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EDITORIAL

Is transient elastography a useful tool for screening liver disease?

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Abstract

Transient elastography (TE) is a new non invasive tool for measuring liver stiffness, which is correlated to the histologic stage of liver fibrosis. Several studies in chronic liver disease (CLD) have determined a good accuracy of TE in predicting significant fibrosis and an optimal accuracy in predicting cirrhosis. Normal liver stiffness ranges between 3.3-7.8 KPa and using a cut off of 7.1 KPa, significant fibrosis and cirrhosis can be excluded with a very high negative predictive value (NPV). Positive predictive value (PPV) for the diagnosis of cirrhosis is lower using just a single scan but increases to 90% if high stiffness values are confirmed by a second independent scan. However the presence of fatty liver and metabolic syndrome slightly increases the readings and may reduce the accuracy of the test. It is uncertain if this increase is related to the presence of steatofibrosis or if it is caused by steatosis itself. TE can be used in screening patients attending the liver clinics to identify those with significant fibrosis or cirrhosis and may be particularly useful in discriminating HBV inactive carriers from chronic hepatitis B patients. TE, however, is not reliable in predicting the presence of esophageal varices in cirrhotics. Another potential indication for TE is the systematic screening of populations at high risk for CLD, such as intravenous drug users and alcoholics, but further studies are needed to determine its diagnostic accuracy in these settings.

Key words: Transient elastography; Screening; Liver disease; Hepatitis B; Hepatitis C; Non alcoholic steatohepatitis; Cirrhosis

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INTRODUCTION

Transient elastography (TE) is a new non invasive tool for measuring liver stiffness, which is correlated to the histologic stage of liver fibrosis[1]. The device (Fibroscan) generates an elastic wave by means of a vibrator applied to the thoracic wall at the level of the right liver lobe. The vibrator produces a shot and a low amplitude shear wave propagating through the liver parenchyma. The velocity of propagation is directly proportional to liver stiffness and is automatically calculated by the instrument. The range of measurements, expressed in kilopascals, varies from 2.5 to 74 KPa.

Many studies have been published on the use of TE in patients with already diagnosed chronic liver disease (CLD) but few have addressed the issue of its possible use as a first line examination in the liver clinic or in facilities where patients at risk of liver disease are attending.

HOW TO TAKE AND INTERPRET THE MEASUREMENTS

In order to obtain valid and reproducible measurements the probe should be placed at the center of the right liver lobe, two intercostal spaces below the upper liver margin and at the level of the anterior or middle axillary line. If measurements are taken below this point and too close to the lower liver edge both the percentage of valid shots and the median stiffness tend to decrease[2]. Ultrasound assistance to locate the upper liver margin is usually unnecessary if the patient is reasonably thin because the liver can be recognized by percussion alone. The device incorporates an M-mode window enabling the operator to locate the liver parenchyma and avoid both ribs and lung. If the shot does not generate a readable wave the software classifies the measurement as unsuccessful. Liver stiffness

is defined as the median of 10 successful measurements and according to the manufacturer's recommendations at least 60% of the shots should be successful for each exam. The main reason for unsuccessful examination in the Western world is patients being overweight, while in the East intercostal spaces which are too narrow often hamper the appropriate contact of the probe. Overall failure rates in different studies range between 2.4% and 9.4%[3-6]. The presence of diabetes and being a transplant recipient have also been identified as independent predictors of failure in a recent study of 215 patients with CLD[7]. TE cannot be performed in ascitic patients because the interposed fluid blocks the progression of the shear wave. Other contraindications are pregnancy and the presence of a cardiac pacemaker because there are no safety studies on the use of TE in these conditions. TE is easy to perform, quick and reproducible although fatty liver and a low fibrosis stage may decrease reproducibility[3]. TE can also be easily learnt and performed by nurses[8] and the results are immediately available, thus saving physician's time and rendering this method particularly suitable for screening a large number of patients.

