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The role of transient elastography in patients with hepatitis B viral disease

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Abstract

This review focuses on the role of ultrasound and transient elastography (TE) in patients with hepatitis B virus (HBV) infection. Among the ultrasonographic signs analyzed, liver surface nodularity has the highest diagnostic accuracy and is particularly useful in confirming the presence of severe fibrosis or cirrhosis, due to its high specificity. The role of TE in patients with hepatitis B virus disease was assessed in inactive carriers and patients with chronic liver disease (CHB). In inactive HBV carriers, mean TE values are similar to normal controls and significantly lower than in patients with CHB. In this latter group, the available studies showed a significant positive correlation between TE values and fibrosis stages at liver histology. However, as for HCV patients, there is a certain degree of overlap among the lower stages of hepatic fibrosis and the accuracy of this technique is not optimal for the diagnosis of significant fibrosis, whereas its diagnostic performances are higher for the diagnosis of liver cirrhosis. The development of diagnostic algorithms, with a confirmatory and an exclusion liver stiffness threshold, seems to be a promising tool for a correct classification of patients.

Keywords: Chronic hepatitis; Fibroscan; HBV inactive carriers; Liver surface nodularity; Transient elastography

1. Introduction

Hepatitis B virus (HBV) infection is a major global cause of morbidity and mortality, with over 350 million people chronically infected worldwide [1]. Persistent HBV infections may be symptomatic or asymptomatic. People with subclinical persistent infection, normal serum aminotransferase levels, and normal or nearly normal findings on liver biopsy are classified as asymptomatic chronic HBV carriers; those with abnormal liver function and histological features have chronic hepatitis B (CHB). Liver cirrhosis develops in about 20% of people with CHB, with hepatic insufficiency and portal hypertension being the most feared consequences of chronic HBV infection [2]. Chronically infected subjects also have a risk of hepatocellular carcinoma that is 100 times as high as that for noncarriers [3]. For an appropriate management of patients with chronic liver disease, it is of primary importance to know the degree of liver fibrosis, since the prognosis is determined by its extent and progression.

Liver fibrosis is a wound-healing response to chronic liver injury, which may lead to cirrhosis and hepatocellular carcinoma (HCC) [4]. A main event in the pathogenesis and progression of fibrosis is the activation of hepatic stellate cells, the major source of the extracellular matrix [5]. Fibrosis is considered irreversible once cirrhosis is established. While the diagnosis of cirrhosis is made clinically on the basis of signs of end-stage liver disease, such as ascites, jaundice, variceal bleeding, encephalopathy and liver failure, the standard method for the assessment of fibrosis remains percutaneous liver biopsy [6]. However, liver biopsy is an invasive and painful procedure [7], that can be followed by severe complications [8,9]: such characteristics limit its acceptance by patients, especially when repeated examinations in difficult-to-treat patients are needed. Moreover, the accuracy of liver biopsy in assessing fibrosis can be questioned because of its poor reproducibility due to sampling errors and to intra- and inter-observer variability, that may lead to the over- or under-staging of fibrosis even in adequately sized specimens, yielding false-negative results in up to 30% of cases [10–12].

Therefore, the increasing need for alternative approaches for the quantification of liver fibrosis has led to the development of several non-invasive techniques for the assessment of liver disease.

This review will focus on the role of non-invasive instrumental techniques, mainly transient elastography (FibroScan®, Echosens, Paris, France), in patients with hepatitis B viral disease.

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1.1. Ultrasound

Ultrasound (US) is a non-invasive, cheap, and repeatable technique. Several US signs have been reported in literature for the non-invasive assessment of liver diseases and, particularly, of liver fibrosis. These US parameters are divided into parenchymal and non-parenchymal (Table 1).

