Digestive and Liver Disease 51 (2019) 1023–1029

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Feasibility and reproducibility of liver and pancreatic stiffness in patients with alcohol-related liver disease

Clara Benedetta Conti[a,*,1], Nina Weiler[b,1], Giovanni Casazza[c], Christopher Schrecker[b], Maximillian Schneider[b], Marcus M. Mücke[b], Alexander Queck[b], Eva Herrmann[d], Dario Conte[a], Massimo Colombo[a], Stefan Zeuzem[b], Mirella Fraquelli[a,1], Mireen Friedrich-Rust[b,1]

[a] Department of Pathophysiology and Organ Transplantation, Maggiore Hospital and IRRCS Foundation, University of Milan, Milan, Italy
[b] Department of Internal Medicine 1, Hospital of the Goethe University, Frankfurt, Germany
[c] Department of Biomedical and Clinical Sciences "L Sacco", University of Milan, Milan, Italy
[d] Department of Medicine, Institute of Biostatistics and Mathematical Modelling, Goethe University Frankfurt, Frankfurt, Germany

ARTICLE INFO

Article history:
Received 18 July 2018
Accepted 21 December 2018
Available online 3 January 2019

Keywords:
Alcoholic cirrhosis
Elastography
Pancreatic alcoholic damage
Shear-wave elastography

ABSTRACT

Background: To date no studies evaluated liver stiffness and pancreatic stiffness by shear-wave elastography, in alcoholic liver disease setting.
Aims: To assess feasibility and reproducibility of Shear-wave elastrography in measuring liver and pancreatic stiffness in alcoholic liver disease and investigate the correlation among liver and pancreatic stiffness and clinical data.
Methods: Liver and pancreatic stiffness were measured by elastography (2 examiners) in patients with alcoholic liver disease and in healthy volunteers, for reference values. Effect of clinical data was evaluated on log-transformed pancreatic or liver stiffness, using univariate and multivariate linear regression model.
Results: 87 patients and 46 healthy volunteers enrolled. Both the stiffness values were higher in patients than healthy volunteers ($p < 0.001$). For liver stiffness: no failure measurements found, the Intraclass correlation coefficient (between 2 examiners) was 0.72 and the variables significantly correlated at multivariate analysis were cirrhosis ($p < 0.0001$) and steatosis ($p = .007$). For pancreatic stiffness: 2 failures found, with ICC 0.40 and the only variable significantly correlated at multivariate analysis was liver cirrhosis ($p = .005$).
Conclusions: Shear-wave elastography feasibility was good for liver and pancreatic stiffness. Reproducibility was good for liver stiffness, whereas fair for pancreatic one. Both the stiffness correlated with alcoholic liver disease severity. Elastography could be a useful tool to detect and monitor alcohol-related liver and pancreatic damage.

1. Introduction

Among the various methods to estimate tissue stiffness [1–3], firstly transient elastography (TE) [4,5] and recently the elastographic techniques as 2D-Shear Wave Elastography (SWE) and point-SWE using acoustic radiation force impulse imaging (ARFI) [6–13], have been applied to estimate liver stiffness (LS) in patients with chronic liver disease (CLD). SWE and ARFI assess LS with a wider applicability than TE in patients with ascites or obesity. A small number of studies evaluated LS in alcoholic liver disease (ALD), and no data are available on the use of 2D-SWE in this setting.

Moreover, SWE gives the opportunity to assess the elasticity of other parenchymal organs, as spleen [14–18] or pancreas.

Pancreatic stiffness (PS) has mainly been investigated using endosonographic (EUS) elastography [19–23] for the characterization of pancreatic masses. PS using transabdominal elastography has been evaluated in patients with cystic fibrosis [24] and in a small number of studies [25–27] in patients with chronic pancreatitis (CP), finding no differences in the median stiffness values between the different regions of the pancreas (i.e. head, body and tail) and observing that CP, alcoholic etiology, and decreased body mass

* Corresponding author at: IRCCS Ospedale Maggiore Policlinico, Italy.
E-mail address: benedetta.conti1@gmail.com (C.B. Conti).
[1] Contributed equally.

https://doi.org/10.1016/j.dld.2018.12.017
1590-8658/

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Age 16–80 years	Age <16 or >80 years
Alcohol-related liver disease	Acute or chronic viral infection
	Autoimmune hepatitis
	Wilson's disease
	Primary sclerosing cholangitis
	Primary biliary cirrhosis
	Non-alcoholic fatty liver disease
	Suspected or ascertained liver cancer
	Autoimmune pancreatitis
	Suspected or ascertained pancreatic cancer
	Pacemaker
	Pregnancy or lactation
Written informed consent	Patients without legal capacity

index (BMI) were all associated with higher PS values [25]. A study of our group [27] assessed PS by point-SWE in CP obtaining both a good reproducibility between two operators, with intraclass correlation cefficient (ICC) of 0.77, and PS values significantly higher in patients than healthy controls. Significantly higher values in the CP were observed in patients with longer disease duration, on chronic analgesic drugs and with lower body weight. At multivariate analysis all the three variables resulted independently associated with PS value.