The validity of the results depends on one important parameter: the variability of measurements. This is reflected by the interquartile range (IQR), representing the range of values including 50% of patients above and below the median. According to the manufacturer's suggestion the IQR/median stiffness ratio should not exceed 30% of the median value, although it seems that 20% could assure the best concordance between liver biopsy and TE[9]. There are no studies specifically dealing with the problem of excessive variability of readings and therefore the interpretation of results is derived more from personal experience and from the manufacturer's advice than from observational data. It is still unknown if variability is observed only in diseased or also in normal livers and how this variability affects the interpretation of the test. The cause may be an improper examination technique or it may be inherent to the liver disease itself e.g. in macronodular cirrhosis stiffness may change in different areas of the liver. When variable readings are obtained it is important to check if the probe is perpendicular to the thoracic wall, that the vibrator is not touching against a rib and if the elastografic wave is straight and narrow. If the wave that has been generated is broad, bifid or angulated the software may reconstruct the velocity curve in different parts of the wave and give variable readings. It is important in these cases to obtain a "good" elastogram. This can be obtained by placing the probe in the middle of the right lobe and avoiding contact with the rib as that may dampen the shot and distort the shear wave.

WHAT ARE THE NORMAL VALUES OF TRANSIENT ELASTOGRAPHY?

Paradoxically many studies have been published in CLD patients, but only three in apparently normal subjects (Table 1): the first as a full paper[10] the second as a letter[11] and the third as an abstract[12]. In the first study, performed by Roulot, 429 apparently healthy subjects attending a free health check were studied by a single operator. Only values with an IQR/median stiffness of less than 30% were considered in the analysis, thus overcoming the problem of variability. Results could be obtained in 93.4% of the subjects, indicating that TE has a low failure rate in the general population. However, the percentage of failures rose to 25% in obese individuals (BMI > 30 kg/m^2) and 88% in morbid obese individuals, confirming that TE is not a good method for screening overweight people. This is a significant drawback, because many obese subjects have fatty livers and need a rapid, non invasive method to rule out significant fibrosis. Using the 5th and 95th centiles normal values were set between 3.3-7.8 KPa in women and 3.8-8 KPa in men. In the main studies of TE in chronic liver disease[13-18] the mean cut-off for significant fibrosis was established between 7 and 8 KPa, (Table 2), which is higher than the 95th centile of normal subjects. TE can thus reliably distinguish normal individuals from patients with significant fibrosis, although overlap exists with mild fibrosis. In addition none of the normal subjects studied by Roulot had values higher than 13-17 KPa, which is considered the cut off range for cirrhosis of all etiologies (Table 3).

Table 1 Liver stiffness in the normal population and factors influencing its measurement

	Corpechot C[11]	Roulot D[10]	Colombo S[12]
Number of subjects	71	429	327
Population	Healthy volunteers	Medical check-up	Blood donors
Mean stiffness (KPa)	4.8 (2.5-6.9)[1]	5.4 ± 1.5[2]	4.9 ± 1.7[2]
95th centile	-	8.6	7.8
Age	No effect	No effect	No effect
Gender	M > F	M > F	M = F
High BMI	Increased	Increased	Increased
Metabolic syndrome	-	Increased[3]	-
Fatty liver	-	-	Increased[3]

[1]Range; [2]Standard deviation; [3]At multivariate analysis.

Our group reproduced the same results in voluntary blood donors[12]: in the absence of fatty liver we observed a mean normal liver stiffness of 4.6 KPa ± 1.52 SD. Using 6.9 as the optimal cut off for normal individuals and comparing it with the cut offs from the literature, we obtained a 96% NPV for ruling out significant fibrosis and a 100% NPV for ruling out cirrhosis. In conclusion, normal subjects can be reliably differentiated from CLD patients. TE could thus be proposed as a good screening tool to detect significant fibrosis and as an optimal tool for the detection of cirrhosis, irrespective of the etiology.

DO STEATOSIS AND TRANSAMINASE LEVELS AFFECT THE READINGS?

