World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i40.14568

World J Gastroenterol 2014 October 28; 20(40): 14568-14580
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (9): Hepatitis B virus

Non-invasive assessment of liver fibrosis in chronic hepatitis B

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Received: November 17, 2013 Revised: January 10, 2014
Accepted: June 2, 2014
Published online: October 28, 2014

Abstract

The goal of this review is to provide a comprehensive picture of the role, clinical applications and future perspectives of the most widely used non-invasive techniques for the evaluation of hepatitis B virus (HBV) infection. During the past decade many non-invasive methods have been developed to reduce the need for liver biopsy in staging fibrosis and to overcome whenever possible its limitations, mainly: invasiveness, costs, low reproducibility, poor acceptance by patients. Elastographic techniques conceived to assess liver stiffness, in particular transient elastography, and the most commonly used biological markers will be assessed against their respective role and limitations in staging hepatic fibrosis. Recent evidence highlights that both liver stiffness and some bio-chemical markers correlate with survival and major clinical end-points such as liver decompensation, development of hepatocellular carcinoma and portal hypertension. Thus the non-invasive techniques here discussed can play a major role in the management of patients with chronic HBV-related hepatitis. Given their prognostic value, transient elastography and some bio-chemical markers can be used to better categorize patients with advanced fibrosis and cirrhosis and assign them to different classes of risk for clinically relevant outcomes. Very recent data indicates that the combined measurements of liver and spleen stiffness enable the reliable prediction of portal hypertension and esophageal varices development.

Key words: Liver fibrosis; Cirrhosis; Hepatitis B virus; Transient elastography; Non invasive markers

Core tip: Several non-invasive techniques for the assessment of liver disease severity, including transient elastography and serological markers, have been developed to overcome the limitations and invasivity of liver biopsy. The application of these techniques in the setting of hepatitis B viral disease for both the assessment of liver fibrosis and the prediction of liver-related complications can lead to improved patient management.

Branchi F, Conti CB, Baccarin A, Lampertico P, Conte D, Fraquelli M. Non-invasive assessment of liver fibrosis in chronic hepatitis B. *World J Gastroenterol* 2014; 20(40): 14568-14580 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i40/14568.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i40.14568

INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health

problem with over 240 million people chronically infected worldwide[1]. The spectrum of the disease and the history of chronic HBV infection are various and variable, ranging from inactive carrier state to progressive chronic hepatitis B (CHB), which can evolve to cirrhosis in up to 20% of the cases, with hepatic insufficiency and portal hypertension being the most serious consequences[2]. Chronically infected subjects also have a 100 times higher risk of hepatocellular carcinoma than non-carriers[3]. The prognosis and management of chronic liver diseases, especially HBV-related chronic hepatitis, strongly depend on the degree of liver fibrosis.

Even if liver biopsy is still considered the reference standard for the staging of hepatic fibrosis, it is an invasive painful procedure. Its diagnostic accuracy decreases because of sampling errors and a significant rate of intra- and inter-observer variability too, this latter leading to the over- or under-staging of fibrosis even in adequately sized specimens, thus yielding false-negative results in up to 30% of cases[4,5].

Therefore, the growing need for alternative approaches to the assessment of liver disease severity has driven the development of several non-invasive methods in order to overcome the limitations of liver biopsy.

This review will focus on the role of non-invasive instrumental techniques -mainly ultra-sound elastography techniques and serum markers - in the diagnosis and assessment of liver disease severity in the complex setting of CHB. CHB shows some peculiarities against other chronic liver diseases, such as its profile of necroinflammation flares, its higher expression as macro-nodular cirrhosis and the natural history of hepatocellular carcinoma (HCC) development in this setting.

ULTRASOUND ELASTOGRAPHIC TECHNIQUES

Transient elastography

Transient elastography (TE) (Fibroscan®-Echosens, Paris, France) is a non-invasive technique developed in 2003. It was conceived to indirectly assess liver fibrosis by measuring liver stiffness (LS)[6]. It is performed with an ultrasound transducer probe mounted on the axis of a vibrator that produces vibrations of mild amplitude and low frequency. This induces an elastic shear wave that propagates through the underlying liver tissues. The velocity of the shear wave is directly related to tissue stiffness: the harder the tissue, the faster the shear wave propagates. TE explores a volume of liver parenchyma which is approximately 1/500 of the total liver mass, at least 100 times bigger and far more representative than a biopsy sample. The examination is painless, rapid, user-friendly and easy to perform at the bedside or in the outpatient clinic[7]. It is worth stressing though that the clinical interpretation of TE results should always be carried out by an expert clinician, aware of patient demographics, disease aetiology and routine laboratory parameters[7]. In fact, an Italian core group study has recently highlighted the need for a very careful quality control in order to better apply TE to clinical practice, with special attention to a patient's conditions and to the success rate of the stiffness measures. That study has also recommended the use of a detailed report form for routine TE results[8].

Reproducibility of TE

TE has been demonstrated to be a highly reproducible technique in terms of inter- and intra-observer agreement with intra-class correlation coefficients of 0.98[9].

Limitations of TE

Absolute contra-indications to TE examination are pregnancy and the presence of implantable devices, such as pacemakers or defibrillators. Liver stiffness measurement (LSM) can be difficult or even impossible in obese patients or in those people with narrow intercostal space or ascites[6]. Several studies in this field have reported failure rates ranging from 2.4% to 9.4%[6,9-16]. Foucher *et al*[16] reported that the only factor associated to failure was a body mass index above 28 (odds ratio 10.0; 95%CI: 5.7-17.9, $P = 0.001$). Further experience has allowed to indicate that, rather than the body mass index, a limiting factor for the success rate may be a fatty thoracic belt[7]. In fact, in over-weight or obese patients the fatty thoracic belt seems responsible for the attenuation of both elastic waves and ultra-sound, making LSM impossible. Dedicated probes and new algorithms based on the attenuation of both ultra-sonic and shear waves have been proposed with some benefits on TE accuracy[10,17].

