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BRIEF ARTICLES

Applicability and variability of liver stiffness measurements according to probe position

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Abstract

AIM: To investigate the liver stiffness measurement (LSM) applicability and variability with reference to three probe positions according to the region of liver biopsy.

METHODS: The applicability for LSM was defined as at least 10 valid measurements with a success rate greater than 60% and an interquartile range/median LSM < 30%. The LSM variability compared the inter-position concordance and the concordance with FibroTest.

RESULTS: Four hundred and forty two consecutive patients were included. The applicability of the anterior position (81%) was significantly higher than that of the reference (69%) and lower positions (68%), (both $P = 0.0001$). There was a significant difference (0.5 kPa, 95% CI 0.13-0.89; $P < 0.0001$) between mean LSM estimated at the reference position (9.3 kPa) *vs* the anterior position (8.8 kPa). Discordance between positions was associated with thoracic fold ($P = 0.008$). The discordance rate between the reference position result and FibroTest was higher when the 7.1 kPa cutoff was used to define advanced fibrosis instead of 8.8 kPa (33.6% *vs* 23.5%, $P = 0.03$).

CONCLUSION: The anterior position of the probe should be the first choice for LSM using Fibroscan, as it has a higher applicability without higher variability compared to the usual liver biopsy position.

Key words: Fibroscan; Fibrotest; Liver fibrosis; Variability; Concordance

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INTRODUCTION

A major clinical challenge is to find the best method to evaluate and to manage the increasing numbers of patients with chronic liver disease[1-4]. Liver biopsy, due to its risks and limitations, is no longer considered mandatory as the first-line indicator of liver injury, and several markers have been developed as non-invasive alternatives[1-4].

The assessment of liver fibrosis by non-invasive techniques such as biomarkers, [FibroTest® (FT)][5] and liver stiffness measurement (LSM) by Fibroscan®[6,7], is now widely performed in countries where these techniques are available and approved[8,9]. It is therefore essential to identify factors associated with a variability of the results of these techniques to reduce the risk of false positives or false negatives. There are no published procedures for the most accurate position of the probe in LSM. In almost all

publications[6,7,9-16], the described method is copied from the original description by Sandrin *et al*[13]: "Because liver biopsies are performed on the right lobe of the liver, so were the elasticity measurements. During the acquisition, patients were lying on their backs with their right arms behind their heads. The physician first proceeded to a sonographic examination to localize the best ultrasonic imaging window between the rib bones. Additionally, regions with large vessels were avoided and a minimal liver parenchyma thickness of 6 cm was sought".

Few studies have examined the variability possibly associated with different positions in the rather vaguely defined area called "the liver biopsy zone". The variability associated with position could be part of the interobserver effect. Only two published studies have estimated the interobserver effect: Sandrin *et al*[13] studied 10 patients involving 3 operators (standardized CV 3.3%) and Coco *et al*[14] compared 2 operators in 40 patients using correlation coefficients (0.92) and paired *t*-tests. Tanne *et al*[17] also observed a significant discordance (25%) between predicted fibrosis stages according to three different positions of the probe and suggested using three different positions, to reduce the "sampling error".

We previously compared 9 different positions in the right lobe in 35 healthy subjects with the same operator and observed a very significant variability[18]. Three positions were therefore selected according to their applicability: the reference position, an anterior position and a lower position.

The aims of this study were to compare the applicability of these three positions, their inter-position concordance, and their concordance alone and relative to FT, a reference biomarker of fibrosis.

MATERIALS AND METHODS

Consecutive patients with chronic liver disease seen in the Hepatology Department of the Pitié-Salpêtrière Hospital in Paris, France were pre-included to undergo LSM and FT. Patients were not included if they did not accept the protocol, or if the quality requirements for FT were not achieved. All patients gave informed consent for the use of data and serum for research purposes in this non-interventional clinical study, which was approved by the local institutional review board. The study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki.

Biochemical markers

FibroTest, and ActiTest (Biopredictive, Paris, France) were performed according to published recommendations[5,19,20].