The present study aimed to assess feasibility and reproducibility of LS and PS measurement by 2D-SWE in a cohort of patients with acute or chronic ALD and to investigate the possible correlation of both stiffness values with clinical and laboratory data.

2. Materials and methods

2.1. Study design

From December 2015 to May 2016, a prospective diagnostic cohort study was performed on patients diagnosed with ALD at the University Hospital Frankfurt, Germany, with the personal and scientific participation of Ospedale Maggiore Policlinico, Milan, Italy. Upon enrollment, all demographic, clinical and laboratory patient data were recorded.

Healthy controls were recruited among the hospital workers.

The study was performed in accordance with the Declaration of Helsinki and with the approval of ethic committees in Frankfurt (30.10.2015, # 412/15). Patient care and study complied with good clinical practice. All participants provided informed written consent before enrollment. Inclusion and exclusion criteria in Table 1.

2.2. Study population

All patients with acute or chronic ALD with a daily ongoing or past alcohol intake of at least 20 g for women and 40 g for men, aged 18–80 years, presenting as in or outpatients, were offered to participate in the study. Past alcohol consumption was defined as last alcohol use more than six months before the enrollment. ALD was diagnosed on the basis of patient clinical history and complete laboratory tests. The diagnosis of liver cirrhosis was based on imaging (US, CT scan or MRI), blood tests and clinical history. A case report form was used to record pseudonymized data.

2.3. Healthy volunteers

Health care workers from the clinic were offered to participate in the study as healthy volunteers (HV). People with previous or concurrent liver disease, US abnormality or abnormal liver function tests were excluded, as medical history was recorded and complete blood tests analysis, including viral hepatitis viruses, have been performed yearly in regular intervals for every heath care worker, starting from the employment. US examination and SWE were performed in accordance with the examination of patients.

2.4. Laboratory tests

Laboratory tests (Table 2) were performed as part of the routine diagnostic workup. The most recent results, for all patients obtained at least one week before enrollment, were recorded. No addictional laboratory tests were performed in HV.

2.5. Ultrasound

A complete evaluation of the liver and pancreas with abdominal US (Toshiba Aplio^{TM} 500, Toshiba Medical Systems Corporation, Otawara, Japan, CE certification according to the Class II a of Medical Devices Act) was performed on all consecutive patients and HV in a fasting condition (at least 6 h) (Table 2).

2.5.1. Liver US

We assessed the homogeneity of the parenchyma, the status of surface nodularity (using a low frequency 5–7 MHz transducer) [28], the presence of caudate lobe hypertrophy, the diameter and flow characteristics of portal vein, hepatic veins and hepatic artery using power-Doppler technology. Hepatic steatosis was defined according to the validated US criteria (the difference in echogenicity between the liver and the right kidney cortex, and the hepatic echo-intensity attenuation rate). The degree of steatosis (I, II, III), was defined for every patient [29].

2.5.2. Pancreatic US

We assessed the dimensions (head, corpus), the echo pattern and pancreatic duct diameter. We searched for the signs of CP (calcifications, duct irregularities, pseudocysts).

2.6. Shear wave elastography

SWE was performed on all consecutive patients in a fasting condition (at least 6 h) using the Toshiba Aplio^{TM} 500 US device. SWE is enabled by 2D quantitative elastography technology, integrated in the US-device and applied with the same probe used for B-mode examination. The assessment of stiffness is based on the generation of short shear wave pulses focused in a selected tissue area. The speed of shear wave propagation is measured using Doppler technology. This process requires Ultrafast^{TM} Imaging, recording frequencies up to 20,000 Hz. The tissue stiffness is calculated by using the formula $E = \rho c^2$: E = tissue elasticity (kPa), ρ = tissue density (kg/m^3), c = shear wave velocity (m/s). A color-coded, two-dimensional real-time map of tissue elasticity is displayed on top of the B-mode image [30]. Mean and standard deviation of tissue stiffness are calculated and displayed by setting a region of interest (ROI) in the tissue, The stiffness measurement by SWE is anatomically oriented, painless, easily feasible and takes five minutes per organ.

