The BARD score and the NAFLD fibrosis score in the assessment of advanced liver fibrosis in nonalcoholic fatty liver disease

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Halina Cichoż-Lach[1ABCDEF], **Krzysztof Celiński**[1ABCDEF], **Beata Prozorow-Król**[1BF], **Jarosław Swatek**[2BCDF], **Maria Słomka**[1BCDEF], **Tomasz Lach**[3BE]

[1] Department of Gastroenterology, Medical University of Lublin, Lublin, Poland
[2] Department of Clinical Pathomorphology, Medical University of Lublin, Lublin, Poland
[3] 2nd Medical Faculty with English Division, Medical University of Lublin, Lublin, Poland

Source of support: Departmental sources

Summary

Background: Non-alcoholic fatty liver disease (NAFLD) refers to a very wide clinical spectrum. Advanced fibrosis that accompanies disease leads to the development of cirrhosis and hepatocellular carcinoma. Thus, identification of patients with advanced fibrosis is essential. The aim of the present study was to compare the usefulness of NAFLD fibrosis and BARD scores in predicting fibrosis in NAFLD and to determine the risk factors of advanced fibrosis.

Material/Methods: The study included 126 patients with NAFLD. Fibrosis in liver biopsy was scored on a 5-point scale. The BARD and the NAFLD fibrosis scores were compared with the biopsy findings.

Results: Liver biopsy revealed 27 patients with advanced and 99 with mild/moderate fibrosis. Advanced fibrosis was statistically significantly more common in older patients with obesity, AST/ALT ratio ≥ 0.8, diabetes mellitus, and thrombocytes $\leq 200 \times 10^3$/L. Positive predictive value, negative predictive value and AUROC curve for BARD score, and NAFLD fibrosis score were 68.57%, 96.70%, 0.865 and 70.59%, 98.11%, 0.919, respectively.

Conclusions: Both scores are capable of ruling out advanced fibrosis and markedly reducing the need for liver biopsies in patients with NAFLD. Obesity, diabetes mellitus, thrombocytes $\leq 200 \times 10^3$/L, advanced age and AST/ALT ratio ≥ 0.8 are the risk factors of advanced fibrosis.

key words: BARD score • liver biopsy • liver fibrosis • NAFLD fibrosis score • non-alcoholic fatty liver disease

Author's address: Krzysztof Celiński, Department of Gastroenterology, Medical University of Lublin, Lublin, Poland, e-mail: celinski.krzysztof@gmail.com

Current Contents/Clinical Medicine • IF(2010)=1.699 • Index Medicus/MEDLINE • EMBASE/Excerpta Medica • Chemical Abstracts • Index Copernicus

CR735

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is considered to be the most common cause of chronic liver dysfunction and the most frequent cause of asymptomatic abnormalities, accounting for 26.4% of positive liver enzymes in laboratory investigations [1]. It is thought that at present NAFLD affects 9%-30% of people in the developed countries; the prevalence of NAFLD is higher than 30% in the adult U.S. population [2–6]. NAFLD has been found to affect 10% of the population under 18 years of age [7].

NAFLD represents a very wide clinical spectrum. It includes: simple fatty liver, in which lipids constitute over 5% of the liver weight; and non-alcoholic steatohepatitis (NASH), which may progress to cirrhosis, with all the dire consequences resulting from the compromised activity of hepatocytes and portal hypertension. It is estimated that NASH is present in 3–5% of the population worldwide [8]. The presence of advanced fibrosis that accompanies NASH will inevitably lead to the development of cirrhosis and hepatocellular carcinoma [9–14]. Thus, identification of patients with advanced fibrosis in the course of NAFLD is essential. To date biopsy has been regarded the "gold standard" for diagnosis and assessment of liver fibrosis [15]. However, the method is expensive, invasive, and has certain limitations; therefore biopsy is no longer considered the obligatory and primary screening for diagnosis of NAFLD [8,16–19].

Introduction of new tests, such as the FibroTest-ActiTest (2001), followed by FibroMax, transient elastography, and other noninvasive fibrosis biomarkers, enabled diagnosticians to change the diagnostic procedures used in patients with NAFLD.

Although the search for other noninvasive markers of liver fibrosis, helpful in identifying patients with advanced fibrosis, has been successful, all the methods have significant limitations. The noninvasive markers of liver fibrosis include: the NAFLD fibrosis score, BARD score, Original European Liver Fibrosis Panel (OELF) score, Enhanced Liver Fibrosis (ELF) score, HAIR score, Palekar's score, BAAT score, Gholam's score, and Nippon score [20–27]. They are based on readily available laboratory tests. Some of them are easy to carry out, while others are merely of scientific value.

