


## HEPATOLOGY

# Comparing point shear wave elastography (ElastPQ) and transient elastography for diagnosis of fibrosis stage in non-alcoholic fatty liver disease

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**Key words**

Fibroscan, Liver stiffness measurement, NAFLD, pSWE, SWE, TE.

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**Abstract**

**Background and Aim:** Transient elastography (TE) and point shear wave elastography (pSWE) are noninvasive methods to diagnose fibrosis stage in patients with chronic liver disease. The aim of this study is to compare the accuracy of the two methods to diagnose fibrosis stage in non-alcoholic fatty liver disease (NAFLD) and to study the intra-observer and inter-observer variability when the examinations were performed by healthcare personnel of different backgrounds.

**Methods:** Consecutive NAFLD patients who underwent liver biopsy were enrolled in this study and had two sets each of pSWE and TE examinations by a nurse and a doctor on the same day of liver biopsy procedure. The medians of the four sets of pSWE and TE were used for evaluation of diagnostic accuracy using area under receiver operating characteristic curve (AUROC). Intra-observer and inter-observer variability was analyzed using intraclass correlation coefficients.

**Results:** Data for 100 NAFLD patients (mean age  $57.1 \pm 10.2$  years; male 46.0%) were analyzed. The AUROC of TE for diagnosis of fibrosis stage  $\geq F1$ ,  $\geq F2$ ,  $\geq F3$ , and  $F4$  was 0.89, 0.83, 0.83, and 0.89, respectively. The corresponding AUROC of pSWE was 0.80, 0.72, 0.69, and 0.79, respectively. TE was significantly better than pSWE for the diagnosis of fibrosis stages  $\geq F2$  and  $\geq F3$ . The intra-observer and inter-observer variability of TE and pSWE measurements by the nurse and doctor was excellent with intraclass correlation coefficient  $> 0.96$ .

**Conclusion:** Transient elastography was significantly better than pSWE for the diagnosis of fibrosis stage  $\geq F2$  and  $\geq F3$ . Both TE and pSWE had excellent intra-observer and inter-observer variability when performed by healthcare personnel of different backgrounds.

**Introduction**

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease and is estimated to affect approximately 25% of the general population worldwide.<sup>1</sup> Traditionally, liver biopsy has been used for the assessment of liver fibrosis in chronic liver disease, but it is invasive and can be associated with severe complications.<sup>2</sup> In recent years, liver biopsy has been largely replaced by noninvasive tests for the assessment of liver fibrosis.<sup>3</sup> Transient elastography (TE) has been shown to be an excellent noninvasive tool for the assessment of liver fibrosis<sup>4</sup> and has been incorporated in several major guidelines on NAFLD.<sup>5–7</sup> However, it has its own limitations, such as failed or unreliable examinations, especially in obese patients.<sup>8</sup> Point shear wave elastography (pSWE) is an acoustic radiation force impulse (ARFI)-based technique and is a relatively new noninvasive tool for assessing liver fibrosis.<sup>9</sup> ARFI uses a

short-duration, high-intensity acoustic pulse to displace tissue perpendicular to the tissue surface.<sup>10</sup> The transducer then detects tissue displacement within a focal spot along the radiation force, and tissue stiffness can be obtained.<sup>11</sup> In pSWE, shear waves perpendicular to the longitudinal waves are measured.<sup>12</sup> Additional equipment is not required for pSWE because it can be incorporated into an ultrasound system with B-mode. Moreover, direct anatomical visualization allows the operator to select a specific area, avoiding large vessels or biliary system.<sup>12</sup> However, a sonographer or radiologist will usually be needed to perform the examination as the ultrasound examination itself requires technical and anatomical expertise.<sup>13</sup> Although recent studies have shown ARFI-based techniques to be promising with similar accuracy as TE, very few studies compared the accuracy of TE and pSWE. The current literature on TE and SWE is summarized in Table S1.<sup>9,14–25</sup> The primary aim of this study was to look at the accuracy of pSWE as a noninvasive tool for assessing liver fibrosis in

patients with NAFLD and to compare it with the more established TE. Our secondary aims were to determine the intra-observer and inter-observer variability of the two modalities in healthcare personnel of different backgrounds, namely, a doctor and a nurse, and to compare the amount of time taken to complete the examinations.

