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High levels of serum hypersensitive C-reactive protein are associated with non-alcoholic fatty liver disease in non-obese people: a cross-sectional study

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Abstract

Introduction Non-alcoholic fatty liver disease (NAFLD) and obesity have become one of the most common chronic diseases, and the global prevalence is increasing year by year. Both are accompanied by hypersensitive C-reactive protein (hs-CRP). At present, there are many predictors of NAFLD. Exploring the relationship between hs-CRP and non-alcoholic fatty liver disease in non-obese people will be helpful for risk prediction and clinical screening in high-risk populations.

Objective To explore the relationship between levels of serum hs-CRP and the presence of NAFLD in non-obese people.

Methods A total of 6558 participants who underwent physical examination from March 2017 to November 2017. Multivariate logistic regression was utilized to analyze the risk factors associated with NAFLD.

Results This study including 4240 males and 2318 females ranging from 20 to 94 years. In 1396 patients with NAFLD, the prevalence rate was 21.3%, among which 1056 (24.9%) males and 340 (14.7%) females had NAFLD. The prevalence of NAFLD was much higher in males compared to females ($\chi^2 = 93.748$, $P < 0.001$). In the nonalcoholic fatty liver group, various factors including hs-CRP, age, WC, BMI, systolic blood pressure and blood pressure diastolic blood pressure were significantly higher than those in the control group. Logistic regression analysis confirmed that hs-CRP was an independent risk factor for NAFLD, even after adjusting for relevant variables.

Conclusions The prevalence of NAFLD increases with the level of hs-CRP in both men and women who are non-obese. Hs-CRP levels are an important risk factor for nonalcoholic fatty liver disease in non-obese individuals.

Keywords Hypersensitive C-reactive protein, Nonalcoholic fatty liver disease, Inflammation, Non-obese people, Cross-sectional

Introduction

About a quarter of the world's population is impacted by this illness, making it the most prevalent liver condition [1]. Non-alcoholic fatty liver disease (NAFLD) may result in inflammation and fibrosis [2]. The prevalence of NAFLD is on the rise in many countries, largely due to the increasing rates of obesity, type 2 diabetes, and metabolic syndrome [3]. The incidence rate of NAFLD varies

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significantly among different regions in China, with some studies reporting an overall prevalence of 15–30%. However, recent data suggest that the prevalence of NAFLD in China may be as high as 40–50% in some regions, such as Shanghai and Guangzhou [4].

If left untreated, NAFLD may progress to cirrhosis, liver failure, and liver cancer [5]. Treatment includes lifestyle modifications such as weight loss, dietary changes, and exercise, as well as medications [6]. Different forms of nonalcoholic fatty liver exist, including basic steatosis and nonalcoholic steatohepatitis (NASH), which includes inflammation, steatosis, and fibrosis. Approximately, 10–30% of individuals diagnosed with NAFLD will progress to NASH, leading to potential complications such as cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality. The clinicopathological mechanism of NAFLD involves a complex interplay of metabolic, genetic, and environmental factors that lead to the accumulation of excess fat in the liver, inflammation, and fibrosis [7, 8]. Insulin resistance, a hallmark of metabolic syndrome, is a key driver of NAFLD [9, 10]. Accumulation of triglycerides in liver cells can lead to dysfunction of mitochondria, stress in the endoplasmic reticulum, and oxidative stress, leading to injury, inflammation, and activation of stellate cells in the liver [11, 12]. For the above reasons, obese patients were excluded and liver function indexes and components of metabolic syndrome were included in the study.

In summary, the incidence of NAFLD is high and the etiology is complex. At present, the specific pathogenesis and natural history of NAFLD are not clear, and there is no exact treatment. Therefore, it is important to explore the risk factors in the progression of NAFLD. hypersensitive C-reactive protein (hs-CRP) is more likely to reflect diseases associated with low inflammatory states, such as diabetes, hypertension, and metabolic syndrome. NAFLD, which is associated with obesity and metabolic syndrome, is also associated with hs-CRP to a certain extent. The relationship between the level of hs-CPR and NAFLD has been reported. However, there are few reports on whether there is also a relationship in non-obese people, and the sample size is small [13]. Therefore, the aim of this study was to explore whether C-reactive protein, a marker of systemic inflammation, can be used as an independent risk factor for NAFLD in non-obese people.

