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A novel web-based online nomogram to predict advanced liver fibrosis in patients with autoimmune hepatitis-primary biliary cholangitis overlap syndrome

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ABSTRACT

Background: Patients with autoimmune hepatitis-primary biliary cholangitis (AIH-PBC) overlap syndrome have a worse prognosis compared to AIH or PBC alone and accurately predicting the severity and dynamically monitoring the progression of disease are therefore essential. We aimed to develop a nomogram-based model to predict advanced liver fibrosis in patients with AIH-PBC overlap syndrome.

Methods: A total of 121 patients with AIH-PBC overlap syndrome were retrospectively included and randomly assigned to a development set and a validation set. Backward stepwise regression's best model with the lowest AIC was employed to create a nomogram. Diagnose accuracy was evaluated using the area under the receiver operator characteristic curve (AUROC), calibration analysis, and decision curve analysis (DCA) and was compared with aspartate aminotransferase-to-platelet ratio (APRI) and fibrosis index based on four factors-4 (FIB-4) score.

Results: The median age of patients was 53.0 years (IQR: 46.0–63.0), and female patients accounted for 95.0 %. Platelets, globulin, total bilirubin, and prothrombin time were associated with advanced fibrosis (≥S3) and used to construct an AIH-PBC overlap syndrome fibrosis (APOSF)-nomogram (available online at https://ndth-zzy.shinyapps.io/APOSF-nomogram/). The AUROCs of APOSF-nomogram were 0.845 (95 % CI: 0.754–0.936) and 0.843 (95 % CI: 0.705–0.982) in development set and validation set respectively, which was significantly better than APRI and FIB-4. Calibration revealed that the estimated risk fits well with biopsy-proven observation. DCA outperformed APRI and FIB4 in terms of net benefit, demonstrating clinical utility.

Abbreviations: AIC, Akaike information criteria; AIH, autoimmune hepatitis; AIH-PBC, autoimmune hepatitis-primary biliary cholangitis; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; APRI, aminotransferase to platelet ratio; ASMA, anti-smooth muscle antibodies; AST, aspartate aminotransferase; AUROC, areas under the receiver operating characteristic curve; CHB, chronic hepatitis B; CI, confidence interval; DCA, decision curve analysis; FIB-4, fibrosis score based on four factors; GGT, gamma-glutamyl transpeptidase; GLB, globulin; IgG, immunoglobulin G; IQR, interquartile range; LASSO, least absolute shrinkage and selection operator; ROC, receiver characteristic curve; NITs, Non-invasive tests; PBC, primary biliary cholangitis; PLT, platelets; PT, prothrombin time; RDW, red cell distribution width; TB, total bilirubin; ULN, upper limit of normal.

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Conclusion: This novel non-invasive web-based online APOSF-nomogram provided a convenient tool for identifying advanced fibrosis in patients with AIH-PBC overlap syndrome. Further prospective, multicenter studies with large sample size are necessary to validate the applicability of APOSF-nomogram.

1. Introduction

Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) are two major autoimmune chronic liver diseases. AIH is an inflammatory liver disease characterized by elevated transaminase levels, interface hepatitis on biopsy, and elevated immunoglobulin G (IgG) levels on serology [1,2]. PBC is a slowly progressing autoimmune disease characterized by interlobular bile duct destruction and nonsuppurative destructive cholangitis [3,4]. Either AIH or PBC harbors a risk of liver fibrosis or cirrhosis progression [5]. The presence of both diseases in the same patient is called the AIH-PBC overlap syndrome [6]. Several studies have reported that patients with AIH-PBC overlap syndrome exhibit more rapid fibrosis and cirrhosis progression, more frequent need for liver transplantation, and more mortality than patients with AIH or PBC alone [6,7]. Thus, accurately predicting the severity and dynamically monitoring the progression of the disease is essential for better managing patients with AIH-PBC overlap syndrome.

Currently, liver biopsy continues to be the gold standard in determining the stage of liver fibrosis. Its broad use in clinical settings is nevertheless constrained by several drawbacks like invasiveness, high cost, and potential complications. Moreover, repeated liver biopsy in patients with AIH-PBC overlap syndrome cannot be routinely performed during long-term follow-up. It is therefore urgent to develop convenient and noninvasive tests (NITs) for accurately staging liver fibrosis. Several NITs have been developed and applied to evaluate the fibrosis stage including aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) [8,9]. Owing to their convenience and efficacy, APRI and FIB-4 are widely used in the clinical evaluation of liver fibrosis and are recommended for use in resource-limited regions in the current treatment guidelines from WHO for chronic hepatitis B (CHB) [10]. However, the performance of these two NITs for assessing the fibrosis stage was not always satisfactory. A fair amount of studies reported moderate or even worse performance of APRI and FIB-4 in assessing liver fibrosis [11–13]. Our previous study also showed a disagreeable performance of APRI and FIB-4 in evaluating the fibrosis stage in patients with AIH [14]. Additionally, it is not yet clear whether they can identify the stages of liver fibrosis in patients with AIH-PBC overlap syndrome.

Therefore, there is an unmet need to develop reliable NITs for the fibrosis stage in the clinical management of AIH-PBC overlap syndrome. The nomogram, a graphical depiction of a complex formula capable of generating individual probabilities of clinical events by integrating most common clinical parameters, is widely used in medicine for prognostic applications [15]. We aimed to develop and validate a nomogram-based noninvasive predictive model to assess the advanced liver fibrosis in patients with AIH-PBC overlap syndrome and to compare the predictive ability of the nomogram with APRI and FIB-4.

