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Noninvasive screening for liver fibrosis and portal hypertension by transient elastography—a large single center experience

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Transiente Elastographie: eine neue nichtinvasive Screeningmethode für Leberfibrose und portale Hypertension

Zusammenfassung

Grundlagen Die transiente Elastographie (TE) ist eine ultraschallbasierte nicht-invasive Methode, um die Lebersteifigkeit (LS) zu messen. Rezente Studien suggerieren, dass die TE als Screeningtool für das Vorliegen einer Leberzirrhose und einer signifikanten portalen Hypertension (≥10 mmHg; CSPH) verwendet werden kann. Die Evidenz durch die aktuelle Datenlage ist jedoch gering.

Methodik Bei 695 Patienten wurde die LS durch eine TE gemessen. Zusätzlich wurden bei 290 Patienten eine Leberbiopsie und bei 502 Patienten eine Pfortaderdruckmessung (HVPG) durchgeführt. Die positiv (PPV) und negativ prädiktiven (PPV) Werte sowie die „area under the curve" (AUC) für die nichtinvasive Diagnostik von histologischen Leberfibrosestadien (F1–F4) sowie einer CSPH wurden in Bezug auf verschiedene LS Grenzwerte berechnet.

Ergebnisse Die Höhe der LS war signifikant mit den histologischen Fibrosestadien assoziiert (R=0.872; $p<0.0001$). Die AUCs lagen für die Diagnose eines Fibrosestadium F2 mit einem TE Grenzwert von >7.2 kPa bei 0.690, für ein F3 Stadium mit einem TE Grenzwert von >9.6 kPa bei 0.737, und für ein F4 Stadium (=Zirrhosestadium) mit einem TE Grenzwert von >12.1 kPa bei 0.904. Mittels einem LS Grenzwert von >12.1 kPa für die Diagnose einer Leberzirrhose (F4) betrugen der PPV 87 % und der NPV 91 %.

Es gab eine signifikante Korrelation zwischen LS und Pfortaderdruck (HVPG): (R=0.794; $p<0.0001$), die bei Patienten mit einer chronischen Virushepatitis (R=0.838; $p<0.0001$) stärker ausgeprägt war als bei Patienten mit alkoholischer Lebererkrankung (R=0.756; $p<0.0001$). Für die Diagnose einer signifikanten portalen Hypertension (CSPH) mittels LS Grenzwert bei >18 kPa lagen der PPV bei 86 % bzw. der NPV bei 80 %.

Schlussfolgerungen Diese Analyse an einem großen Kollektiv von Patienten mit chronischer Lebererkrankung bestätigte die klinische Wertigkeit einer TE als wertvolle nichtinvasive Screeningmethode auf das Vorliegen einer Leberzirrhose. Die klinische Aussagekraft einer TE in Bezug eine nichtinvasive Diagnostik für das Vorliegen einer portalen Hypertension ist jedoch limitiert.

Schlüsselwörter: Transiente Elastographie, Portale Hypertension, HVPG, Fibrose, Zirrhose

Summary

Background Transient elastography (TE) is a noninvasive tool to assess hepatic fibrosis by measuring liver stiffness (LS). Recent studies suggest that TE may be used to screen for liver cirrhosis and clinically significant portal hypertension (≥10 mmHg; CSPH), whereas data on the clinical applicability of TE are limited.

Methods Among 695 patients undergoing measurement of LS, data on liver biopsies and on hepatic venous pressure gradient (HVPG) were available in 290 and 502 patients, respectively. Analysis of the area under the receiver operating curve (AUC) was used to assess the positive (PPV) and negative predictive (NPV) values of LS cut-offs for staging of hepatic fibrosis and for diagnosis of CSPH.

Results LS was significantly associated with fibrosis stage (R=0.872; $p<0.0001$). AUC for diagnosis of fibrosis

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F2 (>7.2 kPa) was 0.690, 0.737 for F3 (>9.6 kPa), and 0.904 for F4 (>12.1 kPa), respectively. At a LS cut-off of 12.1 kPa the PPV and NPV for diagnosis of cirrhosis were 87 and 91 %, respectively. A significant correlation of LS and HVPG was noted (R=0.794; $p<0.0001$), being stronger in patients with viral disease (R=0.838; $p<0.0001$) than in patients with alcoholic disease (R=0.756; $p<0.0001$). The LS cut-off at 18 kPa can identify CSPH with a PPV and NPV of 86 and 80 %, respectively.

Conclusions This large single center study confirms the clinical utility of TE as valuable noninvasive screening tool for liver fibrosis with excellent accuracy to rule out F4 cirrhosis. However, the moderate PPV and NPV limit the diagnostic use of TE for discriminating patients with and without CSPH.

