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ORIGINAL ARTICLE

Elevated serum ferritin level associated with hepatic steatosis and fibrosis in hepatitis C virus–infected patients

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Abstract

Background: Serum ferritin is an indicator of iron accumulation in a human body, and it is frequently elevated in patients with systemic inflammatory state in chronic hepatitis C (CHC). Iron accumulation is associated with hepatic fibrosis, steatosis, and unfavorable outcome in CHC patients. We studied the status of elevated serum ferritin level and its association with the liver fibrosis or steatosis in Taiwanese CHC patients.

Methods: Seven hundred and thirty-eight Taiwanese CHC patients were consecutively included in this study. Laboratory analysis, four indexes of fibrosis (FIB4), histological assessment of fibrosis, and steatosis were assessed by appropriate elevation of serum ferritin level.

Results: Three hundred and one patients (40.8%) had elevated serum ferritin level (sex-specific threshold >1.5 × upper limit of normal). Serum iron level (odds ratio [OR], 1.02; 95% CI, 1.01%-1.03%, $p < 0.001$), female gender (OR, 1.49; 95% CI, 1.07%-2.08%, $p = 0.018$), serum gamma-glutamyl transferase level (OR, 1.007; 95% CI, 1.003%-1.01%, $p < 0.001$), steatosis grade (OR, 1.56; 95% CI, 1.13%-2.16%, $p = 0.006$), and FIB4 ≥3.25 (OR, 1.63; 95% CI, 1.18%-2.27%, $p = 0.003$) indexes were associated with high serum ferritin level by multivariate logistic regression analysis. Patients with steatosis (>5%) were associated with older age (OR, 1.01; 95% CI, 1.00%-1.03%, $p = 0.015$), body mass index (OR, 1.10; 95% CI, 1.05%-1.15%, $p < 0.001$), and elevated serum ferritin level (OR, 1.001; 95% CI, 1.00%-1.001%, $p = 0.024$) by multivariate logistic regression analysis. Serum ferritin level also associated with high FIB4 (≥3.25) (OR, 1.001; 95% CI, 1.001%-1.002%, $p = 0.010$) when multivariate model adjusted together with advanced liver fibrosis by biopsy.

Conclusion: Elevated serum ferritin level was noted in 40.8% of Taiwanese CHC patients, and the serum ferritin level was associated with liver steatosis and high FIB4.

Keywords: CHC; Ferritins; FIB4; HCV; Liver cirrhosis

1. INTRODUCTION

Globally over 170 millions of people were infected by hepatitis C virus (HCV), a prevalence of 2.8% to 3% of the World population, and it is a serious burden to global health.[1] Up to 20% of patients with chronic hepatitis C (CHC) would develop liver cirrhosis, and >25% of patients who had cirrhosis would develop severe liver failure or hepatocellular carcinoma and needed liver transplantation.[2] Host genetic background, HCV viral load and genotype, and environmental factors are the risk for the clinical manifestation and progression of the liver failure. However, HCV interferes with the host iron metabolism, and it is related to the increased hepatic and serum iron components.[3]

An elevated serum ferritin level is associated with some chronic liver diseases such as nonalcoholic fatty liver disease, nonalcoholic steatohepatitis,[4] steatosis caused by HCV, and liver fibrosis progression[5] and is also related to HCV treatment outcome.[6] Elevated serum ferritin level has also been previously observed in obesity-related chronic inflammatory conditions, such as diabetes and metabolic syndrome.[7] Also elevated serum ferritin level can predict early mortality of patients with decompensated liver cirrhosis as a surrogate marker.[8] Cutoff point of the serum ferritin level was calculated as 350 ng/mL in women and 450 ng/mL in men to predict advanced hepatic iron deposit in a report from Italy.[9]

An elevated serum ferritin level has been reported to be linked to *HFE* gene mutation and hereditary hemochromatosis, but the prevalence of *HFE* gene mutations are extremely low in

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Taiwanese CHC patients.[10] However, Lin et al[11] reported that both serum and hepatic iron depositions did not relate to grade or stage of liver histology. Therefore, we studied the status of elevated serum ferritin level and its association with the liver fibrosis or steatosis in a large number of Taiwanese CHC patients.

