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# Point Shear Wave Elastography by ElastPQ for Fibrosis Screening in Patients with NAFLD: A Prospective, Multicenter Comparison to Vibration-Controlled Elastography

## Punkt-Schwerwellen-Elastographie mittels ElastPQ für das Fibrosescreening in NAFLD Patienten: eine prospektive, multizentrische Studie



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### ABSTRACT

**Background** Since nonalcoholic fatty liver disease (NAFLD) has become the leading cause of liver disease in the Western world, clinicians need reliable noninvasive tools for the identification of NAFLD-associated fibrosis. Limited evidence on the performance of the novel shear wave elastography technique Elast-PQ (EPQ) in NAFLD is available. **Method** In this prospective, European multinational study we assessed the diagnostic accuracy of EPQ using vibration-controlled transient elastography (VCTE) as a reference standard. **Results** Among 353 NAFLD patients, 332 (94.1 %) fulfilled reliability criteria of VCTE and EPQ (defined by IQR/median  $\leq 0.3$ ; 41.3 % female, mean age: 59 [IQR: 16.5], mean BMI: 29.0 (7.1)). 4/353 (1.1 %) and 17/353 (4.8 %) had unreliable VCTE and EPQ measurements, respectively. VCTE-based NAFLD fibrosis stages were F0/F1: 222(66.9 %), F2: 41 (12.3 %), F3: 30 (9.1 %), F4:

39 (11.7 %). We found a strong correlation (Pearson  $R = 0.87$ ;  $p < 0.0001$ ) and concordance (Lin's concordance correlation coefficient = 0.792) of EPQ with VCTE. EPQ was able to identify NAFLD-fibrosis risk with the following EPQ cutoffs:  $\geq 6.5$  kPa for significant fibrosis ( $\geq F2$ ) ( $\geq 1.47$  m/s; sensitivity: 78 %; specificity: 95 %; AUROC: 0.94),  $\geq 6.9$  kPa for advanced fibrosis ( $\geq F3$ ) ( $\geq 1.52$  m/s; sens.: 88 %, spec.: 89 %; AUROC: 0.949), and  $\geq 10.4$  kPa for cirrhosis (F4) ( $\geq 1.86$  m/s; sens.: 87 %; spec.: 94 %; AUROC: 0.949). **Conclusion** The point shear wave elastography technique EPQ shows excellent correlation to and concordance with VCTE. EPQ can reliably exclude NAFLD fibrosis  $< 6.0$  kPa ( $< 1.41$  m/s) and indicate a high risk of advanced fibrosis  $\geq 10.4$  kPa ( $\geq 1.86$  m/s).

## ZUSAMMENFASSUNG

**Hintergrund** Die nichtalkoholische Fettleber (NAFLD) ist mittlerweile die häufigste Lebererkrankung in der westlichen Welt. Daher besteht ein Bedarf an nichtinvasiven Methoden zur Einschätzung des Fibrose-Risikos bei NAFLD. Über die Aussagekraft der neuen Scherwellen-Technologie Elast-PQ (EPQ) liegen nur wenige Daten vor. **Methoden** Diese prospektive, europäische multinationale Studie untersuchte die diagnos-

tische Genauigkeit von EPQ bei NAFLD-PatientInnen im Vergleich zur Vibrations-kontrollierten transienten Elastografie (VCTE). **Resultate** Von 353 NAFLD-Patient\*innen erfüllten 332 (94,1 %) die Zuverlässigkeitskriterien für VCTE und EPQ (definiert als IQR/median  $\leq 0,3$ ). Die Studienpopulation war zu 41,3 % weiblich, mit einem medianen Alter von 59 [IQR: 16,5] Jahren und einem medianen BMI von 29 [IQR: 7] kg/m<sup>2</sup>. Es bestand eine starke Korrelation (Pearson  $R = 0,87$ ;  $p < 0.0001$ ) und Konkordanz (Lin-Konkordanz-Korrelationskoeffizient = 0,792) von EPQ mit VCTE. EPQ konnte das NAFLD-Fibrose-Risiko anhand folgender Grenzwerte abschätzen: Signifikante Fibrose ( $\geq F2$ ) ab  $\geq 6,5$  kPa ( $\geq 1,47$  m/s; Sensitivität: 80 %; Spezifität: 95 %; AUROC: 0,940), fortgeschrittene Fibrose ( $\geq F3$ ) ab  $\geq 6,9$  kPa ( $\geq 1,52$  m/s; Sensitivität: 88 %, Spezifität: 89 %; AUROC: 0,949), und Zirrhose (F4) ab  $\geq 10,4$  kPa ( $\geq 1,86$  m/s; Sensitivität: 87 %; Spezifität: 94 %; AUROC: 0,949). **Schlussfolgerungen** Die Punkt-Scherwellen-Elastografie-Methode EPQ zeigt eine exzellente Korrelation und Konkordanz mit der VCTE. Bei NAFLD-Patient\*innen wird durch EPQ  $< 6,0$  kPa ( $< 1,41$  m/s) eine signifikante Fibrose ausgeschlossen und durch EPQ  $\geq 10,4$  kPa ( $\geq 1,86$  m/s) ein hohes Risiko für eine fortgeschrittene Fibrose angezeigt.

