Original papers

Ultrasound-Guided Attenuation Parameter (UGAP) for the quantification of liver steatosis using the Controlled Attenuation Parameter (CAP) as the reference method

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Abstract

Aim: Nonalcoholic Fatty Liver Disease (NAFLD) is increasing in frequency in daily practice and evaluation of liver steatosis, fibrosis and inflammation severity are essential for prognosis assessment. The aim was to evaluate the usefulness of a new liver steatosis quantification system - Ultrasound-Guided Attenuation Parameter (UGAP) from General Electric Healthcare, using Controlled Attenuation Parameter (CAP) as the reference method. **Material and method:** 179 consecutive subjects, in whom liver steatosis was assessed in the same session using UGAP, implemented on LOGIQ E10 system (GE Healthcare), and CAP (FibroScan, EchoSens). To discriminate between steatosis stages by CAP, we used the cut-offs recommended by the manufacturer: S1 (mild) – 230 dB/m, S2 (moderate) – 275 dB/m, S3 (severe) – 300 dB/m. **Results:** We classified our cohort by means of CAP into the following groups: S0 (no steatosis): 48/176 (27.2%), S1 (mild): 56/176 (31.6%), S2 (moderate): 14/176 (7.3%) and S3 (severe): 59/176 (33.9%). The mean UGAP values increased with the steatosis grade and for each group were the following: S0: 198.3±25.7 dB/m, S1: 216.86±26.3 dB/m, S2: 237.79±26.3 dB/m, and S3: 270.8±31.62 dB/m respectively (p<0.001). A very good positive correlation was found between UGAP and CAP values (r=0.73, p<0.0001). The best cut-off values for predicting different grades of liver steatosis using CAP as the reference were: S1 - 192.5 dB/m (AUC 0.83); S2 – 231 dB/m (AUC 0.90) and S3 – 248 dB/m (AUC 0.91). **Conclusion:** UGAP seems to be a good method for liver steatosis quantification and correlates strongly with CAP values.

Keywords: Ultrasound-guided attenuation parameter (UGAP); liver steatosis quantification; Controlled Attenuation Parameter (CAP); NAFLD.

Introduction

The prevalence of liver steatosis has rapidly increased worldwide; currently nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide, with an estimated global prevalence of 1 billion [1]. NAFLD encompasses a wide histological variety with a spectrum that can go from non-evolutive simple steatosis to progressive non-alcoholic steatohepatitis (NASH), which may progress to liver cirrhosis, hepatic failure and hepatocellular carcinoma (HCC) [2].

NAFLD is strongly associated with metabolic syndrome, including type 2 diabetes mellitus (T2DM), dyslipidemia, and obesity. Lifestyles have become increasingly sedentary, and dietary patterns have changed over the past few decades, which has led to an increased prevalence of obesity and insulin resistance in the general population [3], while the number of people with T2DM has quadrupled in the past three decades, diabetes mellitus being the ninth major cause of death [4]. NAFLD has rapidly become the most frequent cause of abnormal liver biochemistry findings in many developed and developing countries [1] and, in the United States, NASH is predicted to become the main indication for liver transplantation [5].

For liver steatosis quantification and the differentiation of simple steatosis from NASH, liver biopsy (LB) is the recommended method [6], but considering the large number of cases, it is not a feasible diagnostic tool in such a large population. In addition, because of its invasiveness, LB is not an appropriate, repeatable method that can be used for follow-up.

Therefore, steatosis detection and quantification using precise, repeatable and noninvasive diagnostic tools are mandatory in NAFLD patients. Moreover, it has been demonstrated that liver steatosis in patients with hepatitis C can lead to more advanced liver fibrosis and a more severe outcome [7].

Imaging techniques are the best and most convenient noninvasive means for liver steatosis evaluation. Conventional B-mode ultrasound was the first used in clinical practice, with 60-94% sensitivity and 88-95% specificity in detecting liver steatosis [8], but its accuracy decreases significantly in the case of mild steatosis [9]. Moreover, a skilled examiner is needed for a correct estimation of the steatosis severity, which is only subjective.

