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Original Article

Predictive Model of Ursodeoxycholic Acid Treatment Response in Primary Biliary Cholangitis

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Abstract

Background and Aims: Although ursodeoxycholic acid (UDCA) treatment in primary biliary cholangitis is effective in many patients, there are still many people who respond poorly to it. Identifying and intervening these patients early is important. Therefore, exploring the risk factors and proposing a predictor index to predict the UDCA treatment nonresponse earlier among primary biliary cholangitis patients were the aims of this research. ***Methods:*** A total of 135 primary biliary cholangitis patients treated with UDCA (13–15 mg/kg/d) were enrolled in this retrospective study. The response to treatment was evaluated based on Paris I criteria. The univariate and logistic multivariate regression analyses were adopted to determine the independent risk factors and propose a predictor index. Receiver operating characteristic curve was used to evaluate the predictive ability of the predictor index. ***Results:*** Total bilirubin, albumin, globulin, immunoglobin M, and aspartate aminotransferase-to-platelet ratio index were the five independent risk factors associating with early biochemical nonresponse to UDCA treatment. Based on these factors, we established a predictor index with the predictive value being 0.886 (sensitivity: 82.80%, specificity: 84.40%). ***Conclusions:*** We developed a predictor index that had an accurate prediction of the early biochemical nonresponse to UDCA treatment, which is expected to provide valuable information for the high-risk group before treatment begins.

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Introduction

Primary biliary cholangitis (PBC) is a kind of autoimmune liver disease marked by destruction of the small bile duct, rising alkaline phosphatase levels and positivity for anti-mitochondrial antibody (AMA) in serum, especially for the AMA-M2 form.[1] The current standard treatment of PBC is ursodeoxycholic acid (UDCA), 13–15 mg/kg/day, which can significantly improve the clinical manifestation, serum profile and histology.[2–4] However, the response to UDCA treatment in some patients is unsatisfactory, which may result in poor prognosis.[5,6]

In recent years, with the increasing prevalence of PBC (39.2 per 100,000),[7] the cases in China have risen up to 19.1 cases per 100,000.[8] Furthermore, because of the uncertainty of UDCA treatment response in some patients, identifying patients at high-risk of poor response to UDCA before the start of treatment and starting the second-line treatment early will help to control disease progression. Therefore, prediction of UDCA treatment nonresponse in PBC is drawing more and more attention.

Several studies have been conducted to identify inadequate response to UDCA.[5,6,9–13] These studies, which are based on 1- or 2-year treatment data, have effectively predicted the long-term outcome but they have not identified the patients earlier. To make up for this deficiency, some criteria have been conducted based upon admission data,[14–16] but the findings still need validation. Given that the risk factors that are associated with early biochemical nonresponse have been subject to misidentification, the aims of our study were to accurately identify the independent risk factors of the early biochemical nonresponse and propose a relatively accurate predictor index for insufficient early biochemical response to UDCA treatment before treatment begins, ultimately providing more evidence of relevant aspects in PBC patients.

Methods

Study design

In total, 241 PBC patients, at admission and in the outpatient setting from January 2010 to July 2018, were identified through search of the electronic medical record system. The 135 patients who met the research needs were enrolled in this retrospective study. The patients were regularly treated with UDCA upon diagnosis. The baseline data were obtained when the patients were first diagnosed with PBC. The follow-up data were obtained at the 1-year regular UDCA treatment appointment (the 1-year follow-up endpoint).

The study was approved by the Ethics Committee of Tongji Medical College, HUST. This Ethics Committee was constituted and still functions in accordance with the Inter-

Keywords: Primary biliary cholangitis; Therapy; Risk factors; Statistical model.
Abbreviations: AMA, anti-mitochondrial antibody; APRI, aspartate aminotransferase- to-platelet ratio index; AUC, area under the ROC curve; ESR, erythrocyte sedimentation rate; FIB-4, fibrosis index based on the four factors; Ig, immunoglobin; PBC, primary biliary cholangitis; ROC, receiver operating characteristic; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
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national Conference on Harmonization-Good Clinical Practice, the Good Clinical Practice in China, and the Declaration of Helsinki. The study is also registered on the Chinese Clinical Trial Registry Platform (http://www.chictr.org.cn/), as ChiCTR1800019712.

