Chapter 4

Clinical Application of Non-Invasive Markers of Liver Fibrosis

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Additional information is available at the end of the chapter

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1. Introduction

Liver is one of the most important organs in our body and any damage on this vital organ may be life threatening. Various factors such as toxins, heavy metals, drugs and infection with hepatitis viruses are able to influence on the function of this organ. One of the most important effects of these factors on liver is gradual necrosis of active liver cells and if this disturbance remained untreated, can lead to liver fibrosis, cirrhosis and finally death. Therefore, it is necessary to diagnose the liver fibrosis. Nowadays physicians rely on liver biopsy to evaluate liver fibrosis. This method was named as 'gold standard' for many years, but it seems researchers prefer to say "The best, not the gold standard". Because of liver biopsy limitations (inter-observer variation amongst pathologists, fibrosis staging systems and sampling errors), patients and also physicians like to estimate the liver fibrosis stages and inflammation grades noninvasively. Therefore we had to find non invasive markers for estimation of liver fibrosis stage.

There are various serum based biomarkers, individually or in an algorithm model for estimation of liver fibrosis stage. The list of serum marker algorithms for assessment of liver fibrosis is increasing. [1-6]. In the last decade, the list of liver fibrosis noninvasive tools is increased rapidly. Some of them (such as transient ultrasound elastography [FibroScan], acoustic radiation force impulse [ARFI], magnetic resonance imaging [MRI], doppler analysis, computed tomography [CT], real-time elastography, tissue strain imaging, supersonic shear imaging, diffusion-weighted MRI, magnetic resonance spectroscopy, positron emission tomography [PET] and single photon emission computed tomography [SPECT] [5-8]) are beyond the scope of this chapter. In this chapter, we will focus on serum noninvasive algorithm-based scores surrogate of liver biopsy.

2. List of serum noninvasive algorithm-based scores

There are some serum-based noninvasive markers individually or in an algorithm-based score that proposed instead of liver biopsy. These markers are usable in clinic, because the physicians are able to request analysis of them frequently, during the treatment and for assessing the treatment efficacy, too.

The lists of individual markers are long. The most common of them that are introduced from the past are: aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase, albumin, prothrombin time and gamma glutamyl transferase [2-6]. Now it is proposed that some of these simple tests are not able to predict liver injury accurately. For example Seto showed that an elevation of serum ALT levels is not able to predict liver injury [9].

There are some markers that newly introduced and most well-known of them are: α-2-macroglobulin, apolipoprotein A1, collagen markers such as procollagen I carboxyl terminal peptide (PICP), procollagen III amino terminal peptide (PIIINP), procollagen IV C peptide, procollagen IV N peptide (7-S collagen) and collagen IV, collagenases (metalloproteinase) and their inhibitors (tissue inhibitors of metalloproteinase), glycoproteins such as human cartilage glycoprotein (YKL-40), fibronectin, laminin, osteonectin, tenascin, glycosaminoglycans such as perlecan, hyaluronic acid, decorin, aggrecan, lumican, fibromodulin and the others [2-4, 10-12]. Some of these parameters increased in various diseases such as cancer; therefore before the using of these parameters for estimation of liver fibrosis, we had to exclude the other diseases [13].

It seems that these serum individual markers are useful for establishing the presence, but not absence of the fibrosis. For overcome on this problem, researchers combined the results of panels of markers and proposed various algorithms. Interestingly, in some algorithms improve in diagnostic accuracy of these noninvasive markers were observed. Again the lists of these markers are long. Some of the most well-known of them are:

AST to platelet ratio index, Age-platelet index, PGA index, Forns, Bonacini, De Ritis, PATEL, Leroy, FibroSpect, European Liver Fibrosis score, Fibrometer, Hepascore, SHASTA Index, FIB-4, SteatoTest, NAFLD Fibrosis Score, Cirrhosis discriminate score, BARD score, Hui model, FibroMeter NAFLD, Fibrosis Probability Index, Lok index, Fibro Q and the others.

