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Sequential algorithms combining non-invasive markers and biopsy for the assessment of liver fibrosis in chronic hepatitis B

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Abstract

AIM: To assess the performance of several non-invasive markers and of our recently proposed stepwise combination algorithms to diagnose significant fibrosis (F $\geqslant$ 2 by METAVIR) and cirrhosis (F4 by METAVIR) in chronic hepatitis B (CHB).

METHODS: One hundred and ten consecutive patients (80 males, 30 females, mean age: 42.6 ± 11.3) with CHB undergoing diagnostic liver biopsy were included. AST-to-Platelet ratio (APRI), Forns' index, AST-to-ALT Ratio, Goteborg University Cirrhosis Index (GUCI), Hui's model and Fibrotest were measured on the day of liver biopsy. The performance of these methods and of sequential algorithms combining Fibrotest, APRI and biopsy was defined by positive (PPV) and negative (NPV) predictive values, accuracy and area under the curve (AUC).

RESULTS: PPV for significant fibrosis was excellent (100%) with Forns and high (> 92%) with APRI, GUCI, Fibrotest and Hui. However, significant fibrosis could not be excluded by any marker (NPV < 65%). Fibrotest had the best PPV and NPV for cirrhosis (87% and 90%, respectively). Fibrotest showed the best AUC for both significant fibrosis and cirrhosis (0.85 and 0.76, respectively). Stepwise combination algorithms of APRI, Fibrotest and biopsy showed excellent performance (0.96 AUC, 100% NPV) for significant fibrosis and 0.95 AUC, 98% NPV for cirrhosis, with 50%-80% reduced need for liver biopsy.

CONCLUSION: In CHB sequential combination of APRI, Fibrotest and liver biopsy greatly improves the diagnostic performance of the single non-invasive markers. Need for liver biopsy is reduced by 50%-80% but cannot be completely avoided. Non-invasive markers and biopsy should be considered as agonists and not antagonists towards the common goal of estimating liver fibrosis.

INTRODUCTION

Chronic hepatitis B (CHB) remains a serious global health concern. Approximately 350 million people are chronically infected, and 500 000 to 1.2 million deaths per year are attributed to HBV-associated complications[1]. Among patients with active viral replication, cirrhosis will develop in 15 to 20 percent within five years[2]. For patients with cirrhosis, acute exacerbation can occur and the disease may progress to end stage complications[2]. The histopathological pathway of progressive liver disease is characterised by the formation and accumulation of fibrosis, leading to increasing distortion of the hepatic architecture, that is the hallmark of evolution to cirrhosis. Liver fibrosis is the result of chronic injury and plays a direct role in the pathogenesis of hepatocellular dysfunction and portal hypertension. Current guidelines recommend that patients with HBV-DNA > 10^5 copies/mL and persistent or intermittent elevation in aminotrasferase levels should be evaluated further with liver biopsy, that is the gold standard for the assessment of fibrosis[3]. This procedure provides information on the severity of necroinflammatory activity and on the stage of fibrosis, features which are essential for estimating prognosis and the need for antiviral therapy[2,4,5]. However, biopsy is a costly procedure associated with side effects and some risks[6-8]. It also has limitations in underestimating liver fibrosis with small samples and is prone to intra- and inter-observer variation[9-12]. Moreover, several studies suggested that liver biopsy is far away from being a perfect gold standard since its performance is size-dependent[9,13-14]. Some studies would suggest that an adequate liver biopsy sample should contain more than 5 portal tracts and be at least 15 mm in length[11,15,16]. In a critical review of the literature concerning the use of liver biopsy in chronic viral hepatitis,

