NON-INVAZIVE METHODS FOR HEPATIC FIBROSIS EVALUATION

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Abstract: *Since it is known that patients with fatty liver and advanced fibrosis are prone to evolution to the final stages of the disease- cirrhosis and liver biopsy is invasive, expensive and marked by multiple complications, there is currently a concern increasingly higher by finding reliable methods of non-invasive diagnosis of the degree of inflammation and liver fibrosis. We evaluated 125 patients with non-alcoholic fatty liver using 7 non-invasive method of calculating the degree of liver fibrosis currently available: AST / ALT ratio, Forns fibrosis score, FIB 4, API, ASPRI, APRI and Fatty Liver Index.*

Cuvinte cheie: *ficat gras non-alcoolic, fibroza hepatică, evaluare non-invazivă*

Rezumat: *Deoarece se ştie că pacienţii cu ficat gras şi fibroză avansată sunt predispuşi la evoluţia spre stadiile finale ale bolii, respectiv spre ciroză, iar biopsia hepatică este invazivă, scumpă şi marcată de multiple complicaţii, există în prezent o preocupare din ce în ce mai mare către găsirea unor metode fiabile de diagnostic non-invaziv al gradului de inflamaţie şi fibroză hepatică. Am evaluat 125 pacienţi cu hepatopatie adipoasă non-alcoolică utilizând 7 metode de calcul non-invaziv al gradului de fibroză hepatică disponibile în prezent, şi anume: raportul ASAT/ALAT, scorurile de fibroză Forns, FIB 4, API, ASPRI, APRI şi evaluarea Fatty Liver Index.*

INTRODUCTION

Considering the quite low predictivity of ALT, GGT and ultrasound as well as risk and variability of liver biopsy results, non-invasive assessment of fibrosis using batteries of biochemical tests seems to be one pertinent solution for correct future assesment of non-alcoholic steatohepatitis. Costs are likely to be similar to those of Fibro Test (about € 100), much cheaper than a liver biopsy or MRI. Patients with high score SteatoTest-imagined by Poynard, Ratziu et al. , showed increased age, BMI, ALT, AST, GGT, glucose, triglycerides but also of haptoglobin, apolipoprotein AI (ApoA1), α2-macroglobulin, bilirubin and cholesterol. (1)

Independent predictor of advanced fibrosis were age, BMI, hyperglycemia, platelet count, albumin level, AST / ALT ratio. A scoring system that uses these 6 parameters obtained an AUC of 0.88 in the estimation group and 0.82 in validation group. A lower cut-off score (-1,455) could exclude fibrosis with relatively high accuracy and negative predictive value of 93% for the estimation group and 88% in the validation group. (2)

Intra-individual variation of biochemical markers proved to be very small and food intake did not significantly affected the results of FibroTest or ActiTest, so this tests allows a very affordable and effective evaluation of patients with chronic liver disease. (3) In this study it was not possible an histological assessment of liver fibrosis by liver biopsy puncture because the patients refused intervention. Therefore we decided to assess the degree of liver fibrosis by non-invasive methods, using clinical data and serum markers.

PURPOSE OF THE STUDY

We aimed to assess the degree of liver fibrosis by non-invasive methods using clinical data and serum markers in 125 patients with non-alcoholic fatty liver.

MATERIAL AND METHODS

We used 7 non-invasive methods of calculating the degree of liver fibrosis that are currently available, in order to assess all the 125 patients, namely: AST / ALT ratio , Forns index , FIB 4, API, ASPRI, APRI and Fatty Liver Index.

RESULTS

Table no. 1. Liver fibrosis Scores of patients (average / std. dev)

INDEX FORNS	3.9	±1.5733
Fib 4	0.00047	±0.00033
SCOR APRI	0.0034	±0.0022
SCOR ASPRI	3.10804	±1.21032
ASAT/ALAT	1.032	±0.622

➢ **FIB 4 SCORE**

To optimize management of patients with chronic HCV liver disease, were developed more non-invasive tests to determine the degree of liver fibrosis. A study by Vallet-Pichard et al. validated non-invasive simple and cheap test called FIB- 4 that combines standard biochemical values (platelets, AST, ALT) and age in a series of 847 liver biopsies performed on patients with VHC infection.The authors compared results of 592 patients in whom determinations were made of FIB-4 and FibroTest in the same day. It was found that FIB-4 test allowed correct identification of patients with severe fibrosis (F3-F4) and cirrhosis with an AUC of 0.85 and 0.91 respectively.