An important finding of Roulot's paper is that mean stiffness was found to be 1.3 KPa higher in subjects with metabolic syndrome than in those without.

Table 2 Diagnostic performance of TE in the diagnosis of significant fibrosis

	Oliveri[14]	Marcellin[13]	Castera[35]	Ziol[15]	Fraquelli[3]	Corpechot[18]	Kelleher[16]	Yoneda[17]
Patients	268	170	183	251	200	95	129	67
F2 or higher (%)	69	50	74	65	50	60	50	49
Etiology	HBV	HBV	HCV	HCV	80% HCV	PBC/PSC	Nafld	Nafld
Cut Off (KPa)	7.5	7.2	7.1	8.8	7.9	7.3	8.7	6.6
Sensitivity (%)	93	70	67	56	72	84	81	82
Specificity (%)	88	83	89	91	84	87	78	81
AUROC	0.96	0.81	0.83	0.79	0.86	0.92	0.86	0.87

Table 3 Diagnostic performance of TE in the diagnosis of cirrhosis

	Olivieri[14]	Marcellin[13]	Castera[35]	Ziol[15]	Fraquelli[3]	Ganne-Carrié[5]	Corpechot[11]	Foucher[33]	Nguyen[36]	Yoneda[17]
Patients	268	202	183	251	200	775	95	354	103	67
Cirrhotics (%)	24	8	25	19	26	15	16	13	32	7.50
Etiology	HBV	HBV	HCV	HCV	80% HCV	All	PBC/PSC	All	Alcohol	Nafld
Cut-off (KPa)	11.8	11	12.5	14.6	11.9	14.6	17.3	17.6	19.5	17
Sensitivity (%)	86	93	87	86	91	79	93	77	91	93
Specificity (%)	96	87	91	96	89	95	95	97	100	95
AUROC	0.97	0.93	0.95	0.97	0.91	0.95	0.96	0.96	0.92	0.99

Metabolic syndrome was also the main predictor of increased stiffness after adjustment for age, sex, BMI and liver enzymes. This finding suggests that the normal ranges for liver stiffness should be shifted upwards in overweight patients with metabolic syndrome. However no ultrasound examination was performed in this study and therefore it was unknown if the increased stiffness was dependent on metabolic syndrome itself or on fatty liver. To answer this question we investigated 327 healthy blood donors using TE and abdominal ultrasound performed on the same day by two operators with good concordant readings[11]. Similarly to Roulot's study we had a very low failure rate (2.4%) confirming the good applicability of TE in population studies. At multiple regression analysis we found that the degree of steatosis, and not BMI, sex, age and liver enzymes, was related to liver stiffness. The central issue is whether steatosis itself increases liver stiffness or if it is caused by an underlying steatofibrosis. Data from the literature are inconclusive: in one study patients with chronic hepatitis C and the same fibrosis stage had increased liver stiffness if they had concomitant fatty liver[19]. In addition, there was a close relationship between the augmentation of liver stiffness and the degree of steatosis. However studies in chronic hepatitis B have shown that patients with the same stage of fibrosis had lower[20] or equal stiffness[21] in the case of accompanying steatosis. It seems unlikely that steatosis might influence liver stiffness in discordant ways depending on the type of hepatitis and therefore further studies are needed to clarify this issue.

Another possible confounding factor is the effect of transaminase (ALT) level. It is well known that acute hepatitis may spuriously cause extreme and transient elevations of liver stiffness[6,22,23], but also minor ALT elevations can alter TE readings and cause discordance with histological stage[24]. If elevated ALT may overestimate fibrosis stage the opposite is also true: e.g. elderly patients with normal or minimally elevated ALT may have their fibrosis stage underestimated. An algorithm has been proposed to correct for the underestimation of fibrosis in the elderly, but this algorithm has not yet been validated[24]. In conclusion, abdominal ultrasound and ALT determination should always be used together with TE in population screening.