The aim of this study was to compare the usefulness of the NAFLD fibrosis score and the BARD score in predicting the results of liver fibrosis in Polish patients with NAFLD, from eastern Poland, and to determine the risk factors of advanced fibrosis. The 2 scores have been chosen because they include 7 parameters (more than the other scores mentioned), and thus are likely to be more reliable. Moreover, the scores are inexpensive and widely available.

MATERIAL AND METHODS

The study encompassed 126 patients with NAFLD, including 53 females (42.1%) and 73 males (57.9%). The patients were recruited from the Department of Gastroenterology, Medical University of Lublin. The study population was an ethnically homogenous Caucasian group of patients from eastern Poland. The mean age of patients was 42.7±13.94 years, 41.2±7.6 in females and 43±11.7 years in males. The study was conducted prospectively. Diagnosis of NAFLD was based on an elevated level of ALT and AST, and liver biopsy showing steatosis in at least 5% of hepatocytes, according to the histological criteria for NAFLD by Kleiner et al. [28] and Tiniakos [29], and alcohol intake lower than 20 g/day in women and 30 g/day in men, obtained during history taking and confirmed by family members.

Other causes of chronic liver diseases (HBV, HCV, autoimmune, primary liver cirrhosis, Wilson disease, hemochromatosis, drug-induced, etc.) were excluded using the specific clinical, biochemical, radiological and histological criteria.

Liver biopsy was evaluated by the same liver pathologist, and fibrosis was scored on a 5-point scale suggested by Kleiner et al. [28], in which stage F0 = absence of fibrosis, F1 = perisinusoidal or periportal fibrosis, F2 = perisinusoidal and portal/periportal fibrosis, F3 = bridging fibrosis, and F4 = cirrhosis. Stages F0, F1, F2 were considered as mild/moderate fibrosis and stages F3 and F4 as advanced fibrosis. On the basis of the histology findings, the studied patients were divided into 2 groups: mild/moderate, and advanced fibrosis.

Levels of AST, ALT, serum albumin and platelet count were determined in all patients. The AST/ALT ratio, BMI, BARD score and NAFLD fibrosis 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/m^2, and overweight when BMI was ⩾25 and <30 kg/m^2.

The NAFLD fibrosis score formula was = –1.675 + 0.037 – age (years) + 0.094 – BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet count (×10^9/l) – 0.66 × albumin (g/dl). Diabetes mellitus was diagnosed when fasting glucose was ⩾126 mg/dl or the patient was treated with anti-diabetic drugs, or had IFG – when the fasting glucose level ranged between 100 and 125 mg/dL. In each patient with diabetes mellitus or IFG, the level of glycosylated hemoglobin (HbA1C) was determined. According to Angulo et al, a score lower than –1.455 (low cutoff) excludes advanced fibrosis, whereas a score higher than 0.676 (high cutoff) predicts advanced fibrosis. Scores between these values are defined as indeterminate [21].

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. According to the results of Harrison et al., BARD scores equaling 0 or 1 are of high (96%) negative predictive value (NPV) for advanced fibrosis [20]. Variables necessary for the assessment of scores (age, BMI) and laboratory analysis (fasting plasma glucose, AST, ALT, platelet count, and serum albumin) were determined the day before the liver biopsy. The results of NAFLD fibrosis score and BARD score were compared with the liver biopsy findings.

The study was approved by the Local Ethics Committee and all the subjects gave written informed consent for examinations.

Statistical analysis

Quantitative variables are presented as a mean and standard deviation (SD). Quantitative variables were compared

Med Sci Monit, 2012; 18(12): CR735-740

Cichoż-Lach H et al – The BARD score and the NAFLD fibrosis score...

Table 1. Clinical, biochemical and histological data of examined patients.

Parameter	Mean ±SD
Age (years)	42.7±13.94
Gender: female/male (n)	53/73
ALT (U/L)	97.51±61.96
AST (U/L)	68.29±51.57
AST/ALT ratio	0.72±0.38
Albumin (g/dL)	4.3±0.47
Platelets (x 10^9/L)	276.94±80.03
BMI (kg/m²)	28.51±2.67
Obesity (n/%) (BMI ≥30 kg/m²)	24/19.05
Overweight (n/%) (BMI ≥25 and <30 kg/m²)	81/64.29
Diabetes mellitus (n/%)	29/23.02
Fibrosis F0/F1/F2/F3/F4 (n)	33/45/21/24/3

n – number of cases; ALT – alanine aminotransferase; AST – aspartate aminotransferase; BMI – body mass index.

