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# A comparison of hepatic steatosis index, controlled attenuation parameter and ultrasound as noninvasive diagnostic tools for steatosis in chronic hepatitis B

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ABSTRACT

*Aims:* To evaluate the value of noninvasive tools for diagnosis of hepatic steatosis in patients with chronic hepatitis B (CHB).
*Methods:* Consecutive treatment-naïve patients with CHB with body mass index less than 30 kg/m$^2$ who underwent liver biopsy, ultrasound and FibroScan® were enrolled. The diagnostic performance of controlled attenuation parameter (CAP), hepatic steatosis index (HSI) and ultrasound for hepatic steatosis compared with liver biopsy was assessed. The areas under receiver operating characteristics curves (AUROCs) were calculated to determine the diagnostic efficacy, with comparisons using the DeLong test.
*Results:* CAP and HSI accuracies were significantly higher than that of ultrasound to detect patients with biopsy-proven mild steatosis (S1, 65.3%, 56.5%, respectively, vs. 17.7%, $\chi^2$ = 46.305, 31.736, both $P$ < 0.05)and moderate-severe (S2-3) steatosis (92.3%, 100%, respectively, vs. 53.8%, $\chi^2$ = 4.887, 7.800, $P$ = 0.037, 0.007, respectively). Both CAP and HSI had lower underestimation rates of steatosis grade than ultrasound (12%, 14.8%, respectively, vs. 29.5%, $\chi^2$ = 9.765, 6.452; $P$ < 0.05 for both), but they exhibited higher overestimation rates (30.5%, 38.2%, respectively, vs. 12.4%, $\chi^2$ = 39.222, 70.986; both $P$ < 0.05). The AUROCs of CAP and HSI were 0.780 (95% confidence intervals [CIs] 0.735–0.822) and 0.655 (95%CI 0.604–0.704) for S ≥1, 0.932 (95%CI 0.902–0.956) and 0.755 (95%CI 0.707–0.799) for S ≥2, 0.990 (95%CI 0.974–0.998) and 0.786 (95% CI 0.740–0.827) for S3, respectively.
*Conclusion:* CAP might be more accurate for detecting hepatic steatosis than HSI and ultrasound in patients with CHB, but further studies are needed to reduce the overestimation rates.


## 1. Introduction

Hepatic steatosis is a frequent finding in patients with chronic hepatitis B (CHB), and its prevalence is increasing with the worldwide epidemic of obesity and type 2 diabetes mellitus [1–4]. Recent studies highlight the impact of hepatic steatosis on accelerating disease progression to liver fibrosis and ultimately cirrhosis [5–7] and reducing the efficacy of antiviral treatment in CHB [8]. Therefore, detection and quantification of hepatic steatosis have increasing relevance both for clinical studies and routine medical care in patients with CHB [9].

Although liver biopsy is traditionally considered the gold standard for steatosis grading, its use has several limitations, including sampling bias, intra- or inter- observer sampling variability and the potential for severe complications [10]. Furthermore, steatosis severity may change within weeks of therapeutic intervention and therefore cannot be sufficiently monitored by repetitive invasive procedures [11]. Imaging techniques provide potential alternatives for noninvasive steatosis characterization because fat deposits alter the physical properties of liver tissue [9]. Magnetic resonance (MR)-based techniques assess triglyceride- specific signal intensity and

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represent sensitive approaches for steatosis detection [12] but are not suitable as point-of-care methods due to high costs and limited comparability between different MR techniques [13,14]. B-mode ultrasound displays a bright echo-pattern in steatotic hepatic tissue and is widely used as a first-line assessment for screening of fatty liver, but it is imprecise in estimating mild steatosis [9,15]. These limitations may be overcome by the controlled attenuation parameter (CAP) software, which has been recently developed to quantify ultrasound attenuation during measurement of liver stiffness vibration-controlled elastography (transient elastography, TE; FibroScan) [16]. CAP measurement is an easy and fast examination providing a numerical value expressed in dB/m, which correlates with the histologic degree of steatosis [17]. According to available published data, CAP exhibits good diagnostic performance for steatosis evaluation in chronic viral hepatitis [18,19] and in multietiology cohorts [20–25]. The hepatic steatosis index (HSI) is also a simple screening tool for hepatic steatosis and is purported to be more accurate than ultrasound [26]. Nonetheless, no data published validate its application in patients with CHB.

Therefore, the study's first objective was to compare CAP's diagnostic accuracy with HSI for hepatic steatosis quantification in patients with CHB using liver biopsy as a reference method. The secondary objective was to evaluate the steatosis detection and misdiagnosis rates of CAP, HSI and ultrasound compared with liver biopsy.

