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Title: Noninvasive diagnosis of fibrosis in non-alcoholic fatty liver disease: diagnostic accuracy of different scores

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is a spectrum of pathologies characterized by liver damage without history of excessive alcohol intake. Advanced fibrosis, generally detected by transient elastography (TE), is the most significant predictor of poor prognosis and mortality among these patients. This study aimed at assessing the accuracy of 5 non-invasive methods, compared to TE, for the evaluation of severity of liver fibrosis in patients with NAFLD.

Methods: The cohort included 41 patients, in whom the result of TE was compared to AST/ALT ratio, BARD score (body mass index, AST/ALT ratio, diabetes), AST to platelet ratio index (APRI), Fibrosis 4 index (FIB 4 index) and NAFLD fibrosis score (NFS).

Results: The severity of fibrosis, assessed by TE, was the following: F0 (absence of fibrosis): 17%, F1 (mild): 39%, F2 (moderate): 17%, F3 (advanced): 10%, F4 (cirrhosis): 17%. Performances of the diagnostic scores were: 49% for AST/ALT ratio, 68% for BARD score, 73% for APRI, 59% and 71% for the lower and upper cut-off of FIB 4 index, 61% and 76% for the lower and upper cut-off of NFS.

Discussion: Considering the scores compared to TE, AST/ALT ratio was not enough sensitive, while BARD score had better diagnostic performance and APRI had a superior accuracy than the formers. However, FIB 4 and NFS were the most useful tests and their performance could be improved through the use of a single cut-off.

Conclusion: These findings demonstrated that the most accurate scores, compared to TE, were NFS and FIB 4.

Keywords: non-alcoholic fatty liver disease; fibrosis; non-invasive diagnosis; diagnostic scores; algorithm.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by steatosis in more than 5% of hepatocytes in patients without excessive alcohol intake, and ranges in severity from simple steatosis, to non-alcoholic steato-hepatitis (NASH), characterized by hepatocellular injury associated to increased risk of evolution, through to advanced fibrosis and cirrhosis. It has been estimated that NAFLD affects 20% of the general population from different Countries.[1-3]

Although it is not uncommon in younger patients[4], the middle-aged and the elderly are more frequently affected from NAFLD, due to the increasing prevalence of risk factors for its development, like obesity and DM, with advancing age.[5]

Most patients with NAFLD are asymptomatic: many cases are diagnosed after finding of increased serum transaminases during routine tests.[6] The progression into the stages of advanced fibrosis and cirrhosis represents the main negative prognostic factor, associated to the reduction of life expectancy. The increased mortality, in patients with advanced fibrosis, is due beyond cardiovascular diseases to liver failure, portal hypertension and hepatocellular carcinoma.[7-9] Hence, it is crucial to identify patients in the early stages of NAFLD.[10]

Liver biopsy remains the gold standard for the diagnosis of NASH and for the assessment of fibrosis. Nevertheless, this procedure is invasive, costly, and is associated with rare but potential complications and sampling errors.[11] Consequently, liver biopsy is not suitable for screening or monitoring in the routinely clinical setting.[12]

Since fibrosis is the key-parameter to predict a poor prognosis, there is a considerable interest in developing non-invasive, simple, accurate and cost-effective methods for its early identification and quantification.[13-16]

Among the existing available methods to detect fibrosis, the most widely used and validated technique is the transient elastography (TE), an ultrasound-based vibration controlled elastography (the most known is the Fibroscan®). This tool allows fibrosis assessment by measuring the velocity of an elastic shear wave propagation through the liver. TE is a painless, quick and non-invasive test which considers liver stiffness as a marker of liver fibrosis: harder the liver tissue is, faster the shear wave propagates.[17] The principal advantages of TE include good reproducibility and high performance for detection of advanced fibrosis. In fact, it measures 1/500 liver samples, compared to biopsy, which samples 1/50000 of the liver, reducing the risk of sampling error.[18]

Since the accuracy of other non-invasive approaches to detect fibrosis, such as diagnostic scores and serologic tests, is controversial, the aim of the present study was to assess the accuracy of five different diagnostic scores in identifying advanced fibrosis in patients with NAFLD.