Keywords: Transient elastography, Portal hypertension, Fibrosis, Hepato-venous pressure gradient, HVPG

Introduction

Fibrosis of the liver is a common consequence of chronic liver diseases which can finally lead to cirrhosis with the risk of developing portal hypertension, end-stage liver disease, (ESLD) and hepatocellular carcinoma (HCC) [1, 2]. Therefore, assessment of liver fibrosis and of portal hypertension is crucial for evaluation of patients with chronic liver disease [3]. Despite its invasiveness and its well-described limitations, liver biopsy still represents the gold standard for staging of fibrosis [4]. Measurement of the hepatic venous pressure gradient (HVPG) is a well-established and valuable tool for the management of all patients with cirrhosis and suspected portal hypertension, since it allows detailed evaluation, targeting of therapeutic interventions, and provides important prognostic information [5, 6]. Since repeated liver biopsy is not feasible to provide information on clinical progression of cirrhosis and is not favored by patients and HVPG measurement is not routinely performed in every center, several noninvasive methods have been developed to substitute these invasive procedures, among those several serum biomarkers [7] or measurement of LS by TE [8]. The potential of TE for assessment of the degree of liver fibrosis has been extensively studied in different forms of chronic liver disease [8–12], in this context TE may also provide prognostic information [13, 14]. An additional application of TE for identifying patients with portal hypertension or with gastroesophageal varices has been suggested in several other studies [15–19]. Its application has not been transferred to clinical practice so far. The technical basis for the use of TE as a tool to investigate fibrosis seems clear, although certain limitations have to be considered: Levels of aminotransferases and bilirubin, sex, being overweight or obese, and food intake have all been described to influence the accuracy of transient elastography for staging liver fibrosis [20–22]. In addition, the basis for the correlation of TE with portal hypertension remains poorly defined, since complex hemodynamic abnormalities and blood flow derangements in the splanchnic and hepatic circulation influence the severity of portal hypertension [2, 23–25]. Prior studies evaluating the correlation of liver stiffness measured by TE and portal pressure measured by HVPG found a good correlation in patients with chronic hepatitis C virus (HCV) infection [19], even after liver transplantation [16] and in patients with alcoholic liver disease (ALD) [18]. Interestingly, the reported cut-offs for predicting moderate fibrosis or cirrhosis and for diagnosis of portal hypertension varied between the studies and were not similar for different etiologies of liver disease [18].

The knowledge about the limitations of TE and the controversial opinions about the clinical value of the proposed cut-offs have to be weighed against the potential of TE in obtaining noninvasive, rapid, and reproducible information about our patients with chronic liver disease. Thus, we aimed to further clarify the clinical applicability of TE for noninvasive evaluation of liver fibrosis and of portal pressure in a large patient cohort with different etiologies of chronic liver diseases.

Patients and methods

Patients

Data on TE measurements were collected prospectively from patients with chronic liver disease managed by the hepatic hemodynamic laboratory of the Medical University of Vienna. Exclusion criteria were presence of pre- and posthepatic causes of portal hypertension, elevated aminotransferases >10× upper limit of normal, average daily alcohol intake >50 g within the last 2 months, and active bacterial infections. Data of portal pressure were recorded, if HVPG was measured simultaneously. No vasoactive drugs were allowed [25]. Results of transjugular or percutaneous liver biopsies were evaluated for this analysis if performed within 3 days prior or after liver stiffness measurement. Etiology of liver disease, age, levels of aminotransferases, platelet counts, and history of variceal bleeding were recorded for each patient. The study was approved by the local Ethics Committee (GZ 2009/0497) and conducted according to the principles of the Declaration of Helsinki.

Transient elastography

Measurement of liver stiffness was performed by transient elastography using Fibroscan (Echosens, Paris, France) after an overnight fasting, as previously described in detail [25–26]. Briefly, the tip of the elastography probe was placed in an intercostal space on the right lobe of the liver with the patient lying in dorsal decubitus position and the right arm in maximal abduction. Vibrations with mild amplitude and low frequency are transmitted to the liver tissue. The velocity of the induced shear wave is directly related to liver stiffness. The measurement of liver stiffness was considered as adequate, if the ratio of

interquartile range to median (IQR/median) was <30 % and the success rate was at least 70 %. The results of the median value and the interquartile range were recorded in kilopascals.

