



# Hepatic steatosis contributes to fibrosis in Asian-American patients with chronic hepatitis B infection

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**Background:** Both hepatitis B and fatty liver are important causes of progressive liver disease. However, the impact of fatty liver on hepatitis B is controversial. The objective of this study is to understand the relationship between these two causes of liver disease within an Asian-American population.

**Methods:** We retrospectively studied consecutive patients who underwent transient elastography (TE) using the Controlled attenuation parameter (CAP) between January 2019 and October 2019 from a community practice in Southern California. Baseline laboratory and clinical data were collected. Univariate analysis, two-sided t-tests and Mann-Whitney U tests were performed, chi-square test for proportions, and logistic regression.

**Results:** One hundred and forty-two patients underwent TE, of which, 112/142 had steatosis present. BMI was significantly higher in the steatosis group (P value <0.01). Most patients with steatosis had S3 fat. A greater number of patients with HBV and steatosis had advanced fibrosis as compared to patients without steatosis as assessed by TE (P=0.04). Patients with both HBV and hepatic steatosis were more likely to be started on HBV therapy.

**Conclusions:** Patients with hepatitis B should be screened for fatty liver disease using noninvasive assessment of hepatic fibrosis. We used a combination of the Fib-4 index and TE with the CAP, which demonstrated advanced fibrosis was greater in Asian patients with both hepatic steatosis and hepatitis B. More studies evaluating the ethnic differences seen in fatty liver disease and HBV is needed to assess the long-term impact on morbidity and mortality.

**Keywords:** Hepatitis B; fatty liver; fibrosis; steatosis

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## Introduction

Hepatitis B virus (HBV) infection is a major public health concern. The infection affects over 257 million people across the globe and is responsible for 887,000 deaths from complications such as hepatocellular carcinoma and

liver failure (1). Most individuals early in their disease are unaware of their infection (2). There are a number of modifiable and non-modifiable risk factors associated with disease progression such as HBV deoxyribonucleic acid (DNA), gender, age, and alanine aminotransferase (ALT) in some patients (3-5). Antiviral therapy is an effective

method to lowering HBV DNA levels and is effective in reversing fibrosis and decrease risk of the hepatic complications of HBV.

Fatty liver is also an important public health issues that has been described in about a quarter of the world's population (6). A specific type of fatty liver termed non-alcoholic steatohepatitis (NASH) can cause progressive liver disease, and now is the second most common indication for liver transplantation in the United States (7). Moreover, fatty liver is the most common underlying risk factor for HCC among patients in the United States with Medicare insurance, a costly burden on the healthcare system (8). The most cost-effective treatment for fatty liver is weight loss, as ten percent of weight loss has been associated with reversing hepatic damage (seen histologically) in patients with NASH (9). However, given the increasing prevalence of this disease, numerous promising pharmaceutical and non-pharmaceutical agents are being investigated including peroxisome proliferator-activated receptor (PPAR)-gamma agonist, glucagon-like peptide (GLP)-1 agonist, obeticholic acid, as well as increased coffee intake (10-12).

There are a number of examples of the interactions between different causes of liver disease. For instance, the alcohol consumption and HBV have been independently described as risk factors for Hepatitis C virus (HCV) progression (13). Given the medical concerns with both HBV and fatty liver, and the global prevalence, we sought to study the interaction between these two disorders. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/dmr-20-75>).

## Methods

### *Setting and study population*

This is a single center retrospective study of consecutive patients with HBV infection at a community-based practice in Southern California who underwent transient elastography (Fibroscan<sup>®</sup> 530, Echosens<sup>™</sup>, Waltham, MA) as routine medical care. Chronic HBV infection was defined by detectable HBsAg. This study includes patients from January 2019 until the end of October of 2019. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board (IRB#19-002283). Informed consent is not applicable since this was a retrospective study.

### *Imaging modalities in the noninvasive assessment of hepatic fibrosis*

Radiological evaluation has significantly improved the estimation of liver fibrosis. Among these imaging modalities are magnetic resonance elastography (MRE) and transient elastography. Each of these techniques are noninvasive when compared to hepatic biopsy, however, in consideration of cost, complications and ease of use in the ambulatory setting, transient elastography has been widely used. Transient elastography was performed by one of the authors (SW). Briefly, a 50 hertz shear wave is passed from the tip of the probe to the patient. It travels through the liver tissue, and its speed is measured through ultrasound pulses as it passes through the liver. The velocity is then used to calculate the liver stiffness, measured in kilopascals, which estimates severity of fibrosis in which Hepatitis B specific thresholds were utilized (14,15). In our study, we made use of the Controlled Attenuation Parameter (CAP), an emerging measurement based on transient elastography with relatively high diagnostic accuracy for detecting hepatic steatosis in patients with liver disease (16).

