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Chronic hepatitis C virus infection

Relationships between inflammatory marker levels and compensated liver cirrhosis

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Abstract

We investigated associations between inflammatory marker levels and hepatitis C virus (HCV)-related compensated liver cirrhosis risk in patients with chronic hepatitis C (CHC) infection in China. We used a case-control design and data from the records of 110 Chinese patients with CHC and cirrhosis for the study; 458 CHC patients who did not have a diagnosis of cirrhosis were matched to the case group by age and sex characteristics. We also investigated fatty liver disease risk factors. The group of patients with CHC infection and cirrhosis had lower platelet-to-lymphocyte ratio (PLR) values (60.63 [44.09, 89.31]) compared with the control group patients (80.24 [57.85, 111.08]). The results indicated that the group of patients with cirrhosis had higher 4-factor fibrosis index and aspartate aminotransferase (AST)-to-platelet ratio index (APRI) values compared with the group of patients with CHC-only (1.66 [0.98, 2.60] vs 0.71 [0.45, 1.17], respectively; $P < .001$ and 2.12 [0.97, 4.25] vs 0.99 [0.51, 2.01], respectively; $P < .001$). Compared with the control group, the AST/alanine aminotransferase ratio (AAR) values in the group of patients with cirrhosis were significantly higher ($P < .001$). Logistic regression analysis that included model adjustment for demographic characteristics and other factors that could affect cirrhosis risk revealed that greater 1/PLR values were associated with an increased odds of having cirrhosis (adjusted odds ratio [AOR], 95% confidence interval [CI] 0.991 [0.985–0.996]); APRI and AAR values were also independent predictors of the presence of compensated cirrhosis. We found that compared with the patients with CHC-only, the triglyceride, cholesterol, and low-density lipoprotein cholesterol levels in the patients with both CHC and fatty liver disease were significantly higher. The multivariate analysis of the risk of fatty liver development in patients with CHC infection found that cholesterol level was a statistically significant risk factor (AOR [95% CI] 1.380 [1.089–1.750], $P = .008$). Increased 1/PLR, APRI, and AAR values were associated with increased risks for development of cirrhosis in this population of Chinese patients with CHC infection. Higher cholesterol levels increased the risk of development of fatty liver disease in patients with CHC.

Abbreviations: AAR = aspartate aminotransferase-to-alanine aminotransferase ratio, ALT = alanine aminotransferase, AOR = adjusted odds ratio, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, CHC = chronic hepatitis C, CI = confidence interval, CT = computed tomography, FIB4 = 4-factor fibrosis index, GGT = gamma-glutamyl transferase, HBV= hepatitis B virus, HDL-C = high-density lipoprotein cholesterol, HCV= hepatitis C virus, LDL-C = low-density lipoprotein cholesterol, MRI = magnetic resonance imaging, NAFL = nonalcoholic fatty liver, NASH = nonalcoholic steatohepatitis, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, TBA = total bile acids, TBIL = total bilirubin, TG = triglyceride.

Keywords: chronic hepatitis C virus, compensated liver cirrhosis, inflammatory marker levels

1. Introduction

The prevalence of cirrhosis, which typifies end-stage chronic hepatic disease, is increasing worldwide.[1,2] Leading causes of cirrhosis in Chinese patients with liver disease include hepatitis C virus (HCV) and hepatitis B virus (HBV) infections, and excessive consumption of alcohol. Compared with other hepatitis virus infections, the effects of HCV infection are more severe and have greater systemic effects.[3]

Hepatitis C virus infection is characterized by gradual progression and the absence of apparent symptoms during the first decade. The liver-related symptoms appear during the later stages of infection.[4] Compared with HBV infection, infection with HCV is more likely to progress to cirrhosis and hepatocellular carcinoma (HCC).[5]

Liver biopsy is invasive and is ineffective for dynamic monitoring of liver disease status. Measurements of the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AAR), the AST-to-platelet ratio index (APRI),[6] and the 4-factor fibrosis index (FIB4)[7] are used for noninvasive monitoring and to assess disease severity. Study results indicate that platelet-to-lymphocyte