Liver biopsy

Liver samples were obtained by transjugular or percutaneous liver biopsy mostly on the same day but at least within 3 days of transient elastography and of HVPG measurement by standard techniques [27, 28]. For transjugular biopsy, a 10 F covering catheter and a 19G biopsy needle (Cook, Bloomington, USA) were used, while percutaneous liver biopsies were carried out using a liver biopsy set with a 17G-needle (Hepafix, LuerLock, Braun, Melsungen, Germany). Specimens were evaluated and scored by an experienced pathologist (J.S.) without knowledge of patients' clinical history. METAVIR score was used for grading necroinflammatory activity and for staging fibrosis in patients with chronic hepatitis C [29]. Liver biopsies of patients with other etiologies were evaluated according to Ludwig's score [30]. The reliability criteria for liver biopsy were a sample length of ≥1 cm including ≥10 portal tracts. Pathologists were blinded of the results of TE and HVPG.

Hepatic venous pressure gradient

Portal pressure was evaluated by measurement of hepatic venous pressure gradient according to international standards [31, 32]. Briefly, under ultrasound guidance and local anesthesia, a catheter introducer set (8.5 F, Arrow International, Reading, USA) was placed in the right internal jugular vein by using the Seldinger technique. A balloon occlusion catheter (7 F, Boston Scientific, Cork, Ireland) was introduced through the upper and lower inferior caval vein into a large liver vein, usually the middle one. Correct placement and adequate wedge position were checked by injection of contrast medium under x-ray control. Permanent tracings were obtained via S/5 Collect Software (General Electric, USA) and digitally recorded for subsequent analysis. At least three repeated measurements of free and wedged hepatic vein pressure were performed to calculate the HVPG. In addition, inferior caval vein pressure as well as systemic blood pressure and heart rate were recorded. Normal portal pressure was defined as an HVPG of 1–5 mmHg, elevated portal pressure as an HVPG of 6–9 mmHg. Clinically significant portal hypertension (CSPH) was present at an HVPG ≥10 mmHg.

Statistical analysis

Quantitative variables are expressed as mean (± standard deviation). Categorical (semiquantitative) variables are expressed as median (± range). Differences between qualitative variables were assessed by Fisher's exact test. Differences between quantitative variables were analyzed by nonparametric tests (Mann-Whitney or Kruskal-Wallis tests). Correlations between parameters were assessed by Spearman's log-rank test and expressed by the Spearman's correlation coefficient. The predictive power of liver stiffness for diagnosing preclinical portal hypertension (HVPG >5 mmHg) and clinically significant hypertension (HVPG ≥10 mmHg) was assessed by calculating the areas under the receiver operator characteristic curves. An area under the curve (AUC) of 1.0 is characteristic of an ideal test, whereas 0.5 indicates a test of no diagnostic value. Best cut-offs for predicting significant fibrosis (F2–F4) and cirrhosis (F4) and for diagnosis of portal hypertension (HVPG >5 mmHg) and clinically significant portal hypertension (HVPG ≥10 mmHg) were selected by the Youden Index (highest sum of sensitivity and specificity). Statistica for Windows version 6.0 (StatSoft, Hamburg, Germany) was used for statistical analysis.

Results

Patients

Among 794 patients undergoing measurement of liver stiffness within the study period, 67 measurements (8 %) showed unreliable results of TE mainly due to obesity or ascites. Twenty patients (3 %) were excluded due to pre- or posthepatic causes of portal hypertension and levels of aminotransferases were >10× upper limit of normal in 12 (2 %) patients. Thus, 695 patients were included in the analysis. Among those 695 patients, 502 patients underwent measurement of HVPG (HVPG-cohort), since portal hypertension was suspected by laboratory parameters or radiologic imaging. Additional transjugular or percutaneous liver biopsies were performed in 302 of those 695 patients (indications: staging of fibrosis in chronic viral hepatitis or assessment of etiology in cases of unknown liver disease). Two hundred and ninety histological results were finally available for analysis (Biopsy-cohort), since 12 (4 %) of liver specimens were too small or insufficient to assess the stage of fibrosis. A total of 227 patients had available data on all three parameters (LS, HVPG, and liver histology: Triple-cohort; Fig. 1, Table 1).

Liver stiffness and portal pressure within certain fibrosis stages

Biopsy Cohort: LS was significantly associated with fibrosis stage (R=0.872; $p<0.0001$). Mean values for LS were calculated for each fibrosis stage: Patients with mild fibrosis showed lower results in TE than patients with moderate fibrosis (F1: 5.1±1.2 kPa vs. F2: 7.2±2.7 kPa; $p=0.006$). Significant differences in LS were present between patients with moderate and severe fibrosis (F2: 7.2±2.7 kPa vs. F3:12.1±7.5 kPa; $p<0.0001$) and with cirrhosis (F3: 12.1±7.5 vs. F4: 32.8±23.4 kPa; $p<0.0001$).