## Methods

This is a prospective study that included consecutive adult NAFLD patients who were scheduled for a liver biopsy at a university hospital between September 2016 and March 2018. The diagnosis of NAFLD was based on ultrasonography finding of fatty liver, and exclusion of significant alcohol intake, use of medications that can cause fatty liver, viral hepatitis B and C infection, and other causes of chronic liver disease were indicated.<sup>5</sup> The study was approved by the local ethics committee (MECID. no: 20170103-4332), and informed consent was obtained from all participating subjects. Demographic, anthropometric, clinical, and laboratory data were recorded using a standard protocol. Using the World Health Organization Western Pacific Regional Office reference standard, subjects with body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> were considered as obese.<sup>26</sup> Central obesity was defined as a waist circumference 90 cm in men and 80 cm in women.<sup>27</sup> Venous blood was drawn after overnight fasting for blood glucose, lipid profile, and liver profile.

**Transient elastography.** Transient elastography was performed after  $\geq 2$  h of fasting using Fibroscan 502 Touch with M probe (Echosens, Paris, France) on the same day of the liver biopsy procedure by two independent operators who were blinded to clinical data. One of the operators was a doctor (operator 1, W. L. L.), while the other operator was a nurse (operator 2, L. L. L.). Both operators have not performed TE previously and have received training to perform TE for the purpose of this study. Following training, each of the operators performed  $\geq 200$  examinations prior to commencement of this study. An examination was considered successful if there were  $\geq 10$  valid measurements and reliable if the interquartile range (IQR)/median for liver stiffness measurement was  $\leq 30\%$  or if the liver stiffness measurement was  $< 7.1$  kPa when the IQR/median was  $> 30\%$ .<sup>28</sup> An examination was considered unsuccessful if  $< 10$  valid measurements were obtained after 30 attempts. Patients who had unsuccessful examination with the M probe were examined using the XL probe and were included in the analysis if the examination was successful. Each of the two operators performed two sets of TE examinations at two different time points on the same day, independent of each other. The time taken to complete each set of examination, from the time the probe was first placed onto the patient until the examination was completed or considered unsuccessful, was recorded.

**Point shear wave elastography.** Point shear wave elastography was performed after  $\geq 2$  h of fasting using Phillips EPIQ 7 ultrasound system with a C5-1 convex probe (Phillips Medical Systems, Bothell, WA, USA) using the ElastPQ technique on the same day of the liver biopsy procedure by the same two operators who performed TE. Both operators have not performed pSWE previously and have received training to perform

pSWE for the purpose of this study. Following training, each of the operators performed  $\geq 200$  examinations prior to commencement of this study. Three measurements were taken for each set of examination based on a similar study in patients with chronic hepatitis B.<sup>19</sup> Each of the two operators performed two sets of pSWE examinations at two different time points on the same day, independent of each other. The time taken to complete each set of examination, from the time the probe was first placed onto the patient until the examination was completed, was recorded. No quality criteria have been established for pSWE at the time of commencement of this study. However, a recent study suggested the use of IQR/median of liver stiffness measurement of  $\leq 30\%$  as a reliability criteria.<sup>9</sup> Therefore, we performed additional *post hoc* analysis using the proposed reliability criteria.

## Liver biopsy and histopathological examination.

Ultrasonography-guided percutaneous liver biopsy was performed by an experienced operator (W. K. C.) using 18G Temno II semi-automatic biopsy needle (Cardinal Health, Dublin, OH, USA). Liver biopsy slides were stained with hematoxylin and eosin stain and Masson's trichrome stain and were examined by a single, experienced histopathologist (N. R. N. M.) who was blinded to clinical data. Histopathological findings were reported according to the Non-Alcoholic Steatohepatitis Clinical Research Network Scoring System.<sup>29</sup> Non-alcoholic steatohepatitis was defined as the presence of steatosis, lobular inflammation, and ballooning with or without fibrosis. Fibrosis stages were graded as follows: F0 = no fibrosis, F1 = perisinusoidal fibrosis, F2 = perisinusoidal with portal/periportal fibrosis, F3 = bridging fibrosis, and F4 = cirrhosis.

