• Liver Fibrosis • Cirrhosis •

Efficiency of FibroScan and FibroTouch in liver stiffness measurement and fat quantification: a comparative analysis

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【**Abstract**】 **Objective** To investigate the efficiency of FibroScan (FS) and FibroTouch (FT) in liver stiffness measurement (LSM) and fat quantification through a comparative analysis. **Methods** The outpatients or hospitalized patients who underwent LSM and fat quantification using FS and FT were enrolled. The differences in success rate and detecting parameters between FS and FT were analyzed, as well as the correlation between FS and FT values. The t-test was used for comparison of normally distributed continuous data between groups, and a one-way analysis of variance or the Kruskal-Wallis test was used for comparison between multiple groups. The Mann-Whitney U test was used for comparison of non-normally distributed continuous data between groups. **Results** A total of 1621 patients were enrolled. The success rates of FT and FS were 100% and 94.96%, respectively, and the success rate of FS was influenced by sex, age, body mass index, and biochemical markers of liver function. FT has a significantly shorter duration of single detection and a significantly lower number of times of single detection than FS (duration of single detection: 190.21±38.78 s vs 220.89±68.36 s, $P < 0.01$; number of single detection times: 10.31±1.32 vs 11.81±3.76, $P < 0.01$), as well as a significantly lower ratio of interquartile range to median of fat quantification in the same patient (5.39%±4.81% vs 17.18%±14.07%, $P < 0.01$). The LSM and fat quantification of FS were significantly correlated with those of FT ($r = 0.645$ and 0.620, both Based on the duration and number of times of single detection, success rate, and stability of fat quantification, FT seems to have a better detection efficiency than FS. The detection values of FT and FS can be calculated with regression equations < 0.01). The equations of linear regression were LSM (FT) = 4.435+0.477×LSM (FS); CAP (FT) = 134.71+0.456×CAP (FS). **Conclusion** Based on the duration and number of times of single detection, success rate, and stability of fat quantification, FT seems to have a better detection efficiency than FS. The detection values of FT and FS can be calculated with regression equations.

【**Keywords**】 Liver cirrhosis; Fatty liver; FibroScan; FibroTouch; Success rate; Influence factors; Linear regression analysis

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With the rapid development of medical imaging technology, new technologies are increasingly being used for the non-invasive diagnosis of liver fibrosis. Among such technologies, elastography is the most widely used in clinical practice. In 2003, Sandrin et al. invented a method, called transient elasticity measurement, for determining tissue elasticity using ultrasonic technology. On this basis, the French company, Echosens, developed FibroScan (FS), a specialized instrument for measuring tissue elasticity. After more than ten years of scientific and technological development, the use of FS has been validated for the assessment of the degree of liver fibrosis in different etiologies of liver diseases, and it has been widely accepted by and incorporated into the guidelines of many experts in China and abroad[1-2]. The FibroTouch (FT), developed by Tsinghua University in 2010, is the first liver stiffness detector developed in China. It measures elasticity through the use of two-dimensional ultrasonic positioning, and it can also measure liver tissue morphology, the degree of fibrosis, and fatty liver levels. The results of existing studies show that FT can

be used for the non-invasive assessment of liver fibrosis caused by chronic hepatitis B, with the test results being consistent with those obtained using FS[3].

The clinical value of FS and FT lies in the non-invasive quantitative measurement of liver fibrosis and hepatic steatosis, and they are expected to be used with respect to liver disease for screening, diagnosis, and follow-up of special populations. At present, FS has been used clinically for over ten years, and it is recommended for the routine diagnosis of liver fibrosis, and even hepatic steatosis, in many countries and regions. As FT is still in the clinical evaluation stage, and the sample sizes in clinical studies comparing FT and FS are relatively small, evidence for its use for clinical diagnosis is insufficient[4]. These two instruments are currently in clinical use in China, and yet a comparison of the measurements of the two different instruments used on the same subjects and the diagnostic threshold of FT are yet to be further studied as part of a study using a large subject population. The purpose of this study is to use the two instruments in a randomized sequence for a comparison of the measurement parameters of FT and FS involving the same operators and subjects, to investigate differences in measurement performance and correlation between the measurements, and to provide some references for the clinical application of the two instruments in the present day.

