NON-INVASIVE MARKERS OF LIVER FIBROSIS IN CHRONIC VIRAL HEPATITIS C

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Abstract: *In assesing liver fibrosis liver biopsy is still considered "gold standard" but since the process of hepatic fibrosis is governed by a series of mediators tried to find non-invasive methods for assessment of hepatic fibrosis, which is devoid of risks and repeated at different stages of disease and treatment.*

Cuvinte cheie: *puncție biopsie hepatică, fibroză hepatică, markeri neinvazivi*

Rezumat: *În evaluarea fibrozei hepatice puncția biopsie hepatică se consideră încă "standardul de aur" dar având în vedere că procesul de fibroză hepatică este guvernat de o serie de mediatori s-a încercat găsirea unor metode de apreciere neinvazivă a fibrozei hepatice, care să fie lipsite de riscuri şi repetitive în diferite stadii de boală şi tratament.*

INTRODUCTION

Conditions should be met by serological marker would ideally be:

1. be specific for liver
2. have adequate statistical value
3. its levels are not influenced of comorbidity (eg. renal disease)
4. measuring one or more of the following:
   - Fibrosis stage,
   - Activity of extracellular matrix deposition,
   - The activity of extracellular matrix degradation.
5. be easily performed
6. have a low cost price
7. be reproductible

POURPUSE OF STUDY

Comparing the results obtained on the degree of fibrosis by liver biopsy and obtained by calculating several noninvasive markers in a group of patients with chronic hepatitis C.

MATHERIAL AND METHOD

We have studied patients with chronic hepatitis C, hospitalized in January 2002 - March 2009, in Sibiu County Emergency Hospital and Emergency Military Hospital Sibiu. All patients were biopsy using Menghini needles of 16 G, which were extracted fragments minim15 mm.

Analysis of liver fragments was made after the score Metavir considering the significant fibrosis ≥ F2 values.

Our study took place in two distinct groups: first group included 184 subjects who fibrosis index compared with values obtained by biopsy obtained by calculating the scores priori FORNS, FIBROINDEX, FIB-4 and a total of 30 subjects was applied and FIBROTEST.

We intend to make partial batch analysis of 30 subjects.

RESULTS AND DISCUSSIONS

It was composed of 22 women (73%) and 8 men (37%).

Distribution of age groups was: 20-29 years 2 subjects (6.66%), 30-39 years 10 subjects (33,33%), 40-49 years four subjects (13.33%), 50-59 years, 11 patients (36.66), 60-65 years three subjects (10%).

Of the entire group to analyze biopsy fragment scale Metavir 4 subjects had F1 fibrosis, 21- F2 and 5 subjects had fibrosis F3. Were considered significant values of the fibrosis ≥ 2.

APRI score (1)

APRI = (AST (/ upper limit of normal) x100) / number of platelets (10^9 / l)

Cut off values used were:

Value ≤ 0.5 = no significant fibrosis.

Value of 1.5 = presence of significant fibrosis.

Values ≥ 2 = cirrhosis

Have been classified a total of 17 subjects (56.6%).

The following parameters were recorded:

Table no. 1. Results obtained at the APRI analysis

SCOR	SENS	SPEC	PPV	NPV	ACC
≤ 0,5	0,85	0,1	0,65	0,25	0,6
> 1,5	1	0,15	0,16	1	0,23

Note that there have been good sensitivity values for both the absence of fibrosis (0.85), and for the presence of fibrosis (1), the NPV for the presence of fibrosis (1), but lower scores for other parameters.

AUROC for detection of significant fibrosis was 0.56.

No significant values were recorded for liver cirrhosis.

Wai's in the original study were obtained as follows:

Table no. 2. Values obtained in the WAI original study

SCOR	SENS	SPEC	PPV	NPV
≤ 0,5	0,91	0,47	0,61	0,86
> 1,5	0,41	0,95	0,88	0,64

AUROC value for detection of significant fibrosis was 0.88.

While numerous studies have been conducted that have examined only APRI score or combination of this and other scores (2-6).

Forns score

FORNS score = 7.811 to 3.131 x ln (no count) + 0.781 × ln (GGT) + 3.467 x age-0.014 x ln (cholesterol).

Values less than 4.2 certify the absence of fibrosis

Higher values of 6.9 signifies the presence of significant fibrosis (7).

They recorded the following results:

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Have been classified a total of 10 subjects (33.3%).