Normal values of liver stiffness

Some studies examined LS values in apparently healthy subjects[18,19] leading to comparable results. In fact, the mean LS values reported by these studies were superimposable and ranged from 4.8 to 6.9 kilopascal (kPa). In addition, LS values were not influenced by age but higher values were reported in men as compared to women and in the presence of steatosis or features of the metabolic syndrome[18,20].

TE in inactive HBV carriers

Inactive HBV carriers are defined as hepatitis B e antigen (HBeAg) negative chronic HBV carriers with normal alanine aminotransferase (ALT) and HBV-DNA persistently at < 2000 international units/mL. Some studies have assessed LS values in inactive HBV carriers showing results superimposable to those of healthy subjects. Oliveri *et al*[21] measured the LS value in 68 inactive HBV carriers. The mean stiffness value was 5.0 ± 1.8 kPa, with a significant difference between subjects with abnormal ALT and steatohepatitis or steatosis at histology ($n = 17$, 6.9 ± 2.3 kPa), and subjects with normal ALT and without dysmetabolic profile ($n = 57$, 4.3 ± 1.0 kPa). Similar results have also been obtained by Maimone *et al*[22] who focused on the usefulness of TE in the discrimination between HBeAg-negative disease and inactive HBeAg-negative carriers. TE was performed in 220 subjects, of

Table 1 Transient elastography performance for the diagnosis of significant fibrosis (F ⩾ 2) in chronic hepatitis B

Ref.	Patients (*n*)	Cut-off (kPa)	Sn	Sp	LR^-	LR^+	AUROC (95%CI)
Oliveri *et al*[21]	188	7.5	93%	88%	0.07	8.2	0.96 (0.94-0.99)
Marcellin *et al*[89]	173	7.2	70%	83%	0.36	2.6	0.81 (0.73-0.86)
Chan *et al*[34]	161	8.4	84%	76%	0.20	3.5	0.87 (0.82-0.93)
Degos *et al*[90]	284	5.2	89%	38%	0.28	1.4	-
Viganò *et al*[25]	217	8.7	64%	92%	0.40	7.5	-
Verveer *et al*[27]	241	6.0	-	-	-	-	0.85
Cardoso *et al*[26]	202	7.2	74%	88%	0.30	6.2	0.86

Sn: Sensitivity; Sp: Specificity; LR^-: Negative likelihood ratio; LR^+: Positive likelihood ratio; AUROC: Area under receiver operating characteristic.

Table 2 Transient elastography performance for the diagnosis of cirrhosis (F4) in chronic hepatitis B

Ref.	Patients (*n*)	Cut-off (kPa)	Sn	Sp	LR^-	LR^+	AUROC (95%CI)
Oliveri *et al*[21]	188	11.8	93%	88%	0.07	8.2	0.97 (0.95-0.99)
Marcellin *et al*[89]	173	11.0	70%	83%	0.36	7.1	0.93 (0.82-0.98)
Chan *et al*[34]	161	13.4	79%	92%	0.20	9.8	0.93 (0.89-0.97)
Viganò *et al*[25]	217	9.4	100%	82%	0.01	5.5	-
Cardoso *et al*[26]	202	11.0	75%	90%	0.20	7.3	0.93

Sn: Sensitivity; Sp: Specificity; LR^-: Negative likelihood ratio; LR^+: Positive likelihood ratio; AUROC: Area under receiver operating characteristic.

whom 125 inactive carriers. LS values resulted significantly lower in the inactive carriers group than in the chronic disease group, with the inactive carriers showing a mean LS value of 4.8 ± 1.2 kPa and a median value of 4.7 kPa (range: 2.4-7.9 kPa).

Castéra *et al*[23] evaluated 201 inactive HBV carriers by means of TE, obtaining LS values (median 4.8 kPa *vs* 6.8 kPa, $P < 0.0001$) significantly lower than in 128 CHB patients, without differences related to HBV DNA levels. Among them, 82 inactive carriers could be evaluated with repeated TE within a median of 21.7 mo (range: 3.3-49.1 mo), showing no significant variation in LS values over time [median intra-patient changes at the end of follow-up -0.2 kPa, range: (-1.2)-(+0.7), $P = 0.12$], pointing to TE as a reliable tool for the follow-up of inactive HBV carriers and for a better selection of patients requiring liver biopsy.

In a recent study[24] performed on a cohort of 361 HBeAg negative HBV carriers who underwent TE at baseline and 3 years later, liver fibrosis progression - which was arbitrarily defined as "an increase in LS by at least 30% to a value suggestive of advanced fibrosis" according to internal diagnostic algorithms - appeared to be rare among patients with a HBV DNA level < 20000 UI/mL (2.8%) and extremely rare in inactive HBV carriers (0.8%)[24].