Liver stiffness measurements

LSM was performed with the non-invasive method of transient elastography (FibroScan, Echosens, Paris, France). The stiffness results were expressed in kilopascal (kPa). The technique was performed by two trained (more than 100 measurements) senior hepatologists, blinded to all other characteristics, and according to the manufacturers' recommendations. During the acquisition, patients were lying on their backs with their right arms behind their heads. The operator firstly proceeded to a sonographic examination to localize the best ultrasonic imaging window between the rib bones in the liver biopsy area. Regions with large vessels were avoided and a minimal liver parenchyma thickness of 6 cm was sought.

The reference position was the region usually recommended for biopsy located at the intersection between the xyphoid line and the median axillary line, where the operator would have performed the biopsy. The second position (lower position) was a more posterior position 2-3 cm in the next intercostal space on the same xyphoid line as the reference position and the third position (anterior position) was an anterior position 2-3 cm ahead of the reference position in the same intercostal space.

Two of the most commonly recommended cutoffs for advanced fibrosis (F2, F3 and F4 in METAVIR staging)[21] *vs* non-advanced fibrosis (F0 and F1) were used: 7.1 kPa[6] and 8.8 kPa[12].

Applicability

The applicability for LSM was defined as: a success rate greater than 60% (SR60)[7,9,12,13], at least 10 valid liver stiffness measurements (V10)[7,9,12,13] and an interquartile range/median LSM < 30% (IQR30)[7,9,14-19].

The applicability for FT was defined as: a security algorithm profile excluding Gilbert's disease, hemolysis, acute inflammation profiles and extreme values of FT components, leading to a change of at least 0.30 in the FT result if the median value of each component was used[5,20].

Statistical analysis

The two main endpoints were the applicability rate and the discordance rate with FT, for the two new positions *vs* the reference position. Because of the number of statistical comparisons for these two endpoints for two positions, a *P* value lower than 0.01 has been taken for a significant difference.

The strength of concordance between each LSM, or their combinations, and FT was assessed using three methods, the kappa reliability test (K) for 2 fibrosis stages (advanced *vs* non-advanced fibrosis), the Spearman rank correlation coefficient (R), and the intraclass coefficient of correlation (ICC)][22].

Applicabilities were compared using Chi square and Fisher's exact tests, quantitative variables were compared using Mann-Whitney test, Wilcoxon signed rank test for paired comparisons, and multivariate analysis using logistic regression analysis. All comparisons were performed separately with subpopulations of operator 1 and 2, as well as with the population of patients with all positions applicable and populations with at least one position applicable. Analyses were performed with NCSS software (Kaysville, Utah, USA)[23].

RESULTS

A total of 468 consecutive patients were pre-included

Table 1 Characteristics of included and non-included patients *n* (%)

Characteristics	Included	Non-included
Number of patients	442	26
Mean age (SE)	49 (1)	50 (2)
Male	293 (66)	17 (65)
Ethnic origin		
Caucasian	285 (65)	17 (65)
Asian	36 (8)	2 (8)
North African	43 (10)	1 (4)
Other African	78 (17)	6 (23)
Anthropometric data		
Height (m)	1.71 (0.05)	1.70 (1.91)
Weight (kg)	71.7 (0.7)	69.7 (2.4)
BMI (kg/m^2)	24.4 (0.2)	24.1 (0.8)
Abdominal fold mm	21.7 (0.5)	26.1 (3.2)
Thoracic fold mm	13.1 (0.3)	13.6 (1.1)
Waist circumference cm	84 (1)	83 (2)
Daily alcohol ≥ 30 g/d	18 (7)	2 (11)
Diagnosis		
HCV	200 (45)	13 (50)
HBV	79 (18)	6 (23)
NAFLD	59 (13)	1 (4)
HIV coinfection	50 (11)	4 (15)
ALD	11 (3)	0 (0)
Other/unknown	93 (21)	2 (8)
Biochemistry		
ALT (IU/L)	58 (3)	151 (100)
AST (IU/L)	48 (2)	45 (6)
	n = 416	*n* = 16
Cholesterol (mmol/L)	4.70 (0.05)	4.50 (0.34)
	n = 381	*n* = 14
Glucose (mmol/L)	5.34 (0.07)	5.28 (0.16)
	n = 404	*n* = 16
Triglycerides (mmol/L)	1.21 (0.06)	1.10 (0.19)
	n = 381	*n* = 14
FibroTest	0.40 (0.01)	0.51 (0.06)
	n = 442	*n* = 18
ActiTest	0.32 (0.01)	0.39 (0.07)
	n = 442	*n* = 18
SteatoTest	0.33 (0.01)	0.27 (0.06)
	n = 378	*n* = 12