An index <1.45 had a negative predictive value of 94.7% to exclude severe fibrosis with a sensitivity of 74.3%, while a score greater than 3.25 showed a positive predictive value of 82.1% to confirm significant fibrosis (F3- F4) with a specificity of 98.2%. Using these limits, 72.8% of 847 biopsies were correctly classified. Also, Fib-4 was correlated closely with results FibroTest for scores <1.45 or> 3.25 (kappa = 0.561, P <0.01). In conclusion, for values outside the range 1.45-3.25, FIB-4 score is a simple, reliable and cheap to assess liver fibrosis, proving consistent with results of FibroTest. (4)

Fib-4 = (age (years) x AST (U / L)) / (count (109 / L) x ALT (U / L) / 2) (5)

We calculated FIB-4 and found that 124 cases (99.2%) had values <1.4, which suggests absence of severe fibrosis

(median of 0482), and only one case shows the index of 1.8 (not fitting into evaluation).

> **FORNS Fibrosis Score**

In a 2006 study published in Gut, the authors used more non-invasive scores of liver fibrosis evaluation in patients with chronic HCV liver disease, Forns score being assessed as the best predictor of non-invasive liver fibrosis. (6)

Forns score = 7.811–3.131 ln (plt (10^9/l)) + 0.781 ln(GGT(UI/l)) + 3.467 ln (age (yrs)) – 0.014x (cholesterol (mg/dl)(6)

They used cut off levels of <4.2 to rule out liver fibrosis. We calculated the Forns score obtaining a mean (average) of 3.78097 (± 1.573306). A total of 78 patients (62.4%) were scored Forns <4.2, 44 patients (35.2%) had a score between 4.2 and 6.9, while only 3 patients scored more than 6.9 suggesting significant liver fibrosis .

Figure no. 1. Distribution of patients according to the score FORNS
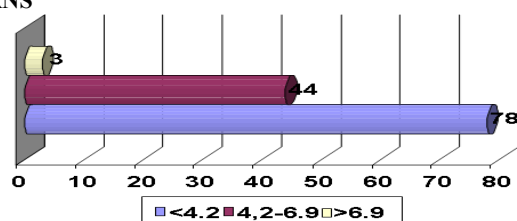

> **AST / ALT RATIO**

Several recently published studies have shown that patients with non-alcoholic steatohepatitis (NASH) and normal transaminases may have liver fibrosis or cirrhosis. In a study on 36 patients with type 2 diabetes and NASH, diabetes was the only factor independently associated with liver fibrosis, the aim being to detect predictors of cirrhosis in patients with NASH and diabetes. In these patients , AST: ALT ratio ranged from 0.41 to 1.85 with an average of 0.98 ± 0.26. Stronger statistical methods that used multiple regression calculations found statistically significant differences between patients with and without fibrosis on AST, ALT and AST / ALT> 1 in approx. 80% of cases, with a sensitivity of 55% and a specificity of 92%, concluding that these parameters can be useful in predicting liver fibrosis in diabetic patients with non-alcoholic steatohepatitis. (7)

In patients with liver steatosis we found an average AST: ALT ratio of 1.087252742. More specifically, 69 patients had a score <1 (55.2%), 50 patients had a score between 1-2 (40%) and 6 patients scored above 2.

Figure no. 2. Distribution of patients according to the AST/ALT ratio
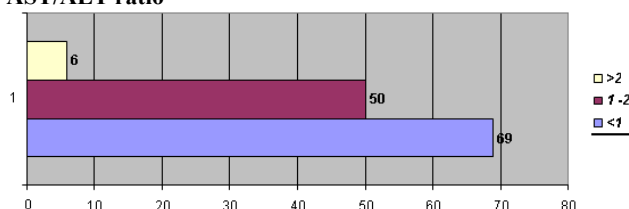
> **APRI SCORE**

Score APRI (AST to Platelets index ratio) was initially described by Wai et al, calculated as **APRI = ((AST / upper limit of normal) / platelet count (10^9 / L)) × 100)**

It is a very simple test using laboratory parameters of wide accessibility and very easy to calculate. Several studies have demonstrated the accuracy of this test to identify significant fibrosis and cirrhosis of liver, so it is considered that using cut-off limits proposed by authors can be classified

approximately 50% of patients with chronic liver diseases, especially those without HCV chronic hepatitis, without the need to conduct liver biopsy. (8) It appears that in patients with HCV hepatitis, but also in patients with liver transplant, the APRI value> 1.4 has a sensitivity of 91% and specificity of 75% in the detection of fibrosis F> 2. (9) All of our subjects had values of APRI <1.4, with an average of 0.341, suggesting the absence of hepatic fibrosis F> 2 in this group of patients.