Materials and Methods

1. Study subjects: Patients with chronic hepatitis and liver fibrosis and healthy volunteers, who arrived at our hospital between June 2014 and December 2014 for transient elasticity measurement of the liver. Exclusion criteria: Patients with recent wounds in the right upper abdomen that have not healed, acute active hepatitis, various space-occupying lesions (tumors, cysts) in the right liver; patients with combined illnesses that may affect the detection of liver diseases, such as severe heart disease and severe infections; and patients with decompensated cirrhosis with ascites.

2. Study methodology: The instruments used were FS (Model 502, Echosens, France) and FT (Type B, Wuxi Hisky Medical Technology Co., Ltd.); the same skilled operators used FS and FT in a randomized sequence to measure the liver stiffness and hepatic steatosis in the same subjects.

FS: When measurements were taken, the subjects were placed in the supine position, with the head held with their right hand to maximize the intercostal spaces. The probe was placed on the 7^{th}, 8^{th} and 9^{th} intercostal spaces between the anterior axillary and mid axillary lines on the right side, keeping the probe perpendicular to the skin surface of the intercostal space, and using ultrasonic modes A and TM to find the appropriate measurement site. Measurement was initiated when the pressure indicator was green, the intensity of the M waveform on the display was consistent and evenly distributed, and the A waveform was linear. Measurement was repeated more than 10 times in the same location.

FT: The B-ultrasound probe of the FT instrument was used initially for positioning, avoiding structures such as cysts and blood vessels in the liver tissue that could interfere with the measurement accuracy. Once the measurement position and angle was determined, the measurement interface was then used for measurement. The other measurement processes were the same as those for FS.

3. Classification of instrument measurement results: For both instruments, the median of all valid measurement results was used as the final result; the unit for liver stiffness measurements (LSMs) was kPa; the quantitative determination of hepatic steatosis was expressed as the controlled attenuation parameter (CAP), expressed in dB/m. The measurement results were divided into three categories: (1) Effective measurement: the ratio of the interquartile range to the median of all measurements (IQR/med) was < 30% and the success rate (successful measurements / total number of measurements) was ≥ 60%. (2) Invalid measurement: IQR/med ≥ 30% or success rate < 60%. (3) A measurement could not be obtained.

4. Relevant data collected: demographic characteristics and clinical information: sex, age, height, body weight, waist circumference, clinical diagnosis, current medical history, past history of disease, history of alcohol consumption, history of hepatitis B; body mass index (BMI), waist to height ratio (WHtR); routine blood test results and blood biochemical indicators of blood collected on the day of examination: white blood cell count, hemoglobin, platelets, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), albumin, total bilirubin (TBIL), total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein; imaging data: B-ultrasound and/or CT examination results.

5. Statistical methods: Following testing for normality, normally distributed measurement data was expressed as the mean ± standard deviation ($\bar{x}$±s), and the *t*-test was used for inter-group comparison; for comparison between multiple groups, testing for homogeneity of variance was performed, and a one-way analysis of variance was used for cases of homogeneity of variance, and the Kruskal-Wallis test was used for cases of heterogeneity of variance. Non-normally distributed measurement data were expressed as the median ± interquartile range; and the Mann-Whitney U

test was used for comparison between groups. Correlation was analyzed using the Pearson correlation. A *P value* of < 0.05 was considered statistically significant. Statistical analysis was carried out using the SPSS 19.0 software package.

Results

1. Basic characteristics of the study population: A total of 1,707 subjects underwent testing using FS and FT during the study period; the success rate of measurement for each subject using FT was 100%; for testing performed using FS, measurement could not be obtained for 86 subjects, and the success rate was 94.96%; a total of 1,621 patients were eventually included in the data analysis, including 841 males and 780 females; ages (53±16 years old) (Figure 1, Table 1).