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 and NAFLD scores were calculated. All calculations were carried out using MedCal software version 12.0.

RESULTS

Clinical, biochemical and histological data of the examined patients are illustrated in Table 1. The histological findings revealed that 27 out of 126 patients were affected with advanced fibrosis (F=3, F=4), whereas 99 had mild/moderate fibrosis (F=0, F=1, F=2). In our study, liver biopsy demonstrated the presence of cirrhosis in 3 patients (F4=3). 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: age, BMI (obesity and overweight), the presence of IFG or diabetes mellitus, AST activity, AST/ALT ratio, and platelet count (Table 2). Diabetes mellitus was diagnosed in 29 patients, and IFG in none. The mean level of HbA1C in this group of patients was 6.93±0.94%.

Advanced fibrosis was statistically significantly more common in the older patients, with BMI usually >30 kg/m² and high AST/ALT ratio. In this group of patients, diabetes mellitus was 6 times more frequent in comparison with the patients with mild/moderate fibrosis. Age ≥50 years, obesity (BMI ≥30 kg/m²), AST/ALT ratio ≥0.8, diabetes mellitus, and platelet count ≤200 (×10^3/L) were the statistically significant risk factors for advanced liver fibrosis (Table 3).

The BARD scores demonstrated 35 patients with high scores – ≥2 points (2 points – 18 patients, 3 points – 13 patients, 4 points – 4 patients), and 91 patients with low scores – 0 points – 52 patients, 1 point – 39 patients). Liver biopsy helped to diagnose advanced fibrosis in 24 patients (F3=21, F4=3) out of 35 whose BARD scores were 2 points or higher. Analysis of BARD scores 0 or 1 revealed advanced fibrosis (F3) in 3 patients; in the remaining 88 patients only mild/moderate fibrosis was diagnosed (F0–30 patients, F1–40 patients and F2–18 patients). Analysis of the NAFLD fibrosis score revealed 34 patients with scores higher than 0.676, 53 patients

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

Parameter	Mild/moderate fibrosis F0-F2 (n=99)	Advanced fibrosis F3-F4 (n=27)	P value
Age (years)*	43.01±13.43	50.89±11.37	0.00618
Gender: female/male (%)	40.4/59.6	44.4/55.6	0.5666
BMI (kg/m²)*	27.85±2.51	32.6±3.36	0.00087
Obesity (%/n) (BMI ≥30 kg/m²)	11.1/11	48.15/13	0.0110
Overweight (%/n) (BMI ≥25 and <30kg/m²)	81.81/70	44.44/12	0.0013
Diabetes mellitus (%/n)	11.1/11	66.6/18	0.0067
ALT (U/L)*	94.81±60.38	104.81±67.71	0.45904
AST (U/L)*	59.41±45.95	94.41±54.16	0.00099
AST/ALT ratio*	0.66±0.29	1.08±0.46	0.000041
Albumin (g/dL)*	4.34±0.48	4.22±0.42	0.2537
Platelet count (×10^9/L)*	292.51±79.73	219.44±69.32	0.00003

* Mean ± standard deviation; ALT – alanine aminotransferase; AST – aspartate aminotransferase; BMI – body mass index; n – number of cases.

Table 3. Assessment of risk factors for advanced fibrosis.

Parameter	Mild/moderate fibrosis F0-F2 (n=99)	Advanced fibrosis F3-F4 (n=27)	P value	OR	95% CI
Age ≥ 50 (years) (n/%)	33/33.33%	18/66.66%	0.0018	4.0	1.50–10.08
Female (n/%)	40/40.4%	12/44.4%	0.7054	1.18	0.80–1.75
Male (n/%)	59/59.6%	16/55.6%	0.9748	0.99	0.67–1.47
BMI ≥25 kg/m^2 (n/%)	81/81.82%	25/92.59%	0.1745	2.78	0.86–8.90
BMI ≥30 kg/m^2 (n/%)	11/11.11%	13/48.15%	0.0000	7.43	4.12–13.37
AST/ALT ratio ≥0.8	9/9.09%	18/66.66%	0.0000	20.00	11.1–36.0
Diabetes mellitus (n/%)	11/11.1%	18/66.6%	0.0000	16.00	8.88–28.8
Platelet count ≤200 (×10^9/L) (n/%)	9/9.09%	11/40.74%	0.0001	6.88	3.82–12.38

n – number of cases; BMI – body mass index.