Methods

Patients

Patients enrollment was carried out at the Hepatology Day Service of the Internal Medicine Unit III of Molinette Hospital (City of Health and Sciences), Turin (Italy), between September 2016 and May 2018. Criteria for eligibility comprehended: NAFLD diagnosed by ultrasonography, elevation of transaminases (aspartate aminotransferase [AST] >45 U/L; alanine aminotransferase [ALT] > 40 U/L; gamma glutamyltranspeptidase [GGT] > 50 U/L) and absence of other standard causes of liver diseases. Exclusion criteria comprehended viral infections, hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency, autoimmune hepatitis, primary biliary cholangitis, and alcohol abuse.[19] Data on age, weight, body mass index (BMI), glycaemia level in serum, platelets count, triglycerides and cholesterol levels were collected.

FibroScan® and diagnostic scores

All patients were examined by TE (FibroScan®, Echosens, Paris, France), as the best known and accurate non-invasive method to detect fibrosis. Liver stiffness measurement was expressed in KiloPascals (kPa), with ranges between 2.5 to 75 kPa, and related to the METAVIR score (F0: absence of fibrosis; F1: mild fibrosis; F2: moderated fibrosis; F3: advanced fibrosis; F4: cirrhosis).[20]

The results of TE were compared to five diagnostic scores: the AST/ALT ratio[21], the BARD score (combination of the following variables: BMI ≥ 28, AST/ALT ratio ≥ 0.8 and Diabetes)[22], the AST to Platelet Ratio Index (APRI)[23], the Fibrosis-4 (FIB-4) index[24,25], and the NAFLD Fibrosis Score (NFS).[26] It has been reported that these scores have a prognostic value in patients affected by NAFLD and they can be easily calculated using laboratory tests and clinical data, as shown in Table I.

Statistical analysis

Statistical analysis was performed using the statistical package for the social sciences (SPSS) software, version 24.0.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were calculated.

The receiver operating characteristics (ROC) curve with the area under the curve (AUC) index was measured to evaluate the diagnostic accuracy of each diagnostic score (AUC < 0.50: fail; 0.50–0.70: fair; 0.70–0.90: good; 0.90–1.00: excellent), which was calculated as follows: diagnostic accuracy = (true positive + true negative) / (true positive + true negative + false positive + false negative).

All data were expressed as median and ranges or mean ± standard deviation. Probability values under 0.05 ($P < 0.05$) were considered as statistically significant.

Results

A total of 41 outpatients with NAFLD were included in the study. Demographic, clinical and biochemical characteristics of the patients are reported in Table II.

In this cohort, 73% of patients (n. 30) had an absent/low stage of fibrosis (F0-F2), while 27% (n. 11) showed an advanced stage (F3-F4).

Among the 41 patients enrolled, 11 (27%) presented at least one of the two most important risk factors associated to advanced NAFLD: obesity (BMI ≥ 30 kg/m^2) or T2DM (glycaemia ≥ 126 mg/dl). One patient presented both conditions. Considering the high rate of patients who had at least one risk factor, we searched for a difference in the fibrosis progression between these two subgroups.

Considering the AST/ALT ratio, patients were divided in two groups. Those (29%, n. 12) who showed AST/ALT > 1 and those (71%, n. 29) who had AST/ALT ≤ 1. Only 1 patient belonging to the first group was affected by advances fibrosis (F3-F4). AST/ALT ratio parameters were the follow: sensitivity 9%, specificity 63%, ROC area 0.36. More detailed data are reported in Table III and Figure 1.

Regarding the BARD score, the cohort was divided in two groups. Those (29%, n. 12) who showed a BARD score ≥ 2 and those (71%, n. 29) who had a value < 2. Five patients with advances fibrosis (F3-F4) were included in the first group. BARD score parameters included a sensitivity of 45%, a specificity of 77% and a ROC area of 0.71 (Table III; Figure 1).

Considering the APRI score, all patients showed APRI ≤ 1, even those affected by advances fibrosis (F3-F4) and the ROC area was 0.66 (Table III; Figure 1).

