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Prediction of Advanced Fibrosis in Nonalcoholic Fatty Liver Disease: An Enhanced Model of BARD Score

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Background/Aims: The BARD score is a model to detect advanced liver fibrosis in nonalcoholic fatty liver disease (NAFLD) patients. The aims of this study were to identify additional factors and then to build an enhanced version of the BARD score. **Methods:** One hundred seven patients with biopsy-proven NAFLD were enrolled retrospectively. Logistic regressions were performed to identify independent risk factors for advanced liver fibrosis (stage 3 or 4). An enhanced model of the BARD score (BARDI score) was built and evaluated with a receiver operating characteristic (ROC) curve. **Results:** In multivariate analysis, age (odds ratio [OR], 0.89; $p=0.04$), aspartate aminotransferase/alanine aminotransferase ratio (OR, 1.73; $p<0.01$), and international normalized ratio (INR) (OR, 8.85; $p<0.01$) were independently significant factors. The BARDI score was created by adding the INR to the BARD. The area under the ROC curve of the BARDI score was significantly larger than that of the BARD score (0.881 vs 0.808, $p<0.01$). A BARDI score of 3 or more showed a positive predictive value (PPV) of 51.0% and a negative predictive value (NPV) of 96.0%. **Conclusions:** The BARDI score had an improved PPV over the BARD score and maintained an excellent NPV. Further study is warranted for its external validation and comparison with other models. (**Gut Liver 2013;7:323-328**)

Key Words: Non-alcoholic fatty liver disease; Liver cirrhosis; International normalized ratio

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common

type of liver disease in the developed countries. About 30% of adults have this disease.¹ The spectrum of NAFLD is diverse, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), which can lead to cirrhosis. The mainstream management strategy for NAFLD is regular follow-up with risk factor modification and early detection of liver fibrosis.² Therefore, the early detection of liver fibrosis is very important.

The gold standard for detecting liver fibrosis is liver biopsy. However this procedure is both risky and expensive, making it difficult for patients to undergo repeated procedures.^{3,4} Further, the NAFLD patients stay asymptomatic usually until its final stages, making it difficult for the clinician to decide when to recommend biopsy, which can result in delayed diagnosis and management of liver cirrhosis. Several imaging methods which use ultrasound, computed tomography or magnetic resonance imaging (MRI) have been introduced to detect liver fibrosis early,⁵⁻¹⁰ but these methods are still expensive and available only in limited places.

Several models using demographic and clinical variables have been developed that can be used to predict liver fibrosis in NAFLD patients. However, some of these were not made specifically for NAFLD patients,¹¹⁻¹³ and some models require a liver fibrosis panel which is not broadly used.^{12,14} The BARD score¹⁵ and the NAFLD fibrosis score¹⁶ are the models which were initially made specifically for NAFLD and do not require a special test. The main strength of the BARD score over the NAFLD fibrosis score is its simplicity. The components of the BARD score: body mass index (BMI), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio and diabetes, are all widely available in clinical practices. The score can be added up simply, without the use of a calculator. Considering the high prevalence

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of NAFLD, it is very important that general physicians have a simple method to routinely screen patients for advanced liver fibrosis. The limitation of the BARD score is its high false positivity. If a patient, for example, has diabetes and a BMI of 28 kg/m² (BARD score, 2), this patient will be classified as having a high risk of advanced liver fibrosis even though the patient has an AST/ALT ratio of less than 0.8 and no liver fibrosis. The positive predictive value (PPV) of a BARD score of 2 or more was 43% for advanced liver fibrosis in its initial development.¹⁵ A prospective study has shown the PPV of a BARD score of 2 or more to be only 36.1% for advanced liver fibrosis, which is lower than PPVs of other clinical models.⁵ This low PPV of BARD score means that a significant number of patients will have false positive results and may end up having unnecessary imaging tests and risky liver biopsies.

In this study, we evaluated the performance of the BARD score in our NAFLD patients and built an enhanced model of the BARD score by finding additional variables in NAFLD patients.