Two different sized probes were utilized depending on the weight of the patient and/or the varying distances between the skin to the center of the liver, also known as the skin-to-capsule distance (17). The medium sized probe measures the median CAP score (amount of fatty change in the liver) and E score (liver stiffness) from 25–65 mm below the surface of the skin, and the XL sized probe measures from 35–75 mm below the surface of the skin. Measurements were performed as previously described (18). The XL probe is used when the skin-liver capsule distance is greater than 25. At least 12 measurements were taken.

Stratification of fibrosis stages and steatosis percentage was done according to manufactural specification (Echosens<sup>™</sup>, Waltham, MA). Briefly, fibrosis stages were categorized as F/0/F1, F2, F3 and F4 depending on the liver stiffness. Similarly, steatosis percentage was defined as S0 (0–<5%), S1 (5–33%), S2 (>34–66%). and S3 (>66%).

### *Operational definitions*

We defined hypertension as blood pressure above 130/80 mmHg or the use of anti-hypertensive medications (19). We defined hyperlipidemia as the used of anti-lipid medications or an LDL value adjusted according to the number of cardiovascular risk factors (20).

Specifically, hyperlipidemia was defined if the LDL value was greater than 190 mg/dL if there were no cardiovascular risk factors, greater than 160 mg/dL if there is one major, or greater than 130 mg/dL if there are two. The risk factors include hypertension, use of tobacco, diabetes, low HDL cholesterol, premature coronary heart disease, and age (males that are 45 years or older and females that are 55 years or older) were also recorded (20). Laboratory data was collected at the time of the transient elastography and before antiviral therapy was started. We recorded the laboratory values such as HBsAg titers, HBV DNA levels, and HBeAg status. We used American Association for the Study of Liver Disease definitions for abnormal ALT values ~ upper limit of normal ALT 33 U/L for men and 25 U/L for women (21,22).

### Statistical Analysis

Continuous data were summarized as mean with standard deviation (SD). All data analysis was conducted using STATA 15 (StataCorp 2015, College Station). Univariate analysis was performed using Fisher's exact test for discrete data and Wilcoxon Rank Sum test for continuous data. All hypothesis tests were two-sided and a p-value below 0.05 was considered statistically significant. We used the Chi-Square Test of Independence to compare proportions of categorical variables. Since we had a larger sample size of greater than 100, the Kolmogorov-Smirnov test was used along with histograms to identify normality. For data that was non-parametric, we used the Mann-Whitney U test.

### Results

One hundred and forty-two patients underwent transient elastography at our office (Table 1). The overall mean ( $\pm$  SD) age of the cohort was 56 ( $\pm$ 12.7) years. Most of the patients were men and all patients were of Asian background. The overall mean ( $\pm$  SD) ALT was 23 ( $\pm$ 16.2) IU/mL. Most patients in our cohort had steatosis noted on transient elastography: one hundred and twelve patients had steatosis, and 30 patients had no evidence of steatosis. The overall and stratification lipid panel values and documentation of metabolic features are shown in Table 1. Patients with fatty liver were more likely to be men (P value =0.010) and have higher ALT values (P value 0.032). None of the patients without steatosis had detectable HBeAg, whereas 13% of patients of patients with steatosis had detectable HBeAg levels (P value =0.264).

Forty percent of our entire cohort were on antiviral therapy. The mean ALT (SD) and HBV DNA (SD) before starting therapy were 82.4 (52.0) IU/L and 136,357,713 (349,301,962) IU/L, respectively. None of the patients in the non-steatosis group were treated with antiviral agents, whereas most patients in the steatosis group were on treatment (49/112). None of the patients on treatment had measurable HBeAg titers. The overall mean ( $\pm$  SD) viral load HBV DNA of patients was 9,579 ( $\pm$ 48,181.7) IU in the patients not on antiviral therapy. The mean viral load was greater in steatosis group than the non-steatosis group (11,427 vs. 5,403 IU, respectively) but not statistically significant (P value 0.59). The mean ALT value was statistically significant higher in the steatosis than non-steatosis group (22 vs. 19 IU, respectively; P value 0.011). Mean Fib-4 results were similar in the steatosis and non-steatosis groups (1.55 vs. 1.25, P value 0.063). The duration of treatment was 53.1 (17.6) months. There was a moderate association between use of antivirals and presence of fatty liver ( $\lambda$ =0.119).