## Introduction

The prevalence of nonalcoholic fatty liver disease (NAFLD) in the general population is 20–30 % and may be up to 70 % in the obese population and 90 % in individuals with diabetes mellitus [1, 2, 3]. Since epidemiological data show a further increase in the prevalence of obesity and diabetes mellitus, the number of NAFLD patients is also expected to increase in the forthcoming years [4]. NAFLD progresses to nonalcoholic steatohepatitis (NASH) in 25 % of cases within 3 years, and NASH already accounts for 12 % of all liver transplantations in Europe [3]. Fibrosis, more than steatosis and inflammatory activity, is associated with portal hypertension and subsequent adverse long-term outcomes, such as hepatocellular carcinoma (HCC) in NAFLD [2, 5, 6]. Thus, reliable noninvasive techniques for the assessment of liver fibrosis risk are of increasing clinical importance. Simple laboratory-based scores (such as the FIB-4 score) can be used to identify patients at risk for fibrosis in low-prevalence populations. However, a sequential algorithm of laboratory-based scores followed by liver elastography techniques is suggested to identify patients with NAFLD-associated fibrosis [7].

Liver biopsy is the gold standard for diagnosing and staging liver fibrosis and can be performed via the transcutaneous or transjugular route [9, 8]. However, it is an imperfect gold standard [8] and associated with periprocedural risks and costs. Ultrasound-based techniques for estimating liver fibrosis offer the advantages of lower-cost, low-risk, quick, and point-of-care assessment. Vibration-controlled transient elastography (VCTE) is a well-validated method of assessing liver fibrosis [7, 9]. However, it requires a dedicated device that cannot perform conventional ultrasound needed in patients with chronic liver disease to screen for HCC

and other liver-related complications. In contrast, acoustic radiation force impulse (ARFI)-based techniques, either point shear wave elastography (pSWE) or two-dimensional SWE, can be included in regular modern ultrasound devices. The diagnostic accuracy and cutoffs for VCTE for different fibrosis stages, portal hypertension, and esophageal varices have been established in multiple liver disease etiologies, including NAFLD [6, 7]. The use of VCTE in NAFLD has been recommended in national and international guidelines [10]. However, VCTE also has relevant limitations: despite the introduction of the XL-probe, failed and unreliable measurements in obese patients remain a problem [11] and measurements cannot be reliably performed in the presence of perihepatic ascites.

pSWE-Elast-PQ (EPQ) is the pSWE technique implemented in Philips ultrasound systems. Its use for liver fibrosis assessment has been validated in various etiologies [12, 13]. In contrast to VCTE, the region of interest (ROI) placement and, therefore, the depth of measurement can be chosen on the B-mode ultrasound image, which allows for more advantageous localization (e. g., avoiding larger blood vessels or other interfering structures). Since abdominal ultrasound devices are needed to screen for liver-related complications, pSWE is potentially more widely and readily available than VCTE. However, reliable cutoffs for ruling in or ruling out significant fibrosis and advanced fibrosis in patients with NAFLD have not yet been sufficiently established.

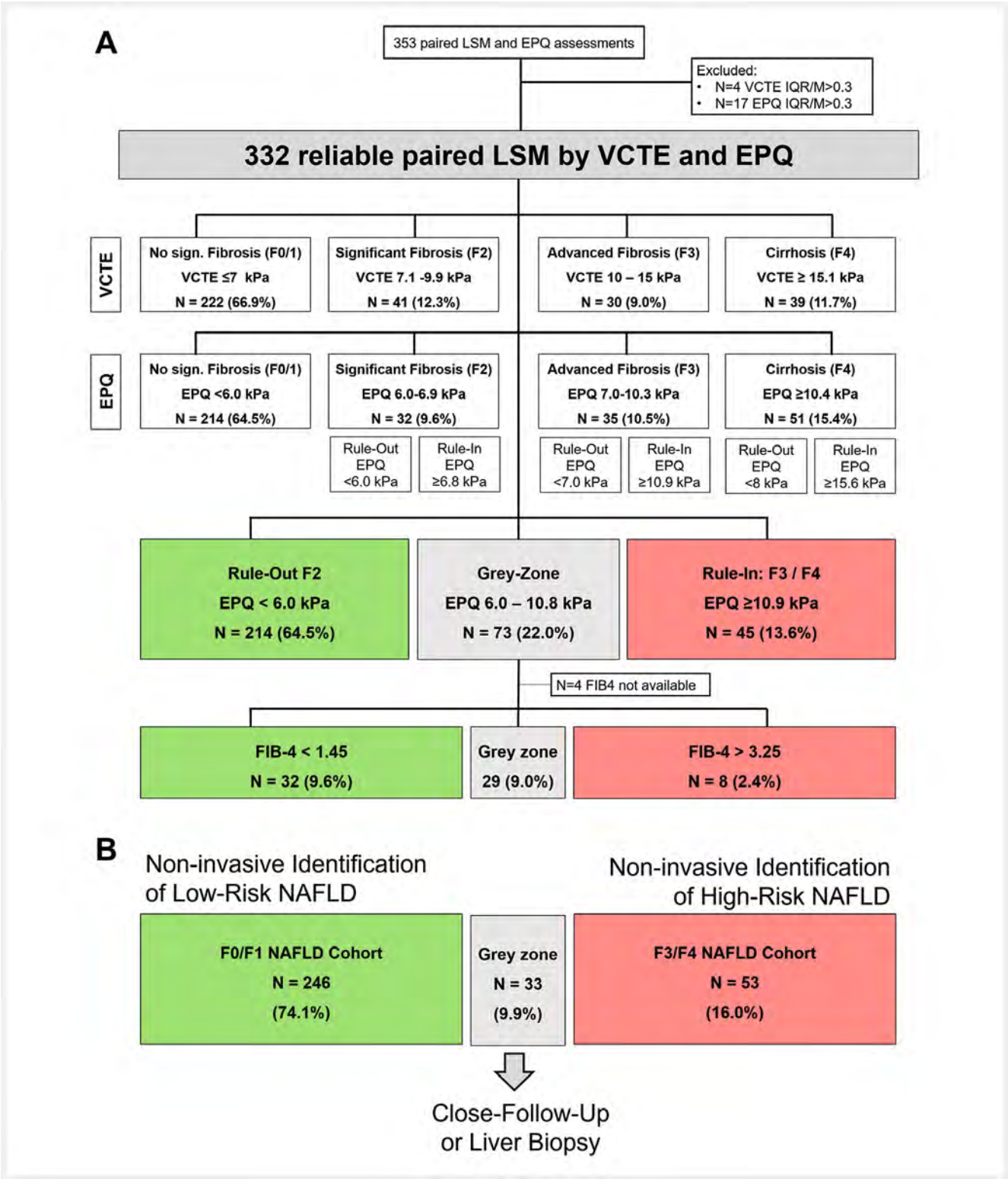
Therefore, we set up a prospective European multicenter study to assess the performance of EPQ for ruling out significant fibrosis and ruling in advanced fibrosis in patients with (suspected) NAFLD using VCTE as a reference standard, exploring factors, which might influence liver stiffness as measured by EPQ and to provide

