**Title**

Optimal thresholds for ultrasound attenuation parameter in the evaluation of hepatic steatosis severity: evidence from a cohort of patients with biopsy-proven fatty liver disease

**Short Title:** UAP cut-offs

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**List of Abbreviations**

UAP, ultrasound attenuation parameter; LSM, liver stiffness measurement; AUROC: area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; FLD, fatty liver disease; NAFLD, non-alcoholic fatty liver disease; AFLD, alcoholic fatty liver disease; TE, transient elastography; IQR, interquartile range; BMI, body mass index; ROC, receiver operating characteristic curve.

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**Conflict of interest**

The authors declare no conflicting interest.

**Abstract**

**Objective:** Fibrotouch® is a newly developed device to assess ultrasound attenuation parameter (UAP) and liver stiffness measurement to quantify hepatic steatosis and fibrosis, respectively. However, there is currently a lack of defined thresholds of UAP to diagnose different stages of hepatic steatosis. We aimed to assess the optimal thresholds of UAP for hepatic steatosis in individuals with biopsy-proven fatty liver disease (FLD).

**Methods:** We enrolled497 adults with FLD undergoing Fibrotouch® and liver biopsy. Area under the receiver operating characteristic curve (AUROC) was performed to calculate the performance of UAP in staging hepatic steatosis. Hepatic steatosis >33% was defined as significant steatosis. We determined the optimal cutoff values of UAP and the sensitivity (Se) or specificity (Sp) higher than 90%. Se, Sp, positive predictive value (PPV) and negative predictive value (NPV) were subsequently calculated.

**Results:** The median UAP for the enrolled patients was 308 dB/m. Multivariable logistic regression analysis showed that UAP was associated with significant steatosis (adjusted-odds ratio 1.05, 95%CI 1.02-1.09, P=0.001). The AUROCs for S≥1, S≥2 and S=3 were 0.88 (95%CI 0.84-0.91), 0.77 (95%CI 0.73-0.81) and 0.70 (95%CI 0.63-0.77), respectively. The optimal UAP cutoffs were 295 dB/m for S≥1, 314 dB/m for S≥2, and 324 dB/m for S=3. Almost identical results were observed in the subgroup of patients with biopsy-confirmed non-alcoholic fatty liver disease (n=435).

**Conclusions:** We found that the AUROC values of UAP by Fibrotouch® were ranging from 0.70 to 0.88 for assessing hepatic steatosis severity. These UAP cutoffs could be applicable for clinical use.

**Keywords:** Ultrasound attenuation parameter, Fatty liver, Steatosis, Diagnosis, Liver biopsy

**Lay summary**

Ultrasound attenuation parameter (UAP) generated by Fibrotouch® is an accurate tool to noninvasively detect and stage the presence of hepatic steatosis. Our proposed UAP cut-off values might be feasible in routine clinical practice.

**Introduction**

Fatty liver disease (FLD) is to date the most common liver disease in the world, which can be generally categorized into non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD) according to the amount of daily alcohol consumption [[1](#_ENREF_1)]. NAFLD can progress to severe liver diseases such as fibrosis and hepatocellular carcinoma [[2-4](#_ENREF_2)]. Liver biopsy is currently the gold standard for diagnosing FLD and distinguishing its histological severity [[5](#_ENREF_5)]. However, due to its associated costs and unwanted complications, it is not practical to undertake liver biopsy in the general population [[5](#_ENREF_5)]. Thus, there is an urgent a need for an accurate methodology to diagnose FLD and assess its severity non-invasively in the general population.

Transient elastography (TE) is a simple methodology that allows non-invasive assessment of the severity of liver steatosis and fibrosis through measuring ultrasonic attenuation of the echo and liver stiffness [[6](#_ENREF_6),[7](#_ENREF_7)]. Fibrotouch® (Wuxi Hisky Medical Technologies Co., Ltd., China) is a 3rd generation device integrating a two-dimensional (2D)-image-guided system for evaluating FLD in China. Fibrotouch® uses a dynamic broadband ultrasound probe to evaluate the liver condition both in normal weight/overweight and obese individuals [[8](#_ENREF_8)]. Fibrotouch® measures liver steatosis and fibrosis by obtaining an ultrasound attenuation parameter (UAP) and a liver stiffness measurement (LSM), and has been used in multiple studies [[8-12](#_ENREF_8)]. However, the large majority of these studies to date have included patients with chronic viral hepatitis, and no studies have extensively examined the diagnostic performance and the best criteria of UAP in a large cohort of non-viral FLD patients.