between April and September 2007. Twenty six patients were not included and 442 patients were included (Table 1). There was no difference between included and non-included patient characteristics.

Applicability

The applicability of LSM according to position is described in Table 2. The applicability of the anterior position (81%) was significantly higher than that of the reference (69%) and lower positions (68%), (both $P = 0.0001$). These differences in applicability were mainly due to an IQR30 obtained more often with the anterior position than with the reference or lower positions for both operator 1 and operator 2 respectively: 82% *vs* 67%, $P < 0.0001$; 82% *vs* 73%, $P = 0.004$ and 91% *vs* 87%, $P = 0.40$; 91% *vs* 76%; $P = 0.004$.

Liver stiffness measurements between positions

Among 268 patients with both anterior and reference positions applicable, the mean LSM estimated at the reference position [9.0 kPa; (0.5)] was significantly higher in comparison to the anterior position [8.5 kPa (0.5); $P < 0.0001$].

Table 2 Liver stiffness measurements applicability

Position, operator and quality criteria	Applicability (%)	Presumed fibrosis stages among applicable patients F0F1/F2/F3/F4 *n* (%)[c]
Reference position	306/442 (69)[a]	167 (55)/59 (19)/ 51 (17)/29 (9)[d]
Operator 1	208/329 (63)	117 (56)/40 (19)/ 32 (15)/19 (9)
Valid10	312/329 (95)	
SR60	300/329 (91)	
IQR30	220/329 (67)	
Operator 2	98/113 (87)	50 (51)/19 (19)/ 19 (19)/10 (10)
Valid10	113/113 (100)	
SR60	113/113 (100)	
IQR30	98/113 (87)	
Anterior position	357/442 (81)[a]	223 (62)/52 (15)/ 49 (14)/33 (9)[d]
Operator 1	255/329 (78)	166 (65)/34 (13)/ 31 (12)/24 (9)
Valid10	300/329 (91)	
SR60	296/329 (90)	
IQR30	271/329 (82)[b]	
Operator 2	102/113 (90)	57 (56)/18 (18)/ 18 (18)/9 (9)
Valid10	111/113 (98)	
SR60	111/113 (98)	
IQR30	103/113 (91)[b]	
Lower position	302/442 (68)[a]	170 (56)/49 (16)/ 47 (16)/36 (12)
Operator 1	224/329 (68)	126 (56)/36 (16)/ 36 (16)/26 (12)
Valid10	299/329 (91)	
SR60	291/329 (88)	
IQR30	240/329 (73)[b]	
Operator 2	78/113 (69)	44 (56)/13 (17)/ 11 (14)/10 (13)
Valid10	96/113 (85)	
SR60	94/113 (83)	
IQR30	86/113 (76)[b]	

[a]Applicability of the anterior position was significantly higher than that of the reference and the lower positions (both $P = 0.0001$); [b]IQR30 was obtained more frequently with the anterior position than with the reference and lower positions for operator 1 (82% *vs* 67% $P < 0.0001$; 82% *vs* 73% $P = 0.004$) and for operator 2 (91% *vs* 87% $P = 0.40$; 91% *vs* 76% $P = 0.004$); [c]Presumed fibrosis stage (METAVIR scoring system) using 7.7 kPa for F2, 8.8 kPa for F3 and 14.5 kPa for F4; [d]Presumed prevalence of non-advanced fibrosis was lower using the reference position than the anterior position ($P = 0.04$).