NEW TECHNIQUES: REAL TIME ELASTOGRAPHY

From the above considerations it would be attractive to use a new device incorporating liver stiffness measurements with conventional ultrasound. This task could be accomplished by real time ultrasonography. This technique is performed with conventional ultrasound probes and equipment such as Hitachi EUB-8500 and EUB-900 machines. The examined tissue is divided into up to 30000 finite elements and compression is applied with the probe itself to the skin overlying the liver. During compression the displacement of each element is measured and recorded: in hard tissue the amount of displacement is low, whereas in soft tissue the amount of displacement is high. The calculation of soft tissue elasticity distribution is performed in real time and the results are presented in a colour-coded scale with a conventional B-mode image in the background. Liver stiffness can thus be determined during a conventional routine upper abdominal utrasonography. This new technique is rapid and cheaper than Fibroscan, but its accuracy should be tested against classic TE and liver biopsy. In one study comparing liver biopsy and real time ultrasonography the areas under the receiver operating curve (AUROC) were inferior to TE: 0.75 for equal or higher than F2 fibrosis, 0.73 for equal or higher than F3, 0.69 for F4 and APRI itself performed better than the new technique[25]. Using heart beats instead of manual

compression for displacement[26] may improve the accuracy and lead to better standardization. Clearly more studies are needed and at this time only TE has sufficient body of evidence to be proposed for screening studies.

WHEN TRANSIENT ELASTOGRAPHY CAN BE USED AS A FIRST LINE EXAMINATION

TE could theoretically be used to screen patients attending the liver clinic in order to identify: (a) patients with chronic hepatitis B and C with significant fibrosis, to establish an indication for antiviral therapy; (b) patients with non alcoholic fatty liver disease (NAFLD) or non alcoholic steatohepatitis with significant fibrosis in which aggressive dietary intervention or new therapies could be proposed; (c) patients with liver cirrhosis, in order to start sonographic surveillance for hepatocellular carcinoma; (d) patients with liver cirrhosis and significant portal hypertension, in order to start endoscopic surveillance of esophageal varices.

Outside the liver clinic TE could also be used to systematically screen populations at high risk for liver disease e.g. intravenous drug addicts or alcoholic patients attending rehabilitation programs.

In the clinical setting accuracy for the diagnosis of cirrhosis is higher than for significant fibrosis with a median AUROC of 0.95 *vs* 0.86 irrespective of the etiology of liver disease (Tables 2 and 3). The best accuracy is achieved in ruling out cirrhosis, with a NPV close to 100%[1]. It should be stressed that despite similar AUROCs, cut offs for significant fibrosis and cirrhosis vary according to etiologies, being lower for hepatitis B, intermediate for hepatitis C and higher for NAFLD or alcoholic liver disease. In chronic hepatitis C and NAFLD there is a continuous spectrum of fibrosis irrespective of ALT levels and therefore it would be preferable to use ranges of values instead of cut-offs[1]. On the contrary, in hepatitis B virus infection there is no spectrum of continuity between the inactive carrier state and the chronic hepatitis B patient[27] and the use of a cut off value would be appropriate. TE can reliably differentiate the inactive carrier from chronic hepatitis B. In a recent paper[14] the mean stiffness value of the liver of an inactive carrier was found to be 5 KPa ± 1.8 SD, which is similar to normal controls and different from chronic hepatitis B patients with significant fibrosis. Therefore, if a patient suspected to be an inactive carrier has normal stiffness and elevated ALT, another cause for the increased ALT levels should be sought e.g. concomitant NAFLD. The capacity of correctly identifying chronic HBV carriers could be of immense value in regions with high prevalence of HBsAg, where it could be used together with ALT measurement as a quick and cheap screening test for a large proportion of the population.