a clinical algorithm comprised of elastography and the laboratory-based noninvasive FIB-4 tests [14].

Patients and methods

Study centers and study population

Patients with suspected or diagnosed NAFLD were prospectively recruited at 4 European centers. We included patients for whom



► **Fig. 1** **A** Study flow chat, showing the fibrosis staging by VCTE and EPQ, as well as resulting cutoffs. **B** Reclassification of patients without rule-out of significant fibrosis and without rule-in of advanced fibrosis, using the FIB-4 index.

the clinical diagnosis of NAFLD was made and who underwent ultrasound evaluation and elastography to assess fibrosis and steatosis. Patients with viral liver disease (as assessed by HBsAg and HCVAb), alcohol intake, hepatic malignancies, and heart failure were excluded.

## Elastography protocol

We consecutively performed liver stiffness measurements (LSM) with pSWE and VTCE on the same day in all included patients. For the pSWE, we used the EPQ module of the Philips EPIQ 7 ultrasound system (Philips Medical System, The Netherlands) with a C5-1 convex probe, and for VTCE, either the FibroScan 502 Touch or Mini 430 (Echosens, Paris, FR) with the M- or XL-Probe, as suggested by the probe selection tool. Patients fasted for at least four hours before the examination. As recommended, both measurements were taken with the patient in a supine position, with the right arm abducted [9]. Both VTCE and EPQ examinations were performed via an intercostal space on the upper right lobe of the liver. Measurements with EPQ and VTCE were performed following guideline recommendations [7]. We considered VTCE and EPQ LSM with an IQR/median ratio  $\leq 0.3$  reliable and included VTCE measures  $< 7.1$  kPa irrespective of IQR/median [15, 16].

## Statistical analysis

The mode of display of the given variables and the statistical tests used are described in the supplementary material.

## Definition of significant and advanced fibrosis and cirrhosis

As VTCE was used as a diagnostic reference standard for risk assessment, published cutoffs [17, 18, 19] were used to differentiate the  $\geq F2$ /significant fibrosis group, the  $\geq F3$ /advanced fibrosis group, and the F4/cirrhosis group. These cutoffs were  $> 7$  kPa for  $\geq F2$ /significant fibrosis,  $\geq 10$  kPa for  $\geq F3$ /advanced fibrosis and  $> 15$  kPa for F4/cirrhosis. Using the grouping described above, the area under the receiver operator characteristic curve (AUROC) and the respective 95 % CI for the ability of EPQ to determine the fibrosis stage defined by VTCE were calculated. To establish cutoffs for the differentiation between fibrosis stages, the Youden Index [20] was used to derive optimal cutoffs. With this method, the optimal cutoff is chosen to maximize the sum of sensitivity (sens.) and specificity (spec.). Additional rule-in and rule-out cutoffs were chosen to maximize sensitivity and specificity. For each cutoff, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), as well as the false positives (FP) and false negatives (FN) for the given population were derived. To further elucidate the fibrosis stage of patients in whom significant fibrosis could not be ruled out and advanced fibrosis could not be ruled in using EPQ, published cutoffs of the FIB-4 score were used [14]. To further elucidate the factors impacting the absolute difference between paired measurements of VTCE and EPQ, we performed univariate linear modelling and multivariate modelling comprising all univariately significant variables and another model of the same kind exploring the impact of factors additional to VTCE-based liver stiffness on EPQ-liver stiffness.