In this study, we aimed to examine the accuracy of Fibrotouch® for diagnosing patients with FLD and identify the optimal diagnostic UAP cutoffs that best predicted the histological severity of hepatic steatosis in these patients.

**Materials and methods**

***Study population***

In this study, 579 consecutive adults with suspected FLD were recruited from the well-characterized Prospective Epidemic Research of NASH (PERSONS) cohort at the First Affiliated Hospital of Wenzhou Medical University from December 2016 to December 2019 [[13](#_ENREF_13)]. Adult patients with suspected FLD (based on imaging methods and/or elevated serum liver enzymes) undergoing Fibrotouch® within two weeks of liver biopsy were enrolled. The exclusion criteria were as follows: (1) patients with liver disease of competing etiologies (i.e. viral hepatitis, autoimmune hepatitis, Wilson’s disease and drug-induced hepatitis); (2) various kinds of cancer; (3) a Fibrotouch® success rate of <60% or an inter-quartile range (IQR) > 30% of UAP. Excessive alcohol consumption was defined as daily alcohol consumption ≥ 20 g/day in women and ≥ 30 g/day in men, respectively.

The study protocol was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University and registered in the Chinese Clinical Trial Registry (ChiCTR-EOC-17013562).

***Clinical and laboratory measurement***

Comprehensive clinical assessment was performed. Body weight, height and blood pressure values were measured in all subjects by well-trained nurses. Blood samples were obtained on the same day as liver biopsy by standard laboratory methods for assessment of the following parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, albumin and fasting glucose levels.

Body mass index (BMI) was calculated as weight (kg) divided by squared height (m) (kg/m2). Known or previously undiagnosed diabetes was defined as a self-reported physician established diagnosis, current use of hypoglycaemic drugs, or fasting glucose level ≥7.0 mmol/L. Hypertension was defined as blood pressure ≥140/90 mmHg or use of any anti-hypertensive agents.

***UAP measurement***

UAP was performed using the Fibrotouch® (Wuxi Hisky Medical Technologies Co., Ltd., China) by a well-trained technician who was blinded to clinical and histological data of participants. The specific operation methods were as follows: The probe is placed below the right 7th, 8th or 9th ribs in the space between the anterior and mid axillary lines to assess the liver continuously. Ten successful reads were required and the median was recorded. The ratio of the interquartile range (IQR) divided by median (IQR/med) of all measurements less than 30% with a success rate (successful tests / total tests) ≥ 60% was regarded as a valid measurement.

***Liver histology measurement***

Ultrasound-guided percutaneous liver biopsy was performed with a 16-gauge Hepafix needle. After stained with hematoxylin-eosin and Masson’s trichrome, all liver specimens were assessed by an experienced liver pathologist (Yang-Yang Li), who was blinded to all clinical and liver imaging data of participants. Histological scoring was based on the NASH-CRN scoring system [[14](#_ENREF_14)]. Hepatic steatosis was graded into S0 (<5%), S1 (5-33%), S2 (34%-66%), S3 (>66%) according to the histological severity of steatosis. Hepatic steatosis >33% (S2 or S3) was defined as significant steatosis.

***Statistical analysis***

We conducted statistical analyses using IBM SPSS version 23.0. Continuous variables were expressed as medians [inter-quartile ranges (IQR)], while categorical variables were expressed as number (%). We constructed a box-plot to illustrate the distribution of UAP values within each histologic steatosis grade. The Kruskal-Wallis test and Dunn’s post-hoc tests were performed to assess the differences of UAP values across increasing steatosis stages. We conducted univariable and multivariable logistic regression analyses to assess the risk factors of significant steatosis (defined as S≥2 on histology). Diagnostic performances of UAP values both in all patients with FLD and in those with NAFLD were assessed by using the areas under the receiver-operating characteristic (AUROC) curves. Optimal cutoff values (i.e., maximum value of Youden’s index) of UAP were determined. The cutoff values were also determined at a sensitivity (Se) >90% and a specificity (Sp) > 90%. Se, Sp, positive predictive value (PPV) and negative predictive value (NPV) were calculated for the cutoff values. P values <0.05 were considered to be statistically significant.