Materials and methods

Subjects

From March 2017 to November 2017, 9837 participants underwent physical examinations at the Health Examination Center of Zhenhai District Refining and Chemical Hospital, Ningbo City. Exclusion criteria for the study encompassed viral hepatitis, Wilson's disease, drug-induced liver injury, autoimmune hepatitis, and other conditions associated with NAFLD. Additionally, participants with a prolonged alcohol consumption history exceeding 140 g per week for men and 70 g per week for women, as well as those who have recently used hepatoprotective drugs, and obesity were also excluded. Patients with hs-CRP > 10 mg/L or acute infections such as acute lung infection or acute gastroenteritis; previous history of myocardial infarction, cerebral infarction, and malignant tumor; incomplete physical examination data not suitable for analysts. Ethics committees of Zhenhai Lianhua Hospital approved this study (no. 20120213).

Methods

General information

After a short training of the investigators, the above subjects were given a uniform questionnaire and relevant examinations, including history of previous liver disease, history of alcohol consumption and smoking, whether they were taking liver protection drugs, and whether they had any recent symptoms of acute infection such as sore throat, cough, and diarrhea. Finally, 6558 participants were included according to the exclusion criteria.

Detection of blood biochemical indicators

10 ml of fasting peripheral venous blood was collected from all subjects in the morning. The same Au640 automatic biochemical detector produced by OLYMPUS Company in Japan was used to test serum biochemical and hs-CRP. The hs-CRP determination was performed using immunoturbidimetry, and the kit was provided by Beijing Liderman Biochemical Technology Co., Ltd.

B-ultrasound examination of liver and definition of obesity

After venous blood sampling, the subjects were examined by B-ultrasound. Two imaging specialists used two ultrasound diagnostic instruments of the same model to perform the operation and issue a report. Diagnosis of Nonalcoholic Fatty Liver Disease is based on the 2010 Chinese Medical Association Guidelines for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease (2010 Revision) [14]. According to this criterion, the subjects were divided into NAFLD group and control group. Obesity criteria were described in our previous study published [15].

Statistical methods

The physical examination data were entered by the hospital staff terminal and statistically analyzed using SPSS22.0 software. Measurement data that conforms to a normal distribution is typically represented as mean ± standard deviation (SD). Multigroup comparisons are performed

using one-way ANOVA (paired comparisons using the LSD method). A chi-square test is applied to the counting data, followed by a multivariate logistic regression to analyze the relationship between different concentrations of hs-CRP and NAFLD. Graphs were created using GraphPad Prism 8.0 (GraphPad Software Inc.). A value of $P<0.05$ indicates a significant difference.

Results

Characteristics of the participants

A total of 6558 patients were included, including 4240 males and 2318 females, with a sex ratio of 1.83:1.The average age was 49.0 ± 14.8 years, ranging from 20 to 94 years. In 1396 patients with NAFLD, the prevalence rate was 21.3%, which was defined as the NAFLD group, among which 1056 (24.9%, 1056/4240) males and 340 (14.7%, 340/2318) females had NAFLD. The prevalence of NAFLD was much greater in males compared to females, ($\chi^2=93.748$, $P<0.001$). 5162 non-NAFLD patients were defined as the control group.

A comparison of medical and laboratory tests in NAFLD and control groups

In Table 1, the NAFLD group had higher values for age, waist circumference, BMI, systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, liver enzymes, fasting glucose, uric acid, glycated hemoglobin, and hs-CRP compared to the control group, with statistically significant differences. The high-density lipoprotein cholesterol was reduced in comparison to the control group.

