BARD SCORE AS A PREDICTIVE VALUE FOR THE DEGREE OF LIVER FIBROSIS IN NON ALCOHOLIC FATTY LIVER DISEASE

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Abstract

Significance:

Non-alcoholic fatty liver disease (NAFLD) has become the most prevalent cause of liver disease, and rising levels of obesity, diabetes and metabolic syndrome render it an important cause of morbidity and mortality. NAFLD refers to a wide clinical spectrum, and advanced fibrosis leads to the development of Cirrhosis and Hepatocellular carcinoma, thus identification of these patients is essential. Liver biopsy is an invasive procedure associated with rare but severe complications, while Transient Elastography (Fibroscan) is limited by cost & wide availability. This study aims to evaluate the usefulness of the BARD score in predicting degree of fibrosis among NAFLD patients, and to determine the risk factors of advanced fibrosis.

Methodology:

Patients records in single outpatient clinic from November 2014-November 2017 were reviewed. Fibrosis in Fibroscan was scored on a 5-point scale. The BARD score was computed and compared with the Fibroscan results. Student's t-test and Chi-square test were done on the data.

Results:

Of the 85 patients, Fibroscan revealed 30 (35.29%) patients with advanced fibrosis and 55 (64.70%) with mild/moderate fibrosis. Advanced fibrosis was statistically & significantly more common in BMI ≥ 28.55, HBA1C ≥6.5, AST/ALT ratio ≥0.77, GGTP ≥96.5 U/L, and Platelet count ≤ 178 $x10^3$/L. The sensitivity, specificity, positive predictive value, negative predictive value for BARD score were 93.30%, 90.90%, 84.80% and 96.20% respectively.

Conclusion:

BARD score is capable of ruling out advanced fibrosis. BMI ≥ 28.55, HBA1C ≥6.5, AST/ALT ratio ≥0.77, GGTP ≥96.5 U/L, and Platelet count ≤ 178 x103/L are risk factors for advanced fibrosis.

Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease ranging from simple steatosis, to inflammatory steatohepatitis (NASH) with increasing levels of fibrosis.[1] Advanced fibrosis that accompanies the disease leads to the development of Cirrhosis and Hepatocellular carcinoma.[2] The development of Nonalcoholic fibrosis also identifies an at-risk group with increased risk of cardiovascular and liver-related death.[1] Thus, identification of patients with advanced fibrosis is essential.

In the great majority of cases, NAFLD arises in association with one or more features of the metabolic syndrome namely insulin resistance, glucose intolerance or diabetes, central obesity, dyslipidemia and hypertension. However, after exclusion of a history of significant alcohol intake which is conventionally <20 g/day, other causes of steatosis including nutritional causes, metabolic disorders and drug induced steatosis were considered.[3]

After diagnosing NAFLD, the next step is to determine the severity, as that provides important information on prognosis. Several subsequent studies have demonstrated that simple steatosis, with no fibrosis, is associated with a similar overall and liver related mortality to that of an age and gender matched general population. This reinforces the need to identify the degree of fibrosis among patients with NAFLD.[1] In practice, most patients with NAFLD do not undergo a liver biopsy. Liver biopsy is an invasive procedure associated with rare but severe complications. Pain and hypotension are major complications of liver biopsy and can lead to increased length of hospital stay and cost.[4] The mortality rate after percutaneous liver biopsy has been reported as 1 in 10000 to 1 in 12000.[5] Therefore, performing liver biopsy for assessment of liver fibrosis is practically not feasible.

Advanced imaging techniques as well as laboratory tests and scoring systems have been studied as means of identifying high-risk patients who should undergo liver biopsy or as potential noninvasive marker of fibrosis. The most studied and widely available has been Transient elastography (Fibroscan) which uses a low amplitude shear wave that propagates through the liver parenchyma. The speed at which the wave moves is correlated with liver stiffness, measured in kilopascals.[6] Using Fibroscan in detecting the level of fibrosis in NAFLD cases has high accuracy and can be a good alternative for liver biopsy among patients who cannot undergo or who cannot assent for invasive procedures, however, it is restricted by its cost and wide availability.[7]

Progress has been made in developing simple, noninvasive, and quantitative tests to estimate the presence and degree of hepatic fibrosis. These tests are best at predicting either absent or advanced fibrosis. The BARD score is an easy & straightforward scoring system that is designed to identify NAFLD patients with a low risk of advanced disease. It combines three variables namely: Body Mass Index (BMI), AST/ALT ratio (AAR) and the presence of diabetes into a weighted sum (BMI ≥ 28 = 1 point, AAR of ≥0.8 = 2 points, DM = 1 point), to generate a score from 0 to 4.[8]

The aim of this study was to compare the usefulness of the BARD score in predicting the results of liver fibrosis among Filipinos with NAFLD, from Manila, Philippines, and to determine the risk factors of advanced fibrosis among NAFLD patients. Compared with the widely accepted Fibroscan, the parameters of BARD score are inexpensive and widely available.