Diagnostic criteria

According to the American Association for the Study of Liver Disease and the European Association for the Study of the Liver,[9,17] a patient meeting any two of following three criteria was diagnosed with PBC: (1) titer of AMA-M2 ≥1:40; (2) alkaline phosphatase elevation of unknown causes (≥1.5 times normal) for 6 months; (3) and liver biopsy findings of non-suppurative cholangitis, interlobular bile duct injury, or bile duct granuloma.[9,17] Positive or weak detection of AMA-M2 was noted when the titer was ≥1:40, according to the equipment system setting.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients diagnosed with PBC; and (2) PBC patients treated with UDCA (13–15 mg/kg/d) regularly following diagnosis. The excluded criteria were as follows: (1) patients complicated with other kinds of hepatitis; (2) patients complicated with liver cancer; (3) pregnant or lactational women; (4) patients who died during this hospitalization; (5) patients with incomplete baseline data; and (6) patients with follow-up less than 1 year.

Data collection

The clinical, laboratory and pathological data were collected from Wuhan Union Hospital and included measures of leukocytes, hemoglobin, platelets, prothrombin time, fibrinogen, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, albumin, globulin, erythrocyte sedimentation rate (referred to as ESR), immunoglobin (Ig) and hepatic-related autoimmune antibodies, as well as findings from liver pathology. Aspartate aminotransferase-to-platelet ratio index (ARP1)[10] and fibrosis index based on the four factors (FIB-4),[11] the two noninvasive liver fibrosis indexes, were analyzed as part of the baseline data. The liver specimens were assessed blindly by two experienced hepatopathologists.

Response to UDCA

The Paris I criteria proposed by Corpechot *et al*.[12] in 2008 was adopted in this study to evaluate the response to UDCA treatment. Early biochemical response was defined as the patients' indexes having met the requirements of the Paris I criteria after a 1-year period of UDCA treatment, in which the level of alkaline phosphatase was ≤3 the upper limit of normal (referred to as ULN), the level of aspartate aminotransferase was ≤2 ULN, and the level of total bilirubin was ≤1 mg/dL.[12] Whereas, the early biochemical nonresponse was defined as the patients' indexes not having met the requirements mentioned above.

Statistical analysis

SPSS software v23.0 (IBM Corp., Armonk, NY, USA) was employed for the data processing. Continuous variables were expressed as median (interquartile range) because of skewed distribution. Categorical variables were described in terms of numbers and percentages. The cut-off value of continuous variables were determined by receiver operating characteristic (ROC) curve, using MedCalc statistical software. Univariate analysis was conducted by χ^2 test or Fisher's exact test, while multivariate analysis was conducted by forward logistic regression analysis based on maximum likelihood estimation, predictor index was obtained by logistic analysis and the ROC curve was measured to evaluate prediction value. Statistical significance was signified by p-value <0.05.

Results

Baseline and follow-up data of PBC patients

In total, 122 females and 13 males (totaling 135 patients) were enrolled, and the gender ratio of female to male was 9.4:1. The median age of the total 135 patients was 51 (range, 45–58) years-old. The liver biopsy had been conducted for 52 (38.5%) of the patients because of the need for diagnosis. The destruction of small bile duct was apparent in all of the patients upon histological examination, with 40 (76.9%) being at stages I and II. Meanwhile, interface hepatitis was apparent in 36 (69.2%) of the patients upon histological examination, but 34 (94.5%) were only at the mild or moderate stages (Table 1).

The follow-up time for this entire group was 1 year. After 1-year of the UDCA treatment, 77 (57%) patients had achieved early biochemical response, whereas 58 (43%) patients had not. The alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase and total bilirubin levels from follow-up were significantly lower than those of baseline (p<0.05), which showed the therapeutic effect of UDCA in our PBC patients (Table 1).

ROC curve and univariate analysis of risk factors

In continuous indexes, the cut-off value for sorting the patients with early biochemical response from those with nonresponse was determined by ROC curve. The indexes which might influence the biochemical response (p<0.05) (Table 2) and the categorical variables were evaluated by univariate analysis. Hemoglobin, prothrombin time, aspartate aminotransferase, total bilirubin, alkaline phosphatase, albumin, globulin, IgG, IgM, IgA, APRI, and FIB-4 were identified as factors that might influence the early biochemical response (p<0.05) (Table 3).