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ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) levels are independent risk factors for various diseases.[8–10] However, few articles on associations between NLR, PLR, and compensated cirrhosis in patients with hepatitis C have been published.[5,11]

Twenty to thirty per cent of patients with chronic HCV infection also have the nonalcoholic fatty liver (NAFL) disease.[12,13] Progressive fibrosis and cirrhosis are more likely to occur in patients with nonalcoholic steatohepatitis (NASH) with chronic HCV infection than in those without HCV infection.[14] Identification of patients with HCV infection and NASH will help predict those at greater risk of the progressive fibrosis, cirrhosis, and HCC, even after the HCV infection is no longer detectable after the use of antiviral therapy.

We performed a case-control study to investigate associations between levels of inflammatory markers and cirrhosis risk in patients with chronic hepatitis C (CHC). The design included controlling for factors associated with cirrhosis risk. We also included an analysis of risk factors for NAFL disease.

2. Methods

2.1. Study design and patient selection

A cross-sectional case-control study design was used to investigate factors associated with an increased cirrhosis risk in patients with CHC infection. The patients had varying lengths of hospital stays (The First Hospital of Jilin University, Changchun, China) between January, 2013 and December, 2016. All methods were carried out in accordance with the approved guidelines. The presence of plasma anti-HCV antibodies and serum HCV RNA for ≥6 months was used to identify the 720 patients with chronic HCV infection who were initially recruited for the study. In all, 110 patients had compensated cirrhosis (ie, cases). After matching the other patients with the patients in the case group by sex and age, there were 458 patients in the control group.

The criteria used to exclude subjects were: HBV co-infection or human immunodeficiency virus co-infection; clinical evidence or history of cancer; clinical evidence or history of infection with 1 or more other hepatitis virus; other hepatic disease (eg, alcoholic liver disease [alcohol consumption for males ≥40 g/d and for females ≥20 g/d]).

2.2. Diagnosis of compensated cirrhosis, fatty liver disease

Liver biopsy results or endoscopy with esophageal varices, excluding noncirrhotic portal hypertension,[15] or combined clinical findings, biochemistry, and radiology results were used to diagnose the presence of compensated cirrhosis. A Child-Pugh score of A was a requirement for inclusion in the compensated cirrhosis group.

Abdominal ultrasonography findings of areas of liver brightness and diffuse echogenic changes in the hepatic parenchyma were required for the diagnosis of fatty liver.

The study protocol, including the procedures used for the recruitment of human subjects, was approved by the Independent Institutional Review Board of The First Hospital of Jilin University. Each patient provided written informed consent at the time of enrollment in the study.

2.3. FIB4 index and AST-to-platelet ratio index scores

The FIB4 score was calculated using[7]:

$$\text{FIB4 Index} = [\text{age (years)} \times \text{AST(U/L)}]/[\text{platelet count(PLT)}\,(10^9/\text{L}) \times \text{ALT(U/L)}^{1/2}]$$

The APRI score was calculated using[6]:

$$\text{APRI} = (\text{AST}/\text{upper limit of normal})/\text{PLT}(10^9/\text{L}) \times 100$$

$$\text{Upper limit of AST} = 40(\text{range } 7-40\,\text{U/L})$$

2.4. Study variables

The analysis included variables such as sex, age, hypertension, and presence of diabetes mellitus as demographic, lifestyle, and health-related variables. We also examined the biochemical parameters neutrophil, lymphocyte, and platelet counts, triglycerides (TGs), cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), AST, ALT, gamma-glutamyl transferase (GGT), total bilirubin (TBIL), and total bile acids (TBA).