Ultrasound attenuation for the quantification of liver steatosis has been developed and studied in the past years. The Controlled Attenuation Parameter (CAP) is a relatively new technique, implemented on the FibroScan device (Echosens, Paris, France), that enables steatosis quantification by measuring ultrasound beam attenuation throughout the liver and has shown a good correlation with histologic grades in adults [10-12]. Moreover, guidelines recommend CAP as an accurate alternative to abdominal ultrasonography for the detection of liver steatosis [13,14].Thus, in the latest WFUMB guidelines on ultrasound elastography, CAP has been recommended as a point-of-care, standardized and reproducible technique for the detection of liver steatosis [15], although its accuracy may be affected by variations in cut-off values of different steatosis grades and different covariates [16]. While CAP does not have the B-mode guidance for choosing the area of liver steatosis measurement, in the last few years ultrasound system manufacturers have developed technologies to quantify the ultrasound beam attenuation incorporated into standard ultrasound machines [17-19]. The advantage of such ultrasound systems is that they can perform steatosis quantification during a standard B-mode abdominal ultrasound examination when the liver seems to be steatosic ("bright liver" with posterior attenuation and an increased hepato-renal index). It is an objective estimation of liver steatosis severity, which can be repeated during follow-up in order to see treatment results.

Ultrasound-guided attenuation parameter (UGAP) measures the attenuation coefficient based on a reference phantom that includes glass bead particles of attenuating materials with known attenuation coefficient. In the UGAP mode, the transmission and reception conditions are fixed to the same values used on the reference phantom, and the acquired echo profiles of the liver are compensated by the reference data. As a result, the compensated sound profiles represent only decay caused by attenuation. If the compensated sound profile is flat, the attenuation is the same as the reference phantom. UGAP includes an automated measurement algorithm to find and analyze the optimum measurement range. The diaphragm is also automatically excluded and the slope is measured across this optimum range to provide a representative attenuation coefficient.

In this study, we aimed to evaluate the usefulness of a new liver steatosis quantification system – Ultrasound-Guided Attenuation Parameter (UGAP) from General Electric Healthcare, using the Controlled Attenuation Parameter (CAP) as the reference method.

Material and methods

Subjects

A prospective study was conducted between June 2019 and October 2019 in a tertiary Department of Gastroenterology and Hepatology. The study population comprised of 179 consecutive subjects with or without chronic liver disease (mostly NAFLD), who had undergone in the same session UGAP, CAP, Transient Elastography (TE)for liver fibrosis and liver steatosis assessment.

Inclusion criteria for all subjects were the ability to provide informed consent, age ≥ 18 years old. Inclusion criteria for healthy liver subjects were: no history of liver disease, a normal abdominal ultrasound examination, previously tested negative for hepatitis B/C virus and LS values by TE <6.5 kPa [6]. The diagnosis of NAFLD was based on the latest guidelines established by the American Association for the Study of Liver Diseases [14], as follows: fatty changes of the liver observed by imaging; no heavy alcohol consumption (ethanol intake <210 g per week for men and <140 g per week for women); no other factors inducing fatty changes of the liver such as medications; and no chronic liver disease with clear etiology (hepatitis B virus, hepatitis C virus, primary biliary cholangitis, primary sclerosing cholangitis or autoimmune hepatitis).

Exclusion criteria were: undergoing antiviral treatment, patients with ascites, patients with signs of biliary obstruction and liver congestion secondary to heart failure and patients with focal liver lesions.

Three operators with good experience in abdominal ultrasound (US), liver fibrosis and steatosis quantifica-

tion (operator 1: 9 years of experience, operator 2: 5 years of experience, operator 3: 4 years of experience), performed all investigations in the following order: abdominal ultrasound, UGAP measurements followed by TE and CAP measurements so that UGAP measurements could not have been influenced.

All subjects signed informed consent. The study was approved by the Ethics Committee and by the institutional review board (32/16.05.2019) and was performed according to the World Medical Association Declaration of Helsinki.

UGAP measurements

UGAP measurements were performed using a LOGIQ E10 ultrasound machine (GE Healthcare, Wauwatosa, WI, USA), using a C1-6-D convex array probe. All measurements were performed in fasting conditions for more than 4 hours, on patients in a supine position, with the right arm in maximum abduction, by intercostal approach, in the right liver lobe. A large colored-coded attenuation map, automatically adjusted by the system, was positioned in the right liver lobe, in a homogenous area of the liver, free of large vessels (fig1). Using the quality map option, the best image was selected in order to acquire the attenuation coefficient measurement. Ten measurements were performed using one or two selected images of the liver and the values were automatically stored in the system. Reliable UGAP measurements were defined as the median value of 10measurements performed in a homogeneous area of liver parenchyma, with an IQR/M <0.30. UGAP values are expressed in dB/cm/MHz or in dB/m.