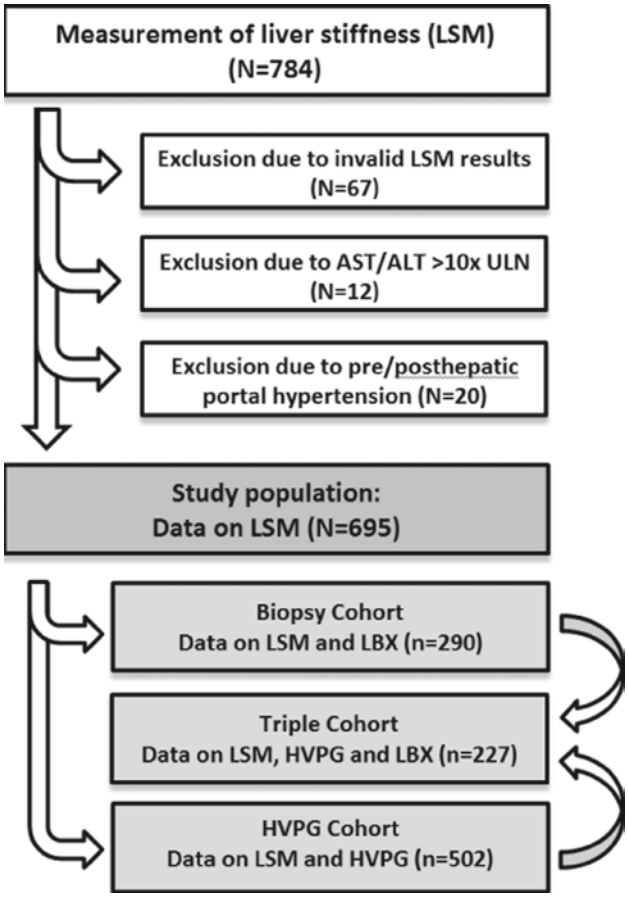

Fig. 1 Patients' flowchart

Table 1. Patients' characteristics

Parameter	
Patients, *n*	695
Sex, m/f	497/198
BMI (kg/m²)	23.1 (±1.4)
Age (year)	50 (±12)
Disease	
Viral Hepatitis, *n* (%)	390 (56)
Alcoholic liver disease, *n* (%)	227 (33)
Autoimmune hepatitis, *n* (%)	31 (4)
Nonalcoholic steatohepatitis (NASH), *n* (%)	47 (7)
Liver stiffness, (kPa) (±SD)	26.4 (±24.2)
Fibrosis stage (Biopsy-cohort)[a] (median (range))	3 (1–4)
F1, *n* (%)	39 (13)
F2, *n* (%)	102 (35)
F3, *n* (%)	41 (14)
F4, *n* (%)	108 (37)
HVPG (HVPG-cohort)[b] (±SD) (mmHg)	12.6 (±7.6)
Normal (HVPG ≤5 mmHg), *n* (%)	136 (27)
PHT (HVPG ≥6 and <10 mmHg), *n* (%)	90 (18)
CSPH (HVPG ≥10 mmHg), *n* (%)	276 (55)

SD standard deviation, *HVPG* hepatovenous pressure gradient, *PHT* portal hypertension defined as HVPG ≥6 mmHg, *CSPH* clinical significant portal hypertension defined as HVPG ≥10 mmHg
[a]290 liver biopsies were available
[b]502 HVPG measurement were performed

Triple Cohort: Fibrosis stages significantly correlated to HVPG (R=0.701; p=0.012). HVPG gradually increased in patients with severe fibrosis (F2: 3.6±1.5 mmHg vs. F3: 7.6±4.3 mmHg; p<0.0001) and cirrhosis (F3: 7.6±4.3 mmHg vs. F4: 12.3±6.9 mmHg; p<0.0001), while patients with mild and moderate fibrosis showed similar

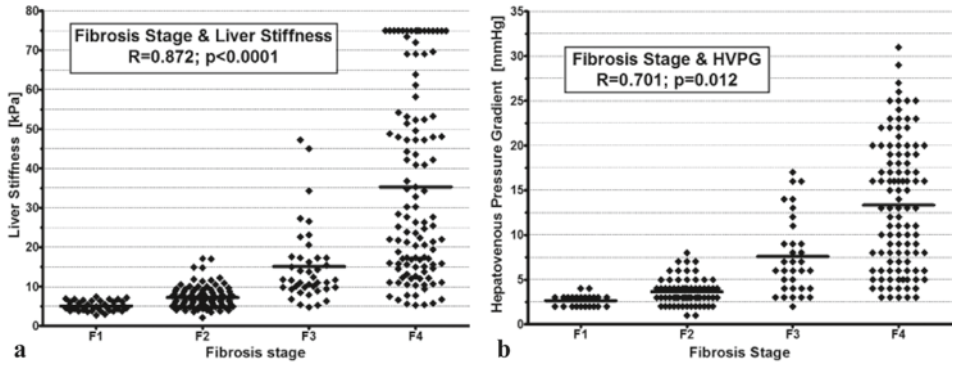

Fig. 2 **a** Fibrosis stage and liver stiffness R=0.872; p<0.0001. **b** Fibrosis stage and HVPG R=0.701; p<0.012