2.6.1. Liver SWE

Carried out in the supine decubitus position with the right arm extended above the head. The ROI was set 1 cm underneath the organ surface avoiding main blood vessels, within the right hepatic lobe in the midaxillary line (Fig. 1A).

2.6.2. Pancreas SWE

Carried out in the supine decubitus position. A pre-defined ROI, 1 cm × 1 cm in size, was set in the pancreatic head or body, avoiding ductal structures, calcifications or lesions (Fig. 1B).

Table 2
Recorded data.

Demography	Sonogramm	Laboratory data
Age (years)	Liver surface nodularity (regular/irregular)	AST(U/l)
Sex (male/female)	Liver pattern (homogenous/inhomogeneous)	ALT (U/l)
BMI (kg/m^2)	Steatosis (degree)	GGT (U/l)
Diabetes (yes/no)	Caudate lobe hypertrophy (yes/no)	Bilirubin (mg/dl)
Active smoking (yes/no, pack years)	Portal vein diameter (cm)	INR
Active alcohol consume (yes/no, g/day)	Portal vein velocity (cm/sec)	Lipase (U/l)
Ascites (yes/no)	Hepatic artery diameter (cm)	Glucose (mg/dl)
Gastrointestinal bleeding history (yes/no)	Hepatic artery velocity (cm/sec)	Cholesterol (mg/dl)
Hepatic encephalopathy (yes/no)	Hepatic vein diameter (cm)	Triglycerides (mg/dl)
	Pancreas head dimension (cm)	Creatinine (mg/dl)
Acute pancreatitis (yes/no)	Pancreas body dimension (cm)	Platelets (mm^3)
Chronic pancreatitis (yes/no)	Pancreaticpattern (homogenous/inhomogeneous)	
Pancreatic insufficiency (yes/no)	Pancreatic calcification (yes/no)	
	Pancreatic duct irregularities (yes/no)	

Pancreatic and liver SWE was performed by two independent examiners, blinded to each other's results. Each examiner performed 5 consecutive measurements per organ, asking the patient to stop breathing in an indifferent breathing phase.

2.6.3. Risks and side effects

No side effects or risks have been reported in connection with SWE. As the technique has never been performed in pregnant women, pregnancy was considered an exclusion criterion.

2.7. Statistical analysis

Descriptive analyses were performed by calculating means, medians and proportions, with their 95% confidence intervals (CI) or interquartile ranges (IQR), as appropriate.Due to a not negligible degree of skewness, all stiffness measurements were log-transformed before performing the analyses.

The intra- and inter-observer reproducibility of LS and PS measurements in ALD patients were assessed by the ICC, classifying the agreement as poor (ICC = 0.00–0.19), fair (ICC = 0.20–0.39), good (ICC = 0.40–0.75), excellent (ICC > 0.75) [30].

We compared stiffness values between ALD patients and HV. Two separate analyses of variance were performed for the comparison of LS and PS between ALD and HV, after adjusting for age.

The effect of clinical data on log-transformed LS and PS measurements was evaluated by fitting the univariate and the multivariate linear regression model, with LS or PS as dependent variable. Only the variables statistically significant at univariate analysis were included in the multivariate analysis. A stepwise procedure was used to find the best multivariate model. Clinical and laboratory data put into the model to evaluate LS were: age, BMI, smoking, active drinking, daily alcohol intake (g/dl), time of alcohol abuse (years), diabetes, liver cirrhosis, liver steatosis, liver surface nodularity, presence of ascites, AST, GGT, MELD score >14 [31]. For PS were placed: sex, age, BMI, smoking, active drinking, daily alcohol intake (g/dl), time of alcohol abuse (years), diabetes, liver cirrhosis, chronic alcoholic pancreatitis, presence of pancreatic calcifications, lipases (U/l), MELD score >14 [31].

The performance of the linear models was evaluated by the determination coefficient (R^2). P values lower than 0.05 (two-tailed) as statistically significant.

All statistical analyses were carried out by SAS statistics software (release 9.4; SAS Institute Inc., Cary, NC).

Table 3
Clinical, relevant US and laboratory data of patients and HV.