**Statistical analysis.** Data were analyzed using a standard statistical software program, SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean  $\pm$  standard deviation or median (IQR), while categorical variables were presented as absolute numbers and percentages. Univariate and multivariate linear regression analyses using the different histological components were performed to look for independent factors associated with TE and pSWE. Factors that were significant on univariate analysis were included in multivariate analysis. Significance was assumed if  $P < 0.05$ . The diagnostic accuracy for TE and pSWE for the diagnosis of fibrosis stages was determined using area under receiver operating characteristic curve (AUROC) using the median of the four sets of examinations. AUROC was interpreted as follows: 0.90–1.00 = excellent, 0.80–0.90 = good, 0.70–0.80 = fair, and 0.70 = poor. The pROC package of the R Statistical Software (R 3.4.3, R Foundation for Statistical Computing, Vienna, Austria) was used to determine the 95% confidence interval for AUROCs and for pairwise comparison of AUROCs. Thirty-five patients with fibrosis stage equal to or greater than the fibrosis stage of interest and another 35 patients with lower fibrosis stages are required in order to detect a difference of 0.15 in AUROC between two diagnostic tests on the same patients with 95% confidence level and 80% power.<sup>30</sup> The optimal cutoff for liver stiffness measurement for diagnosis of a particular fibrosis stage was the liver stiffness measurement that provided the highest sum of sensitivity and specificity for the diagnosis of that fibrosis stage. The sensitivity, specificity, positive predictive value, and negative predictive value of liver

stiffness measurement for the diagnosis of a particular fibrosis stage were determined based on the optimal cutoff for that fibrosis stage. Intra-observer and inter-observer reliability was analyzed using intraclass correlation coefficient. Intraclass correlation coefficient was interpreted as follows: 0.90–1.00 = excellent, 0.80–0.90 = good, 0.70–0.80 = fair, and 0.70 = poor.

## Results

**Patient characteristics and examination sets included for analysis.** One hundred patients who underwent liver biopsy during the study period were included in this study. Patient characteristics are shown in Table 1. Each of the patients underwent two sets of TE and pSWE examinations by the same operator and another two sets of TE and pSWE examinations by a second operator, giving a total of 400 sets of TE and pSWE examinations. There were eight failed or unreliable TE examinations. The M probe was used in most of the examinations (92.3%). There were no failed pSWE examination. On multivariate analysis using the different histological components, only fibrosis stage was independently associated with TE and pSWE (Tables S2,S3).

**Liver stiffness measurement according to fibrosis stages.** The median liver stiffness measurement for fibrosis stages F0, F1, F2, F3, and F4 using TE was 5.9 (5.2–7.6) kPa, 8.8 (7.0–11.1) kPa, 10.0 (8.5–15.7) kPa, 13.4 (9.8–15.8) kPa, and 19.5 (14.7–23.3) kPa, respectively. The corresponding median liver stiffness measurement using pSWE was 6.0 (4.0–6.8) kPa, 6.9 (6.0–8.6) kPa, 8.5 (6.8–10.7) kPa, 7.7 (6.8–10.5) kPa, and 13.0 (7.4–16.6) kPa, respectively. Boxplots depicting the liver stiffness measurements for fibrosis stages F0, F1, F2, F3, and F4 using TE and pSWE can be found in Figures S1 and S2, respectively.