Table 2. Data on liver stiffness and HVPG in different fibrosis stages (triple-Cohort)

Fibrosis stage	Patients (*n*)	Age (year)	Liver stiffness (kPa)	HVPG (mmHg)	Normal HVPG (%)	PHT ≥5 mmHg (%)	CSPH ≥10 mmHg (%)
F1	39	41±13	5.1±1.2	2.7±0.6	100	0	0
F2	102	41±12	7.2±2.7	3.6±1.5	88	12	0
F3	41	46±10	12.1±7.5	7.6±4.3	36	40	24
F4	108	53±10	32.8±23.4	12.3±6.9	17	20	63

HVPG hepatovenous pressure gradient, *PHT* portal hypertension defined as HVPG ≥6 mmHg, *CSPH* clinical significant portal hypertension defined as HVPG ≥10 mmHg

HVPG results (F1: 2.7±0.6 mmHg vs. F2: 3.6±1.5 mmHg; p=0.132). No patient with F1 had portal hypertension (HVPG >5 mmHg) or CSPH (HVPG >10 mmHg). Patients with moderate fibrosis (F2) showed HVPG >5 mmHg in 12 % of cases but no patient had CSPH. The 40 and 24 % of patients with F3 in liver biopsy were diagnosed with portal hypertension and CSPH, respectively. In patients with histologically proven cirrhosis, the prevalence of portal hypertension and CSPH was 20 and 63 %, respectively (Fig. 2, Table 2).

Noninvasive discrimination between fibrosis stages

Biopsy Cohort: Best cut-offs for discriminating between certain stages of liver fibrosis were calculated by ROC curve analysis: 7.2 kPa and 9.6 kPa were the best cut-offs to diagnose moderate fibrosis (F≥2) and severe fibrosis (F≥3) with an AUC of 0.690 and 0.737, respectively. Using a cut-off at 12.1 kPa, the AUC for diagnosis of cirrhosis (F4) was 0.904. The PPV for moderate fibrosis was 78.9 % (F≥2) using 7.2 kPa as cut-off, while the NPV for exclusion of cirrhosis (F<4) was 90.8 % using a cut-off at 12.1 kPa (Table 3).

Table 3. Liver stiffness cut-offs to discriminate between fibrosis stages (Biopsy-Cohort)

	F1 vs. F2/3/4	F1/2 vs. F3/4	F1/2/3 vs. F4
	>7.2 kPa	>9.6 kPa	>12.1 kPa
AUC	0.690 (0.541–0.781)	0.737 (0.703–762)	0.904 (0.847–0.944)
p-value	0.0344	0.0044	0.0001
Specificity (%)	77.4	82.9	86.8
Sensitivity (%)	73.3	86.9	84.8
PPV (%)	78.9	78.5	87.4
NPV (%)	75.2	86.4	90.8

AUC area under the receiver operating characteristics curve, *PPV* positive predictive value, *NPV* negative predictive value

Correlation of liver stiffness and portal pressure

HVPG-Cohort: Clear associations between the results of TE and the results of HVPG were present in all patients with different etiologies of liver diseases, since liver stiffness showed a significant correlation with portal pressure (n=502; R=0.799; p<0.0001; Fig. 3a). This