**Results**

***Patient characteristics***

Of 579 enrolled patients, 82 were initially excluded (51 for hepatitis B virus, 19 for invalid measurement of UAP value, 4 for hepatitis C virus, 2 for autoimmune hepatitis, 4 for drug-induced hepatitis, 1 for thyroid cancer, and 1 for breast cancer). The baseline characteristics of the 497 participants with biopsy-proven FLD are summarized in **Table 1**. They were predominantly of male sex (n=376, 75.7%) and had a median age of 44 years and a median BMI of 26.6 kg/m2. **Twelve and half percent** of these subjects (n=62) had an excessive alcohol consumption. In the whole cohort the median UAP values were 308 dB/m. The percentage and number of patients within each grade of hepatic steatosis were as follows: S0 9.9% (n=49), S1 41.6% (n=207), S2 33.8% (n=168) and S3 14.7% (n=73), respectively.

***Distribution of UAP values according to steatosis grade***

The median UAP values for patients with S0, S1, S2 and S3 steatosis were 286 dB/m (IQR, 280.5-293.5), 310 dB/m (IQR, 296.5-318.5), 319 dB/m (IQR, 307-326) and 324 dB/m (IQR, 309-339), respectively. As shown in **Figure 1,** values of UAP progressively increased according to the histological severity of hepatic steatosis (P<0.001 for trend by the Kruskal-Wallis test; P=0.48 between S2 and S3, and P<0.001 for all other inter-group differences by the Dunn’s post hoc test).

***Univariable and multivariable logistic regression analyses for association with significant steatosis***

In univariable logistic regression analysis (model 1), UAP was significantly associated with presence of significant steatosis (defined as S≥2 on histology) (OR: 1.06, 95%CI: 1.05-1.07, P<0.001). In Model 2, UAP values were independently associated with the presence of significant steatosis after adjusting for age, sex, BMI and excessive alcohol consumption (adjusted-OR: 1.06, 95%CI: 1.04-1.08, P<0.001). In Model 3, this association remained statistically significant even after additional adjustment for LSM (adjusted-OR: 1.05, 95%CI: 1.02-1.09, P=0.001) (**Table 2**).

***Diagnostic performance of UAP***

The diagnostic performance of UAP for accurately identifying the histological severity of hepatic steatosis is summarized in **Figure 2** and **Table 3**. The optimal UAP cutoff values were 295 dB/m for S≥1 (Se 83.3%, Sp 79.6%, PPV 97.4% and NPV 34.4%), 314 dB/m for S≥2 (Se 61.8%, Sp 79.3%, PPV 73.8% and NPV 68.8%), and 324 dB/m for S=3 (Se 50.7%, Sp 80.4%, PPV 30.8% and NPV 90.4%). In addition, the cutoff values for 90% sensitivity were 289 dB/m for S≥1 (Se 90.0%, Sp 61.2%, PPV 95.5% and NPV 40.2%), 298 dB/m for S≥2 (Se 90.0%, Sp 42.2%, PPV 59.5% and NPV 81.8%), and 296 dB/m for S=3 (Se 91.8%, Sp 25.7%, PPV 17.6% and NPV 94.8%). The cutoff values for 90% specificity were 305 dB/m for S≥1 (Se 63.8%, Sp 93.9%, PPV 99.0% and NPV 22.2%), 324 dB/m for S≥2 (Se 39.8%, Sp 90.6%, PPV 79.9% and NPV 61.5%), and 331 dB/m for S=3 (Se 34.2%, Sp 90.3%, PPV 37.8% and NPV 88.8%). The diagnostic performance of UAP in detecting and staging hepatic steatosis only among patients with NAFLD was similar to that of the pooled cohort (as detailed in **Table 3**).