2. Methods

2.1. Patients

We conducted a multicenter retrospective cross-sectional study which included patients with AIH-PBC overlap syndrome who underwent liver biopsy at four medical centers (Nanjing Drum Tower Hospital; Nanjing Second Hospital; Infectious Disease Hospital of Soochow University; and Wuxi Fifth People's Hospital) between January 2014 and December 2020. The diagnosis of AIH and PBC was strict in accordance with at least two of the three recognized criteria of AIH and PBC [16]. The criteria for AIH were defined as follows: (1) Elevated levels of Alanine aminotransferase (ALT) exceeding five times the upper limit of normal (ULN); (2) Presence of serum IgG levels at least twice the ULN or a positive result for anti-smooth muscle antibodies (ASMA); and (3) Identification of moderate to severe periportal or periseptal piecemeal lymphocytic necrosis in liver biopsy specimens. The criteria for PBC were defined as: (1) Alkaline phosphatase (ALP) levels at least two times higher than the ULN or gamma-glutamyltransferase (GGT) levels exceeding five times the ULN; (2) Positive test result for anti-mitochondrial antibodies (AMA); and (3) The presence of florid bile duct lesions in liver biopsy specimens. We excluded patients with following conditions: (1) Patients with hepatic occupying lesions; (2) Patients with AIH-PBC- Primary sclerosing cholangitis overlap syndrome; (3) Patients with CHB; (4) Patients without sufficient data; (5) Patients lack Scheuer grading scores. The study received approval from the ethics committees of local hospitals and was carried out in alignment with the ethical principles outlined in the Declaration of Helsinki.

2.2. Data acquisition

A retrospective review of the medical records of patients diagnosed with the AIH-PBC overlap syndrome was conducted, and data was gathered on clinical characteristics and laboratory measurements such as AST, ALT, platelet (PLT) count, and total bilirubin (TB) levels.

APRI index was calculated using the formula (AST (U/L)/ULN considered as 40 IU/L)/PLT count (10^9/L) × 100 [8], FIB-4 index was calculated using the formula (age × AST (U/L))/((PLT count (10^9/L) × (ALT (U/L))$^{1/2}$) [9].

2.3. Liver histological assessment

Liver biopsies were performed in patients using 16-gauge disposable needles under ultrasound guidance. The specimens were subjected to hematoxylin and eosin staining and analyzed by two experienced pathologists, who were blinded to the patient information. The liver fibrosis stage was assessed according to the Scheuer scoring system (S0, no fibrosis; S1, portal fibrosis without septa; S2, portal fibrosis with rare septa; S3, numerous septa without cirrhosis; and S4, cirrhosis) [17]. Fibrosis stage ≥ S3 was defined as advanced fibrosis.

2.4. Statistical analysis

Patients were randomly assigned to the development set or validation set in a ratio of 2:1. Continuous data were presented as median and inter-quartile range (IQR) while categorical data were expressed as frequencies and proportions. For comparisons between two groups of continuous and categorical variables, Mann–Whitney *U* test or chi-square test were used, as appropriate. Variables selection was performed in the development set, and candidate variables of $P < 0.05$ in the univariate logistic analysis were introduced into multivariate analysis. The best model with the minimum Akaike information criteria (AIC) through stepwise backward regression was confirmed. Subsequently, a nomogram based on the best model was constructed using the "rms" package and uploaded as an online dynamic nomogram on the website (https://ndth-zzy.shinyapps.io/APOSF-nomogram/) by the "shiny" package. We next applied several methods to validate the performance of the nomogram internally in both the development and validation sets. The calibration was evaluated by the Hosmer-Lemeshow test and a calibration bar plot. The clinical applicability of the nomogram was evaluated using decision curve analysis (DCA). Discrimination was measured through the calculation of the area under the receiver

operating characteristic curve (AUROC), and AUROC values were compared using the DeLong test method. The correlation between the nomogram, APRI, and FIB-4 scores with fibrosis stages was assessed using the Spearman rank correlation analysis. A two-tailed p-value of less than 0.05 was considered statistically significant. The statistical analyses were performed using R software version 4.2.0 (https://www.r-project.org/).

3. Results

3.1. Clinical characteristics of patients

As shown in Fig. S1, 121 patients who met the inclusion and exclusion criteria were utilized for the final analysis. For the overall patients, the median age was 53.0 (IQR: 46.0–63.0) years, and female patients were in a proportion of 95.0 %. The median levels of ALT, IgG, red cell distribution width (RDW) and PLT were 65.0 (IQR: 44.0, 122.2) U/L, 18.1 (IQR: 14.7, 23.4) g/L, 13.9 (IQR: 13.0, 14.9) % and 150.0 (IQR: 111.0, 201.0) $\times 10^9$/L, respectively. The percentages of patients with fibrosis stage S0-1, S2, S3, and S4 were 5.0 % (6 patients), 28.9 % (35 patients), 28.9 % (35 patients), and 37.2 % (45 patients), respectively. Eighty-two patients (71.9 %) were positive for antinuclear antibody and 61 (57.5 %) were positive for AMA-M2. The characteristics of patients were given in Table 1. Among 121 patients with AIH-PBC overlap syndrome, 81 patients were divided into the development set randomly, and the rest of patients (n = 40) formed the validation set. The development and validation sets were well-matched for the distribution of fibrosis stages, and no significant differences of patient characteristics were found in the two datasets.

3.2. Comparison of biochemical and clinical features of patients with and without advanced fibrosis in the development set

Fifty (61.7 %) patients in the development set had advanced liver fibrosis. The characteristics of patients with and without advanced fibrosis in the development set were shown in Table S1. Patients with advanced liver fibrosis had higher median levels of RDW (14.2 % vs. 13.5 %, P = 0.003), TB (22.2 μmol/L vs. 15.1 μmol/L, P = 0.009), and prothrombin time (PT) (13.0s vs. 12.3s, P = 0.005) compared to patients with non-advanced liver fibrosis, while the median levels of albumin (ALB) (36.4 g/L vs. 40.4 g/L, P = 0.001) and PLT (132.5 $\times 10^9$/L vs. 188.0 $\times 10^9$/L, P < 0.001) were lower in patients with advanced liver fibrosis. However, similar gender distribution and median age were found between patients with and without advanced fibrosis.