MATERIALS AND METHODS

1. Data sources and elements

All patients with NASH, whose diagnoses were confirmed by liver biopsy between 2002 and 2006 at Cabell Huntington Hospital/Marshall University Medical Center, were enrolled retrospectively. The diagnostic criteria for NASH were used as described in literature previously.¹⁷ Any patients who had a history of alcohol abuse in their medical records, serologic evidence of hepatitis virus infection, or history of other liver disease, such as hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, or primary sclerosing cholangitis, were excluded. Also the patients who had an age of less than 18 years old at the time of biopsy were excluded.

Demographics (age, sex, weight, and height), comorbidities (hypertension, diabetes, and hyperlipidemia), and laboratory information (liver profile, lipid profile, serum creatinine, and international normalized ratio [INR]) tested within a month before the biopsy were obtained from the medical records. Hypertension, diabetes, and hyperlipidemia patients were defined as those who were previously diagnosed with these diseases by physicians, or those who took antihypertensive medications, hypoglycemic agents/insulin, or lipid-lowering agents at the time of biopsy. The liver profile, lipid profile and serum creatinine level were measured using ADVIA[®] 1650 Chemistry System (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Protamine was measured using BCS[®] System (Siemens Healthcare Diagnostics). The INR was calculated from the protamine level by SoftLab[®] (SCC Soft Computer, Clearwater, FL, USA). Pathological reports made by two pathologists for clinical purposes were used. The extent of fibrosis was staged as follows: stage 0 was defined as no fi-

bro sis. Enlarged fibrotic portal tracts were classified as stage 1. Periportal or portal-portal septa but intact architecture was classified as stage 2. Fibrosis with architectural distortion without cirrhosis as stage 3, and probable or definite cirrhosis as stage 4.¹⁷ We classified stages 3 and 4 fibrosis as advanced fibrosis and stages 0, 1, and 2 as nonadvanced fibrosis. This study was approved by Marshall University Institutional Review Board.

2. Statistical method

The chi-square test and Fisher's exact test were used for the categorical variables as appropriate, and a Wilcoxon rank sum test was used for the continuous variables to compare between advanced and nonadvanced fibrosis groups. A box plot was created to show the relationship between variables and the severity of fibrosis. The variables which were significantly associated with the severity of fibrosis in univariate analyses were selected for the multivariate logistic regression. A Wald chi-square test was used for the statistical significance testing in the logistic regression.

The independent predictors in our multivariate model were incorporated into the BARD score model to make an enhanced model. A receiver operating characteristics (ROC) curve was plotted for both the BARD score model and our enhanced model to evaluate their abilities to identify advanced fibrosis in NAFLD patients. The area under the ROC curve (AUROC) was calculated and a likelihood ratio test was performed to compare the models. As an independent validation data set was not available, a 20-fold cross validation was performed as internal validation.¹⁸

A p-value of 0.05 was used as the cutoff of statistical significance. Statistical analyses were conducted using the SAS 9.1 statistical software package (SAS Institute, Cary, NC, USA). SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) was used to create the box plot and ROC curve.

RESULTS

Of the 135 patients who were identified initially, 28 of patients were excluded because of our exclusion criteria: 10 alcoholic hepatitis, nine viral hepatitis, six pediatric patients, two hemochromatosis, and one patient with lack of data. Finally, 107 patients were included in this study. Twenty-two patients had stage 0 fibrosis, 20 patients had stage 1, 31 patients had stage 2, 18 patients had stage 3, and 16 patients had stage 4 fibrosis. As shown in Table 1, the median age was 48.9. Most (79%) of the patients had a BMI of more than 28 kg/m² and there were more females than males in both of nonadvanced and advanced fibrosis groups. Age, BMI, and sex did not show any significant difference between the two groups. Of the laboratory test results, ALT, AST/ALT ratio, bilirubin, INR, cholesterol, and high density lipoprotein levels were significantly different between the advanced and nonadvanced liver fibrosis groups.