If TE is a useful tool to diagnose significant fibrosis and cirrhosis in CLD patients and to define the inactive HBsAg carrier, it is not so for predicting portal hypertension and esophageal varices. In fact a good correlation between stiffness and hepatic-vein portal gradient (HVPG) was found only up to HVPG values of 10-12 mmHg, whereas for higher values the correlation was suboptimal[28]. This could be explained by the fact that TE measures the initial rise of portal pressure caused by the accumulation of a fibrillar matrix, but not the complex hemodynamic changes of late portal hypertension[29]. Accordingly TE was not accurate in prediction of esophageal varices, with an AUROC ranging from 0.76 to 0.84 in various studies[29-31]. Although sensitivity was good (71%-96%) , specificity and positive predictive values (PPV) were low (60%-80% and 48%-54%) and overall accuracy was inferior compared to simple tests like platelet count/spleen diameter ratio[32]. Another problem arising from these studies is the wide range of proposed cut offs, varying from 13.9 to 21.3 KPa for all varices and from 19 to 30 KPa for F2 varices[30,31]. The optimal cut offs therefore are still to be defined.

It would also be interesting to determine a cut off for liver stiffness associated with an increased risk for hepatocellular carcinoma, thus warranting enhanced surveillance for this type of patient. This issue was addressed in only one study[33] in which 144 patients with cirrhosis or advanced fibrosis of varying etiologies were studied with TE and appropriate imaging. According to the authors, a cut of 53.7 KPa could identify cirrhotics harbouring hepatocellular carcinoma with good specificity (87%) and high NPV (90%). PPV and sensitivity were however too low (around 30%) to propose TE as a screening tool for determining the risk of hepatocellular carcinoma. Moreover the conclusions were drawn from only 19 liver cancer patients and clearly more studies are needed in larger cohorts of patients.

In different settings from liver clinics, TE has been studied in IVDU[34] and alcoholics participating in a rehabilitation program (Melin P, personal communication). In the first study, conducted in Denmark, 434 IVDU from 6 methadone clinics were studied[34]. Among the 394 subjects in which TE could be performed, 11 % had cirrhosis (> 12 KPa) and 16% significant fibrosis (8-12 KPa). Twenty-five patients with stiffness > 12 KPa had a repeated TE measurement at the time of liver biopsy. It is interesting to note that 6 patients had a stiffness < 12 KPa at the second scan and all of them had mild fibrosis at biopsy, while only 1 out of 19 patients confirmed at the second scan had mild fibrosis. The authors conclude that two consecutive and concordant scans are needed in order to establish a confident diagnosis of cirrhosis. In fact, PPV for the diagnosis of cirrhosis increased from 50% to 94% after 2 independent scans. The take home message of this study is that in population screening, it is advisable to confirm all elevated results with a second independent scan.

CONCLUSION

In conclusion, there are not enough data to recommend TE as a screening tool outside of liver clinics and

specific studies are needed on high risk populations. On the basis of existing evidence we can conclude that TE has a high NPV to exclude cirrhosis. PPV is low with a single scan but can increase to 90% if high stiffness values are confirmed by a second independent scan. Accuracy for diagnosing significant fibrosis is lower than for cirrhosis and different cut offs must be taken into account. However, TE is not useful for the prediction of esophageal varices, because PPV is low and cut-offs are still undefined.

REFERENCES

1 **Castera L**, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol* 2008; **48**: 835-847

2 **Abergel A**, Bonny C, Randl K, Nicolas C, Roszyk L, Noirfalise C, Massoulier S, Chauterame B, Sapin V, Bommelaer G. Fibroscan measures according to intercostal space: validity andconcordance. *J Hepatol* 2008; **48** Suppl 2: S268

3 **Fraquelli M**, Rigamonti C, Casazza G, Conte D, Donato MF, Ronchi G, Colombo M. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. *Gut* 2007; **56**: 968-973

4 **Castera L**, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Ledinghen V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; **128**: 343-350

5 **Ganne-Carrie N**, Ziol M, de Ledinghen V, Douvin C, Marcellin P, Castera L, Dhumeaux D, Trinchet JC, Beaugrand M. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. *Hepatology* 2006; **44**: 1511-1517

