

Review paper

# Evaluation of hepatic fibrosis – access to non-invasive methods, national practice/guidelines in Central Europe

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## Abstract

Noninvasive methods have improved diagnostic tools of liver fibrosis. Although liver biopsy is the gold standard for diagnosis of hepatic fibrosis, the noninvasive tests are usually much less expensive than liver biopsy, better tolerated, and can be repeated without any risk for the patient.

Two groups of these noninvasive tests are included in clinical practice: serum biomarkers and elastography. In our paper we summarize noninvasive diagnostic options for liver fibrosis in the Czech Republic, Hungary, Poland and Slovakia. Noninvasive diagnostic methods, especially elastography, are widely accessible in all countries.

**Key words:** liver fibrosis, serum biomarkers, elastography, hepatitis C.

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## Introduction

Liver-related mortality is caused mainly by cirrhosis and its complications; thus the major determinant for prognosis of patients with chronic liver disease is the degree and progression of liver fibrosis leading to cirrhosis. Up to 29 million members of the European population could suffer from chronic liver disease. The most frequent chronic liver diseases in Europe are non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease and chronic infection with hepatitis C virus (HCV) [1]. Prognosis and complications of chronic liver diseases strongly depend on the degree of liver fibrosis. The evaluation of liver fibrosis has an essential role in the management of chronic liver diseases. Stage of liver fibrosis determines the indication for treatment, the choice of treatment option, duration, and the necessity of co-administration of ribavirin in patients with chronic hepatitis C.

The gold standard for the evaluation of liver fibrosis is the liver biopsy, but it is an invasive, painful procedure,

and carries a significant, although small risk of life-threatening complications [2]. Hypotension is the most common as a result of vasovagal reaction, while other complications, such as hemobilia and larger intraperitoneal bleeding, occur rarely. Mortality of this procedure is about 0.001% [3]. It may have contraindications, and it is certainly not the ideal procedure for serially repeated assessment of disease progression. But due to its invasiveness, intra- and inter-observer variability, sampling error and costs, liver biopsy has been substituted by non-invasive tests in many situations including the evaluation of liver fibrosis [4]. The non-invasive tests are usually much less expensive than liver biopsy, better tolerated and can be repeated without any risk for the patient. European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C, 2015, stating that “fibrosis stage can be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional aetiologies”, were included in the Polish Recommendations for treatment of hepatitis C

[5, 6]. Recently several noninvasive methods have been designed to measure liver stiffness/fibrosis. Two groups of these non-invasive tests are included in clinical practice: serum biomarkers and elastography.

## Noninvasive laboratory tests for liver cirrhosis

Circulating markers of liver fibrosis progression can be divided into Class I and Class II biomarkers of fibrosis. The markers in Class I directly represent the intensity of fibrogenesis or fibrinolysis. Frequently, they involve costly laboratory tests and are the result of translation of fibrogenic mechanisms into clinical

application. Thus, their selection is hypothesis-driven. Class II biomarkers are empirically derived indexes which include proteins, enzymes, coagulation factors, and other various biochemical and cytological markers often combined into a mathematical formula. They usually represent the stage of fibrosis or the extent of fibrotic transformation of liver parenchyma. These two groups of biomarkers are useful for different purposes. Class I markers are generally (but not always) more sensitive in determining intensity of fibrogenesis, or grade of the disease. Class II markers can help us estimate the extent of fibrosis or stage of the disease [3, 7]. A summary of laboratory tests using for evaluation of stage of liver fibrosis is presented in Tables 1-3.

**Table 1.** Liver fibrosis scoring systems using standard laboratory tests (adapted from Jarcuska *et al.* [3])

Index	Parameters	Sensitivity (%)	Specificity (%)
Sheth index (De Ritis)	AST/ALT ratio	53	100
Bonacini index	ALT/AST-ratio, INR, platelet count	46	98
Pohl score	AST/ALT ratio, platelet count	41	99
Forns index	Age, platelet count, GMT, cholesterol	94	51
WAI index (APRI)	AST, platelet count	89	75
Testa index	Platelet count/Spleen diameter ratio	78	79
FIB-4	Platelet count, AST, ALT, age	70	74

**Table 2.** Liver fibrosis scoring systems using non-standard laboratory tests (adapted from Jarcuska *et al.* [3])

Scoring systems	Parameters	Sensitivity (%)	Specificity (%)
PGA index	Prothrombin time, GMT, apolipoprotein	91	81
PGAA index	Prothrombin time, GMT, apolipoprotein A1, $\alpha$ 2-macroglobulin	79	89
Fortunato score	Fibronectin, prothrombin time, PCHE, ALT, Mn-SOD, $\beta$ -NAG		94
Fibrotest (Fibro-score)	Haptoglobin, $\alpha$ 2-macroglobulin, apolipoprotein A1, GGT, bilirubin	75	85
Actitest	fibrotest + ALT		
Sud index (fibrosis probability index – FPI)	Age, AST, cholesterol, insulin resistance (HOMA), past alcohol intake	96	44