There was no significant difference between LSM measured at the reference in comparison to the lower position [9.5 kPa (0.5) *vs* 9.3 kPa (0.5), $n = 253$, $P = 0.36$].

Presumed prevalence of fibrosis

Among 268 patients with both applicable anterior and reference positions, using a 7.1 kPa cutoff, 121/268 (45%) of patients had advanced fibrosis using the reference position *vs* 102/268 (38%) using the anterior position ($P = 0.10$). Using an 8.8 kPa cutoff, 73/268 (27%) of patients had advanced fibrosis using the reference position *vs* 58/268 (24%) using the anterior position ($P = 0.40$).

When the prevalence of presumed fibrosis stages was compared according to the probe position of all applicable patients, prevalence of non-advanced fibrosis (7.1 kPa cutoff) was lower using the reference position (55%) than the anterior position (62%, $P = 0.04$) (Table 2).

Table 3 Strength of concordance between stiffness measurements assessed in three positions in the biopsy area

Position (No. of patients)	Method assessing concordance	
Quantitative concordance	Spearman mean (95% CI)	Intra class coefficient mean (95% CI)
Reference *vs* anterior (196)	0.81 (0.75-0.85)	0.90 (0.86-0.94)
Reference *vs* lower (196)	0.77 (0.70-0.82)	0.86 (0.79-0.93)
Anterior *vs* lower (196)	0.77 (0.70-0.82)	0.87 (0.80-0.94)
Two classes concordance	Discordance rate (%)	Kappa mean (SE)
Advanced *vs* non advanced fibrosis		
7.1 cutoff		
Reference *vs* anterior (196)	35 (17.9)[a]	0.63 (0.07)
Reference *vs* lower (196)	33 (16.8)[b]	0.66 (0.07)
Anterior *vs* lower (196)	34 (17.3)[c]	0.64 (0.07)
8.8 cutoff		
Reference *vs* anterior (196)	22 (11.2)	0.71 (0.07)
Reference *vs* lower (196)	28 (14.3)	0.65 (0.07)
Anterior *vs* lower (196)	20 (10.2)	0.74 (0.07)

[a]P = 0.06 *vs* 8.8 kPa cutoff; [b]P = 0.50 *vs* 8.8 kPa cutoff; [c]P = 0.04 *vs* 7.1 kPa cutoff.

Using an 8.8 kPa cutoff, there was no difference between the prevalence of non-advanced fibrosis using the reference position (226/306, 74%) than the anterior position (275/357, 77%; P = 0.34).

Concordance between positions

The discordance rates and strength of concordance between LSM assessed in three positions are detailed in Table 3. The discordance rate between the anterior and the lower probe positions was higher (17.3%) when the 7.1 kPa cutoff was used to define advanced fibrosis, instead of 8.8 kPa (10.2%; P = 0.04), and for the anterior *vs* the reference position (17.9% *vs* 11.3%; P = 0.06). There was no significant operator effect.

The factors significantly associated with discordance between the reference and the anterior positions were thoracic fold (P = 0.0008) thickness and non-alcoholic fatty liver disease (NAFLD) as the cause of liver disease (P = 0.008) (Table 4). BMI (P = 0.02), abdominal (P = 0.03) and waist circumference (0.047), and SteatoTest (P = 0.04) were not significantly associated when protected for multiple statistical comparisons (Table 4). In multivariate analysis, only thoracic fold was significantly associated with position discordance (regression coefficient beta= 0.07; 95% CI 0.02-0.13; P = 0.01). Same results were observed in the population with three positions applicable.

Concordance with FT

Discordance rates and strength of concordance between LSM assessed in three positions and FT are detailed in Table 5. There were no significant differences between the discordances rates and the strength of concordance between the three probe positions at a sufficient P value protected for multiple testing.

The discordances rates between probe positions and FT were higher when the 7.1 kPa cutoff was used to define advanced fibrosis instead of 8.8 kPa for the reference position (33.6% *vs* 23.5%, P = 0.03) in the 196 patients with all 3 positions applicable and also among the 306 patients with only the reference position applicable (34.9% *vs* 26.8%, P = 0.03).