Role of TE in chronic hepatitis B

In CHB the assessment of the extent of fibrosis is crucially important to take appropriate therapeutic decisions on whether to start antiviral treatment or to evaluate the need for HCC surveillance. Because of the complex natural history of CHB, which frequently displays fluctuating patterns in term of necroinflammation, differences evidently exist between CHB and other chronic liver diseases such as chronic hepatitis C (CHC). Several studies have analysed the diagnostic accuracy of TE in predicting the stage of fibrosis in CHB patients: the main results are summarized in Table 1. For the purpose of diagnosing significant fibrosis (*i.e.*, F ⩾ 2 or S ⩾ 3) the LS cut-off used ranged from 5.2 to 8.7 kPa. The sensitivity estimates ranged from 70% to 93% and specificity estimates from 38% to 92%. Corresponding positive and negative likelihood ratios (LR^+ and LR^-) ranged from 1.4 to 8.2 and from 0.07 to 0.40, respectively. For the purpose of diagnosing liver cirrhosis, the proposed LS cut-off values varied from 10.3 to 13.4 kPa with sensitivity estimates ranging from 59% to 100% and specificity from 79% to 94% and corresponding LR^+ and LR^- from 0.07 to 0.3 and from 2.0 to 9.9 respectively, as shown in Table 2.

These wide variations in diagnostic accuracy estimates among the studies available in the literature can be related to differences in the spectrum of the population analysed and in the prevalence of the disease and particularly to the different LS cut-off values used. In fact, the main limitation to the use of the technique in clinical practice is the definition of LS cut-off values that help reliably classify patients in a given fibrosis stage: it is widely known that a substantial degree of overlap exists among patient groups of adjacent fibrosis stages. Usually, the cut-off value is derived from the receiver operating characteristics (ROC) curve and it is the one optimizing both sensitivity and specificity. An available different approach is about choosing two different cut-offs, one that maximizes sensitivity to exclude the diagnosis and the other that maximizes specificity for a confirmation strategy. Viganò *et al*[25] validated an algorithm with two distinct cut-offs for the positive and negative prediction of significant fibrosis and cirrhosis in treatment-naïve patients with CHB. Patients were examined by percutaneous liver biopsy and TE: a > 13.1 kPa positive and a ⩽ 9.4 kPa negative cut-off for cirrhosis had a > 90% sensitivity and

specificity, with an overall accuracy prediction of 94%, independent of alanine aminotransferase values.

Only a few studies have carried out direct comparisons between CHB and CHC patients. Both Cardoso *et al*[26] and Verveer *et al*[27] have assessed - in a cross-sectional study - treatment-naive patients with CHB or CHC who underwent TE measurement and liver biopsy, showing that the overall TE diagnostic performance was similar in the two patient groups. In the meta-analysis by Tsochatzis *et al*[28] the reported LS cut-offs were globally lower in CHB as compared to CHC group (on average 7.0 *vs* 7.6 for F ⩾ 2, 8.2 *vs* 10.9 for F ⩾ 3 and 11.3 *vs* 15.3 for F4). The authors have suggested that a possible logical explanation for this finding is that fibrosis septa are usually thinner in CHB patients than in those with CHC. In addition, because CHB tends to result in cirrhosis with larger nodules, *i.e.*, macro-nodular cirrhosis, than CHC does, TE waves are more likely to pass the normal liver parenchyma between fibrotic bands leading to lower stiffness values.

TE and possible confounders - the role of necroinflammation in HBV

Liver stiffness is a physical parameter primarily related to fibrosis, but it can also be influenced by other factors that modify liver elasticity, such as inflammatory infiltrate variations[15], oedema, vascular congestion[29], cholestasis[30] and, even if still controversial, hepatic steatosis[31]. Some earlier reports have suggested the influence of steatosis on LS be negligible but this association has possibly been attenuated by the low prevalence of steatosis[32]. Data from literature seems to show a poorer association between steatosis and CHB than between steatosis and CHC, with lower LS values and corresponding cut-offs in CHB. By contrast, liver inflammation clearly contributes to LS and may be more pronounced in CHB patients, especially during a hepatitis flare or viral reactivation. In their prospective study Verveer *et al*[27] confirmed that necroinflammation may induce higher LS values in both CHC and CHB. A demonstration that the presence of elevated ALT levels can increase LS values descends from the evidence that after the introduction of an antiviral therapy there is a rapid decrease of LS in parallel with ALT normalization[33]. A question remains unsolved about whether ALT levels, which frequently fluctuate in CHB, should be taken into consideration to adapt the cut-offs used for LS categorization: Chan *et al*[34] have proposed an algorithm which uses higher cut-offs in patients with elevated ALT levels, to avoid the overestimation of fibrosis because of the inflammation. Interestingly, adapting cut-offs on ALT did not improve the overall percentage of patients correctly classified. From all these data one can possibly conclude that, since LS is the consequence of multiple intra-hepatic events, including steatosis and inflammation, it will never be a perfect marker of fibrosis by itself, especially in the context of CHB but it can more usefully used as an overall marker of hepatic "well-being".

In a study by our own group[31], we have made a comprehensive evaluation of the factors that would account for any discrepancies in diagnostic accuracy between TE and the standard-of-care liver biopsy in CHB as compared to CHC patients. The results of the study evidenced that fibrosis stage and liver cell necroinflammatory activity were independently associated with TE results in both HBV and HCV patients, whereas steatosis was independently associated with TE only in HCV. Fibrosis over-estimation was predicted by severe/moderate necroinflammatory activity in HBV and by older age (41-60 years or > 60 years *vs* < 40 years), > 2 upper limit of normal (UNL) AST and > 2 UNL GGT, as well as severe/moderate necroinflammatory activity and severe/moderate steatosis in HCV.

