

## Do Non-Invasive Markers of Fibrosis have a Place in the Evaluation of Fibrosis in Overlap Syndrome?

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### Abstract

**Introduction:** The non-invasive markers of fibrosis are currently validated in viral hepatopathies but less validated in other dysimmune liver diseases. Very few studies have focused on the place of non-invasive markers of fibrosis in the overlap syndrome. The aim of our study is to determine the correlation between non-invasive markers of fibrosis and histological fibrosis scores in overlap syndrome.

**Methods:** We conducted a retrospective study that collected all patients with an overlap syndrome: primary biliary cholangitis - autoimmune hepatitis or primary sclerosing cholangitis - autoimmune hepatitis. The APRI and FIB-4 scores were calculated at the time of diagnosis and one year after treatment. A liver biopsy specifying the degree of fibrosis according to Metavir was performed at the time of diagnosis. Liver elastography was done after one year of treatment. Fibrosis was considered significant from F2 for hepatic elastography and Metavir score and a cut-off > 1.5 and > 3.25 for APRI and FIB-4, respectively. The Spearman correlation test and the ROC curve were used to analyze the data.

**Results:** Our study involved 56 patients divided into 52 women and 4 men of average age 51.1 years (30 - 73 years). Autoimmune hepatitis was associated with primary biliary cholangitis in 89.3% of cases and primary sclerosing cholangitis in 10.7% of cases. Spearman's correlation analysis did not show a correlation between serum markers measured at the time of diagnosis and the degree of histological fibrosis ( $r = 0.5$ ,  $p = 0.001$ ). Among the 52 patients who would have significant fibrosis according to the APRI score, 20 patients had no significant histological fibrosis (F0, F1). Among the 48 patients who would have significant fibrosis according to the FIB-4 score, 30 actually had significant fibrosis ( $\geq F2$ ). After one year of treatment, 54 patients underwent hepatic elastography, which showed significant fibrosis in 70.3% of cases (38 patients). Correlation analysis did not show any correlation between serum markers of fibrosis and hepatic elastography. Among the 38 patients with significant fibrosis according to the measurement of hepatic elastography, 16 patients and 12 others were presumed to have no significant fibrosis according to the APRI and FIB-4 scores, respectively.

**Conclusion:** In our study, we did not find any correlation between the different non-invasive markers of fibrosis and the results of the liver biopsy, which remains to this day the gold standard for assessing liver fibrosis in dysimmunitary disorders like overlap syndrome.

**Keywords:** Non-Invasive Markers; Fibrosis; Overlap Syndrome

### Abbreviations

OS: Overlap Syndrome; AIH: Autoimmune Hepatitis; PBC: Primary Biliary Cholangitis; PSC: Primary Sclerosing Cholangitis; ALP: Alkaline Phosphatase; GGT: Gamma Glutamyl-Transpeptidase; ULN: Upper Limit of Normal; AMA: Anti-Mitochondrial Antibody; ALT: Alanine Aminotransferase; ASMA: Anti-Smooth Muscle Antibody; EASL: European Association for the Study of the Liver; SPSS: Statistical Package for the Social Sciences; NAFLD: Non Alcoholic Fatty Liver Disease

### Introduction

The overlap syndrome (OS) is an uncommon liver disease. It's a variant of hepatopathy in which characteristics of autoimmune hepatitis (AIH) are simultaneously or consecutively associated with primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) criteria. AIH-PBC OS diagnosis is mostly based on "Paris criteria" [1,2] which requires the presence of at least two of three features for the diagnosis of PBC and AIH.

The PBC criteria are as follows:

- 1) ALP > 2 times ULN or GGT > 5 times ULN;
- 2) presence of AMAs;
- 3) florid bile duct lesions in the liver biopsy specimen.

For AIH, the criteria are as follows:

- 1) ALT levels >5 times ULN;
- 2) Serum immunoglobulin G levels >2 times ULN or positive ASMAs;
- 3) Moderate or severe periportal or periseptal lymphocytic piecemeal necrosis in the liver biopsy specimen.

AIH-PSC OS diagnosis is less codified and is based on the combination of biologic, immunologic, radiological and histological arguments.

The assessment of the fibrosis degree and detection of cirrhosis represent the most relevant clinical endpoint in every hepatopathy but since liver biopsy is an invasive procedure, it was performed only in few patients. Thus, non invasive tests have emerged: the measurement of liver stiffness or elastography and scores based on biological markers. The non-invasive markers of fibrosis are currently validated in viral hepatopathies but less validated in other dysimmune liver diseases [3]. Very few studies have focused on the place of non-invasive markers of fibrosis in the OS. The aim of our study is to determine the correlation between non-invasive markers of fibrosis such as the APRI and FIB-4 scores and histological fibrosis scores in OS.