**Accuracy of transient elastography and point shear wave elastography for the diagnosis of the different fibrosis stages.** The receiver operating characteristic curves for TE and pSWE for the diagnosis of the different fibrosis stages are shown in Figure 1. The AUROC, optimal cutoff, sensitivity, specificity, positive predictive value, and negative predictive value of TE and pSWE for the diagnosis of fibrosis stages  $\geq$  F1,  $\geq$  F2,  $\geq$  F3, and F4 are shown in Table 2. TE was good for the diagnosis of fibrosis stages  $\geq$  F1,  $\geq$  F2,  $\geq$  F3, and F4, while pSWE was good for the diagnosis of fibrosis stage  $\geq$  F1, fair for the diagnosis of fibrosis stages  $\geq$  F2 and F4, and poor for the diagnosis of fibrosis stage  $\geq$  F3. TE was significantly better than pSWE for the diagnosis of fibrosis stages  $\geq$  F2 and  $\geq$  F3. An additional *post hoc* analysis including only pSWE examinations with IQR/median  $\leq$  30% and corresponding TE examinations was performed (Table 3). TE was good, while pSWE was fair for the diagnosis of all fibrosis stages. TE was significantly better than pSWE for the diagnosis of fibrosis stages  $\geq$  F2 and  $\geq$  F3.

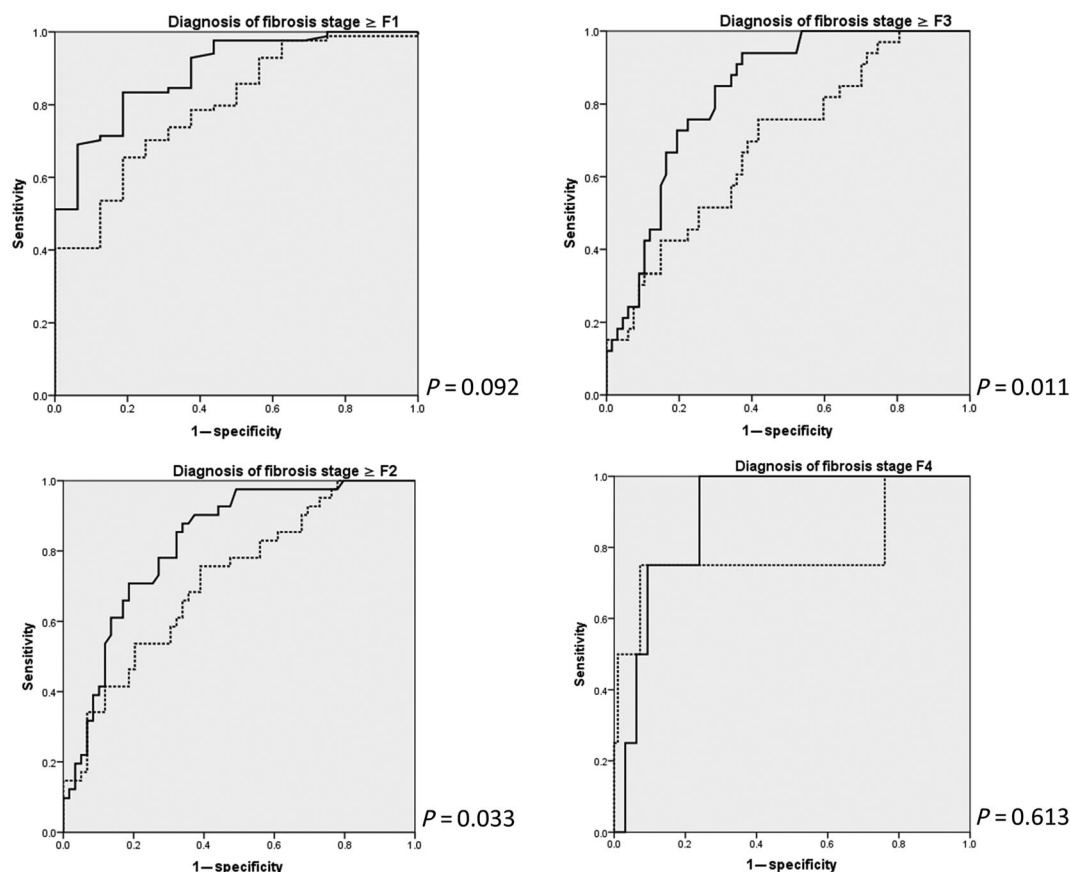
**Table 1** Characteristics of the study population