2. METHODS

In total, 738 Taiwanese patients who underwent a diagnostic liver biopsy before treatment at Kaohsiung Medical University Hospital, a tertiary medical center, were included in this study. All patients infected with HCV were proven seropositive for anti-HCV antibody. None of the patients included in this study were positive for hepatitis B virus and human immunodeficiency virus; we also excluded patients who drink >60 g of alcohol per day, and those with hereditary hemochromatosis and hepatocellular carcinoma.

Before the initiation of HCV treatment, general demographic characteristics and serum biochemical analyses using commercial tests were performed. These included glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), gamma-glutamyl transferase (GGT), alpha fetoprotein (AFP), and platelet counts. Biochemical tests and complete blood counts including serum ferritin and iron levels were performed using a standard autoanalyzer. The serum level of HCV-RNA was measured using RT-PCR method and Cobas Amplicor HCV test, V2.0 (Roche Diagnostics, Branchburg, NJ). For calculating body mass index (BMI), we used following formula: weight in kilogram/(height in meter)^2. Liver biopsy was performed by a single pathologist who was blind to the treatment. Liver biopsy was evaluated according to the METAVIR scoring system, and the degree of steatosis was graded in four stages (grade 0, <5%; grade 1, 5%-33%; grade 2, 34%-66%; grade 3, >66%). Serum ferritin was considered elevated if it was >350 ng/mL in women and >450 ng/mL in men. The four indexes of fibrosis (FIB4) were calculated to describe advanced fibrosis. We used following formula to calculate FIB4[12]:

$$\text{FIB4} = \frac{(\text{age [years]} \times \text{GOT [U/L]})}{(\text{Platelet } [10^9/\text{L}] \times \sqrt{\text{GPT}}\ \text{[U/L]})}.$$

Aspartate aminotransferase to platelet ratio index (APRI) was calculated by the following formula.[13]

$$\frac{(\text{GOT [U/L]}/\text{GOT [upper limit of normal range]})}{\text{Platelet } [10^9/\text{L}]}.$$

2.1. Statistical analysis

Analyzing the relation between serum ferritin level and other variables of interest, we defined sex-specific serum ferritin level as a dichotomous variable with 350 ng/mL in women and >450 ng/mL in men, a 1.5-fold increased value of normal ferritin level in serum. Descriptive statistics were applied for data distribution, mean, and standard deviation. Group means were compared using analyses of variance and Students *t* test for parametric or nonparametric test. For association between baseline predictors of both serum ferritin level and hepatic steatosis score, we used a multiple logistic, linear regression, and Fishers exact or chi-square tests were performed when appropriate. All statistical analyses were performed using the IBM SPSS Statistics, version 20 and original patient's data gathered in Microsoft Excel software. All statistical analyses were based on two-sided hypothesis tests with a significance level of $p < 0.05$.

3. RESULTS

3.1. Associated factors for sex-specific high ferritin level

All patients were separated into two groups by sex-specific, 1.5-fold increased serum ferritin level, and the basic characteristics of 738 patients are summarized in Table 1. The percentage of female patients with 1.5-fold high serum ferritin level was higher compared with the percentage of those with lower serum ferritin level (48.8% vs 40.5%; $p = 0.025$). An elevated ferritin level was associated with older age (55.3 ± 9.2 vs 52.0 ± 11.2; p=0.0001), the presence of diabetes (21.4% vs 13.9%; $p = 0.008$), the presence of steatosis (13.3% vs 5.9%; $p = 0.001$), and the stage of fibrosis ($p = 0.044$). Therefore, BMI, HCV genotype, and viral load were not so important for high ferritin level. However, serum biochemical parameters were associated with sex-specific high ferritin level and simple, noninvasive predictor

