Original Article

# Association between Hepatic Steatosis and Fibrosis in Chronic Viral Hepatitis B and C Patients

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***Background***: Chronic viral hepatitis B (CHB) and chronic viral hepatitis C (CHC) are important causes of chronic liver disease and cancer development in patients with progressive fibrosis, which are often associated with hepatic steatosis.

***Objective***: To evaluate the prevalence of hepatic steatosis in Thai CHB and CHC patients and its correlation with fibrosis stage.

***Materials and Methods***: The authors examined the liver biopsy findings of CHB and CHC patients diagnosed at Srinagarind Hospital between 2016 and 2018. Routine Hematoxylin and Eosin staining with PAS, and Masson trichrome staining were used to evaluate fibrosis and steatosis histology according to the METAVIR and SAF scoring systems. The association were evaluated by chi-square, Fisher's exact, and Spearman's correlation tests with statistical significance defined as p-value less than 0.05.

***Results***: One hundred thirty-eight cases were examined. The mean age of the patients was 45 years. Chronic hepatitis C was detected in 96 patients (69.6%), and CHB was detected in 42 patients (30.4%). Liver biopsies showed steatosis in 73 patients (52.9%; grade 1: 67.1%, grade 2: 19.2%, and grade 3: 13.7%). Steatosis was associated with viral hepatitis profile (OR 2.534, 95% CI 1.087 to 5.904, p=0.031); however, the METAVIR fibrosis stage associated with the age of the patient (OR 1.059, 95% CI 1.012 to 1.109, p=0.014) and METAVIR activity (OR 4.924, 95% CI 2.443 to 9.967, p<0.0001).

***Conclusion***: Hepatic steatosis is commonly present in Thai CHC and CHB patients, and especially in the former. Steatosis was associated with viral hepatitis profile. Hepatic fibrosis is associated only with the age of the patient and METAVIR activity.

***Keywords***: Chronic hepatitis B, Chronic hepatitis C, Steatosis, Fibrosis, METAVIR, SAF score, Liver biopsy

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Chronic viral hepatitis B (CHB) and chronic viral hepatitis C (CHC) are common diseases and important public health problems worldwide, including in Thailand. According to the Thailand's Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, there are about two to three million CHB patients and about 0.5 to one million CHC patients in the country[1]. Both diseases are major causes of chronic liver disease and carcinogenesis in patients with advanced fibrosis[2]. Hepatic steatosis is commonly found in CHB and CHC patients. Hepatic steatosis is defined as fat exceeding 5% of the liver by weight, more commonly, as fat identifiable in more than 5% of hepatocytes by liver histopathology[3]. Previous studies have found the prevalence of steatosis to be 14% to 70% in CHB patients[4] and 35% to 81% in CHC patients[5]. Hepatic steatosis is one of the factors involved in fibrosis progression and a risk factor for hepatocellular carcinoma[6]. Currently, according to the 2018 guidelines for managing hepatitis B and hepatitis C issued by the Thai Association for the Study of the Liver, one of the criteria for treatment is evidence of fibrosis on liver biopsy[7]. The aims of the present study were to evaluate the prevalence of hepatic steatosis on liver biopsy in Thai CHB and CHC patients and its association with fibrosis stage.

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## Materials and Methods

The present study was a retrospective study conducted among 138 CHB and CHC patients diagnosed of CHB or C that underwent liver biopsy at Srinagarind Hospital between 2016 and 2018. Patients with co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV), co-infection of HBV/HCV and HIV, or hepatocellular carcinoma or

