How to Screen?

6

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Introduction

The Baveno V consensus conference recommended 5 years ago that all patients with newly diagnosed cirrhosis should undergo screening endoscopy for assessing gastroesophageal varices in order to begin primary prophylaxis, if required, and hepatic vein pressure gradient (HVPG) measurement should be obtained for prognostic aims whenever available [1]. However, in the meantime noninvasive methods have been increasingly validated and used not only for staging liver fibrosis but also to predict complications of cirrhosis including those related to portal hypertension [2]. Among noninvasive methods, transient elastography (TE) (FibroScan™, Echosens, Paris, France) has reached an established role in clinical practice, particularly in viral hepatitis-induced chronic liver diseases and is now routinely used worldwide [3]. Several meta-analyses [4–8] have confirmed the excellent performance of liver stiffness (LS) measurement using TE for diagnosing cirrhosis in patients with chronic liver disease, with mean AUROC values of 0.94 and a suggested optimal cut-off of 13 kPa [6]. In clinical practice, TE is better at ruling out than ruling in cirrhosis with negative and positive predictive values of 96 % and 74 %, respectively [9]. Although different cut-offs have been proposed for cirrhosis according to etiologies (ranging, for instance, from 11 kPa in chronic hepatitis B [10] to 22.6 kPa in alcoholic liver disease [11]), it should be kept in mind that these cut-off values have been defined in a single population using ROC curves in order to maximize sensitivity and specificity – and not applied to a validation cohort. Difference between cut-offs may be simply related to difference in cirrhosis

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prevalence in the studied populations, known as the spectrum bias [12]. Finally, the cut-off choice should also consider the pretest probability of cirrhosis in the target population (varying from less than 1 % in the general population to 10–20 % in tertiary referral centers). For instance, it has been shown that in a population with a pretest probability of 13.8 %, at a cut-off <7 kPa, cirrhosis postestprobability ranged from 0 to 3 %, whereas at a cut-off >17 kPa cirrhosis probability was 72 % [13]. Interestingly, several recent studies have shown that in patients with chronic liver disease, LS could also predict clinical decompensation as well as survival [14–17]. For instance, Robic et al. [15] found that TE was as effective as HVPG measurement in predicting clinical decompensation in 100 patients with chronic liver disease with a 2 years follow-up. Both HVPG $\leq$ 10 mmHg and liver stiffness $\leq$21.1 kPa had 100 % negative predictive value for portal-hypertensive complications. However in clinical practice, TE results should always be interpreted being aware of the risk of overestimating liver stiffness values with confounding factors such as ALT flares, food intake, extrahepatic cholestasis, congestive heart failure, and excessive alcohol intake [18].

Thanks to the improvements in the noninvasive methods, most patients are currently diagnosed in a very initial stage of cirrhosis, in which CSPH and esophageal varices (EV) are often absent. In this new scenario, a large proportion of HVPG measurements and screening endoscopies may be unnecessary. Therefore, efforts should be directed at limiting these procedures to those patients at higher risk of CSPH and varices, so as to reducing healthcare cost and lessen patients' discomfort [19]. There are two clinically relevant questions when screening for portal hypertension: first, identification of patients at high risk for clinically significant portal hypertension (CSPH) defined by an HVPG $\geq$ 10 mmHg [20]; second, identification of patients at high risk for EV.

Detection of Patients at High Risk for CSPH

Among available noninvasive tests, LS measurement using TE has been the most extensively studied. There is substantial evidence indicating that TE can be quite effective in detecting patients with a high risk of having (or not having) developed CSPH. Several studies have shown that there is a good correlation between liver stiffness values and HVPG in patients with advanced liver diseases [21–24]. According to a recent meta-analysis (based on 5 studies including 420 patients), the diagnostic performance of TE for predicting CSPH in the setting of patients with compensated chronic liver disease/cirrhosis is excellent, with an AUROC of 0.93 [25]. TE was very informative with 81 % probability of correctly detecting significant portal hypertension following a "positive" measurement (over the threshold value) and lowering the probability of disease to as low as 11 % when "negative" measurement (below the threshold value) was found when the pretest probability was 50 %. However, it should be noted that when the pretest probability of significant portal hypertension was as low as 25 %, the probability of correctly identifying significant portal hypertension decreased markedly. The studies addressing the