Age, years	57.1 $\pm$ 10.2
Male, <i>n</i> (%)	46 (46.0)
Body mass index, kg/m <sup>2</sup>	30.8 $\pm$ 4.8
Obesity, <i>n</i> (%)	92 (92)
Waist circumference, cm	100.6 $\pm$ 11.4
Central obesity, <i>n</i> (%)	97 (97.0)
Hypertension, <i>n</i> (%)	70 (70.0)
FBS, mmol/L	7.6 (6.1–9.0)
Triglyceride, mmol/L	1.6 (1.2–2.3)
Total cholesterol, mmol/L	4.3 (3.6–4.9)
HDL, mmol/L	1.2 (1.0–1.4)
LDL, mmol/L	2.3 (1.7–2.8)
ALT, IU/L	36 (24–53)
AST, IU/L	31 (23–41)
GGT, IU/L	55 (28–94)
Liver biopsy length, mm	14 (12–15)
Number of portal tracts	6 (4–7)
NASH, <i>n</i> (%)	80 (80)
Steatosis, <i>n</i> (%)	
S0	1 (1.0)
S1	42 (42.0)
S2	53 (53.0)
S3	4 (4)
Lobular inflammation, <i>n</i> (%)	
0	1 (1.0)
1	77 (77.0)
2	21 (21.0)
3	1 (1.0)
Ballooning, <i>n</i> (%)	
0	24 (24.0)
1	54 (54.0)
2	22 (22.0)
Fibrosis, <i>n</i> (%)	
F0	16 (16.0)
F1	43 (43.0)
F2	8 (8.0)
F3	29 (29.0)
F4	4 (4.0)

Continuous variables are presented as mean  $\pm$  standard deviation or median (interquartile range).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, fibrosis stage; FBS, fasting blood sugar; GGT,  $\gamma$ -glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NASH, non-alcoholic steatohepatitis; S, steatosis grade.

**Intra-observer and inter-observer agreement and time taken to complete transient elastography and point shear wave elastography examinations.** There was excellent correlation in repeated measurements by different operators and by the same operator for TE and pSWE (Table 4). The time taken to perform pSWE was significantly longer than the time taken to perform TE for both operators (95 vs 52 s,  $P < 0.001$  for operator 1; 93 vs 50 s,  $P < 0.001$  for operator 2). Operator 1 took longer to perform TE compared with operator 2 (52 vs 50 s,  $P = 0.004$ ). However, there was no difference in the time taken to perform pSWE by the two operators (95 vs 90 s,  $P = 0.199$ ).



**Figure 1** Receiver operating characteristic curves for transient elastography (TE) and point shear wave elastography (pSWE) for the diagnosis of fibrosis stage  $\geq$  F1 ( $\text{—}$ , TE;  $\cdots$ , pSWE),  $\geq$  F2 ( $\text{—}$ , TE;  $\cdots$ , pSWE),  $\geq$  F3 ( $\text{—}$ , TE;  $\cdots$ , pSWE), and F4 ( $\text{—}$ , MedTE;  $\cdots$ , MedpSWE).

**Table 2** The AUROC, optimal cutoff, sensitivity, specificity, PPV, and NPV of TE and pSWE for the diagnosis of steatosis grade  $\geq$  F1,  $\geq$  F2,  $\geq$  F3, and F4