3.3. Development of a nomogram estimating advanced fibrosis

The construction of nomogram was conducted in the development set. Firstly, we performed the univariate logistic regression for advanced fibrosis and the results were given in Fig. 1. Of all the 12 variables, 6 significant variables significantly associated with advanced liver fibrosis were included in the multivariate analysis. The final model was selected according to backward stepwise regression based on lower AIC. Four variables containing globulin (GLB), PLT, PT, and TB were incorporated into the best model which was presented in the form of a nomogram (Fig. 2A) and designated the "AIH-PBC Overlap Syndrome Fibrosis" (APOSF)-nomogram, which is available as an online dynamic nomogram at https://ndth-zzy.shinyapps.io/APOSF-nomogram/as screenshotted in Fig. 2B. For instance, a patient with a PLT of 164 $\times 10^9$/L, TB of 35 μmol/L, GLB of 36 g/L, and PT of 13s has about a 73.8 % probability of being predicted to have advanced liver fibrosis.

3.4. Validation of the APOSF-nomogram for predicting advanced fibrosis

We calculated predicted risk by quartiles of APOSF-nomogram in both the development and validation sets. In the development set, predicted risk and observed frequency for advanced fibrosis were in good agreement in the quartiles of APOSF-nomogram (Hosmer-Lemeshow: $\chi^2 = 2.986$, P = 0.225, Fig. 3A) and in the validation set, APOSF-nomogram prediction and actual observation likewise demonstrated a good consistency (Hosmer-Lemeshow: $\chi^2 = 0.529$, P = 0.767, Fig. 3B).

The DCA was used to evaluate the clinical utility for APOSF-nomogram predicting advanced fibrosis. As presented in Fig. 3C, we could obtain more benefits compared to treat-all or treat-none methods as well as APRI and FIB-4 when using APOSF-nomogram to predict advanced liver fibrosis for a threshold range from 4.7 % to 86.6 % in the development set. Similarly, more net benefits were gained when employing APOSF- nomogram in a considerably large range of threshold probability compared to other strategies in the validation set (Fig. 3D).

Fig. 3E and F showed the ROC curves of the APOSF-nomogram, APRI, and FIB-4 for differentiating advanced fibrosis and non-advanced fibrosis in two sets. In both sets, the APOSF-nomogram can accurately predict advanced liver fibrosis in patients with AIH-PBC overlap syndrome by more than 80 %, which was an exceptional performance (Table 2). The cutoff point of the APOSF-nomogram in the development

Table 1
Characteristics for patients with autoimmune hepatitis-primary biliary cholangitis overlap syndrome.

	Total (n = 121)	Development set (n = 81)	Validation set (n = 40)	P value
Age (yr)	53.0 (46.0, 63.0)	52.0 (46.0, 62.0)	56.0 (47.5, 67.2)	0.213
Female (%)	115 (95.0)	78 (96.3)	37 (92.5)	0.646
RDW (%)	13.9 (13.0, 14.9)	13.9 (13.0, 14.7)	13.9 (13.0, 15.0)	0.699
PLT (× 10^9/ L)	150.0 (111.0, 201.0)	150.0 (115.0, 202.0)	161.0 (91.0, 199.2)	0.779
TB (μmol/L)	19.0 (14.0, 31.4)	18.0 (14.0, 31.6)	19.3 (15.0, 30.5)	0.710
ALB (g/L)	37.7 (34.5, 39.8)	37.4 (34.5, 40.7)	38.0 (34.6, 38.6)	0.864
GLB (g/L)	34.9 (31.1, 39.7)	35.0 (31.5, 39.7)	34.6 (29.9, 38.3)	0.450
ALT (U/L)	65.0 (44.0, 122.2)	61.0 (40.0, 123.0)	71.0 (47.2, 119.8)	0.256
AST (U/L)	68.2 (45.0, 113.8)	67.0 (43.4, 100.0)	74.5 (48.2, 128.4)	0.300
ALP (U/L)	176.0 (118.0, 293.0)	176.0 (111.0, 295.0)	173.0 (122.1, 285.5)	0.941
GGT (U/L)	147.5 (86.0, 250.0)	150.3 (86.0, 256.0)	145.2 (90.5, 199.6)	0.888
PT (s)	12.7 (11.9, 13.5)	12.7 (11.9, 13.4)	12.6 (11.9, 13.5)	0.825
APRI	1.2 (0.7, 2.2)	1.1 (0.7, 2.0)	1.7 (0.8, 2.9)	0.101
FIB-4	3.2 (1.9, 5.6)	2.9 (1.8, 5.1)	4.5 (2.0, 6.6)	0.141
Fibrosis stage (%)				0.203
0–1	6 (5.0)	4 (4.9)	2 (5.0)	
2	35 (28.9)	27 (33.3)	8 (20.0)	
3	35 (28.9)	25 (30.9)	10 (25.0)	
4	45 (37.2)	25 (30.9)	20 (50.0)	
IgG (g/L)	18.1 (14.7, 23.4)	18.4 (15.1, 23.2)	17.6 (14.3, 23.7)	0.717
IgM (g/L)	3.2 (1.7, 5.0)	2.9 (1.9, 5.0)	3.4 (1.6, 4.9)	0.808
ANA (+)	82 (71.9)	55 (74.3)	27 (67.5)	0.579
ASMA (−)	20 (100.0)	11 (100.0)	9 (100.0)	
AMA-M2 (+)	61 (57.5)	39 (56.5)	22 (59.5)	0.932
APOSF-score	91.4 (78.6, 105.1)	92.2 (78.9, 103.4)	88.1 (74.5, 109.4)	0.908

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA-M2, anti-mitochondrial antibody-M2; ANA, antinuclear antibody; APRI, aminotransferase to platelet ratio; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; FIB-4, fibrosis score based on four factors; GGT, gamma-glutamyl transferase; GLB, globulin; IgG, immunoglobulin G; IgM, immunoglobulin M; PLT, platelets; PT, prothrombin time; RDW, red cell distribution width; TB, total bilirubin.

