CLINICAL PRACTICE ARTICLE

Prognostic Value of Noninvasive Fibrosis Scores in Primary Biliary Cholangitis

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Abstract

Objective: To explore the prognostic value of several widely used noninvasive fibrosis scores (NIFS) for the mortality due to liver-related events in Chinese primary biliary cholangitis (PBC) population.

Study Design: An observational study.

Place and Duration of Study: Department of Infectious Diseases and Hepatology, the Second Hospital of Shandong University, Jinan, China, from August 2008 to July 2018.

Methodology: Patients were diagnosed as PBC when they fulfilled at least two of the following criteria: presence of anti-mitochondrial antibodies (AMA), or other PBC-specific autoantibodies; and/or biochemical evidence of cholestasis; and/or histological evidence of liver biopsy. Patients were excluded if they were just started UDCA administration within last year, followed up for less than a year, diagnosed as overlap syndrome, or suffered from other coexisting hepatic diseases. Clinical data were recorded and scores of 11 generally accepted NIFS were calculated. Cox proportional hazards model was performed to explore independent predictors of liver-related mortality.

Results: Sixty-five PBC patients were included in the current cohort. Five patients died due to liver-related events during a median of 35-month follow-up. The 5-year cumulative survival rate was 88.4%. Non-survival patients were characterised with lower platelet count (p=0.049), lower level of albumin (p=0.018), higher fibrosis index (p<0.001) and higher Doha score (p=0.006). Multivariate Cox regression analysis identified fibrosis index (HR 17.449, 95% CI 1.410-215.989, p=0.026) and Doha score (HR 1.782, 95% CI 1.146-2.771, p=0.010) as independent predictors for liver-related mortality of PBC patients.

Conclusion: Fibrosis index and Doha score could serve as valuable prognostic factors for liver-related mortality in Chinese PBC population.

Key Words: *Primary biliary cholangitis, Noninvasive fibrosis scores, Mortality.*

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INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic auto-immune liver disease and cholestasis is confirmed as a feature of disease course.[1,2] The etiology of PBC is still unknown, genetic predisposition and environmental factors have been indicated as important pathogenic factors.[3] Outcomes in PBC generally rested on the development of cirrhosis and its complications.[1,2]

Ursodeoxycholic acid (UDCA) is the first line drug approved for the treatment of patients with PBC, which has been proven to ameliorate biochemical indices, delay histologic progression and improve long term survival.[1,4] However, about one-third of PBC patients may not obtain perfect biochemical response after 12 months' therapy with UDCA and there may be factors independently associated with disease progression and death due to liver-related events.[4,5] Several models have been designed to evaluate biochemical response to UDCA, including the Rotterdam criteria,[6] Barcelona criteria,[7] Paris I criteria,[8] Paris II criteria,[5] and Toronto criteria.[9] These models are based on the improvement of several biochemical markers after 6-12 months of UDCA treatment, such as alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), albumin and total bilirubin (TB). Recently, two new models (the GLOBE score and the UK-PBC score),[10,11] have been introduced by including some other factors, such as age and platelet count, to predict long-term outcomes of PBC. However, as the above predictive models including indices of the baseline and 1 year after UDCA therapy, it is difficult to judge the prognosis of PBC patients prior to initiating therapy.

Several noninvasive fibrosis scores (NIFS), which could be calculated from liver function tests and other routine blood tests, such as aspartate aminotransferas (AST)-platelet ratio index (APRI) and Lok score, have been widely used for determination of liver fibrosis. These noninvasive score systems have also been shown a

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good prognostic value for prognosis of patients with chronic hepatitis C (CHC).[12] However, only a few studies in literature have evaluated prognostic value of NIFS for the long-term survival of PBC population.

The present study was performed to explore prognostic value of several widely used NIFS for the mortality due to liver-related events in Chinese PBC population.