LOGIQ E10 ultrasound machine can also perform liver stiffness measurements for fibrosis evaluation using an accurate 2D-Shear Wave Elastography (2D-SWE) technique [20-23], but this type of evaluation was not included in the present study.

TE and CAP measurements

TE and CAP measurements were performed in fasting conditions for more than 4 hours, on patients in supine position, with the right arm in maximum abduction, by intercostal approach, in the right liver lobe. In each patient, we aimed for 10 valid LS measurements, using the M probe (standard probe – transducer frequency 3.5 MHz) or the XL probe (transducer frequency 2.5 MHz). M and XL probes were chosen according to the EFSUMB recommendation on M and XL probe selection [24]. The median value of 10 valid LS measurements was calculated and the results were expressed in kiloPascals (kPa). Reliable measurements were defined as the median value of 10 valid LS measurements, with an interquartile range interval/median ratio (IQR/M) <30% [24]. To discriminate between fibrosis stages, we used the following TE
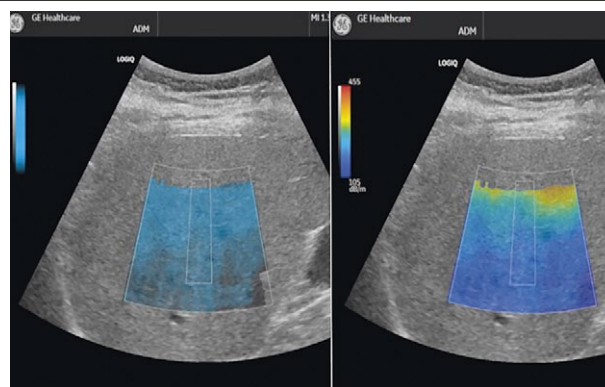

Fig 1. UGAP measurement using the Attenuation map (left) and the quality map (right).

cut-off values [25]: significant fibrosis (F≥2) - 7 kPa, severe fibrosis (F ≥ 3) – 9 kPa and cirrhosis (F=4) – 11.8 kPa. To discriminate between steatosis stages by CAP we used the cut-offs recommended by the manufacturer: S1 (mild) – 230dB/m, S2 (moderate) – 275dB/m, S3 (severe) – 300dB/m.

Statistical analyses

The statistical analysis was performed using MedCalc Software, version 12.5.0.0 (MedCalc program, Belgium), SPSS, Version 17.0 (IBM Statistics) and R software packages (v.3.3). Collected data were presented as mean (±SD) for continuous variables with a normal distribution, median (IQR) for continuous variables without normal distribution, or absolute frequency (percentage) for nominal variables. The normality of continuous variable distributions was tested using the Kolmogorov–Smirnov's test. The significance of the difference between groups was assessed by using the Student's t-test (means, normal populations), Mann–Whitney U test (medians, non-normal populations), and Pearson's chi-squared or Fisher's exact test (proportions). The correlation between two variables was assessed with Pearson's r correlation coefficient. For method performance and thresholds, receiver operating curve (ROC) analysis was used. We considered a p-value of 0.05 as the threshold for statistical significance and a confidence level of 95% for estimating intervals.

Results

A total of 179 consecutive patients were screened during the study period. Of these patients, 2 were excluded due to unreliable CAP and UGAP results, so that 177 patients were included in the final analyses (fig 2). The success rates for CAP and UGAP were similar, 98.8% (177/179). The reason for failure for CAP and UGAP was BMI >40 kg/m² in both patients. The main charac-
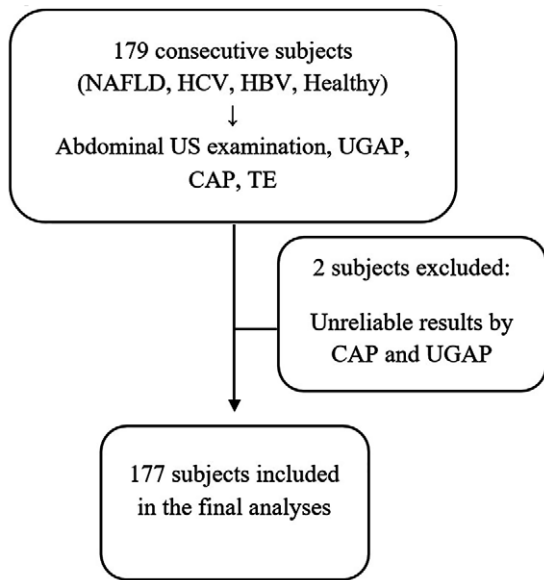
Fig 2. Flow diagram of the study population. NAFLD = non-alcoholic fatty liver disease; HCV = hepatitis C virus; HBV = hepatitis B virus; US = ultrasound; UGAP = ultrasound-guided attenuation parameter; CAP = control attenuation parameter; TE= transient elastography.