Of the comorbidities, only hypertension was significantly

Table 1. Demographic and Clinical Characteristics of Patients

Characteristic	Total	Nonadvanced (n=73)	Advanced (n=34)	p-value*
Age, yr	48.9 (40.9–50.0)	48.2 (39.7–54.5) n=73	50.5 (42.3–58.2) n=34	0.14
BMI, kg/m ²	35.9 (29.6–44.7)	35.08 (28.82–43.82) n=63	40.97 (31.35–52.78) n=31	0.08
Male sex	41 (38.3)	27 (37) n=73	14 (41) n=34	0.68
AST, U/L	55.0 (36.0–81.0)	55.0 (39.0–81.0) n=65	54.5 (30.0–80.0) n=34	0.48
ALT, U/L	63.0 (29.0–105.0)	75.0 (42.0–122.0) n=65	33.5 (26.0–69.0) n=34	<0.01
AST/ALT ratio	0.90 (0.68–1.31)	0.74 (0.62–1.08) n=65	1.25 (0.99–1.56) n=34	<0.01
Bilirubin, mg/dL	0.50 (0.40–0.80)	0.40 (0.30–0.60) n=64	0.60 (0.40–1.00) n=34	0.01
INR	1.02 (0.95–1.14)	0.97 (0.94–1.05) n=64	1.14 (1.05–1.46) n=31	<0.01
Creatinine, mg/dL	1.00 (0.90–1.10)	1.00 (0.90–1.10) n=62	1.00 (0.90–1.10) n=33	0.44
Total cholesterol, mg/dL	183.5 (162.0–219.0)	202.0 (168.0–222.0) n=35	172.0 (151.0–199.0) n=21	0.05
LDL, mg/dL	106 (85.5–133.0)	116.0 (87.0–145.0) n=35	101.0 (82.0–117.0) n=21	0.10
HDL, mg/dL	42.5 (35.0–50.5)	47.0 (35.0–57.0) n=35	38.0 (35.0–43.0) n=21	0.03
Triglyceride, mg/dL	157.0 (115.0–255.0)	159.0 (128.5–278.5) n=36	140.0 (98.0–207.0) n=21	0.15
Diabetes	34 (32.7)	21 (29.2)	13 (40.6)	0.25
Hypertension	51 (49.0)	30 (41.7)	21 (65.6)	0.02
Hyperlipidemia	30 (28.9)	17 (23.6)	13 (41.6)	0.08

Data are presented as medians (interquartile ranges) or number (%).

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; LDL, low density lipoprotein; HDL, high density lipoprotein.

*Comparison between nonadvanced vs advanced disease. Chi-square tests for sex, diabetes, hypertension, and hyperlipidemia. Wilcoxon Rank-Sum tests for other variables.

different between the two fibrosis groups. About 33% of the patients had diabetes. The difference in frequencies of diabetes and hyperlipidemia between the two fibrosis groups didn't reach a level of statistical significance (Table 1).

Age, BMI, AST/ALT ratio, INR, bilirubin, cholesterol, diabetes, and hypertension were included initially in multivariate logistic regression. Age, BMI, and diabetes were included because these had been the important variables in the previous studies. After stepwise selection, age, AST/ALT ratio, and INR were the independently significant factors for advanced fibrosis. Bilirubin, diabetes, and hypertension were not independently significant, even though these variables remained in the final model (Table 2).

The BARD score was calculated and its ROC curve was created using our study sample. An enhanced model of BARD score, BARDI score, was generated by adding the INR to the

components of the BARD score model. To keep the character of the BARD score, the same criteria (BMI ≥ 28 kg/m² and AST/ALT ratio ≥ 0.8) were used in the BARDI score. For the INR, the ROC curve was generated and the maximum point of sensitivity plus specificity was chosen as a cutoff (INR, 1.07). Forced entry multivariate logistic regression was performed again using BMI, AST/ALT ratio, diabetes and INR. The coefficients (β) of variables in this multivariate logistic regression were used for the BARDI scoring system. AST/ALT ≥ 0.8 ($\beta=3.21$) received three credits, diabetes ($\beta=1.22$) received one credit, and an INR ≥ 1.07 ($\beta=2.01$) received two credits. A BMI ≥ 28 kg/m² ($\beta=0.12$) received one credit even with a low β in order to keep the character of the BARD score in the BARDI score. The ROC curve of this BARDI model showed better performance than the BARD model (Fig. 1). The AUROC of the BARDI model was significantly better than the AUROC of the BARD model (0.881 vs