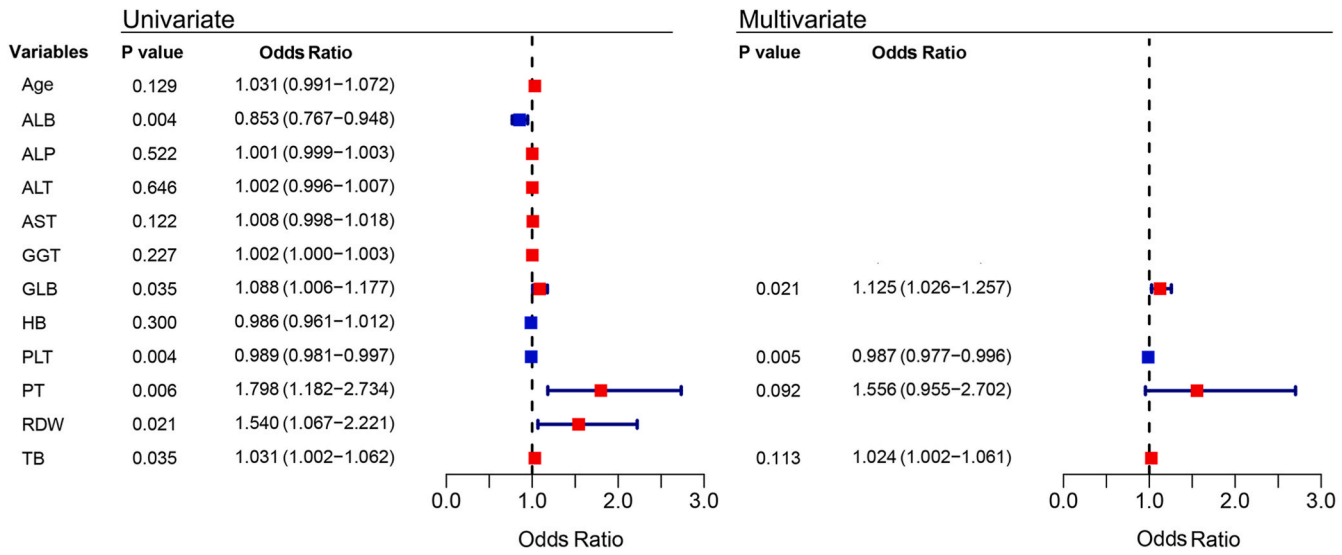


Fig. 1. Forestplot depicting the results of univariate and multivariate logistic regression analysis of advanced liver fibrosis in patients with AIH-PBC overlap syndrome. AIH, Autoimmune hepatitis; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; GLB, globulin; HB, hemoglobin; PLT, platelets; PBC, primary biliary cholangitis; PT, prothrombin time; RDW, red cell distribution width; TB, total bilirubin.

set was 86.574 and the sensitivity and specificity were 86.0 % and 71.0 %, respectively. The AUC of APOSF-nomogram for predicting advanced fibrosis was 0.845 (95 % confidence interval [CI]: 0.754–0.936) in the development set which was significantly better than APRI (0.714, 95% CI: 0.598–0.830, P = 0.011) and a barely detectable statistically significant difference was found compared with FIB-4 (0.768, 95%CI: 0.651–0.884, P = 0.073). In the validation set, the AUROC of the APOSF-nomogram was 0.843 (95 % CI: 0.705–0.982), and the cutoff point was 79.302, with a sensitivity of 86.7 % and a specificity of 80.0 %. The discrimination ability of the APOSF-nomogram was substantially superior to APRI (0.553, 95%CI: 0.320–0.787, P = 0.016) and FIB-4 (0.600, 95%CI: 0.409–0.791, P = 0.005).