Considering the FIB-4 index, patients were divided in three groups. Most of them (61%, n. 25) had a FIB-4 index < 1,45, one patient showed a FIB-4 index > 3,25 and the remaining ones (37%, n. 15) presented intermediate values. No patients with advanced fibrosis (F3-F4) showed a FIB-4 index > 3.25, as they were all included in the other groups: 6 in the FIB-4 index < 1,45 group and 5 in the intermediate one. The only patient included in the FIB-4 index > 3.25 group was affected by mild fibrosis. Parameters and diagnostic accuracy were calculated for the lower and the upper cut-offs: they had respectively 63% and 0% of sensitivity, 46% and 97% of specificity (Table III; Figure 1).

Considering the NFS, patients were divided in three groups. While 7% of patients (n. 3) showed a NFS > 0.676, the majority presented NFS ≤ 1.45 (44%, n. 18) or intermediate values (49%, n. 20). Two patients with advanced fibrosis (F3-F4) showed a NFS > 0.676, while the other 9 were included in the NFS ≤ 1.45 group (n. 2) or in the intermediate one (n. 7). Parameters and diagnostic accuracy were calculated for the lower and the upper cut-offs: they had respectively 53% and 18% of sensitivity, 82% and 98% of specificity (Table III; Figure 1).

Compared to TE, among the investigated tests, NFS presented the best performance for advanced liver fibrosis diagnosis.

Discussion

With the increased prevalence of risk factors as obesity, T2DM and metabolic syndrome, NAFLD is becoming a disease diffused worldwide.[1,6] Despite the knowledge that proper dietary and pharmacological treatment is essential for preventing NAFLD consequences[27], until now, scarce results have been reported with these strategies. Furthermore, the presence of concomitant risk factors facilitates the progression of steatosis into NASH, advanced fibrosis and cirrhosis. The staging of the disease, by the assessment of liver fibrosis, is a crucial clinical requirement, permitting its appropriate management. The limitations of liver biopsy led to the development of others diagnostic methods such as TE and scores based on the elaboration of different variables such as BMI, patients' age, blood exams.

Our study included 41 patients affected by NAFLD and managed according to International guidelines.[28] The percentage of patients with advanced fibrosis was higher in obese and diabetic patients. This suggests the need of a closer follow up of this cohort. Considering the

scores compared to TE, the AST/ALT ratio, even though it is very economic, was not enough sensitive in identifying patients with advanced fibrosis. The BARD score, on the contrary, had a higher sensitivity to identify patients with advanced disease and a better diagnostic performance. The accuracy of APRI was superior than that of AST/ALT ratio and BARD score. The two last scores analysed, FIB4 and NFS, were the most useful tests: their performance could be improved through the use of a single cut off in order to avoid the grey area of diagnostic indeterminate. Our findings are in agreement with a recently published paper from Malmö, Sweden, showing that in patients with NAFLD NFS and FIB-4, can be used to identify patients at risk of future liver-related events, overall mortality, metabolic comorbidities and chronic kidney disease.[29]

Conclusions

In conclusion, our findings demonstrated that the most accurate score, compared to TE, was NFS. It will be interesting to evaluate, in future studies, if the combined employment of NFS with others scores, such as BARD score and FIB 4 score, in larger cohorts, could ameliorate diagnostic accuracy in term of fibrosis staging, in patients with NAFLD.

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Conflicts of interest. The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors contributions. Conceptualization: Marilena Durazzo, Letizia Marzari; methodology: Marilena Durazzo, Letizia Marzari; data collection: Letizia Marzari, Silvia Bonetto, Arianna Ferro, Paola Belci, Alessandro Collo; writing: Marilena Durazzo, Letizia Marzari, Sharmila Fagoonee; review and editing: Sharmila Fagoonee, Maria Cristina Ghigo

All authors read and approved the final version of the manuscript.

TABLES

Table I - Diagnostic scores calculation formula.