The aim of this chapter is describing the formula, usability and diagnostic accuracy of some of the most common and available serum noninvasive algorithm-based scores in various liver diseases in a simple manner.

3. Age-Platelet (AP) index

Age and platelet counts are major constituents of this index. This index is calculated according to the following instruction:

Platelets counts $(10^9/l)$: 225 = 0; 200-224 = 1; 175-199 = 2; 150-174 = 3; 125-149 = 4; <125 = 5

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Age (years) <30 = 0; 30-39 = 1; 40-49 = 2; 50-59 = 3; 60-69 = 4; 70 = 5

Sum of age and platelets counts scores are AP index [14]. Various studies proposed that this index is a good index for estimating liver fibrosis stage. For example in a study that carried out by Lackner [15] on HCV patients, area under the ROC curve (AUROC) was 0.740 for prediction of significant fibrosis and for prediction of cirrhosis, AUROC was 0.910 (according to Ishak score). In another study on 62 hepatitis patients, Parsian et al reported an AUROC of 0.818 for discrimination of patients with liver fibrosis vs. control group and an AUROC of 0.518 for discrimination of patients with mild from those with significant fibrosis [16]. There are other studies that discussed diagnostic accuracy of this simple index [17].

4. AST to Platelet Ratio Index (APRI)

APRI score was initially described by Wai et al [18]. This index is dependent to two routine tests, i.e. aspartate aminotransferase and platelet count and simply calculated by this formula:

$$APRI = [(AST, \text{upper limit of normal}) / \text{platelet count } (10^9/L)] \times 100$$

Several studies have suggested that the APRI may be a useful noninvasive marker of hepatic fibrosis. Shin et al showed that in chronic hepatitis B patients, the predictive power of detecting significant fibrosis based on the AUROC is 0.850–0.950 and concluded that this index is a useful indirect marker for estimating significant fibrosis [19].

The AUROC of APRI in HCV patients was reported better in female (0.871) than in male (0.753). Among female cases, an APRI value >1.4 was 91% sensitive and 75% specific in detecting a staging score >2. The corresponding values among male cases were 60% and 77%, respectively [8].

5. AAR index (Deritis index)

There is another simple index that used for evaluation of liver fibrosis and researchers named it AAR index. By dividing the levels of two routine enzymes, i.e. AST and ALT, we are able to calculate it [20].

In a study that carried out on 111 NAFLD patients, researchers found an AUC of 0.61 with an AST/ALT ratio of 0.8 for the prediction of advanced fibrosis [21]. Park et al reported that AST/ALT > or = 1 is highly specific but not diagnostic for the presence of cirrhosis in patients with chronic HCV infection and concluded that the ratio reflects the grade of fibrosis in these patients [22].

6. Fibro Q

Fibro Q is a index that is more complicated than previous indices and is dependent to age (years), AST level, platelet count and also PT International Normalized Ratio (INR). PT INR

measures the extrinsic pathway of coagulation. We are able to calculate this index by the following formula [23].

Fibro Q = [(10 × age (years) × AST × PT INR)/ (PLT × ALT)].

In 2012, Hsieh et al showed that FibroQ is a simple and useful test for predicting significant fibrosis in patients with chronic hepatitis C [24]. In our previous study, we found that this index had a reasonable AUROC for discrimination of patients with liver fibrosis vs. control and not for discrimination of patients with severe liver fibrosis vs. mild liver fibrosis [11].

7. FIB4

Other simple index that related to age (years), AST and ALT levels (U/L) and platelet count, is FIB-4 [25]. By the following formula, one can calculate its value:

FIB-4 = [age (year) × AST (U/L)] / [PLT $(10^9/L)$ × ALT (U/L))$^{1/2}$].

Yang et al reported that FIB-4 index had a significant power for differentiation between patients with mild and significant fibrosis in nonalcoholic fatty liver disease (0.24 ± 0.12 vs. 0.31 ± 0.21, P = 0.010) and the AUROC of FIB4 was 0.810. They reported that FIB4 might be useful as a noninvasive hepatic fibrosis scores for predicting hepatic fibrosis in patients with NAFLD [6]. Shah et al [8] in a study on 541 NAFLD adults found that among various serum based algorithms, FIB4 had better diagnostic accuracy for estimation of liver fibrosis.