Multivariate analysis of the risk factors and development of the predictor index

Multivariate logistic regression analysis was employed to determine the independent risk factors. The analysis included all the factors that were statistically significant in the univariate analysis. Collinearity diagnostics was employed and the multi-collinearity of the indexes of those factors were excluded. After adjusting for sex and age, the forward logistic regression analysis based on maximum likelihood estimation indicated that total bilirubin ≥1.98 mg/dL, albumin ≤35.30 g/L, globulin ≥33.00 g/L, IgM ≥3.10 g/L and APRI ≥1.63 were independent risk factors of early biochemical nonresponse in PBC patients, with the

Table 1. Characteristics of the PBC patients in our study cohort

Variables	Total patients	Response patients	Nonresponse patients
Gender, male (%)	13 (9.6%)	9 (11.7%)	4 (6.9%)
Age, years	51 (45, 58)	53 (45, 58)	50.5 (44, 56)
Leukocyte, 4–10*10^9/L	4.64 (3.49, 5.84)	4.809 (3.53, 5.67)	4.245 (2.89, 6.15)
Hemoglobin, male: 120−160 g/L; female: 110−150 g/L	111 (99, 122)	116 (106, 125)	102.5 (85,115)
Platelet, 100−300*10^9/L	150 (95, 240)	158 (106.5, 243.5)	138.5 (78.0, 235.5)
Prothrombin time, 11–16 s	12.7 (12.0, 13.5)	12.5 (12.0, 13.2)	12.8 (12.0, 15.0)
Fibrinogen, 2−4 g/L	3.10 (2.57, 3.63)	3.10 (2.71, 3.60)	3.15 (2.49, 3.69)
Alanine aminotransferase, 5−35 U/L	67.0 (41.0, 115.0)	67.0 (39.5, 115.5)	70.5 (45.5,108.8)
Aspartate aminotransferase, 8−40 U/L	86.0 (52.0, 129.0)	63.0 (45.0, 99.5)	113.0 (74.8, 159.3)
Total bilirubin, 0.1−1 mg/dL	1.44(0.82, 2.59)	16.95 (10.93, 27.60)	41.75(25.05, 87.55)
Alkaline phosphatase, 40−150 U/L	318.0 (209.0, 537.0)	264.0 (181.5, 484.0)	387.5(250.5,638.3)
γ-glutamyl transpeptidase, 7−32 U/L	346.0 (160.0, 612.3)	325.0 (156.8, 568.5)	380.5 (177.3, 670.3)
Albumin, 35−55 g/L	37.8 (33.2, 41.3)	39.7 (36.6, 42.2)	35.1 (30.9, 39.6)
Globulin, 20−30 g/L	33.7 (28.1, 38.9)	31.8 (27.0, 36.6)	36.5 (31.1, 42.2)
ESR, male <15 mm/h; female <20 mm/h	33.0 (17.8, 67.5)	25.0 (16.0, 67.0)	46.0 (27.0, 73.0)
IgG, 7.51−15.60 g/L	16.89 (12.60, 21.00)	14.65 (11.93,18.73)	18.89 (15.90, 25.20)
IgM, 0.460−3.040 g/L	4.24 (2.94, 5.49)	3.61 (2.33, 5.47)	4.68 (3.94, 5.66)
IgA, 0.82−4.53 g/L	2.65 (1.92, 3.79)	2.47 (1.87, 3.37)	3.46 (2.21, 4.55)
Complement 3, 0.790−1.520 g/L	1.03 (0.79, 1.23)	1.00 (0.81, 1.16)	1.09 (0.67, 1.33)
Complement 4, 0.160−0.380 g/L	0.18 (0.14, 0.22)	0.18 (0.14, 0.21)	0.17 (0.13, 0.22)
APRI	1.25 (0.81, 2.48)	1.05 (0.70, 1.70)	1.98 (1.04, 3.54)
FIB-4	3.49 (1.97, 6.09)	2.57 (1.70, 4.65)	4.38 (2.47, 8.02)
ANA, *n* (%)	119 (89.5%)	67 (89.3%)	52 (89.7%)
ASMA, *n* (%)	4 (3.00%)	2 (2.67%)	2 (3.45%)
AMA-M2, *n* (%)	111 (83.5%)	60 (80.0%)	51 (87.9%)
Anti-sp100 antibody, *n* (%)	8 (25.00%)	4 (17.39%)	4 (44.44%)
Anti-gp210 antibody, *n* (%)	16 (50.00%)	11 (47.83%)	5 (55.56%)
Anti-3E-BPO antibody	25 (78.10%)	17 (73.91%)	8 (88.89%)
Interface hepatitis, *n* (%)	36 (69.2%)	27 (71.1%)	9 (64.3%)
Cholangitis (Ludwig)			
I−II	40 (76.9%)	32 (82.1%)	8 (61.5%)
III−IV	12 (23.1%)	7 (17.9%)	5 (38.5%)
Alanine aminotransferase T12	30.0 (21.0, 47.5)	25.0 (19.0, 33.3)	49.0 (30.0, 83.0)
Aspartate aminotransferase T12	42.0 (29.5, 77.5)	33.0 (27.0, 41.3)	83.0 (54.0, 114.0)
Total bilirubin T12	1.02 (0.75, 2.03)	13.85 (11.40, 17.00)	42.00 (26.80, 74.20)
Alkaline phosphatase T12	174.0 (108.5, 264.5)	119.5 (86.8, 183.5)	277.0 (201.0, 386.0)
γ-glutamyl transpeptidase T12	129.0 (62.0, 308.0)	99.0 (40.0, 195.8)	234.0 (104.0, 454.0)
Albumin T12	39.0 (34.1, 43.0)	41.9 (38.0, 44.0)	35.0 (27.3,38.8)
Globulin T12	33.0 (28.4, 38.6)	32.2 (28.6, 35.5)	35.1 (28.1, 43.0)