6 **Coco B**, Oliveri F, Maina AM, Ciccorossi P, Sacco R, Colombatto P, Bonino F, Brunetto MR. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. *J Viral Hepat* 2007; **14**: 360-369

7 **Marin-Gabriel JC**, De-la-Cruz JB, Tocado M, Rodriguez-Gil Y, Fernandez-Vasquez I, Manzano-Alonso ML, Martin-Algibez AM, Meneu-Diaz JC, Coline-Ruiz Delgado F, Moreno-Gonzales E, Solis-Herruzo JA, Castellano-Tertajada G. Failure of liver stiffness measurement with fibroscan: prevalence and determinants. *J Hepatol* 2008; **48** Suppl 2: S279

8 **Kettaneh A**, Marcellin P, Douvin C, Poupon R, Ziol M, Beaugrand M, de Ledinghen V. Features associated with success rate and performance of FibroScan measurements for the diagnosis of cirrhosis in HCV patients: a prospective study of 935 patients. *J Hepatol* 2007; **46**: 628-634

9 **Lucidarme D**, Foucher J, Le Bail B, Castera L, Villars S, Forzy G, Filoche B, Couzigou P, deLedinghen V. Ratio interquartile range / median value of liver stiffness measurement is a key factor of accuracy of transient elastography (FIBROSCAN®) for the diagnosis of liver fibrosis. *Hepatology* 2007; **46** Suppl: A318

10 **Roulot D**, Czernichow S, Le Clesiau H, Costes JL, Vergnaud AC, Beaugrand M. Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome. *J Hepatol* 2008; **48**: 606-613

11 **Corpechot C**, El Naggar A, Poupon R. Gender and liver: is the liver stiffness weaker in weaker sex? *Hepatology* 2006; **44**: 513-514

12 **Colombo S**, Belloli L, Buonocore M, Jamoletti C, Zaccanelli M, Badia E, Del Poggio P. Liver Stiffness values in the normal population: a studying voluntary blood donors. *Hepatology* 2008; **48** Suppl: A995

13 **Marcellin P**, de Ledinghen V, Dhumeaux D, Poupon R, Ziol M, Bedossa P, Beaugrand M. Non invasive assessment of liver fibrosis in chronic hepatitis B using Fibroscan. *Hepatology* 2005; **42** Suppl: A715

14 **Oliveri F**, Coco B, Ciccorossi P, Colombatto P, Romagnoli V, Cherubini B, Bonino F, Brunetto MR. Liver stiffness in the hepatitis B virus carrier: A non-invasive marker of liver disease influenced by the pattern of transaminases. *World J Gastroenterol* 2008; **14**: 6154-6162

15 **Ziol M**, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, de Ledinghen V, Marcellin P, Dhumeaux D, Trinchet JC, Beaugrand M. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology* 2005; **41**: 48-54

16 **Kelleher T**, MacFarlane C, de Ledinghen V, Beaugrand M, Foucher J, Castera L. Risk factors and hepatic elastography (FibroScan) in the prediction of hepatic fibrosis in non-alcoholic steatohepatitis. *Gastroenterology* 2006; **130**: A736

17 **Yoneda M**, Yoneda M, Fujita K, Inamori M, Tamano M, Hiriishi H, Nakajima A. Transient elastography in patients with non-alcoholic fatty liver disease (NAFLD). *Gut* 2007; **56**: 1330-1331

18 **Corpechot C**, El Naggar A, Poujol-Robert A, Ziol M, Wendum D, Chazouilleres O, de Ledinghen V, Dhumeaux D, Marcellin P, Beaugrand M, Poupon R. Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. *Hepatology* 2006; **43**: 1118-1124

19 **Lupsor M**, Stefanescu H, Sparchez Z, Serban A, Grigorescu M, Iancu S, Suten T, Badea R. The influence of fatty load on liver stiffness in chronic hepatitis C patients. *J Hepatol* 2008; **48** Suppl 2: S278