diagnostic performances of TE for the detection of CSPH [22–24, 26–31] are summarized in Table 6.1. The results of these studies deserve several comments: most if not all of them have been conducted in European expert centers where HVPG is available with a likely referral bias. Indeed, studied populations are heterogeneous in terms of etiologies and Child-Pugh classes (ranging from 20 to 100 % for Child-Pugh class A) with small sample size (<100 patients) and high prevalence of CSPH (51–86 %). These are limitations that are inherent to the HVPG technique and thus will be difficult to overcome but that hamper the applicability of these results to the target population of patients with early cirrhosis eligible for screening. Finally, TE cut-offs vary from 13.6 to 34.9 kPa, making the optimal TE cut-offs for prediction of CSPH difficult to be defined. In the largest studied population ($n = 502$), Reiberger et al. [29] have shown that at a cut-off of 18 kPa, TE was better at ruling in than ruling out CSPH (positive and negative predictive values of 86 and 81 %) [29]. Other authors [27] have proposed a dual cut-off strategy (<13.6 kPa with a 90 % sensitivity for CSPH diagnosis and ≥21 kPa with a 90 % specificity), allowing a correct stratification of presence/absence of CSPH in patients with compensated cirrhosis and potentially resectable hepatocellular carcinoma, reducing the need for invasive hemodynamic assessment in around 50 % of patients. However, while the correlation is excellent for HVPG values between 5 and 10–12 mmHg (typical of cirrhosis without evident clinical manifestations related to portal hypertension), it hardly reaches statistical significance for values above 12 mmHg [22]. This is because,

Table 6.1 Diagnostic performance of transient elastography for the detection of clinically significant portal hypertension (HVPG ≥10 mmHg)

Authors	Year	Patients (*n*)	Etiologies	CP A (%)	CSPH (%)	Cut-offs (kPa)	AUROC	Se (%)	Sp (%)	CC (%)
Vizzutti et al. [22]	2007	61	HCV	46	77	13.6	0.99	97	92	95
Lemoine et al. [24]	2008	44 48	HCV alcohol	100	77 83	20.5 34.9	0.76 0.94	63 90	70 88	98 98
Bureau et al. [23]	2008	150	CLD	20	51	21.0	0.94	90	93	83
Sanchez-Condé et al. [26]	2011	38	HIV-HCV	71	74	14.0	0.80	93	50	81
Llop et al. [27]	2011	79	CLD	100	40	13.6/21	0.84	91/58	57/91	53
Reiberger et al. [29]	2012	502	CLD	NA	55	18.0	0.82	83	82	72
Colecchia et al. [28]	2012	100	HCV	68	65	16.0 / 24.2	0.92	95/52	69/92	65
Berzigotti et al. [30]	2013	117 56	CLD CLD	88 70	67 86	13.6 / 21.1 13.6 / 21.1	0.88 0.91	91/65 NA	56/92 NA	62 70
Kitson et al. [31]	2015	95	CLD	91	74	29.0	0.90	72	100	-

with the progression of cirrhosis, the mechanisms of portal hypertension (PH) become less and less dependent on the intrahepatic resistance to portal flow due to tissue fibrosis and progressively more dependent on extrahepatic factors (i.e., hyperdynamic circulation, splanchnic vasodilatation) [32]. This observation sets a key limitation to the use of liver stiffness measurements as a noninvasive surrogate of HVPG beyond the prediction of clinically significant (HVPG ≥ 10 mmHg) and severe (HVPG ≥ 12 mmHg) PH, and, accordingly, TE of the liver is unlikely to be useful in monitoring the hemodynamic response to the administration of beta-blockers or disease progression in the decompensated phase.

Several biological parameters have been proposed for the noninvasive detection of clinically significant portal hypertension including prothrombin time [23], a score combining platelet count and total bilirubin [33], and FibroTest® [34]. In particular, a score combining platelet count with total bilirubin had an AUROC of 0.91 for predicting clinically significant portal hypertension with 88 % sensitivity and 86 % specificity at a cut-off of −1.0.

Finally, in order to increase diagnostic accuracy, some authors have proposed scores combining LS with platelet count and spleen diameter by ultrasound, referred as LSPS for LSM-spleen diameter to Platelet ratio score [35] or PH risk score [30]. For instance, in a population of 117 patients with compensated cirrhosis, more than 80 % of patients were accurately classified for CSPH using LSPS and PH risk score. These promising results require further external validation but could represent an attractive strategy for screening patients for CSPH as proposed by some authors [36].