**Table 3.** Liver fibrosis scoring systems using Class I fibrosis markers (adapted from Jarcuska *et al.* [3])

Index	Parameters	Sensitivity (%)	Specificity (%)
Patel index	hyaluronic acid, TIMP-1, $\alpha$ 2-macroglobulin	77	73
Leroy score	PIIINP, MMP-1	60	92
Rosenberg score (ELF score)	PIIINP, hyaluronic acid, TIMP-1	90	41
Fibrometer test	platelet count, prothrombin index, AST, $\alpha$ 2-macroglobulin, hyaluronic acid, urea, age	81	84
Hepascore	bilirubin, GMT, hyaluronic acid, $\alpha$ 2-macroglobulin, age, gender	63	89

Noninvasive laboratory tests are not widely used in Central Europe for diagnostics of liver fibrosis. The Fibrotest is most popular, and it is used especially in Poland. In Slovakia only 2 centers have personal experiences with noninvasive tests for liver fibrosis. Koller *et al.* created a noninvasive fibrosis score algorithm for patients with chronic hepatitis C. For its semiquantitative calculation, age,  $\alpha$ 2-macroglobulin, APRI (AST to platelet ratio index) score, serum AST, serum ferritin and serum insulin were used. The noninvasive fibrosis score has AUROC (area under the receiver operating characteristic) 89-90%, sensitivity 78-85% and specificity 92-100% [8].

## Elastography

Elastography utilizes decrease of liver elasticity with progression of fibrosis. Various types of elastography are used in clinical practice.

Ultrasound elastography:

- transient elastography (TE),
- acoustic radiation force impulse imaging (ARFI),
- shear wave elasticity imaging (SWEI),
- supersonic shear imaging (SSI),
- quasi-static elastography.

## Magnetic resonance elastography

The procedure is painless, rapid, and needs no preparation. The use of this technique is easy to perform, reproducible in about 95% of patients, safe, and inexpensive. So far, transient elastography has been mostly validated in chronic hepatitis C, but it is applicable in liver diseases with other etiologies. The diagnostic accuracy of transient elastography increases with stage of fibrosis and is more accurate in advanced fibrosis ( $F \geq 2$ , Metavir score) and cirrhosis. Indication of antiviral therapy for chronic viral hepatitis B and C is the main field of application of transient elastography, and it is also a useful tool for follow-up of disease progression.

Result of elastography examination not only closely correlates with the liver fibrosis score but also predicts survival and liver cirrhosis complications of patients with liver disease [9, 10].

Transient elastography is the almost exclusively used method for evaluation of liver fibrosis in Hungary, and it is available across the country [11]. Ultrasound-based elastography is widely available in the Czech Republic. Only dynamic elastography has been accepted by the Polish Association for Study of Liver, the Polish Expert Group of HCV and the Polish Expert Group of HBV for liver fibrosis assessment. Transient Elastography-

Vibration Controlled Transient Elastography “FibroScan” (15 devices in Poland) and more recently Ultrasound Imaging Innovative ShearWave Elastography “Aixplorer-MultiWave” (10 devices in Poland in hepatological practice) have successfully entered clinical practice in our country. Both these techniques are now reimbursed in Poland by the NHF (programs: Therapy of chronic HCV infection, IFN-free therapy of chronic HCV infection, and Therapy of chronic HBV infection) [12]. Four transient elastographies and 1 ARFI in four centers (Bratislava, Banská Bystrica, Košice, Bardejov Spa) are used for evaluation of the liver fibrosis score in Slovakia, but only 1 center has a pediatric device. Every center examines more than 1000 patients per year. The Health Care System does not reimburse elastography examination, but the results of the investigation are accepted for the patient’s prioritization for IFN-free chronic hepatitis C treatment. Results of the examination are not generally accepted for IFN-based treatment of chronic hepatitis B and C by the health care insurance in Slovakia.

A novel non-invasive diagnostic tool, called the “controlled attenuated parameter” (CAP), is also discussed. CAP measures the attenuation of ultrasound waves generated by FibroScan, and based on this parameter we can quantitatively assess the hepatic fat content and distinguish several steatosis grades. The relevance of the examination of hepatic steatosis in CHC: CHC can cause steatosis, steatosis progression is often observed after successful treatment of CHC, and steatosis may prevent fibrosis regression after eradication of HCV [13].

Spleen elastography predicts severity and bleeding risk of esophageal varices in cirrhotic patients [14].

Combination of elastography and one laboratory liver fibrosis scoring system could be the best noninvasive scoring system to assess the liver fibrosis score, but in Central Europe there are only limited data on its application in clinical practice.

## Conclusions

Noninvasive methods for diagnosis of liver fibrosis are widely accessible in Central Europe. The implementation of a noninvasive method in the detection of significant liver fibrosis improved diagnostic options and led to a reduction in the number of liver biopsies in many centers across Central Europe.

## Disclosure

Authors report no conflict of interest.

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