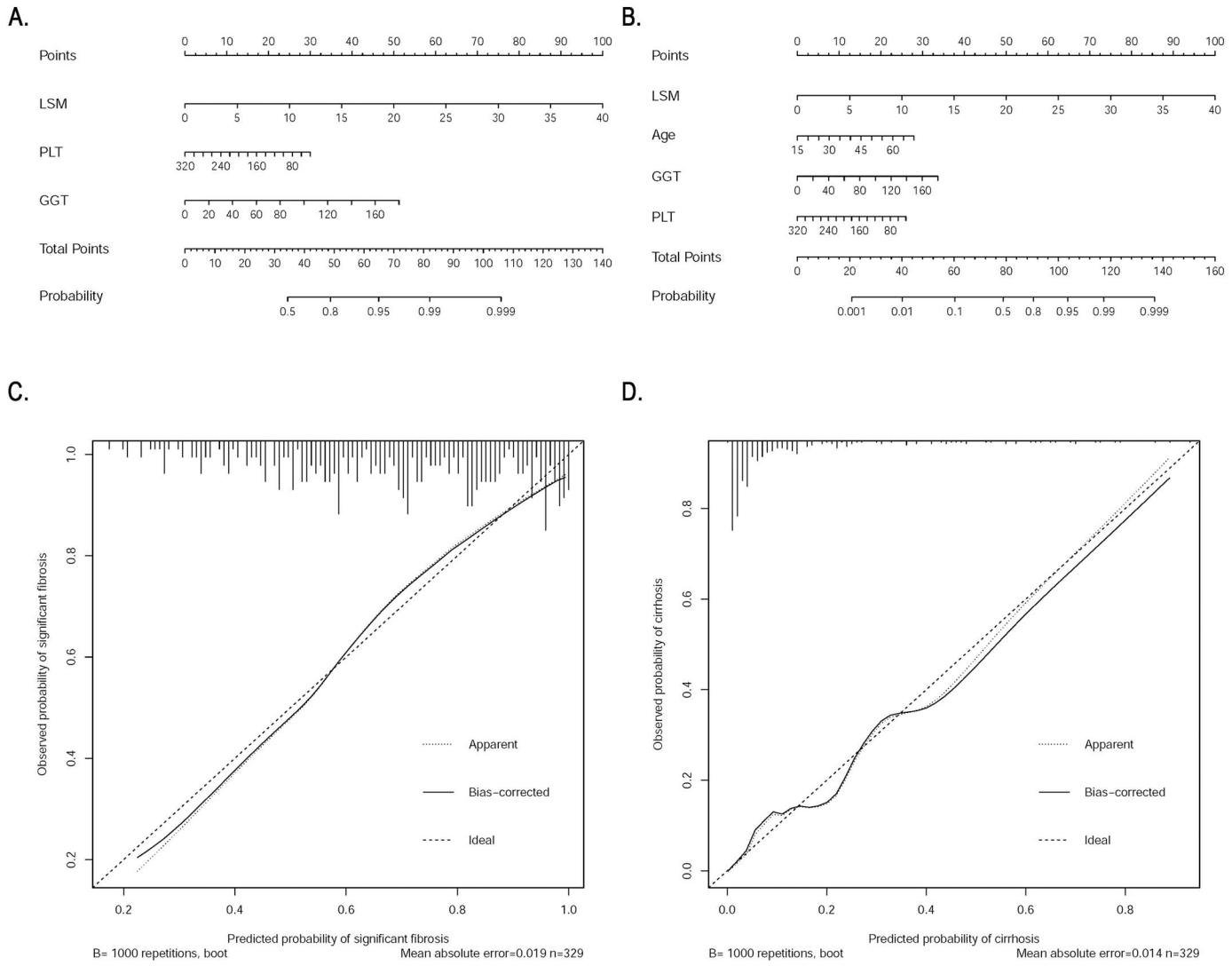

Fig. 2. Nomograms and calibrations for assessment of significant liver fibrosis and cirrhosis in CHB patients with ULN < ALT < 2 ULN. The Nomogram-Fibrosis (A) and the Nomogram-Cirrhosis (B) were constructed for the assessment of significant fibrosis and cirrhosis. Each variable is assigned a score on the top scale, and the total points can be converted to a predicted probability of significant fibrosis or cirrhosis in the lowest scale for patients with CHB. Calibrations curves were plotted for Nomogram-Fibrosis (C) and Nomogram-Cirrhosis (D). The dashed line represents an ideal evaluation. LSM, liver stiffness measurement.

patients with clinically significant liver fibrosis or cirrhosis would be misdiagnosed by APRI or FIB-4 scores [43]. Moreover, worse correlation between APRI or FIB-4 score and Ishak change of fibrosis was observed after 240-week antiviral therapy [43]. Indeed, in our study, the accuracy of FIB-4 were better than APRI in discriminating significant fibrosis and cirrhosis, but still lower than a simple indicator of LSM by ROC analysis let alone the nomograms.