2.5. Statistical analysis

Median, 25th percentile, and 75th percentile values were calculated from the data for continuous variables. Number and percentage values were calculated from the data for categorical variables. Independent-sample *t* tests were used to examine the statistical significance of the between-group differences for continuous variables that were normally distributed. Chi-square tests were used to determine whether between-group differences for categorical variables were statistically significant. All tests were 2-tailed. Multivariate logistic regression analysis was used to adjust for possible confounding effects and to calculate adjusted odds ratios (AORs) and 95% confidence intervals (CIs). We used SPSS (version 13.0) software (SPSS Inc., Chicago, IL) for the analyses. A P value $<.05$ indicated a statistically significant result.

3. Results

3.1. Demographic and clinical characteristics of the study population

Complete sets of diagnostic records were obtained for the 568 study participants. The results for the demographic and clinical variables are presented in Table 1. A total of 110 patients had a diagnosis of CHC and HCV-associated cirrhosis (compensated cirrhosis, case group); 458 patients had a diagnosis of CHC without cirrhosis (CHC-only, control group). The median (25th, 75th percentile) age of the cirrhosis group was 60.00 (51.75, 67.25) years, and 40% were male. The median age of the patients in the CHC-only control group was 57.00 (51.00, 63.00) years; 47.2% of the patients in this group were male. The patients in the CHC-only (control) group were age and sex-matched to patients in the cirrhosis group. We found statistically significant differences in the prevalence of diabetes mellitus in the cirrhosis group (21.8%) compared with the CHC-only group (14.2%) ($P=.048$). The between-group difference between the values for prevalence of hypertension was not statistically significant.

Table 1

Demographic and clinical characteristics of the case and control groups.

Variable	CHC (n = 458)	Liver cirrhosis (n = 110)	P
Male, n (%)	216 (47.2)	44 (40.0)	.176
Age (y)	57.00 (51.00,63.00)	60.00 (51.75, 67.25)	.066
Hypertension, n (%)	111 (24.2)	22 (20.0)	.346
Diabetes mellitus, n (%)	65 (14.2)	24 (21.8)	.048
Neutrophils (10^9/L)	2.49 (1.75, 3.40)	1.79 (1.22, 2.70)	<.001
Lymphocytes (10^9/L)	1.70 (1.33, 2.24)	1.27 (0.91, 1.74)	<.001
Platelet count (10^9/L)	144.00 (105.00, 184.00)	81.00 (54.75, 119.25)	<.001
Triglyceride	1.14 (0.84, 1.58)	0.96 (0.72, 1.17)	<.001
Cholesterol	3.85 (3.25, 4.52)	3.63 (3.10,4.20)	.004
HDL-C	1.16 (0.90, 1.43)	1.19 (0.95, 1.51)	.316
LDL-C	2.29 (1.84, 2.83)	2.11 (1.69, 2.63)	.005
AST (IU/L)	52.50 (31.00, 90.25)	59.00 (40.00, 101.60)	.029
ALT (IU/L)	64.00 (29.00, 126.00)	60.00 (30.00, 91.15)	.192
TBIL (μmol/L)	15.80 (11.38, 22.73)	21.30 (15.78, 33.73)	<.001
GGT (IU/L)	52.00 (24.10, 110.50)	53.00 (28.73,90.93)	.695
TBA	10.70 (6.00, 19.65)	22.55 (13.85, 49.50)	<.001

Continuous variables are expressed as median (25th, 75th percentiles). Categorical variables are displayed as numbers and percentages.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHC = chronic hepatitis C, GGT = gamma-glutamyl transpeptidase, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TBA = total bile acid, TBIL = total bilirubin.

The results of the analysis indicated that the median values for the levels of AST, TBIL, and TBA were elevated in the group of patients with cirrhosis compared with the control group patients. The median values for neutrophil, lymphocyte, and platelet counts were greater, and triglyceride, cholesterol, and LDL-C levels were higher, in the control group compared with the cirrhosis group. The median values for the levels of HDL-C, ALT, and GGT were similar between the 2 groups.