3.5. Correlation analysis between the APOSF-nomogram, APRI, FIB-4, and liver fibrosis stage

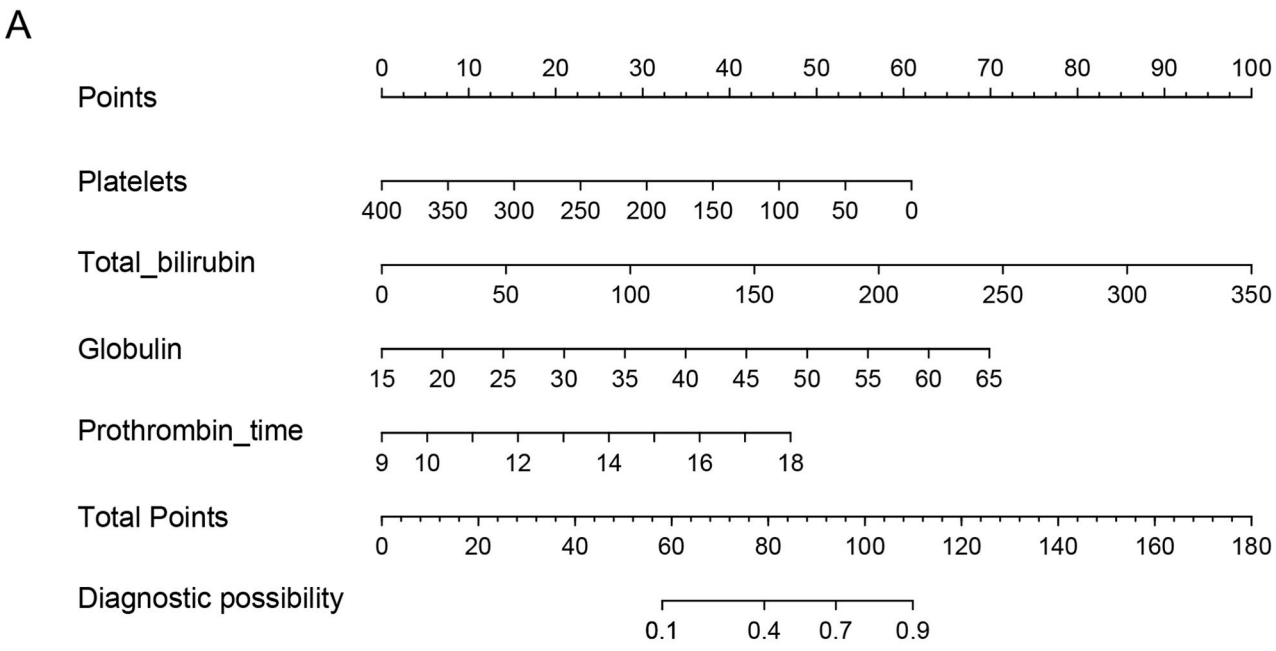
We calculated the total points of each patient in the APOSF-nomogram to evaluate the correlation between APOSF-nomogram scores, APRI, and FIB-4 with fibrosis stages. The median APOSF-score levels were 92.2 (78.9, 103.4) in the development set and 88.1 (74.5, 109.4) in the validation set. The APOSF-scores were comparable between these two sets (Table 1). Correlation analysis showed a positive correlation trend of APRI (r = 0.29, P = 0.008) and FIB-4 (r = 0.44, P < 0.001) with fibrosis stages in the development set while no such correlation was found in the validation set (Table S2). Generally, APOSF-nomogram scores were step-wisely increased across fibrosis stages and strong positive correlations were observed in both the development (r = 0.58, P < 0.001) and validation sets (r = 0.60, P < 0.001) (Fig. 4A and B). Patients with advanced liver fibrosis had significantly higher APOSF-nomogram scores than patients with non-advanced fibrosis in both datasets (Both P < 0.001) (Fig. 4C and D).

4. Discussion

Previous studies suggested patients with AIH-PBC overlap syndrome had a faster cirrhotic progression and worse clinical outcomes than patients with AIH or PBC alone [18,19]. This is consistent with the current study's findings that 66.1 % of patients had advanced fibrosis and 37.2 % had cirrhosis, both of which were much higher than in our earlier analysis of AIH patients [14]. Therefore, an accurate and timely assessment of fibrosis stages is essential to better guide clinical treatment and improve patients' prognosis. In the present study, we constructed an APOSF-nomogram for accurately predicting the advanced liver fibrosis in patients with AIH-PBC overlap syndrome as well as compared the predictive performance with APRI and FIB-4. The APOSF-nomogram comprising PLT, TB, GLB, and PT was more consistent with biopsy-proven results and more accurate than APRI and FIB-4 in differentiating advanced fibrosis stages from non-advanced fibrosis stages.

Liver biopsy has a non-negligible role and is considered the gold standard for liver fibrosis detection. However, some drawbacks limit its wide clinical application. Therefore, the development of NITs for the assessment of the fibrosis stage deserves more attention. NITs scores such as APRI and FIB-4 were originally developed to assess liver fibrosis in patients with chronic hepatitis C with high accuracy and have been used in other liver diseases, including autoimmune liver diseases [8,9]. However, the two NITs did not perform as well as expected in some AIH sets. Xing et al. [20] reported the AUROCs of FIB-4 and APRI detecting advanced fibrosis in patients with AIH were 0.63 (95 % CI: 0.53–0.72) and 0.57 (95 % CI: 0.47–0.67), respectively. Our previous study also indicated that FIB-4 had a poor performance in identifying fibrosis stage while APRI could not predict liver fibrosis stage in AIH patients [14]. A similar study by Osman et al. [21] showed a moderate AUROC of APRI in diagnosing advanced liver fibrosis in PBC patients. However, the performance of APRI and FIB-4 in patients with AIH-PBC overlap syndrome remains unclear. Due to the low prevalence of AIH-PBC overlap syndrome, few studies have reported the performance of APRI and FIB-4 in the assessment of liver fibrosis stage in patients with AIH-PBC overlap syndrome. Wu et al. [22] reported fair performance for FIB-4 (AUROC = 0.715) and moderate performance for APRI (AUROC = 0.616) in evaluating advanced fibrosis in patients with AIH-PBC overlap syndrome. However, the study was limited by its small sample size of only 70 patients. There is a need for further development of reliable non-invasive tests for the assessment of liver fibrosis in patients with AIH-PBC overlap syndrome.

Nomograms are straightforward graphical representations of predictive models that produce probability in numbers for clinical events via conversion by formula. In the multivariate logistic regression analysis, we created the APOSF-nomogram based on the backward stepwise regression of the best model with the lowest AIC in the development set.