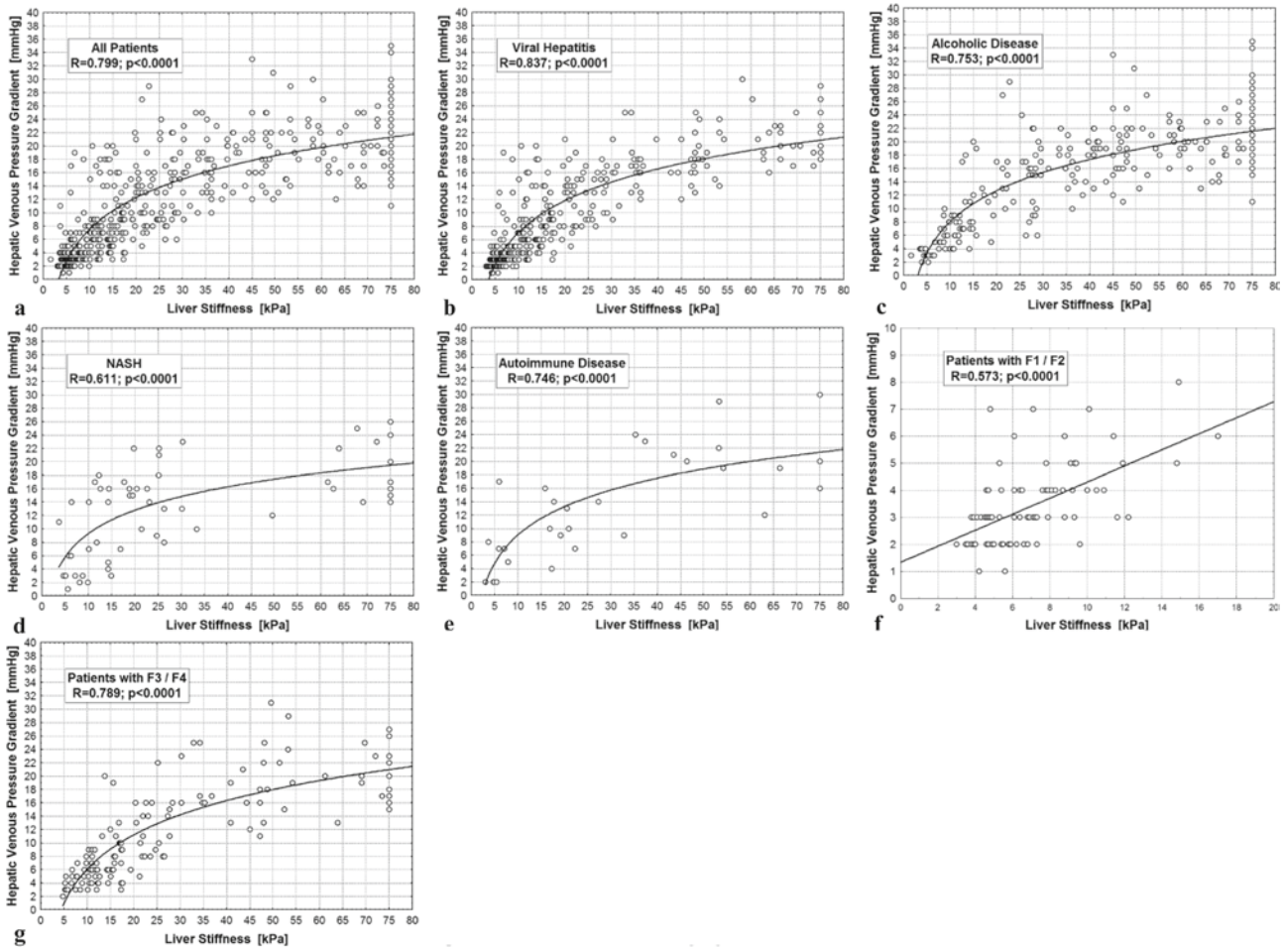

Fig. 3 **a** All patients R=0.799; p<0.0001. **b** Viral Hepatitis R=0.837; p<0.0001. **c** Alcoholic Disease R=0.753; p<0.0001. **d** NASH R=0.611; p<0.0001. **e** Autoimmune Disease R=0.746; p<0.0001. **f** Patients with F1/F2 R=0.573; p<0.0001. **g** Patients with F3/F4 R=0.789; p<0.0001

correlation was more pronounced in patients with viral hepatitis (R=0.837; $p<0.0001$; Fig. 3b) compared to patients with ALD ($n=227$; R=0.753; $p<0.0001$, Fig. 3c). Spearman's correlation coefficient was (R=0.581; $p<0.0001$; Fig. 3d) for patients with nonalcoholic steatohepatitis (NASH) and (R=0.571; $p<0.0001$; Fig. 3e) for patients with autoimmune hepatitis, respectively. Patients with histological mild or moderate fibrosis (F1 and F2) showed a significant linear correlation of liver stiffness and HVPG (R=0.573; $p<0.0001$; Fig. 3f), while the correlation was more logarithmic in patients with severe fibrosis or cirrhosis (F3 and F4; R=0.790; $p<0.0001$; Fig. 3g).