Table 1

Demographic comparison between patients with and without increase of ferritin

Characteristics	Total, N = 738	<1.5 × ULN, ng/mL, N = 437	≥1.5 × ULN, ng/mL, N = 301	*p*
Sex, N (%)				
Male	414 (56.1)	260 (59.5)	154 (51.2)	0.025
Female	324 (43.9)	177 (40.5)	147 (48.8)	
Age, mean ± SD, y	53.3 ± 10.6	52.0 ± 11.2	55.3 ± 9.2	0.0001
BMI, mean ± SD, kg/m^2	25.0 ± 3.4	24.9 ± 3.4	25.3 ± 3.3	0.119
HCV type, n (%)				
1	373 (50.5)	228 (52.2)	145 (48.2)	0.285
Other	365 (49.5)	209 (47.8)	156 (51.8)	
Diabetes, n (%)				
Yes	123 (17)	59 (13.9)	64 (21.4)	0.008
No	600 (83)	365 (86.1)	235 (78.6)	
HCV-RNA, log IU/mL, mean ± SD	5.4 ± 2.1	5.3 ± 2.2	5.4 ± 2.0	0.431
Steatosis, n (%)				
>34%	66 (8.9)	26 (5.9)	40 (13.3)	0.001
<33%	672 (91.1)	411 (94.1)	261 (86.7)	
Fibrosis grade, n (%)				
F0	78 (10.6)	54 (12.4)—69.2%	24 (8)—30.8%	0.044
F1	220 (29.8)	140 (32)—63.6%	80 (26.6)—36.4%	
F2	223 (30.2)	120 (27.5)—53.8%	103 (34.2)—46.2%	
F3	119 (16.1)	63 (14.4)—52.9%	56 (18.6)—47.1%	
F4	98 (13.3)	60 (13.7)—61.2%	38 (12.6)—38.8%	

BMI = body mass index; HCV = hepatitis C virus; ULN = upper limit of normal.

Table 2

Comparison of laboratory parameters in sex-specific 1.5-fold increase of ferritin

Characteristics	Total, N-738	<1.5 × ULN, ng/mL, N = 437		≥1.5 × ULN, ng/mL, N = 301		p
		N	Value	N	Value	
GOT, U/L	106.2 ± 55.3	437	99.7 ± 54.8	301	115.7 ± 54.7	<0.0001
GPT, U/L	157.4 ± 83.8	437	147.7 ± 81.3	301	171.5 ± 85.5	<0.0001
GGT, U/L	66.0 ± 48.1	437	58.4 ± 41.4	301	77.1 ± 54.7	<0.0001
Platelet, 10^9/L	161.5 ± 58.6	437	168.1 ± 62.3	301	151.9 ± 51.3	<0.0001
AFP, ng/mL	16.0 ± 24.1	437	12.6 ± 18.3	301	21.1 ± 30.0	<0.0001
Iron, μg/dL	42.3 ± 19.7	433	38.7 ± 16.1	301	47.5 ± 23.1	<0.0001
Triglycerides, mg/dL	103.5 ± 55.6	320	99.1 ± 60.3	219	109.8 ± 47.3	0.027
Cholesterol, mg/dL	168.5 ± 33.2	319	168.1 ± 34.0	220	169.0 ± 32.1	0.750
APRI	1.7 ± 1.4	437	1.6 ± 1.3	301	1.9 ± 1.4	<0.0001
FIB4	3.5 ± 2.9	437	3.3 ± 3.0	301	3.9 ± 2.8	0.010

Results in mean ± standard deviation.

AFP = alpha fetoprotein; APRI = aspartate aminotransferase to platelet ratio index; FIB4 = four indexes of fibrosis; GGT = gamma-glutamyl transferase; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; ULN = upper limit of normal.

Table 3

Multivariate analysis of associated factors for the sex-specific increase of serum ferritin

Characteristic	OR	95% CI	p
Female gender	1.49	1.07-2.08	0.018
GGT	1.007	1.003-1.011	<0.0001
Iron	1.02	1.01-1.03	<0.0001
Steatosis score (>5%)	1.56	1.13-2.16	0.006
FIB4 (≥3.25)	1.63	1.18-2.27	0.003
BMI	1.02	0.97-1.06	0.400

BMI = body mass index; FIB4 = four indexes of fibrosis; GGT = gamma-glutamyl transferase.

of liver fibrosis FIB4 (3.9 ± 2.8 vs 3.3 ± 3.0; p = 0.010) and APRI (1.9 ± 1.4 vs 1.6 ± 1.3; p = 0.0001) (Table 2). Multivariate logistic regression analysis revealed that female gender, serum GGT, iron level, the presence of steatosis, and FIB4 (>3.25) scores were significantly associated with the sex-specific high ferritin level (Table 3).