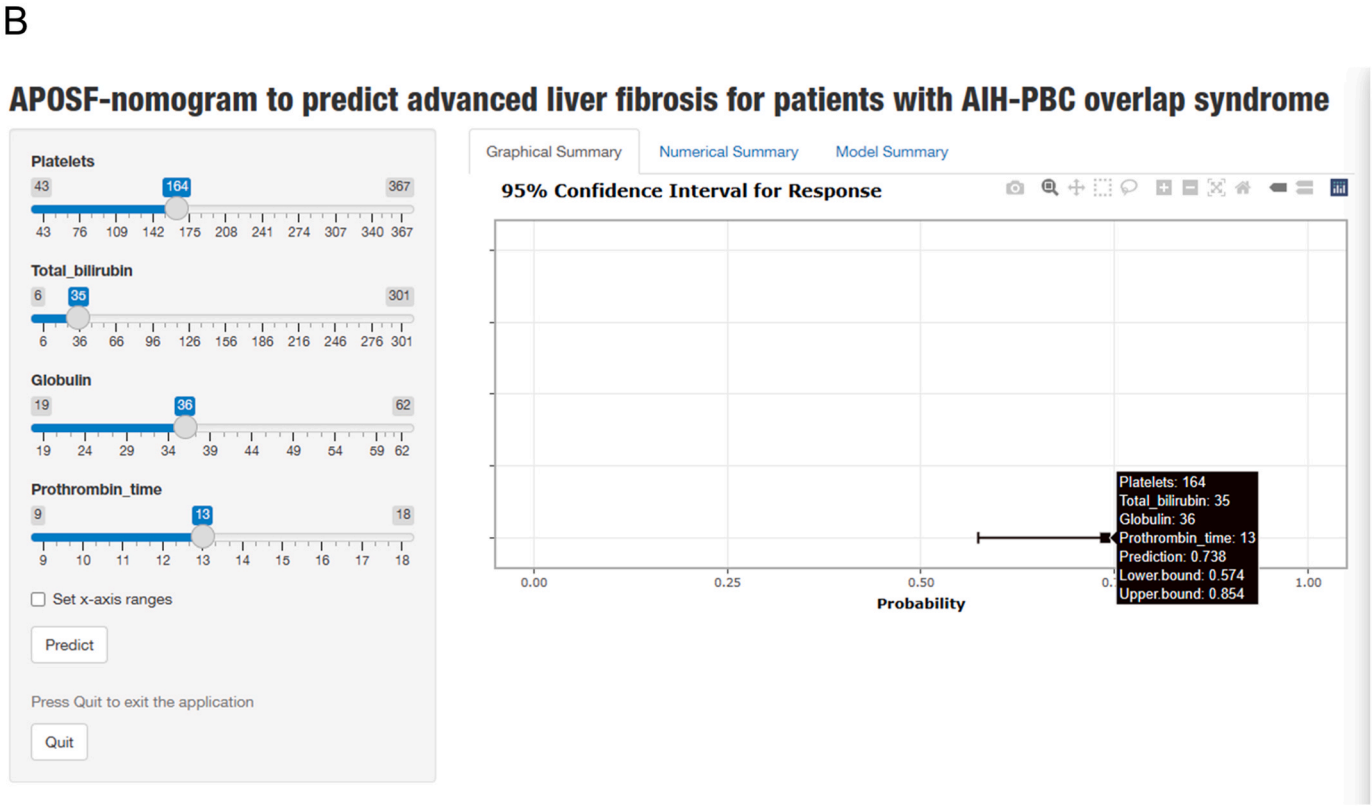


Fig. 2. Development of nomogram. (A) APOSF-nomogram for the prediction of advanced liver fibrosis in patients with AIH-PBC overlap syndrome. To use the nomogram, first determine the position of the first variable. Then a vertical line was drawn upward, which gave the corresponding single points for the variable in APOSF-nomogram. This process was repeated for the other three variables, and then the individual points for each variable were summed to obtain the total points. The position of the total points was determined, and then a vertical line was drawn down to the probability axis to determine the likelihood of advanced liver fibrosis. (B) A screenshot of the web-based online nomogram. For example, a patient with the platelets of 164 $\times$ 10^9/L, total bilirubin of 35 μmol/L, globulin of 36 g/L, and prothrombin time of 13s has about a 73.8 % probability of being predicted to have advanced liver fibrosis. AIH, Autoimmune hepatitis; PBC, primary biliary cholangitis. Units for the variables: platelets, $\times$ 10^9/L; total bilirubin, μmol/L; globulin, g/L; prothrombin time, s.