8. BARD score

In 2008, Harrison et al proposed an index and named it BARD score. The constituents of this score are body-mass index (BMI), AST/ALT ratio (AAR), and presence of type 2 diabetes mellitus (DMt2). They combined these three simple variables to propose a score for predicting advanced fibrosis. Calculating of this score is simple:

BMI ≥ 28 kg/m^2 = 1 point, BMI <28 kg/m^2 = 0 point; AST/ALT ratio ≥ 0.8 = 2 points, AST/ALT ratio < 0.8 = 0 points; freshly recognized or preexisting DMt2 = 1 point.

A total of 2-4 points (sum of the score of BMI, AST/ALT ratio and presence or absence of DMt2) indicate significant fibrosis [26]. In a study that carried out by Wyszomirska in 2010, validation of this score on nonalcoholic fatty liver disease (NAFLD) evaluated. They reported that this scoring system has value for diagnosis of advanced fibrosis in NAFLD patients and if it is possible using of this system in clinic, most patients don't need to undergo liver biopsy [27]. As another try to determine the validation of this score, Ruffillo et al, evaluated the diagnostic accuracy of this score in NAFLD patients and concluded that this score is useful in identifying patients without severe fibrosis [28].

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9. Enhanced Liver Fibrosis (ELF)

This liver fibrosis score is derived from markers that are not available in routine clinical laboratories [29-30]. It was shown that this score has good diagnostic accuracy for the detection of moderate and severe fibrosis [31].

ELF panel constituents are matrix metalloproteinase 1 inhibitor, hyaluronic acid, and amino-terminal peptide of pro-collagen III.

ELF score can calculate by this formula [32]:

Discriminant score = - 7.412 + [ln (HA) × 0.681) + ln (PIIINP) × 0.775) + ln (TIMP1) × 0.494] + 10

In a study that carried out by Nobili et al on 112 NAFLD subjects, concluded that the ELF test is able to accurately discriminate patients with liver fibrosis and can be used for assessing the level of liver fibrosis in pediatric patients [30].

10. Cirrhosis Discriminate Score (CDS) Bonacini

This simple score is proposed by Bonacini [33] and its constituents are AST/ALT, PT-INR and platelet count in a simple manner as described in table 1 [34]. According to this score, different points are given to ingredients of this index and ultimately they added together.

Parametes/Score	0	1	2	3	4	5	6
INR	<1.1	1.1-1.4	>1.4				
ALT/AST ratio	>1.7	1.7-1.2	1.19-0.6	<0.6			
PLT ×1 000 /mm^3	>340	340-280	279-220	219-160	159-100	99-40	<40

Table 1. Determinants of Bonacini score.

There are various studies that analyzed the accuracy of this index for assessing liver fibrosis. For example in a study by Colli et al [34] on 176 patients with chronic HCV infection, they observed that this score was able to identify 67% of patients with a high (>75%) or low (<10%) probability of cirrhosis, and ultimately 33% of the HCV patients need liver biopsy for assessing their liver fibrosis score. Against the above study, there are some studies that found this score was not able to detect severe fibrosis and observed this score has low power of discrimination [35].

11. Fibrotest (FT)

Fibrotest is consisting of a panel of five biomarkers that proposed for evaluation of liver fibrosis stage. Constituents of this index are alpha2-macroglobulin, haptoglobin, apolipoprotein A1, gamma glutamyl transpeptidase and total bilirubin [36] and the formula of this index is:

Fibrotest=4467 × log [alpha2-macroglobulin (gr/l)] – 1357 × log [haptoglobin (gr/l)] + 0.0821 × [age (years)] +1737 × log [bilirubin (μmol/l)] - 1184 × [apolipoprotein A1 (gr/l)] + 0.301 × sex (male=1, female=0) – 5.054

FT is the most studied test and now there are various studies that proposed this test has considerable ability for discrimination of liver fibrosis without significant divergence among liver diseases. For example its ability on hepatitis C, hepatitis B, alcoholic and nonalcoholic fatty liver disease was shown [37-40].