METHODOLOGY

It was observational study where all patients diagnosed with PBC and treated at the Second Hospital of Shandong University were recruited between August 2008 and July 2018. The diagnosis of PBC should fulfill at least two of the following criteria:[1] (1) presence of anti-mitochondrial antibodies (AMA), or other PBC-specific autoantibodies, including anti-sp100 or anti-glycoprotein 210 (anti-gp210); (2) biochemical evidence of cholestasis (elevated ALP levels); and (3) histological evidence of liver biopsy, such as non-suppurative destructive cholangitis and destruction of interlobular bile ducts. Patients were excluded if they were: just started UDCA administration within last year, followed up for less than one year, diagnosed as overlap syndrome, suffered from other coexisting hepatic diseases including chronic hepatitis B (CHB) and CHC infection, alcoholic liver disease, steatohepatitis, and hereditary metabolic liver disease.

Patients' age, gender, platelet count, liver biochemistry, creatinine, and international normalised ratio (INR) were recorded. Scores of 11 NIFS deriving from blood tests for pre-treatment assessment of liver fibrosis were calculated, including fibrosis-4 index, Lok score, Fibro-alpha, GUCI score, AST-ALT ratio (AAR), Fibrosis index, Fibro-Q score, Doha score, Age platelet count index, King's score and AST-platelet count ratio index (APRI) (Table I).[12,13]

The endpoint event was set as death due to liver-related events, such as hepatocellular carcinoma (HCC), hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome and gastrointestinal bleeding. The protocol of the current study followed guidelines of the Helsinki Declaration and has been approved by the Ethical Committee of the Second Hospital of Shandong University.

All data were analysed using IBM SPSS Statistics Version 22.0 (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov test was performed to calculate the normality of continuous variables. Data were expressed by using mean ± standard deviation (SD) or median [interquartile range (IQR)] for continuous variables. Student t-test or Mann-Whitney test were selected for the comparisons of continuous statistics. Cox proportional hazards model was performed to explore independent predictors of liver-related mortality. Covariates brought into multi-variable analysis included: age at diagnosis of PBC, gender, alanine aminotransferase (ALT), aspartate aminotransferas (AST), GGT, TB, albumin, platelet count, INR, creatinine, and a specific NIFS. If some covariates were included in the given NIFS, they were removed from the multivariable analysis. A p-value less than 0.05 was considered as statistically significant.

Table I: Calculations of included noninvasive fibrosis scores (NIFS).[12,20]

NIFS	Calculations
Fibrosis-4 index	(Age × AST) / (PLT × ALT(1/2))
Lok score	Log odds = -5.56 - 0.0089 × platelet count+1.26 × (AST/ALT) + 5.27×INR; Predicted probability = [exp (log odds)]/[1 + exp (log odds)]
Fibro-alpha	1.35 + [AFP × 0.009584] + [(AST)/(ALT) × 0.243] - (PLT × 0.001624)
GUCI score	Normalized AST × INR × 100/PLT
AST-ALT ratio (AAR)	AST/ALT
Fibrosis index	8.0 - (0.01 × PLT) - serum albumin
Fibro-Q score	(Age × AST × INR)/(ALT × PLT)
Doha score	8.5 - 0.2 × albumin + 0.01 × AST - 0.02 × PLT
Age platelet count index	Age/PLT
King's score	(Age × AST × INR)/PLT
AST-platelet count ratio index (APRI)	(Normalized AST/PLT) × 100

NIFS, Noninvasive fibrosis scores; ALT, alanine aminotransferase; AST, aspartate aminotransferas; GGT, gamma-glutamyl transferase; INR, international normalised ratio; PLT, platelet count.
Normalised AST = observed AST/upper limit of normal AST.
Age was expressed as years; ALT and AST were expressed as U/L; PLT was expressed as 10^9/L; AFP was expressed as IU/ml; albumin was expressed as g/dl.

Table II: Characteristics of included patients.