Data	Patients (n = 87)	Healthy volunteers (n = 46)
Male/female	63/24	14/32
Age [years; median (range)]	59 (52–65)	33 (24–57)
BMI [kg/m^2; median (range)]	26 (23–28)	22 (15–33)
Diabetes (n, %)	21 (24)	0 (0)
Active smokers (n, %)	44 (51)	4 (9)
Pack years [n; median (range)]	3 (0–63)	0 (0–8)
Active drinkers (n,%)	12 (14)	40 (87)
Abstinence from alcohol at least from 6 months (n,%)		–
Alcohol consumption/d [g; median (range)]	80 (24–800)	1.4 (0–15)
Duration of alcohol consumption [years; median (range)]	25 (20–30)	10 (0–40)
Liver cirrhosis (n, %)	75 (86)	0 (0)
MELD [median (range)]	12 (0–30)	–
MELD > 14 n (%)	23 (26)	–
Previous hepatic decompensation (n, %)	63 (72)	0 (0)
Previous bleeding episodes (n, %)	12 (14)	0 (0)
Previous hepatic encephalopathy (n, %)	32 (37)	0 (0)
Pancreatic insufficiency	1 (1)	0 (0)
Pancreatic calcifications n (%)	3 (3)	0 (00
Pancreatic duct irregolarities n (%)	7 (8)	0 (0)
AST [U/1; median (range)]	36 (16–155)	–
ALT [U/1; median (range)]	27 (6–292)	–
GGT [U/1; median (range)]	92 (12–1148)	–
Bilirubin [mg/d1; median (range)]	1.3 (0.3–9.8)	–
INR [median (range)]	1.2 (0.8–2.1)	–
Platelets [mm^3; median (range)]	122 (3–299)	–
Lipase [U/1; median (range)]	46 (7–465)	–
Glucose [mg/dl; median (range)]	105 (68–327)	–
Cholesterol [mg/dl; median (range)]	156 (50–375)	–
Triglycerides [mg/dl; median (range)]	81 (32–277)	–
Creatinine [mg/; median (range)]	0.9 (0.5–2.3)	

3. Results

3.1. Patient demographics

We enrolled 87 patients and 46 HV. Data in Table 3. The percentages of patients stratified for present or past alcohol intake (g/dl) were: 66% between 60 and 100, 21% between 100 and 200