**Table 1.** Demographic data

| Parameter | Total, n=138 (100); n (%) | CHB, n=42 (30.4); n (%) | CHC, n=96 (69.6); n (%) | p-value |
|---|---|---|---|---|
| Age (years); median (range) | 45 (19 to 69) | 36 (20 to 61) | 50 (19 to 69) | <0.001 |
| Sex | | | | <0.001 |
| Male | 74 (53.6) | 10 (23.8) | 64 (66.7) | |
| Female | 64 (46.4) | 32 (76.2) | 32 (33.3) | |
| Body mass index | | | | n.s. |
| Underweight | 8 (5.8) | 4 (9.5) | 4 (4.2) | |
| Normal weight | 62 (44.9) | 20 (47.6) | 42 (43.8) | |
| Overweight | 23 (16.7) | 7 (16.7) | 16 (16.7) | |
| Obesity class I | 41 (29.7) | 10 (23.8) | 31 (32.3) | |
| Obesity class II | 4 (2.9) | 1 (2.4) | 3 (3.1) | |
| Alcohol intake | | | | n.s. |
| Yes | 12 (8.7) | 2 (4.8) | 10 (10.4) | |
| No | 126 (91.3) | 40 (95.2) | 86 (89.6) | |
| Other metabolic disease | | | | n.s. |
| None | 122 (88.4) | 38 (90.5) | 84 (87.5) | |
| DM | 7 (5.1) | 2 (4.8) | 5 (5.2) | |
| HT | 5 (3.6) | 0 (0.0) | 5 (5.2) | |
| DLD | 2 (1.4) | 2 (4.8) | 0 (0.0) | |
| DM and HT | 1 (0.7) | 0 (0.0) | 1 (1.0) | |
| DM and DLD | 1 (0.7) | 0 (0.0) | 1 (1.0) | |

CHB=chronic viral hepatitis B; CHC=chronic viral hepatitis C; DM=diabetes mellitus; HT=hypertension; DLD=diffuse liver disease; n.s.=not significant

cholangiocarcinoma were excluded. Demographic data were collected including age, gender, weight, height, alcohol intake, other metabolic diseases, and CHC genotype. Body mass index (BMI) was calculated as weight (kg)/[height (m)]$^2$. Hematoxylin and Eosin, Periodic Acid-Schiff, and Masson's trichrome stains were used to evaluate liver biopsy histology according to the SAF and METAVIR scoring systems. Patients' SAF scores were calculated as follows: 1) steatosis grade 0 to 3 (0=steatosis less than 5%, 1=steatosis 5% to 33%, 2=steatosis more than 33% to 66%, 3=steatosis more than 66%), 2) activity grade 0 to 3 (0=no activity, 1=mild, 2=moderate, 3=severe), and 3) stage 0 to 4 (0=no fibrosis, 1a=mild perisinusoidal fibrosis, 1b=moderate perisinusoidal fibrosis, 1c=portal/periportal fibrosis without perisinusoidal fibrosis, 2=perisinusoidal and portal/periportal fibrosis, 3=bridging fibrosis, 4=cirrhosis). Participants' METAVIR scores were calculated as: 1) stage 0 to 4 (0=no fibrosis, 1=portal fibrosis without septa, 2=portal fibrosis with few septa, 3=bridging or septal fibrosis, 4=cirrhosis), and 2) activity grade 0 to 3 (0=no activity, 1=mild, 2=moderate, 3=severe).

Statistical analyses were performed using chi-square, Fisher's exact, and Spearman's correlation tests in IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). The univariate and multivariate analyses by logistic regression were also performed to indicate the clinicopathologic variables potentially associated with dependent variables, for instance the present of steatosis and fibrosis METAVIR. The values of p-value less than 0.05 were considered statistically significant.