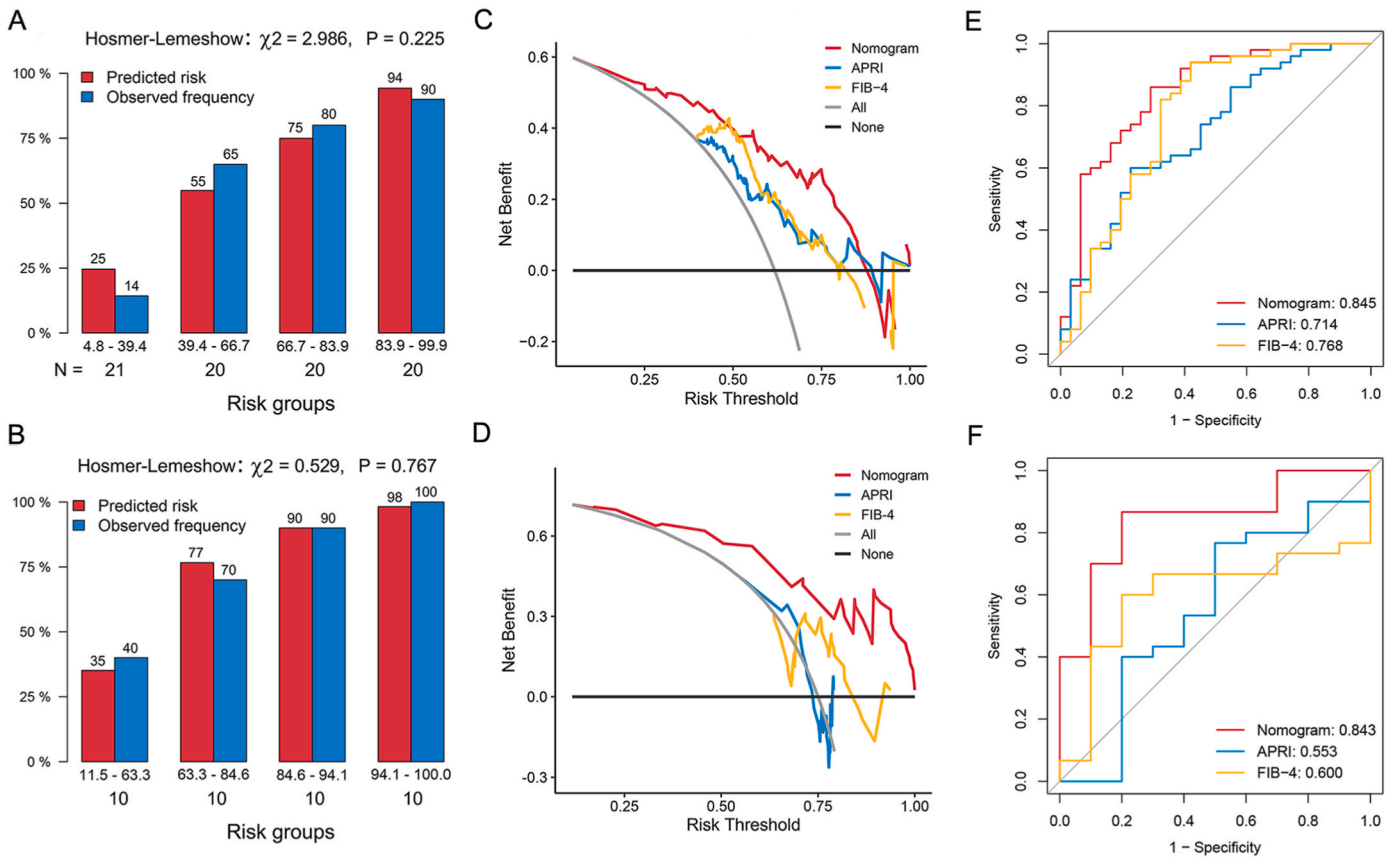


Fig. 3. Performance of the APOSF-nomogram for predicting advanced liver fibrosis in patients with AIH-PBC overlap syndrome. Calibration analysis in the development set (A) and validation set (B). Decision curve analysis in the development set (C) and validation set (D). Receiver operating characteristic curves in the development set (E) and validation set (F). AIH, Autoimmune hepatitis; APRI, aminotransferase to platelet ratio; FIB-4, fibrosis score based on four factors; PBC, primary biliary cholangitis.

Table 2
Diagnostic performances of the APOSF-nomogram, APRI, and FIB-4 in the development and validation sets.

	Cutoff	AUROC (95%CI)	DeLong test	ACC (%)	SEN (%)	SPE (%)	PPV (%)	NPV (%)
Development set (n = 81)								
APOSF-nomogram	86.574	0.845 (0.754–0.936)	reference	80.2	86.0	71.0	82.7	75.9
APRI	1.230	0.714 (0.598–0.830)	0.011	66.7	60.0	77.4	81.1	54.5
FIB-4	1.815	0.768 (0.651–0.884)	0.073	80.2	94.0	58.1	78.3	85.7
Validation set (n = 40)								
APOSF-nomogram	79.302	0.843 (0.705–0.982)	reference	85.0	86.7	80.0	92.9	66.7
APRI	0.934	0.553 (0.320–0.787)	0.016	70.0	76.7	50.0	82.1	41.7
FIB-4	4.465	0.600 (0.409–0.791)	0.005	65.0	60.0	80.0	90.0	40.0

ACC, accuracy; APRI, aminotransferase to platelet ratio; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; FIB-4, fibrosis score based on four factors; NPV, negative predictive value, PPV, positive predictive value; SEN, sensitivity; SPE, specificity.

We certified the good performance of the APOSF-nomogram for predicting advanced liver fibrosis in patients with AIH-PBC overlap syndrome, with an AUROC of 0.845 in the development set, which was superior to APRI (0.714) and FIB-4 (0.768). The performance of the APOSF-nomogram was also surprisingly excellent in the validation set with an AUROC of 0.843. Moreover, both APRI (0.553) and FIB-4 (0.600) were significantly inferior to our APOSF-nomogram in the validation set. The predicted risk was in good fit with the observed frequency in the calibration analysis. Besides, the Hosmer-Lemeshow test yielded a nonsignificant P value of 0.225 in the development set and a P value of 0.767 in the validation set indicating the model was the goodness of fit. The DCA results demonstrated more net benefits were provided than APRI and FIB-4 under a large range of thresholds when using APOSF-nomogram in the development and validation set.

Compared to conventional nomogram-based prediction model, one of the remarkable highlights of our study was a web online nomogram. It is very convenient for clinicians to use the online nomogram to diagnose advanced fibrosis stage in patients with AIH-PBC overlap syndrome. This online nomogram is quite practical in clinical practice and can serve as the foundation for personalized and accurate treatment.

In the current study, variables included in the APOSF-nomogram were PLT, TB, GLB, and PT. Moreover, all the variables included in the APOSF-nomogram were easily obtained, which facilitates the use of the APOSF-nomogram in clinical settings, especially in the source-limited regions. Low PLT counts have always played a significant role in the prediction of hepatic fibrosis in numerous studies, consistent with our present study that patients with advanced liver fibrosis had lower PLT counts compared to those without advanced liver fibrosis, which may be interpreted that the hypersplenism observed in liver fibrosis is related to thrombocytopenia [23–25]. Our previous study also found