## Results

In total, 353 concomitant, paired VTCE, and EPQ-based liver stiffness measurements were obtained in the four participating centers. Of these, 21 (6.0 %) were excluded, as they did not fulfill the reliability criterion of IQR/median  $\leq 0.3$  % for either VTCE or EPQ (see **Supplementary Table-ST1**). Consequently, 332 (94.1 %) patients were included in the analysis. Among these, 222 (66.9 %) had no significant fibrosis (F0–1), 41 (12.4 %) had significant fibrosis (F2), 30 (9.0 %) were diagnosed with advanced fibrosis ( $\geq F3$ ), and 39 (11.8 %) were diagnosed with cirrhosis (F4). A summary of the included patients, the calculated cutoffs, and the resulting fibrosis staging is shown in ► **Fig. 1A**.

The population defining characteristics for all patients, patients without significant fibrosis, patients with significant and advanced fibrosis, and cirrhosis patients are displayed in ► **Table 1** and the patient characteristics by center in **Supplementary Table-ST2**. The patient populations were heterogeneous between centers, differing in age, sex distribution, BMI, markers of disease severity, such as laboratory values and liver stiffness, steatosis grade, and liver stiffness. The included patients were 59 [IQR: 16.5] years old and predominantly males. The median BMI was 29 [IQR: 7] kg/m<sup>2</sup> and did not increase with the fibrosis stage. The blood work was mostly obtained on the same day as the elastography [IQR: 1 day]. Platelet count, cholesterol, albumin, and the CAP decreased, while the international normalized ratio (INR), alkaline phosphatase (ALP), and aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), and FIB-4 increased with each fibrosis stage. Liver stiffness as measured with EPQ significantly increased with the fibrosis stage as defined by VTCE (► **Table 1**).

The correlation between reliable measurements of VTCE and EPQ was high, with a Pearson's  $R = 0.87$  (95 % CI: 0.83–0.89,  $p < 0.0001$ ). This is shown in a scatterplot of the reliable measurements of VTCE and EPQ in ► **Fig. 2**.

The concordance between VTCE and EPQ was high, as shown by Lin's CCC = 0.792 (95 % CI: 0.623–0.889). To display the effect of increasing liver stiffness on the concordance of the two compared methods, a Bland-Altman-Leh plot is provided in ► **Fig. 3**. It shows that the numeric difference between absolute liver stiffness as measured by VTCE and EPQ increased with increasing liver stiffness leading to a converse monotonous decrease in the Pearson's correlation coefficient (► **Fig. 4**). Multivariate analysis to predict the absolute difference in liver stiffness as measured by EPQ and VTCE revealed that higher VTCE, EPQ-based liver stiffness, BMI and EPQ IQR are associated with a larger absolute difference in measured liver stiffness (compare **Supplementary Table-ST3**). A second analysis aimed at factors that might impact EPQ-based liver stiffness, in addition to VTCE-based liver stiffness, showed an association of VTCE IQR and probe with EPQ-based liver stiffness (see **Supplementary Table-ST4**).

To assess the accuracy of EPQ for fibrosis risk assessment in NAFLD, we calculated the AUROC values for the detection of significant fibrosis and advanced fibrosis, as well as respective rule-in and rule-out cutoffs. EPQ can identify significant fibrosis with an AUROC of 0.94 (95 % CI: 0.910–0.969). The optimal (Youden) cutoff was determined at  $\geq 6.5$  kPa ( $\geq 1.47$  m/s; sens.: 80 %,



► **Table 1** Patient characteristics.