3.2. Associated factors for the presence of steatosis

The presence of steatosis was associated with older age (54.4 ± 10.9 vs 52.3 ± 10.2; p = 0.007), BMI (25.6 ± 3.3 vs 24.4 ± 3.4; p = 0.0001), and advanced fibrosis (34% vs 25%; p = 0.007). Therefore, gender, HCV genotype, and viral load were not so important for the presence of steatosis (Table 4). However, serum biochemical parameters such as GGT, triglycerides, and ferritin were associated with steatosis (Table 5). Multivariate logistic regression analysis revealed that age (OR, 1.01; 95% CI, 1.00%-1.03%; p = 0.015), BMI (OR, 1.10; 95% CI, 1.05%-1.15%; p = 0.0001), and serum ferritin (OR, 1.001; 95% CI, 1.0000%-1.001%; p = 0.024) were significantly associated with the presence of steatosis (Table 6).

3.3. Associated factors for the advanced fibrosis

We used FIB4 score to adjust patients by a cutoff point of 3.25 to reveal associated factors for advanced fibrosis. All patients were separated into two groups by FIB4 score, and the basic characteristics of 738 patients are summarized in Table 7. The percentage of female patients with high serum ferritin was higher compared with that of male patients (57.8% vs 34.3%; p = 0.0001). Advanced fibrosis was associated with older age (59.5 ± 7.7 vs 49.1 ± 10.2; p = 0.0001; FIB4 score included age), the presence of diabetes (21.2% vs 14.1%; p = 0.012), and moderate fibrosis grade (46.8% vs 17.4%; p = 0.0001). Therefore, BMI, HCV genotype, and viral load were not so important for fibrosis. However, serum biochemical parameters such as GOT, GPT, and platelet were associated with FIB4 score because of its component. GGT, AFP, ferritin, and noninvasive maker for fibrosis APRI were associated with FIB4 but not serum iron level (Table 8). Multivariate logistic regression analysis revealed that female gender, serum AFP, fibrosis by biopsy, the presence of diabetes, and ferritin were significantly associated with high FIB4 score (Table 9).

4. DISCUSSION

In this study, we show that serum ferritin was independently associated with the presence of steatosis and high FIB4 score. We adopted a cutoff point of 350 ng/mL in women and 450 ng/mL in men to calculate the association from the study by Sebastiani et al.[9] The sex-specific cutoff for serum ferritin maybe useful to predict liver steatosis and fibrosis, but additional studies are needed for validation.

In our study, high serum ferritin levels were strongly associated with steatosis and fibrosis in CHC patients. Also Vagu et al[14] reported that an elevated serum ferritin level can represent an early marker for the severity of chronic liver disease, related to the degree of liver steatosis grade. In multivariate model, these associations remained strongly significant. However, Rubbia-Brandt et al[15] described that HCV genotype 3 is important for liver steatosis, but HCV genotype 3 is rare in Taiwan. In our study, according to subanalyses, the association between serum ferritin and steatosis remained significant in both univariate and multivariate analyses in patients with HCV genotypes 1 and 2.

We focused on to investigate the possible role of serum iron and ferritin in the development of liver steatosis. The mechanism of steatosis in HCV infection remains uncertain, which is considered including multifunctional iron overload and insulin resistance (IR). Bugianesi et al[16] studied that the IR has association with both serum ferritin level and steatosis grade. However, our study generally supports that elevated serum ferritin level occurs in type 2 diabetes, and diabetes is one of the main risk factors of increased ferritin level in HCV-infected patients by univariate analysis. In other hand, HCV may induce IR by itself in disease progression and genotype specific way.[17]

In CHC, serum ferritin can be elevated because of HCV-induced downregulation of hepcidin. Liu et al[18] proved that HCV can inhibit hepcidin mRNA in Huh7.5 cell line followed by increased hepatic iron. Accumulated iron can lead to oxidative stress, hepatic fibrosis, and cirrhosis. They also reported that hepcidin reduced HCV replication in Huh7.5 cell line.[19] Increased iron can influence the HCV replication but is more likely to contribute to disease by potentiating oxidative stress,

Table 4

Univariate analysis of associated factors with the steatosis <5% vs >5%

Characteristics	Total, N = 738	Steatosis 0%-5%, N = 376	Steatosis >5%, N = 362	*p*
Sex, N (%)				
Male	414 (56.1)	219 (58.2)	195 (53.9)	0.231
Female	324 (43.9)	157 (41.8)	167 (46.1)	
Age, mean ± SD, y	53.3 ± 10.6	52.3 ± 10.2	54.4 ± 10.9	0.007
BMI, mean ± SD, kg/m^2	25.0 ± 3.4	24.4 ± 3.4	25.6 ± 3.3	0.0001
HCV type, n (%)				
1	373 (50.5)	195 (51.9)	178 (49.2)	0.465
Other	365 (49.5)	181 (48.1)	184 (50.8)	
Diabetes, n (%)				
Yes	123 (17)	55 (14.8)	68 (19.3)	0.108
No	600 (83)	316 (85.2)	284 (80.7)	
HCV-RNA, log IU/mL, mean ± SD	5.4 ± 2.1	5.3 ± 2.2	5.4 ± 2.1	0.691
Fibrosis grade				
F0-F2	521 (70.6)	282 (75)	239 (66)	0.007
F3-F4	217 (29.4)	94 (25)	123 (34)	

BMI = body mass index; HCV = hepatitis C virus.