3.2. Factors associated with development of cirrhosis development in patients with chronic hepatitis C infection

The results of the univariate analyses suggested that the prevalence of diabetes was greater in the group of patients with cirrhosis (Table 2). However, the patients with cirrhosis had lower PLRs and higher FIB4, APRI, and AAR values. The variables sex, age, diabetes, hypertension, and the PLR, NLR, FIB4, APRI, and AAR values were included in a multivariate analysis that included adjustment for potential confounding variables. The results indicated that the APRI, AST/ALT, and PLR levels were the factors with the strongest associations with cirrhosis. The results of the analysis indicated that the factors associated with a greater odds of having cirrhosis were higher AAR ($P < .001$), higher APRI ($P < .001$), and lower PLR ($P = .001$) values.

Higher AAR levels and higher APRI scores were associated with a 1-to-2-fold increase in the odds of having cirrhosis (AOR 1.180, 95% CI 1.081–1.288; AOR 2.150, 95% CI 1.477–3.130, respectively). Lower PLR levels were associated with a greater odds of having cirrhosis (AOR 0.991, 95% CI 0.985–0.996).

Table 2

Univariate and multivariate analyses of variables associated with liver cirrhosis in patients with chronic hepatitis C infection.

Variable	CHC (n = 458)	Liver cirrhosis (n = 110)	P*	AOR (95% CI)†	P‡
Sex			.176	—	—
Female, n (%)	242 (52.8)	66 (60.0)			
Male, n (%)	216 (47.2)	44 (40.0)			
Age	57.00 (51.00, 63.00)	60.00 (51.75, 67.25)	.066	—	—
Hypertension			.346	—	—
No, n (%)	347 (75.8)	88 (80.0)			
Yes, n (%)	111 (24.2)	22 (20.0)			
Diabetes mellitus			.048	—	—
No, n (%)	393 (85.8)	86 (78.2)			
Yes, n (%)	65 (14.2)	24 (21.8)			
PLR	80.24 (57.85, 111.08)	60.63 (44.09, 89.31)	<.001	0.991 (0.985–0.996)	.001
NLR	1.37 (1.00, 2.00)	1.38 (0.97, 2.31)	.841		
FIB4	0.71 (0.45, 1.17)	1.66 (0.98, 2.60)	<.001		
APRI	0.99 (0.51, 2.01)	2.12 (0.97, 4.25)	<.001	1.180 (1.081–1.288)	<.001
AAR	0.85 (0.65, 1.18)	1.12 (0.87, 1.39)	<.001	2.150 (1.477–3.130)	<.001

AAR = AST-to-ALT ratio, AOR = adjusted odds ratio, APRI = aspartate aminotransferase-to-platelet ratio index, CHC = chronic hepatitis C, CI = confidence interval, FIB4 = 4-factor fibrosis index, NLR = neutrophils-to-lymphocyte ratio, PLR = platelets-to-lymphocyte ratio.
* *P* value for univariate analysis.
† Adjusted for sex, age, TBIL, DM, liver disease etiology, liver cirrhosis.
‡ *P* value for multivariate analysis.

The results of the multivariate analysis indicated that there were no statistically significant between-group differences for NLR or FIB4 values.

3.3. Factors associated with development of fatty liver in patients with chronic hepatitis C infection

Because patients with CHC usually have fatty liver disease, we analyzed the risk factors for fatty liver in these patients. The livers of patients with cirrhosis usually do not have the typical imaging changes consistent with fatty liver, so we only included data from the patients with CHC in the analysis. The results for the demographic and clinical characteristics for the group of patients with CHC-only are presented in Table 3 and Fig. 1.

Data from the 92 patients with CHC and fatty liver, and the 366 patients with CHC and no fatty liver (control group) were included in the analysis. The univariate analyses revealed that the factors associated with a greater risk of fatty liver development were higher triglyceride concentrations ($P < .001$); higher cholesterol concentrations ($P = .005$); higher TG/HDL-C ratios ($P < .001$); and younger age ($P = .017$).