lower than –1.455, and 39 patients with indeterminate scores (30.9%). In the group of patients with high NAFLD fibrosis score (over 0.676), 24 had advanced fibrosis (F3=21, F4=3), and another 10 patients had mild/moderate fibrosis (2 patients-F0, 5 patients –F1 and 3 patients-F2). In the group of patients with low scores (lower than –1.455) 1 patient had advanced fibrosis demonstrated by liver biopsy. The accuracy of BARD and NAFLD fibrosis scores is presented in Table 4.

Discussion

Assessment of advanced fibrosis in the course of NAFLD is of vital practical and prognostic significance; therefore, identification of these patients is of utmost importance. To avoid liver biopsy, a highly invasive procedure, new simple and noninvasive diagnostic methods to diagnose advanced liver fibrosis are being searched for (30). Among the tests that could be useful, the NAFLD fibrosis score and the BARD score give promising results.

Harrison et al. [20] found high values of NPV (96%) in patients with low BARD scores, which enabled identification of patients without advanced fibrosis. According to Angulo et al [21], NPV and PPV for the NAFLD fibrosis score were high – NPV ≥87% and PPV – >78%, respectively. Some results were still indeterminate (NAFLD fibrosis scores between –1.455 and 0.676); thus, these patients require liver biopsy to assess liver fibrosis severity.

Our studies have shown that both the BARD and NAFLD fibrosis scores have relatively high sensitivity and specificity. Moreover, both of them showed very high values of NPV (ie, 96.70% and 98.11%, respectively) and were very similar to the results reported by McPherson's et al. [31], Raszeja-Wyszomirska et al. [32], and a Chinese study [33]. Compared to our findings, NPV found in Argentinian patients was lower – 81.3% for both BARD and NAFLD fibrosis scores [34]. Moreover, PPV was lower than NPV, comparable to other study results – 68.57% for the BARD score and 70.59% for the NAFLD score. Our findings identified 30.9% of patients whose results were indeterminate. The percentage of such patients was similar to the results of other studies [33,34].

Table 4. Accuracy of BARD and NAFLD fibrosis scores for predicting advanced fibrosis.

Parameter	BARD score	NAFLD fibrosis score
Sensitivity	88.89%	96.00%
Specificity	88.89%	83.87%
PPV	68.57%	70.59%
NPV	96.70%	98.11%
AUROC curve	0.865 (p<0.0001) OR=9.479 95%CI=0.793–0.920	0.919 (p<0.0001) OR=17.81 95%CI=0.841–0.967

PPV – positive predictive value; NPV – negative predictive value; AUROC curve – area under receiver operator characteristic curve.

According to Wong et al. [33], implementation of the NAFLD fibrosis score to the Chinese population should help avoid liver biopsy in 79% of patients. The researchers emphasize the role this parameter plays in primary health care, since it provides certain data necessary for identification of those patients with NAFLD who require livery biopsy for diagnosis of advanced fibrosis and assessment of its severity [1].

Otherwise, McPherson et al. [31] believe that the FIB-4 test has the best diagnostic value, although only slightly better than that of the BARD and NAFLD fibrosis scores (age × AST [IU/l]/platelet count [×10^9/litre] × radical ALT [IU/l]). In the FIB-4 test, the AUROC curve is 0.86, while in the BARD and NAFLD fibrosis scores were 0.77 and 0.81, respectively. According to the authors, FIB-4 tests can rule out advanced liver fibrosis beyond any doubt; thus liver biopsy is avoidable in 62% of patients, as compared to 52% based on the NAFLD fibrosis score (69.1% in our study) and only 38% based on the BARD score. Moreover, Shah et al. [35] also found the FIB-4 index superior to 7 other non-invasive markers of fibrosis in NAFLD [32]. In their study, the AUROC curve for the BARD and the NAFLD fibrosis scores, and the FIB-4 index, were 0.700, 0.768 and 0.802, respectively. Importantly,

Med Sci Monit, 2012; 18(12): CR735-740

Cichoż-Lach H et al – The BARD score and the NAFLD fibrosis score...