Liver stiffness and the complications of liver cirrhosis

Patients with cirrhosis need strict follow-up for the surveillance of hepatic decompensation, portal hypertension and its complications and the early detection of HCC. Hepatic vein pressure gradient (HVPG) and upper gastro-intestinal endoscopy are the current reference standards in the assessment of portal hypertension, both techniques being expensive and invasive. Several groups have tried to develop non-invasive methods to stage the grade of portal hypertension and possibly predict its complications. Literature data suggest TE be a simple and reliable method to use in every-day clinical practice[35].

Portal hypertension and the presence of varices

TE has showed a good correlation with HVPG in different studies[36-40]. The main objectives on which the studies focused have been the detection of clinically significant portal hypertension and the presence of esophageal varices (EV): in CHC and other aetiology settings, TE accuracy seems to be satisfactory in predicting significant portal hypertention whereas its diagnostic performance in predicting the presence and severity of EV is lower and often sub-optimal.

In HBV settings some groups, mainly from Asia, have tried to assess the role of liver stiffness measurement by TE in predicting the presence of varices in cirrhotic patients, especially high-grade EV. Data are summarized in Table 3. Chen *et al*[41] performed both TE and upper endoscopy in 238 HBV cirrhotic patients. As TE alone could not predict EV with satisfactory efficiency (area under receiver operating characteristic curve, AUROC 0.73, 95%CI: 0.66-0.80), they tried to create a novel algorithm to improve the performance: USLS, an ultrasonic score calculated on the morphologic parameters reflecting hepatic fibrosis progression. The AUROC comparison thus showed an improved performance in predicting the presence of high-grade EV in the sub-group of patients with ALT > 5 ULN (0.85, 95%CI: 0.76-0.94). Kim *et al*[42] enrolled and evaluated 401 consecutive CHB patients, developing a prediction model to detect high-grade EV by means of combining LS, spleen diameter and platelet count, showing a good overall accuracy (AUROC 0.953).

Table 3 Transient elastography performance for the detection of portal hypertension and esophageal varices in various settings including chronic hepatitis B

Ref.	Prevalence	Aetiology	Patients (*n*)	Cut off (kPa)	Sn	Sp	LR⁻	LR⁺	AUROC
	Significant PH[1]								
Bureau *et al*[91]	51%	Mixed	150	21.0	90%	93%	0.10	12.8	0.94 (0.90-0.98)
Robic *et al*[38]	51%	Mixed	100	21.1	100%	65%	0.00	2.8	0.84 (0.76-0.82)
	EV								
Kazemi *et al*[40]	41%	Mixed	165	13.9	95%	43%	0.13	1.7	0.83 (0.78-0.90)
				19	91%	60%	0.14	2.3	0.84 (0.76-0.89)
Bureau *et al*[91]	72%	Mixed	150	21.1	84%	71%	0.22	2.9	0.85 (0.77-0.82)
	48%[2]			29.3	81%	61%	0.31	2.1	0.76 (0.67-0.85)
Nguyen-Khac *et al*[92]	22%	Mixed	183	48	73%	73%	0.37	2.7	0.76 (0.69-0.82)
Kim *et al*[42]	32%[2]	HBV	280	5.5[3]	94%	94%	0.06	15.7	0.95 (0.93-0.97)
Sporea *et al*[39]	35%[2]	Mixed	1000	31	83%	62%	0.27	2.2	0.78
Chen *et al*[41]	80%[2]	HBV	222	17.1	90%	44%	0.22	1.6	0.73 (0.66-0.80)
Wang *et al*[93]	38%	HBV	126	12	67%	77%	0.43	2.89	0.73 (0.65-0.80)
	10%[2]			21	77%	87%	0.27	5.79	0.86 (0.79-0.91)

[1]Hepatic vein pressure gradient > 12 mmHg; [2]Large/high risk esophageal varices; [3]LSPS. Sn: Sensitivity; Sp: Specificity; LR⁻: Negative likelihood ratio; LR⁺: Positive likelihood ratio; AUROC: Area under receiver operating characteristic; HBV: Hepatitis B virus.

The same group[43] assessed the cumulative risk of future EV bleeding in 577 consecutive HBV cirrhosis patients without history of EV bleeding. The combination of LS, spleen diameter and platelet count was useful in identifying a sub-group of patients at significantly higher risk of bleeding among the patients with so-defined high-risk EV ($P < 0.001$).

Hepatocellular carcinoma and hepatic decompensation

LS has been evaluated also as a possible predictor of the development of HCC. Several groups assessed this aspect, mainly in CHC settings, showing a good correlation between high basal values of LS and the increased risk of HCC development during follow-up[44-46].

In HBV settings Chon *et al*[47] compared the accuracy of several non-invasive liver fibrosis panels [age-spleen-platelet ratio index, LS, SSM; LS-spleen diameter-platelet ratio index (LSPI), P2/MS, and fibrosis score 4 (FIB-4)] in predicting the development of HCC or hepatic decompensation - defined as variceal bleeding, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome - in a large cohort of CHB patients ($n = 1126$). During a median follow-up of 30.7 mo the accuracy of LS values and LSPI in predicting the development of HCC or hepatic decompensation was higher than that of other parameters, although with a relatively low predictive capacity (AUROC = 0.789 and 0.788 *vs* 0.729, 0.756, 0.696, 0.744 for HCC development; AUROC = 0.820 and 0.848 *vs* 0.787, 0.799, 0.812, 0.784 for hepatic decompensation). By multivariate analysis including demographic and laboratory data, LS was found to be an independent predictor of HCC development (HR 1.040; 95%CI: 0.012-1.070, $P = 0.006$) together with age, male gender, and HBeAg positivity. Both LS (HR 1.033 95%CI: 1.007-1.060, $P = 0.013$) and LSPI (HR 1.002; 95%CI: 1.001-1.004, $P = 0.003$) were independent predictors of hepatic decompensation.