**Discussion**

To our knowledge, this is the first study aimed at establishing the appropriate cutoff values of UAP obtained by Fibrotouch® for diagnosing and staging hepatic steatosis in a large cohort of adult patients with biopsy-confirmed FLD. We showed that Fibrotouch® is an effective technique for assessing and staging non-invasively the severity of hepatic steatosis in patients with FLD. In our study, the AUROC values of UAP by Fibrotouch® was ranging from 0.70 to 0.88 for assessing the severity of hepatic steatosis on liver histology. We found that the optimal cutoff values of UAP (i.e., the maximum value of Youden’s index) were 295 dB/m for S≥1, 314 dB/m for S≥2, and 324 dB/m for S=3, respectively, for detecting hepatic steatosis in these patients. Interestingly, the diagnostic performance of UAP and the optimal cutoff values in patients with NAFLD were essentially superimposable to those observed in the pooled cohort of patients with FLD. It has to be mentioned that the AUROC value of UAP for detecting S3 is relatively low in our study (AUROC=0.70, 95%CI: 0.63-0.77). Nonetheless, in clinical practice, it is valuable to detect whether a patient has any hepatic steatosis [[15](#_ENREF_15)] and performance was very good in detecting S1 and S2. Our data also showed that UAP was significantly correlated with significant steatosis, independent of other potential confounders (i.e., age, sex, BMI, alcohol consumption and LSM). Collectively, we believe that the aforementioned results may be of clinical importance, especially for the follow-up of those patients with significant FLD (S≥2) in routine clinical practice.

Although liver biopsy remains the current gold standard for diagnosing and staging FLD, it is not suitable for widespread clinical screening. Liver ultrasonography is widely accepted as first-line screening method for FLD due to its non-invasiveness and inexpensiveness [[16](#_ENREF_16),[17](#_ENREF_17)]. However, ultrasonography may also have some disadvantages. First of all, this method provides only a qualitative (or semi-quantitative) assessment of liver steatosis and fibrosis [[18](#_ENREF_18)]. Furthermore, its diagnostic performance is highly operator dependent [[19](#_ENREF_19)]. Conversely, Fibrotouch® is a newly introduced technology that may overcome these limitations. In particular, the intra- and inter-observer variability of TE by Fibrotouch® are negligible and the measurements are highly reproducible. Moreover, Fibrotouch® is also less likely to provide sampling errors due to its continuous coverage of the general liver area compared to liver biopsy examination, which is usually 1/50,000 of the total liver mass [[19](#_ENREF_19)]. Of note, TE by Fibrotouch® issimilar to techniques used in FibroScan®, which utilizes the controlled attenuation parameter (CAP) and liver stiffness measurement to quantify liver steatosis and fibrosis, and has been widely used in detecting liver steatosis and fibrosis outside of China [[20-22](#_ENREF_20)]. However, Fibrotouch® differed slightly in that the new generation of TE uses a dynamic broadband ultrasound probe to overcome errors encountered clinically for detecting patients with varying degrees of subcutaneous fat accumulation, making it possible to achieve higher successful rate in detection of liver steatosis than Fibroscan® [[23](#_ENREF_23),[24](#_ENREF_24)].

Our study has some important limitations that should be mentioned. First, the diagnostic performance of UAP is not satisfactory in distinguishing patients with S3. This result might have been influenced by the relatively small number of S3 patients (14.7%, n=73) in our study sample. The low PPVs of the S3 cutoff values may be also influenced by the low proportion of patients with S3. These results need to be confirmed in other studies with a larger proportion of S3 patients. Second, patients recruited in our cohort (tertiary center) are likely to have more advanced liver disease. However, the NPVs to exclude significant steatosis are expected to be higher in community-based settings. Finally, FLD patients enrolled in this study are of Chinese Han ethnicity and our results may not be generalizable to other ethnicities. Future validation studies involving different ethnic populations are needed.

In conclusion, Fibrotouch® is a good method for noninvasively diagnosing patients of FLD, irrespective of the etiology. The optimal cutoff values of UAP established by our study could be used to effectively diagnose patients with hepatic steatosis ranging from S1 to S3 in primary care settings.

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**FIGURE LEGENDS**

**Figure 1**. Boxplot of UAP values in relation to the histologic grade of hepatic steatosis. UAP values increased progressively with increasing steatosis grade (P<0.001 for trend by the Kruskal-Wallis test).

**Figure 2**. ROC curves of UAP values for the severity of hepatic steatosis: (A) ≥ 5%; (B) ≥33%; (C) ≥ 66% of steatotic hepatocytes on liver biopsy.

**TABLE LEGENDS**

**Table 1**. Baseline characteristics of participants.

**Table 2**. Association between UAP values and presence of significant steatosis (defined as S≥2).

**Table 3**. Diagnostic performances of UAP values for grading hepatic steatosis both in the whole cohort of patients with FLD and in patients with NAFLD**.**