Guido and Rugge suggest that in an era of evidence-based medicine the use and interpretation of liver biopsy is very often flawed by unacceptable methodological limits and that a biopsy sample of 20 mm or more containing at least 11 complete portal tracts should be considered reliable for adequate grading and staging[14]. Other authors have recommended even bigger samples[17]. The pathologist need for obtaining a liver sample of adequate size is in contrast with the patient's need of a procedure causing limited pain and with the clinician's need of a safe procedure. A French survey which interviewed 1177 general practitioners concluded that liver biopsy may be refused by up to 59% of patients with chronic hepatitis C and that 22% of the physicians share the same concern regarding this invasive procedure[18]. In this regard, a recent survey assessing the consensus among Italian hepatologists on when and how to take a liver biopsy in chronic hepatitis C showed great divergence in the management of the same subgroup of patients[19]. Considering these limitations and patient reluctance to undergo liver biopsy, a great interest and many studies have been recently dedicated to the development of non-invasive markers as surrogates of liver biopsy. Most of the studies on non-invasive markers of liver fibrosis have been conducted in chronic hepatitis C and few data are available on the applicability of this approach to patients with CHB. Several markers have been described with variable diagnostic accuracy in hepatitis C, but the expected rate of misdiagnosis for each single test is still around 20%[11,20]. To overcome this limitation, recently we have developed and validated sequential algorithms that combine non-invasive markers with liver biopsy[21]. This approach allowed us to reach excellent diagnostic accuracy (> 95%) for both significant fibrosis and cirrhosis in patients with chronic hepatitis C with around 50%-70% reduced need of taking a liver biopsy. We have now assessed the performance of several non-invasive markers and of our stepwise algorithms in patients with CHB.

MATERIALS AND METHODS

Patients

This study included 110 consecutive patients with a diagnosis of chronic HBV infection, as defined by positive hepatitis B surface (HBsAg) for at least 6 mo, who underwent a diagnostic percutaneous liver biopsy at the Department of Clinical and Experimental Medicine at the University of Padova between March 2003 and June 2005. All patients were positive for serum HBV-DNA by polymerase chain reaction (PCR) and had compensated chronic HBV infection. The exclusion criteria were any other cause of chronic liver disease, and clinical signs of liver cirrhosis, co-infection with HCV or HIV and co-morbidities that could confound the results of the non-invasive markers adopted, clinical signs of liver cirrhosis. These included current alcohol intake (> 20 g/die), haemolysis, Gilbert's syndrome, and hematologic causes of thrombocytopenia. All biopsies were obtained with the 16G Menghini type needle. To limit the risk of fibrosis underestimation, patients with biopsy samples shorter than 1.5 cm or containing less than 7 portal tracts were excluded[11,15,16,22]. Informed consent was obtained from all patients participating in the study that was conducted according to the rules of the Declaration of Helsinki.

Virologic assays

HBsAg, hepatitis Be antigen (HBeAg), and antibodies to HBeAg and HDV were determined using commercial assays (Roche Diagnostics, Basel, Switzerland). HBV DNA level was measured by real-time PCR and expressed as $\log_{10}$ copies/mL.

Histological assessment

Liver biopsies were fixed in formalin and embedded in paraffin. The slides were stained with hematoxylin-eosin, van Gieson stain for collagen, PAS after diastase digestion and Perls' Prussian blue method. The slides were evaluated by a single Pathologist (MG) who was unaware of the clinical data. Fibrosis was scored according to the METAVIR system, which was previously applied in other reports on CHB[23-25]. Fibrosis was staged from F0 to F4: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Significant fibrosis was defined as a METAVIR score of F2 or more ($F \geqslant 2$), cirrhosis was defined as a METAVIR score of F4.

Non-invasive markers of liver fibrosis

All patients were evaluated for AST-to-Platelet Ratio Index (APRI), Forns' index, AST-to-ALT ratio (AAR), Hui's model, Goteborg University Cirrhosis Index (GUCI), Fibrotest. The rationale for the choice of the non-invasive markers was their simplicity together with a reported good performance for APRI, Forns' index, AAR and GUCI, and the high number of validation studies reported together with a good performance for Fibrotest[26-30]. Hui's model, based on a combination of body mass index, total bilirubin, platelets and albumin, was chosen since it is the only non-invasive marker developed in patients with hepatitis B[31]. The markers were all calculated using fasting serum samples obtained on the same day of liver biopsy. For this purpose platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamiltranspeptidase (γGT), cholesterol levels, haptoglobin, apolipoprotein A1, alpha-2-macroglobulin, total bilirubin, prothrombin time (international normalised ratio, INR), albumin were routinely determined using validated methods. Fibrotest results were kindly provided by T. Poynard, Universite Paris VI, Paris, France. For all the non invasive methods the cut-off values indicated in the original reports were applied[26-31].

Stepwise combination algorithms for liver fibrosis

The algorithms recently developed by us for patient with chronic hepatitis C were applied to this cohort of hepatitis B patients. The diagnostic algorithms were developed by modelling the best algorithm for liver fibrosis in different clinical scenarios, as described in a previous study[21]. Algorithm A (for significant fibrosis, $F \geqslant 2$ by METAVIR) and algorithm B (for cirrhosis, F4 by METAVIR) are described in Figure 1A and B.