In a study that carried out by Sebastiani et al [41] the ability of several noninvasive markers including FT on 110 CHB patients were assessed. They found that the Fibrotest and APRI had the highest diagnostic accuracy for discrimination of patients with severe stage of liver fibrosis. In another study on 221 chronic alcoholic liver disease patients, Naveau et al [42] reported that in heavy alcohol drinkers, this test is able to estimate the liver fibrosis stage and by this test is possible to decrease the need for liver biopsy.

12. Fibrometer

Fibrometer is a regression algorithm that proposed for evaluation of liver fibrosis stage in liver diseases. Glucose, AST, ferritin, platelet, ALT, body weight and age are the variables that this score is derived from them. First time, this score proposed by Cales et al [43]. Calculation of this score is simple by the following formula:

Fibrometer= 0.4184 glucose (mmol/l) + 0.0701 AST (IU/l) + 0.0008 ferritin (μg/l) - 0.0102 platelet (G/l) - 0.0260 ALT (UI/l) + 0.0459 body weight (kg) + 0.0842 age (yr) + 11.6226.

Various groups of researchers determined the diagnostic accuracy of this index versus liver biopsy in liver disease. For example Cale et al [44] analyzed the accuracy of this index on 235 NAFLD patients. They observed that this score, in comparison with the other scores such as APRI, had higher accuracy rate for significant fibrosis and had lower misclassification rate. Finally, they concluded that Fibrometer had a reasonable performance.

13. Fibrosis Probability Index (FPI) or sud index

This index is depended on: any history of alcohol use, patient age, cholesterol level, AST activity and HOMA-IR index (Homeostasis model assessment: insulin resistance) [45]. First time Sud et al proposed this index and published the results of their study in hepatology journal [46]. They considered and analyzed thirty-five variables in 176 HCV patients and proposed a fibrosis probability index (FPI) for estimation of the liver fibrosis stages by some of these parameters. In addition, they tested the accuracy of this index in another study consists of 126 patients.

Fibrosis probability index (FPI) = 10.929 + (1.827 × Ln AST) +(0.081 × age) + (0.768 × past alcohol use) + (0.385 × HOMA-IR) – (0.447 × cholesterol).

It seems, this index that proposed by this research team can be used as a noninvasive tools for estimation of liver fibrosis and this confirmed by others [47].

14. Forns score

Another score for assessing the liver fibrosis score is Forn score [48]. Constituents of this score are age, platelet count, GGT, and cholesterol. One can calculate this index by this equation:

Forns index: [7.811 - 3.131 × ln(platelet count) + 0.781 × ln(GGT) + 3.467 × ln(age) - 0.014 × cholesterol]

In their study on 476 CHC patients, Forn et al reported the AUROC of this score was 0.86 for the estimation group and 0.81 for the validation group. Yang et al [6] evaluated the accuracy of Forn score in 77 NAFLD children and according to the severity of their necroinflmmatory injuries, divided the patients to two groups: mild fibrosis (stage 0-1) vs. significant fibrosis (stage 2-4). They analyzed diagnostic accuracy of some simple algorhitms such as AAR, APARI and FIB-4, in addition to Forn score. They observed that among these algorithms, only APRI and FIB4 had a significant difference between patients with mild and significant fibrosis.

15. Hepascore

Hepascore is a more complicated score for estimation of liver fibrosis stage. Age, gender, bilirubin, GGT, hyaluronic acid and alpha2-macroglobulin are constituents of this score [49]. In this score that was proposed by Adams et al for the first time, they added a single direct biomarker of hepatic fibrosis i.e. hyaluronic acid in their algorithm.

By this formula, we can calculate this score:

Hepascore = y/(1 + y), where y = exp (-4.185818 –0.0249 × age + 0.7464 ×gender (male = 1, female = 0) + 1.0039 ×α2-macroglobulin + 0.0302 ×hyaluronic acid + 0.0691 × bilirubin – 0.0012 × GGT.