Multivariate analyses were also used to examine the associations between sex; age; diabetes mellitus; hypertension; PLR; NLR; TG; cholesterol; and TG/HDL-C and the odds of having CHC and fatty liver (Table 4). Patients with CHC and higher cholesterol levels had greater odds of having fatty liver (AOR 1.380, 95% CI 1.089–1.750, $P = .008$). Conversely, we did not find that TG levels or the TG/HDL-C ratio affected the odds of having fatty liver in patients with CHC. We also found no statistically significant correlations between PLR values, NLR values, and the risk of having fatty liver.

4. Discussion

This study found that the PLR was lower in patients with CHC and compensated cirrhosis compared with sex and age-matched control group patients with CHC-only. These findings are consistent with the findings of previous studies.[11,16] Meng et al[11] investigated the correlation between PLR and disease progression in patients with HCV-associated liver disease and the virological response. They found a statistically significant association between PLR and disease severity. A cohort study also revealed that PLR is an independent predictor of liver fibrosis and cirrhosis in patients with CHB infection.[17]

The PLR is a comprehensive indicator of changes in immune status during disease because it is calculated as the platelet count/lymphocyte count, and accounts for variations in platelet and lymphocyte numbers.[11] Preoperative PLR values are associated with the prognosis of aggressive tumors for different cancer types.[18] PLR values are also associated with the progression and prognosis of vestibular neuritis, sudden deafness, cardiovascular disease, and thrombosis-related disease.[19–21] A persistent chronic inflammatory response is a characteristic of chronic infectious diseases (eg, types of viral hepatitis). PLR values are associated with the prognosis and progression of HCC associated with viral hepatitis infection.[18,22] The function of platelets as a carrier medium for immune cells and responses is being investigated.[23] The relationships between PLR and NLR values, and HCV infection-associated diseases remain undetermined.

The NLR includes the variation in neutrophil count as an indicator of inflammation and in lymphocyte count as an indicator of physiologic stress. The NLR has many uses as a prognostic marker, including assessment of liver disease severity in patients with HBV infection.[24] However, white blood cell, lymphocyte, neutrophil, and platelet values fluctuate during response to infection and other clinical disease. This variation might explain why we found no statistically significant differences between the CHC-only and CHC-related compensated cirrhosis groups. Compared with use of single NLR values, continuous monitoring of the changes in the NLR will be a more valid approach for estimation of disease severity.

The HCV life cycle includes reliance on host lipids. Disease progression is affected by viral factors that interact with the host's immune and metabolic pathways.[25] However, the validity of the use of serum lipids for assessment of CHC severity needs further investigation. In this study, we found that patients with CHC who had higher cholesterol levels had an increased risk of NAFL. Therefore, monitoring the values of blood lipid parameters is

Table 3

Demographic and clinical characteristics patients with chronic hepatitis C infection (no cirrhosis), with and without accompanying fatty liver disease.

Variable	CHC (nonfatty liver) n = 366	CHC (fatty liver) n = 92	*P*
Male, n (%)	169 (46.2)	47 (51.1)	.399
Age (y)	57.00 (51.00, 64.00)	54.50 (50.00, 60.00)	.017
Hypertension, n (%)	87 (23.8)	24 (26.1)	.643
Diabetes mellitus, n (%)	51 (13.9)	14 (15.2)	.753
Neutrophils (10^9/L)	2.47 (1.72, 3.31)	2.54 (1.82, 3.53)	.476
Lymphocytes (10^9/L)	1.68 (1.30, 2.22)	1.83 (1.42, 2.46)	.028
Platelet count (10^9/L)	144.00 (104.00, 185.25)	150.00 (109.25, 182.00)	.555
Triglyceride	1.09 (0.80, 1.52)	1.42 (1.05,1.81)	<.001
Cholesterol	3.77 (3.22, 4.48)	4.13 (3.52, 4.85)	.005
HDL-C	1.20 (0.92,1.43)	1.08 (0.87, 1.42)	.102
LDL-C	2.22 (1.81, 2.77)	2.55 (2.02,3.02)	.002
AST (IU/L)	51.25 (29.00, 89.20)	57.00 (34.98, 94.50)	.098
ALT (IU/L)	58.00 (27.00, 123.85)	77.50 (38.40, 139.88)	.012
GGT	49.10 (23.00, 107.00)	66.55 (34.93, 122.73)	.009