Abbreviations: ANA, anti-nuclear antibody; anti-3E-BPO antibody, anti-BCOADC-E2PDC-E2OGDC-E2 antibody; ASMA, anti-smooth muscle antibody; dsDNA antibody, double stranded DNA antibody.

area under the ROC curve (AUC) values for each being 0.804, 0.704, 0.676, 0.640 and 0.711, respectively (Tables 2 and 4).

In assigning the independent risk factors that were men-

Table 2. ROC curve of continuous variations of baseline data

Variables	AUC	Cut-off value	*p*-value
Age, years	0.554	51.00	0.286
Leukocyte, 4−10*10^9/L	0.520	4.50	0.7
Hemoglobin, male: 120−160 g/L; female: 110−150 g/L	0.710	108.00	<0.001***
Platelet, 100−300*10^9/L	0.570	104.00	0.173
Prothrombin time, 11−16 s	0.605	13.90	0.042*
Fibrinogen, 2−4 g/L	0.524	2.80	0.651
Alanine aminotransferase, 5−35 U/L	0.545	53.00	0.362
Aspartate aminotransferase, 8−40 U/L	0.732	107.00	<0.001***
Total bilirubin, 0.1−1 mg/dL	0.804	1.98	<0.001***
Alkaline phosphatase, 40−150 U/L	0.668	317.00	<0.001***
γ-glutamyl transpeptidase, 7−32 U/L	0.554	440.00	0.285
Albumin, 35−55 g/L	0.704	35.30	<0.001***
Globulin, 20−30 g/L	0.676	33.00	<0.001***
ESR, male <15 mm/h; female <20 mm/h	0.622	23.00	0.062
IgG, 7.51−15.60 g/L	0.710	15.20	<0.001***
IgM, 0.460−3.040 g/L	0.640	3.10	0.013*
IgA, 0.82−4.53 g/L	0.646	3.30	0.01*
Complement 3, 0.790−1.520 g/L	0.527	1.31	0.656
Complement 4, 0.160−0.380 g/L	0.509	0.18	0.887
APRI	0.711	1.63	<0.001***
FIB-4	0.686	3.33	<0.001***

*p<0.05, ***p<0.001.