Noninvasive prediction of portal hypertension by TE

HVPG-Cohort: AUROC analysis identified 8 kPa as the best cut-off for identification of patients with PHT (HVPG >5 mmHg). This PHT cut-off at a liver stiffness of 8 kPa showed an AUC of 0.794 ($p=0.0001$) with a specificity and sensitivity of 66.7 and 95.6 %, respectively. For diagnosis of CSPH (HVPG ≥10 mmHg), the best cut-off was identified at 18 kPa with an AUC of 0.817 ($p=0.0001$). The TE cut-off at 18 kPa for diagnosis of CSPH yielded a PPV of 85.7 % and an NPV of 80.2 %. Patients at risk of variceal bleeding (HVPG ≥12 mmHg) could be identified with an AUC of 0.790 ($p=0.0012$) using a TE cut-off at 20 kPa. The AUC for diagnosis of high-risk portal hypertension (HVPG ≥20 mmHg) with a liver stiffness cut-off at 40 kPa showed an AUC of 0.712 ($p=0.0435$). Notably, the NPV for excluding high-risk portal hypertension was 92.5 % using the TE cut-off at 40 kPa (Table 4, Fig. 4).

Considering only patients with ALD, the ideal TE cut-offs for prediction of portal hypertension and CSPH were identified at 10 and 19 kPa, respectively. The noninvasive prediction of CSPH in ALD using the cut-off at 19 kPa showed a PPV and NPV of 89.3 and 84.1 %, respectively. In patients with viral hepatitis, AUROC analysis showed a PPV of 84.1 % and a NPV of 86.2 % for diagnosis of CSPH using a TE cut-off at 18 kPa. All TE cut-offs for diagnosis of portal hypertension or CSPH, and high risk of variceal bleeding were higher in patients with alcoholic liver disease compared to patients with viral hepatitis.

Figure 3 shows the proportion of patients that were correctly and incorrectly classified by the cut-offs selec-

Table 4. Liver stiffness cut-offs to diagnose stages of portal hypertension (HVPG-cohort)

	HVPG			
	>5 mmHg	≥10 mmHg	≥12 mmHg	≥20 mmHg
All patients				
Cut-offs	8 (kPa)	18 (kPa)	20 (kPa)	40 (kPa)
AUC	0.794 (0.729–0.896)	0.817 (0.752–0.891)	0.790 (0.725–0.862)	0.712 (0.586–0.793)
p-value	0.0001	0.0001	0.0012	0.0435
Specificity (%)	66.7	82.2	80.7	75.2
Sensitivity (%)	85.6	83.4	84.2	79.9
PPV (%)	84.2	85.7	81.8	42.9
NPV (%)	85.3	80.2	83.2	92.5
Patients with viral hepatitis				
Cut-offs	8 (kPa)	18 (kPa)	20 (kPa)	39 (kPa)
AUC	0.830 (0.796–0.855)	0.892 (0.857–0.941)	0.899 (0.867–0.947)	0.731 (0.697–0.765)
p-value	0.0001	0.0001	0.0001	0.0001
Specificity (%)	71.0	86.9	86.5	79.8
Sensitivity (%)	95.3	80.3	84.4	80.3
PPV (%)	83.5	84.1	78.2	49.1
NPV (%)	89.9	86.2	89.6	93.8
Patients with alcoholic liver disease				
Cut-offs	10 (kPa)	19 (kPa)	23 (kPa)	40 (kPa)
AUC	0.739 (0.697–0.764)	0.798 (0.718–0.845)	0.793 (0.731–0.859)	0.659 (0.599–0.713)
p-value	0.0001	0.0001	0.0001	0.0001
Specificity (%)	79.4	72.8	77.0	58.9
Sensitivity (%)	85.0	89.1	91.3	85.9
PPV (%)	85.6	89.3	86.9	44.0
NPV (%)	75.0	84.1	80.3	91.7

HVPG hepatovenous pressure gradient, *AUC* area under the receiver operating characteristics curve, *PPV* positive predictive value, *NPV* negative predictive value

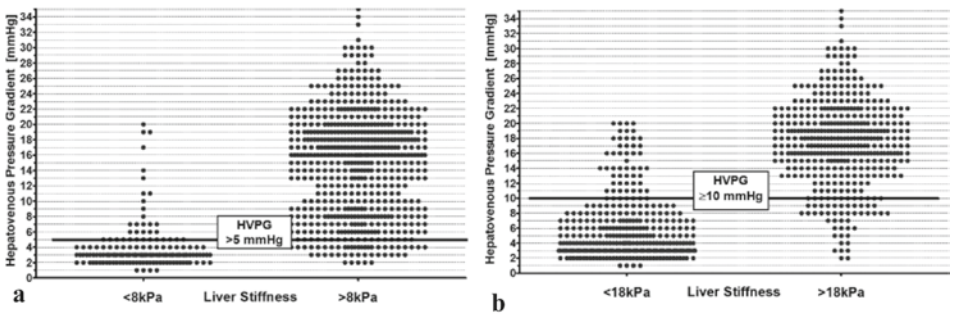

Fig. 4 **a** Prediction of portal hypertension (HVPG >5 mmHg) by transient elastography. **b** Prediction of clinically significant portal hypertension (HVPG ≥10 mmHg) by transient elastography

ted by AUROC analysis. Using a TE cut-off at 8 kPa 15 % (20/136) with predicted normal portal pressure had portal hypertension and 12 % (58/494) with predicted portal hypertension actually had normal portal pressure. For diagnosis of CSPH, a TE cut-off at 18 kPa was identified by AUROC, through which 17 % (48/286) and 11 % (39/344) of patients were wrongly classified with absence and presence of CSPH, respectively.