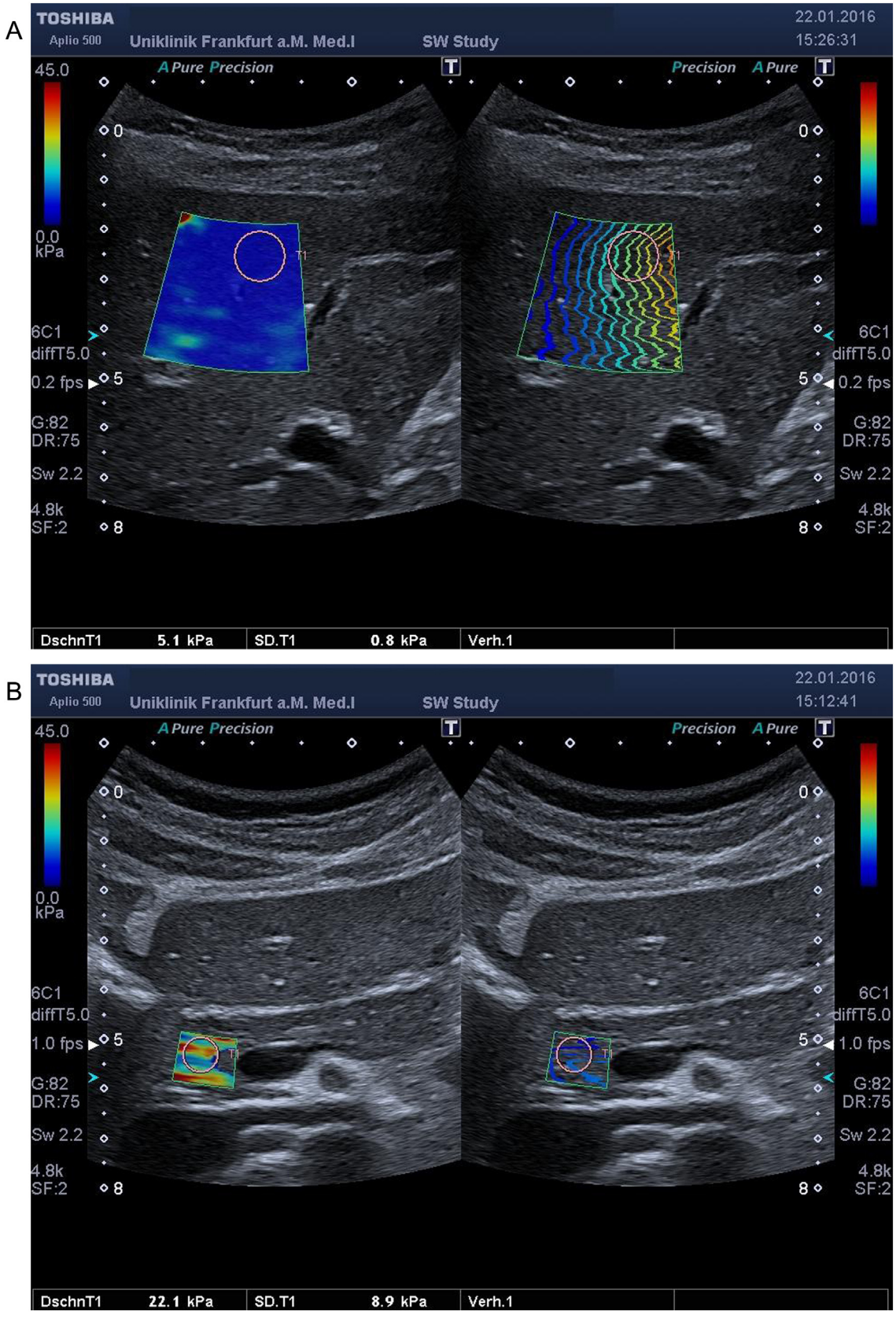

Fig. 1. (A) Liver SWE in a HV. (B) Pancreatic SWE in a HV.

and 13% > 200. Regarding the period of alcohol consume (years): 6 patients (7%) for less than 10, 37 (42%) for more than 10, and 44 (51%) for more than 20. One patient had ongoing acute alcoholic hepatitis; one patient had ongoing acute alcoholic pancreatitis. Three patients, had concomitant alcoholic CP, diagnosed by clinical history and EUS or MRI data.

Table 4
LS in ALD, stratified according to degree of steatosis.

Degree of liver steatosis	Patients; cirrhotics (#;%)	Median LS (kPa)	IQR
0	42 (98)	21.9	17.3–33.2
I	30 (80)	23.0	18.0–45.1
II	8 (75)	44.0	20.5–62.3
III	7 (38)	7.6	5.2–22.0

Table 5
PS in cirrhotic and non-cirrhotic ALD.

	Number of patients	Median PS (kPa)	IQR
No liver cirrhosis	12	12.5	9.7–14.1
Liver cirrhosis	75	16.4	12.9–20.1

3.2. Liver stiffness

3.2.1. Feasibility
In all patients and HV we obtained valid measurements of liver SWE. No measurement failures.

3.2.2. Reproducibility
The inter-observer agreement on LS measurements was good, with overall ICC of 0.72.

3.2.3. Comparison: ALD group vs. HV group
LS was significantly higher in ALD patients (median 22.1 kPa; IQR, 16.9–36.2) than in HV (median 5.7 kPa; IQR CI 5.2–6.4) ($p < 0.001$).

3.2.4. Correlation with clinical data
We stratified the population into four subgroups, one without steatosis and three according to the US degrees of steatosis (Table 4).

At univariate analysis, the variables associated with LS were: presence of liver cirrhosis ($p < 0.001$), presence of liver steatosis ($p = 0.0003$),surface nodularity ($p = 0.0003$), active alcohol consume ($p = 0.015$), alcohol consumption/day ($p = 0.013$), AST (IU/ml) ($p = 0.035$), diabetes ($p = 0.022$).

At multivariate analysis, only the presence of liver cirrhosis ($p < 0.0001$) and steatosis ($p = 0.007$) remained independently associated with LS.

3.3. Pancreatic stiffness

3.3.1. Feasibility
In 85 patients and in all HV we obtained valid measurements of pancreatic SWE. Only two measurement failures were found.

3.3.2. Reproducibility
The inter-observer agreement on PS measurements was fair, with overall ICC of 0.48.

3.3.3. Comparison: ALD group vs. HV group
PS was significantly higher in ALD patients (median 15.4 kPa; IQR 12.2–19.9) than in HV (median 11.8 kPa (95% CI 10.4–12.8) ($p < 0.001$)).

3.3.4. Correlation with clinical data
At univariate analysis, PS was significantly correlated with the presence of liver cirrhosis ($p = 0.005$), active alcohol consume ($p = 0.039$) and CP ($p = 0.044$). At multivariate analysis, only the presence of liver cirrhosis remained independently associated with PS. The median values of PS in cirrhotic and non-cirrhotic patients are in Table 5.

4. Discussion

To date, the present study represents the first series focusing on the assessment of LS and PS in ALD patients, using SWE. The sample size is small and this possibly affects the chances of external application of our results, especially as concerns the pancreatic stiffness. However, the topic of our pilot study is new and of great interest, the alcohol-related diseases (pancreatic and hepatic) being widely present in all countries and the liver alcohol-related diseases featuring among the main causes of liver cirrhosis and decompensation.