In a separate study[48] 128 patients with CHB underwent TE and liver biopsy before starting nucleot(s)ide analogues (38.3% lamivudine, 61.7% entecavir); all the patients were viremics (HBV DNA > 2000 IU/mL) with histological fibrosis ⩾ F3. All the patients were followed up regularly to detect decompensation (variceal bleeding, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome) and HCC. During a median follow-up period of 27.8 mo, 19 patients developed major events (14.8% of all patients): hepatic decompensation ($n = 5$), HCC ($n = 13$) and both conditions ($n = 1$). Serum albumin, prothrombin time, and platelet count were significantly higher in those patients without liver related events; AFP, and LSM values were significantly higher among those who developed liver-related events. Multivariate analysis including demographic data, laboratory tests, liver biopsy data, type of antiviral treatment and HBV DNA levels after treatment initiation, identified LS as the only independent predictor of liver related events (HR 1.038; 95%CI: 1.002-1.081, $P = 0.044$), especially for patients with LS ⩾ 19 kPa (HR 7.176; 95%CI: 2.257-22.812, $P = 0.001$).

Finally, also the large study by Jung *et al*[49] assessed the new role of TE in predicting the risk of HCC development in 1130 patients with CHB. Between May 2005 and December 2007, 672 (59.5%) patients were treated with antiviral drugs before or after enrolment. All 1130 patients underwent LSM with a median value of 7.7 kPa and then attended regular follow-up for HCC surveillance. During a median period of 30.7 mo (range: 24.0-50.9 mo), 57 patients developed HCC with cumulative incidence rates of HCC development in the first, second and third year of 0.80%, 3.26%, and 5.98%, respectively. The data collected showed that the patients with higher LS value (> 8 kPa) were at a significantly greater risk of HCC development: HR were: 3.07 (95%CI: 1.01-9.31, $P = 0.047$) for LS 8.1-13 kPa, 4.68 (95%CI: 1.40-15.64, $P = 0.012$) for LS 13.1-18 kPa, 5.55 (95%CI: 1.53-20.04, $P = 0.009$) for LS 18.1-23 kPa and 6.60 (95%CI: 1.83-23.84, $P = 0.004$) for LS > 23 kPa, encouraging the regular use of TE in clinical practice to stratify the risk of development

of HCC also in the HBV subset.

Liver stiffness and survival in chronic HBV

Some studies in HCV settings[38,50] have recently showed that TE as well as other non-invasive tests can predict clinically relevant outcomes, including survival, even better than liver biopsy[50].

In HBV setting de Lédinghen *et al*[51] first investigated the prognostic role for liver fibrosis of TE and other non-invasive tests (FibroTest, APRI, FIB-4) as compared to liver biopsy. The Authors assessed the 5-year overall survival in a consecutive cohort of 600 patients with CHB (inactive carriers 36%, n = 209). After a 5 years long observation period they had 25 deaths of which 13 for liver-related factors and four patients underwent OLT. Among inactive carriers no liver-related deaths were observed. Survival without liver-related death was 96.3%, overall survival 94.1%, and it resulted significantly low in patients with severe fibrosis, detected by both non-invasive method ($P < 0.0001$) and liver biopsy ($P = 0.02$). At year 5, 97.1% of patients with a LSM < 9 kPa was alive *vs* 38.5% of patients with a LSM > 20 kPa. In the multivariate analysis, FibroTest and LS were both independent predictors of survival: LS showed a HR of 6.8 (1.6-28.7), $P < 0.001$ with a prognostic AUROC of 0.80 (0.70-0.87).

TE and HBV: Monitoring treatment response

HBV-related liver cirrhosis is a complex clinical field, in which recent clinical trials have suggested that CHB treatment may lead to cirrhosis improvement. A recent study was performed on CHB patients with advanced fibrosis or cirrhosis prior to treatment with nucleoside/nucleotide analogue for at least one year; they underwent LS measurement by means of TE at follow-up[52]. LS cut-off levels for diagnosing fibrosis stage F2, F3 and F4 were ⩾ 7.2 kPa, ⩾ 8.1, and ⩾ 11.0 kPa, respectively. Eighty percent of the patients had cirrhosis and 20% advanced fibrosis (F3) prior to treatment. The median treatment duration was 50.5 mo. Among the patients with cirrhosis prior to treatment, 26 (49%) had LS below 11.0 kPa at follow-up, suggesting cirrhosis regression. Among the patients with advanced fibrosis (F3) prior to treatment, 10 (77%) had LS below 8.1 kPa after treatment, suggesting fibrosis improvement.

Other elastographic techniques for the assessment of liver stiffness

Acoustic radiation force impulse: Acoustic radiation force impulse (ARFI) quantification (Virtual Touch™ Siemens ACUSON S2000™, Siemens Medical Solution, Mountain View, CA, United States; ElastoQ Philips iU22, Philips, Bothell, United States) is obtained by means of short-duration acoustic pulses around 2.6 mHz. The pulses induce the compression of the tissue and consequently the development of shear waves that propagate at a certain velocity proportional to tissue stiffness; the propagation velocity of the shear wave is detected by the ultrasound probe and is displayed on the screen. Basically, the speed of the shear wave propagation correlates with the stiffness of the tissue and thus with the severity of liver fibrosis in the context of liver disease[53]. The advantage of this technique is that ARFI can be included in the standard B-mode liver ultra-sound equipment, becoming an easy immediate complement to abdominal ultra-sound examination.