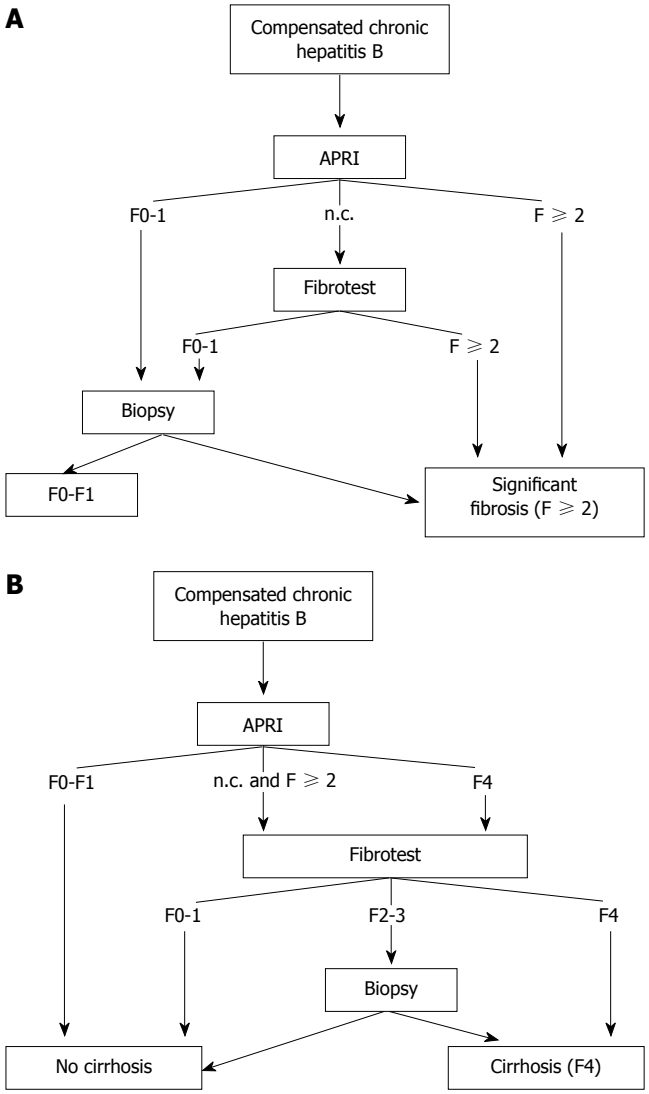

Figure 1 **A**: Algorithm A for detection of significant fibrosis (F ⩾ 2 by METAVIR) in HBV patients. F0-1 by APRI is intended as APRI < 0.5. F ⩾ 2 by APRI is intended as APRI > 1.5. n.c. by APRI is intended as APRI > 0.5 and < 1.5; **B**: Algorithm B for detection of cirrhosis (F4 by METAVIR) in HBV patients. F0-1 by APRI is intended as APRI < 0.5. F ⩾ 2 by APRI is intended as APRI > 1.5. F4 by APRI is intended as APRI ⩾ 2. n.c. by APRI is intended as APRI > 0.5 and < 1.5.

Statistical analysis

The primary endpoints were the detection of significant fibrosis (F ⩾ 2) and cirrhosis (F4). These thresholds were selected since the first is generally considered an indication for antiviral therapy and the second requires a specific management and follow-up. Descriptive results were expressed as mean ± standard deviation (SD) or number (percentage) of patients with a condition. Kappa statistics was used to measure intra-observer variation in the histopathological evaluation of the degree of fibrosis. The performance of the non-invasive methods for liver fibrosis was measured as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and likelihood ratios (LR). Sensitivity, specificity, PPV, NPV and accuracy were expressed as percentage. The diagnostic value of the non-invasive methods was expressed using the Area Under the receiver operating characteristic Curve (AUC) and its corresponding 95% confidence intervals (CI).