The mean of the 3 positions (a total of 30 LSM), did not increase the strength of concordance with FT.

Table 4 Factors associated with discordance between reference and anterior positions *n* (%)

Characteristics	Concordant	Discordant	*P*
Number of patients	221	47	
Mean age (SE)	47 (1)	49 (2)	0.16
Male	151 (68)	34 (72)	0.59
Ethnic origin			
Caucasian	134 (61)	30 (64)	0.69
Asian	16 (7)	4 (8)	0.68
North African	27 (12)	6 (13)	0.87
Other African	44 (20)	7 (15)	0.38
Anthropometric data			
Height (m)	1.71 (0.01)	1.71 (0.10)	0.96
Weight (kg)	69.8 (0.9)	73.6 (2.2)	0.12
BMI (kg/m^2)	23.7 (0.2)	25.0 (0.5)	0.02
Abdominal fold (mm)	19.2 (0.6)	23.0 (1.6)	0.03
Thoracic fold (mm)	11.4 (0.4)	14.5 (0.9)	0.001
Waist circumference (cm)	82 (1)	86 (2)	0.047
Daily alcohol ⩾ 30 g/d	18/137 (13)	2/23 (9)	0.55
Diagnosis			
HCV	102 (46)	18 (38)	0.29
HBV	44 (20)	9 (19)	0.88
NAFLD	21 (10)	11 (23)	0.002
HIV coinfection	29 (13)	5 (11)	0.63
ALD	8 (4)	0 (0)	0.16
Other	46 (20)	9 (19)	0.88
Biochemistry			
ALT (IU/L)	55 (3) *n* = 221	81 (19) *n* = 47	0.56
AST (IU/L)	47 (2) *n* = 221	57 (6) *n* = 47	0.54
Cholesterol (mmol/L)	4.63 (0.08) *n* = 186	4.85 (0.13) *n* = 42	0.06
Glucose (mmol/L)	5.26 (0.09) *n* = 197	5.42 (0.17) *n* = 46	0.15
Triglycerides (mmol/L)	1.15 (0.06) *n* = 186	1.37 (0.19) *n* = 42	0.10
FibroTest	0.40 (0.01) *n* = 221	0.41 (0.06) *n* = 47	0.76
ActiTest	0.32 (0.02) *n* = 221	0.34 (0.04) *n* = 18	0.59
SteatoTest	0.30 (0.01) *n* = 183	0.38 (0.04) *n* = 42	0.04

DISCUSSION

This study provides an improved assessment of the variability of LSM due to the position of the probe in the right liver lobe. We confirmed the preliminary results we had observed in 35 healthy subjects, in whom 9 different positions had been assessed[18].

The diagnostic value of LSM and FT has been validated in the most common chronic liver diseases and FT has shown at least a similar prognostic value as liver biopsy (which is also an imperfect gold-standard[24]) in patients with chronic hepatitis C[25] and B[26]. We demonstrated previously that the strength of concordance between LSM and FT could be used to identify LSM

Table 5 Strength of concordance between LSM and FibroTest (FT) according to positions