Data on several patients with chronic liver disease of different aetiology show that ARFI quantification has a good performance for liver fibrosis staging with slightly better results with regard to the assessment of severe fibrosis (AUROC 0.91) and cirrhosis (AUROC 0.93) than for significant fibrosis, coherently with the results of TE. Proposed optimal cut-offs are 1.34 m/s for the diagnosis of significant fibrosis, 1.55 m/s for severe fibrosis and 1.8 m/s for cirrhosis[54]. A recent study assessed ARFI in 114 CHB patients undergoing liver biopsy and showed a significant correlation between ARFI quantification and histological fibrosis stage. The overall diagnostic accuracy expressed as areas under ROC curves for ARFI imaging was 0.75 for the diagnosis of significant fibrosis (F ⩾ 2), 0.93 for severe fibrosis (F ⩾ 3) and 0.97 for cirrhosis, without any significant difference between ARFI and TE performed in 92 out of 114 patients, thus confirming the reliability of this technique also in the HBV setting[55]. To our knowledge, there is still a lack of data to support the prognostic value of ARFI quantification of LS in terms of prediction of mortality or liver-related complications, especially in chronic HBV settings.

OTHER INSTRUMENTAL TECHNIQUES

Magnetic resonance elastography

Magnetic resonance elastography (MRE) is a MRI-based technique which has been extensively evaluated and demonstrated as an accurate predictor of liver fibrosis with very high diagnostic performances[56-60].

Most of the studies were performed in populations with chronic liver disease of various aetiologies, such as CHC and alcohol-related cirrhosis and NASH. One study by Venkatesh *et al*[61] assessed the performance of MRE in 63 CHB patients, showing a good performance in the diagnosis of significant fibrosis (AUROC 0.99), and cirrhosis (AUROC 0.98).

Spleen stiffness measurement

Very recently a further promising use of TE has been found to be the measurement of spleen stiffness (SS) in assessing liver disease severity in CLD patients, considering the well-known role of splenomegaly as an indicator of cirrhosis, related to portal hypertension and splenic congestion in increased vascular resistance, leading to fibrosis of the spleen. In the last four years many studies have focused on this application of TE or ARFI elastography in clinical practice[62-64]. In CHC settings the correlation of SS with fibrosis stage has been assessed, showing a good correlation between SS values > 60 kPa and the presence of cirrhosis[63]. PH and varices presence have

Table 4 Major biochemical markers evaluated in chronic hepatitis B setting

Serum panel	Parameters
Fibrotest	Haptoglobin, a2macroglobulin, apolipoprotein-A1, gGT, total bilirubin, gammaglobulin
APRI	AST, platelets
FIB-4	Age, AST, ALT, platelets
Forn's	Age, platelets, gGT, cholesterol
GUCI	AST, INR, platelets
Hui's	Body mass index, platelets, albumin and bilirubin

gGT: Gammaglutamyltranspeptidase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferaese; INR: Intrnational normalised ratio; APRI: AST to platelet ratio index; FIB-4: Fibrosis score 4.

also been evaluated in this setting, showing a significant correlation between HVPG values and both LS and SS and an association between SS values and EV presence. Data from our group[62] suggest a good inter-observer agreement for SS measurement in chronic hepatitis settings and a positive correlation between SS, as well as LS, and EV presence, thus suggesting that the combined use of the two parameters can reliably predict the presence of varices and be useful in assessing liver disease severity.

Spleen stiffness in HBV setting

Most studies on SS assessment have been conducted in HCV settings, but the interest in its role for HBV positive patients is increasing. The main studies conducted in this population have measured SS using ARFI technology.

In fact, preliminary results indicated that the ARFI measurement of SS can be used as a non-invasive tool to rule out cirrhosis (AUROC = 0.91, accuracy = 87.1%) and to predict the presence of EV[65-67].

Chen *et al*[68] evaluated the diagnostic role of SS measurement, using ARFI technology, for liver fibrosis assessment in patients with CHB (n = 61) or C (n = 102), performing also LSM and percutaneous liver biopsy. Intra-observer correlations coefficients (ICC) were evaluated: ICC for LSM and SSM were 0.993 (95%CI: 0.981-0.997, $P < 0.001$) and 0.834 (95%CI: 0.627-0.931, $P < 0.001$), respectively. Using the METAVIR fibrosis scoring system, 138 patients were scored as F1-F3 (47 HBV$^+$, 91 HCV$^+$): 62 F1, 56 F2, 20 F3 and 25 as F4 (14 HBV$^+$ and 11 HCV$^+$). A significant correlation was obtained between LSM and SSM (r^2 = 0.574, $P < 0.0001$); AUROC 0.839 (95%CI: 0.780-0.898) for METAVIR F1 *vs* F2-4, 0.936 (95%CI: 0.898-0.975) for F1-2 *vs* F3-4 and 0.932 (95%CI: 0.893-0.971) for F1-3 *vs* F4, all $P < 0.001$.

Considering the role of SS in predicting complications, Ye *et al*[69] evaluated the performance of liver and spleen stiffness, by ARFI elastography, for the assessment of liver fibrosis and esophageal varices in 66 patients with CHB, who underwent liver biopsy, and 138 with cirrhosis HBV related, examined by upper endoscopy. They obtained a significant linear correlation between liver (ρ = 0.87; $P < 0.001$) and spleen (ρ = 0.76; $P < 0.001$) stiffness and liver fibrosis. A fairly significant linear correlation (ρ = 0.65; $P < 0.001$) was found between SS and the varices grade, promising an important role of this technique also in HVB related cirrhosis, although further studies are required.