Table 1
Ultrasound parameters of hepatic fibrosis

Parenchymal
– Liver surface nodularity (LSN)
– Caudate or left lobe hypertrophy (CLH, LLH)
– Echotexture
– Hepatic veins doppler flow pattern (HVF)
Non-parenchymal (mainly related to portal hypertension)
– Presence of splenomegaly, ascites, collateral vessels etc.
– Venous and arterial splanchnic evaluation by Doppler US technique

The former are the most useful in the assessment of patients with compensated chronic liver disease whereas the non-parenchymal ones, such as the presence of splenomegaly, ascites, collateral vessels, and alterations in the venous and arterial splanchnic circulation by Doppler US, are mainly related to the presence of portal hypertension, and therefore present in the most advanced phases of liver disease, when liver decompensation occurs. For this reason, in this review we will focus only on the parenchymal US signs. Several studies analyzed the diagnostic accuracy of these US signs, achieving results that showed great heterogeneity, mainly due to differences in technique (technological advances in recent years, different US equipment and transducers), enrolled population (different prevalence of severe fibrosis and cirrhosis) and study design (most of the studies are case series or case control studies). In addition, most of the studies included in our review were performed in patients with chronic liver disease of mixed aetiology, including only a minority of patients with HBV infection.

1.2. Liver surface nodularity

Liver surface nodularity (LSN) is a sonographic feature often found in patients with chronic liver disease [13–17]. This parameter is more accurately evidenced with the use of high frequency transducers. The finding is considered positive if, during US examination, the liver surface appears as a dotted or irregular line instead of a straight and regular hyperechoic line, and/or the liver parenchyma is not homogeneous, but shows areas with different echogenicity, reflecting an underlying nodularity [13]. This parameter has been evaluated for the diagnosis of liver cirrhosis, showing a sensitivity between 54% and 92% and a specificity between 80% and 95% [13–17]. In a recent prospective series of consecutive patients with liver disease of different aetiology (including patients with HBV chronic infection) [13], alone or in combination with other imaging features, the LSN sign showed, among the US signs analyzed, the highest accuracy for the diagnosis of severe fibrosis-cirrhosis with a sensitivity of 54% and a specificity of 95% and corresponding negative likelihood ratio (LR–) of 0.5 and positive likelihood ratio (LR+) of 11.5, respectively (Table 2). These results suggest that, when LSN sign is positive, it is very useful in confirming the presence of the disease, whereas its negativity does not allow to confidently exclude it. The role of this sign in acute liver disease is questionable, as a recent study has proved that LSN is often positive also in patients with fulminant hepatic failure, usually reflecting a combination of foci of regenerative nodules and necrosis [18]; an incorrect radiologic diagnosis of cirrhosis in this setting could thus affect the clinical management of these patients.

1.3. Caudate or left lobe hypertrophy

The ultrasound evidence of hypertrophy of the caudate lobe (CLH) or the left hepatic lobe (LLH), defined as relative enlargement of those structures along with reduction in volume of the right lobe (measured either through the ratio of transverse caudate/left lobe width to transverse right lobe width or through multidimensional indexes), has been shown to be a useful criterion for the diagnosis of liver cirrhosis [19–23]. The diagnostic performances of CLH and LLH signs vary widely in sensitivity ranging from 43% to 95% and specificity from 94% to 100%.

Table 2
Diagnostic performances of liver surface nodularity (LSN) sign

Prospective study	Probe (MHz)	Prevalence of cirrhosis (%)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Di Lelio 1989 [14]	5	76	88	94	14.6	0.1
Gaiani 1997 [15][a]	5	22	82	80	3.9	0.2
Simonovsky 1999 [16]	7.5	49	92	84	5.7	0.09
Hung 2003[17][b]	3.5	36–40	77–82	70–92	2.7–10	0.2
Colli 2003 [13]	5–12	36	54	95	11.6	0.5

[a] LSN + portal velocity.
[b] LSN + echotexture + vascular structure + splenic size.

1.4. Echotexture

Specific ultrasound patterns, such as a coarse echopattern [24], or the attenuation of the ultrasound beam [22,25], have been assessed in different studies reporting ranges of sensitivity of 20–58% and 78–88%, respectively, for the diagnosis of liver cirrhosis.