## Results

### Demographic data

One hundred thirty-eight CHB and CHC patients were included in the present study. The demographic data is shown in Table 1. Ninety-six of the participants (69.6%) had CHC and the remaining 42 (30.4%) had CHB. The mean age was 45 years with a range of 19 to 69 years old and was higher in CHC patients than in CHB patients. There were 76 males (53.6%) and 64 females (46.4%), with CHC being more predominant in the males (p<0.001). The highest proportion of patients had normal BMI (44.9%), followed by obesity class I (29.7%). Most patients did not consume alcohol (91.3%) and most had no other known metabolic diseases (88.4%). Patients in

**Table 2.** Histological evaluation regarding of SAF and METAVIR score in the overall population

| Parameter | Total, n=138 (100); n (%) | CHB, n=42 (30.4); n (%) | CHC, n=96 (69.6); n (%) | p-value |
|---|---|---|---|---|
| SAF steatosis grade | | | | 0.01 |
| Grade 0 | 65 (47.1) | 28 (66.7) | 37 (38.5) | |
| Grade 1 | 49 (35.5) | 12 (28.6) | 37 (38.5) | |
| Grade 2 | 14 (10.1) | 1 (2.4) | 13 (13.5) | |
| Grade 3 | 10 (7.2) | 1 (2.4) | 9 (9.4) | |
| SAF activity grade | | | | 0.01 |
| Grade 0 | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Grade 1 | 2 (1.4) | 1 (2.4) | 1 (1.0) | |
| Grade 2 | 68 (49.3) | 29 (69.0) | 39 (40.6) | |
| Grade 3 | 68 (49.3) | 12 (28.6) | 56 (58.4) | |
| SAF fibrosis stage | | | | 0.04 |
| Stage 0 | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Stage 1a | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Stage 1b | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Stage 1c | 20 (14.5) | 8 (19.0) | 12 (12.5) | |
| Stage 2 | 99 (71.7) | 33 (78.6) | 66 (68.8) | |
| Stage 3 | 8 (5.8) | 1 (2.4) | 7 (7.3) | |
| Stage 4 | 11 (8.0) | 0 (0.0) | 11 (11.5) | |
| METAVIR fibrosis stage | | | | <0.001 |
| Stage 0 | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Stage 1 | 71 (51.4) | 33 (78.6) | 38 (39.6) | |
| Stage 2 | 48 (34.8) | 8 (19.0) | 40 (41.7) | |
| Stage 3 | 8 (5.8) | 1 (2.4) | 7 (7.3) | |
| Stage 4 | 11 (8.0) | 0 (0.0) | 11 (11.5) | |
| METAVIR activity grade | | | | <0.001 |
| Grade 0 | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Grade 1 | 32 (23.2) | 19 (45.2) | 13 (13.5) | |
| Grade 2 | 36 (26.1) | 15 (35.7) | 21 (21.9) | |
| Grade 3 | 70 (50.7) | 8 (19.1) | 62 (64.6) | |

CHB=chronic viral hepatitis B; CHC=chronic viral hepatitis C

the CHB and CHC groups did not differ in terms of BMI, alcohol intake, or presence of other metabolic diseases. Of the 93 patients with CHC, 31.2% had genotype 1, 39.8% had genotype 3, and 29.0% had genotype 6 (29.0%).

## Histological evaluation

Overall liver biopsy histology is shown in Table 2. Hepatic steatosis was present in 73 patients (52.9%), 67.1%, 19.2%, and 13.7% of whom had grade 1, 2, and 3, respectively. Steatosis was presented in 61.5% of CHC patients and 33.3% of CHB patients. Steatosis grade was higher in the CHC patients (p=0.01). A total of 14.5%, 71.7%, 5.8%, and 8.0% of patients had SAF fibrosis stage 1c, 2, 3, and 4, respectively, and 51.4%, 34.8%, 5.8%, and 8.0% had METAVIR fibrosis stage 1, 2, 3, and 4, respectively. Both SAF and METAVIR fibrosis stage were higher in CHC patients than in CHB patients (p=0.04 and <0.001, respectively).

A total of 1.4%, 49.3%, and 49.3% of patients had SAF activity grade 1, 2, and 3, respectively, and 23.2%, 26.1%, 50.7%. had METAVIR activity grade 1, 2, and 3, respectively. Both were higher in CHC patients than in CHB patients (p=0.01 and <0.001, respectively).

