Original Article

Correlation between Serum Iron Markers and Liver Fibrosis in Treatment-Naive Urban Patients with Chronic Hepatitis C Infection in Vajira Hospital

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Objective: To study the correlation between serum iron markers and liver fibrosis in treatment-naive chronic hepatitis C urban patients.

Material and Methods: Fifty patients with treatment-naive chronic hepatitis C from database (E-phis) in the Liver Clinic from January to December 2017, aged between 18 to 80 years, were examined for serum iron markers, laboratory investigations and measurement of the liver stiffness.

Results: Eleven patients (22%) had normal serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) levels. Thirty-four patients (68%) had a normal serum iron level, and 31 (62%) had a normal ferritin level. The mean serum levels of iron (p = 0.003, p<0.001), ferritin (p = 0.020, p = 0.035) and transferrin saturation (p = 0.007, p = 0.015) showed significant positive correlations with AST and ALT. The mean levels of AST, ferritin, total iron binding capacity (TIBC) and transferrin saturation were significantly higher in patients of the significant fibrosis group than in the no/minimal fibrosis group (p = 0.013, 0.006, 0.049 and 0.030, respectively). Seventy-five percent of the patients with elevated serum ferritin had progressed to a stage of advanced fibrosis. In the hepatocellular carcinoma group, the mean ferritin was significantly higher than in the non-HCC group (p = 0.010).

Conclusion: Serum ferritin was normal in all treatments-naive chronic hepatitis C with no-minimal fibrosis. Even with a low sensitivity, a higher level may be useful to identify patients at risk of advanced fibrosis but not for necroinflammation. However, in extremely high levels of ferritin, medical professionals need to beware of the possibility of hepatocellular carcinoma.

Keywords: Chronic hepatitis C infection, Serum iron markers, Liver stiffness

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Chronic hepatitis C (CHC) infection is a chronic disease, which is attributed to 0.58 to 1.22% of the Thai population survey and HCV seropositivity is higher in Northeast regions than urban central regions[1]. From the long-term follow-up, 20% of the patients could develop liver fibrosis, cirrhosis and in an advanced stage, 1 to 3% could develop hepatocellular carcinoma (HCC). Chronic hepatitis C infection causes a disruption of the hepcidin synthesis which result an increase of intestinal iron absorption and iron storage in hepatocyte. The process of storage iron comprises transporting protein in terms of transferrin and ferritin, respectively. Elevated serum iron level induces an increase of ferritin and transferrin saturation and reduction the blood capacity to bind iron with transferrin. All of them are composed of serum iron markers. More excessive iron will produce oxidative stress, lipid peroxidation, induce hepatocyte apoptosis, and can progress to advanced fibrosis[2]. Previous studies showed that patients with elevated serum iron markers may worsen a liver injury in terms of more fibrosis and poor response to treatment[3-5].

In chronic hepatitis C, a significant proportion of patients are in stage of significant fibrosis and asymptomatic[6]. Currently, transient elastography is an efficient and standard instrument which is used to estimate the degree of liver fibrosis but it might not be provided in all hospitals[7]. The objective of the present study was to find the relationship between level of serum iron markers and disease severities in terms of necroinflammation, liver fibrosis, cirrhosis and HCC in treatment-naive urban patients with chronic hepatitis C.

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Materials and Methods

Study population

A cross-sectional study was conducted in the Liver Clinic at Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand, between January to December 2017. A total of 50 treatment-naive-chronic hepatitis C patients were