In their study, Adams et al on 221 HCV patients reported AUROCs of 0.82, 0.90 and 0.89 for the diagnosis of significant fibrosis, extensive fibrosis and cirrhosis, respectively.

In another study on patients with chronic hepatitis C virus, Becker et al [50] reported that Hepascore is able to predict liver fibrosis and maybe by this score a need for liver biopsy is decrease. Bourliere et al reported that the accuracy of Hepascore for excluding the cirrhosis was excellent [51].

16. HUI model

Hui et al performed a retrospective study on 235 CHB patients and by univariate analysis and multivariate logistic regression generated this predictive model. They concluded that this model is able to predict absence of significant fibrosis, accurately. Body mass index (BMI), platelet count,

serum albumin, and total bilirubin levels are the constituents of this model [52]. Calculation of this model is very simple and we can calculate this model score by this following formula.

Hui score = 3.148 + 0.167× BMI + 0.088×bilirubin - 0.151× albumin - 0.019 × platelet

In a study that carried out by Sebastiani on 110 CHB patients, some indices such as, APRI, Forns' index, Hui's model and Fibrotest were determined. They reported that performance of these methods for discrimination of patients with significant fibrosis as positive predictive values (PPV) was excellent, i.e. 100% for Forns and greater than 92% for APRI, GUCI, Fibrotest and Hui model [41].

17. Leroy score or MP3 model

Leroy et al used extracellular matrix component i.e. procollagen III amino terminal peptide (PIIINP) and matrix metalloproteinases-1 (MMP-1) for proposing this model. They determined serum levels of hyaluronate (HA), PIIINP, MMP-1, MMP-2, MMP-9 and their tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2) in 194 chronic hepatitis C patients and 194 healthy people. They found that six markers (MMP-2, TIMP-1, HA, PIIINP, MMP-1 and MMP-9) were significantly correlated with liver fibrosis and by using regression model they proposed their index according to the following formula:

MP3= 0.5903 × log PIIINP (ng/mL) - 0.1749 × log MMP-1 (ng/mL)

They showed that their scoring system is able to differentiate between mild and significant fibrosis and pointed that maybe this score can provide a useful tool for evaluating liver fibrosis [53].

18. Lok index

Another simple scoring system for estimation of liver fibrosis stage that proposed by Lok et al is Lok index [54]. This index is based on serum AST and ALT levels, platelet count and PT-INR. One can calculate this index according to a simple formula:

Lok index = - 5.56 - 0.0089 × platelet $(10^3 mm^3)$ + 1.26 × AST/ALT ratio + 5.27 × INR

For this scoring system two cut points introduced: 0.2 to rule out cirrhosis and 0.5 to confirm cirrhosis. All values that are between these cut points are considered indeterminate. Lok et al in their cohort study on 1,141 patients with CHC, introduced this score and reported an AUROC of 0.78-0.81 to detect cirrhosis.

There are various studies that used this score for estimation of liver fibrosis stage. Castera et al reported that this index has a reasonable performance [55]. Masuzaki studied 386 CHC patients for determining the diagnostic accuracy of this index in comparison with the other noninvasive indices such as APRI. They reported that Lok index and APRI were correlated with histological fibrosis stages (rho=0.581, and 0.460, respectively) and reported an AUROC (95% CI) of Lok index and APRI of 0.787 (0.741-0.832) and 0.692(0.639-0.745), respectively [56].

19. FIBROSpect or PATEL index

Patel et al [57] by combing the serum levels of hyaluronic acid (HA), tissue inhibitors of metalloproteinase 1 (TIMP-1) and alpha2-macroglobulin (A2M), introduced this index that is also has another name, FibroSpect. Against the much scores that are based on the routine and simple laboratory tests, this score is based on the specific and non routine laboratory test. In a study that carried out by their research team on 696 HCV patients, they introduced this scoring system and reported an AUROC of 0.830 for the diagnosis of significant fibrosis.

There are some studies that confirmed the diagnostic accuracy of this scoring system and reported the excellency of this scoring system for estimation of liver fibrosis [58].