4.1. Liver

SWE feasibility was excellent and reproducibility was good, also in presence of ascites and in patients with advanced CLD, in contrast to TE, where the presence of ascites precludes accurate assessment of LS.

LS using SWE was easy to obtain due to the size of the liver, which reduced the influence of the minimal movements created by breathing on the capture of stiffness. In agreement with Yashima et al. [25], LS values in patients with ALD were higher compared with HV.

SWE confirmed the ability of elastography to both detect and exclude the presence of liver cirrhosis.

The lack of correlation of LS with blood tests confirms its value as a detector of liver fibrosis: SWE measurements are not affected by hepatic inflammation – very common in the ALD – or cholestasis, again in contrast to TE [32]. The correlation between LS and steatosis and the median values in the subgroups of patients stratified according to degree of steatosis, highlights the importance of assessing LS by SWE at different time points in the course of the disease [33]. LS values increased with the severity of steatosis (Table 4), and its drop in patients with degree III is justified by the fact that between these eight patients only three had cirrhosis, whereas the others five had chronic ALD. LS mean value of the cirrhotic patients with severe steatosis was 25 kPa. This data support the ability of LS as fibrosis detector.

4.2. Pancreas

SWE feasibility was good, with only two failures in the ALD cohort, but with fair reproducibility. The assessment of PS measurements required an excellent US window, difficult to obtain, especially in obese patients (mean value of BMI in ALD cohort was 26.4 (range [23–28])) or in presence of large volume of ascites. Mainly, the presence of ascites can be avoided just by putting the ROI in a space that is free of liquid, as also done during the liver stiffness measurement. Regarding obesity or overweight, these interfered with the measurements as the pancreas can be located deep, this making the acquisition difficult and in some cases impossible (in such cases the measurements were regarded as indeterminate). In the presence of interfering intestinal air, an approach that has already been frequently used for the B-mode examination, can be that of achieving a side shift of the air by turning the patient and then putting him again in the supine position. The measurement was always acquired with the patient in the supine position. The presence of large cysts or ductal pancreatic irregularities can clearly interfere with the acquisition of the measurement. In our population we have always been able to avoid ductal dilation and cysts, as the size of these latter ones were small (<20 mm). However, when unavoidable, this should be notified and the examination considered as unsuccessful. As a general consideration, it should also be noted that the presence of very large cysts leads to a reduction of the pancreatic parenchyma, which has also to be always notified during the pancreas examination, in order to add infor-

mation towards the final evaluation of the pancreatic damage. In our cohort the operators reported difficulties in finding a homogeneously colored spectrum in the ROI due to the limited size of the examined area and the influence of minimal breathing movements or pulsation of aorta on scan quality, creating small shifts of the pancreatic B-mode image. This could partially explain the lower reproducibility in the assessment of PS in the present cohort. In a previous study by our group [27] we obtained a higher reproducibility for PS. However, this data could be explained by the different populations investigated, as in the previous study [27] none had ascites and the prevalence of obese patients was significantly lower than in the present cohort. Moreover, we used different techniques in the two studies: in the present cohort we performed the measurement by SWE, whereas in the previous onbe [27] we used point-SWE. However, all these data have to be confirmed in further series.

The significantly higher PS values in ALD compared to HV, agrees with the data from Yashima et al. [25].

The presence of liver cirrhosis was the only independent variable significantly associated with PS at multivariate analysis and we also found a statistical correlation between PS and LS in our population ($r = 0.24$, $p = .0225$), to support this data. The meaning of this association is not clear, but is supported by recent histomorphological data: the pancreatic parenchymal fibrosis is more frequently observed in alcoholic cirrhosis than in non-cirrhotic ALD [34]. Thus, it could be hypothesized that the presence of severe ALD also induces chronic pancreatic cell damage and scarring. PS values appear to depend on the degree of liver damage, and elevated PS values may indicate the presence of severe alcohol-related pancreatic damage and fibrosis in patients with advanced ALD.

Accordingly, we hypothesize that the presence of high pancreatic stiffness can be a surrogate marker of the pancreatic damage in terms of fibrosis, in line with previously published data on LS measurements and hepatic fibrosis [35]. The possibility to non-invasively assess alcohol-induced pancreatic parenchymal damage and to study the degree of pancreatic fibrosis, in a series of complex decompensated patients, opens up new avenues in the management of chronic pancreatic disease. It may also be possible to predict clinical worsening of alcohol-related pancreatic disease using elastography. Regarding the correlation with pancreatic exocrine insufficiency, we had about a quarter (24%) of patients with diabetes. However, interestingly, the correlation between diabetes and PS did not result statistically significant. Only two patients has exocrine pancreatic insufficiency preventing any possible correlation. However, all these interesting aspects could better be investigated in further larger series.