Correlation between hs-CRP levels and the development of NAFLD

To investigate the relationship between hs-CRP levels and NAFLD prevalence rates, the level of hs-CRP was stratified by the quartile. And then grouped according to it, the values of different groups were Q1 ≤ 0.3 mg/L, Q2 > 0.4 mg/L- ≤ 0.5 mg/L, Q3 > 0.5 mg/L- ≤ 1.0 mg/L, and Q4 > 1.1 mg/L. According to Table 2, the prevalence of NAFLD gradually increased with the increase of

Table 1 A comparison of clinical and laboratory indicators between subjects in the control and NAFLD groups

Clinical characteristics	Control ($n=5162$)	NAFLD ($n=1396$)	*t* value	*P* value
Age (years)	48.4 ± 15.3	51.5 ± 12.8	7.092	< 0.001
Waist circumference (cm)	77.9 ± 6.7	82.8 ± 5.4	25.091	< 0.001
BMI (kg/m^2)	21.5 ± 2.1	23.7 ± 1.8	34.406	< 0.001
Systolic blood pressure (mmHg)	123.3 ± 16.4	130.9 ± 16.5	15.528	< 0.001
Diastolic blood pressure (mmHg)	73.4 ± 10.4	79.2 ± 10.8	18.602	< 0.001
Total cholesterol (mmol/L)	4.7 (4.2,5.3)	5.0 (4.4,5.6)	4.843*	< 0.001
Triacylglycerol (mmol/L)	1.1 (0.8,1.5)	1.8 (1.3,2.6)	13.833*	< 0.001
HDL-C (mmol/L)	1.5 (1.3,1.8)	1.3 (1.1,1.5)	− 7.562*	< 0.001
LDL-C (mmol/L)	2.7 (2.3,3.2)	2.8 (2.4,3.3)	2.316*	< 0.001
ALT (U/L)	16 (13,22)	25 (18,36)	11.691*	< 0.001
AST (U/L)	20 (17,24)	23 (19,28)	6.716*	< 0.001
ALP (U/L)	79 (67,94)	87 (74,100)	5.068*	< 0.001
GGT (U/L)	19 (14,27)	30 (21,47)	12.114*	< 0.001
Fasting blood glucose (mmol/L)	5.2 (4.9,5.5)	5.3 (5.0,5.8)	5.635*	< 0.001
Uric acid (μmol/L)	324.3 ± 77.0	373.3 ± 81.1	31.656	< 0.001
Glycosylated hemoglobin (%)	5.31 (5.1,5.5)	5.4 (5.2,5.8)	5.849*	< 0.001
hs-CRP	0.5 (0.3,0.9)	0.9 (0.5,1.5)	8.863*	< 0.001

1 mmHg = 0.133 kPa; *z value, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol

Table 2 Relationship between hs-CRP levels and incidence of NAFLD [*n* (%)]

	Serum hypersensitive C-reactive protein					
	Q1 ($n=2080$)	Q2 ($n=1339$)	Q3 ($n=1589$)	Q4 ($n=1550$)	X^2 value	*P* value
Male	149 (11.8)	201 (22.9)	324 (30.8)	382 (36.6)	173.447	< 0.001
Female	42 (5,2)	42 (9.1)	91 (16.9)	165 (32.5)	153.752	< 0.001
Total	191 (9.2)	243 (18.1)	415 (26.1)	547 (35.3)	308.278	< 0.001

hs-CRP level in both men, women and the general population, showing statistical significance ($P < 0.001$).

Clinical characteristics of indicators related to hs-CRP levels

6558 subjects were stratified and compared according to hs-CRP levels. Levels of age, waist circumference (WC), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), LDL cholesterol (LDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), fasting plasma glucose (FPG), uric acid (UC), and hemoglobin A1c (HbA1c) all rose as hs-CRP levels increased ($P < 0.001$).As hs-CRP level increased, HDL cholesterol (HDL-C) levels decreased significantly ($P < 0.001$), Table 3.

Elevated hs-CRP levels are associated with a higher risk of developing NAFLD in non-obese people

We employed the risk factors associated with NAFLD. Multivariate analysis revealed that being male, age, WC, BMI, DBP, TC, TG, LDL-C, AST, ALT, GGT, FPG, UC, HbA1c, and hs-CRP levels were associated with an increased risk of NAFLD (Fig. 1).

To investigate the relationship between hs-CRP and NAFLD, the hs-CRP level was divided into quartiles, with NAFLD (1 = present, 0 = absent) as the outcome variable. The risk of NAFLD increases when considering hs-CRP concentration (Q1, Q2, Q3, Q4), age, sex, WC, BMI, SBP, DBP, FPG, TC, TG, HDL-C, AST, ALT, GGT, UC, and HbA1c as predictors. This trend remained statistically significant after adjusting for related factors ($P < 0.01$, Fig. 2).