### Patients and Methods

We conducted a retrospective study that included all patients with an OS in the gastro-enterology department in Sahloul hospital. In our study, we chose to assess the APRI and FIB-4 scores to evaluate fibrosis degree. APRI or AST to Platelet Ratio corresponds to  $AST (/ULN)/platelet (10^9/L) \times 100$ . FIB-4 score is  $age (yr) \times AST [U/L]/(platelets [10^9/L] \times (ALT [U/L])^{1/2})$ . These two scores were calculated at the time of diagnosis and one year after treatment. A liver biopsy specifying the degree of fibrosis according to Metavir was performed at the time of diagnosis. Liver elastography was performed one year after treatment. Fibrosis was considered significant from F2 for hepatic elastography and Metavir score and a cut-off > 1.5 and > 3.25 for APRI and FIB-4, respectively. These cut-offs were the ones validated in EASL in chronic hepatitis C [8]. The Spearman correlation test and the ROC curve were used to analyze the data using the SPSS version 20 software.

**Results**

Our study involved 56 patients divided into 52 women and 4 men of average age 51.1 years (30-73 years). AIH was associated with PBC in 89.3% of cases (50 patients) and PSC in 10.7% of cases (6 patients).

Variable	Before treatment	One year after treatment
Age (years)	51,1 ± 13,01	52,1 ± 13,01
ASAT (u/l)	188,66 ± 159,65	58,33 ± 53,43
ALAT (u/l)	169,18 ± 159,05	53,85 ± 63,87
BT (µmol/L)	71,18 ± 89,74	-
PLQ (*10 <sup>3</sup> µL)	243 ± 138	215 ± 100
ALB (g/l)	29,71 ± 5,43	-
APRI score	2,68 ± 2,82	0,73 ± 0,61
FIB4 score	5,29 ± 4,93	2,34 ± 1,62

**Table 1:** Demographic, biological characteristics and fibrosis scores before and after treatment.

Spearman’s correlation analysis did not show a correlation between serum markers measured at the time of diagnosis and the degree of histological fibrosis (r = 0.5, p = 0.001). Among the 52 patients who would have significant fibrosis according to the APRI score, 20 patients had no significant histological fibrosis (F0, F1). Among the 48 patients who would have significant fibrosis according to the FIB-4 score, 30 actually had significant fibrosis (> = F2).

After one year of treatment, 54 patients underwent hepatic elastography, which showed significant fibrosis in 70.3% of cases (38 patients). Correlation analysis did not show any correlation between serum markers of fibrosis and hepatic elastography. Among the 38 patients with significant fibrosis according to the measurement of hepatic elastography, 16 patients and 12 others were presumed to have no significant fibrosis according to the APRI and FIB-4 scores, respectively.

**Discussion**

Overlap syndrome is a rare hepatopathy. The frequency of AIH-PBC OS varies from 2.1 to 20% of all CBP and HAI diagnosed as such. The mean age in the study of Chazouillères, *et al.* was 51 years [1,4-6]. The frequency of AIH-PSC OS within cohorts of AIH patients ranges from 1.7 - 12.5% [7-9]. The average diagnosis age in AIH/PSC ranged from 24 - 27 years [7,8]. The AIH-PBC OS was more frequent in females [1,4,5] as demonstrated in our study while the AIH/PSC OS concerned mainly men [7].

Many serum biomarkers have emerged for the assessment of liver fibrosis, mainly in patients with chronic hepatitis C. their advantages are their good reproducibility, their no cost availability and their safety compared to liver biopsy. However, none are liver specific and they may be influenced by any intercurrent condition [3]. The most widely used and validated tests are the Fibrotest and APRI score mainly in chronic hepatitis C and they are reliable in the diagnosis of either significant fibrosis and cirrhosis. The FIB-4 score was validated as well. APRI and FIB-4 scores were validated in alcoholic liver disease and NAFLD respectively [3]. Since the Fibrotest require the measurement of α-2-macroglobulin, apolipoprotein A1, haptoglobin which are costly and not available in our hospital, we based our study on the APRI and FIB-4 scores. As mentioned by the EASL, no single serum biomarker was able to differentiate between early and advanced fibrosis in PBC [3]. There was not enough data for the PSC patients. In AIH, non-invasive tests may be useful for monitoring response to treatment. However, they are still not validated in evaluating fibrosis degree. Our study showed no correlation between these scores and Metavir score nor elastometry in detecting advanced fibrosis.

## Conclusion

In our study, we did not find any correlation between the different non-invasive markers of fibrosis and the results of the liver biopsy which remains until this day the gold standard for assessing liver fibrosis in dysimmunitary disorders like overlap syndrome.

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