The prevalence of diabetes, and hypercholesterolemia was similar in the two groups. A diagnosis of hypertension was almost three times more common in patients with hepatic steatosis as compared to those patients without steatosis (P value 0.024). Values of HDL were also lower in patients with hepatic steatosis (P value <0.01). The median BMI was higher in patients with hepatic steatosis than those without steatosis (24.0 vs. 21.0, P value <0.01). The distribution of BMI according to the presence of steatosis in patients with chronic hepatitis B is shown in Figure 1.

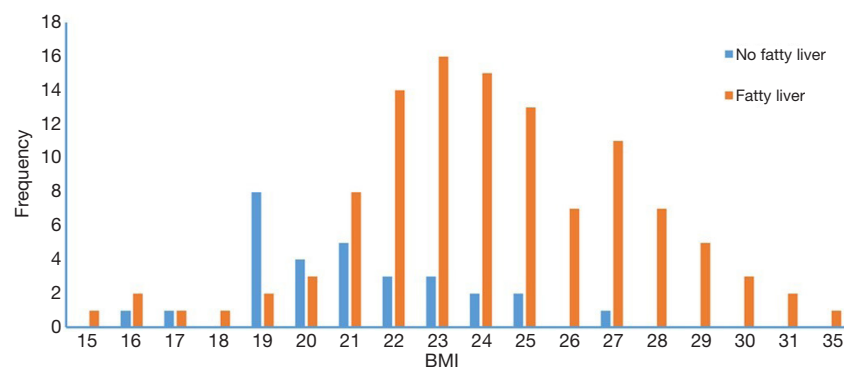
### Discussion

As expected, our manuscript provides further evidence that the presence of steatosis not only increases liver enzymes in patients with hepatitis B but increases viral loads as well. HBeAg was more likely to be detectable in patients with fatty liver disease, in which hepatic steatosis contributed to a greater likelihood of advanced fibrosis. However, an unexpected finding of our study was the large cohort of patients with fatty liver disease using of the CAP measurement. Approximately 2/3 of our entire cohort had hepatic steatosis. This is higher than expected in the general population where approximately 25% of patients have non-alcoholic fatty liver disease. Originally this was thought to be attributed to our selected cohort of Asian-Americans, however, our prevalence is also higher than that reported by Golabi *et al.* in Asian American adults in the United

**Table 1** Demographic and baseline laboratory values

Variables	All patients	No fatty liver	Fatty liver	P value
Total	142	30	112	
Gender				0.010
Male	77 (54.2%)	10 (33.3%)	67 (59.8%)	
Female	65 (45.7%)	20 (66.7%)	45 (40.2%)	
BMI	23.6±3.4	21.0±2.5	24.3±3.3	0.000
Age, years	55.7±12.7	52.8±13.2	56.4±12.4	0.166
ALT, U/L	23.0±16.2	19.3±8.7	24.3±17.5	0.032
HBV DNA, U/mL	6,282±37,903	5,403±12,332	6,520±42,286	0.808
HBeAg +	14/136 (10.3%)	0/30 (0%)	14/106 (13.2%)	0.264
Total cholesterol, mg/dL	173.1±33.5	175.3±33.1	172.5±33.9	0.590
LDL, mg/dL	97.2±27.3	91.6±25.7	98.7±27.6	0.369
HDL, mg/dL	55.1±15.4	67.4±15.2	51.8±13.8	0.000
AFP, ng/mL	1.8±1.8	2.4±2.6	1.7±1.6	0.169
Glucose, mg/dL	99.1±22.9	98.4±26.9	99.4±21.8	0.832
Hemoglobin a1c	6.0±0.9	6.0±0.8	6.0±0.9	1.000
Mean Fib-4	1.38±0.9	1.54±1.3	1.34±0.7	0.423
HTN	37 (26.1%)	3 (10%)	34 (30.4%)	0.024
Diabetes	13 (9.1%)	2 (6.7%)	11 (10.4%)	0.543
Hypercholesterolemia	71 (50.0%)	15 (50%)	56 (50%)	1.000

Normal ALT values: <33 U/L for men and <25 U/L for women. ALT, alanine aminotransferase; aspartate aminotransferase; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; AFP, alpha fetoprotein; LDL, low-density lipoprotein; HDL, high density lipoprotein; HTN, hypertension; Fib-4, fibrosis-4 index.