Table I. Main characteristics of the study population

Parameter	Value
n	177
mean age (years)	52.5 ± 17.3 (20-88)
gender (male/female)	88/89
mean BMI (kg/m^2)	28.2 ± 5.5 (17.1- 47.6)
BMI< 25 kg/m^2	25.4% (45/177)
BMI 25-30 kg/m^2	35% (62/177)
BMI ≥ 30 kg/m^2	39.6% (70/177)
Liver disease etiology	
Healthy liver subjects	20.3% (36/177)
NAFLD	48.5% (86/177)
HCV	14.6% (26/177)
HBV	10.1% (18/177)
ALD	6.2% (11/177)
Steatosis stage using CAP	
S0	27.1% (48/177)
S1	31.6% (56/177)
S2	8% (14/177)
S3	33.3% (59/177)
Fibrosis stage using TE	
F0-F1	68.3% (121/177)
F2	9.6% (17/177)
F3	8% (14/177)
F4	14.1% (25/177)

Numerical variables with normal distribution are presented as mean value ± standard deviation, while variables with non-normal distribution are presented as median values and range intervals. n = number; BMI = body mass index; NAFLD = non-alcoholic fatty liver disease; HCV = hepatitis C virus; HBV = hepatitis B virus; ALD = alcoholic liver disease; CAP = controlled attenuation parameter; TE = transient elastography.

teristics of the study population are presented in Table I. We classified our cohort by means of CAP into 4 groups according to the liver steatosis severity.

The mean UGAP values in our study cohort were significantly lower than the mean CAP values: 231.5 ± 40.9 dB/m vs. 268.6 ± 61.7 dB/m, $p < 0.001$. Considering CAP as the reference for liver steatosis quantification, the mean UGAP values increased according to steatosis severity (fig 3).

A good positive correlation was found between UGAP and CAP values ($r = 0.73$, $p < 0.0001$) (fig 4).

The best UGAP cut-off values for predicting different grades of liver steatosis, using CAP as the reference were: S1 - 192.5 dB/m; S2 – 231 dB/m; S3 – 248 dB/m (Table II, fig 5).
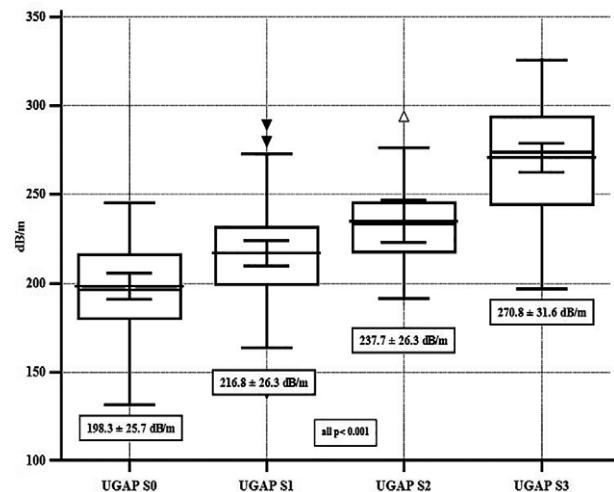