Discussion

Recently published studies support the use of transient elastography for evaluating patients with portal hypertension. We assessed (1) the performance of TE for staging liver fibrosis and (2) the correlation of LS and portal pressure measured by HVPG in a large cohort of patients with chronic liver diseases. Together, we present a large dataset of almost 700 LS measurements performed in patient suffering from different etiologies of liver disease (most of them with viral hepatitis or with ALD).

Although TE represents a novel, rapid, and noninvasive method to assess liver fibrosis, the current enthusiasm should not prevent critical evaluation of possible applications of TE in daily clinical practice. Our study clearly demonstrates the limitations of TE for the evaluation of the degree of liver fibrosis or of portal hypertension, despite the significant correlation of liver stiffness with portal pressure and with liver fibrosis, which was comparable to previous studies [8, 11, 15, 16, 19].

However, the PPV of 79 % and NPV of 75 % for diagnosis of significant fibrosis (F≥2), which would be useful in clinical practice to evaluate the indication for antiviral treatment in patients with chronic hepatitis C or hepatitis B virus infection [33], seem to be insufficient to replace liver biopsy. A substantial proportion of patients would be treated in absence of significant fibrosis or would not be treated despite significant fibrosis.

The accuracy of TE for diagnosis of liver cirrhosis (F4) was better with a PPV of 87 and an NPV of 91 %, respectively. These results support the clinical use of TE for establishing and even more for exclusion of histological cirrhosis.

In accordance to prior studies, the correlation of liver stiffness and portal pressure was highly significant in our large dataset including 502 concomitant measurements of TE and HVPG. This correlation was stronger in patients with viral hepatitis than in patients with ALD. This study provides the first evidence of a positive association between portal pressure and liver stiffness in patients with NASH and autoimmune hepatitis.

However, the clinical utility of TE for evaluation of patients with portal hypertension seems limited, since the accuracy of TE for prediction of portal hypertension, reflected by a PPV of 84 % and an NPV of 85 % was rather weak. The PPV and NPV for noninvasive prediction of CSPH, which would be even more important for clinicians, were again poor with 85 and 80 %, respectively. Using a TE cut-off at 8 kPa for diagnosis of portal hypertension 27 % of patients would be wrongly classified. Twenty-eight percent of patients were not correctly classified when using a TE cut-off at 18 kPa for noninvasive prediction of CSPH by TE. In summary, we have to face that 1 out of 4 patients cannot be correctly evaluated for the presence of portal hypertension or of CSPH by TE.

Portal pressure is influenced by both structural and functional abnormalities within the hepatic and splanchnic circulation [23, 24]. Functional abnormalities account for approximately 20–30 % of the increase in hepatic resistance [2]. Transient elastography mainly measures the structural components of portal hypertension, while the dynamic component of portal hypertension may not be assessed, as shown by the improvement of the correlation between LS and HVPG under treatment with β-blocker treatment [25]. Compared to TE, the HVPG measures both the structural and functional (dynamic) components, and this limits the use of TE for noninvasive assessment of portal pressure in the individual patient.

Therefore, TE may be used as a screening tool for liver fibrosis and portal hypertension, as long as users are aware of its limitations as reflected by moderate PPV and NPV in this large scale single center experience. Several parameters, like etiology of liver disease, age, sex, levels of aminotransferases, and intake of vasoactive drugs that all influence the results of TE have to be considered in clinical practice. Both HVPG measurement and liver biopsy are invasive procedures with potential associated complications, and the limitations of costs, sampling error and availability. TE as noninvasive tool overcomes these limitations, but has questionable prognostic value in the clinical setting being insufficiently accurate for diagnosis of significant fibrosis (F≥2) or of CSPH (HVPG ≥10 mmHg). In summary, we would not recommend to generally apply the previously published cut-offs for all patients with different etiologies of chronic liver disease. Both liver biopsy and measurement of HVPG are still necessary to correctly diagnose different stages of liver fibrosis and of portal hypertension.

Conflicts of interest
The authors do not have conflicts of interest to disclose.

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