Table 2. Multivariate Logistic Regression Analysis for the Prediction of Advanced Liver Fibrosis

	Multivariate	
	OR (95% CI)	p-value*
Age	0.89 (0.79–1.00)	0.04
AST/ALT ratio	1.73 (1.17–2.56) [†]	<0.01
Bilirubin	0.09 (0.01–1.04)	0.05
INR	8.85 (1.77–44.11) [‡]	<0.01
Diabetes	9.08 (0.62–131.93)	0.11
Hypertension	13.80 (0.82–233.29)	0.07

Stepwise selection after including age, body mass index, AST/ALT ratio, INR, bilirubin, cholesterol, diabetes, and hypertension. The AST/ALT ratio and INR were multiplied by 10 to match the interval scale with other variables.

OR, odds ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.

*Wald chi-square test; [†]OR for the 0.1 change of AST/ALT ratio; [‡]OR for the 0.1 change of INR.

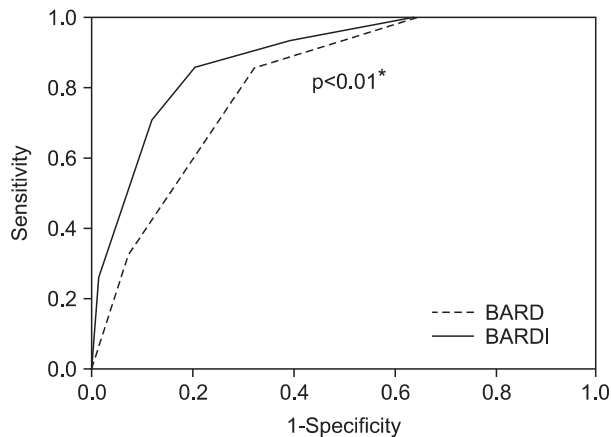


Fig. 1. Receiver operating characteristic (ROC) curve of BARD and BARDI score for advanced liver fibrosis. Area under ROC curve for BARDI model, 0.881 (95% confidence interval [CI], 0.804 to 0.958). Area under ROC curve for BARD model, 0.808 (95% CI, 0.712 to 0.904). Seventy-six patients were used for this ROC curve after the exclusion of patients with missing values.

*Likelihood ratio test.

0.808, $p < 0.01$). Comparing a BARD score of 2 or more with a BARDI score of 2 or more, the PPV was 45.8% for the BARD and 45.0% for the BARDI, which were not much different in our subjects. The negative predictive values (NPV) were 100% in both the BARD and BARDI scores. When comparing a BARDI score of 3 or more with a BARD of score 2 or more, the BARDI score showed higher specificity (49.0% vs 34.7%) without losing much sensitivity (96.3% vs 100%). The PPV for a BARDI score of 3 or more was 51.0%, while the PPV for a BARD score of 2 or more was 45.8%. The NPV for a BARDI score of 3 or more was 96.0% and NPV for a BARD score of 2 or more was 100%

Table 3. Comparison between BARD and BARDI Scores Using Our Study Sample

	Sensitivity	Specificity	PPV	NPV
BARD				
≥0	1.000	0.000	0.355	1.000
≥1	1.000	0.082	0.375	1.000
≥2	1.000	0.347	0.458	1.000
≥3	0.852	0.673	0.590	0.892
≥4	0.333	0.918	0.692	0.714
BARDI				
≥0	1.000	0.000	0.355	1.000
≥1	1.000	0.082	0.375	1.000
≥2	1.000	0.327	0.450	1.000
≥3	0.963	0.490	0.510	0.960
≥4	0.926	0.612	0.568	0.938
≥5	0.852	0.796	0.697	0.907
≥6	0.704	0.878	0.760	0.843
≥7	0.259	0.980	0.875	0.706

BARD area under receiver operating characteristic curve 0.808. BARDI area under receiver operating characteristic curve 0.881. BARDI score is the sum of the points below.