Table 1 Demographic, laboratory and histological characteristics of the 110 patients with chronic hepatitis B

Males *n* (%)	80 (72.7)
Age (mean yr ± SD)	42.6 ± 11.3
BMI (kg/m^2)	24.2 ± 3.3
AST (mean IU/L ± SD)	73.4 ± 61.2
AST / ULN ratio (mean ± SD)	1.75 ± 1.47
ALT (mean IU/L ± SD)	144.5 ± 148.0
ALT / ULN ratio (mean ± SD)	3.14 ± 3.3
γGT (mean IU/L ± SD)	46.4 ± 49.1
γGT / ULN ratio (mean ± SD)	0.81 ± 0.84
Bilirubin (mean μmol/L ± SD)	13.9 ± 6.48
PLT (mean 10^9/L ± SD)	194.6 ± 56.9
Albumin (mean g/L ± SD)	42.7 ± 5
Cholesterol (mean mg/dL ± SD)	177.5 ± 32.9
INR (mean value ± SD)	1.12 ± 0.1
Haptoglobin (mean g/L ± SD)	1.05 ± 0.6
α_2M (mean g/L ± SD)	2.67 ± 0.84
ApoA1 (mean g/L ± SD)	1.48 ± 6.48
Viral load (mean log$_{10}$ cp/mL ± SD)	2.15 ± 1.18
HBeAg positive cases (%)	20 (18.2)
HDV co-infected cases (%)	8 (7.3)
Staging *n* (%)	
F0	15 (13.6)
F1	20 (18.2)
F2	40 (36.4)
F3	13 (11.8)
F4	22 (20.0)

SD: standard deviation; ULN: upper limits of normal;PLT: platelets; INR: international normalised ratio; α_2M: alpha-2-macroglobulin; ApoA1: apolipoprotein A1.

RESULTS

Demographic, laboratory and histological features of the 110 patients with CHB are described in Table 1. Mean age was 42.6 ± 11.3 years and 80 patients (72.7%) were males. Twenty cases (18.2%) were HBeAg positive and 8 cases (7.3%) were co-infected with HDV. Prevalence of significant fibrosis (F ⩾ 2) and cirrhosis was 68.2% and 20%, respectively. The mean length of liver specimens was 1.69 ± 0.29 cm and mean complete portal tracts number was 9.9 ± 3.6. Intra-observer agreement was assessed by re-evaluating a subset of 50 randomly chosen samples: k value was higher than 0.90.

Performance of non-invasive methods for the diagnosis of significant fibrosis (F ⩾ 2)

Seventy-five patients (68.2%) had significant fibrosis as defined by METAVIR fibrosis stage F ⩾ 2. The performance of the non-invasive markers in diagnosing significant fibrosis is shown in Table 2. AAR was not included here since it identifies cirrhosis but does not discriminate significant fibrosis. Fibrotest, GUCI and Hui' s model classified all cases while both APRI and Forns' index were unable to classify one third of the patients. All the methods showed high PPV (> 90%) for significant fibrosis. Forns' index had an excellent 100% PPV with a 6.9 cut-off but its diagnostic value was quite low, at 0.63 AUC (95% CI: 0.50-0.76). The NPV was quite low for all the non-invasive markers (always < 65%), so that significant fibrosis could not be reliably excluded by any of these markers. Fibrotest, APRI and GUCI showed good overall

Table 2 Performance of the non-invasive methods and of the algorithm A in detecting significant fibrosis (≥ F2 by METAVIR) in patients with CHB

	Fibrotest	Forns		APRI		GUCI	Hui's model	Algorithm A
Classified cases (%)	100	63.3		66.2		100	100	100
Cut-off	F2	4.2	6.9	0.5	1.5	0.2	0.15	na
Sensitivity (%)	80.8	58.3	14.6	70.8	27.1	66.7	50	100
Specificity (%)	90	78.3	100	87	95.7	95.7	90.9	91.3
PPV (%)	95.5	90.6	100	94.1	97.9	97.9	96.3	96
NPV (%)	64.3	53.5	35.9	62.2	39.7	58.9	45.8	100
LR +	8.1	2.69	0.146	5.45	6.3	15.5	5.49	11.49
LR -	0.21	0.53	0.85	0.36	0.76	0.35	0.55	0
Accuracy (%)	83.3	64.8	42.3	76.1	49.3	76.1	62.2	97.2
AUC (95% CI)	0.85 (0.75-0.95)	0.63 (0.50-0.76)		0.72 (0.58-0.86)		0.81 (0.70-0.92)	0.71 (0.56-0.86)	0.96 (0.92-1)

APRI: aspartate aminotransferase to platelets ratio; GUCI: Goteborg University Cirrhosis Index; na: not available; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; AUC: area under the curve; CI: confidence interval.