4.3. Limitations of the study

The fair reproducibility of PS is the main limitation of the present study. The assessment of PS requires a learning period, with an extensive induction to the methodology. The small sample size of the cohort examined could be a limitation to generalize the results obtained and the elevated proportion of patients with cirrhosis could represent a spectrum variation that could influence especially liver stiffness diagnostic performances. The absence of a pancreatic histological examination may be a weakness of the study; however, pancreatic histology is not usually performed in clinical practice in absence of a focal mass.

Author contributions

Study concept and design: MF, MFR, CBC, NW, GC. Acquisition of data CBC, NW, CS, MS, MMM, AQ. Analysis and interpretation of data: GC, CBC, NW, EH. Drafting of the manuscript: CBC, NW. Critical revision of the manuscript for important intellectual content: MF, MFR, DC, MC, SZ. Statistical analysis: GC, EH. All the authors approved the final version of the Manuscript.

Conflict of interest

None deaclared.

List of abbreviations

ALD, Alcoholic liver disease; ALT, Alanine transaminase; ARFI, Acoustic radiation force imaging; AST, Aspartate transaminase; BMI, Body mass index; CI, Confidence intervals; CP, Chronic pancreatitis; CT, Computer tomography; EUS, Endoscopic ultrasound; GGT, γ-glutamyl transferase; HV, Healthy volunteers; ICC, Intraclass correlation coefficient; INR, International normalized ratio; IQR, Interquartile ranges; LS, Liver stiffness; MELD, Model for end-stage liver disease; MRI, Magnetic resonance imaging; PS, Pancreatic stiffness; PTL, Platelets; ROI, Region of interest; SWE, Shear wave elastography; SS, Spleen stiffness; TE, Transient elastography; US, Ultrasound.

References

[1] Gerber L, Kasper D, Fitting D, Knop V, Vermehren A, Sprinzl K, et al. Assessment of liver fibrosis with 2-D shear wave elastography in comparison to transient elastography and acoustic radiation force impulse imaging in patients with chronic liver disease. Ultrasound Med Biol 2015;41:2350–9.
[2] Nightingale K, Bentley R, Trahey G. Observations of tissue response to acoustic radiation force: opportunities for imaging. Ultrason Imaging 2002;24:129–38.
[3] Hoyt K, Parker KJ, Rubens DJ. Real-time shear velocity imaging using sonoelastographic techniques. Ultrasound Med Biol 2007;33:1086–97.
[4] Lupsor M, Badea R, Stefanescu H, et al. Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the non invasive assessment of chronic hepatitis C. Preliminary results. J Gastrointestin Liver Dis 2009;18(September (3)):303–10.
[5] Sporea I, Bota S, Grădinaru-Taşcău O, Şirli R, Popescu A. Comparative study between two point Shear Wave Elastographic techniques: Acoustic Radiation Force Impulse (ARFI) elastography and ElastPQ. Med Ultrason 2014;16(December (4)):309–14.
[6] Friedrich-Rust M, Lupsor M, de Knegt R, Dries V, Buggisch P, Gebel M, et al. Point Shear Wave Elastography by Acoustic Radiation Force Impulse quantification in comparison to transient elastography for the noninvasive assessment of liver fibrosis in chronic hepatitis C: a prospective international multicenter study. Ultraschall Med 2015 Jun;36(3):239–47.
[7] Ferraioli G, Filice C, Castera L, Choi BI, Sporea I, Wilson SR, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: part 3: liver. Ultrasound Med Biol 2015;41:1161–79.
[8] Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 2012;56:2125–33.
[9] Bavu E, Gennisson JL, Couade M, Bercoff J, Mallet V, Fink M, et al. Noninvasive in vivo liver fibrosis evaluation using supersonic shear imaging: a clinical study on 113 hepatitis C virus patients. Ultrasound Med Biol 2011;37:1361–73.
[10] Samir AE, Dhyani M, Vij A, Bhan AK, Halpern EF, Méndez-Navarro J, et al. Shear-wave elastography for the estimation of liver fibrosis in chronic liver disease: determining accuracy and ideal site for measurement. Radiology 2015;274:888–96.
[11] Zheng J, Guo H, Zeng J, Huang Z, Zheng B, Ren J, et al. Two-dimensional shear-wave elastography and conventional US: the optimal evaluation of liver fibrosis and cirrhosis. Radiology 2015;275:290–300.
[12] Friedrich-Rust M, Buggisch P, de Knegt RJ, Dries V, Shi Y, Matschenz K, et al. Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B. J Viral Hepat 2013;20:240–7.
[13] Bota S, Herkner H, Sporea I, Salzl P, Sirli R, Neghina AM, et al. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. Liver Int 2013;33:1138–47.
[14] Abraldes JG, Reverter E, Berzigotti A. Spleen stiffness: toward a noninvasive portal sphygmomanometer? Hepatology 2013;57:1278–80.
[15] Colecchia A, Montrone L, Scaioli E, Bacchi-Reggiani ML, Colli A, Casazza G, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology 2012;143:646–54.