BIO-CHEMICAL MARKERS

Several non-invasive markers have been developed in recent years, as an alternative to liver biopsy, for the evaluation of chronic liver disease severity. A few of them have been validated as diagnostic and prognostic markers of liver disease severity in HBV setting, as summarised in Table 4.

FibroTest (Biopredictive, Paris, France; FibroSure-Labcorp, Burlington, NC, United States) is a non-invasive marker which has been widely validated as a tool for the detection of liver fibrosis in the setting of CHC. The FibroTest is a scoring algorithm which combines various simple serum markers (serum haptoglobin, beta2-macroglobulin, apolipoprotein A1, gamma-glutamyl-transferase and bilirubin) with an adjustment for age and sex[70]. It was shown to have a high degree of accuracy and reproducibility in predicting bridging fibrosis and cirrhosis in patients with chronic liver diseases, its only theoretical limit being the inclusion of very sensitive fluctuating parameters such as bilirubin and platelet count[71]. It is known that liver disease aetiology can influence the performance of non-invasive serum markers as well as it does with liver stiffness measurement. In a study by Sebastiani *et al*[72], however, the performance of Fibrotest was good in all aetiologies including HCV, HBV and NASH for both F $\geqslant$ 2 and F4 (AUROC adjusted for DANA - difference between advanced and non-advanced fibrosis - AdjAUROC > 0.73), except for $\geqslant$ F2 in NASH (AdjAUROC = 0.64). In fact, Fibrotest has been recently validated for the diagnosis of significant fibrosis and cirrhosis in the setting of CHB. With an area under the ROCs (AUROCs) of 0.84-0.90 for the diagnosis of significant fibrosis and an AUROC of 0.85-0.87 for the diagnosis of cirrhosis, its performance seems to be of high significance[73,74]. A recent study on 330 Asian patients with CHB compared FibroTest and liver biopsy, showing that the detection of advanced fibrosis (F3-4) is the only independent factor of discordance between the two techniques[75].

Some studies have recently tested FibroTest as a prognostic index in different settings of liver disease, showing that this tool has a 5-year long prognostic value similar to liver biopsy for the prediction of cirrhosis decompensation and survival in patients with CHC virus (HCV)[50,76,77]. A recent meta-analysis concluded that Fibrotest can be considered a validated bio-marker for predicting liver disease mortality in the setting of chronic liver disease[78]. As for hepatitis B, Ngo *et al*[79] demonstrated that the evaluation of HBV carriers with FibroTest is useful in terms of definition of inactive carrier state and prediction of prognosis in CHB patients. de Lédinghen *et al*[51] recently evaluated the prognostic value of several non-invasive

Table 5 Performances of Fibrotest for the diagnosis of fibrosis (F2-F4) and assessment of prognosis in chronic hepatitis B

Outcome	Patients (*n*)	Cut-off (kPa)	Sn	Sp	LR^+	LR^-	AUROC (95%CI)	Ref
Significant fibrosis F ⩾ 2	194	0.32	79.3%	93.3%	11.8	0.2	0.90 (0.84-0.97)	[74]
	254	0.48	54.2%	83.3%	3.3	0.6	0.69 (0.63-0.75)	[72]
Cirrhosis F4	194	0.68	80.0%	84.0%	5	0.2	0.87 (0.82-0.92)	[74]
	254	0.75	42.1%	91.4%	4.9	0.6	0.68 (0.63-0.73)	[72]
Prediction of 5-yr survival	600	⩽ 0.73 > 0.85	-	-	-	-	0.82 (0.71-0.89)	[51]

Sn: Sensitivity; Sp: Specificity; LR^-: Negative likelihood ratio; LR^+: Positive likelihood ratio; AUROC: Area under receiver operating characteristic.

tests, concluding that FibroTest can be useful in predicting 5-year mortality and liver transplantation in chronic hepatitis B patients, with a hazard ratio similar to TE (overall prognostic performance: AUROC 0.82, 95%CI: 0.71-0.89 for Fibrotest) and far more significant than that of liver biopsy. Operating characteristics of FibroTest in CHB settings are detailed in Table 5.

APRI The aspartate aminotransferase (AST) to platelet ratio index (APRI) is a simple non-invasive marker also developed in the setting of CHC, combining AST and platelet count[80]. In other chronic hepatitis settings, APRI score does have a significant performance in assessing fibrosis and cirrhosis and its prognostic value in predicting mortality has been tested also in patients with HCV/HIV co-infection[81]. In their study, de Lédinghen *et al*[51] aimed at assessing the prognostic value of several non-invasive methods in HBV settings: APRI score did not reach the prognostic performance of LSM or FibroTest.

FIB-4 is another non-invasive test which combines standard bio-chemical values (platelets, ALT, AST) and age, also validated in the context of CHC[82]. Like APRI, it is a relatively simple score but its diagnostic and prognostic performance does not seem as promising as that of liver stiffness or FibroTest, as recently demonstrated in chronic HBV patients[51].

Forn's index is a non-invasive test that includes the evaluation of age, platelet count, gamma-glutamyl-tranferase and cholesterol levels. It shows a lower diagnostic performance in CHB as compared to CHC settings, with an 0.79 AUROC for the diagnosis of significant fibrosis (*i.e.,* F2-F4) and 0.86 for the diagnosis of severe fibrosis (F3-4) in 78 CHB patients[83].