20. PGA index

PGA index can be calculated by the sum of three tests, i.e., P, prothrombin time; G, gamma-glutamyl transpeptidase and A, apoliprotein AI and is ranged from 0 to 12 [59].

There are various studies that showed the accuracy of this index in patients with various chronic liver diseases [60-61]. These studies reported that this score has highest accuracy for detecting cirrhosis in patients with alcoholic liver disease.

Against the above mentioned studies, Yang et al didn't find similar results [6]. In their study on 77 NAFLD children, diagnostic accuracy of PGA index (AUROC=0.45) in addition to the other tests such as AAR (0.53), APRI (0.70), Forns index (0.73) and FIB-4 (0.81) were compared. They concluded that among these indices, APRI and FIB4 had the highest performance for discrimination of patients with mild from significant fibrosis.

21. SHASTA index

This index first time introduced by Kelleher et al [62]. They studied 95 patients that had HIV/HCV co-infection and determined the serum levels or activity of ALT, AST, APRI, albumin, total bilirubin, hyaluronic acid (HA) and YKL-40. They observed that among these tests, only serum HA, albumin and AST were useful for discrimination of mild from advanced fibrosis. Finally they constructed a predictive model by these factors (HA, albumin and AST) and named it SHASTA Index. This index can be calculated by the following formula:

Risk score = -3.84 +1.70 (1 if HA 41–85 ng/ml, 0 otherwise) +3.28 (1 if HA>85 ng/ml, 0 otherwise) +1.58 (albumin <3.5 g/dl, 0 otherwise) +1.78 (1 if AST >60 IU/l, 0 otherwise).

A cut off of 0.8 of this index showed specificity and positive predictive value of 100%. A cutoff of <0.30 was associated with a sensitivity and negative predictive value of 88% and 94%, respectively.

22. STEATO test panel

This index is an index that proposed by researchers for estimation of liver steatosis in alcoholic, NAFLD, hepatitis C and B patients. By combining the simple parameters such as age, sex, and BMI with AST, ALT, bilirubin, GGT, alpha2-macroglobulin, apolipoprotein AI, haptoglobin, glucose, cholesterol, and triglyceride this index proposed. First time, Poynard et al proposed this index by the above mentioned variables. They found that steatoTest is able to predict liver steatosis and can decrease the need for liver biopsy [63].

In a study that carried out by Lassailly, diagnostic accuracy of this panel confirmed on two hundred and eighty-eight patients with morbid obesity and concluded that this panel is able to reduce the need for biopsy [64].

23. NAFLD fibrosis score

Components of this score that proposed by Angulo et al are age (years), body mass index, impaired fasting glucose (IFG) or presence the diabetes, AST, ALT, platelet count, and serum albumin levels [65]. They proposed this index as a predictive model for estimation of liver fibrosis. By using the following formula, we are able to calculate this scoring system.

NAFLD fibrosis score =-1.675 + 0.037× age (years) + 0.094 ×BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 ×platelets $(10^9/l)$ – 0.66×albumin (gr/dl)

A score value < -1.455 (lowest cut point) is able to exclude advanced liver fibrosis and a value > 0.676 (high cutoff) is able to predict advanced liver. Values between these two values are considered as indeterminate liver fibrosis and maybe patients with this result had to undergo liver biopsy.

Shah et al studied diagnostic accuracy of this scoring model in 541 adults with NAFLD for estimation of liver fibrosis and found an AUROC (95% confidence interval [CI]) of 0.768; (0.720 – 0.816) for this model [8]. In another study that carried out by Ruffillo et al on 138 NAFLD patients, they concluded that this scoring model is useful for identifying patients without severe fibrosis, but it has some indeterminate results [28]. In another study that carried out by Yang et al on 77 NAFLD children, AUROC of NAFLD fibrosis score was determined 0.58 for discrimination of mild from significant liver fibrosis [65].