If body mass index ≥ 28 kg/m², then 1 point. If aspartate aminotransferase/alanine aminotransferase ratio ≥ 0.8 , then 3 points. If diabetes present, then 1 point. If international normalized ratio ≥ 1.07 , then 2 points.

PPV, positive predictive value; NPV, negative predictive value.

(Table 3). Twenty fold cross validation of the BARDI model showed 80.39% accuracy with a standard error of 0.75%. We tried to incorporate age, bilirubin, and hypertension respectively into the BARDI model. However, these variables did not increase the AUROC significantly and were not included in the final model (data not shown).

DISCUSSION

We developed an enhanced model (BARDI score), by adding the INR, which was known to have correlation with liver fibrosis.^{13,16} As shown in Table 3, the BARDI score kept the simplicity and strength of the BARD score. All patients with a BARD score of 2 or more should have a BARDI score of 2 or more. A BARDI score of 2 or more performed similarly to a BARD score of 2 or more. When a BARDI score of 3 or more was compared with a BARD score of 2 or more, the BARDI score showed an improved PPV and kept an excellent NPV for detecting advanced liver fibrosis.

Using 2 or more of the BARD score is just the same as having one of either two risk factors (obesity and diabetes) or an AST/ALT ratio ≥ 0.8 as criteria for advanced fibrosis. If the patient has two risk factors with an AST/ALT ratio less than 0.8, the patient will be classified as high risk for advanced fibrosis. Usually,

Table 4. Previously Reported Models for Advanced Liver Fibrosis in NAFLD

Model	Variable	Cut-off	AUROC	Sensitivity, %	Specificity, %	PPV, %	NPV, %
BAAT ^{11,*}	BMI, age, ALT, triglycerides	1	0.84	100	47	45	100
FIB-4 ^{5,1}	Age, AST, ALT, platelet	1.30	0.80	65.1	80.2	50.6	88.0
OELF ¹⁴	Age, P3NP, TIMP-1, HA	0.375	0.87	89	96	80	98
ELF ¹⁴	P3NP, TIMP-1, HA	0.3576	0.90	80	90	71	94
NAFLD fibrosis score ¹⁶	Age, BMI, IFG or DM, AST/ALT, platelet, albumin	-1.455	0.88	82	77	56	93
ELF+NAFLD fibrosis score ¹⁴	P3NP, TIMP-1, HA, BMI, IFG or DM, AST/ALT, platelet, albumin	-0.2826	0.98	91	96	77	99
BARD score ¹⁵	BMI, AST/ALT, DM	≥2	0.81	NA	NA	43	96

NAFLD, nonalcoholic fatty liver disease; AUROC, area under receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; P3NP, amino-terminal propeptide of type III collagen; TIMP-1, tissue inhibitor of matrix metalloproteinase 1; HA, hyaluronic acid; IFG, impaired fasting glucose; DM, diabetes mellitus; NA, not available.

*AUROC, PPV, NPV were calculated to detect stage 2 or higher; ¹AUROC, PPV, NPV data were from the study.

diabetic patients have a high prevalence of obesity.¹⁹ All these obese diabetic patients will be classified into the high risk group for advanced fibrosis, which will result in a lot of false positivity. In our study, we had a skewed population in terms of BMI and most patients received a credit due to obesity (BMI ≥28). Among the patients with both diabetes and obesity in our study (n=27), many patients (n=11, 40.7%) would have a BARD score of 2, even though they did not have advanced liver fibrosis. In contrast, a BARDI score of 3 or more cannot be made from the risk factors alone. Risk factors need to be combined with an INR ≥1.07 to reach a score of 3 or more. This combination is the main reason why the BARDI score can decrease the false positivity (increase PPV) of the BARD score. The role of AST/ALT ratio was kept the same in the BARDI score as in the BARD score. Any patient with an AST/ALT ratio of 0.8 or more should be classified into the possible advanced liver fibrosis group in either scoring system.