TE	$\geq$ F1	$\geq$ F2	$\geq$ F3	F4
<i>n</i>	84	41	33	4
AUROC (95% CI)	0.89 (0.81–0.97)	0.83 (0.74–0.91)	0.83 (0.75–0.91)	0.89 (0.80–0.99)
Optimal cutoff (kPa)	7.68	9.13	9.28	13.45
Sensitivity	83.3% (70/84)	87.8% (36/41)	90.9% (30/33)	100% (4/4)
Specificity	81.3% (13/16)	66.1% (39/59)	64.2% (43/67)	76.0% (73/96)
PPV	95.9% (70/73)	64.3% (36/56)	55.6% (44/54)	14.8% (4/27)
NPV	48.1% (13/27)	88.6% (39/41)	93.5% (43/46)	100% (73/73)
pSWE	$\geq$ F1	$\geq$ F2	$\geq$ F3	F4
AUROC (95% CI)	0.80 (0.68–0.91)	0.72 (0.62–0.82)	0.69 (0.58–0.80)	0.79 (0.48–1.00)
Optimal cutoff (kPa)	6.83	6.98	7.02	11.52
Sensitivity	65.5% (55/84)	75.6% (31/41)	75.8% (25/33)	75.0% (3/4)
Specificity	81.3% (13/16)	61.0% (36/59)	47.2% (25/53)	92.7% (89/96)
PPV	94.8% (55/58)	57.4% (31/54)	58.2% (39/67)	30.0% (3/10)
NPV	31.0% (13/42)	78.3% (36/46)	83.0% (39/47)	98.8% (89/90)
<i>P</i> value for AUROC between TE and pSWE	0.092	0.033	0.011	0.613

The number of patients with F0 fibrosis was 16, F1 fibrosis was 43, F2 fibrosis was 8, F3 fibrosis was 29, and F4 fibrosis was 4. Optimal cutoff is the kPa value that provided the greatest sum of sensitivity and specificity for estimation of fibrosis stage equal to or greater than the respective stage. AUROC, area under receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; pSWE, point shear wave elastography; S, steatosis grade; TE, transient elastography.



**Table 3** The AUROC, optimal cutoff, sensitivity, specificity, PPV, and NPV of TE and pSWE for the diagnosis of steatosis grade  $\geq$  F1,  $\geq$  F2,  $\geq$  F3, and F4 including only pSWE examinations with IQR/median  $\leq$  30% and corresponding TE examinations

TE	$\geq$ F1	$\geq$ F2	$\geq$ F3	F4
<i>n</i>	64	32	27	3
AUROC (95% CI)	0.89 (0.80–0.98)	0.85 (0.76–0.93)	0.84 (0.75–0.93)	0.86 (0.76–0.96)
Optimal cutoff (kPa)	8.78	9.13	9.73	10.45
Sensitivity	71.9% (46/64)	90.6% (29/32)	85.2% (23/27)	100.0% (3/3)
Specificity	91.7% (11/12)	65.9% (29/44)	71.4% (35/49)	61.6% (45/73)
PPV	97.9% (46/47)	65.9% (29/44)	62.2% (23/37)	9.7% (3/31)
NPV	37.9% (11/29)	90.6% (29/32)	89.7% (35/39)	100.0% (45/45)
pSWE	$\geq$ F1	$\geq$ F2	$\geq$ F3	F4
AUROC (95% CI)	0.79 (0.65–0.92)	0.74 (0.62–0.85)	0.71 (0.59–0.83)	0.72 (0.31–1.00)
Optimal cutoff (kPa)	6.22	6.98	7.30	11.52
Sensitivity	81.3% (52/64)	78.1% (25/32)	74.1% (20/27)	66.7% (2/3)
Specificity	66.7% (8/12)	61.4% (27/44)	63.3% (31/49)	93.2% (68/73)
PPV	92.9% (52/56)	59.5% (25/42)	52.6% (20/38)	28.6% (2/7)
NPV	40.0% (8/20)	79.4% (27/34)	81.6% (31/38)	98.6% (68/69)
<i>P</i> value for AUROC between TE and pSWE	0.129	0.044	0.043	0.621

The number of examinations of patients with F0 fibrosis was 12, F1 fibrosis was 32, F2 fibrosis was 5, F3 fibrosis was 24, and F4 fibrosis was 3. Optimal cutoff is the kPa value that provided the greatest sum of sensitivity and specificity for estimation of fibrosis stage equal to or greater than the respective stage.

AUROC, area under receiver operating characteristic curve; CI, confidence interval; IQR, interquartile range; NPV, negative predictive value; PPV, positive predictive value; pSWE, point shear wave elastography; S, steatosis grade; TE, transient elastography.