The GUCI index was first developed by a Scandinavian group[84] as a simple non-invasive tool to exclude liver cirrhosis in CHC patients. It can be easily computed by using these variables: normalized AST × prothrombin-international normalized ratio × 100/platelet count ($\times 10^9$/L). In 2007 Sebastiani *et al*[85] evaluated the GUCI index in CHB settings, obtaining a good overall performance for the detection of significant fibrosis (AUROC 0.81, 95%CI: 0.70-0.92) but not cirrhosis (AUROC 0.56). Moreover, a recent study[86] on 221 CHB showed poor performances of the GUCI score for CHB staging.

Hui's model[87] is another simple bio-chemical panel including BMI, platelet count, serum albumin and bilirubin levels. It was developed in 2005 and it was demonstrated to accurately predict the absence of significant fibrosis with a high degree of accuracy. Sebastiani *et al*[85] reported a moderate overall accuracy of this model for the detection of significant fibrosis (AUROC 0.71), whereas the model performances for the detection of cirrhosis resulted sub-optimal.

Furthermore, some of the aforementioned non-invasive markers have been tested as possible tools for evaluating the response to HBV treatment. In the study by Basar *et al*[88] several bio-chemical markers such as APRI, FIB-4, Forn's index, were assessed before and after treatment, reporting significantly lower values of these indexes in post-treatment CHB patients in comparison to pre-treatment patients.

Diagnostic algorithms

Interestingly, almost all the mentioned bio-chemical markers have been evaluated in combination with one another or with elastographic techniques in order to build sequential algorithms, aiming at correctly allocating and staging CHC and CHB patients. In CHB settings, Sebastiani *et al*[85] evaluated a series of possible algorithms combining various non-invasive markers concluding that the sequential combination of APRI, FibroTest and liver biopsy turned out the most promising approach.

CONCLUSION

Non-invasive methods for the assessment of liver disease severity have witnessed major advancements in the last few years. The great interest in developing more and more accurate non-invasive methods for the assessment and management of chronic liver disease can be explained by several reasons: first of all, the well-known limitations of liver biopsy, the increasing awareness of its unreliability to predict liver disease severity, partly because of its being an "imperfect gold standard", partly because of the new data on its poor correlation with mortality and development of liver-related complications.

In the setting of chronic HBV-related liver disease, which has a peculiar clinical history of frequent flares of necroinflammation and a histological pattern of macronodularity after its shift to cirrhosis, it is extremely important to define novel methods to assess the stage of fibrosis and the stage of liver disease in an acceptable cost-effective safe way.

Among the non-invasive methods TE is a simple

user-friendly reproducible technique for the non-invasive evaluation of LSM as a surrogate marker of liver fibrosis.

In inactive HBV carriers, mean FS values are similar to those in healthy controls and significantly lower than in CHB patients. In this setting TE can be introduced as an adjunct to transaminase levels and HBV DNA determination in order to discriminate inactive HBV carriers and to select subjects in need for further characterisation, as for HBV carriers with inactive viral profile when the increased LS values suggest the presence of liver damage caused by other causes. HBV inactive carriers can also be monitored with periodic LSM for a better surveillance of disease reactivation.

In patients with chronic liver disease LSM is accurate especially for the diagnosis of severe fibrosis and cirrhosis whereas its ability to diagnose significant fibrosis is lower. In CHB settings, the LS cut-off values proposed for the diagnosis of significant liver fibrosis and cirrhosis are lower than those used in CHC patients, partly because of differences in the pathogenesis and progression of liver damage (*i.e.*, differences in extent and structure of the collagen septa, and in type and extent of liver inflammatory infiltrate). The proposed cut-offs range from 7.2 to 8.4 kPa for significant fibrosis and from 10.3 to 13.4 for cirrhosis.

For the proper assessment of treatment naïve patients - a category of patient who need a correct management in terms of therapy and biopsy timing - the development of diagnostic algorithms with a confirmatory and an exclusion LS threshold may provide a promising tool for a correct classification of patients, keeping liver biopsy as the reference standard for patients with ambiguous LS values. As to the follow-up of CHB patients undergoing treatment, the regular monitoring of LS by means of TE can add more knowledge about the mechanisms of fibrosis progression and regression. Given the proved influence of necroinflammation on LS values, the pattern of bio-chemical activity must be taken into account in the interpretation of TE before and during treatment. Cirrhotic HBV patients would benefit from the recent advances in assessing the correlation between LS values and the development of complications, especially portal hypertensions and HCC.

Other elastography techniques have yet to be fully studied but have shown promising results in terms of reproducibility and applicability in clinical practice, especially ARFI quantification which can be added to any standard liver ultra-sound examination. Both ARFI and MRI show a good performance in the assessment of liver fibrosis in several settings, including CHB. Available data on their prognostic performance in HBV setting is however still insufficient.

SS measurement, both by TE and ARFI, is currently under investigation by various groups in order to achieve sufficient results also in the setting of CHB after showing promising results in terms of prediction of portal hypertension, EV and variceal bleeding in HCV settings.

Serum markers such as FibroTest, APRI and FIB-4 are simple non-invasive tests which can be computed by means of simple mathematical algorithms and carried out with a few blood tests, most of which are usually collected during routine controls. The minimal invasiveness and costs together with the optimal accuracy profile of Fibrotest lead to expect that it will be widely adopted in a near future, along with elastography techniques, in order to assess and follow up the complications of chronic HBV related disease.

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ISSN 1007-9327
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