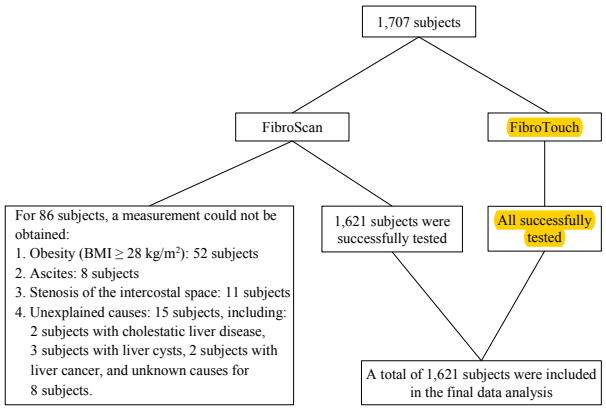


Figure 1 Overview of measurement of the study population

Table 1 Basic characteristics of the study population ($\bar{x}$±s)

Demographic characteristics	$\bar{x}$±s
Age (years)	53.00±16.00
Height (cm)	165.21± 9.91
Body mass (kg)	65.54±13.93
Body Mass Index (kg/m²)	23.82±3.82
Waist circumference (cm)	87.63±10.85
Hip circumference (cm)	98.24±9.62
Waist to height ratio	0.53±0.06

2. Comparison between the measurement performance of FS and FT: The FT single measurement time was (190.21±38.78) s, and the FS measurement time was (220.89±68.36) s; the number single FT measurements was (10.31±1.32), and the number of FS measurements was (11.81±3.76); the success rate for obtaining a measurement using FT single measurements was 100%, while the success rate for FS was 84.31%. The difference was statistically significant (P<0.01). There was no statistically significant difference in the interquartile range (IQR) and IQR/med between the FT and FS liver stiffness results for the same subjects. However, the difference in the IQR and IQR/med of CAP values for the two fat quantitative measurement results was statistically significant (P<0.01). For the two instruments, the performance of FT was superior to that of FS with respect to single measurement time, number of single measurements, success rate and stability of CAP quantitative measurement etc. See Table 2.

The success rates of FS and FT measurement were compared by age, sex, BMI, and WHtR. The results showed that the FT measurement success rate for different subjects was 100%. In the FS test, however, the success rate of measurement for those aged ≥50 years was lower; the measurement success rate for female subjects was lower than that of males; for subjects with a BMI ≥ 28 kg/m², the measurement success rate was significantly lower than those with a BMI < 28 kg/m²; for subjects with a WHtR ≥ 0.5, the measurement success rate was significantly lower than those with a WHTR <0.5 (Table 3).

Table 3 Comparison of FibroScan measurement success rates for different ages, sex and BMI populations

Group	Number of subjects	FibroScan measurement success rate (%)	*t* value	*P* value
Sex				
Male	841	85.50±21.21	2.832	0.005
Female	780	83.03±23.58		
Age (years)				
< 50	529	89.90±17.42	7.061	<0.01
≥ 50	1092	81.62±24.02		
BMI (kg/m²)				
< 28	1446	85.32±21.57	5.312	<0.01
≥ 28	175	75.86±27.11		

Note: BMI refers to Body Mass Index

Table 2 Comparison of FibroScan and FibroTouch measurement performance parameters ($\bar{x}$±s)

Group	Single measurement time (s)	Total number of single tests	Success rate (%)	LSM-IQR (kPa)	LSM-IQR/med (%)	CAP-IQR (dB/m)	CAP-IQR/med (%)
FibroScan	220.89±68.36	11.81±3.76	84.31±22.41	1.78±2.82	18.00±14.62	36.75±24.10	17.18±14.07
FibroTouch	190.21±38.78	10.31±1.32	100.00±0	1.68±2.76	17.62±21.17	13.07±11.98	5.39±4.81
t value	5.29	15.56	-28.19	1.240	0.596	35.613	32.667
P value	<0.01	<0.01	<0.01	0.552	0.215	<0.01	<0.01