PROGNOSTIC SCORE	CALCULATION	
AAR	$\frac{\text{AST}}{\text{ALT}}$	
BARD SCORE	Parameters	Score
	AST/ALT ratio ≥ 0.8	2
	BMI ≥ 28	2
	Diabetes type	1
APRI	$\frac{\frac{\text{AST (patient)}}{\text{AST (normal value)}}}{\text{PLTS}} \times 100$	
FIB-4	$\frac{\text{Age} \times \text{AST}}{\text{PLTs} \times \sqrt{\text{ALT}}}$	
NFS	-1.675 + (0.037×Age) + (0.094×BMI) + (1.13×IFG/Diabetes) + (0.99×AST/ALT) – (0.013×PLTs) – (0.66×Albumin)	

Abbreviations. AAR: AST to ALT ratio; APRI: AST to platelet ratio index; NFS: NAFLD fibrosis score; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: body mass index [kg/m^2]; PLTs: platelet count [x10^9/L]. Units. AST: UI/L; ALT: UI/L; BMI: kg/m^2; PLTs: x10^9/L; Age: years; Albumin: g/dl. Interpretation. IFG/Diabetes: yes = 1, no = 0.

Table II - Patients demographic, clinical and biochemical characteristics.

Patients	**N (%)**	**41 (100)**
Age (years)	Mean ± SD	55±12
Gender	M/F	8/33
BMI (kg/m^2)	Mean ± SD	28±4
BMI < 25	N (%)	10 (24)
25 ≤ BMI < 30	N (%)	23 (56)
BMI ≥ 30	N (%)	8 (20)
AST (U/L)	Mean ± SD	32±15
ALT (U/L)	Mean ± SD	50±41
GGT (U/L)	Mean ± SD	68±67
Glycaemia (mg/dl)	Mean ± SD	102±38
Glycaemia ≥ 126	N (%)	5 (12)
Platelets (x10^9/L)	Mean ± SD	213±53
Triglycerides (mg/dl)	Mean ± SD	137±57
Cholesterol (mg/dl)	Mean ± SD	195±32
Fibrosis stage:		
F0	N (%)	7 (17)
F1	N (%)	16 (39)
F2	N (%)	7 (17)
F3	N (%)	4 (10)
F4	N (%)	7 (17)

Abbreviations. SD: standard deviation; BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyltranspeptidase.

Table III - Accuracy parameters of each diagnostic score.

		IC 95%
AST/ALT Ratio		
Sensitivity	9.00%	0.20% - 41.30%
Specificity	63.00%	43.90% - 80.10%
PPV	8.00%	0.20% - 38.50%
NVP	66.00%	45.70% - 82.10%
LR +	0.25	0.04 - 1.70
LR -	1.44	1.03 - 2.00
ROC area	0.36	0.16 - 0.54
BARD Score		
Sensitivity	45.00%	16.70% - 76.60%
Specificity	77.00%	57.70% - 90.10%
PPV	42.00%	15.20% - 72.30%
NVP	79.00%	60.30% - 92.00%
LR +	1.95	0.78 - 4.87
LR -	0.71	0.40 - 1.26
ROC area	0.71	0.53 - 0.89
APRI		
ROC area	0.66	0.46 - 0.86
FIB-4 Index (lower cut-off < 1,45)		
Sensitivity	63.00%	43.90% - 80.10%
Specificity	46.00%	16.70% - 76.60%
PPV	76.00%	54.90% - 90.60%
NPV	31.00%	11.00% - 58.70%
LR+	1.16	0.64 - 2.12
LR-	0.81	0.36 - 1.80
FIB-4 Index (upper cut-off > 3,25)		
Sensitivity	0.00%	0.00% - 28.50%
Specificity	97.00%	82.80% - 99.90%
VVP	0.00%	0.00% - 97.50%
VVN	73.00%	56.10% - 85.40%
LR+	0.00	0.00
LR-	1.03	0.97 - 1.11
NFS (lower cut-off < 1,45)		
Sensitivity	53.00%	34.30 % - 71.70 %

Specificity	82.00%	48.20 % - 97.70 %
PPV	89.00%	65.30 % - 98.60 %
NPV	39.00%	19.70 % - 61.50 %
LR+	2.93	0.80 – 10.70
LR-	0.57	0.36 – 0.92
NFS		
(upper cut-off > 0,676)		
Sensitivity	18.00%	2.30% - 51.80%
Specificity	97.00%	82.80% - 99.90%
PPV	67.00%	9.40% - 99.20%
NPV	76.00%	59.80% - 88.60%
LR+	5.45	0.55 – 54.30
LR-	0.85	0.64 – 1.13

Abbreviations. AST: aspartate aminotransferase; ALT: alanine aminotransferase; APRI: AST to platelet ratio index; FIB-4: fibrosis-4; NFS: NAFLD fibrosis score; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio.