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enrolled aged between 18 to 80 years. The patients had been diagnosed with chronic hepatitis C from the presence of a serum HCV antibody for at least six months with a qualitative microplate chemiluminescence assay (CLIA). All were examined by laboratory investigations that included liver function test (LFT), complete blood count (CBC), gamma globulin (GGT), interleukin-6 (IL-6), alpha-fetoprotein (AFP), quantitative HCV viral load by using a real-time polymerase chain reaction assay (The COBAS® AmpliPrep/ COBAS® Taqman HCV Test) and HCV genotype. Serum iron, serum ferritin and total iron binding capacity (TIBC) were measured using the reagent from Siemens Healthcare Diagnostics Limited and a Dimension EXL 200 analyser. Transferrin saturation was calculated by the ratio of the serum iron and TIBC values. The exclusion criteria were signs of metabolic syndrome diagnosed by at least three out of five of the following factors (≥90 cm waist circumference in men and ≥80 cm for women, triglycerides ≥150 mg/dl, HDL level ≤40 mg/dl in men and ≤50 mg/dl in women, blood pressure >130/85 mmHg and blood sugar >100 mg/dl), chronic hepatitis B, obesity (body mass index ≥30 kg/m^2), non-HCC malignancy, thalassemia or a transfusion-dependent condition and other chronic diseases; such as HIV infection, chronic renal failure, autoimmune or rheumatologic disease and patients with tense ascites. Diagnosis of HCC was conducted by the use of standard criteria[8].

Measurement of liver stiffness (LS)

The researchers used transient elastography for the measurement of liver stiffness (LS) after the patient had fasted for at least six hours. The transient elastography measured the shear wave velocity (in meters per second). A wave of 50-MHz was transmitted to the liver from a small transducer on the end of an ultrasound probe and converted into liver stiffness, which was expressed in kilopascals. The validation of the measurements was performed by the number of at least 10 valid shots in which the success rate was greater than 60% and the interquartile range (IQR) was less than 30% of the median value. The staging of liver fibrosis was done according to no/mild fibrosis (F0 to F1): 2.5 to 7 kPa, significant fibrosis (F2): 7.1 to 8.8 kPa, advanced fibrosis (F3/F4): 9.5 to 9.6, and 12.5 to 14.6 kPa, respectively[9].

Statistical analysis

Most patients' characteristics were categorized as mean ± standard deviation (SD). Liver stiffness, AFP and GGT were presented as a median (range). The Pearson's product-moment correlation coefficient was used to test the relationship between the aminotransferase level with the serum iron markers. An independent t-test was used to compare the differences between the no/mild fibrosis (F0 to F1) and significant fibrosis (F2 to F4). One-way ANOVA was used to compare the serum iron markers with the subgroups of the serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT). The data analysis was performed with SPSS for Windows version 22.0. The levels of the statistical significance was less than 0.05.

Results

The mean age of the patients was 56.7±11 years and

Table 1. Baseline characteristics of chronic hepatitis C patients (n = 50)

Characteristics	Value
Sex, n (%)	
Male	28 (56)
Female	22 (44)
Age (years)	56.7±11
BMI (kg/m^2)	25.1±4
Platelet (x10^9/L)	175±97
<100	13 (26%)
>100	37 (74%)
Albumin (g/dL)	3.6±0.7
AST (U/L)	76.2±56
<40	11 (22%)
40 to 80	26 (52%)
>80	13 (26%)
ALT (U/L)	78.9±62
<40	11 (22%)
40 to 80	23 (46%)
>80	16 (32%)
AFP (ng/ml)[a]	5.45 (1.0 to 334)
GGT (U/L)[a]	75.5 (43.5 to 169)
Ferritin (ng/mL)	393±377
Serum iron (µg/dL)	110.4±59
Total iron binding capacity (µg/dL)	309±75
Transferrin saturation (%)	37.8±21
Interleukin-6 (pg/ml)	12.2±26
HCV genotype (n = 39)	
No band	8 (20.5%)
1	15 (38.5%)
3	16 (41%)
HCV viral load (log IU/mL)	5.2±2
<6.0	27 (54%)
>6.0	23 (46%)
No cirrhosis	21 (42%)
Child Pugh Score of cirrhosis	
A	19 (38%)
B	10 (20%)
C	0 (0%)
Liver stiffness (kPa)[a]	20.4 (13 to 75)
Stage of liver fibrosis	
F0 to 1	12 (24%)
F2	4 (8%)
F3	5 (10%)
F4	29 (58%)
Hepatocellular carcinoma	
Yes	4 (8%)
No	46 (92%)