	All NAFLD N = 332 (100 %)	No/Mild Fibrosis F0/F1 N = 222 (66.9 %)	Significant Fibrosis F2 N = 41 (12.3 %)	Severe Fibrosis F3 N = 30 (9.0 %)	Cirrhosis F4 N = 39 (11.7 %)	P-value
Age, years, median [IQR]	59.0 [16.5]	56.5 [19.0]	59.0 [12]	59.5 [16.0]	63.0 [10.5]	<b>0.001</b>
Sex, N (%)						
Female	137 (41.3)	92 (41.4)	17 (41.5)	12 (40.0)	16 (41.0)	0.999
Male	195 (58.7)	130 (58.6)	24 (58.5)	18 (60.0)	23 (59.0)	
Center, N (%)						
Pavia	27 (8.1)	24 (10.8)	1 (2.4)	0 (0.0)	2 (5.1)	
Timișoara	57 (17.2)	39 (17.6)	6 (14.6)	8 (26.7)	4 (10.3)	<b>&lt;0.001</b>
Vienna	112 (33.7)	58 (26.1)	15 (36.6)	12 (40.0)	27 (69.2)	
Zagreb	136 (41.0)	101 (45.5)	19 (46.3)	10 (33.3)	6 (15.4)	
BMI, kg/m <sup>2</sup> , median [IQR]	29.0 [7.1]	28.6 [6.3]	30.7 [10.9]	26.9 [6.0]	31.2 [8.9]	<b>0.025</b>
Platelets, G/L, mean (SD)	224 (75)	240 (70)	228 (64)	200 (62)	149 (72)	<b>&lt;0.001</b>
INR, median [IQR]	1.0 [0.2]	1.0 [0.1]	1.0 [0.2]	1.1 [0.3]	1.0 [0.20]	<b>&lt;0.001</b>
Bilirubin, mg/dL, median [IQR]	0.76 [0.42]	0.76 [0.37]	0.83 [0.49]	0.76 [0.25]	0.77 [0.54]	0.913
Albumin, g/dL, median [IQR]	41.9 [8.1]	43.1 [8.4]	40.5 [7.1]	40.75 [6.9]	39.2 [5.7]	<b>0.027</b>
AST, U/L, median [IQR]	30 [21]	27 [18]	29 [34]	38 [35]	45 [22]	<b>&lt;0.001</b>
ALT, U/L, median [IQR]	35 [38]	35 [39]	32 [33]	44 [38]	33 [22]	0.275
GGT, U/L, median [IQR]	50 [74]	40 [60]	64 [68]	73 [60]	112 [193]	<b>&lt;0.001</b>
FIB-4, points, median [IQR]	1.33 [1.12]	1.17 [0.75]	1.36 [1.05]	1.81 [1.68]	3.62 [3.27]	<b>&lt;0.001</b>
VCTE, kPa, median [IQR]	6 [4.33]	5 [1.8]	8.4 [1.3]	12.7 [3.1]	22.8 [16.0]	<b>&lt;0.001</b>
VCTE IQR/median, %, median [IQR]	15.0 [10.0]	15.0 [10.0]	16.0 [11.0]	14.5 [7.2]	17.5 [11.6]	0.284
CAP, dB/m, median [IQR]	298 [78]	298 [73]	305 [89]	299 [70]	272 [122]	0.42
CAP IQR, dB/m, median [IQR]	29 [20]	30 [19]	29 [10]	30 [12]	30 [34]	0.855
EPQ, kPa, median [IQR]	5.2 [2.8]	4.6 [1.5]	7.0 [3.1]	9.4 [4.3]	13.6 [9.2]	<b>&lt;0.001</b>
EPQ IQR, kPa, median [IQR]	1.23 [0.02]	1.24 [0.51]	1.53 [0.33]	1.77 [0.42]	2.13 [0.68]	<b>&lt;0.001</b>

► **Table 1** (Continuation)

	All NAFLD N = 332 (100 %)	No/Mild Fibrosis F0/F1 N = 222 (66.9 %)	Significant Fibrosis F2 N = 41 (12.3 %)	Severe Fibrosis F3 N = 30 (9.0 %)	Cirrhosis F4 N = 39 (11.7 %)	P-value
EPQ IQR/median, %, median [IQR]	22.9 [10.4]	22.0 [10.0]	24.6 [9.6]	25.0 [12.6]	26.0 [7.3]	<b>0.033</b>

P-values were calculated using the Kruskal-Wallis test comparing the values of patients with no significant fibrosis, F2, F3, and F4. Significant p-values are bold.

#### Abbreviations

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CAP: continuous attenuation parameter; EPQ: Elast PQ:F0/F1: fibrosis stage 0 or 1; F2: fibrosis stage 2; F3: fibrosis stage 3; F4: fibrosis stage 4; GGT: gamma glutamyl transferase; INR: international normalized ratio; IQR: interquartile range; kPa: kilopascal; M: median; N: number; VCTE: vibration-controlled transient elastography

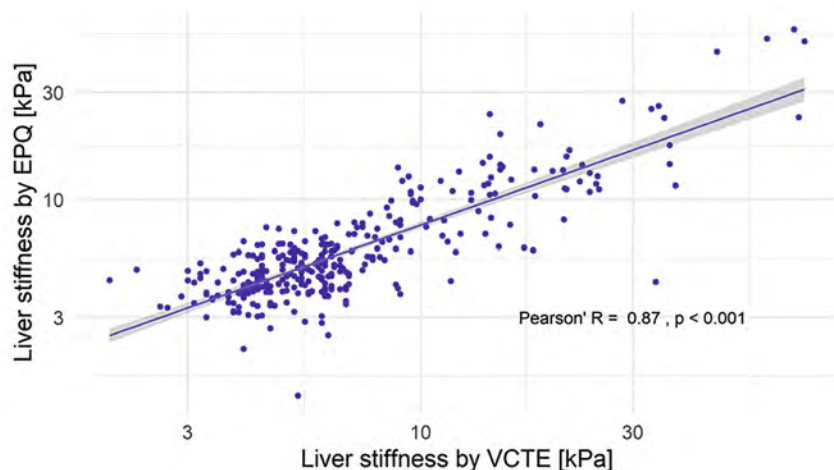
spec.: 95 %), the specific rule-in cutoff at  $\geq 6.8$  kPa ( $\geq 1.51$  m/s; sens.: 77 %, spec.: 97 %), and the sensitive rule-out cutoff at  $< 6$  kPa ( $< 1.41$  m/s; sens.: 86 %, spec.: 89 %). The AUROC for advanced fibrosis was 0.949 (95 % CI: 0.919–0.979). The optimal cutoff was  $\geq 6.9$  kPa ( $\geq 1.52$  m/s; sens.: 88 %, spec.: 89 %), while the respective rule-in and rule-out cutoffs were  $\geq 10.9$  kPa ( $\geq 1.91$  m/s; sens.: 61 %, spec.: 99 %) and  $< 7$  kPa ( $< 1.53$  m/s; sens.: 86 %, spec.: 90 %). EPQ detected cirrhosis with an AUROC of 0.949 (95 % CI: 0.91–0.989). The optimal rule-in and rule-out cutoffs were  $\geq 10.4$  kPa ( $\geq 1.86$  m/s; sens.: 87 %, spec.: 94 %),  $\geq 15.6$  kPa ( $\geq 2.28$  m/s; sens.: 36 %, spec.: 99 %), and  $< 8$  kPa ( $< 1.63$  m/s; sens.: 90 %, spec.: 90 %), respectively. These cutoffs and the corresponding measures are summarized in ► **Table 2**.