## 2. Materials and methods

### 2.1. Patients

Among all patients who underwent a series of laboratory tests, liver biopsy, ultrasound and FibroScan at Tianjin Second People's Hospital, China, between July 2012 and April 2014, those who were positive for serum hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA for at least 6 months and did not undergo antiviral treatment were prospectively enrolled in this study. The exclusion criteria were as follows: (1) co-infection with other hepatitis virus and HIV; (2) daily alcohol consumption >20 g for women and >30 g for men; (3) any type of positive autoantibody above 1:160; (4) age <18 years; (5) presence of hepatocellular carcinoma; (6) immune suppressive treatment within 1 year; (7) an interval between liver biopsy, ultrasound and FibroScan examination longer than 2 weeks; (8) liver biopsy specimen <15 mm length or <0.8 mm diameter; and (9) body mass index (BMI) $\geq$30 kg/m$^2$. The study protocol was approved by the hospital Ethics Committee and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before the study.

### 2.2. Clinical, laboratory data collection

Demographic information, such as age, sex, history of diseases (such as arterial hypertension, diabetes mellitus and cardiovascular disease), daily alcohol consumption, smoking status and drug use were recorded from patient interviews before liver biopsy. The anthropometric measurements, including body weight (kilogram), height (meter) and BMI were obtained. Fasting blood samples were collected on the same day or within 3 days before and after liver biopsy. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, fasting plasma glucose, total cholesterol and triglycerides were measured by a Hitachi 7600–110 automatic analyzer (Hitachi Co., Tokyo, Japan). HSI was calculated according to the following formula: 8 $\times$ (ALT/AST ratio) + BMI (+2, if female; +2, if diabetes mellitus) [26]. Serum HBsAg, HBV e antigen (HBeAg) and HBV DNA were measured using an electrochemiluminescence assay (Roche COBAS e 411, Sandhofer Stasse 116, 68305 Mannheim, Germany) and quantitative PCR (Roche, light Cycler® 480 II/96, Rotkreuz, Switzerland), respectively.

### 2.3. Ultrasound examination

Abdominal ultrasound was performed with a Philips ultrasound machine (Model No. IU22, 22100 Bothell Everett Highway Bothell, WA, USA), by one senior radiologist (Zhou), using a C5-1 scanner with a 5 MHz convex probe. Hepatic steatosis was quantified during examination according to Hamaguchi's ultrasonographic score, from 0 to 6 points, based on the hepatorenal contrast, bright hepatic echoes, deep attenuation and vessel blurring [27,28]. A score <2 was defined as without steatosis, a score $\geq$2 and <4 was defined as mild steatosis, a score $\geq$4 and <6 was defined as moderate steatosis and the score = 6 was defined as severe steatosis.

### 2.4. Measurement of liver stiffness values and CAP

All patients were examined using FibroScan-502 (Echosens, Paris, France) with a 3.5 MHz M probe, which measures liver stiffness 25–65 mm underneath the skin surface [28–30]. The results of liver stiffness measurements (LSMs) were expressed as kPa. Examinations were considered unreliable if fewer than 10 valid measurements were obtained and/or the ratio of the interquartile range (IQR) over the median of 10 measurements (IQR/M) of LSM and CAP was 0.30, and skin capsular distance >25 mm. The CAP values were expressed in dB/m and were provided only if the LSM examination was successfully performed. One senior operator (Xu) was blinded to the patients' clinical and histologic data.

### 2.5. Liver biopsy

All patients underwent a percutaneous ultrasound-guided liver biopsy. Each liver specimen was fixed in formalin, embedded in paraffin and stained with hematoxylin-eosin, Masson's trichrome and collagen. Two experienced hepatic pathologists (Shi and Liu) blinded to the clinical data independently reviewed the histologic findings. Consensus was reached in case of disagreement. The Knodell histologic activity index was used to describe the hepatocellular necro-inflammatory activity [31]. Liver fibrosis was semi-quantitatively assessed according to the Ishak system and was graded from stage 0 to stage 6 [32]. Hepatic steatosis was graded from 0 to 3 based on the number of hepatocytes with steatosis at histology: S0: <5%; S1: 5–33%; S2: 34–66%; S3: >66% [33].

### 2.6. Statistical analysis

All data were presented as number (%) and median (range) values. A Mann–Whitney test (two-group comparison) or Kruskal–Wallis test (more than two group comparison) was used for continuous variables. Multivariate analyses of variance were performed to study interactions between the histologic steatosis grades and CAP. The distribution of CAP values and HSI values for each degree of histologic steatosis was evaluated using box plots. Comparisons of the detection rates, coincidence rates and discordance rates of hepatic steatosis in CAP, HSI and ultrasound according to liver biopsy were made using the chi-squared or Fisher's exact test. The diagnostic performances of CAP and HSI were analyzed by computing the AUROCs and their 95% CIs. The optimal diagnostic cutoff value for each degree of histologic steatosis was found by maximizing the Youden Index. For each cutoff, a corresponding positive predictive value (PPV), negative predictive value (NPV) and positive and negative likelihood ratios (LR+ and LR−, respectively) were also calculated. The diagnostic performances between two measures were compared using the DeLong