Detection of Patients at High Risk for GOV

More uncertain and controversial is the possibility of predicting the presence and the size of OV based on LS measurements (LSM). In a recent meta-analysis [25] (based on 18 studies and 3644 patients), the diagnostic performance of TE for predicting OV and large OV (LOV) was not as good as for CSPH with AUROCS of 0.84 and 0.78, respectively. The studies addressing the performance of TE for prediction of OV [22–24, 28, 37–52] are summarized in Table 6.2. AUROCs range from 0.62 to 0.90 and cut-offs from 13.9 to 48.0 kPa. Although the sensitivity for the prediction of the presence of OV was high (56–100 %), specificity was much lower (32–87 %) and less satisfactory. Regardless, the general features of these studies, i.e., single-center retrospective, heterogeneous etiology of cirrhosis and stages of disease progression, and subjective assessment of OV size, do not allow any sound conclusion on the utility of liver stiffness assessment in predicting the presence of OV and to screen cirrhotic patients without endoscopy [54].

Similarly, several biomarkers have been proposed for the detection of OV including routine biological parameters [55], FibroTest® [56], and combination of simple biological and ultrasound parameters [57]. In the largest study to date comparing retrospectively a panel of serum markers (platelet count, AST/ALT ratio, APRI, Forns index, Lok index, FIB-4, and Fibroindex) in more than 500 patients with

Table 6.2 Diagnostic performance of transient elastography for the detection of esophageal varices (OV and LOV) in cirrhotic patients

Authors	Year	Patients (*n*)	Etiologies	CP A (%)	Endpoint	OV (%)	Cut-offs (kPa)	AUROC	Se (%)	Sp (%)	CC (%)
Kazemi et al. [37]	2006	165	CLD	NA	OV LOV	45 38	13.9 19.0	0.83 0.84	95 91	43 60	66 69
Foucher et al. [38]	2006	144	CLD	NA	LOV	29	27.5	0.73	88	53	NA
Vizzutti et al. [22]	2007	47	HCV	60	OV	66	17.6	0.76	90	43	74
Bureau et al. [23]	2008	89	CLD	34	OV LOV	72 48	21.1 29.3	0.85 0.76	84 81	71 61	81 71
Castera et al. [39]	2009	70	HCV	100	OV LOV	36 19	21.5 30.5	0.84 0.87	76 77	78 85	73 79
Pineda et al. [40]	2009	102°	HIV-HCV	76	LOV	13	21.0	0.71	100	32	44
Nguyen et al. [41]	2010	183	CLD	63	LOV	22	48.0	0.76	73	73	73
Malik et al. [42]	2010	124	CLD	NA	OV	51	20.0	0.85	NA	NA	NA
Pritchett et al. [43]	2011	211	CLD	NA	OV LOV	NA 37	19.5 19.8	0.74 0.76	76 91	66 56	NA 69
Sporea et al. [44]	2011	1000	CLD	NA	LOV	35	31.0	0.78	83	62	NA
Stefanescu et al. [45]	2011	231	HCV/ALD	76	OV LOV	68 29	19.0 38.0	0.66 0.69	84 56	32 75	67 68
Colecchia et al. [28]	2012	100	HCV	68	OV	53	16.4 / 25.0	0.90	96/57	60/98	NA
Chen et al. [46]	2012	222	HBV	49	OV	37	17.1	0.73	90	44	NA
Wang et al. [53]	2012	126	HBV	NA	OV LOV	38 10	12.0 21.0	0.79 0.86	67 77	77 87	73 86
Calvaruso et al. [48]	2013	96	HCV	100	OV LOV	57 27	17.0 19.0	0.70 0.71	71 72	57 55	63 56
Sharma et al. [51]	2013	174	CLD	31	OV	71	27.3	0.91	91	72	86

(continued)

Table 6.2 (continued)