20 **Gaia S**, Carenzi S, Brunello F, Barilli AL, Lagger M, Bugianesi E, Smedile A, Rizzetto M. Is liver stiffness measurement different in patients with NASH or with viral hepatitis? *Dig Liver Dis* 2008; **40**: A128

21 **Kim SU**, Kim DY, Park JY, Ahn SH, Paik YH, Choi EH. The impact of steatosis on liver stiffness measurement using fibroscan in patients with hepatitis B virus related chronic liver disease in Korea. *Hepatology* 2008; **48**: Suppl 4: A994

22 **Arena U**, Vizzutti F, Corti G, Ambu S, Stasi C, Bresci S, Moscarella S, Boddi V, Petrarca A, Laffi G, Marra F, Pinzani M. Acute viral hepatitis increases liver stiffness values measured by transient elastography. *Hepatology* 2008; **47**: 380-384

23 **Sagir A**, Erhardt A, Schmitt M, Haussinger D. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. *Hepatology* 2008; **47**: 592-595

24 **Calvaruso V**, Cammà C, Di Marco V, Maimone S, Bronte F, Enea M, Pleguezuelo M, Xirouchakis E, Misseri M, Manousou P, Dusheiko M, Burroughs A, Craxi A. Error factors for transient elastography in chronic hepatitis C. *Hepatology* 2008; **48** Suppl: A313

25 **Friedrich-Rust M**, Ong MF, Herrmann E, Dries V, Samaras P, Zeuzem S, Sarrazin C. Real-time elastography for noninvasive assessment of liver fibrosis in chronic viral hepatitis. *AJR Am J Roentgenol* 2007; **188**: 758-764

26 **Yoshioka K**, Kawabe N, Hashimoto S. Transient elastography: Applications and limitations. *Hepatol Res* 2008; **38**: 1063-1068

27 **Lok AS**, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007; **45**: 507-539

28 **Vizzutti F**, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, Petrarca A, Moscarella S, Belli G, Zignego AL, Marra F, Laffi G, Pinzani M. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology* 2007; **45**: 1290-1297

29 **Lim JK**, Groszmann RJ. Transient elastography for diagnosis of portal hypertension in liver cirrhosis: is there still a role for hepatic venous pressure gradient measurement? *Hepatology* 2007; **45**: 1087-1090

30 **Castera L**, Bernard PH, Le Bail B, Foucher J, Merrouche W,

Couzigou P, de Ledinghen V. What is the best non invasive method for early prediction of cirrhosis inchronic hepatitis C? Prospective comparison between Fibroscan and serum markers. *Hepatology* 2007; **46** Suppl: A581

31 **Kazemi F**, Kettaneh A, N'kontchou G, Pinto E, Ganne-Carrie N, Trinchet JC, Beaugrand M. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. *J Hepatol* 2006; **45**: 230-235

32 **Giannini E**, Botta F, Borro P, Risso D, Romagnoli P, Fasoli A, Mele MR, Testa E, Mansi C, Savarino V, Testa R. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. *Gut* 2003; **52**: 1200-1205

33 **Foucher J**, Chanteloup E, Vergniol J, Castera L, Le Bail B, Adhoute X, Bertet J, Couzigou P, de Ledinghen V. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 2006; **55**: 403-408

34 **Klemmensen Mossner B**, Riis Jorgensen T, Skamling M, Pedersen C, Christensen PB. Outreach screening of drug users with fibroscan identifies a high proportion of severe fibrosis not previously recognized. *J Hepatol* 2008; **48** Suppl 2: S276

35 **Castera L**, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Ledinghen V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; **128**: 343-350

36 **Nguyen-Khac E**, Chatelain D, Tramier B, Decrombecque C, Robert B, Joly JP, Brevet M, Grignon P, Lion S, Le Page L, Dupas JL. Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan: prospective comparison with seven non-invasive laboratory tests. *Aliment Pharmacol Ther* 2008; **28**: 1188-1198

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