24. Göteborg University Cirrhosis Index (GUCI index)

First time, this index proposed by Kandemir et al [66].They analyzed blood samples from 68 CHC patients for aspartate aminotransferase, prothrombin INR, and platelet count and found

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a strong association between the fibrosis stage and their proposed index. The GUCI index can be calculate by this formula:

GUCI = Normalized AST× prothrombin-INR ×100 / Platelet count $(\times 10^9/L)$

They concluded that this index can discriminate patients with severe fibrosis (stage 3-4) from those without severe fibrosis (stage 0-2).

25. King score

This score introduced by Cross et al and is a simple index that derived from age, AST activity INR and platelet count, as follow for the estimation of liver fibrosis.

King's Score = [age (years) × AST (IU/l) × INR] / platelets$(10^9/L)$

Cross et al in their study on 923 CHC patients introduced this scoring model. They reported AUROCs for predicting of cirrhosis and significant fibrosis of 0.91 and 0.79 (respectively) and the results was confirmed in a validation study. They concluded that this scoring is an applicable index for predicting of cirrhosis in chronic hepatitis C patients [67].

Diagnostic accuracy of this scoring model determined in another study. Cross et al performed another study on 187 CHC patients and evaluated the diagnostic accuracy of King score (KS) model and Fibroscan (FS). For diagnosis of significant fibrosis, AUROCs for FS, KS and FS + KS were 0.83, 0.82 and 0.85 (respectively) and for the diagnosis of cirrhosis these values were 0.96, 0.89 and 0.93, respectively [68].

26. Predicted Liver Fibrosis score (PLF score)

Bota et al in their study on 212 CHC patients proposed a scoring system for estimation of liver fibrosis and named it predicted liver fibrosis score [69]. Constituents of their score are transient elastography (TE), APRI score, Forns score, FIB-4 score and King score. Their scoring formula is:

Predicted liver fibrosis score (PLF score) = 0.956 + 0.084 × TE – 0.004 × King Score + 0.124 × Forns score + 0.202 × APRI score.

They found a good correlation (r = 0.68) for their score with liver fibrosis and concluded that this complex formula that derived from the other algorithms, is able to predict sever fibrosis and its performance is better than TE.

The cut off values, AUROC, positive and negative predictive values of the above mentioned algorithms for estimation of liver fibrosis severity in chronic viral hepatitis and/or NAFLD/NASH is summarized in the table 2.

Noninvasive Test	Variables	Disease	Cut off	AUROC	PPV	NPV	Explanations
AAR	AST and ALT	HCV	≥1	NA	73.7	88.1	
AP	Age and platelets counts	HCV	≥6	t=0.76 v=0.69	96	NA	
APRI	AST and platelets counts	HCV	≥1.5 ≤0.5	t=0.80 v=0.88	91	90	≈Ishak 3-6 ≈Ishak 0-2
BARD score	BMI, AST, ALT and type 2 diabetes mellitus	NAFLD/ NASH	2-4 2	NA	43 27-81	96 45-95	Advanced liver fibrosis (F3-4)
CDS	PT-INR, AST, ALT and platelets counts	HCV	>8	NA	92.6	NA	≈Knodell 3-4
ELF	Matrix metalloproteinase 1 inhibitor, hyaluronic acid, and aminoterminal peptide of pro-collagen III	HBV HCV NAFLD	>0.102 <0.102	0.8	35	92	≈ Scheuer 3-4 ≈ Scheuer 0-2
FIB4	Age, AST, ALT and platelet count	HCV	<1.45 >3.25	0.76	65	90	≈Ishak <4-6 ≈Ishak ≥4-6
Fibro Q	Age, AST, platelet count and PT-INR	HBV HCV	1.6 2.6	F2-4= 0.783 F4=0.791	93 11.3	41 100	
Fibrometer	Glucose, AST, ferritin, platelet, ALT, body weight and age	NAFLD	NA	NA	88	92	
FIBROSpect	Hyaluronic acid, tissue inhibitors of metalloproteinase 1 and alpha2-macroglobulin	HCV	0.82-0.97	NA	90	58	For stage ≥F2
FORNS SCORE	Age, platelet count, GGT, and cholesterol	HCV	≥6.9 <4.2	t=0.86 v=0.81	66	96	≈ Scheuer 2-4 ≈ Scheuer 0-1
FPI	Alcohol use, age, cholesterol, AST and HOMA-IR index	HCV	<0.2 ≥0.8	t=0.84 v=0.77	87	77.4	≈F0-F1 ≈F2-F4
FT	Alpha2-macroglobulin, haptoglobin, apolipoprotein A1, gamma glutamyl transpeptidase and bilirubin	HCV HBV	0.75-1.00 ≈F4 0.73-0.74≈F3-F4 0.59-0.72≈F3 0.49-0.58≈F2 0.32-0.48≈F1-F2 0.28-0.31≈F1 0.22-0.27≈F0-F1 0.00-0.21≈F0	t=0.83 v=0.87	78 76 76 67 61	- - - - 85 91 92 94	