Table no. 3. Results obtained in the FORNS analysis

SCOR	SENS	SPEC	PPV	NPV	ACC
<4,2	0,95	0,27	0,69	0,75	0,7
> 6,9	1	0,18	0,31	1	0,4

AUROC for the detection of significant fibrosis was 0,63.

The original Forns study was obtained AUROC 0.94.

Have been developed and other studies that have found lower results in patients with genotype 3, which call lower cholesterol values (8, 9).

FIB-4

4 FIB score combines the following elements: **age (years) x AST (U / l) / platelets (10^9 / l) x √ ALT (U / l)**

Values **<1.45** excluded the presence of significant fibrosis.

Values> **3.25** confirms the presence of significant fibrosis (10).

They obtained the following results:

Could not be classified a total of 10 subjects (33.3%).

Table no. 4. Results obtained in the FIB-4 analysis

SCOR	SENS	SPEC	PPV	NPV	ACC
<1,45	0,92	0,18	0,46	0,75	0,5
> 3,25	1	0,15	0,16	1	0,23

AUROC value for detection of significant fibrosis was 0.59.

FIBROINDEX

Formula: 1.738 to 0.064 (Tr x 10^4 / mm $^{3)}$ + 0.005 (AST (U / l)) + 0.463 (gamma globe. (G / dl))

Values **<1.25** are representative of the absence of significant fibrosis.

Values> 2.25 are representative of the presence of significant fibrosis (11).

They obtained the following results:

Could not be classified a total of 19 subjects (63.3%)

Table no. 5. Results obtained in the FIBROINDEX analysis

SCOR	SENS	SPEC	PPV	NPV	ACC
<1,25	1	0,4	0,77	1	0,8
> 2,25	1	0,14	0,04	1	0,17

AUROC value for detection of significant fibrosis was 0.55.

Fibro Test team imagined Imbert-Bismuth and associates in 2001 met several determinations of markers, much less used in practice (12).

Index calculation is made according to a formula, after determining the following components:

- Alpha 2-macroglobulin;
- Total bilirubin;
- Gamma-GT;
- A1 apolipoprotein;
- Haptoglobin

combined with age and sex of the patient, a computer algorithm (USPTO 6,631,330). This test has not let quality unclassified subjects.

They obtained the following data:

Tabelul nr. 6. Results obtained in the FIBROTEST analysis

SCOR	SENS	SPEC	PPV	NPV	ACC
	1	0,31	0,65	1	0,7

AUROC for significant fibrosis detection: 0,66. The initial studies were obtained range from 0,84 to 0,87.

While comparative studies have been conducted on large groups of patients with high PPV affirming significant fibrosis, especially in subjects with elevated values of Fibrotest (13, 14).

APRI score is the quality that uses routine determinations in clinical practice and is easy to calculate, with good results in the original study, AUROC 0,88 for detection of significant fibrosis in our study were much lower values are obtained-0,56. Forns index also uses the usual laboratory tests, mentioning the possibility of results due to the high values of GGT change (alcohol) or cholesterol which may be dependent on genotype (3). AUROC for detection of significant fibrosis was the study's original Forns 0,94. In our study had a value of only 0,66. They won, but good values of both sensitivity and excluding significant fibrosis in affirming it. FIBROINDEX and Fib-4 used in calculation routine determinations in clinical practice, but in our study were obtained low values for AUROC affirmation fibrosis, significant increased sensitivity to both assertion and the absence of this fibrosis.

A negativ element in the use of these scores is that they show a range of values that do not qualify subjects, this limiting their use. In our study, remained unclassified 56.6% (APRI), 33.3% (Forns), 33.3 % (Fib-4) and 63.3% (FIBROINDEX).

Fibrotest-has the advantage that it can classify all patients, with sensitivity in the detection of fibrosis, but the PPV of moderate value.

Shows the important disadvantage of cost, using determinations are not routinely performed and a particular algorithm.

Clearly very different values obtained in subgroup analysis presented is also due to small number of subjects analyzed, the impossibility of analyzing using Fibrotest a more representative group.

CONCLUSIONS

Using non-invasive markers for assessing liver fibrosis in chronic hepatitis C can be used in a limited number of cases; are frequent cases when subjects can not be classified, some of them shows the high cost price. It is possible that a conjunction of several tests to ensure more correct classification of a larger number of patients, in this sense there is more and more studies.

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