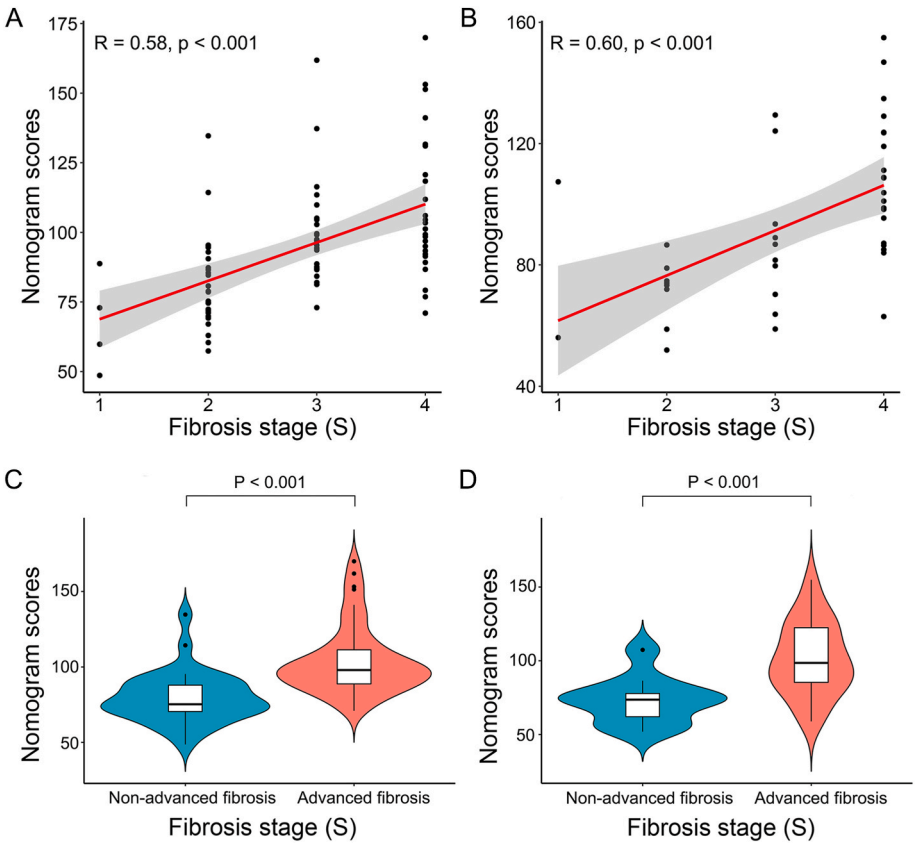


Fig. 4. Correlation between APOSF-nomogram scores and liver fibrosis stages in the development set (A) and validation set (B). Distribution of APOSF-nomogram scores in patients with and without advanced liver fibrosis of the development set (C) and validation set (D).

PLT count was an independent risk factor of significant fibrosis in patients with CHB [26]. TB is part of the liver function tests, and the widely used albumin-bilirubin index containing TB is a promising non-invasive score in differentiating liver fibrosis stage, and we have previously validated its accuracy for CHB-related liver cirrhosis [27,28]. In terms of GLB, several studies have reported the correlation between GLB and liver fibrosis stage, which was a predictor of significant liver fibrosis or cirrhosis in patients with chronic HBV infection [29–31]. In addition, we previously reported GLB as a risk factor for the development of significant liver fibrosis in patients with CHB [26]. Due to decreased generation of coagulation factors in the advanced stages of liver fibrosis, a prolonged PT is also a sign of a worse prognosis in liver fibrosis [32]. Cheng et al. [24] constructed a nomogram containing PT and other indexes with an excellent prediction capability in diagnosing liver fibrosis in patients with CHB.

Several limitations should be acknowledged. First, the study population was not as large due to a low prevalence of AIH-PBC overlap syndrome. However, we believe the results of our multicenter study may truly reflect the actual liver fibrosis in patients with AIH-PBC overlap syndrome. Second, we only verified the study internally and all the patients were Asian. Thus, a large sample size for external validation and in other ethnic populations is warranted. In addition, we did not acquire sufficient data on liver stiffness. Therefore, we could not compare the performance of APOSF-nomogram with liver stiffness in diagnosing advanced liver fibrosis in patients with AIH-PBC overlap syndrome. Third, due to the lack of follow-up data, the predictive value of APOSF-nomogram for long-term outcomes of patients with AIH-PBC overlap syndrome is not yet clear.

In conclusion, we established a nomogram-based prediction model which could well predict advanced liver fibrosis for patients with AIH-PBC overlap syndrome. Variables contained in the APOSF-nomogram were easily obtained, and the model performed well in both the development and validation sets. Moreover, the online nomogram provided clinicians with a user-friendly platform for identifying patients with advanced liver fibrosis, which was helpful for the better management of patients with AIH-PBC overlap syndrome. We deem the APOSF-nomogram to be useful in facilitating the individualized prediction of advanced liver fibrosis in patients with AIH-PBC overlap syndrome.

Credit author statement

All authors contributed to this study at different levels. All authors read and approved the final version. Study concept and design (Chao Wu, Rui Huang); acquisition of data (Zhiyi Zhang, Jian Wang, Yun Chen, Yiguang Li, Li Zhu, Huali Wang, Yilin Liu, Jiacheng Liu, Shengxia Yin, Xin Tong, Xiaomin Yan, Yuxin Chen, Chuanwu Zhu, Jie Li, Yuanwang Qiu); statistical analysis and interpretation of data (Zhiyi Zhang, Jian Wang, Yun Chen); drafting of the manuscript (Zhiyi Zhang, Jian Wang, Rui Huang); critical revision of the manuscript for important intellectual content (Rui Huang, Chao Wu).

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Declaration of competing interest

Zhiyi Zhang, Jian Wang, Yun Chen, Yiguang Li, Li Zhu, Huali Wang, Yilin Liu, Jiacheng Liu, Shengxia Yin, Xin Tong, Xiaomin Yan, Yuxin Chen, Chuanwu Zhu, Jie Li, Yuanwang Qiu, Chao Wu, Rui Huang. The authors declare they have no conflict of interest.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2023.100215.

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