Note: LSM-IQR refers to the interquartile range of the liver stiffness measurements; LSM-IQR/med refers to the ratio of the interquartile range to the median of the liver stiffness measurements; CAP-IQR: the interquartile range of the controlled attenuation parameter values; CAP-IQR/med: the ratio of the interquartile range to the median of the controlled attenuation parameter values

A Pearson correlation analysis showed that the success rate of FS measurement and the subject age (r = -0.195, P<0.01), BMI (r = -0.103, P<0.01), waist circumference (r = -0.182, P<0.01), and WHtR (r = -0.140, P<0.01) were negatively correlated, and the success rate and ALT (r = 0.117, P<0.01), AST (r = 0.110, P<0.01), GGT (r = 0.110, P<0.01), and TBIL (r = 0.076, P<0.01) levels were positively correlated (Table 4).

Table 4 Analysis of the correlation between the FibroScan measurement success rate with patient clinical information and laboratory indicators ($\bar{x}$±s)

Characteristics	Success rate(%)	*r* value	*P* value
Age (years)	53.17±15.99	-0.195	<0.000
BMI (kg/m^2)	23.82±3.82	-0.103	<0.000
Waist circumference (cm)	87.63±10.85	-0.182	<0.000
WHtR	0.53±0.06	-0.140	<0.000
Hemoglobin (g/L)	134.83±23.98	-0.100	0.088
Platelets (10^9/L)	181.86±78.35	0.041	0.170
ALT (U/L)	74.22±148.82	0.117	<0.000
AST (U/L)	52.91±85.77	0.110	<0.000
ALP (U/L)	117.63±100.91	0.044	0.124
GGT (U/L)	100.53±169.17	0.110	<0.000
Total bilirubin (μmol/L)	24.46±47.72	0.076	0.007
Albumin (g/L)	40.02±5.44	0.036	0.203
Total cholesterol (mmol/L)	4.75±2.55	0.001	0.988
Triglycerides (mmol/L)	2.03±7.18	0.012	0.742
HDL (mmol/L)	1.35±0.42	-0.103	0.101

Note: BMI: Body mass index; WHtR: Waist to height ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyltranspeptidase; ALP: alkaline phosphatase; HDL: High-density lipoproteins

3. Comparison of the characteristics of invalid measurement populations for FS and FT: In this study, there were 86 subjects for which measurements could not be obtained using FS, accounting for 5.04% of the total number of subjects tested; based on the instrument's definition of effective measurement, there were 108 cases of invalid LSM, accounting for the total 6.33% of the total number of subjects tested; there were 180 cases of invalid CAP measurements, accounting for 10.54% of the total number of subjects tested; there were 64 cases of invalid LSM and CAP measurements, accounting for 3.75% of the total number of subjects tested.

There were 0 cases where a value could not be obtained using FT; there were 101 cases of invalid LSM, accounting for 5.92% of the total number of subjects tested; there were 10 cases of invalid CAP measurements, accounting for 0.59% of the total number of subjects tested; there was 1 case where LSM and CAP values were simultaneously invalid, accounting for 0.06% of the total number of subjects tested. The failure rates of LSM using both FS and FT instruments was related to age, BMI, and WHtR (P values all <0.05); with respect to CAP measurement efficiency, the measurement performance using FT was superior to FS. See Table 5 and Table 6.

Table 5 Population characteristics of invalid FibroScan measurements

Group	Number of subjects	Invalid liver stiffness measurements (n = 108)	*P* value	Invalid controlled attenuation parameter values (n = 180)	*P* value
Sex					
Male	841	56	0.454	68	<0.01
Female	780	52		112	
Age (years)					
< 50	529	21	<0.01	41	<0.01
≥ 50	1092	87		139	
Body Mass Index (kg/m^2)					
< 28	1446	70	<0.01	161	0.141
≥ 28	175	38		19	

Table 6 Population characteristics of invalid FibroTouch measurements

Group	Number of subjects	Invalid liver stiffness measurements (n =101)	*P* value	Invalid controlled attenuation parameter values (n = 10)	*P* value
Sex					
Male	841	48	0.054	6	0.608
Female	780	53		4	
Age (years)					
< 50	529	20	0.037	6	0.663
≥ 50	1092	81		4	
Body Mass Index (kg/m^2)					
< 28	1446	75	0.015	10	0.268
≥ 28	175	26		0	