Materials and Methods

Patients in a single outpatient clinic at Chinese General Hospital & Medical Center from November 2014-November 2017 were identified and included in the study. The study population was ethnically Asian composed of purely Filipino or Chinese, and Filipino-Chinese group of patients from the Philippines.

The study was a restrospective cross-sectional study and approved by the Review Board of Chinese General Hospital, Section of Gastroenterology. To establish a diagnosis of NAFLD, alcoholic liver disease was excluded and NAFLD was entertained only in the absence of significant alcohol use (consumption of < 20 to 40 g of alcohol per day in most clinical studies) obtained during history taking and confirmed by family members. Patients should have mild to moderate (1.5- to 4-fold) elevation of the serum AST and/or ALT level with the serum ALT level usually greater than the AST level or a hepatic Ultrasound revealing a "bright" liver of increased echogenicity or CT/MRI, with which fat appears bright on T1-weighted imaging which is consistent with hepatic steatosis.[9] Other causes of chronic liver diseases were excluded.

Fibroscan was performed by the same Radiologic Technician and results were automated. Liver elasticity was indirectly related to Fibrosis which is measured in kilopascals and scored on a 5-point scale. The Liver Stiffness Measurement (LSM) of patients with F0, F1, F2, F3, and F4 disease were 5.7 ±1.8, 6.8 ±2.4, 7.8 ±2.4, 11.8 ±5.2, and 25.1 ±17.1 kPa, respectively (P 0.0001 by analysis of variance). In a study by Wong et al, the best LSM cutoff for F2 or greater disease was 7.0 kPa with negative predictive value to exclude F2 or greater disease at 84% (95% confidence interval [CI], 78%-90%). The best cutoff for F3 or greater disease was 8.7 kPa with negative predictive value to exclude F3 or greater disease at 95% (95% CI, 91%-98%). The best cutoff for F4 disease was 10.3 kPa with negative predictive value to exclude cirrhosis at 99% (95% CI, 98%-100%). The study confirmed that transient elastography works well in both white and Asian NAFLD patients and it is reasonable to consider advanced liver fibrosis and liver biopsy in patients whose LSM is 7.9 kPa or above.[10]

Age, weight, height, levels of AST, ALT, Fasting Blood Sugar (FBS), Hemoglobin A1C (HBA1c), Platelet count and GGTP were determined in all patients. Diagnosis of Diabetes Mellitus was based on history of known disease or FBS ≥ 126 mg/dL or HBA1c ≥ 6.5%.[11] The AST/ALT ratio, BMI and BARD score were calculated for each patient. BMI was calculated using the formula: weight (in kilograms)/height (in meters^2). Obesity was diagnosed when BMI was ≥30 kg/m2, and overweight when BMI was ≥25 and <30 kg/m2.[12]

The BARD score was composed of 3 variables: AST/ALT ratio ≥0.8 =2 points; a BMI ≥28 =1 point; and the presence of diabetes = 1 point. The possible score ranges from 0 to 4 points.[2] BARD scores equaling 0 or 1 are of high (96%) negative predictive value (NPV) for advanced fibrosis. The high negative predictive value

(96%) indicates that patients not achieving a positive score are at low risk for having advanced fibrosis. Additionally, patients with a positive BARD score (>2 points) are 17 times more likely to have advanced fibrosis than those without a positive score.[11]

Variables necessary for the assessment of scores (age, BMI) and laboratory analysis (FBS, AST, ALT and platelet count) were determined within a month before the Fibroscan test. The BARD scores were compared with the Fibroscan findings.

Statistical analysis

Quantitative variables are presented as a mean and standard deviation (SD). Quantitative variables were compared between the groups using Student's t-test, and qualitative variables using the chi-square test. Statistical significance was assumed at $p<0.05$. Adjusted odds ratios (OR), 95% confidence intervals (95% CI), negative and positive predictive values, and AUROC (area under receiver operator characteristic) curve for BARD score were calculated. All calculations were carried out using SPSS.

Results

The study encompassed 85 patients with NAFLD, including 40 (53%) females and 45 (47%) males. The mean age of patients was 60 in females and 52 in males. The clinical, biochemical and histological data of the examined patients are illustrated in Table 1. The Fibroscan findings revealed that 30 out of 85 patients were affected with advanced fibrosis (F=3, F=4) *(or kpa with ≥8.7)*, whereas 55 had mild/moderate fibrosis (F=0, F=1, F=2) *(or kpa < 8.7)* . Comparison of the selected biochemical and clinical features between the studied groups of patients with advanced and mild/moderate fibrosis showed statistically significant differences in the following parameters: BMI of ≥ 28.55, HBA1C ≥6.5, AST/ALT ratio of ≥0.77, GGTP of ≥96.5 U/L, Platelet count of ≤178 10^3/L. (Table 2).