	Total (n=65)	Alive (n=60)	Death (n=5)	p-value
Age (years)	61.1 ±10.9	61.0 ±10.6	63.2 ±15.0	0.662
Gender (male / female)	7/58	6/54	1/4	0.488
ALT (U/L)*	72.0 (40.0-102.0)	71.0 (38.5-102.5)	72.0 (57-364)	0.510
AST (U/L)*	70.0 (53.0-97.0)	69.5 (49.3-96.5)	73 (63.5-398.5)	0.272
GGT (U/L)*	224.0 (127.5-381.0)	217.5 (123.8-390.5)	275 (186-383.5)	0.747
Bilirubin (umol/L)*	22.0 (14.7-37.7)	21.9 (13.6-38.7)	30.5 (17.0-43.9)	0.464
Platelet count (10^9/L)	158.8 ±63.1	163.3 ±63.0	105.6 ±36.5	0.049
INR*	0.96 (0.93-1.00)	0.96 (0.93-1.00)	0.92 (0.88-0.99)	0.203
Albumin (g/L)	34.8 ±6.5	35.4 ±6.4	28.3 ±3.6	0.018
Creatinine (umol/L)*	53.6 (47.2-60.2)	53.6 (46.9-60.2)	51.3 (47.6-208.6)	0.858
Fibrosis-4 index*	3.46 (2.22-6.00)	3.29 (2.19-5.69)	6.28 (4.31-21.7)	0.062
Lok score	0.43 ±0.24	0.43 ±0.25	0.48 ±0.12	0.657
Fibro-alpha*	1.42 (1.29-1.51)	1.41 (1.28-1.51)	1.50 (1.43-1.60)	0.154
GUCI score*	1.04 (0.63-1.95)	1.01 (0.61-1.82)	1.62 (1.07-14.45)	0.103
AST-ALT ratio (AAR)*	1.03 (0.82-1.48)	1.03 (0.79-1.48)	1.08 (0.99-1.47)	0.510
Fibrosis index	2.92 ±1.05	2.83 ±1.04	4.11 ±0.26	<0.001
Fibro-Q score*	0.44 (0.27-0.68)	0.41 (0.26-0.65)	0.67 (0.45-1.11)	0.114
Doha score	5.68 ±1.86	5.50 ±1.65	7.82 ±2.97	0.006
Age platelet count index*	0.37 (0.29-0.59)	0.37 (0.28-0.57)	0.66 (0.36-1.11)	0.092
King's score*	26.2 (16.4-48.8)	26.1 (16.1-47.6)	48.5 (31.6-488.3)	0.120
AST-platelet count ratio index (APRI)*	1.10 (0.65-1.91)	0.98 (0.64-1.83)	1.67 (1.17-14.68)	0.074

ALT, alanine aminotransferase; AST, aspartate aminotransferas; GGT, gamma-glutamyl transferase; INR, international normalized ratio; IQR, interquartile range.
**Median (interquartile range).*

Table III: Univariate and multivariate cox regression analysis revealing predictive value of 11 selected NIFS.

	Univariate analysis			Multivariate analysis		
	B	HR (95% CI)	p-value	B	HR (95% CI)	p-value
Fibrosis-4 index	0.110	1.116 (1.028-1.212)	0.009	1.320	3.744 (0.146-95.759)	0.425
Lok score	0.767	2.154 (0.064-72.126)	0.668			
Fibro-alpha	1.269	3.559 (0.095-132.658)	0.492			
GUCI score	0.134	1.143 (1.026-1.273)	0.015	2.414	11.181 (0.015-8183.793)	0.473
AST-ALT ratio (AAR)	-0.127	0.880 (0.256-3.027)	0.840			
Fibrosis index	2.712	15.056 (2.000-113.317)	0.008	2.859	17.449 (1.410-215.989)	0.026
Fibro-Q score	0.626	1.871 (0.582-6.018)	0.293			
Doha score	0.467	1.594 (1.120-2.271)	0.010	0.578	1.782 (1.146-2.771)	0.010
Age platelet count index	2.832	16.979 (1.395-206.673)	0.026	Not in the equation		
King's score	0.004	1.004 (1.001-1.007)	0.008	0.050	1.052 (0.966-1.145)	0.246
AST-platelet count ratio index (APRI)	0.133	1.143 (1.027-1.272)	0.015	1.292	3.639 (0.211-62.873)	0.374

NIFS: Noninvasive fibrosis scores; ALT: Alanine aminotransferase; AST: Aspartate aminotransferas.