Using the established EPQ cutoffs, we could not rule-out significant fibrosis and could not rule-in advanced fibrosis in some patients. Here we applied a FIB-4 cutoff of  $< 1.45$  to rule-out significant fibrosis and a cutoff of 3.45 to rule in advanced fibrosis [14]. The FIB-4 (available in 69/73, 94.5 %) allowed a further stratification of patients in the EPQ gray zone, since significant fibrosis could be ruled out in 32 (46.4 %) patients, and advanced fibrosis could be ruled in in 8 (11.6 %). Finally, after considering EPQ and FIB-4 results, only 33 (9.9 %) patients remained in the indeterminate "gray zone" (Fig-1B).

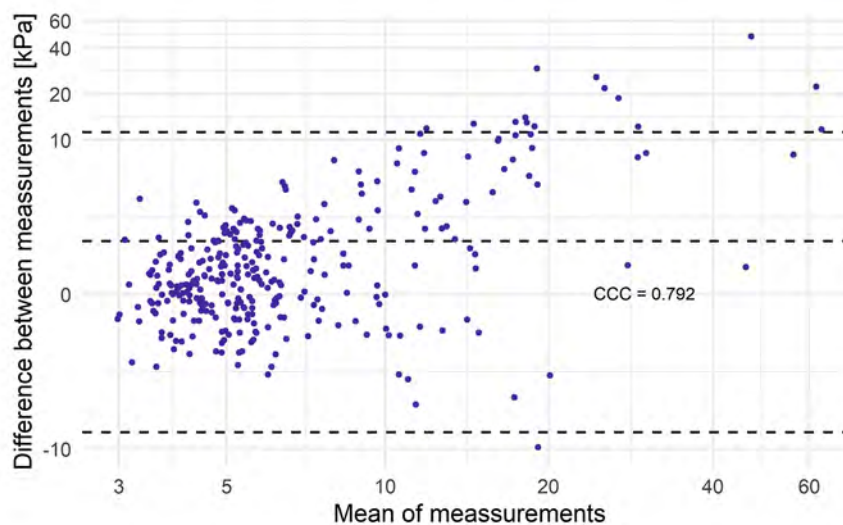
## Discussion

While different noninvasive tools for the diagnosis and staging of NAFLD are available, ultrasound-based methods are a very attractive screening option since the first suspicion of NAFLD is often based on detecting a hyperechogenic liver texture on abdominal ultrasound. Subsequent pSWE of the liver – readily available in mid-and high-end ultrasound devices – could represent a valuable one-stop assessment for diagnosing hepatic steatosis and further risk stratification according to fibrosis grade. It is crucial to identify significant liver fibrosis and cirrhosis as early as possible to initiate effective measures to prevent disease progression and HCC screening. Furthermore, pSWE may allow for noninvasive, longitudinal monitoring of the effects of lifestyle modification and potential future medical therapies for NASH in the academic and routine clinical setting.

As of today, among all the available pSWE techniques, only Virtual Touch Quantification (VTQ) has been extensively evaluated for use in NAFLD/NASH: A 2015 ARFI meta-analysis [23] reported only moderate sensitivity (80.2 %) and specificity (85.2 %). pSWE is not recommended as an endpoint in patients with NAFLD by the 2017 update to the EFSUMB guidelines [9], while the 2018 update to the WFUMB guidelines on the use of liver shear wave elastography recommends SWE – a term that includes VCTE, pSWE, and two-dimensional SWE – for liver stiffness measurements in NAFLD, in particular, to rule-out advanced fibrosis and to select patients for further investigation [7]. A more recent meta-analysis (2020) on pSWE (VTQ) including 1,147 patients reported a better diagnostic value of VTQ for significant fibrosis ( $\geq$  F2; AUROC: 0.89; sens.: 85 %, spec.: 83 %) and for cirrhosis (F4; AUROC: 0.94; sens.: 90 %, spec.: 95 %) in NAFLD patients [24].



► **Fig. 2** Pearson correlation of reliable liver stiffness measurements by VCTE and EPQ, with CI 95 % shown, on a log-10 scale.



► **Fig. 3** Bland-Altman-Leh plot comparing the difference between VCTE and EPQ measurements for a given mean of a measurement with lines of average difference and two 95 % CI lines, with the Lin's concordance coefficient shown on a pseudo-log10 scale.