Table 3. Results of univariate analysis of risk factor between the response group and nonresponse group

Variables	Response group	Non-response group	Statistics	*p* value
Hemoglobin >108.00 g/L, *n* (%)	55 (71.4%)	20 (34.5%)	18.29	<0.001***
Prothrombin time >13.90 s, *n* (%)	6 (7.8%)	20 (34.5%)	15.16	<0.001***
Aspartate aminotransferase >107.00 U/L, *n* (%)	13 (16.9%)	31 (53.4%)	20.13	<0.001***
Total bilirubin >1.98 mg/dL, *n* (%)	10 (13.0%)	38 (65.5%)	39.84	<0.001***
Alkaline phosphatase >317.00 U/L, *n* (%)	29 (37.7%)	39 (67.2%)	11.58	0.001**
Albumin <35.30 g/L, *n* (%)	11 (14.3%)	30 (51.8%)	21.93	<0.001***
Globulin >33.00g/L, *n* (%)	29 (37.7%)	41 (70.7%)	14.45	0.001**
IgG >15.20 g/L, *n* (%)	29 (37.7%)	35 (60.3%)	6.83	0.009**
IgM >3.10 g/L, *n* (%)	40 (51.9%)	41 (70.7%)	4.84	0.028*
IgA >3.32 g/L, *n* (%)	17 (22.1%)	24 (41.4%)	5.83	0.016*
APRI >1.63, *n* (%)	20 (26.0%)	36 (62.1%)	17.76	<0.001***
FIB-4 >3.33, *n* (%)	29 (37.7%)	41 (70.7%)	14.45	<0.001***
AMA-M2, *n* (%)	60 (80.0%)	51 (87.9%)	1.49	0.222
Anti-sp100 antibody, *n* (%)	4 (17.4%)	4 (44.4%)		0.176
Anti-gp210 antibody, *n* (%)	11 (33.3%)	5 (55.6%)		1
Anti-3E-BPO antibody, *n* (%)	17 (73.9%)	8 (88.9%)		0.64
Interface hepatitis	27 (71.1%)	9 (64.3%)	0.017	0.896
Cholangitis (Ludwig)				
III−IV, *n* (%)	7 (17.9%)	5 (38.5%)	1.30	0.254

*p<0.05, **p<0.01, ***p<0.001.

Table 4. Result of logistics regression analysis of risk factor between response group and nonresponse group

Variables	Assignment	Multivariate analysis				
		B	S.E.	Wald	Exp(B) (95%CI)	Sig.
X1 (total bilirubin)	>1.98 mg/dL=1; <1.98 mg/dL=0	2.456	0.539	20.794	11.66 (40.56, 33.49)	<0.001***
X2 (globulin)	>33.00 g/L=1; <33.00 g/L=0	1.156	0.516	5.023	3.18 (1.16, 8.73)	0.025*
X3 (IgM)	>3.10 g/L=1; <3.10 g/L=0	1.217	0.561	4.695	3.38 (1.12, 10.15)	0.03*
X4 (APRI)	>1.63=1; <1.63=0	1.217	0.489	6.2	3.38 (1.30, 8.80)	0.013*
X5 (albumin)	<35.30 g/L=1; >35.30 g/L=0	1.533	0.573	7.162	4.63 (1.51, 14.23)	0.007**
Constant		−3.548	0.646	30.183	0.03	<0.001***

*p<0.05, **p<0.01, ***p<0.001.

tioned above (Table 4), the logistic equation was established and the predictor index was formed (Table 4). The ROC curve was adopted to evaluate the prediction value of the predictor index, and the obtained value of the AUC was 0.886, which was better than that obtained for any of the single independent risk factors, with the cut-off value being 0.3102 (Fig. 1). Transferring the logistic equation, the predictor index was obtained.

The logistic equation was:

$$\text{logit}(p) = -3.548+2.456*X1+1.156*X2 +1.217*X3+1.217*X4+1.533*X5$$

$$\text{predictor index} = 1/e^{(-3.548+2.456*X1 +1.156*X2+1.217*X3+1.217*X4+1.533*X5)}$$

Discussion

In this study, we adopted univariate analysis, logistic multivariate regression analysis and ROC curve analysis to identify the risk factors of UDCA nonresponse and propose a predictor index to predict treatment response of PBC patients to UDCA. We observed that total bilirubin, albumin, globulin, IgM, and APRI were independent risk factors and the cut-off value of the predictor index was 0.3102, with the AUC being 0.886, indicating good predictive value.