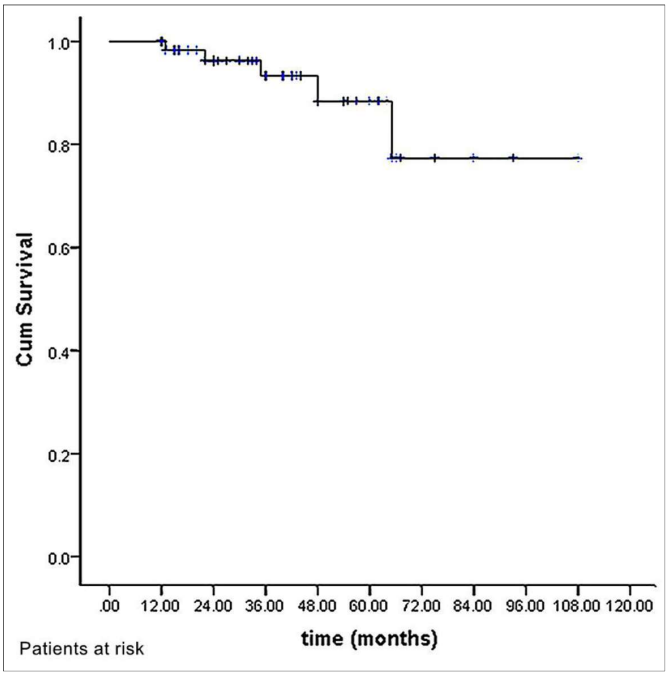

Figure 1: Cumulative survival curve of included primary biliary cholangitis patients.

RESULTS

Eighty-four patients were preliminarily identified and 19 patients were not recruited in the present cohort because of exclusion criteria. Hence, the present study included 65 PBC patients. Twelve patients (18.5%) were diagnosed as PBC on liver biopsy. Most of the included patients were females (58 patients, 89.2%) and the mean age at diagnosis of PBC was 61.1 years. Data of ultrasound, computer tomography (CT) or MRI were available for all included patients. Typical imaging findings of liver cirrhosis were observed in 39 patients, of whom 11 patients, 13 patients and 15 patients were evaluated as Child-Pugh Class A, B and C, respectively. Other 26 patients were diagnosed as chronic liver diseases or no obvious abnormality by ultrasound, CT or MRI. HCC occurred in two patients (3.1%) after 12 and 48-month follow-up, respectively. During a median of 35-month (IQR 19 to 51 months) follow-up, five patients (7.7%) died because of liver-related events and the 5-year cumulative survival rate was 88.4% (Figure I). Non-survival patients were characterised with lower platelet count (p=0.049) and lower level of albumin (p=0.018, Table II).

The predictive value of 11 generally accepted NIFS were evaluated (Table I). Fibrosis index (p<0.001) and Doha score (p=0.006) were significantly higher in non-survival PBC patients (Table II). Univariate analysis revealed that higher Fibrosis-4 index (p=0.009), GUCI score (p=0.015), Fibrosis index (p=0.008), Doha score (p=0.010), Age platelet count index (p=0.026), King's score (p=0.008) and APRI (p=0.015) may be related to worse clinical prognosis (death because of liver-related events). However, in multivariate Cox regression analysis, only Fibrosis index (HR 17.449, 95% CI 1.410-215.989, p=0.026) and Doha score (HR 1.782, 95% CI 1.146-2.771, p=0.010) were identified as independent predictors for liver-related mortality of PBC population (Table III).

DISCUSSION

Although several models including baseline characteristics and biochemical response to UDCA have been approved to predict long-term outcomes of PBC, the prognostic value of parameters prior to initiating therapy is still unknown. Cirrhosis has been identified as an independent predictor for transplant-free survival in Chinese PBC patients;[3,14] however, the diagnosis of cirrhosis made by imaging features or findings of portal hypertension (including ascites, splenomegaly and varices) may be delayed and have low sensitivity. NIFS are routinely available in clinical practice and have been widely used for the evaluation of liver fibrosis and cirrhosis.[12,13] Therefore, the evaluation of NIFS prior to UDCA therapy for long-term survival of PBC patients is promising and should be of great clinical significance.