Table 3 Performance of the non-invasive methods and of the algorithm B in detecting cirrhosis (F4 by METAVIR) in patients with CHB

	Fibrotest	APRI	AAR	GUCI	Algorithm B
Classified cases (%)	100	66.2	100	100	100
Cut-off	F4	2	1	1	na
Sensitivity (%)	55.6	42.9	7.1	21.4	92.9
Specificity (%)	96.3	85.4	94.7	91.2	96.5
PPV (%)	90	53.8	82.4	73.7	87.5
NPV (%)	87.1	91.1	81.4	83.8	98.3
LR +	15	2.94	1.34	2.43	26.5
LR -	0.46	0.67	0.98	0.86	0.07
Accuracy (%)	86.1	79.2	77.5	77.5	95.8
AUC (95% CI)	0.76 (0.67-0.85)	0.64 (0.53-0.75)	0.51 (0.39-0.62)	0.56 (0.47-0.65)	0.95 (0.90-1)

accuracy (83.3%, 76.1% and 76.1% respectively). Among the non-invasive methods, Fibrotest showed the best diagnostic value as indicated by an AUC of 0.85 (95% CI: 0.75-0.95).

Performance of non-invasive methods for the diagnosis of cirrhosis (F4)

Twenty-two patients (20%) had cirrhosis as defined by METAVIR fibrosis stage F4. The performance of the non-invasive markers in diagnosing cirrhosis is shown in Table 3. Forns' index and Hui's model were not considered here since they do not discriminate between significant fibrosis and cirrhosis. Fibrotest had the best PPV (90%) and very good accuracy (86.1%). The overall diagnostic value of Fibrotest was quite good, with 0.76 AUC (95% CI: 0.67-0.85). APRI showed good NPV and accuracy but the diagnostic value, described by AUC, was rather low (0.64; 95% CI: 0.53-0.75). The other markers showed an even lower diagnostic value, with AUCs around 0.5.

Performance of stepwise algorithms for the diagnosis of significant fibrosis and cirrhosis

The performance of stepwise algorithms for the detection of significant fibrosis (algorithm A) and cirrhosis (algorithm B) is reported in Tables 2 and 3, respectively. Table 4 describes in details the number of tests and of liver biopsies needed when the two algorithms were applied to our cohort of patients with CHB. The stepwise algorithm for significant fibrosis (algorithm A) excluded the presence of F ≥ 2 by METAVIR with excellent 100% NPV. It also showed a very high accuracy, with excellent 97.2%, and it presented with an excellent diagnostic value, with 0.96 AUC (95% CI: 0.92-1). This algorithm permitted avoidance of liver biopsy in about half of the cases (Table 4). Algorithm B showed excellent 95.8% accuracy and 0.95 AUC (95% CI: 0.90-1) in the identification of cirrhosis. Furthermore, this algorithm reduced by more than 80% the need for liver biopsy (Table 4).

DISCUSSION

Several non-invasive markers of liver fibrosis have been recently described, mainly in patients with hepatitis C, but their implementation in clinical practice as a substitute for invasive liver biopsy has been delayed by lack of adequate accuracy in assessing individual patients. Indeed, according to the most recent International Guidelines and Recommendations, inter-laboratory variability, lack of reproducibility and, most important, an expected rate of misdiagnosis of at least 20% do not yet allow the use of these methods in clinical practice[11,32]. Since the diagnostic performance of described non-invasive markers is variable depending on the stage of fibrosis and other patient characteristics, they can be used to reduce rather than completely substitute the need for liver biopsy. Recently we have described stepwise combination algorithms based on