1.5. Hepatic veins Doppler flow pattern

The normal hepatic vein waveform is triphasic as a result of transmitted cardiac activity. In chronic liver disease, alterations of hepatic vein flow profile may be observed: several studies have demonstrated that the flattening of Doppler waveform, with loss of reverse flow component, correlates with the presence of severe fibrosis, but the results in terms of sensitivity and specificity of this test are controversial [26–29]. Flattening of the flow profile in the right hepatic vein in cirrhotic patients also correlates with a poorer prognosis [28]. However, this abnormal waveform can occur in diseases such as Budd–Chiari syndrome, diffuse hepatic metastases and steatosis [30]. Moreover, the hepatic flow profile may be influenced by deep inspiration, obesity or ascites. Sensitivity and specificity ranges of this sign for the diagnosis of severe fibrosis or cirrhosis vary from 50% to 82% for sensitivity and from 49% to 100% for specificity.

2. Transient elastography

Transient elastography (TE) (Fig. 1) is a simple, non-invasive technique developed in 2003 for the assessment of liver fibrosis by measurement of liver stiffness [31]. It is performed with an US transducer probe mounted on the axis of a vibrator. Mild-amplitude, low-frequency vibrations (50 mHz), transmitted from the vibrator toward the tissue, induce an elastic shear wave that propagates through the tissue. The propagation of the shear wave and its velocity are measured by means of pulse-echo US acquisition. 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 (a cylinder 1 cm wide and 4 cm long, between 25 and 65 mm below the body surface) which is approximately 1/500 of the total liver mass, at least 100 times bigger and far more representative than a biopsy sample. It is a painless and rapid examination, easy to perform at the bedside or in the outpatient clinic [32]. It can be performed after a short learning curve (about 100 examinations) [33] and the results are immediately available and operator-independent [34]. The clinical interpretation of TE results, however, should always be done by an expert clinician, aware of patients' demographics, disease aetiology and routine laboratory parameters [32].

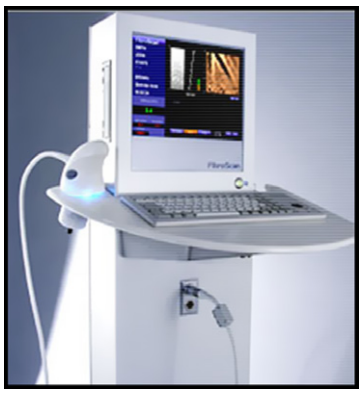

Fig. 1. Fibroscan® (Echosens, Paris, France).

2.1. Reproducibility of TE

Reproducibility of TE is an important prerequisite for the widespread use of this technique in clinical practice. In a recent Italian study, 800 TE examinations were performed by two operators in 200 patients with various chronic liver diseases: TE reproducibility was proven excellent for both inter-observer and intra-observer agreement, with intra-class correlation coefficients (ICC) of 0.98 [35]. However, interobserver agreement was significantly reduced in patients with lower degrees of hepatic fibrosis (ICC for F0–F1 0.60 versus 0.99 for FP 2), with hepatic steatosis (ICC for the presence of fat involving more than 25% of hepatocytes 0.90 versus 0.98 for the presence of fat in less than 25% of hepatocytes) and with increased body mass index (ICC for BMI >25 kg/m^2 0.94 versus 0.98 for <25 kg/m^2).

2.2. Limitations of TE

Contraindications to the examination are pregnancy and presence of implantable devices, such as pacemakers or defibrillators. Liver stiffness measurements can be difficult or even impossible in obese patients or in those with narrow intercostal space or ascites [31]. Several studies in this field have reported failure rates ranging from 2.4% to 9.4% [31,33–41]. Foucher et al. [41] report that the only factor associated with failure was a body mass index above 28 (odds ratio 10.0; 95% confidence interval 5.7–17.9, P = 0.001). Further experience suggested that, rather than body mass index, a limiting factor for the success rate may be a fatty thoracic belt [32]. Indeed, in overweight or obese patients, the fatty thoracic belt seems responsible for the attenuation of both elastic waves and ultrasound making liver stiffness measurement impossible. Dedicated probes and new algorithms based on attenuation of both ultrasonic and shear waves have been proposed, with some benefits on TE accuracy [33].

2.3. Normal values of liver stiffness

Four studies have examined liver stiffness values in apparently healthy subjects [42–45]. Roulot et al. [42] examined 429 healthy subjects, without overt causes of liver disease and with normal liver function tests, undergoing a medical check-up. The mean liver stiffness value in these patients was 5.5±1.6 kPa, with significant differences between men and women (5.8±1.5 vs. 5.2±1.6 kPa, respectively;

Table 3
Diagnostic performance of transient elastography in CHB patients in diagnosing significant fibrosis (F ⩾ 2 or S ⩾ 3).