We compared the accuracy of the established nomograms with APRI, FIB-4 and LSM alone for evaluation of fibrosis severity. It was suggested that the Nomogram-Fibrosis provided a better sensitivity and specificity than the other indexes for estimating significant liver fibrosis according to the ROC analysis. The Nomogram-Cirrhosis was likely to yield the most accurate evaluation for cirrhosis diagnosis. It should be underlined that sensitivity and specificity were not enough to assess the usefulness of models for fibrosis staging in clinical application. Due to the calibration curve analysis, the predicted significant fibrosis or cirrhosis proportion using Nomogram-Fibrosis and Nomogram-Cirrhosis closely agreed with the observation. Furthermore, the decision curve analysis revealed that the maximum net benefit would be gained by using nomogram scoring systems in the training cohort.

Nevertheless, there are some limitations in the present study. First, the nomograms wereestimated with a single resource. The results needed to be confirmed in larger, more ethnically and geographically diverse population. Second, the study excluded patients with ALT at normal range or over 2ULN activities, so the discrimination abilities of the nomograms were not clear in these conditions.

5. Conclusions

The Nomogram-Fibrosis and the Nomogram-Cirrhosis scoring systems based on LSM were constructed for CHB patients with ALT near the threshold for initiating treatment. A total point of 65 in Nomogram-Fibrosis and 104 in Nomogram-Cirrhosis strongly suggest significant fibrosis and cirrhosis, which could be helpful when considering antiviral therapy. Although, future validation in other cohorts is needed, these two nomograms could be promising tools for fibrosis stage assessment in a non-invasive manner and referential to avoid unnecessary liver biopsy in clinical practice.

Table 4
Nomogram scoring system for significant fibrosis and cirrhosis evaluation.

Total points	Probability of significant fibrosis	LSM (kPa)	Points	PLT (g/l)	Points	GGT (mmol/l)	Points
34	0.500	0	0	40	30	0	0
49	0.800	5	12	80	26	20	6
65	0.950	10	25	120	21	40	11
82	0.990	15	38	160	17	60	17
106	0.999	20	50	200	13	80	23
		25	62	240	9	100	28
		30	75	280	4	120	34
		35	87	320	0	140	40
		40	100			160	46
						180	51

Total points	Probability of cirrhosis	LSM (kPa)	Points	Age (y)	Points	GGT (mmol/l)	Points	PLT (g/l)	Points
21	0.001	0	0	15	0	0	0	40	26
40	0.010	5	12	20	3	20	4	80	22
60	0.100	10	25	25	5	40	7	120	19
79	0.500	15	38	30	8	60	11	160	15
90	0.800	20	50	35	10	80	15	200	11
104	0.950	25	62	40	13	100	19	240	7
117	0.990	30	75	45	15	120	22	280	4
137	0.999	35	88	50	18	140	26	320	0
		40	100	55	20	160	30		
				60	23	180	34		
				65	25				
				70	28				

Probability of significant fibrosis and cirrhosis corresponding to total points not shown in the table can be obtained by linear interpolation. The same approach could be followed for points corresponding to values of LSM, age, GGT and PLT not included here.LSM, liver stiffness measurement.