Data are presented as mean±standard deviation or number (%)
[a] Data are presented as median (range)
BMI = Body mass index; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; AFP = Alpha-fetoprotein; GGT = Gamma-glutamyltransferase; HCV = Hepatitis C virus
Reference value: Ferritin 13 to 150 ng/mL, Serum iron 60 to 180 mg/dL, Total iron binding capacity 250 to 450 mg/dL, Transferin saturation 15 to 50%

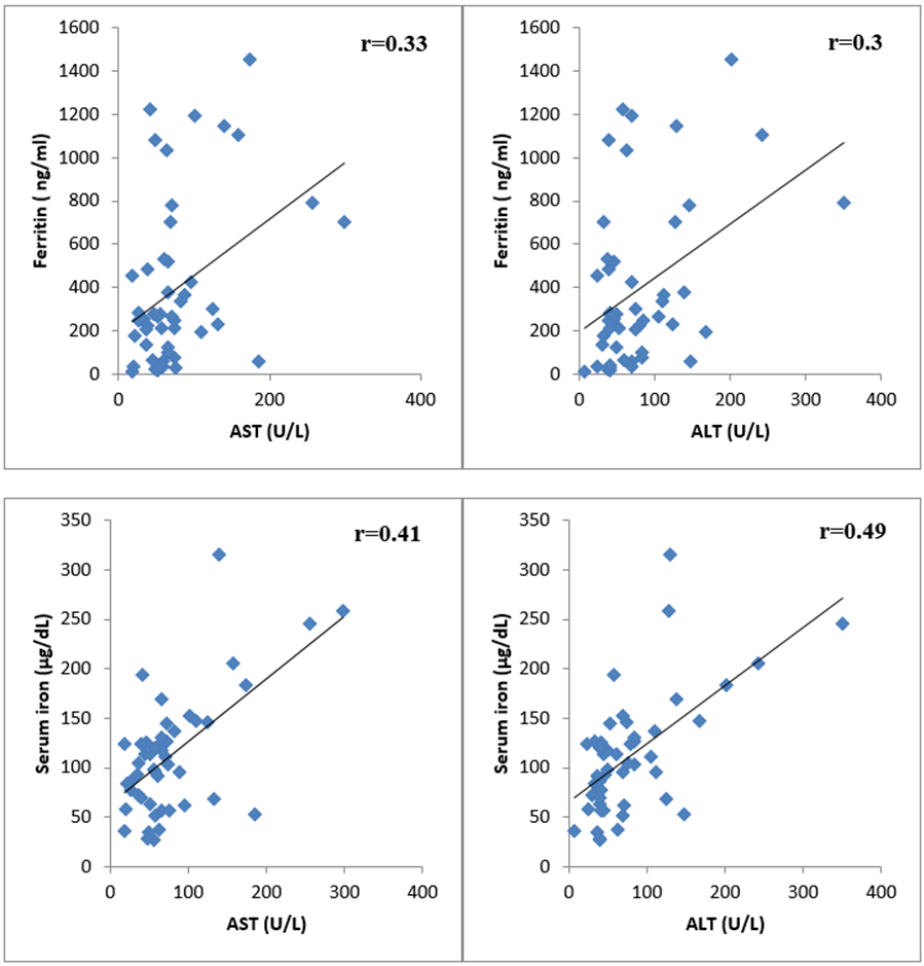

Figure 1. Correlation between serum iron markers and AST, ALT. A) Ferritin and AST. B) Ferritin and ALT, C) Serum iron and AST, D) Serum iron and ALT.