	Oliveri 2008 [46]	Marcellin 2009 [52]	Chan 2009 [51]
Patients	188	173	161
HBeAg + (%)	11	NR	69
Prevalence (%)	69	50	NR
Cut off (kPa)	7.5	7.2	8.4
Sensitivity	93	70	84
Specificity	88	83	76
LR+[a]	8.2	2.6	3.5
LR–[a]	0.07	0.36	0.20
AUROC	0.96	0.81	0.87

LR+, positive likelihood ratio, LR–, negative likelihood ratio, AUROC, area under the receiver operating curve.
[a] Optimal LR+ ⩾10 and LR– ⩽0.1.

p = 0.0002) and in subjects with body mass index >30 kg/m^2 (6.3±1.9 kPa; p = 0.0003). Even after adjustment for gender and body mass index, liver stiffness values remained higher in subjects with metabolic syndrome (n = 59; 13.7%) than in those without (6.5±1.6 vs. 5.3±1.5 kPa, respectively; p < 0.0001) [42]. A study of another group [44] reproduced the same results in voluntary blood donors, observing a mean normal liver stiffness of 4.9 kPa±1.7 SD.

A recent large study [45] assessing more than one thousand North-Italian blood donors, evidenced that the 50th and 95th centiles of liver stiffness measurements distribution were 4.1 and 7.4 kPa in females and 4.6 and 7.8 kPa in males, respectively. Interestingly in this study, liver stiffness values higher than 8 kPa were found in about 3% of the blood donor population.

It must be pointed out that in these studies the value of liver stiffness corresponding to the 95th centile of normal subjects was lower than the mean cut-off for significant fibrosis established in the main studies of TE in chronic liver disease [34–37,43,46–49], which is between 7 and 8 kPa.

3. Role of transient elastography in HBV settings

3.1. Inactive HBV carriers

Oliveri et al. [46] measured liver stiffness in 68 inactive HBV carriers, defined as chronic HBV carriers with HBV-DNA persistently <10^5 copies/mL and IgM anti-HBc levels <0.200. The mean stiffness value was 5.0±1.8 kPa, with significant difference between subjects with abnormal alanine transaminase (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 been obtained by Maimone et al. [50], who have focused on the utility of TE for the discrimination between HBeAg-negative disease and inactive HBeAg-negative carriers. Liver stiffness measurements were performed on 220 subjects, of whom 125 inactive carriers, defined as patients with a negative HBeAg and positive anti-HBe in serum, persistently normal ALT and AST and HBV-DNA <10^5 copies/mL. Liver stiffness was significantly different between the inactive carriers group and the chronic disease group, with the inactive carriers showing a mean TE value of 4.8±1.2 kPa and a median value of 4.7 kPa (range 2.4–7.9 kPa).

3.2. Chronic hepatitis B

Transient elastography has been evaluated extensively as a non-invasive tool to assess liver fibrosis in patients with chronic hepatitis C infection [31,32,34–39]. Also in patients with chronic hepatitis B (CHB), the available studies [40,46, 49–54] have shown a significant positive correlation between TE values and fibrosis stages at liver histology. Coco et al. [40] showed that mean values of liver stiffness were correlated with fibrosis stage both in chronic hepatitis C (CHC) and CHB patients subsets. CHC patients with US signs of cirrhosis had higher liver stiffness values than HBV patients (28.6 versus 19.2 kPa), but the profiles of biochemical activity of the two groups were different (8 of 74 patients with CHC were in biochemical remission at the time of liver stiffness measurements as compared with 17 of 41 patients with CHB).

In another Italian study [46], 188 untreated CHB patients were examined with TE to identify optimal cut-offs for fibrosis ⩾S3 (according to Ishak staging system) and cirrhosis (Ishak ⩾S5 or US cirrhosis). The identified cut-off values were 7.5 kPa for fibrosis ⩾S3 and 11.8 kPa for cirrhosis. The areas under the ROC curve (AUROCs) for fibrosis ⩾S3 and cirrhosis were 0.966 and 0.973 (95% CI 0.942–0.989 and 0.952–0.994), respectively.