Continuous variables are expressed as median (25th, 75th percentiles). Categorical variables are displayed as numbers and percentages.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHC = chronic hepatitis C, GGT = gamma-glutamyl transpeptidase, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

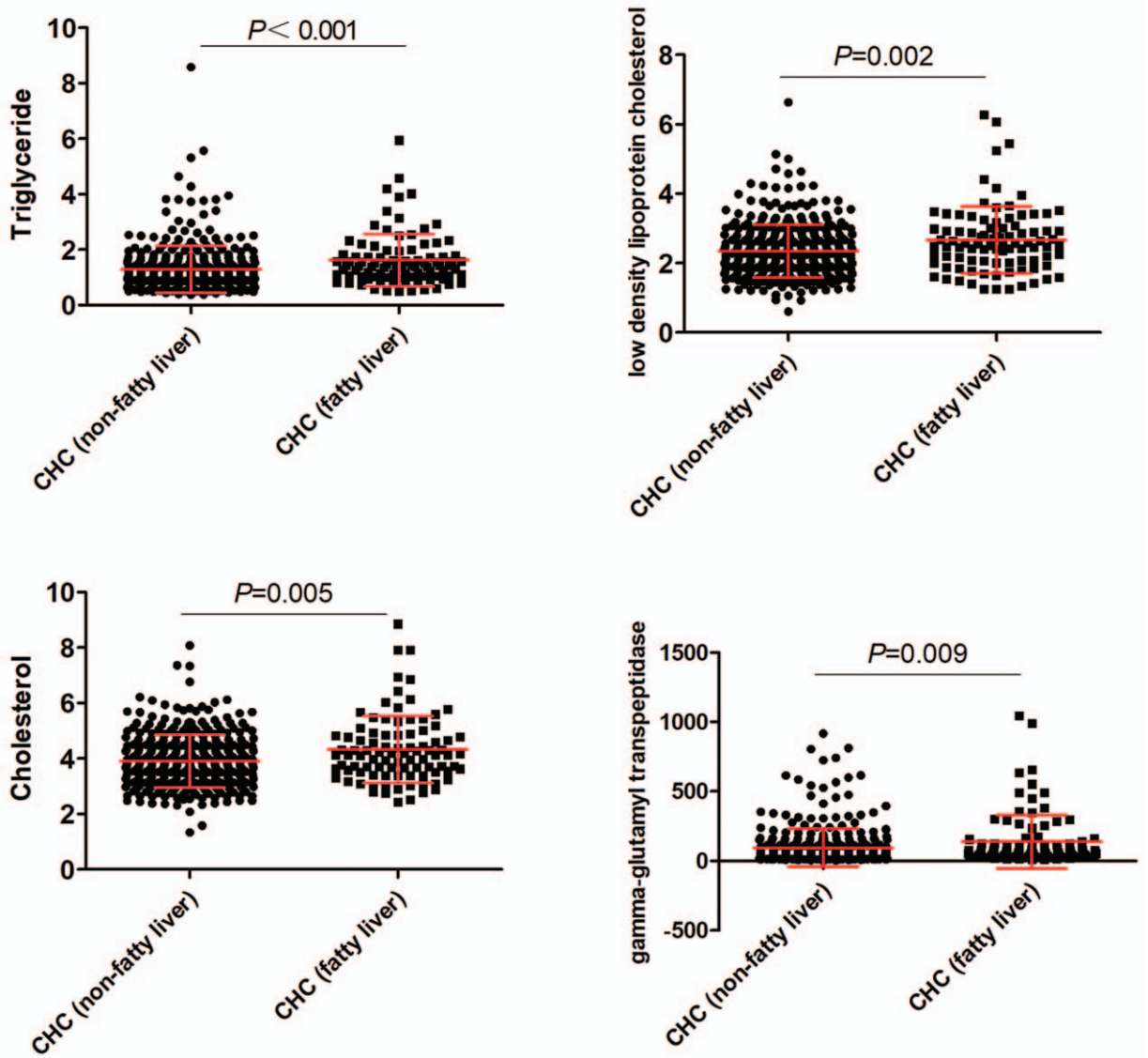

Figure 1. Demographic characteristics patients with chronic hepatitis C infection (no cirrhosis), with and without accompanying fatty liver disease. The median values for triglyceride, cholesterol, low-density lipoprotein cholesterol, and gamma-glutamyl transpeptidase were higher, in the fatty liver group compared with the nonfatty liver group.

Table 4

Univariate and multivariate analyses of variables associated with fatty liver disease in patients with chronic hepatitis C infection.

Variable	CHC (n = 366)	CHC/fatty liver (n = 92)	P*	AOR (95% CI)†	P‡
Sex			.399	—	—
Female, n (%)	197 (53.8)	45 (48.9)			
Male, n (%)	169 (46.2)	47 (51.1)			
Age	57.00 (51.00, 64.00)	54.50 (50.00, 60.00)	.017	—	—
Hypertension			.643	—	—
No, n (%)	279 (76.2)	68 (73.9)			
Yes, n (%)	87 (23.8)	24 (26.1)			
Diabetes			.753	—	—
No, n (%)	315 (86.1)	78 (84.8)			
Yes, n (%)	51 (13.9)	14 (15.2)			
PLR	82.01 (58.47, 113.35)	73.51 (55.33, 100.69)	.111	—	—
NLR	1.37 (0.99, 2.11)	1.29 (1.01, 1.83)	.348	—	—
TG/HDL-C	0.89 (0.61, 1.45)	1.27 (0.82, 2.05)	<.001	—	—
Triglyceride	1.09 (0.80, 1.52)	1.42 (1.05, 1.81)	<.001	—	—
Cholesterol	3.77 (3.22, 4.48)	4.13 (3.52, 4.85)	.005	1.380 (1.089–1.750)	.008

AOR = adjusted odds ratio, CHC = chronic hepatitis C, CI = confidence interval, NLR = neutrophils-to-lymphocyte ratio, PLR = platelets-to-lymphocyte ratio, TG/HDL-C = triglycerides-to-HDL-cholesterol ratio.

* *P* value for univariate analysis.