more than half (56%) were male. Eleven patients (22%) had normal serum AST and ALT levels. Twenty-six (52%) and 23 of the patients (46%) had serum AST and ALT levels between 1 to 2 times higher than the upper limit of normal (ULN), respectively while another 13 (26%) and 16 patients (32%) had high serum AST and ALT 2 times higher than ULN. Thirty-seven of the patients (74%) had a platelets level more than $100x10^9$/L. The mean albumin was 3.6±0.7 g/dL. Thirty-four (68%) and 31 patients (62%) had normal serum iron and ferritin levels with a mean of 110.4±59 µg/dL and 393±377 ng/mL, respectively. Forty (80%) and 26 of the patients (52%) had normal TIBC, and the transferrin saturation had a mean of 309±75 µg/dL and 37.8±21%, respectively. Twelve (24%) and 38 patients (76%) had a stage of no/minimal fibrosis and significant fibrosis (F2 to F4), respectively with the median of liver stiffness being 20.4 (13 to 75) kPa. Twenty-nine patients (58%) were diagnosed with cirrhosis, which contributed to Child Pugh score A and Child Pugh score B (38% and 20%, respectively). The researchers did not find any Child Pugh score C in the present study due to the exclusion of ascites. The mean viral load was 5.2±2 log IU/mL, and 54% had a viral load less than 6 log IU/mL. HCV genotype 3 was the most prevalent (41%) followed by genotype 1 (38.5%). In the present study, there were four patients (8%) who were diagnosed with hepatocellular carcinoma.

Correlation between the serum iron markers and severity of liver disease

The mean serum levels of iron ($r = 0.41$, $p = 0.003$; $r = 0.49$, $p<0.001$), ferritin ($r = 0.33$, $p = 0.02$; $r = 0.30$, $p = 0.035$) and transferrin saturation ($r = 0.37$, $p = 0.007$; $r = 0.34$, $p = 0.015$) had significant positive correlations with AST and ALT, respectively (Figure 1). There was an inverse correlation between the mean serum iron ($p = 0.134$), ferritin ($p = 0.827$) and transferrin saturation ($p = 0.163$) and the platelet counts, although a correlation did not reach statistical significance.

A total of 50 patients, 12 (24%) and 38 patients (76%), had no/minimal fibrosis (F0 to F1) and significant fibrosis (F2 to F4), respectively. There was a significant lower number of mean platelets and mean albumin in the significant fibrosis group than in the no/minimal fibrosis group (140.4±70 vs. 284.5±91 x10^9/L, p<0.001) (3.5±0.7 vs. 4±0.6 g/dL, p = 0.028). In the significant fibrosis group, the mean serum levels of AST were significantly higher than in patients of the no/minimal fibrosis group (87.2±58 vs. 41.3±32 U/L, p = 0.013). The mean ALT was also higher in the significant fibrosis group more than in the other groups, but did not reach statistical significance (87.5±65 vs. 51.7±40 U/L; p = 0.08).

The researchers observed significantly higher levels of mean ferritin (445.5±414.6 vs. 226.6±126.1%; p = 0.006), transferrin saturation (40.6±23.6 vs. 29.1±11.8%; p = 0.03) and lower levels of TIBC (297.3±71.7 vs. 346.0±76 µg/dL; p = 0.049) in patients with significant fibrosis than in the group of no/mild fibrosis. The mean serum iron in the significant fibrosis group was higher than in the minimal fibrosis group but did not reach a statistical significant (115.0±65.1 vs. 95.7±37.6 µg/dL, p = 0.33). There was no difference in the HCV viral load between the two groups (5.4±2 vs. 4.8±2 log IU/mL, p = 0.39) (Table 2).

The levels of each aminotransferase were divided in 3 groups (group 1: AST, ALT within normal limit (<40 U/L); group 2: AST, ALT 1 to 2 times above normal limit (40 to 80 U/L), and group 3: AST, ALT more than 2 times above normal limit (>80 U/L). There was a higher ferritin in group 3 than group 1 significantly according to AST (638.3±457 vs. 228.6±147 ng/mL; p = 0.024), but not according to ALT levels (513.7±430 vs. 353.5±336 ng/mL; p = 0.3). In both AST and ALT, the serum iron was also higher in group 3 as compared with group 1 (159.1±80 vs. 84.4±26 µg/dL, p = 0.001), (150.7±74 vs. 73.6±33 µg/dL; p = 0.001) respectively (Figure 2).