Table 5

Univariate analysis of laboratory parameters with the steatosis <5% vs >5%

		Steatosis 0%–5%, N = 376		Steatosis >5%, N = 362		
Characteristics	Total, N = 738	N	Value	N	Value	*p*
GOT, U/L	106.2 ± 55.3	376	106.4 ± 58.2	362	106.1 ± 52.3	0.943
GPT, U/L	157.4 ± 83.8	376	156.7 ± 87.2	362	158.1 ± 80.2	0.827
GGT, U/L	66.0 ± 48.1	376	60.0 ± 44.9	362	72.3 ± 50.5	0.0001
Platelet, 10^9/L	161.5 ± 58.6	376	163.3 ± 59.5	362	159.6 ± 57.6	0.395
AFP, ng/mL	16.0 ± 24.1	376	15.2 ± 27.1	362	17.0 ± 20.6	0.319
Ferritin, ng/mL	392.6 ± 245.2	376	368.1 ± 237.1	362	418.0 ± 251.1	0.006
Iron, μg/dL	42.3 ± 19.7	374	43.5 ± 20.9	360	41.0 ± 18.4	0.092
Triglycerides, mg/dL	103.5 ± 55.6	255	95.3 ± 41.8	284	110.7 ± 64.8	0.001
Cholesterol, mg/dL	168.5 ± 33.2	255	166.9 ± 35.5	284	169.8 ± 31.1	0.319

Results in mean ± standard deviation.

AFP = alpha fetoprotein; GGT = gamma-glutamyl transferase; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase.

Table 6

Multivariate analysis for the associated factors for steatosis

Characteristic	OR	95% CI	*p*
Age	1.01	1.00-1.03	0.015
Advanced fibrosis	1.29	0.92-1.80	0.133
Ferritin	1.001	1.00-1.001	0.024
BMI	1.10	1.05-1.15	0.0001

BMI = body mass index.

which leads to chronic inflammation. In most studies, HCV viral load does not correlate with disease.[20]

Sumida et al[5] described that there was a significant strong relations does exist between hepatic fibrosis and steatosis analyzed by linear modeling. The mechanism of this theory is steatosis that has positive correlation in lipid peroxidation and hepatic fibrosis. In fact, the elevation of marker of oxidative stress, serum thioredoxin, has an association with hepatic fibrosis and the serum lipid peroxide level in HCV-infected patients.[5] In our study, there was significant correlation between liver steatosis and hepatic fibrosis grade in univariate analysis but not in multivariate logistic regression analysis.

Steatosis and elevated serum ferritin levels were associated with elevated GGT level as a result of lipid peroxidation and development of hepatocellular carcinoma.[21] Serum GGT level is considered a marker of severe liver diseases in CHC[22] and liver fat deposition.[23] An elevated serum ferritin level served to predict the sign of hepatic steatosis in nonalcoholic fatty liver disease,[4] and also elevated serum GGT level is considered to be associated with liver steatosis in HCV-infected patients.[24]

In this study, advanced fibrosis and serum ferritin correlated with steatosis. However, Fierbinţeanu-Braticevici et al[25] described that severe steatosis predicted advanced fibrosis in CHC patients and IR contributed to fibrosis progression.

Fibrosis, steatosis, and serum ferritin are important in CHC progression. Interaction between fibrosis, steatosis, and serum ferritin in pathogenesis of CHC still remains uncertain. FIB4 is an accurate noninvasive marker to predict liver fibrosis.[12] This is the first study to investigate the relations between serum ferritin and liver fibrosis by using FIB4 score. Serum ferritin level was significantly associated with high FIB4 score in univariate and multivariate analyses.

