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Prediction of Liver Cirrhosis in Patients with HCV Chronic Infection through Routine Laboratory Parameters: Myth or Reality?

Ivan Gentile* and Guglielmo Borgia

Department of Clinical Medicine and Surgery, University of Naples Federico II, Italy

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About 150,000,000 people worldwide are estimated to be chronic carriers of Hepatitis C virus (HCV) [1]. Roughly, a quarter of these patients evolve toward liver cirrhosis [2]. Once cirrhosis has been established, 4% per year of these patients progress toward a decompensated disease with an annual death rate as high as 30%, and about 1.6% per year develop a hepatocellular carcinoma (HCC) [3]. Therefore the presence of cirrhosis is a boundary layer that marks a dramatic drop in the life expectancy and quality of life of HCV-positive patients. Moreover, the diagnosis of cirrhosis prompts mandatory screening for esophageal varices and HCC, and influences decisions about timing of antiviral treatment.

How do physicians diagnose liver cirrhosis? Excluding the most advanced stages of the disease, in which the diagnosis is based on clinical observation (e.g. presence of ascites) and, in the absence of clear signs of cirrhosis on ultrasound examination, endoscopy or on blood count (e.g. low platelet count), liver biopsy, and the subsequent histological evaluation of the liver tissue, is the most widely used method for the assessment of liver cirrhosis. However, liver biopsy is invasive and consequently it is associated with a not negligible rate of complications (0.3-0.8%) and even death (0.01-0.3%) [4-7].

Several researchers have proposed non-invasive means to diagnose liver cirrhosis [8-10]. Some procedures need an expensive machine to measure liver stiffness (FibroScan) [11], others are based on a panel of blood tests and a proprietary algorithm called "Fibro Test" [12]. On the other hand, other groups have devised scores based on routinely available analytes [8,13-28]. Some scores were devised and validated to predict advanced fibrosis (e.g., AP, FIB-4, CDS, the Pohl score and the Forns score); some scores were able to predict also or exclusively liver cirrhosis (e.g., GUCI, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, platelet count (PLT), APRI, CISCUN, the Lok score, the Fibrosis index and the King's College score).

The most frequently used scores able to predict cirrhosis and the formulae used to calculate them are reported in Table 1. The table also shows the sensitivity and specificity as calculated in the original report of each method. No score has both 100% sensitivity and specificity. However, some of these scores can be useful in diagnosing cirrhosis, namely those with a high positive predictive value (PPV), and others in ruling out it, namely those with a high negative predictive value (NPV). Almost all scores listed in the table have a relatively low PPV. Only the AST/ALT ratio by Sheth et al. [16] had a PPV of 100%. This finding was not confirmed in other studies [27,29]. Although some scores have a high NPV, but this value should be very close to 100% to make this score a reliable screening test. Notably, positive likelihood ratios(i.e. the probability of a positive test in patients with the disease divided by the probability of the same finding in patients without the disease) are quite low except in the cases of the Fibrosis index and CISCUN ≥ 4, and the negative likelihood ratio(i.e. the probability of a negative test in patients with the disease divided by the probability of the same finding in patients without the disease) are acceptably low only for CISCUN ≤ 1 and APRI ≤ 1.Interestingly, some scores (namely, Lok, CISCUN and APRI) provide two cutoff values to identify patients at a high and low risk of cirrhosis, respectively [13,27]. According to the authors, the patients in the two tails could be spared liver biopsy because of their high or low risk of cirrhosis. Patients in the middle ("gray zone") should undergo liver biopsy because they have an intermediate *a priori* calculated risk of cirrhosis. However, neither of these scores had a NPV of 100% for the low-risk cutoff value and even the PPV was relatively low.

The real drawback of all these studies is that the comparison was made with the standard method for assessing cirrhosis (i.e. liver biopsy) which is *per se* in accurate [30]. The "true gold standard" is the histological evaluation of large surgical biopsies [31], which is difficult to obtain in everyday clinical practice. Classical liver biopsy had a 20% false negative rate for the diagnosis of liver cirrhosis when compared with laparoscopic biopsy in an Italian study [32]. This can occur because the distribution of fibrosis is patchy, and a liver biopsy sample represents only from one hundred-thousandth to one thirty-thousandth of the whole organ, and gives no information about the remaining part of the liver. In fact, histology of long and thick samples provides a better estimate of liver fibrosis than histology of short and thin samples [31,33,34].

In conclusion, the ideal non-invasive procedure for the evaluation of cirrhosis, namely one that is based on routinely-available markers, that is easy-to-calculate, and, above all, that accurately discriminates between patients with or without cirrhosis is not yet within our grasp. Therefore, studies comparing the diagnostic accuracy of the above-described scores with that of the Fibro scan or the Fibro test and liver biopsy are needed to identify the best, if not the ideal, score with which to diagnose non-invasively liver cirrhosis in patients with chronic hepatitis C.

***Corresponding author:** Ivan Gentile, Department of Clinical Medicine and Surgery (Ed. 18), University of Naples Federico II, I-80131 Naples, Italy, Tel: +390817463178; Fax: +390817463094; E-mail: ivan.gentile@unina.it

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Test	Formula	Cut-off value	SE	SP	PPV	NPV	DA	PLR	NLR
AAR [16]	AST/ALT	>1	53.2	100	100	80.7	84.2	NC	0.47
APRI [18]	([AST/ULN]/PLT [10^9/L]) ×100	≤ 1 >1	89.3	75	37.9	97.6	77.1	3.57	0.14
		≤ 2 >2	57.1	92.7	57.1	92.7	87.5	7.81	0.46
CISCUN [27]	Age+AST+PLT+ Prothrombin Activity (Range, 0–4) Age: ≤ 40 years=0; > 40 years=1 AST: ≤ 2 ULN=0; >2 ULN=1 Platelet count(10^9/L): ≥ 160=0; < 160=1; prothrombin activity: ≥ 100%=0; <100%=1	≤ 1 >1	94.1	50.5	32.9	97.1	59.4	1.90	0.12
		<4 ≥ 4	37.3	98.5	86.4	85.9	85.9	24.59	0.64
GUCI [26]	normalized ASTxINRx100/platelet count (10^9/L)	>1	80	78	31.4	96.9	78.2	3.63	0.26
Fibrosis index [28]	8- 0.001×Platelet count (10^9/L) – Albumin (g/dL)	≥ 3.3	67.7	97.9	75	97.1	95.4	32.61	0.33
Lok [13]	log odds= - 5.56 -0.0089 x platelet count (10^3/mm^3) + 1.26 × AST/ALT ratio + 5.27 × INR Formula to calculate final probability: exp (logodds)/(1+exp (logodds))	≤ 0.2	92.2	30	46.2	85.5	54.5	1.32	0.26
		>0.5	54	85.2	70.5	74	72.9	3.66	0.54
Platelet count [20]		<150 (× 10^9/L)	77	88	56	95	NA	6.42	0.26

AAR: AST/ALT Ratio; APRI: AST To Platelet Ratio Index; CISCUN: Cirrhosis Score University Of Naples; GUCI: Göteborg University Cirrhosis Index; ULN: Upper Limit Of Normal Range; SE: Sensitivity; SP: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; DA: Diagnostic Accuracy (Rate Of Correctly-Classified Patients); PLR: Positive Likelihood Ratio; NLR: Negative Likelihood Ratio.

Table 1: Scores used to predict cirrhosis based on noninvasive, routinely-available parameters.

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