the use of two non-invasive markers (APRI and Fibrotest) and liver biopsy[16]. When applied to patients with chronic hepatitis C these algorithms were proven to correctly identify significant fibrosis and cirrhosis with high (> 95%) accuracy and 50%-70% reduction in liver biopsy. Very few studies have investigated the role of non-invasive markers of liver fibrosis in hepatitis B. Indeed, significant differences exist between CHB and chronic HCV infection in natural history, laboratory parameters, liver histology and associated comorbidities. For example, elevated ALT reflects accurately the necroinflammatory activity of CHB and is used as one of the criteria for antiviral therapy while the same could not be applied to hepatitis C[3]. Steatosis is an important feature of chronic HCV infection while its role in CHB is unclear[33]. The association of diabetes mellitus with chronic hepatitis C has not been found in CHB[34]. Since CHB has specific pathogenetic mechanisms and is associated strongly with liver disease, the results of the studies on hepatitis C cannot be directly transferred to hepatitis B and a dedicated validation of the markers should be provided. The latest AASLD guidelines on management of chronic hepatitis B recommend that patients with HBV-DNA > 10^5 copies/ml and persistent or intermittent elevation in transaminase levels should be evaluated further with liver biopsy[3]. Moreover, prior to consider of antiviral treatment, liver biopsy is still recommended. Assessment of the stage of liver disease is indeed fundamental for treatment decision in any patient presenting with compensated chronic HBV infection. The available evidences suggest that non-invasive markers of liver fibrosis in hepatitis B present with a similar accuracy to hepatitis C. Lebensztejn *et al*[35] assessed the value of some non-invasive markers of liver fibrosis in few children with chronic hepatitis B and found that a combination of hyaluronan and laminin had 0.84 AUC. Hui and colleagues developed a predictive model based on body mass index and three routine laboratory tests, which showed 0.79 AUC[31]. Two recent reports applied Fibrotest in CHB showing 0.77 and 0.78 AUC for detection of significant fibrosis and cirrhosis, respectively[24,25]. Our results, based on an independent application of Fibrotest to CHB patients, showed an accuracy that is similar to that reported by Poynard's group. A very recent study by Zeng *et al*[36] proposed a non-invasive combination model based on alpha-2-macroglobulin, hyaluronan, age and γGT and it showed an AUC between 0.77 and 0.84. For all these markers, the expected rate of misdiagnosis was around 20%, thus similar to that reported for hepatitis C which is considered not satisfactory by many clinicians. Very recently the use of "proteome" technology has been introduced in studying liver fibrosis. In 46 patients with chronic hepatitis B, 30 features predictive of significant fibrosis and cirrhosis were identified. The AUC for this analysis was very promising, being 0.906 and 0.921 for advanced fibrosis and cirrhosis, respectively[37]. However, this is a quite complicated method that might not be available for large scale testing. Moreover, the excellent performance reported in that preliminary study should be confirmed by others. In our study we found that Fibrotest had the best performance when compared to other non-invasive methods. However, none of the investigated non-invasive markers of liver fibrosis had adequate accuracy for universal use in substitution of liver biopsy, the expected rate of misdiagnosis being 15%-35% for significant fibrosis and 25%-45% for cirrhosis. On the other hand, when APRI and Fibrotest were combined with liver biopsy in sequential algorithms, we could reach > 95% accuracy for detecting significant fibrosis or cirrhosis, with a 50%-80% reduced need for liver biopsy, as already described previously in patients with compensated chronic hepatitis C. With this approach, the number of liver biopsies needed decreased especially for the patients at higher risk of cirrhosis and this appears particularly important since the risk of liver biopsy complications is increased in cirrhotic cases. The overall cost of these algorithms appears favourable compared to universal use of liver biopsy. Indeed, for a cohort of one hundred patients algorithm A requires 100 APRIs, 34 Fibrotests and 52 biopsies while algorithm B requires 100 APRIs, 52 Fibrotests and 19 biopsies (Table 4). A cost-benefit analysis indicates that in the US a liver biopsy costs 1032 USD, which increases to 2745 USD when a complication occurs[8]. Fibrotest-Fibrosure is a commercialised method with a cost of around 90 euros (Biopredictive, Houilles, France). According to these values, algorithm A and algorithm B would result in a 50% and 75% reduction in cost compared to liver biopsy, respectively.

Table 4 Features of clinical interest of stepwise algorithms in chronic hepatitis B

	Algorithm A	Algorithm B
Saved biopsies (%)	48	81
APRI performed (%)	100	100
Fibrotest performed (%)	34	52
Under-diagnosed and unclassified (%)	0	0
Over-diagnosed (%)	3	3

Algorithm A: algorithm for significant fibrosis (F ⩾ 2 by METAVIR); Algorithm B: algorithm for cirrhosis (F4 by METAVIR); APRI: aspartate aminotransferase to platelets ratio.

There are some limitations in our study. This was in fact a retrospective study, with a quite limited number of cases. Another limitation could be in the choice of the dimension of biopsy sample. We have here included specimens of at least 1.5 cm length and containing 7 portal tracts on the basis of the recommendations of some authors[11,15,16,22]. However, several observations from the pathologists would suggest even bigger samples for a correct staging of liver fibrosis[13,14,17]. Finally, recent criticisms suggested that liver biopsy is not a perfect gold standard for fibrosis evaluation due to its large variability (sampling error plus observer error). Indeed, Bedossa *et al*[13] indicated that biopsy is an estimate of liver fibrosis which, when compared with the whole liver, showed a coefficient of variation greater than 40% with length greater than 15 mm with 80% accuracy.