[16] Takuma Y, Nouso K, Morimoto Y, Tomokuni J, Sahara A, Takabatake H, et al. Portal hypertension in patients with liver cirrhosis: diagnostic accuracy of spleen stiffness. Radiology 2016;279:609–19.
[17] Takuma Y, Nouso K, Morimoto Y, Tomokuni J, Sahara A, Takabatake H, et al. Prediction of oesophageal variceal bleeding by measuring spleen stiffness in patients with liver cirrhosis. Gut 2016;65:354–5.
[18] Elkrief L, Rautou PE, Ronot M, Lambert S, Dioguardi Burgio M, Francoz C, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. Radiology 2015;275:589–98.
[19] Kongkam P, Lakananurak N, Navicharern P, Chantarojanasiri T, Aye K, Ridtitid W, et al. Combination of EUS-FNA and elastography (strain ratio) to exclude malignant solid pancreatic lesions: a prospective single-blinded study. J Gastroenterol Hepatol 2015;30:1683–9.
[20] Dyrla P, Gil J, Florek M, Saracyn M, Grala B, Jędrzejewski E, et al. Elastography in pancreatic solid tumours diagnoses Prz. Gastroenterol 2015;10:41–6.
[21] Itoh Y, Itoh A, Kawashima H, Ohno E, Nakamura Y, Hiramatsu T, et al. Quantitative analysis of diagnosing pancreatic fibrosis using EUS-elastography (comparison with surgical specimens). J Gastroenterol 2014;49:1183–92.
[22] Dietrich CF, Hirche TO, Ott M, Ignee A. Real-time tissue elastography in the diagnosis of autoimmune pancreatitis. Endoscopy 2009;41:718–20.
[23] Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. EUS elastography for the characterization of solid pancreatic masses. Gastrointest Endosc 2009;70:1101–8.
[24] Friedrich-Rust M, Schlueter N, Smaczny C, Eickmeier O, Rosewich M, Feifel K, et al. Non-invasive measurement of liver and pancreas fibrosis in patients with cystic fibrosis. J Cyst Fibros 2013;12:431–9.
[25] Yashima Y, Sasahira N, Isayama H, Kogure H, Ikeda H, Hirano K, et al. Acoustic radiation force impulse elastography for noninvasive assessment of chronic pancreatitis. J Gastroenterol 2012;47:427–32.
[26] Llamoza-Torres CJ, Fuentes-Pardo M, Alvarez-Higueras FJ, Alberca-de-Las-Parras F, Carballo-Álvarez F. Usefulness of percutaneous elastography by acoustic radiation force impulse for the non-invasive diagnosis of chronic pancreatitis. Rev Esp Enferm Dig 2016;108:450–6.
[27] Pozzi R, Parzanese I, Baccarin A, Giunta M, Conti CB, Cantù P, et al. Point shear-wave elastography in chronic pancreatitis: a promising tool for staging disease severity. Pancreatology 2017 Nov;17(November–December (6)):905–10.
[28] Colli A, Fraquelli M, Andreoletti M, Marino B, Zuccoli E, Conte D. Severe liver fibrosis or cirrhosis: accuracy of US for detection–analysis of 300 cases. Radiology 2003;227:89–94.
[29] Kelly EM, Feldstein VA, Etheridge D, Hudock R, Peters MG. Sonography predicts liver steatosis in patients with chronic hepatitis B. J Ultrasound Med 2017;36:925–32.
[30] Garra BS. Elastography: history, principles, and technique comparison. Abdom Imaging 2015;40(April (4)):680–97.
[31] Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005;5(February (2)):307–13.
[32] Fraquelli M, Baccarin A, Casazza G, Conti CB, Giunta M, Massironi S, et al. Liver stiffness measurement reliability and main determinants of point shear-wave elastography in patients with chronic liver disease. Aliment Pharmacol Ther 2016;44:356–65.
[34] Agrawal P, Vaiphei K. Histomorphological features of pancreas and liver in chronic alcoholics–an analytical study in 390 autopsy cases. Indian J Pathol Microbiol 2014;57(January–March (1)):2–8.
[35] EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237–64.