Noninvasive Test	Variables	Disease	Cut off	AUROC	PPV	NPV	Explanations
Göteborg University Cirrhosis Index (GUCI index)	AST,PT-INR, and platelet count	HCV	NA	F4=0.85	F4=31	F4=97	
Hepascore	Age, gender, bilirubin, GGT, hyaluronic acid and alpha2-macroglobulin	HCV	≥0.5 <0.5	t=0.85 v=0.82	88	98	≈F2-F4 ≈F0-F1
HUI model	BMI, platelet count, albumin and bilirubin	HBV	<0.15	t=0.803 v=0.765 entire cohort=0.791	NA	NA	
King Score	Age, AST, INR and platelet count	HCV	≥12.3 ≥16.7	F3-6=0.79 F5-6=0.91	81 56	77 96	
Leroy score or MP3 model	Procollagen III amino terminal peptide and matrix metalloproteinases-1	HCV	NA	≥F2, 0.82	≥F2=89	≥F2=84	
Lok index	AST, ALT, platelet count and PT-INR	HCV	NA	F4=0.78-.0.81	F4=32-75	F4=84-91	
NAFLD fibrosis score	Age, BMI, impaired fasting glucose (IFG) or presence the diabetes, AST, ALT, platelet count, and serum albumin levels	NAFLD/NASH	-1.455 0.676	NA	30-56 82-90	88-93 85-86	
PLF score	Transient elastography, APRI score, Forns score, FIB-4 score and King score	HCV	F ≥ 1= 1.77 F ≥ 2= 2.88 F ≥ 3=2.47 F=4, = 2.98	0.76 0.78 0.86 0.97	99.5 96.4 85.1 70.7	18.1 21.4 78.6 99.4	
SHASTA index	ALT, AST, APRI, albumin, total bilirubin, hyaluronic acid and YKL-40	HCV	>.08 <0.3	0.87	100	94 21.4	Ishak ≥3 Ishak ≤2
STEATO test panel	ALT, α2-macroglobulin , apolipoprotein A-I, haptoglobin, total bilirubin, GGT, cholesterol, triglycerides, glucose, age, gender and BMI	NAFLD	0.3 0.5 0.7	NA	22 29 33	100 95 92	For predicting liver steatosis greater than 5%.

Table 2. An alphabetical order of various noninvasive serum indices to detect liver fibrosis in patients with chronic viral hepatitis and/or NAFLD/NASH.

Abbreviations

AUROC, area under receiver operating characteristic curve; NA, Not available; PPV, positive predictive value; NPV, negative predictive value; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MMP, metalloproteinases TIMP, tissue inhibitors of matrix metalloproteinases; HOMA-IR, homeostasis model assessment of insulin resistance; INR, international normalized ratio for prothrombie; t, training group; v, validation group [3, 15, 22,23, 52, 63, 67, 69, 71].

27. Conclusion

Liver biopsy still has an important role in the estimation of liver fibrosis stage, but it is not very far that this invasive method will completely replace with the other noninvasive methods such as serum based biomarkers [70]. Therefore development of non-invasive methods is still needed and we should work harder for finding an appropriate method. Maybe with finding some appropriate biomarkers, we can completely obsolete the liver biopsy.

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