Table 1 *Clinical, biochemical and Fibroscan data of examined patients.*

Parameter	Mean ± SD
Age (Years)	55.7±14.18
Gender (F/M)	40/45
BMI	27.09±3.46
HBA1C	6.40±1.01
AST/AUL ratio	0.90+0.29
GGTP	93.59+23.49
Fibrosis F0/F1/F2/F3/F4	28/14/13/17/13

Table 2 *Comparison of selected clinical and biochemical parameters between patients with mild/moderate and advanced fibrosis.*

Parameter	Mild/moderate fibrosis F0-F2 *n=55*	Advanced fibrosis F3-F4 *n=30*	P value
Age (Years)	55.55±13.29	56.07±15.92	0.873
Gender (F/M)	49.1/50.9	43.3/56.7	
BMI	26.29±2.72	28.55.07±4.17	0.003
HBA1C	6.05±0.74	7.03±1.15	0.00001
AST/AUL ratio	0.77±0.22	1.14±0.26	0.00001
GGTP	81.92±16.18	113.61±20.47	0.00001
Platelet Count	288.27±83.19	178.90±55.51	0.00001

The BARD scores demonstrated 42 patients with high scores ≥2 points (2 points, 9 patients; 3 points, 22 patients; 4 points ,11 patients), and 43 patients with low scores 0-1 point (0 point, 28; 1 point,15). Fibroscan helped to diagnose advanced fibrosis (*Advanced Fibrosis are those with kpa> 8.7)* in 30 patients (F3=17, F4=13) out of 33 whose BARD scores were 2 points or higher. Analysis of BARD scores 0 or 1 revealed advanced fibrosis in 2 patients

The sensitivity of BARD score in assessing fibrosis is high at 93.3% with a specificity of 90.9%. Ultimately, the positive predictive value and negative predictive value are also high at 84.8% and 96.2%., respectively. (Table 3)

Table 3. Accuracy of BARD score in assessing Liver Fibrosis

Parameter	BARD Score
Sensitivity	93.30%
Specificity	90.90%
PPV	84.80%
NPV	96.20%

PPV – positive predictive value; NPV – negative predictive value

Discussion

The worldwide increase in prevalence of metabolic syndrome, obesity, diabetes, and consequently of NAFLD poses a very difficult challenge for the public and private health systems and also for the general practitioners in everyday practice. Currently, NAFLD is considered the most frequently encountered chronic liver disease which then may eventually evolve into advanced fibrosis, cirrhosis, end-stage liver disease, and liver-related mortality.[13] Patients with NASH and severe fibrosis are the most prone to present clinical complications in the short-term and they should undergo closer follow-up and should be included in clinical trials of experimental therapies.[14] For this reason, it is desirable to know the stage of disease in most of the patients with NAFLD.

In the study by Harrison et al. a low BARD score (0 or 1 point) had a very interesting negative predictive value (96%) to identify patients without advanced fibrosis while the positive predictive value of a high score was not so good (43%). The test however was not very sensitive (51.4%) and had a low PPV (45.2%), but the negative predictive value was 81.3%.[8]

In the study where BARD score was compared with NAFLD Fibrosis score, it was concluded that both scoring systems had more specificity than sensitivity and that they were more useful to identify patients without advanced fibrosis. However, it was also stated that it seems convenient to apply the BARD score, which is easier to estimate in everyday practice, to identify patients without severe liver fibrosis, with a negative predictive value of 81.2%.[14] The main limitation of the BARD score is that it is likely to exhibit high false positive results. Patients with a BARD score of ≥2 are predicted to have severe fibrosis, if they have a BMI of ≥28 kg/m2 and presence of diabetes despite having a normal level of AST/ALT ratio.[15]

This study shows that BARD score is useful in predicting fibrosis in NAFLD. The sensitivity of BARD score in assessing fibrosis is high at 93.3% with a specificity of 90.9%. Ultimately, the positive predictive value and negative predictive value are also high at 84.8% and 96.2%., respectively. The accuracy of BARD in assessing fibrosis is statistically significantly.

The literature contains only a few reports concerning the risk factors of advanced fibrosis. According to our study, the following risk factors are statistically significant in assessing advance fibrosis: BMI of ≥ 28.55, HBA1C ≥6.5, AST/AUL ratio of ≥0.77, GGTP of ≥96.5 U/L, Platelet count of ≤178 10^3/L.

Conclusion

Our study results validate that BARD score have high negative predictive value and is capable of excluding advanced liver fibrosis and markedly reducing the incidence of liver biopsies in patients with NAFLD. BMI ≥ 28.55, HBA1C ≥6.5, AST/ALT ratio ≥0.77, GGTP ≥96.5 U/L, and Platelet count ≤ 178 x10^3/L are considered the risk factors of advanced fibrosis in patients with NAFLD.

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