## Variables associated with presence of steatosis

The variables associated with presence of steatosis in the overall sample population are shown

**Table 3.** Univariate and multivariate regression analyses of clinicopathologic variables potentially associated with the present of steatosis in chronic hepatitis patient

| Variables | n | Univariate regression | | Multivariate regression | |
|---|---|---|---|---|---|
| | | OR (95% CI) | p-value | Adjusted OR (95% CI) | p-value |
| Age | 138 | 0.972 (0.944 to 1.002) | 0.068 | | |
| Sex | 138 | 1.397 (0.713 to 2.736) | 0.329 | | |
| Viral profile | 138 | 3.189 (1.489 to 6.832) | 0.003* | 2.534 (1.087 to 5.904) | 0.031* |
| Genotype of hepatitis C | 138 | 1.417 (0.306 to 2.545) | 0.356 | | |
| Weight | 138 | 0.937 (0.904 to 0.972) | 0.0005* | 1.005 | 0.887 |
| Body mass index | 138 | 0.778 (0.687 to 0.882) | 0.0001* | 0.763 | 0.015* |
| HT | 138 | 0.976 (0.940 to 1.023) | 0.082 | | |
| Alcohol drinking | 138 | 1.877 (0.538 to 6.551) | 0.324 | | |
| Activity METAVIR | 138 | 1.462 (0.292 to 2.002) | 0.292 | | |
| Fibrosis METAVIR | 138 | 1.448 (0.181 to 1.721) | 0.125 | | |
| Activity SAF | 138 | 0.333 (0.279 to 0.822) | 0.099 | | |
| Fibrosis SAF | 138 | 0.512 (0.299 to 0.879) | 0.015* | 0.518 (0.288 to 0.932) | 0.028* |

HT=hypertension; OR=odds ratio; CI=confidence interval

* p<0.05 is considered statistically significant

Variables found insignificant by univariate regression were not included in the multiple regression model

**Table 4.** Univariate and multivariate regression analyses of clinicopathologic variables potentially associated with the fibrosis METAVIR (Stage 0 to 1 vs. stage 2 to 4) in chronic hepatitis patient

| Variables | n | Univariate regression | | Multivariate regression | |
|---|---|---|---|---|---|
| | | OR (95% CI) | p-value | Adjusted OR (95% CI) | p-value |
| Age | 138 | 1.074 (1.037 to 1.112) | <0.0001* | 1.059 (1.012 to 1.109) | 0.014* |
| Sex | 138 | 0.382 (0.192 to 0.763) | 0.006* | 0.404 (0.164 to 0.993) | 0.048* |
| Viral profile | 138 | 5.596 (2.409 to 13.002) | <0.0001* | 0.779 (0.277 to 2.675) | 0.691 |
| Genotype of hepatitis C | 138 | 0.912 (0.737 to 1.128) | 0.395 | | |
| Weight | 138 | 1.009 (0.979 to 1.040) | 0.572 | | |
| Height | 138 | 1.035 (0.991 to 1.080) | 0.119 | | |
| Body mass index | 138 | 0.988 (0.892 to 1.095) | 0.821 | | |
| Systolic blood pressure | 138 | 0.997 (0.971 to 1.024) | 0.827 | | |
| Alcohol drinking | 138 | 1.356 (0.409 to 4.501) | 0.619 | | |
| Activity METAVIR | 138 | 4.589 (2.635 to 7.991) | <0.0001* | 4.924 (2.443 to 9.967) | <0.0001* |
| Activity SAF | 138 | 1.714 (1.021 to 2.876) | 0.041* | 0.573 (0.272 to 1.206) | 0.142 |
| Present of steatosis | 138 | 0.361 (0.181 t o0.721) | 0.004* | 0.395 (0.164 to 0.953) | 0.039* |

OR=odds ratio; CI=confidence interval

* p<0.05 is considered statistically significant

Variables found insignificant by univariate regression were not included in the multiple regression model

in Table 3. The viral profile, weight, BMI, and SAF fibrosis were associated with steatosis in univariate analysis. Only for viral profile was associated in multivariate analysis (OR 2.534, 95% CI 1.087 to 5.904, p=0.031). Age, gender, alcohol intake, and presence of other metabolic disease were not associated with the presence of steatosis.