Discussion

Our study shows that the prevalence of NAFLD increases with the level of hs-CRP in both men and women who are non-obese. hs-CRP levels are an important risk factor for the development of nonalcoholic fatty liver disease in non-obese people. In the nonalcoholic fatty liver group, various factors including hs-CRP, age, WC, BMI, systolic blood pressure and blood pressure diastolic blood pressure were significantly higher than those in the control group. Logistic regression analysis confirmed that hs-CRP was an independent risk factor for NAFLD, even after adjusting for relevant variables. These findings suggest that hs-CRP may independently increase the risk of NAFLD in non-obese individuals.

Hs-CRP serves as an indicator of widespread inflammation [16]. Multiple studies have linked the progression and worsening of NAFLD and obesity to inflammation [17, 18]. A prior investigation revealed a correlation between elevated hs-CRP levels and increased severity of liver disease in individuals with NAFLD when compared to those without the condition [18, 19]. Patients diagnosed with NASH had notably elevated hs-CRP levels compared to individuals with simple NAFLD, in contrast to those with simple steatosis [20]. The hs-CRP and inflammatory cytokines are both engaged in the inflammatory process, although they have diverse functions

Table 3 Clinical characteristics of elderly people after hs-CRP stratification

Clinical characteristics	Q1 ($n = 2080$)	Q2 ($n = 1339$)	Q3 ($n = 1589$)	Q4 ($n = 1550$)	*F* value	*P* value
Age (years)	46.1 ± 14.3	48.8 ± 14.3	50.5 ± 14.9	51.7 ± 15.4	94.179	< 0.001
WC (cm)	77.2 ± 6.9	79.1 ± 6.6	79.6 ± 6.6	80.7 ± 6.1	67.349	< 0.001
BMI (kg/m^2)	21.2 ± 2.2	21.9 ± 2.1	22.3 ± 2.2	22.7 ± 2.1	31.091	< 0.001
SBP (mmHg)	121.4 ± 15.4	124.4 ± 16.3	126.7 ± 17.0	128.3 ± 17.4	76.263	< 0.001
DBP (mmHg)	72.5 ± 10.2	74.4 ± 10.5	75.5 ± 10.8	76.7 ± 11.0	45.601	< 0.001
TC (mmol/L)	4.6 (4.1,5.2)	4.8 (4.2,5.4)	4.9 (4.2,5.5)	5.0 (4.3,5.6)	39.517	< 0.001
TG (mmol/L)	1.0 (0.8,1.4)	1.2 (0.9,1.7)	1.3 (1.0,1.9)	1.4 (1.0,2.1)	86.322	< 0.001
HDL-C (mmol/L)	1.3 (1.2,1.5)	1.3 (1.1,1.5)	1.3 (1.1,1.6)	1.3 (1.1,1.4)	8.395	< 0.001
LDL-C (mmol/L)	2.7 (2.3,3.1)	2.7 (2.4,3.2)	2.8 (2.4,3.3)	2.8 (2.4,3.3)	27.343	< 0.001
ALT (U/L)	16 (12,22)	18 (13,24)	19 (14,26)	19 (14,28)	34.872	< 0.001
AST (U/L)	20 (17,24)	21 (18,25)	21 (18,26)	22 (18,27)	32.023	< 0.001
ALP (U/L)	76 (63,89)	79 (68,94)	83 (70,96)	88 (75,103)	28.246	< 0.001
GGT (U/L)	18 (14,24)	20 (15,29)	22 (16,33)	26 (18,39)	50.333	< 0.001
FPG (mmol/L)	5.1 (4.9,5.4)	5.2 (4.9,5.5)	5.2 (4.9,5.6)	5.2 (4.9,5.7)	20.319	< 0.001
UC (μmol/L)	315.7 ± 74.8	331.3 ± 75.8	339.8 ± 76.9	358.1 ± 88.2	75.689	< 0.001
HbA1c (%)	4.9 (4.7,5.2)	5.0 (4.7,5.3)	5.1 (4.8,5.4)	5.2 (4.9,5.5)	11.290	< 0.001