This study has few strengths and limitations. The strengths include the large sample size and all patients with the liver biopsy to diagnose steatosis and available data to calculate FIB4. Therefore, the multivariate regression analysis was accurately calculated to evaluate association between serum ferritin and moderate steatosis, advanced fibrosis by FIB4. On the other hand, there were limitations, including we did not consider about hereditary hemochromatosis and *HFE* gene because of extremely rare occurrence in Taiwan; also *HFE* gene mutations played minor role in elevating serum ferritin or iron in Taiwanese CHC patients.[10] It is also unclear that our findings may be extrapolated to the patients for other ethnicities; however, in this study we included Taiwanese patients.

Table 7

Univariate analysis of associated factors with high FIB4

Characteristics	Total, N = 738	FIB4 <3.25, N = 437	FIB4 ≥3.25, N = 301	*p*
Sex, N (%)				
Male	414 (56.1)	287 (65.7)	127 (42.2)	<0.0001
Female	324 (43.9)	150 (34.3)	174 (57.8)	
Age, mean ± SD, y	53.3 ± 10.6	49.1 ± 10.2	59.5 ± 7.7	<0.0001
BMI, mean ± SD, kg/m^2	25.0 ± 3.4	25.1 ± 3.5	25.0 ± 3.3	0.856
HCV type, n (%)				
1	373 (50.5)	225 (51.5)	148 (49.2)	0.536
Other	365 (49.5)	212 (48.5)	153 (50.8)	
Diabetes, n (%)				
Yes	123 (17)	60 (14.1)	63 (21.2)	0.012
No	600 (83)	366 (85.9)	234 (78.8)	
HCV-RNA, log IU/mL, mean ± SD	5.4 ± 2.1	5.4 ± 2.2	5.3 ± 2.0	0.652
Fibrosis grade, n (%)				
F0-F2	521 (70.6)	361 (82.6)	160 (53.2)	<0.0001
F3-F4	217 (29.4)	76 (17.4)	141 (46.8)	
Steatosis, n (%)				
Yes	66 (8.9)	36 (8.2)	30 (10)	0.419
No	672 (91.1)	401 (91.8)	271 (90)	

BMI = body mass index; FIB4 = four indexes of fibrosis; HCV = hepatitis C virus.

Table 8

Univariate analysis of laboratory parameters with high FIB4

		FIB4 <3.25, N = 437		FIB4 ≥3.25, N = 301		
Characteristics	Total, N = 738	N	Value	N	Value	*p*
GOT, U/L	106.2 ± 55.3	437	85.9 ± 43.7	301	135.7 ± 57.2	<0.0001
GPT, U/L	157.4 ± 83.8	437	151.0 ± 85.0	301	166.6 ± 81.2	0.013
GGT, U/L	66.0 ± 48.1	437	61.6 ± 44.9	301	72.5 ± 51.8	0.003
Platelet, 10^9/L	161.5 ± 58.6	437	192.7 ± 49.1	301	116.2 ± 38.1	<0.0001
AFP, ng/mL	16.0 ± 24.1	437	8.6 ± 8.9	301	26.9 ± 33.4	<0.0001
Ferritin, ng/mL	392.6 ± 245.2	437	362.2 ± 223.7	301	436.7 ± 267.6	<0.0001
Iron, μg/dL	42.3 ± 19.7	436	41.4 ± 20.9	298	43.6 ± 17.9	0.133
APRI	1.7 ± 1.4	437	1.0 ± 0.5	301	2.8 ± 1.5	<0.0001

Results in mean ± standard deviation.

AFP = alpha fetoprotein; APRI = aspartate aminotransferase to platelet ratio index; FIB4 = four indexes of fibrosis; GGT = gamma-glutamyl transferase; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase.

Table 9

Multivariate analysis for the associated factors for high FIB4 (≥3.25)

Characteristics	OR	95% CI	*p*
Female	2.40	1.67-3.44	<0.0001
AFP	1.05	1.04-1.07	<0.0001
Fibrosis F3, F4	3.23	2.20-4.76	<0.0001
Diabetes	1.29	0.82-2.04	0.263
Ferritin	1.00	1.00-1.002	0.010

AFP = alpha fetoprotein; FIB4 = four indexes of fibrosis.

In conclusion, we show that serum ferritin is strongly associated with the presence of steatosis in liver and high noninvasive fibrosis marker FIB4. The sex-specific cutoff for serum ferritin maybe used to evaluate the steatosis in clinic, but further investigation is needed.

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