Fig 3. Box plots representing the mean values of UGAP measurements for different stages of liver steatosis.
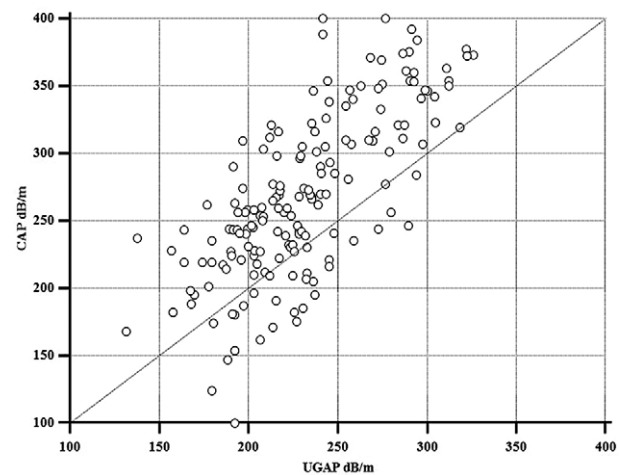

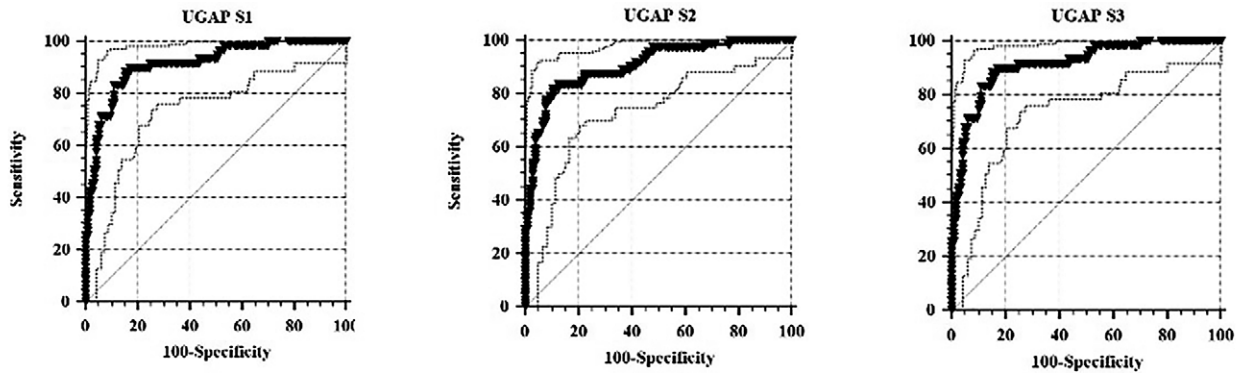**Fig 4.** The scatterplot shows the correlation between UGAP and CAP.

Fig 5. Diagnostic accuracy of UGAP for predicting different grades of liver steatosis.

Table II. UGAP cut-off values for predicting different grades of liver steatosis.

Steatosis stage	Cut-off (dB/m)	Cut-off (dB/cm/MHz)	AUC	Se (%)	Sp (%)	PPV (%)	NPV (%)	p value
S ≥ 1	192.5	0.55	0.83	93.7	47.9	82.8	74.2	<0.0001
S ≥2	231	0.66	0.90	83.3	83.7	75.0	87.5	<0.0001
S = 3	248	0.70	0.91	71.1	94.2	85.7	86.8	<0.0001

AUC = area under the curve; Se = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value.

Discussions

NAFLD has become an emerging and challenging medical problem nowadays due to its increased prevalence, becoming a subject of extensive research in the last years. The need for screening and evaluation of these patients is very high. The main issues regarding populational screening in NASH are to decide how to perform the screening and which population to screen–the general population or the population at risk. It is quite impossible to screen the general population and, maybe, for the moment, we must focus on the population at risk to develop NAFLD, which includes patients with type 2 diabetes mellitus, obese patients, individuals with a metabolic syndrome [26-28]. The screening of this population at risk should be performed, assuredly, by means of non-invasive methods, among which ultrasound-based ones have become very popular in the last 10 years.

Transient Elastography (TE) is a shear wave elasto-graphic technique that allows rapid evaluation of liver fibrosis [24]. CAP was subsequently developed, first implemented on the M probe and later on the XL probe, in order to simultaneously assess liver steatosis [16,29]. In the latter years, CAP has been thoroughly studied and demonstrated a high accuracy for liver steatosis quantification, in comparison with liver biopsy [30,31], subsequently becoming a reference method. However, some problems have been raised regarding CAP, mainly regarding the proposed cut-off values for different groups of patients and regarding the need to use quality criteria [32,33].