The diagnostic performances of these studies for the diagnosis of significant and severe fibrosis are summarized in Tables 3 and 4: the 7.5 kPa cut-off for fibrosis ⩾S3 shows a LR+ of 4.2 and an optimal LR– of 0.07, while the 11.8 cut-off for cirrhosis has a LR+ of 23.6 and a LR– of 0.14.

In a study performed in China [51], TE was performed in 161 consecutive CHB patients undergoing liver biopsy. CHB was defined by positive serology tests for serum hepatitis B surface antigen (HBsAg) for at least 6 months. Median liver stiffness values were 5.9 kPa (3.1–8.9 kPa) for F0, 5.9 kPa

Table 4
Transient elastography (TE) diagnostic performance in CHB patients in diagnosing cirrhosis (F = 4 or S = 6)

	Oliveri 2008 [46]	Marcellin 2009 [52]	Kim 2009 [53]	Chan 2009 [51]
Patients	188	173	99	161
HBeAg +ve (%)	11	NR	59	69
Prevalence (%)	24	8	40	23
Cut off (kPA)	11.8	11	10.3	9–13.4
Sensitivity	86	93	59	79
Specificity	96	87	78	92
LR+[a]	23.1	7.1	2.0	9.8
LR−[a]	0.14	0.08	0.5	0.23
AUROC	0.97	0.93	0.80	0.93

LR+, positive likelihood ratio, LR−, negative likelihood ratio, AUROC, area under the receiver operating curve.
[a] Optimal LR+ $\geqslant$10 and LR− $\leqslant$0.1.

(2.5–10.2 kPa) for F1, 7.0 kPa (3.9–19.6 kPa) for F2, 8.8 kPa (4.8–34.3 kPa) for F3 and 14.2 kPa (8.0–36.9 kPa) for F4 fibrosis. As in other studies, there was a significant overlap of TE values among patients with lower stages of fibrosis. Four optimal cut-off values (at least 90% sensitivity, a maximum sum of sensitivity and specificity, at least 90% specificity and a maximum diagnostic accuracy) were defined for the assessment of different stages of fibrosis. For no fibrosis (METAVIR stage F0 vs F1–4), these optimal cut-off values ranged from 4.2 to 9.0 kPa. For bridging fibrosis (F0–2 vs F3–4), the range was from 6.0 to 11.3 kPa. For cirrhosis (F0–3 vs F4), optimal cut-off values were between 8.4 and 13.4 kPa. In patients with elevated ALT levels, optimal cut-off values tended to be higher. For this reason, an algorithm was derived for the assessment of liver fibrosis according to ALT levels and TE values.

A recent French study [52] was designed to assess the accuracy of TE in patients with chronic hepatitis B by comparing liver stiffness measurements and histological fibrosis stage. 173 HBsAg positive patients, with HBV-DNA $>10^5$ copies/ml and liver histology compatible with chronic hepatitis, were evaluated. Liver stiffness showed significant correlation with both METAVIR and Ishak fibrosis stage. The median value of liver stiffness compared with METAVIR fibrosis stage was 5.1 (2.5–8.5) kPa for F0, 6.0 (2.7–35.3) kPa for F1, 7.0 (2.8–17.6) kPa for F2, 12.8 (5.9–45.1) kPa for F3 and 23.7 (6.4–59.3) kPa for F4. With ROC curves of 0.81 (0.73–0.86), TE proved to discriminate well patients with significant fibrosis (METAVIR F0–F1 vs F2–F4) and even better those with severe fibrosis (F0–F2 vs F3–F4, ROC curves 0.93, 0.82–0.98).

Overall, in CHB patients the cut-offs identified from the studies currently available in the literature vary from 7.2 to 8.4 kPa for diagnosing significant fibrosis and from 10.3 to 13.4 for the detection of liver cirrhosis (Tables 3 and 4).

A further possible approach to assess the diagnostic performances of non-invasive techniques, such as TE, in the setting of CHB patients is the development of diagnostic algorithms.