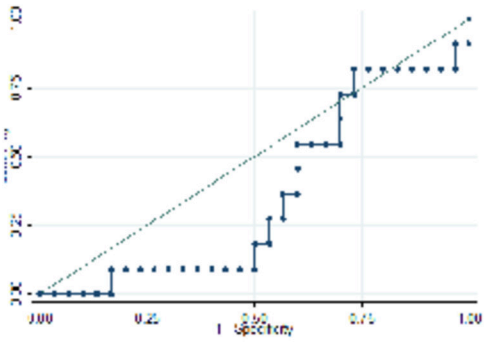
TITLES OF FIGURES

Figure 1- Accuracy parameters of each diagnostic score.

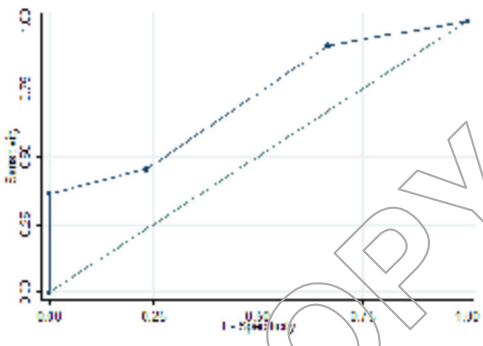
Legend. ROC curve for diagnostic accuracy of each considered diagnostic score (IC 95%).

Abbreviations. ROC: receiver operating characteristics; AST: aspartate aminotransferase; ALT: alanine aminotransferase; APRI: AST to platelet ratio index; FIB-4: fibrosis-4; NFS: NAFLD fibrosis score.

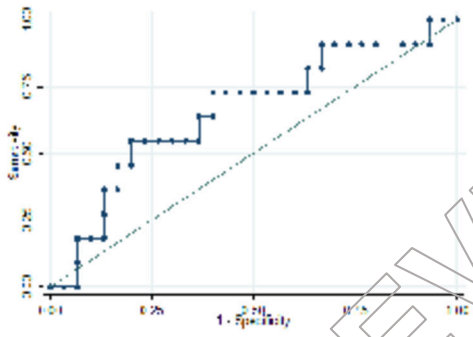
Abbreviations. ROC: receiver operating characteristics; AST: aspartate aminotransferase; ALT: alanine aminotransferase; APRI: AST to platelet ratio index; FIB-4: fibrosis-4; NFS: NAFLD fibrosis score.



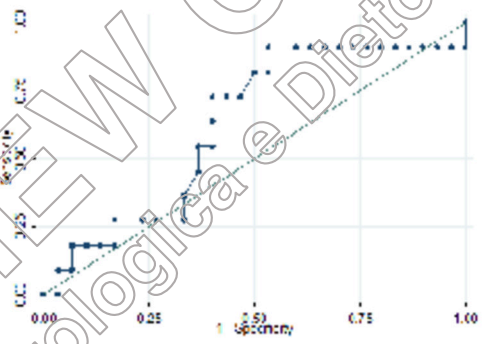
AST/ALT ratio



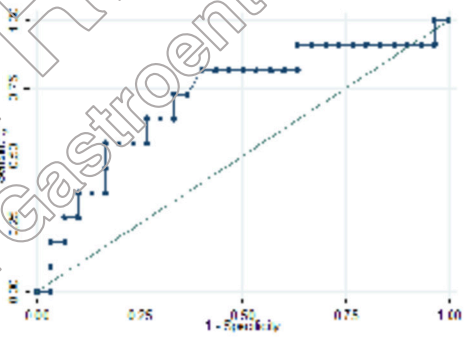
BARD score



APRI



FIB-4 score



NFS