† Adjusted for sex, age, TBIL, DM, liver disease etiology, liver cirrhosis.

‡ *P* value for multivariate analysis.

useful during assessment of patients with HCV because patients who have co-occurring HCV infection and NAFL are at greater risk of progression of their liver disease. We found no statistically significant correlations between TG/HDL-C levels and fatty liver development in this population of CHC patients. Advanced fibrosis is associated with TG values that include higher LDL and HDL concentrations, and lower very-low-density lipoprotein concentrations.[26,27] We did not stratify the analysis by the presence of liver fibrosis because we used a retrospective study design and did not detailed liver biopsy and fibroscan data.

The main limitations of this study were the use of the retrospective design and the lack of fibroscan data. Further study of the associations between TG/HDL-C values and fatty liver development during the stages of liver fibrosis is needed. We also did not include evaluation of some potential confounding variables (eg, the presence of idiopathic thrombocytopenic purpura and spontaneous peritonitis).

5. Conclusions

In conclusion, we found statistically significant correlations between the PLR, an inexpensive and easily calculated index, and HCV infection-associated compensated cirrhosis among Chinese patients with CHC. Monitoring PLR values can be used to assess disease development. These results also suggested that patients with CHC and higher cholesterol concentrations may be at greater risk of developing fatty liver disease.

Author contributions

Data curation: Xu Li, Le Wang.
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Writing – original draft: Xu Li.
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