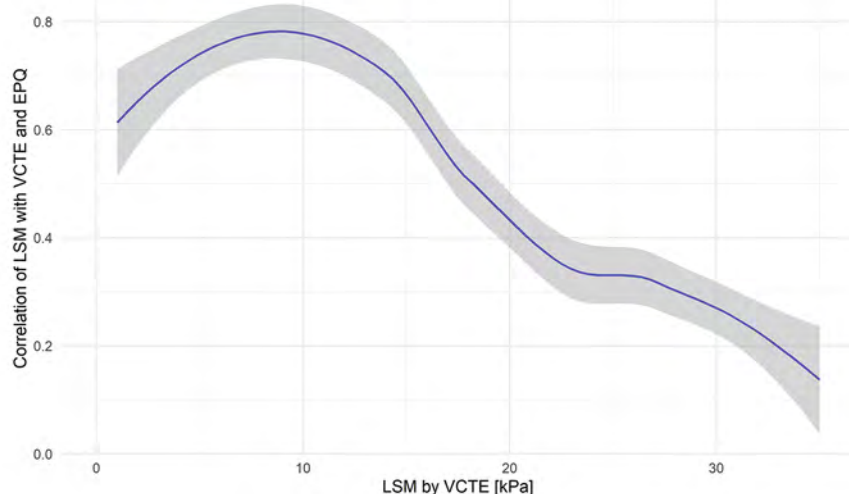
EPQ has previously been evaluated for use in other etiologies [13] but only in a small group of NAFLD/NASH patients against liver biopsy [21]. VCTE was found to be superior to EPQ for fibrosis screening, indicating a diagnostic performance for EPQ for significant fibrosis ( $\geq F2$ ) with an AUROC: 0.74 (sens.: 78.1 %, spec.: 61.4 %) and for cirrhosis (F4) with an AUROC: 0.72 (sens.: 66.7 %, spec: 93.2 %). However, this study included only a very limited number of patients with F0 and F4 fibrosis, which might have impacted this study's ability to assess the "true" diagnostic accuracy in NAFLD fibrosis staging. Furthermore, the authors state that the histology specimens, on average, did not fulfill recommended standards, introducing potential sampling bias [21]. Therefore, although we applied liver stiffness measurement by VCTE instead of liver biopsy as a diagnostic gold standard, our study provides im-

portant results regarding the concordance of EPQ and VCTE in a large cohort of prospectively recruited NAFLD patients from four European centers. While the largest group of patients was classified as having no significant fibrosis, the significant and advanced fibrosis and cirrhosis groups were sufficiently powered, thereby reflecting the clinical spectrum of NAFLD seen at specialized centers.

Furthermore, VCTE is known to sometimes fail in patients with a higher BMI. Because obese patients in whom VCTE failed or delivered unreliable results, despite using the XL-probe, were excluded from the analysis, the present study cannot provide information on the accuracy of EPQ in patients in the higher BMI range.

We found a high correlation between VCTE and EPQ (Pearson's correlation coefficient: 0.87) as well as a high concordance (CCC:





► **Fig. 4** Correlation of VCTE with EPQ at different VCTE liver stiffnesses. The figure shows the Pearson correlation coefficient of the LSM by VCTE and EPQ (y-axis) at the liver stiffness as determined by VCTE  $\pm$  10 kPa (x-axis). This does not indicate the correlation at this point but illustrates how increasing liver stiffness affects the correlation.

0.792). Therefore, EPQ can correctly identify significant and advanced fibrosis and cirrhosis, as expressed by respective AUROCs of  $\geq$  F2: 0.940,  $\geq$  F3: 0.949, and F4: 0.949. Optimal Youden's index-derived cutoffs for stages of fibrosis were defined at  $\geq$  6.5 kPa ( $\geq$  1.47 m/s) for significant fibrosis ( $\geq$  F2), at  $\geq$  6.9 kPa ( $\geq$  1.52 m/s) for advanced fibrosis ( $\geq$  F3), and at  $>$  10.4 kPa ( $>$  1.86 m/s) for cirrhosis (F4). To further increase clinical applicability, we also provide specific rule-in and specific rule-out cutoffs for the clinically relevant NAFLD-fibrosis stages. The subsequent use of the FIB-4 score on the 69/73 patients in the EPQ gray zone, where the FIB-4 was available, could rule-out significant fibrosis in 32 (9.6%) patients and rule-in advanced fibrosis in 8 (2.4%), finally leaving only 33 (9.9%) patients with an indeterminate fibrosis stage. This algorithm combining noninvasive EPQ liver stiffness measurement and broadly available blood tests of fibrosis is a valuable tool for noninvasive fibrosis risk discrimination.

In concordance with previous studies [27, 26], we noted an increase in the discrepancy in numerical values between VCTE and EPQ above 20–25 kPa. To explore the factors impacting the discrepancy between VCTE and EPQ, we performed a regression modeling of factors that may impact the absolute difference between VCTE and EPQ. Next to higher VCTE-LSM values, higher BMI and higher IQR of EPQ were significantly associated with a discrepancy between VCTE-LSM vs. EPQ-LSM in multivariate analysis. Still, liver stiffness values above 20 kPa would indicate advanced chronic liver disease (ACLD) using both VCTE and EPQ, and the divergence above this range does not question the ability to detect ACLD. However, since EPQ may not be in concordance with VCTE within high stiffness ranges, useful cutoffs or relevant delta/changes in EPQ stiffness to monitor improvement or worsening of liver cirrhosis/portal hypertension remain to be explored. Importantly, EPQ was still useful for assessing the fibrosis risk in

NAFLD and predicting clinical outcomes [22, 25, 26]. Importantly, our cohort was acquired at tertiary centers, as evident from the high proportion of patients with advanced fibrosis and cirrhosis. Therefore, the cutoffs derived here might not be directly applicable to the primary care setting.