In conclusion, this study suggests that in hepatitis B currently available non-invasive tests do not show a diagnostic performance that would be considered adequate by many clinicians. However, their stepwise combined use can be most useful to reduce the need for liver biopsy

without loosing diagnostic accuracy. In this respect liver biopsy and non-invasive markers should be considered as agonists and not as antagonists towards the common goal of correctly classifying the stage of liver fibrosis. Priority should be given to large scale validation studies of these algorithms in different patient populations inclusive of all major etiologies of chronic liver disease and most frequent cofactors, which may affect the diagnostic performance of fibrosis markers.

COMMENTS

Background

Non-invasive markers of liver fibrosis have been recently proposed as substitutes for liver biopsy but their reported accuracy was around 80%. They have been mostly validated in hepatitis C while few studies have been conducted in hepatitis B. We have recently shown that stepwise combination of non-invasive markers and liver biopsy permitted to obtain excellent accuracy (> 95%) by saving 50%-70% liver biopsies in hepatitis C. We applied our method to a cohort of patients with chronic hepatitis B.

Research frontiers

Nowadays many clinicians show concerns about the role of liver biopsy in chronic viral hepatitis due to side effects, intra- and inter-observer variation and costs. Some non-invasive methods for liver fibrosis have been proposed but International Guidelines still do not recommend a routine use of the markers due to lack of reproducibility and an expected misdiagnosis rate of 20%. Thus, a trusted method that avoides a number of liver biopsies by maintaining excellent accuracy is urgently needed.

Innovations and breakthroughs

In this article we validated in hepatitis B a recently proposed method for the detection of liver fibrosis and cirrhosis in hepatitis C. This is the first sequential approach based on a first line assessment by non-invasive markers of liver fibrosis followed by liver biopsy in unclassified cases or cases in which non-invasive methods do not reach a satisfactory accuracy. The overall accuracy of this method is > 95% and it saved 50%-80% liver biopsies. This is a rational and practical way to apply non-invasive markers in hepatitis B and it introduces a new concept: non-invasive markers and liver biopsy are agonists and not antagonists towards the common goal of classifying liver fibrosis.

Applications

The most accurate non-invasive markers should be used as a first line assessment, limiting liver biopsy to the cases in whom they are unclassified or show low predictive value. For the future, priority should be given to large scale validation studies of these algorithms and the most promising non-invasive markers in different patient populations inclusive of all major etiologies of chronic liver disease and most frequent cofactors which may affect the diagnostic performance of fibrosis markers.

Terminology

(1) Fibrotest: a commercial panel of serum markers combining γGT, alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin for the non invasive assessment of liver fibrosis. It has been extensively validated in hepatitis C. The overall accuracy of the panel is good but it combines also uncommon parameters. Only two, not independent, validation studies on hepatitis B have been so far conducted. (2) APRI: a simple test combining AST and platelet count group for the non-invasive prediction of significant fibrosis and cirrhosis in hepatitis C. It is a very simple and economic tool but it is somehow less accurate than fibrotest and it presents with a significant percentage of unclassified cases. To our knowledge, this is the first validation of APRI in an independent series of HBV patients. (3) Forns' index: an index combining, age, platelet, γGT, cholesterol for the non-invasive prediction of significant fibrosis in hepatitis C. It is a quite simple index, combining common parameters (except for cholesterol) but it showed a significant number of unclassified cases. To our knowledge, this is the first application of Forns' index to a cohort of patients with CHB. (4) GUCI: a simple index combining AST, platelets and INR. It showed good accuracy in hepatitis C for both significant fibrosis and cirrhosis. It has never been applied to HBV cases. (5) Hui's model: a panel combining albumin, BMI, total bilirubin and platelet count for the prediction of significant fibrosis. It has been developed for hepatitis B patients and no validation study has to date been conducted.

Peer review

Evaluate the applicability and prognostic value of a previously developed algorithm that includes a combination of two different serum marker tests for the detection of liver fibrosis to avoid liver biopsies in patients with chronic HBV infection. This is an excellent paper that investigates the performance of non-invasive tests for estimating liver fibrosis in patients with chronic hepatitis B. The study is timely and provides useful information.

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