There were four patients who developed HCC in this study and all of them were male in a stage of F4 fibrosis. In the HCC group, the mean ferritin was significantly higher than in the non-HCC group (851.3±519 vs. 353.1±341 ng/mL, p = 0.01) (Figure 3a). The researchers also found a trend of higher transferrin saturation in the HCC group without any significance (57.5±33% vs. 36.1±20%; p = 0.06) (Figure 3b). Three of four HCC patients (75%) had a ferritin level of more than 1,000 ng/mL, but in only four of 46 of the non-HCC patients (8.7%) had a ferritin level of more than 1,000 ng/mL.

Discussion

In this real-life study, the researchers had a 76% naive CHC patients were in a stage of significant fibrosis. For significant fibrosis, the subgroup of advanced fibrosis contributed to 87% which were waiting for therapy with direct acting antiviral regimens. From current knowledge, there are many non-invasive tools for detecting liver fibrosis; such as, the AST to Platelet Ratio Index (APRI) and transient elastography measurement, but transient elastography machine is not available in every center. In the present study, the mean ALT in the significant fibrosis group was higher than in the no/minimal fibrosis group but not statistical significant, moreover, 5 of 38 (13.2%) patients in this group had a normal range of ALT. Huang et al studied CHC with persistent normal ALT by following up for 72 weeks and found that almost two-thirds had develop portal fibrosis and 10% had bridging fibrosis[10]. Also, Ahmed et al. found that some proportion of the patients (15%) with normal or mild elevated ALT had initial significant fibrosis[11]. On the other hand, Roshan et al found that a more percentage of patient with persistently normal ALT who had advanced fibrosis compared to those with elevated ALT[12]. So that fibrosis of CHC can develop non-concurrent with necroinflammation.

Thirty-four of 38 (89.4%) patients in the significant fibrosis group were in an advanced fibrotic stage that caused a significantly higher level of AST compared with the no/minimal fibrosis group. As supported in previous studies of

Table 2. Association between stage of liver fibrosis and biochemical markers of chronic hepatitis C

	F0 to F1 (n = 12)	F2 to F4 (n = 38)	p-value
Platelet (x10^9/L)	284.5±91	140.4±70	0.001
Albumin (g/dL)	4±0.6	3.5±0.7	0.028
AST (U/L)	41.3±32	87.2±58	0.013
ALT (U/L)	51.7±40	87.5±65	0.082
AFP (ng/ml)	51.9±109	24.0±43	0.407
Ferritin (ng/mL)	226.6±126	445.5±414	0.006
Abnormal Ferritin >1.5 UNL, n (%)	0 (0)	12 (31.6)	0.049
Serum iron (µg/dL)	95.7±37	115.0±65	0.335
Total iron binding capacity (µg/dL)	346.0±76	297.3±71	0.049
Transferrin saturation (%)	29.1±11	40.6±23	0.031
HCV viral load (log IU/mL)	4.8±2	5.4±2	0.391

Data are presented as mean ± standard deviation
AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; AFP = Alpha-fetoprotein; HCV = Hepatitis C virus