VCTE has been found to have lower sensitivity and specificity in NAFLD-associated fibrosis for distinguishing lower fibrosis stages [27]. Subsequently, using VCTE as a reference standard for fibrosis staging may have led to overly optimistic results since VCTE and EPQ are based on the same diagnostic principle (i. e., elastography), which may indicate a higher concordance as compared to using liver biopsy as a reference. Furthermore, fibrosis staging by VCTE is not regarded as the gold standard, and thus, the comparator of VCTE-based LSM represents a limitation of this study. However, by using VCTE as a reference standard, we ensured that the results of EPQ-based LSM could be assessed in the context of VCTE as the currently most widely used liver stiffness measurement technique. In addition, this strategy also allowed us to recruit a larger number of NAFLD patients.

Ultimately, the EPQ cutoffs identified in our study only suggest the risk of having the respective NAFLD-associated fibrosis stages. However, a previous study using histopathological evaluation of liver biopsy – as the (imperfect) diagnostic gold standard – reported similar cutoff values for fibrosis staging as in our study [21], which suggests the validity of our EPQ NAFLD fibrosis stage cutoffs. Importantly, in our diagnostic algorithm, we specifically focused on the clinically relevant questions of ruling out significant fibrosis and ruling in advanced fibrosis/ cirrhosis.

Future studies on the utility of EPQ to assess the risk of compensated advanced chronic liver disease (cACLD) – validated by the diagnostic gold standards, i. e., varices detection by endoscopy, HVPG  $\geq$  6 mmHg, or liver biopsy showing F3/F4 fibrosis – are desirable.

► Table 2 Elast-PQ cutoffs.

Stage	Cutoff	AUROC	EPQ cutoff, stiffness (kPa)	EPQ cutoff, shear wave (m/s)	Sensitivity, %	Specificity, %	PPV, %	NPV, %	FP, N	FN, N
≥F2	Youden	0.940 (95 %CI: 0.910–0.969, Power: 1)	≥ 6.5	≥ 1.47	80	95	90	91	10	21
	Rule-in		≥ 6.8	≥ 1.51	77	97	92	89	7	25
	Rule-out		< 6.0	< 1.41	86	89	80	92	24	16
≥F3	Youden	0.949 (95 %CI: 0.919–0.979, Power: 1)	≥ 6.9	≥ 1.52	88	89	69	97	28	8
	Rule-in		≥ 10.9	≥ 1.91	60	99	93	96	3	27
	Rule-out		< 7.0	< 1.53	86	90	71	96	25	9
F4	Youden	0.949 (95 %CI: 0.91–0.989, Power: 1)	≥ 10.4	≥ 1.86	87	94	65	98	18	5
	Rule-in		≥ 15.6	≥ 2.28	36	99	93	92	1	25
	Rule-out		< 8	< 1.63	90	90	54	99	30	4

EPQ cutoffs for the diagnosis of significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4). **Abbreviations:** AUROC: area under the receiver operator characteristics; F2: fibrosis stage 2; F3: fibrosis stage 3; F4: fibrosis stage 4; FN: false negative; FP: false positive; kPa: kilopascal; NPV: negative predictive value; PPV: positive predictive value

In conclusion, this prospective, multinational study showed an excellent diagnostic accuracy of EPQ-pSWE liver stiffness measurements for assessing fibrosis risk in a large cohort of NAFLD patients. We found a divergence between absolute values of VCTE and EPQ, which monotonously increases above 20 kPa, but does not impact the ability of EPQ to stratify NAFLD fibrosis risk. Importantly, we provide optimized EPQ cutoffs to rule-in and rule-out significant fibrosis, advanced fibrosis, and cirrhosis in patients with NAFLD in daily clinical practice.

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## Conflict of Interest

DB served as a speaker and/or consultant and/or advisory board member for AbbVie and received travel support from AbbVie and Gilead. VM, RM, LM, SM: nothing to declare. DC served as a speaker and/or consultant and/or advisory board member for AbbVie, Gilead, and MSD, and received travel support from AbbVie, MSD, ViiV Healthcare, and Gilead. TB has received travel support from BMS, Gilead, and AbbVie. MM served as a speaker and/or consultant and/or advisory board member for AbbVie, Bristol-Myers Squibb, Gilead, Collective Acumen, and W. L. Gore & Associates and received travel support from AbbVie, Bristol-Myers Squibb, and Gilead. IS served as speaker for AbbVie, BMS, Gilead, Janssen, Echosens, Philips; and received advisory board fees by AbbVie, Merck; Siemens, Canon, Toshiba; and received research support by Philips. GF served as speaker for Canon Medical Systems, Hitachi Ltd., Mindray Medical Systems, and Philips. IG served as speaker for Echosens and Philips. TR served as a speaker and/or consultant and/or advisory board member for AbbVie, Bayer, Boehringer Ingelheim, Gilead, Intercept, MSD, Siemens, and W. L. Gore & Associates and received grants/research support from AbbVie, Boehringer Ingelheim, Gilead, MSD, Philips, and W. L. Gore & Associates as well as travel support from Boehringer Ingelheim and Gilead.

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