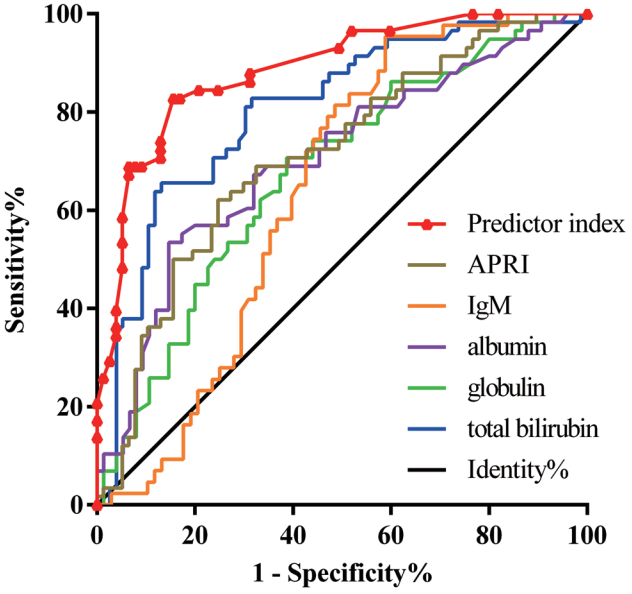

Fig. 1. ROC curve of the five independent risk factors and the predictor index established by the five variables. The AUCs of total bilirubin, globulin, IgM, albumin and APRI were 0.804, 0.67, 0.640, 0.704 and 0.711, respectively. The AUC of the predictor index was 0.886.

UDCA is widely recommended as the first-line treatment for PBC, and the disease can be effectively delayed if the patient responds well to the UDCA. But, unfortunately, there are still some patients whose response is poor to this treatment. To evaluate the treatment response to UDCA, a number of criteria have been published, such as Barcelona, Paris-I/II, GLOBE score, UK-PBC score and so on, which are all based on data from 1 or 2 years of UDCA treatment.[5,6,12,13,18–20] Among the published criteria which identified the treatment response of UDCA, Paris I has been the widely used.[1] The GLOBE score and UK-PBC score were proposed recently and are considered to be better than the Paris I criteria but they both still need further validation.[21] Compared to the Barcelona, Rochester, Rotterdam, Ehime and Toronto criteria, the Paris I criteria has a relatively better predictive value and has been validated by several large studies.[21–23] In our study, we compared the criteria and found the response rate in Paris I was close to the Guideline.[1] With the intent of providing a supplement of Paris I, we tried to use Paris II criteria to decide on the biochemical response of early-stage patients, but the response rate was no different from that of the Paris I criteria. Considering the situation above and the Paris I criteria being recommended by the Chinese Guideline,[24] so we chose Paris I to determine the early biochemical response.

Consistent with previous studies, total bilirubin, albumin, and APRI were found to be associated with biochemical nonresponse to UDCA treatment.[9,25,26] The elevation of total bilirubin level associated with the adverse outcome of PBC patients has been confirmed by many other surveys.[9–11,27-30] The elevation of total bilirubin might reflect progression of PBC.[9] Therefore, there is no doubt that bilirubin is one of the risk factors of early biochemical nonresponse. Albumin, as a protective factor, has already been reported as associated with the adverse long-term outcome in PBC.[13,18,31] As is known, albumin is synthesized by the liver; hence, the decline of albumin reflects the decline of hepatic function, which represents the severity of the disease. APRI is a non-invasive measurement of liver fibrosis in chronic hepatitis of C, and is calculated by Wai's formula.[10] The previous studies showed that APRI could act as a non-invasive diagnostic tool for hepatitis C virus-related liver fibrosis[32] and are associated with Ludwig's stages of PBC.[33] Moreover, the APRI was supposed to be able to predict UDCA treatment response.[25]

A key difference between our and other studies is that the globulin and IgM were identified as independent risk factors in ours and each was determined to significantly influence the UDCA response (odds ratio of 3.38); most of the previous studies did not include the Igs in their analyses. IgM is the one of the established biomarkers of PBC.[34] Moreover, increase of globulin is related to liver inflammation and