4. Comparison of FS and FT measurements: The LSM values obtained using FS and FT are significantly correlated (r = 0.645, P<0.01; Figure 2); the CAP values are also significantly correlated (r = 0.620, P<0.01; Figure 3). At the same time, the LSMs for FS and their CAP values (r = -0.108, P<0.01) and the LSMs for FT and CAP values (r=-0.059, P=0.018) were negatively correlated, and the differences were statistically significant.

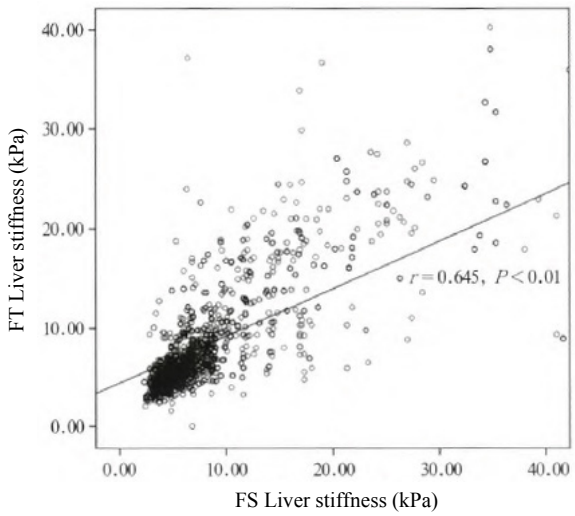
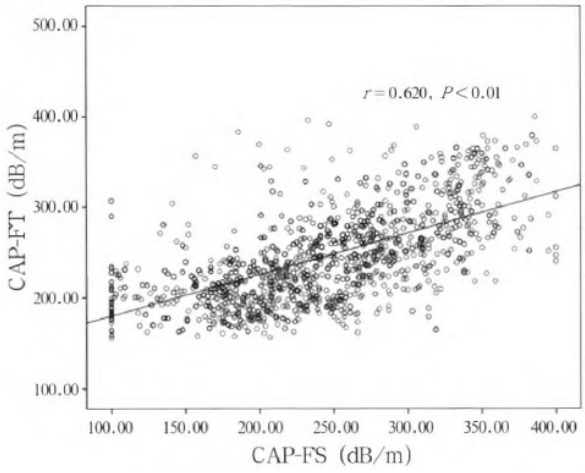


Figure 2 Scatter plot of FibroScan and FibroTouch liver stiffness measurements



Note: CAP: Controlled attenuation parameter

Figure 3 Scatter plot of CAP value measurements using FibroScan and FibroTouch

Following linear regression analysis of the LSMs of FS and FT, it was found that: LSM (FT) = 4.435 + 0.477 × LSM (FS); following linear regression analysis of CAP values measured using FS and FT, it was found that: CAP (FT) = 134.71 + 0.456 × CAP (FS).

Discussion

The instrument model used in this study, FS-502, can detect both LSM and CAP values. The CAP value is a parameter defined by the principle of ultrasonic attenuation, which can be used to quantitatively analyze liver fat content. In recent years, the clinical application of FS has been extensively validated by many studies, but it still has some limitations that affect the accuracy of measurement. As early as 2007, Sagir et al.[5] found that in patients with acute liver damage, even when there was no obvious fibrosis in the liver tissue, the liver stiffness measurement was elevated, and even exceeded the critical value for diagnosing cirrhosis. The reason may be that liver stiffness is affected by the acute increase of ALT. [6] Therefore, Sagir concluded that FS is not suitable for the detection of active hepatitis. Through a retrospective analysis of 13,369 subjects, Castéra et al.[7], found that when FS was used to measure liver stiffness, it was difficult to obtain effective measurement in about one-fifth of patients. The success rate of measurement was affected by factors including patient obesity, intercostal space, ascites, sex, age, hyperglycemia, high blood pressure, food intake, and operator experience. In this study, for 86 of the 1,707 subjects tested using FS, no measurements could be obtained. Therefore, the success rate was 94.96%. A stratified analysis of the subjects revealed that for subjects ≥50 years old, female subjects, and those with a BMI ≥ 28 kg/m^2 all had a significant reduction in the success rate of measurement; the success rate of FS measurement was also related to the levels of ALT, AST, GGT, and TBIL, which is consistent with previous studies.