CR

our results showed that the AUROC curve for the BARD and NAFLD fibrosis scores was much higher compared to the 2 other studies. The AUROC curve for both scores was as high as for the FIB-4 in the study by McPherson et al. [31] and much higher than that reported by Shah et al. [35].

Another useful technique for assessment of advanced liver fibrosis is ultrasound-based transient elastography (Fibroscan), which shows a significant correlation between liver stiffness measurements and fibrosis staging confirmed by liver biopsy in NAFLD patients [36]. It is a non-invasive procedure, but has some significant limitations in obese patients [37]. The failure rate is 2–10% of patients with BMI ⩾30 kg/m². The currently available procedure is designed only for patients with standard morphology. A newly developed XL probe provides higher accuracy of advanced fibrosis evaluation in patients with increased BMI and shows promising results, yet has not been widely used. In the near future it is likely to become the gold standard for diagnosis of advanced fibrosis, and can eliminate the need for liver biopsy and the other non-invasive markers.

The literature contains only a few reports concerning the risk factors of advanced fibrosis. According to our findings, age ⩾50 years, obesity (BMI ⩾30 kg/m²), diabetes mellitus, and the platelet count ⩽200 (×10⁹/L) favored the development of advanced fibrosis. The AST/ALT ratio ⩾0.8 was a particularly important factor – OR for it was 20. Likewise, Ong et al. [38] demonstrated that obesity, as a component of metabolic syndrome, was independently associated with advanced fibrosis. There are reports, however, that found no relationship between BMI, diabetes mellitus, and aced fibrosis [32,38]. In one of them the differences can be related to the fact that BMI ⩾28 kg/m² was considered a risk factor of advanced fibrosis, and not BMI ⩾30 kg/m² as in our study [32]. We found that only obesity and not overweight was associated with advanced liver fibrosis. In the other study statistical significance was not demonstrated due to the small number of patients [39].

CONCLUSIONS

Our study results reveal that BARD and NAFLD fibrosis scores have high NPV values, are capable of excluding advanced liver fibrosis and markedly reducing the incidence of liver biopsies in patients with NAFLD. This invasive procedure is required only in a certain group of patients. Obesity, diabetes mellitus, more advanced age, platelet count ⩽200×10⁹/L, and AST/ALT ratio = 0.8 or higher are considered the risk factors of advanced fibrosis in patients with NAFLD.

REFERENCES:

1. Armstrong MJ, Houlihan DD, Bentham L et al: Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. J Hepatol, 2012; 56: 234–40

2. Browning JD, Szczepaniak LS, Dobbins R et al: Prevalance of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology, 2004; 40: 1387–95

3. Wieckowska A, Feldstein AE: Diagnosis of nonalcoholic fatty liver disease: invasive versus noninvasive. Semin Liver Dis, 2008; 28: 386–95

4. Das K, Das K, Mukherjee PS et al: Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. Hepatology, 2010; 51: 1593–602

5. Nomura H, Kashiwagi S, Hayashi J et al: Prevalence of fatty liver disease in a general population of Okinawa, Japan. Japn J Med, 1998; 27: 142–49

6. Bedogni G, Miglioli L, Masutti F et al: Prevalence of and risk foactors for nonalcoholic liver disease. The Dyonisos nutrition and liver study. Hepatology, 2005; 42: 44–52

7. Adams LA, Feldstein AE: Non-invasive diagnosis of nonalcoholic fatty liver and nonalcoholic steatohepatitis. Dig Dis, 2011; 12: 10–16

8. Estep JM, Birerdinc A, Younossi Z: Non-invasive diagnostic tests for nonalcoholic fatty liver disease. Curr Mol Med, 2010; 10: 166–72

9. Sanyal AJ, Banas C, Sargeant C et al: Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology, 2006; 43: 682–89

10. Bugianesi E, Leone N, Vanni E et al: Expanding the natural history of nonalcoholic steatohepatitis from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology, 2002; 123: 134–40

11. Marrero JA, Fontana RJ, Su GL et al: NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. Hepatology, 2002; 36: 1349–54

12. Farrell GC, Larter CZ: Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology, 2006; 43: S99–112

13. Lu P, Liu H, Yin H, Yang L: Expression of angiotensinogen during hepatic fibrogenesis and its effect on hepatic stellate cells. Med Sci Monit, 2011; 17(9): BR248–56