Authors	Year	Patients (*n*)	Etiologies	CP A (%)	Endpoint	OV (%)	Cut-offs (kPa)	AUROC	Se (%)	Sp (%)	CC (%)
Fraquelli et al. [49]	2014	110	HCV/HBV	NA	OV	10	19.0	0.62	73	47	NA
Hu et al. [50]	2015	200	HBV	NA	OV LOV	55 34	20.2 25.2	0.85 0.84	84 86	72 72	NA NA
Stefanescu et al. [52]	2015	90	CLD	62	LOV	52	38.0	0.70	60	71	65

chronic liver diseases, the combination of Lok index (cut-off = 1.5) and Forns index (cut-off = 8.8) had the best diagnostic performance (AUROC of 0.80 and negative predictive value of 90 %) for predicting clinically relevant OV [55]. Finally, as mentioned before for CSPH, scores combining LS with platelet count and spleen diameter by ultrasound such as LSPS or variceal risk score have been proposed [30, 35]. For instance, in 401 Korean patients with HVB cirrhosis (280 in the training set and 121 in the validation set), the LSPS had a significantly better AUROC than TE alone for prediction of high-risk OV (0.95 vs. 0.88 in the training set, respectively, $p < 0.001$) [35]. At a cut-off < 3.5, LSPS had a 94.0 % negative predictive value and a 94.2 % positive predictive value at a cut-off > 5.5. Overall, upper GI endoscopy could be saved in 90.3 % patients. Interestingly, LSPS appeared as a reliable predictor of OV bleeding risk [58]. The performance of LSPS has also been confirmed externally [28, 30]. Using a similar strategy in 173 patients, Berzigotti et al. [30] have shown that only 3 of 70 with varices (4 %; all with small varices) would have been missed if endoscopy was delayed using the varices risk score. These scores appear thus as an attractive strategy in clinical decision making for detecting patients with high-risk OV.

Spleen Stiffness: A New Surrogate of Portal Hypertension?

Recently, studies employing different technical approaches have highlighted the potential utility of spleen stiffness (SS) assessment for the prediction of the presence of OV and the degree of portal hypertension in cirrhotic patients [28, 51, 59]. Colecchia et al. measured SS and LS by TE in 100 consecutive patients with hepatitis C virus-induced cirrhosis patients who underwent measurement of HVPG and upper GI endoscopy [28]. The ability of both SS and LS to predict CSPH and the presence of OV was compared to that of the previously proposed methods, i.e., LSPS and platelet count to spleen diameter [35, 57, 60]. SS and LS were more accurate than other noninvasive parameters in identifying patients with OV and different degrees of portal hypertension. However, TE may not be the most appropriate tool for SS measurement, as ultrasound examination of the spleen was mandatory before performing TE to ensure that the ultrasound beam remained within the spleen parenchyma. Indeed, SS could not be measured in 13 % of patients particularly those with an anteroposterior spleen diameter measuring <4 cm. Alternative ultrasound-based elastography techniques such as acoustic radiation force impulse imaging (ARFI) (Virtual touch tissue quantification™, Siemens) or 2D-shear-wave elastography (2D-SWE) (Aixplorer™, Supersonic Imagine, France) have been proposed for measuring SS with much lower failure rates of 4.5 % [61] and 3 % [62], respectively. Another technical advantage of ARFI and 2D-SWE over TE is that they can be performed using a regular ultrasound machine, allowing during a single procedure to choose the region of interest where the shear-wave velocity is measured under direct visualization of the spleen [63]. Although not clearly demonstrated in the study by Colecchia et al. [28], the study by Takuma et al. [61] in 340 patients showed that SS was better than LS measurement, particularly for ruling out

the presence of OV. Finally, there may be a ceiling effect with TE that showed significantly higher kPa values (up to 70 kPa) with SS values compared with LS at any given HVPG level, suggesting that even an upper detection limit of 75 kPa could be too restrictive for a satisfactory SS measurement and would need to be extended as proposed by some authors [48]. Thus, SS is not ready yet for "prime time," and further validation is needed before its exact place in clinical practice can be defined.

Conclusions and Perspectives

In conclusion, the evidence accumulated so far indicates that noninvasive methods cannot replace HVPG for a detailed portal hypertension evaluation and upper GI endoscopy for detecting OV. However, in settings where HVPG is not available, TE could be considered to stratify the risk of CSPH. Similarly, strategies combining LS measurement with platelet count and spleen diameter could be useful to rule out OV in patients at low risk of having portal hypertension. One would foresee different levels of invasiveness, starting with simple laboratory tests, followed by measurements of LS and, only in a minority of patients, would we need to perform an invasive test.

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