On the other hand, FibroScan is a machine used only for fibrosis and steatosis quantification and it is expensive. As an alternative, besides imaging of the abdominal organs (size, structure, focal lesions), modern new ultrasound systems can evaluate liver fibrosis (using point Shear wave elastography or 2D Shear wave elastography) [20,22,34,35]and more recently, can quantify liver steatosis [17-19]. Considering all these capabilities, and also including Contrast-Enhanced Ultrasound, newer ultrasound systems have become really multiparametric ultrasound (MPUS) tools [36].

In this current study, the feasibility of UGAP was very high (98.8%) and similar to CAP. Unreliable results by means of UGAP were observed in only two patients. The reason for failure in both patients was BMI > 40 kg/m^2. In a previously published study, Fujiwara et. al reported an excellent feasibility of UGAP for liver steatosis quantification (100%) and demonstrated a negative association between BMI and UGAP [18]. In our study, almost 40% of the subjects included were obese, thus demonstrating a very good feasibility of UGAP for liver steatosis assessment in obese patients.

In our study the correlation between CAP measurements and UGAP was 0.73, corresponding to a strong correlation. Moreover, the UGAP values increased with the steatosis severity. The AUROC of UGAP for predicting grade 3 liver steatosis was higher than 0.90, corresponding to high diagnostic accuracy. Furthermore, the AUROCs for predicting grade 2 and grade 1 liver steatosis were 0.90 and 0.83, demonstrating that UGAP has

a very good diagnostic ability to detect and discriminate among different grades of liver steatosis.

Previously published studies also showed a very high diagnostic accuracy of UGAP for liver steatosis quantification. In a study that included 182 subjects with NAFLD and HCV, using liver biopsy as the reference, the AUROCs of UGAP for diagnosing liver steatosis grade 1, 2 and 3 were 0.90, 0.95 and 0.95 respectively [18]. Another published study that enrolled 126 subjects with chronic liver disease, in which magnetic resonance imaging proton density fat fraction (MRI-PDFF) was used as the reference method, UGAP demonstrated AUROCs of 0.92, 0.87 and 0.92 for diagnosing liver steatosis grade 1, 2 and 3, respectively [37].

Finally, we calculated the best UGAP cut-off values for predicting different stages of liver steatosis, using CAP as the reference method. The cut-off values for predicting liver steatosis grade 1,2 and 3 were 192.5 dB/m (0.55 dB/cm/MHz), 231 dB/m (0.66 dB/cm/MHz) and 248 dB/m (0.7 dB/cm/MHz). Comparing the results in dB/cm/MHz with previously published studies [18,37], the cut-off values seem quite similar. Although the US machine can express and record the US attenuation either in dB/m or dB/cm/MHz, we recommend for future publications the usage of dB/m in order to have more homogenous results and easily compare them with other methods (CAP).

UGAP is an emerging technique that has been recently developed for liver steatosis quantification. The scientific background supporting its usefulness is still weak, with only a few studies published so far, but with promising results. New elastographic and attenuation quantification techniques are rapidly developing and the pressure to release them on the market is increasing. Using liver biopsy in order to validate these methods can be difficult to achieve, taking into account the concerns and the lack of compliance of the patients towards its invasiveness and also the large amount of time needed to recruit subjects. Therefore, many published studies used TE as a reference method for liver fibrosis evaluation. Considering that CAP has been also validated for liver steatosis quantification, with a very good accuracy demonstrated in prospective studies and meta-analyses, we think that CAP can be used as a reference method for liver steatosis quantification [16,29-31]. Some studies used MRI-PDFF as a new standard for liver steatosis quantification. Despite the fact that this technique is very sensitive and specific, the cost of this evaluation is high. On the other hand, ultrasound-based steatosis quantification, as well as liver stiffness estimation, are seen as point of care methods, that can be used in the examination room, immediately after an ultrasound examination in subjects at risk.

Several limitations are associated with our study. The main limitation is the lack of liver biopsy or MRI-PDFF as the reference method for liver steatosis quantification. As mentioned before, we used CAP as the reference method since it is a validated and a recommended method for liver steatosis quantification in clinical practice. Another limitation of the study is the number of subjects included, which is quite small for the different etiologies. Taking this into account, there is a need for further studies, with larger cohorts of patients in order to validate our results.

In conclusion, UGAP seems to be a good method for liver steatosis quantification and correlates strongly with CAP values. Feasibility is very good and the examination can be performed immediately after a standard ultrasound examination, being connected with the liver stiffness evaluation.

Conflict of interest: none

Acknowledgements

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