The FT, developed by Tsinghua University in 2010, is the first stiffness detector developed in China. It integrates two-dimensional imaging and transient elasticity technologies. It guides the accurate positioning for measurement of elasticity through its built-in B-mode ultrasound, which compensates for the limitation of lack of positioning using FS. Xia Changhong et al.[8] compared liver elasticity values measured using FS and FT in a hepatitis B liver fibrosis group, chronic hepatitis B group and healthy volunteers, with the results showing that the FT measurement success rate (100%) was higher than that of FS (92.5%), and its diagnostic efficiency was slightly better than FS. From a technical point of view, FT's algorithm uses optimized parallel computing, and a built-in parallel data processing algorithm to speed up the measurement time while simultaneously eliminating irrelevant data; its built-in liver capsule detection module can utilize the characteristics of the internal and external sound signals of the liver capsule to obtain more accurate positioning of the liver capsule and automatically adjust

the depth of measurement. Considering that the subcutaneous measurement range using the FS M probe is 2.5 - 6.5 cm, existing studies suggested that a BMI ≥ 28 kg/m^2 may affect the measurement accuracy [9-10]; A skin-liver capsule depth (SCD) of ≥ 25 mm in patients with non-alcoholic fatty liver disease affects the accuracy of diagnosing progressive fibrosis using LSM[11-12]. Therefore, the corresponding probe should be selected according to the patient's SCD to improve the success rate. Although FS has three probe types (S-type, M-type, and XL-type), it can be used on persons of different ages and body types. However, only M-type probes are used in clinical testing in China, which affects the success rate of measurement and the accuracy of the final diagnosis, in addition to adding a certain level of inconvenience to clinical work. Liver capsule detection module technology can be used with FT to further ensure the accuracy of the measurement range, so that subject SCD does not interfere with the measurement results. Possible reasons for the difference between the two instruments in terms of measurement success rates and stability may be due to: The use of ultrasound in FS to track the transmission of shear waves in the liver. Although the ultrasonic frequency is high (3.5 MHz) and the spatial resolution is high, the accompanying attenuation, however, is also large and there is low penetration. In obese subjects, the attenuation of high-frequency ultrasound signals caused by subcutaneous fat and the low signal-to-noise ratio can lead to measurement failures. For FT, the broadband frequency probe emits a wider ultrasonic band (2 to 7 MHz) with both high-frequency and low-frequency components, therefore the penetration force and resolution can be adjusted according to different subjects. Overall, this improves the success rate and accuracy of measurement, resulting in FT having certain advantages for measurement in obese patients. In this study, the success rate of FT measurement was 100%, with the duration of single measurements shorter than FS, and the number of measurements fewer than FS. Factors including sex, age, BMI had no significant effect on the measurement success rate. Moreover, the stability in detecting CAP values using FT was significantly higher than FS. The measurement effective rate was high and the measurement efficiency was significantly better than FS.