Position (No. of patients)	Method assessing	Kappa
	Discordance rate (%)	
Quantitative concordance	Spearman mean (95% CI)	Intra class coefficient mean (95% CI)
All positions applicable		
Reference (196)	0.46 (0.34-0.56)	0.55 (0.33-0.67)
Anterior (196)	0.46 (0.34-0.56)	0.56 (0.34-0.68)
Lower (196)	0.40 (0.27-0.51)	0.50 (0.38-0.62)
Mean of positions (196)	0.47 (0.35-0.57)	0.56 (0.34-0.68)
At least one position applicable		
Reference (306)	0.44 (0.35-0.53)	0.51 (0.39-0.63)
Anterior (357)	0.46 (0.38-0.54)	0.54 (0.32-0.66)
Lower (302)	0.39 (0.29-0.49)	0.50 (0.38-0.62)
Two classes concordance	Discordance rate *n* (%)	Kappa mean (SE)
Cutoff 7.1 kPa		
All positions applicable		
Reference (196)	66 (33.6)[a]	0.30 (0.07)
Anterior (196)	61 (31.1)	0.32 (0.07)
Lower (196)	71 (36.2)	0.24 (0.07)
Mean of positions (196)	67 (34.2)	0.28 (0.07)
At least one position applicable		
Reference (306)	107 (34.9)[b]	0.28 (0.06)
Anterior (357)	112 (31.6)	0.33 (0.05)
Lower (302)	109 (36.1)[c]	0.24 (0.06)
Cutoff 8.8 kPa		
All positions applicable		
Reference (196)	46 (23.5)[a]	0.45 (0.07)
Anterior (196)	54 (27.6)	0.33 (0.07)
Lower (196)	56 (28.6)	0.34 (0.07)
Mean of positions (196)	52 (26.5)	0.37 (0.07)
At least one position applicable		
Reference (306)	82 (26.8)[b]	0.38 (0.06)
Anterior (357)	108 (30.2)	0.30 (0.05)
Lower (302)	84 (27.8)[c]	0.34 (0.06)

[a,b,c]$P = 0.03$ between 7.1 and 8.8 kPa.

variability factors[27].

The results strongly suggest that the reference position for LSM has two weaknesses in comparison with a more anterior position: a significantly lower applicability and a possible higher variability for the diagnosis of advanced fibrosis using the 7.1 kPa cutoff. The third position analyzed at a lower level compared to the reference position had no advantage either in terms of applicability or in strength of concordance with FT.

The main significant weakness of the reference position in this population was the low applicability rate: 69% compared to 81% in the anterior position. There may be several explanations for the difference in this rate compared to the rates observed in the largest series already published.

Firstly, most Fibroscan validation studies do not apply the strict recommendations for applicability. Foucher *et al*[11] achieved in 758 patients a 93.8% applicability rate but used weak criteria: less than 5 valid measurements and a success rate lower than 30%, without taking into account the IQR/median percentage. Kettaneh *et al*[12] obtained, in 935 patients, 10 LSM in 91.6%, and did not specify the rate of patients with a success rate lower than 60% and with an IQR/median higher than 30%. In applying only the criteria of 10 valid measurements, we also observed in the present study 95% and 100% applicability for the two operators. There is a major risk of false positive or false negative conclusions for the diagnosis of advanced fibrosis if LSM results with a low success rate or a high dispersion (IQR) are interpreted[19].

Secondly, the design of the present study was to start at the usual position for liver biopsy and then move to a more anterior and then to a lower position. Skilled operators probably automatically make the small change of position, when they are not satisfied with the first LSM results. Our results suggest that they must probably start with the anterior position first.

The mean LSM was significantly lower (0.5 kPa) at the anterior position *vs* the reference position. This difference was also clinically significant. When using the anterior position instead of the reference position, 7% of patients changed status from advanced fibrosis to non-advanced fibrosis when a cutoff of 7.1 kPa was chosen. The difference of 0.5 kPa is particularly clinically relevant in the zone of 7 to 9 kPa for the risk of a false negative/positive diagnosis of advanced fibrosis; it is less relevant for the diagnosis of cirrhosis as LSM cutoffs are usually recommended at a 12.5 kPa or 14 kPa cutoff with a range to 75 kPa. From these data it is possible to say that the reference position using 7.7 kPa cutoff for F2 and 8.8 kPa for F3 increases the risk of false positive conclusions in comparison with 8.8 and 12.5 kPa cutoffs, respectively.

Several anthropometric factors were associated with discordance between the reference and the anterior positions but the most significant factor was the thoracic skin fold thickness. More studies must now be conducted to better understand the role of these anthropometric factors both with regard to the applicability and to the variability of LSM.