The current study attempts to explore the prognostic value of several widely used NIFS for the mortality due to liver-related events in Chinese PBC population. Based on a long-term observational cohort recruiting 65 PBC patients, the present research selected 11 NIFS

arriving from liver function tests and other routine blood tests to identify Fibrosis index and Doha score as valuable prognostic factors.

Parameters contained in both Fibrosis index and Doha score included serum albumin and platelet count. Albumin could reflect the synthetic ability of hepatocytes. Lower levels of albumin at the time of diagnosis have been proven to identify PBC patients with a worse prognosis.[4,10,11,15] A 10-year observational UDCA-treated PBC cohort also revealed that the long-term survival of PBC population with normal levels of bilirubin and albumin could be comparable to that of general population.[16] The above findings emphasised the prognostic value of albumin. Platelet counts could reflect the level of portal hypertension and has been considered as a serum marker of liver fibrosis and cirrhosis. Previous studies also revealed the prognostic value of platelet count for adverse events.[2,10,11] The baseline levels of albumin and platelet count were also evaluated in two recently developed scoring systems for outcomes of PBC (the GLOBE,[10] and UK-PBC systems),[11] revealing the validated prognostic value of the two parameters.

Trivedi *et al*. concluded that higher APRI is associated with risk of liver transplant (LT) or death.[2] In this study, the prognostic value of APRI was also significant in univariate analysis (p=0.015); however, in multivariate Cox regression analysis, ARPI was not related to the mortality due to liver-related events. The difference might be because of the interaction of different parameters (e.g. AST, bilirubin, albumin and platelet count). Discrepancy of PBC patients between Western and Asian countries should also be considered. Further validation with larger cohort is needed in the future.

Yang *et al*. reported that anti-gp210 could serve as a predictive indicator for the prognosis of Chinese PBC population and should be an important supplement to the GLOBE score and UK-PBC score.[15] As positive anti-gp210 in PBC patients is correlated with more severe cholestatic manifestations and higher risk of liver failure,[15,17] the combined prognostic value of anti-gp210 and Fibrosis index or Doha score should be investigated. However, only a small proportion of included PBC patients in our cohort were examined with anti-gp210 and this parameter was not brought into the current statistical analysis.

In the present cohort, 5 patients died because of liver-related events during a median of 35-month follow-up. The 5-year cumulative survival rate was 88.4%, which was consistent with previous studies performed in Asian populations.[14,18] The incidences of HCC were as low as 0.76%-5.9% in PBC patients,[19] and were mainly found in patients with advanced stage of the disease.[17] In the current study, HCC occurred in 2 patients (3.1%) after 12 and 48 months' follow-up, respectively, which was also similar to previous studies.[14,18,19] Both of HCC patients were diagnosed in cirrhotic status before the start of UDCA. The present study did not explore the risk factors for HCC because of the limited number of carcinoma patients.

There are several limitations of the present study. First, the sample size was relatively small. However, the results were valid, which were consistent with the performance of various prognostic models. Second, the relatively short follow-up time (range 12 to 108 months) may restrict some prognostic models in predicting clinical outcomes after long-term follow-up, which may omit some valuable NIFS.

CONCLUSION

Two valuable NIFS (Fibrosis index and Doha score) arriving from routine pretreatment laboratory parameters were identified for the evaluation of liver-related mortality in Chinese PBC population. These predictive NIFS can be applied easily before treatment of PBC and may be helpful in the evaluation of long-term prognosis.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
YQ: Conception of the manuscript, study design, patients' follow-up, data collection, statistical analysis, manuscript writing and revision.
LW: Patients' follow-up and manuscript revision.
QY: Patients' follow-up and data collection.
YZ: Study design, statistical analysis, and manuscript revision.
JX: Study design, statistical analysis.
TL: Conception of the manuscript, study design, patients' follow-up, data collection, statistical analysis, manuscript writing and revision.

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