**Figure 1** Distribution of body mass index (BMI) in patients with chronic hepatitis B with and without steatosis.

States (23,24). We believe this could be attributed to our use of the CAP when screening for fatty liver disease, as our results indicate the use of the CAP may prove to be a better

diagnostic indicator than previously reported. Nevertheless, as expected, patients with hepatic steatosis were more likely to have metabolic risk factors such as lower HDL,

hypertension, and greater BMI. An unexpected finding was that a substantial number of patients in our cohort had steatosis even at BMI below 30 and 25, the threshold value for defining obesity and overweight respectively among individuals from Asia (“Mean Body” 2017 and “Appropriate Body-Mass” 2014). In fact, over 63.3% of our patients had a BMI below 25. 95.8% of our patients had a BMI below 30. This is consistent with current healthcare disparities research which demonstrates metabolic risk factors differ by ethnicity, as Asian patients develop fatty liver disease more readily and at a lower BMI than Caucasian cohorts (25). We believe further health disparities research is needed to investigate this finding in other underrepresented populations, which would help determine if treatment for steatosis should be used in patients with a BMI below 25 (26).

The relationship between fatty liver and hepatitis B has been controversial. Several studies have shown that hepatitis B is either a risk factor for fatty liver disease or has no impact at all (27-29). Zhu *et al.* seem to suggest that viral replication is not related to fatty liver disease, but rather the etiology of steatosis (30). No suggested mechanisms were reported, although some confounding factors could include type and severity of metabolic features and the degree of steatosis. Fibrosis being the hallmark of chronic liver disease, measuring the severity remains important to help define the natural history of HBV. Although, direct measurements through hepatic biopsy are invasive, costly and poses significant risk for patients, histological evaluation and linear regression modeling for active viral hepatitis against the degree of steatohepatitis has also shown to have no correlation, concordant with Worland *et al.* manuscript (31).

As in other causes of liver disease, there have been a number of studies assessing the utility of non-invasive tools to measure hepatic fibrosis, including serological [aspartate aminotransferase to platelet ratio (APRI) score, FibroTest/FibroSure and Fib-4 index] and radiologic (TE and MRE) test. We used in our study two different measures of fibrosis. One was laboratory based, and the other based on imaging. We used the Fib-4 as a laboratory assessment based on the results of a recent systematic review, which found it more accurate than APRI and select proprietary tests to predict the presence of fibrosis (32). We also employed transient elastography with use of the CAP measurement as our imaging modality. The results of a meta-analysis highlighted the varied specificity and sensitivity according to fibrosis stage, but the overall accuracy was quite good (15). A limitation of our study could be the lack of data on MRE in our population since this radiographic modality has the

highest accuracy for detecting fibrosis (33).

We suggest based on our results that patients with hepatitis B be screened for fatty liver utilizing Fib-4 and TE with the CAP, as this can be easily done in the outpatient setting with high accuracy. Although the presence of steatosis is invariably related to the presence of metabolic features and not necessarily hepatitis B, the majority of patients with hepatitis B did have fatty liver. Although we were able to demonstrate differences in fibrosis between the 2 groups, we are unable to comment on the long-term effect of steatosis in patients with hepatitis B such as prognosis or the risk of morbidity and mortality (29). Since steatosis did increase liver enzymes independent of hepatitis B viral replication, as noted in other studies, we believe further research is necessary to consider the timeline to initiate antiviral therapy (34).

In conclusion, fatty liver disease occurs more frequently in patients with HBV infections than previously thought when using the CAP. Patients with hepatitis B should be screened for fatty liver using any of the aforementioned modalities, however, we used the Fib-4 index and TE with the CAP. Liver enzyme elevation may occur independent of viral replication, as suggested by our study and other published literature, therefore the initiation of antiviral therapy should incorporate this phenomenon. Advanced fibrosis was greater among Asian patients with both hepatic steatosis and hepatitis B. More studies evaluating the ethnic differences seen in fatty liver disease and HBV is needed to assess the long-term impact on morbidity and mortality.

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## Footnote

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**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board (IRB#19-002283). Informed consent is not applicable since this was a retrospective study.

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