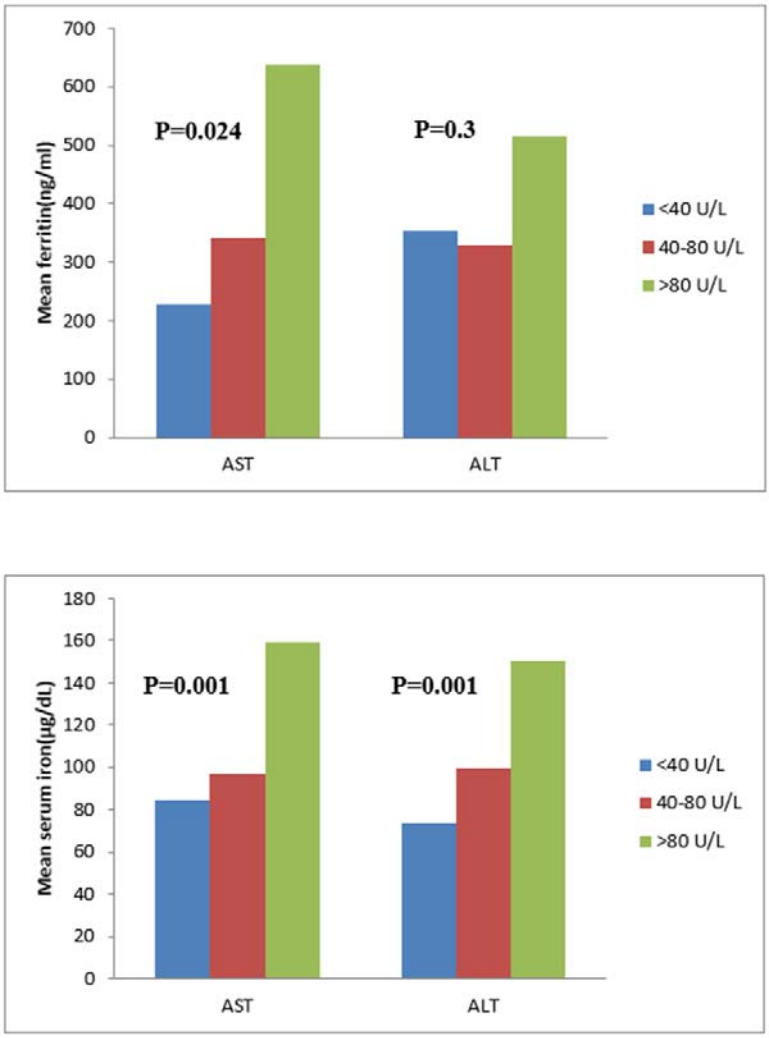

Figure 2. Comparison of (a) ferritin with the groups of both AST and ALT and (b) serum iron with the groups of both AST and ALT.
AST = Aspartate aminotransferase; ALT = Alanine aminotransferase.

naive CHC that found higher AST levels in advanced fibrosis compared with no/minimal fibrosis[13], the researchers of this study could not find any differences of the HCV viral load between the two groups. Neither was there any correlation between the HCV viral load with liver fibrosis nor iron markers. Poynard et al studied that the HCV viral load was not independently associated with the progression of fibrosis progression[14].

Excessive accumulation of iron in the hepatocyte caused an increase in liver apoptosis by the mechanism of oxidative stress induced stellate cells activation, proliferation and finally occurrence of liver fibrosis in CHC. Even the present study showed more than half of the serum iron markers were in a normal range but there was a positive moderate correlation between the level of the mean serum iron and necroinflammation in terms of ALT level. The present study also found mean serum iron was higher in the significant fibrosis group than in the minimal fibrosis group even though not significant according to the small population. Supported by Fujita et al. demonstrated that liver iron deposition was associated with more progression in terms of necroinflammation and fibrosis[15].

Ferritin is a protein that transports iron in the liver. The present study showed the low impact of ALT and ferritin level by demonstrated of nearly one-third (31.2%) of those with elevated ferritin had normal ALT. This can be explained that ferritin may elevated due to chronic infectious process irrespective of necroinflammation.

Thrombocytopenia is an early sign of portal hypertension. This study showed a non-significant inverse