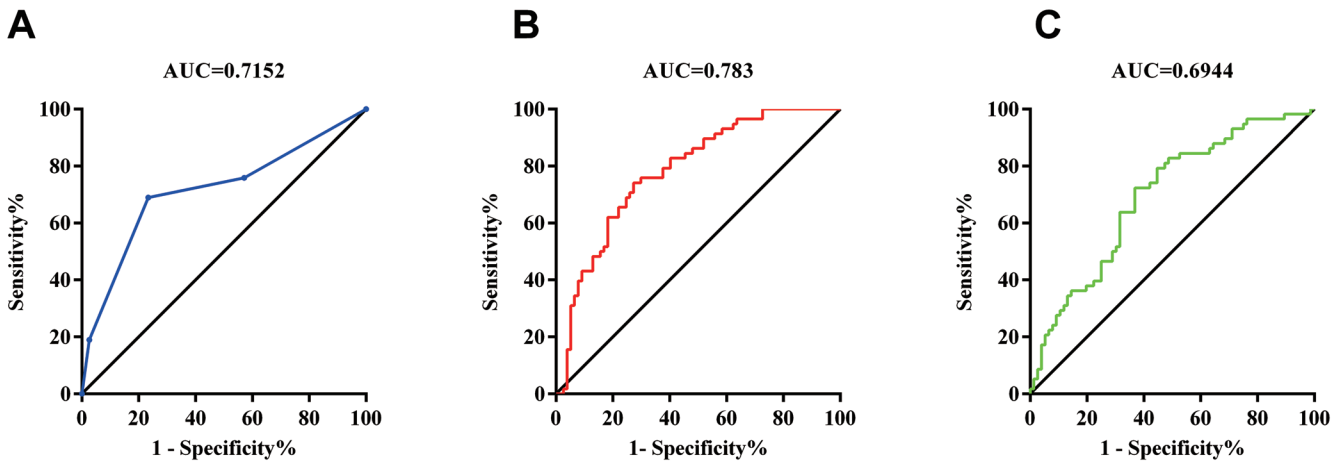

Fig. 2. Predictive value of the proposed criteria in our cohort. (A) The model proposed by Chen *et al*.[15] (B) The model proposed by Tian *et al*.[16] (C) The model proposed by Carbone *et al*.[14]

fibrosis in chronic hepatitis patients, including those with autoimmune liver disease.[35] Therefore, we supposed that the elevations of globulin and IgM were predictive for complicated conditions of patients or a longer diagnostic delay of such patients, linking them to early biochemical nonresponse.

What interested us most was that alkaline phosphatase was not included in the last predictor index. In previous studies, alkaline phosphatase was included in many published models established from the data of European and North American patients.[9,13,18] When involving Chinese patients, we found that alkaline phosphatase was not included in some groups for predicting early biochemical response[15] or long-term outcome.[30] The reasons that might account for this phenomenon are small sample size, different populations of PBC patients and the different natural histories of Chinese and European or North American patients.

The model established by the five risk factors mentioned above had a relatively high predictive ability, with AUC being 0.886 (sensitivity: 82.80%, specificity: 84.40%). Compared to the previous studies that established the predictive model,[14–16] our study has some key distinctions. First of all, the independent risk factors that formed the predictor index were different. The risk factors in our study were total bilirubin, albumin, globulin, IgM, and APRI. Among them, the IgM and globulin were first discovered by us, both of which showed great influence on the response to UDCA (odds ratio for them was 3.38) (Table 4). Second, we screened more factors that were probably associated with the response to UDCA, including complement 3, complement 4, IgA, IgM, IgG, ESR, ANA, ASMA, AMA-M2, interface hepatitis and so on, among which the IgM showed significant relevance to the UDCA treatment response. Furthermore, we tested the predictive value of the model proposed by previous studies[14–16] in our cohort. It turned out that the predictive ability of them was relatively low (Fig. 2).

This retrospective study established a relatively accurate predictor index for the response of PBC patients to UDCA treatment, but there might be some limitations. Mainly, our sample size was small, so there might exist selection bias and we did not have validation data. Because of the short-term follow-up, we also could not identify the predictive value for long-term outcomes.

In conclusion, we found that total bilirubin, albumin, globulin, IgM, and APRI were independent risk factors of early biochemical nonresponse in PBC patients after 1-year of UDCA treatment. The predictive value of the predictor index established based on those five variables was excellent, and it is expected to contribute to the future recognition of high-risk patients before the start of treatment and provide important information for the physician.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception and design of the study (JY, FD), data collection and analysis (YYS, YHS, TB, HTS), review of patient charts and data interpretation (XLP, LY), statistical analysis (YYS, YHS), and manuscript preparation (YYS, FD, JY).

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