Improved knowledge of LSM variability is also important for the definition of normal values of LSM. In contrast to FT, very few studies have assessed the normal range of LSM with biopsy without fibrosis (F0 in the METAVIR scoring system). Roulot *et al*[16] proposed the 95% percentile of a healthy non-obese population as the upper normal limit; 7.8 for females and 8.0 kPa for males. If these definitions of normal range are widely validated, the usual recommended cutoffs values of 7.1 and even 8.8 kPa for stage F2 must be re-assessed, as well the performance of Fibroscan to identify the F1 stage.

Before attributing the observed variability to a specific position, the following confounding factors must be discussed: an order effect, an operator effect, and another factor associated with LSM variability such as skin fold thickness or steatosis.

The order of LSM measurements began with the reference position first, followed by the lower and finally the anterior position. There was no systematic order effect for applicability rates or strength of concordance estimates and this bias can be excluded.

Two operators participated in the present study. The study was not designed as an inter-operator study and

therefore the two operators measured LSM in different patients. There was a difference between operators for the applicability rate of the reference position due to a lower IQR30 percentage. This was not a systematic operator effect, as this lower IQR30 percentage was not observed for the anterior or the lower positions. Operator 1 had twice as many NAFLD patients [50/329 (15.2%)] as operator 2 [9/113 (8%) $P = 0.05$], which could explain the greater variability of LSM and lower applicability in comparison to operator 2. As with other authors[7,12,15,16], we previously observed that the non-applicability and the variability of LSM at the reference position were higher in patients with NAFLD *vs* non-NAFLD patients.

We acknowledge that the number of comparisons increased the risk of false positives. The comparison between the strength of concordance anterior position-FT and the strength of concordance reference position-FT did not reach a high statistical significance ($P < 0.01$).

However, all the comparisons indicated the same direction and at least a lower concordance of the anterior position with FT in comparison with the reference position can be excluded.

In conclusion, our results suggest that the anterior position of the probe, 2-3 cm ahead of the usual position of liver biopsy, should be the first choice for LSM using FibroScan for liver fibrosis estimates. Compared with the reference position, the anterior position improved the applicability of FibroScan without decreasing its concordance with FibroTest.

COMMENTS

Background

Liver fibrosis describes the phenomenon of scarification of the liver tissue in chronic liver diseases. The common final path of chronic liver damage is liver cirrhosis with a high morbidity and mortality and the risk of developing liver cancer. Liver biopsy has always been the traditional gold-standard to "measure" liver fibrosis. Recently, new non-invasive methods of measurement such as serum markers (i.e. FibroTest®) or elastometry (FibroScan®) have emerged to replace liver biopsy in the clinical setting.

Research frontiers

Liver stiffness measurement (LSM) by transient elastometry is now widely used in countries where the method is accessible and approved. However, the best location to perform the liver elastometry has not been identified and recommendations are derived from an estimated "best spot" defined in an earlier study. In this study, the authors showed that applicability rates may change in a significant way depending where the measurements are done and that results tend to vary.

Innovations and breakthroughs

This is the first systematic research to identify applicability and variability limits of transient elastometry. The study has shown that applicability rates are higher when a more anterior position is chosen compared to the recommended position. A trend towards higher fibrosis rates measured in the recommended position compared to the anterior position has also been seen in this study. Moreover, the LSM results were compared with a well established biomarker (FibroTest®) and the anterior position was not inferior with regard to concordance rates.

Applications

This study implies that Fibroscan® examinations reach higher applicability rates when performed at a more anterior position that the hitherto recommended position.

Terminology

Liver fibrosis is the process of collagen septa production in the hepatic tissue. Liver biopsy gives a pathologist the possibility to examine the liver tissue but samples are potentially too small. Transient elastometry uses the change in liver stiffness due to collagen content to estimate the liver damage. Biomarkers use direct or indirect blood markers associated with liver fibrosis.

Peer review

This study arouses interest for readers and provides an important clue to evaluate liver stiffness by using non-invasive probe techniques. Liver biopsy is day-after-day decreasing in importance when dealing with patients suffering from HCV-related chronic hepatitis mainly because all in all the therapeutic approach does not change. In this light the elastography plays a new extraordinary role and the present study contributes to its better applicability, defining rigorously the positions of the probe.

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