**Table 4** The ICCs and 95% CIs for TE and pSWE

	TE	SWE
	Average measure (95% CI)	Average measure (95% CI)
Op 1 (1) vs Op 2 (1)	0.97 (0.96–0.98)	0.99 (0.98–0.99)
Op 1 (1) vs Op 2 (2)	0.97 (0.96–0.98)	0.98 (0.97–0.99)
Op 2 (1) vs Op 1 (2)	0.98 (0.98–0.99)	0.98 (0.97–0.99)
Op 2 (2) vs Op 1 (2)	0.99 (0.98–0.99)	0.98 (0.96–0.98)
Op 1 (1) vs Op 1 (2)	0.98 (0.97–0.99)	0.98 (0.97–0.99)
Op 2 (1) vs Op 2 (2)	0.99 (0.99–0.99)	0.98 (0.98–0.99)

ICCs, intraclass correlation coefficients; Op 1 (1), operator 1 first set of examination; Op 2 (1), operator 2 first set of examination; Op 1 (2), operator 1 second set of examination; Op 2 (2), operator 2 second set of examination; pSWE, point shear wave elastography; TE, transient elastography.

## Discussion

We found that TE was good for the diagnosis of fibrosis stages  $\geq$  F1,  $\geq$  F2,  $\geq$  F3, and F4, whereas pSWE was good for the diagnosis of fibrosis stage  $\geq$  F1, fair for the diagnosis of fibrosis stages  $\geq$  F2 and F4, and poor for the diagnosis of fibrosis stage  $\geq$  F3. Although there have been several studies comparing the diagnostic performance of TE and SWE, these studies were on patients with chronic liver disease of various etiologies.<sup>9,16,19–22,25,31</sup> Moreover, some of these studies did not use liver biopsy as a reference standard.<sup>9,21,22</sup> To the best of our knowledge, there are only four published studies to date that compared the diagnostic performance of TE and SWE, using liver biopsy as the reference standard, in a cohort that consisted exclusively of NAFLD patients.<sup>14,15,17,32</sup> However, the studies used different techniques of SWE, such as pSWE using Virtual Touch™ Quantification (VTQ) and supersonic imaging (SSI). To the best of our

knowledge, our study is the first to compare TE and pSWE using ElastPQ that used liver biopsy as the reference standard in a pure NAFLD cohort. This is notable because although ElastPQ, VTQ, and SSI are ultrasound elastography techniques, they vary in terms of fundamental techniques.<sup>10,33</sup> In the study by Cassinotto and colleagues, TE was found to be good across fibrosis stages  $\geq$  F2,  $\geq$  F3, and F4, which is consistent with the findings of our study. Their study showed that pSWE using VTQ was fair for the diagnosis of fibrosis stage  $\geq$  F2 and good for the diagnosis of fibrosis stages  $\geq$  F3 and F4. Our results on pSWE using ElastPQ were not as promising. This may have been due to the different pSWE techniques used. Moreover, the mean BMI of our study population was 30.8 kg/m<sup>2</sup>, much higher than that in the recent studies investigating the accuracy of pSWE technique, which ranged from 23.7 to 27.3 kg/m<sup>2</sup>.<sup>16,21,22,25</sup> It is known that thick subcutaneous tissue may attenuate ultrasound beam, and this may explain the poorer diagnostic performance of pSWE in our study.<sup>34</sup> Existing studies comparing TE and pSWE consisted of patients with chronic liver disease of various etiologies, in which the proportion of NAFLD patients were very small. For example, the study by Ferraioli and colleagues found that pSWE was good to excellent for the diagnosis of significant liver fibrosis ( $\geq$  F2) with AUROC of 0.85 to 0.96. However, only 5% of the study population consisted of NAFLD patients, and the mean BMI was only 25.8 kg/m<sup>2</sup>.