In a recent study performed in 197 treatment-naïve CHB patients [Viganò et al., unpublished data] a TE-based algorithm for the classification of different stages of liver fibrosis was developed in a training cohort of 128 CHB patients and subsequently validated in a prospective internal validation cohort of 69 CHB patients. All patients underwent, on the same day, TE and liver biopsy. The cut-offs of 6.2 and 9.4 kPa were predefined for the confirmation and the exclusion, respectively, of significant fibrosis (METAVIR F $\geqslant$ 2). Similarly, the cut-offs of 9.4 and 13.1 kPa were predefined for the diagnosis and exclusion, respectively, of cirrhosis (METAVIR F4). According to the results of liver histology, representing the reference standard for the staging of liver fibrosis, the application of this algorithm led to the correct classification of 68% of patients, with 93% overall accuracy, for the diagnosis of significant fibrosis, and to the correct classification of 85% of patients, with 95% overall accuracy, for the diagnosis of cirrhosis.

3.3. Influence of necroinflammation: acute B hepatitis and recurrent hepatitis B flares

Liver stiffness is a physical parameter primarily related to fibrosis, but it could also be influenced by other factors that modify liver elasticity, such as variations of inflammatory infiltrate, oedema and vascular congestion [40,42,55–57].

In HBV setting the role of necroinflammation has been extensively investigated.

Coco et al. [42] observed that both in patients with CHB and in patients with CHC there was a significant correlation between FS and ALT levels. In fact, significant fluctuations of TE values paralleled ALT values during hepatitis flares in patients with acute or chronic hepatitis.

Independent studies [46,54] confirmed these observations in patients with acute liver damage of different etiology. Interestingly, in these patients TE peak values frequently exceeded the thresholds values proposed for cirrhosis in patients who did not have any stiffness component other than fibrosis. Furthermore, also necroinflammation assessed by histological grading (both Ishak and METAVIR systems), has been proved to significantly and independently affect TE

results in patients with liver disease of mixed aetiology [34, 41,45,58].

Thus, intrahepatic inflammation has important implications for TE values, and the ALT pattern has to be taken into account when interpreting the results of TE measurements to avoid the overestimation of liver fibrosis in patients with elevated ALT.

4. Conclusion: When is transient elastography useful?

Transient elastography is a simple, user-friendly and reproducible technique for the non-invasive evaluation of liver stiffness as a surrogate marker of liver fibrosis. Liver stiffness measurements on subjects with chronic liver disease have a significant positive correlation with fibrosis stages at liver histology, regardless of the aetiology. Current data suggest that in the setting of hepatitis B viral disease, TE can play a role in clinical practice.

In *inactive HBV carriers*, mean FS values are similar to those in normal controls and significantly lower than in CHB patients. TE could be introduced as an adjunct to the determination of ALT levels and HBV-DNA, to identify inactive HBV carriers and to select subjects in need of further characterisation, for instance, HBV carriers with inactive viral profile whose increased liver stiffness values suggest the presence of liver damage from other causes. HBV inactive carriers could also be monitored with periodic liver stiffness measurements for a better surveillance of disease reactivation.

In *CHB* settings, TE cut-off values proposed for the diagnosis of significant liver fibrosis and cirrhosis are lower than 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). Further data are needed in order to identify single TE cut-off values for the diagnosis of fibrosis and cirrhosis in CHB, with the proposed cut-offs ranging from 7.2 to 8.4 kPa for significant fibrosis and from 10.3 to 13.4 for cirrhosis.

For a proper assessment of *treatment-naïve patients*, a category of patients who need a correct management in terms of therapy and biopsy timing, the development of diagnostic algorithms, with a confirmatory and an exclusion liver stiffness threshold, could be a promising tool for a correct classification of patients, keeping liver biopsy as reference standard for patients with ambiguous TE values.

Given the proven influence of necroinflammation on liver stiffness values, the pattern of biochemical activity must be taken into account in the interpretation of TE.

Promising but still unexplored issues in the setting of HBV patients will be the possible role of TE in the assessment of CHB immune-tolerant patients and patients with advanced liver disease, for whom TE monitoring could be predictive of prognosis or development of complications. Finally, another possible interesting topic will be the assessment of the role of TE in monitoring CHB patients during antiviral therapy.

Conflict of interest

The authors do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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