After nearly a decade of development, the use of FS has been validated for the assessment of liver fibrosis in various liver diseases, including chronic hepatitis C, chronic hepatitis B, and non-alcoholic fatty liver disease. However, a large number of liver biopsies are lacking for the clinical diagnostic threshold of FT to be clarified. After examining the pathological staging in liver biopsies in 45 patients with chronic hepatitis B, Yuan Lichao et al. [3] from China found that in an analysis of the receiver operating characteristic curves for liver fibrosis diagnosis using FT: For the degrees of liver fibrosis diagnosed as ≥S1, ≥S2, ≥S3 and ≥S4, the areas under the receiver operating characteristic curves were 0.889, 0.941, 0.908 and 0.911, respectively. This indicates that FT is effective for the staging diagnosis of liver fibrosis. This study analyzed the data on 1,621 subjects. The results showed that the liver stiffness measurements using FS and FT were significantly correlated with the measured fat quantitative values. A linear regression analysis on the measured liver stiffness values and fat quantitative values was performed, and the following was obtained: LSM (FT) = 4.435 + 0.477 × LSM (FS); CAP (FT) = 134.71 + 0.456 × CAP (FS). At present, both instruments are in clinical use in China. The establishment of regression equations for the measurements obtained using both instruments can provide a reference for clinicians for the comparison and conversion of measurements for the two different instruments for the same subjects.

It is worth noting that, following linear correlation analysis, it was found that the LSM values of both FS and FT alike were negatively correlated with CAP values in this study. In a study of 112 subjects with chronic liver disease, the French researchers de Lédinghen et al.[13] found a significant positive correlation between CAP values and LSM values (r = 0.173, P = 0.0007). Following a linear correlation analysis, Lu Jiafa et al.[14], also found a significant positive correlation between LSM and CAP values; on the other hand, the Portuguese researchers Carvalhana et al.[15] found no significant correlation between the two in a study of the general population. A possible reason for the difference in study results could be that the correlation between CAP and LSM values is weak, and that the heterogeneity of the study populations for each study was too large to reach a definitive conclusion. The true relationship between LSM and CAP values remains to be further studied.

In summary, FS and FT offer good prospects in terms of clinical value for the non-invasive quantitative measurement of liver fibrosis and hepatic steatosis, clinical disease diagnosis and follow-up for special populations. Although FT is still in the clinical evaluation stage and the sample size used was small, the study above compares the measurement parameters and the measurements using the two instruments on the same subjects. In terms of measurement time, number of measurements, measurement success rate and CAP measurement stability, the results show that the measurement performance of FT with B-ultrasonic positioning, parallel algorithms, built-in liver capsule detection modules and broadband technology is slightly better in comparison to FS.

Conflicts of interest None

Author contribution statement Zeng Jing, Sun Wanlu, Yan Shiyan, Fan Jiangao: Responsible for the preparation and design of the experiments; Chen Guangyu, Pan Qin, Xu Zhengjie: Responsible for the implementation of the study; Zeng Jing, Sun Wanlu: Responsible for data collection, processing and statistical analysis; Zeng Jing, Sun Chao: Responsible for article drafting; Fan Jiangao: Responsible for reviewing articles

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2. Website registration (Please note that your user name and password are synchronized with your Chinese Medical Association login information. If you forget your password, you can request it by filling in the email address);
3. Apply to be published in the journal;
4. Log on to the system, then click on "Remote Manuscript Management System" in the left menu bar. The corresponding functions are displayed below;
5. Click on “Author Submission” and fill in the required content for submission;
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7. Click “Save” to add the manuscript to the "My Drafts" section.
8. Authors can also submit an inquiry on the manuscript status, communicate with the editorial department, modify the manuscript after it is returned, and pay fees such as the manuscript processing fee and layout fee online.

Description of the expert review for the "Chinese Journal of Hepatology"

1. Visit http://www.cma.org.cn/ywzx/ywzx.asp.
2. Click “Login” to enter the information management platform of the Chinese Medical Association;
3. Enter “Login Name” and “Password” and click “Login” to enter the system. A login and password for experts can be obtained in two ways: (1) direct expert log in provided by the editorial department of the journal, and (2) activation of the

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6. After verifying your current role is as the expert tasked with processing the journal's manuscripts, click on “Unrevised Manuscripts” to view all the unrevised manuscripts of the current journal;
7. Click on the link in the “Manuscript Number” column to go to the page where the review comments are submitted;
8. Fill in the corresponding content and click “Submit Review Opinion” to complete the revision;
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The editorial department advises authors to submit manuscripts online. If you have any questions, please contact the editorial department at 023-63727251 or by email at hepnet@163.com.