> **API SCORE**

Originally studied in order to evaluate the degree of non-invasive liver fibrosis in patients with viral hepatitis HBV, API score (Age / Platelets Index) has demonstrated statistic viability, showing a significant correlation with the the degree of liver fibrosis proven by liver biopsy. (r = o.669, p <0.001). **Cut off limit is <1.5,** and a higher API score (eg 4, 6, 8) is considered to prove an even more severe degree of liver fibrosis. (10)

Table no. 2. API score calculation method

API	Age(years) <30=0; 30-39=1; 40-49=2; 50-59=3; 60-69=4; ≥70=5
	Platelets (10^9/l): ≥225=0; 200-224=1; 175-199=2; 150-174=3; 125-149=4; <125=5
	AP index(API) is the sum of the above (possible values = 0-10)

In our study we found an API score > 1.5 in 119 patients (95.2%) with values predominantly between 4 and 8.
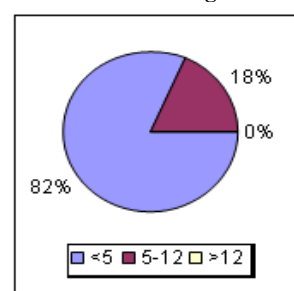
> **ASPRI SCORE**

Three independent factors: age, the long axis of the spleen and platelet count were used in designing this score. To exclude the effect of fluctuations in transaminases (as the case of AST in the APRI score, widely accepted as a non-invasive test) this parameter was replaced with spleen size.

Regarding the age factor, a score was calculated a gravity score as follows:<30 years-0 points., between 30-40 years-1 pt., 40-50ani-2pt, 50-60 years-3pt., 60-70 years-4pt. Over 70 years-5 points

SPRI = spleen diameter (cm) / platelets count (10^9 / l) x 100 ASPRI = age score + SPRI

Figure no. 3. Distribution according to the ASPRI score

In a study published in 2007 were demonstrated statistical significant correlation with liver fibrosis using all the tests: APRI, API, SPRI and AST / ALT , but ASPRI showed the highest correlation with fibrosis (r = 0.703, P <0.001). Using a cutoff score> 12 , the cirrhosis was identified correctly by 96.3% positive predictive value and a score below 5 this was of 100% negative predictive value. (10)

Our patients had the following ASPRI scores:ASPRI <5 = 102 patients - 81.6%, ASPRI> 12 = 0 patients, ASPRI between 5 and 12 = 23 patients - 18.4%.

> **FATTY LIVER INDEX**

Fatty Liver Index (FLI) or steatosis prediction index is presented by Italian researchers using a simple formula including triglycerides levels (mg / dl), BMI (kg/m2), GGT (U /

L) and waist circumference (cm) resulting in a numerical value.

One result of FLI over 60 signifies a 85% possibility of having steatosis while a FLI value below 30 means more than 86% probability of not having fatty liver. (11)

$$FLI = (e^{0.953*\log(\text{triglycerides}) + 0.139*IMC + 0.718*\log(GGT) + 0.053*\text{waist} - 15.745}) / (1 + e^{0.953*\log(\text{triglycerides}) + 0.139*BMI + 0.718*\log(GGT) + 0.053*\text{waist} - 15.745}) * 100$$

FLI calculation showed that only 13 subjects had levels of FLI score below 30, but these patients demonstrated mild steatosison liver ultrasound with posterior attenuation, most patients - 77.6% (n = 97) having FLI values> 60, confirming thus also by this method the presence of fatty liver.

Figure no. 4. Distribution of patients according to FLI

☐ FLI ■ <30 ☐ 30-60 ☐ >=60
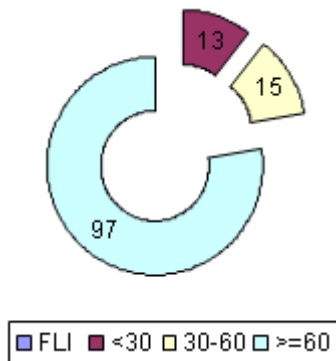
- Non-invasive calculation of the degree of liver fibrosis using proprietary formulas for other chronic liver diseases had slightly different results depending on the formula used: no patient with severe fibrosis (APRI and FIB- 4), 3 patients with severe fibrosis (Forns score), 44.8% - liver fibrosis (AST / ALT ratio > 1), 102 patients (81.6%) in whom can be surely excluded hepatic cirrhosis –according to ASRI score, 119 patients with API score values> 1.5 , which signifies the existence of a degree of liver fibrosis.
- Calculation of FLI (Fatty Liver Index) confirm the applicability of this assay based on triglyceride levels, BMI, GGT and waist circumference in the prediction of fatty liver, most patients (n = 97) having FLI values> 60, confirming the existence of fatty liver.
- In patients with non-alcoholic fat liver, non-invasive assessment of liver fibrosis by the methods described above may be a step up in the diagnostic algorithm, following that in subjects with elevated or inconclusive results to perform a biopsy liver.

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