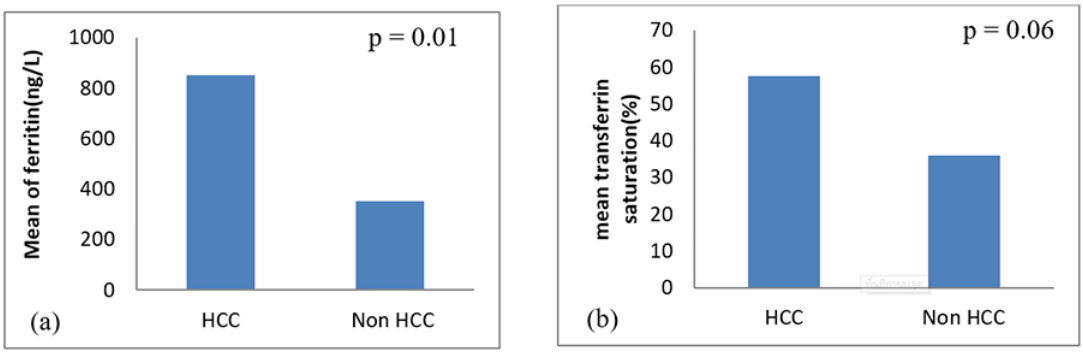

Figure 3. Comparison of (a) mean serum ferritin with the present of HCC and (b) mean transferrin saturation with the present of HCC.
HCC = hepatocellular carcinoma.

correlation between the mean serum iron, ferritin and transferrin saturation and the platelet counts supported by Ripoll et al who found that there was no correlation between ferritin and the hepatic venous pressure gradient and portal hypertension[16].

Significant serum ferritin was reported by Lange et al that high levels were independently associated with advanced liver fibrosis in chronic hepatitis C[17]; furthermore, Kowdley et al reported that serum ferritin above 1.5 of the upper normal limit in nonalcoholic fatty liver disease patients was associated with hepatic iron deposition, worsened histological activity and was an independent predictor of advanced liver fibrosis[18]. None of the patients in the group of no/minimal fibrosis had a serum ferritin above 1.5 UNL compared with 31.6% of those in the significant fibrosis group (p = 0.046), moreover, most of significant fibrosis patients (75%) had advanced fibrosis. This corresponded with the statistical significance between the ferritin and different group-levels of AST, which may conclude that ferritin is one of many indirect biomarkers in which a high level represents a stage of advanced fibrosis. However, most of the patients in the significant fibrosis group (68.5%) and cirrhotic group (70%) still had serum ferritin below 1.5 UNL. Angulo et al reported that the serum levels of ferritin correlated with more severe liver fibrosis, but the levels alone had a low sensitivity for the presence of liver fibrosis in patients with NAFLD[19]. A study of Insiripong et al reported that nearly half (46.7%) of non-hemochromatosis cirrhotic Thai patients had extremely elevated ferritin levels (>1,000 ng /ml)[20]. An extremely high ferritin level contributed to five out of 29 of the cirrhotic patients (17.2%) of this present study, which was the lesser incidence than previous reported. Uchino et al reported that serum ferritin level is an independent risk factor for HCC development in male patients with chronic hepatitis C[21]. Even though there was a low percentage of extremely high ferritin in this study, three out of seven of the patients (42.9%) with very high ferritin developed HCC. The researchers found four cases of HCC and all of them had a serum AFP less than 200 ng/ml. Three out of four HCC patients (75%) had extremely elevated ferritin levels compared with four out of 46 non-HCC patients (8.7%). Patil et al found an independent association between the serum ferritin levels and HCC occurrence in chronic liver disease of viral etiology[22].

The limitations of the present study were having an inadequate sample size in each group to conduct a multivariate analysis. Also, the present study could not include Child Pugh score C cirrhotic ascites due to the inability to measure liver stiffness, which is a more advanced liver disease.

Conclusion

Serum ferritin is normal in all treatments-naive chronic hepatitis C with no/minimal fibrosis. Even though there could be low sensitivity, a higher level may be useful to identify patients at risk for advanced fibrosis but not for degree of necroinflammation. Ferritin may be a benefit in the center which transient elastography was not available. Furthermore, medical professionals need to be aware that patients with an extremely high level of ferritin may be looking for hepatocellular carcinoma, especially in cases that are non-diagnosed by AFP.

What is already known on this topic?

There was a moderate positive relationship between serum iron/serum ferritin and degree of liver fibrosis in chronic hepatitis C.

What this study adds?

An extremely high level of ferritin in chronic hepatitis C may be looking for hepatocellular carcinoma.

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Potential conflicts of interest

The authors declare no conflict of interest.

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