### Variable associated with METAVIR fibrosis

Variable associated with fibrosis are shown in Table 4. The METAVIR fibrosis was associated with age, gender, viral profile, METAVIR/SAF activity score, and presence of steatosis. Age and MEVATIR activity variable were associated with METAVIR fibrosis in multivariable analysis (OR 1.059, 95%

CI 1.012 to 1.109, p=0.014) and (OR 4.924, 95% CI 2.443 to 9.967, p<0.0001).

## Discussion

Hepatic steatosis was found in 73 patients (52.9%), 59 with CHC and 14 with CHB. The prevalence of steatosis in CHC patients was 61.5%, which is within the range found in previous studies[5,8]. Similar to findings of a meta-analysis by Machado et al, 33.3% of CHB patients in the present study had steatosis, 28.6%, 2.4%, and 2.4% with grade 1, 2, and 3, respectively[4]. Several studies have found an association between steatosis and host metabolic factors[9-11]. Although various studies have demonstrated an association between steatosis and viral factors, especially in CHC genotype 3[8,12], some have found association of steatosis with host metabolic factors in patients with CHC genotype 1 and CHB[8,13]. There were 93 CHC patients in the present study, 31.2%, 39.8%, and 29.0% had genotype 1, 3, and 6, respectively. While genotype 3 was most common among CHC patients, a higher percentage of patients had genotypes other than 3. The present study also showed a strong association between steatosis and viral profile in chronic viral hepatitis, which was supported by the present study finding that steatosis grade, are higher in viral hepatitis C but not the viral hepatitis C genotype and alcohol drinking.

METAVIR fibrosis stage was higher in CHC patients than in those with CHB. Previous studies regarding the prediction of fibrosis progression in chronic viral hepatitis found several factors associated with increased risk of progression such as older age, male gender, viral factors, alcohol intake, steatosis, and metabolic disease[14,15]. In the present study, there were several factors higher in CHC patients than in those with CHB, which supports the present study finding that fibrosis stage was higher in CHC patients. In addition, it was found that fibrosis was correlated with age, viral profile, METAVIR activity, and SAF activity, but age and METAVIR activity were significant in multivariate analysis. Previous studies have shown that alcohol intake and host metabolic factors to be associated with fibrosis[16,17]. Several previous studies have also found an association between steatosis and fibrosis in CHC, but no association in CHB[8,12,18,19].

Inflammatory activity grade of METAVIR and SAF were higher in CHC patients than in CHB patients. Fujita et al found that inflammatory activity induced by oxidative stress was also common in CHC patients[20]. Steatosis grade was correlated with SAF activity grade in CHC patients. The authors also found the METAVIR activity associated with higher fibrosis grade. Previously studies found association between alcohol intake/host metabolic factors and inflammatory activity[21,22].

## Conclusion

Hepatic steatosis is common in Thai CHC and CHB patients, and especially in the former. Steatosis was associated with viral profile. When combined METAVIR activity, it also appeared to be related to fibrosis. These findings may be applicable in the treatment of Thai CHC patients to reduce the risk of fibrosis progression and cancer development.

### What is already known on this topic?

The prevalence of steatosis in CHC was 61%. Genotype 3 was commonly found around 39.8%. METAVIR activity grade and SAF activity grade were higher in CHC patients than in CHB patients.

### What this study adds?

Hepatic steatosis grade was higher in chronic hepatitis C, genotype 3 patients than in chronic hepatitis B patients. Association of viral profile, age, and some host metabolic factors appear to relate to inflammatory activities that affect the steatosis and fibrosis.


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### Conflicts of interest

The authors declare no conflict of interest.

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