Age,^{11-13,16} platelet count,¹³ albumin,¹⁶ bilirubin,^{13,16} triglyceride,¹¹ impaired fasting glucose level,¹⁶ and hypertension^{15,16} are known to be associated with advanced liver fibrosis and some of them have been used in other models, as shown in Table 4. In our study, we didn't have enough data for platelet, albumin and were not able to compare BARDI score directly with other models including NAFLD fibrosis score¹⁶ or FIB-4 score.¹³ As our patients did not have liver fibrosis panel, it was also not possible to compare the BARDI score with any models (OELF,^{12,14} ELF¹⁴ models) that used the liver fibrosis panel. Indirect comparison of PPV and NPV was also not possible because the PPV and NPV would be affected by the prevalence of advanced liver fibrosis in each study. However, the indirect comparison of sensitivity and specificity between models showed promising results. For example, an NAFLD fibrosis score showed 82% sensitivity and 77% specificity. A BARDI score of 3 or more showed 96% sensitivity and 49% specificity. When it comes with the BARDI score of 5 or more, the BARDI showed 85% sensitivity and 79.6% specificity. When the AUROC was compared using the

previously reported AUROCs of other models, the AUROC 0.881 of the BARDI score was at least comparable with other models (Table 4).

Other imaging studies including ultrasound based transient elastography (FibroScan), MR spectroscopy, diffusion weighted MRI, and MR elastography have been developed.⁹ It has been shown that these imaging methods have slightly better or comparable results to clinical models. In the case of transient elastography, the AUROC was reported to be 0.904⁷ and 0.94.⁵ In particular, Wong *et al.*⁵ showed the superiority of transient elastography to other previous clinical models for the diagnosis of advanced liver fibrosis. However, these imaging techniques cost more expenses and limited to only a small number of centers. Considering that NAFLD is a very common disease with a prevalence of about 30%,¹ there should be a way that clinicians can evaluate a patient's risk of liver fibrosis in their offices before they refer them to specialized centers. If the assessment can be done using simple usual lab tests, many at risk patients can be detected or excluded before they go for an imaging test. After first screening with a clinical model, a physician still can perform imaging tests, which can give some information before the liver biopsy. An imaging test can differentiate a diffuse lesion from a local lesion and can also provide information about the character of a localized lesion, including possible mass like lesion, infection and so on. Then patient can opt for biopsy if it is indicated through the clinical model and imaging test.

Our study had several limitations. We had only 107 patients to analyze, which made it hard to split our subjects for external validation. Instead, we performed 20-fold cross validation, which showed a good performance of the BARDI score. Another limitation was derived from the restrictions of retrospective study. All information was gathered using the medical records which had been produced for clinical purposes only. The information was not complete enough to compare several previous models using our study subjects. We were able to calculate only the BARD score for our subjects. Also some medical records

were not detailed regarding alcohol consumption. We had to exclude any patients who drank unspecified amounts of alcohol from our study. Also, our study was based on patients who had already had liver biopsies, indicating that the studies subjects may be sicker than the general population. Actually, all previous clinical models were made using the patient population who had received or had decided to have liver biopsy as well. The performance of these models should be evaluated prospectively in general population.

In conclusion, the INR was an independently significant factor for advanced liver fibrosis. We developed the BARDI score by adding the INR to the BARD score, resulting in an enhanced model that was still easy to calculate and had better performance than the BARD in predicting advanced liver fibrosis. Using the BARDI score would decrease false positivity with an excellent NPV, and eventually prevent unnecessary imaging tests or risky liver biopsies. Further external validation study and prospective study are needed to confirm this finding.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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