14. Colak Y, Ozturk O, Senates E et al: SIRT1 as a potential therapeutic target for treatment of nonalcoholic fatty liver disease. Med Sci Monit, 2011; 17(5): HY5–9

15. Vizzutti F, Arena U, Nobili V et al: Non-invasive assessment of fibrosis in non-alcoholic fatty liver disease. Ann Hepatol, 2009; 8: 89–94

16. Vuppalanchi R, Chalasani N: Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. Hepatology, 2009; 49: 306–17

17. Ratziu V, Charlotte F, Heurtier A et al: Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology, 2005; 128: 1898–906

18. Merriman RB, Ferrell LD, Patti MG et al: Correlation of paired liver biopsies in morbidly obese patients with suspected nonalcoholic fatty liver disease. Hepatology, 2006; 44: 874–80

19. Pais R, Lupşor M, Poantă L et al: Liver biopsy versus noninvasive methods-fibroscan and fibrotest in the diagnosis of non-alcoholic fatty liver disease: a review of the literature. Rom J Intern Med, 2009; 47: 331–40

20. Harrison SA, Oliver D, Arnold HL et al: Development and validation of a simple NALFD clinical scoring system for identifying patient without advanced disease. Gut, 2008; 57: 1441–47

21. Angulo P, Hui JM, Marchesini G et al: The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology, 2007; 45: 846–54

22. Guha IN, Parkes J, Roderick P et al: Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: validating the European Liver Fibrosis Panel and exploring simple markers. Hepatology, 2008; 47: 455–60

23. Dixon JB, Bhathal PS, O'Brien PE: Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology, 2001; 121: 91–100

24. Palekar NA, Naus R, Larson SP et al: Clinical model for distinguishing nonalcoholic steatohepatitis from simple steatosis in patients with nonalcoholic fatty liver disease. Liver Int, 2006; 26: 151–56

25. Ratziu V, Giral P, Charlotte F et al: Liver fibrosis in overweight patients. Gastroenterology, 2000; 118: 1117–23

26. Gholam PM, Flancbaum L, Machan JT et al: Nonalcoholic fatty liver disease in severely obese subjects. Am J Gastroenterol, 2007; 102: 399–408

27. Miyaaki H, Ichikawa T, Nakao K et al: Clinicopathological study of nonalcoholic fatty liver disease in Japan: the risk factors for fibrosis. Liver Int, 2008; 28: 519–24

28. Kleiner DE, Brunt EM, Natta MV et al: Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology, 2005; 41: 1313–21

29. Tiniakos DG: Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis: histological diagnostic criteria and scoring systems. Eur J Gastroenterol Hepatol, 2010; 22: 643–50

30. Wieckowska A, McCullough AJ, Feldstein AE: Noninvasive diagnosis and monitoring of nonalcoholic steatohepatitis: present and future. Hepatology, 2007; 46: 582–89

31. McPherson S, Stewart SF, Henderson E et al: Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut, 2010; 59: 1265–69

32. Raszeja-Wyszomirska J, Szymanik B, Ławniczak M et al: Validation of the BARD scoring system in Polish patients with nonalcoholic fatty liver disease (NAFLD). BMC Gastroenterol, 2010; 10: 67

33. Wong VW, Wong GL, Chim AM et al: Validation of the NAFLD fibrosis score in a Chinese population with low prevalence of advanced fibrosis. Am J Gastroenterol, 2008; 103: 1682–88

34. Ruffillo G, FassioE, Alvarez E et al: Comparison of NAFLD fibrosis score and BARD score in predicting fibrosis in nonalcoholic fatty liver disease. J Hepatol, 2011; 54: 160–63

35. Shah AG, Lydecker A, Murray K et al: Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroterol Hepatol, 2009; 10: 1104–12

36. Yoneda M, Yoneda M, Mawatari H et al: Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with nonalcoholic fatty liver disease (NAFLD). Dig Liv Dis, 2008; 40: 371–78

37. De Ledinghen V, Vergniol J, Foucher J et al: Feasibility of liver transient elastography with FibroScan using a new probe for obese patients. Liver Int, 2010; 30: 1043–48

38. Ong JP, Elariny H, Collantes R et al: Predictors of nonalcoholic steatohepatitis and advanced fibrosis in morbidly obese patients. Obes Surg, 2005; 15: 310–15

39. Uslusoy HS, Nak SG, Gulten M: Noninvasive predictors for liver fibrosis in patients with nonalcoholic steatohepatitis. World J Hepatol, 2011; 3: 219–27