The optimal cutoff values for diagnosis of fibrosis stages  $\geq$  F2 and  $\geq$  F3 were close to each other for both TE and pSWE. This could have been due to the relatively high BMI and the relatively small number of patients with F2 fibrosis in our study population. TE may be affected by increased skin capsular distance in obese subjects. Although the use of XL probe has been increasingly recommended for patients with greater BMI, for example,  $\geq$  30 kg/m<sup>2</sup>, this was not standard practice at the time of commencement of this study. Using the computer recommendation on probe choice was also not something routine at the time of commencement of this

study, and we have used the XL probe in cases of failed or unreliable examination with the M probe instead. A more precise use of probe size would have increased the accuracy of TE for the diagnosis of the different fibrosis stages. This would only increase the already observed difference in the diagnostic accuracy of TE compared with pSWE.

To be fair, pSWE is a relatively new method and has yet to have validated reliability criteria at the time of commencement of this study. Two recent studies have shown that the highest accuracy of pSWE is obtained when the quality criterion IQR/median  $\leq 30\%$  was followed.<sup>9,22</sup> Therefore, we have performed additional *post hoc* analysis using the reliability criteria of IQR/median  $\leq 30\%$ . However, the results were mixed, with marginally higher AUROC for the diagnosis of fibrosis stages  $\geq F2$  and  $\geq F3$  and lower AUROC for the diagnosis of fibrosis stages  $\geq F1$  and  $F4$ . Nevertheless, TE remained significantly better than pSWE for the diagnosis of fibrosis stages  $\geq F2$  and  $\geq F3$ . One of the important quality of a good diagnostic tool is that its result should be consistent and reproducible when used by the same operator and by different operators. Ultrasound-based techniques are often operator dependent because of its subjective assessment by different operators.<sup>35</sup> Our study showed that both TE and pSWE are highly reliable methods for assessing fibrosis stages with high intra-observer and inter-observer correlation coefficients, even in healthcare personnel of different background. While pSWE required a statistically significantly longer time to be performed compared with TE, the magnitude of difference is probably not clinically important.

Despite our best efforts, this study has several limitations. Firstly, when assessing the inter-observer and intra-observer variability, the repeat examinations of TE and pSWE for both operators were performed on the same day. Although ideally these should have been performed at least several days apart to minimize operator bias, this was not possible because of logistic reasons. Furthermore, we wanted to ensure the interval between examinations and liver biopsy date were not too far apart for the examination results to be truly representative of the liver biopsy results. Secondly, the number of patients with F0 and F4 fibrosis was small, and this may have resulted in the difference in the diagnostic accuracy of TE and pSWE to be not statistically significant for the diagnosis of fibrosis stages  $\geq F1$  and  $F4$ . Lastly, as in any study that used liver histology as reference standard, our study may be limited by sampling and observer variability. Although none of the liver biopsy specimens were deemed inadequate for assessment by our pathologist, the mean length of the liver biopsy specimens and number of portal tracts in our study did fall short of the recommended international standards, which may have affected the interpretation of diagnostic accuracy in our study.<sup>36</sup> In summary, our study showed that TE was good for the diagnosis of all fibrosis stages and was superior compared with pSWE for the diagnosis of fibrosis stages  $\geq F2$  and  $\geq F3$ . Further studies with a larger number of patients with F0 and F4 fibrosis will be required for a more conclusive comparison of the accuracy of TE and pSWE for the diagnosis of fibrosis stages  $\geq F1$  and  $F4$ . Both TE and pSWE were found to have excellent intra-observer and inter-observer reliability when performed by trained healthcare personnel of different background. pSWE required a longer time to be performed compared with TE, but the magnitude of difference is probably not clinically important.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Boxplot showing distribution of TE according to fibrosis stages. The number of examinations for each of the fibrosis stages is indicated above the corresponding boxplot.

**Figure S2.** Boxplot showing distribution of pSWE according to fibrosis stages. The number of examinations for each of the fibrosis stages is indicated above the corresponding boxplot.

**Table S1.** Summary of studies on SWE for the diagnosis of the different fibrosis stages in patients with chronic liver disease.

**Table S2.** Univariate and multivariate analyses using the different histological components for TE.

**Table S3.** Univariate and multivariate analyses using the different histological components for pSWE.

**Data S1.** Supporting information.