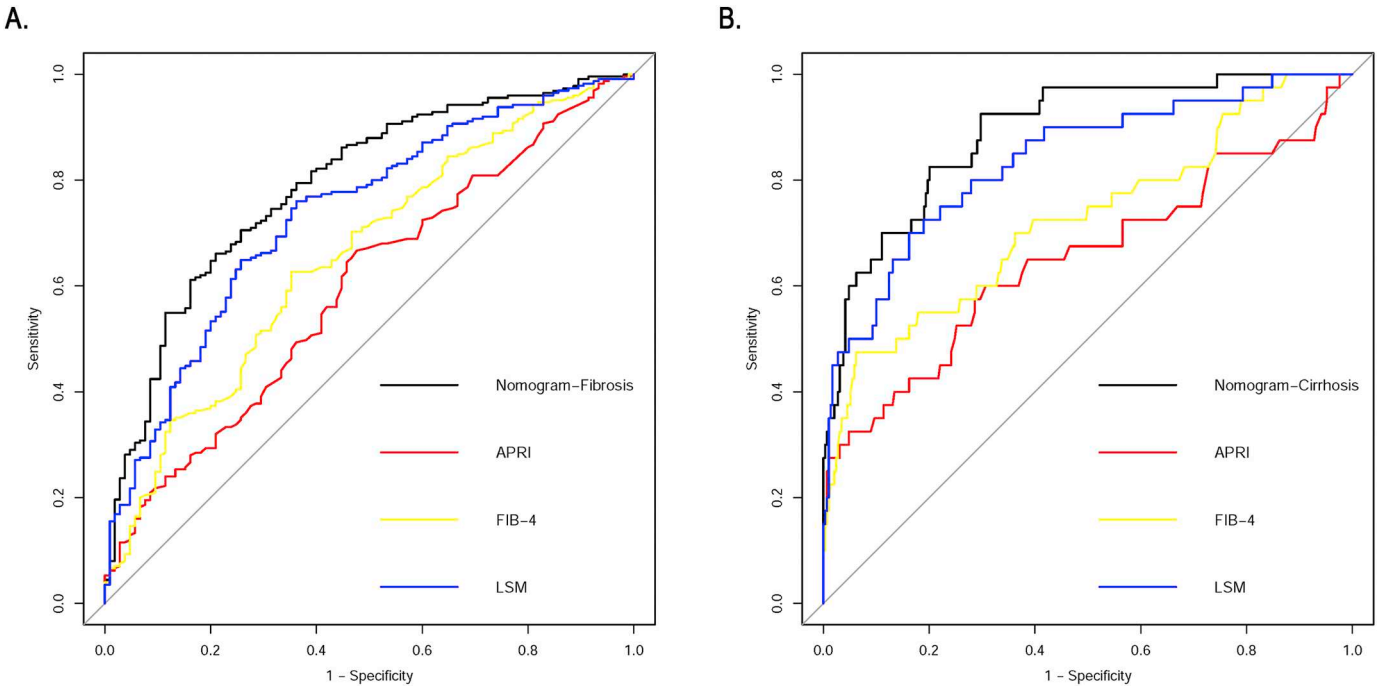

Fig. 3. ROC analysis for the assessment of significant fibrosis and cirrhosis. The ROC curves of the established nomogram, APRI, FIB-4 and LSM alone wereseparately plotted as black, red, yellow and blue lines. APRI, aspartate aminotransferase to platelet count ratio index; FIB-4, age-aspartate aminotransferase-platelet count-alanine aminotranferase index; LSM, liver stiffness measurement; (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

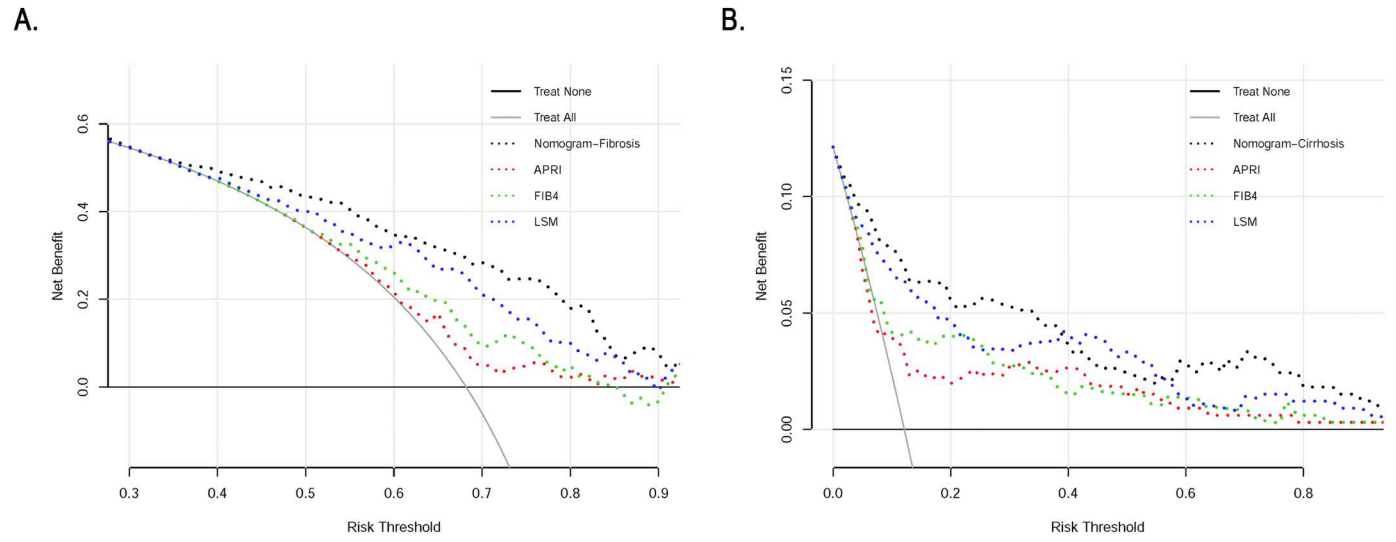

Fig. 4. Decision curves for prediction of net benefit of the constructed nomograms, APRI, FIB-4 and LSM. Solid grey line: net benefit of treating all patients. Solid black line: net benefit of treating no patient. Dotted lines: net benefit of treating patients according to the constructed nomogram, APRI, FIB-4 and LSM alone. APRI, aspartate aminotransferase to platelet count ratio index; FIB-4, age-aspartate aminotransferase-platelet count-alanine aminotranferase index; LSM, liver stiffness measurement.

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