1 mmHg = 0.133 kPa; *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol

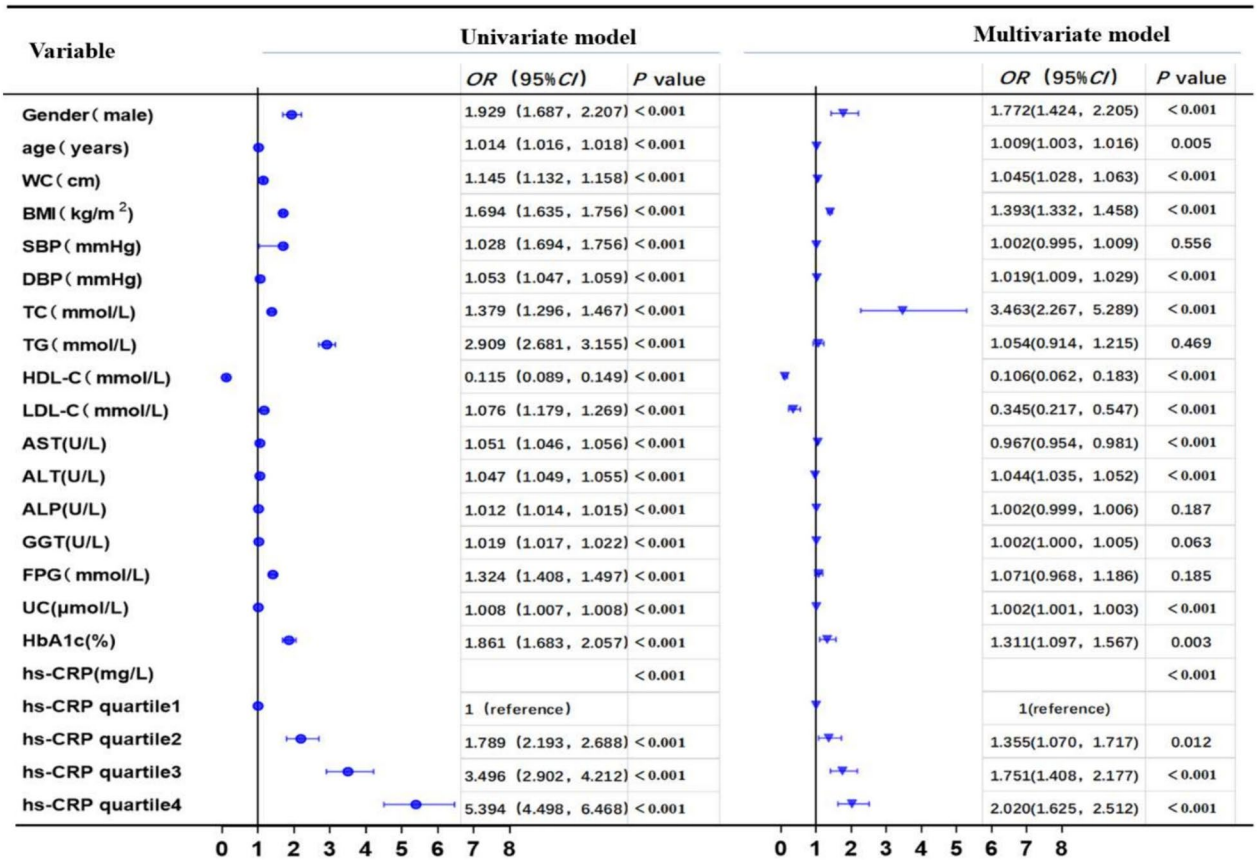

Fig. 1 Univariate and multivariate logistic regression analysis of risk factors for NAFLD

and are controlled by various mechanisms. Hs-CRP is considered a marker of systemic inflammation, used in clinical tests to assess the risk of cardiovascular disease and other illnesses associated with chronic inflammation. The generation of hs-CRP is stimulated by inflammatory cytokines, which demonstrates the intimate relationship between inflammatory cytokines and hs-CRP [20, 21].

The possible mechanisms by which C-reactive protein is associated with nonalcoholic fatty liver disease are as follows. Activation of toll-like receptor 4 (TLR4) signaling is a crucial molecular mechanism that drives inflammation in NAFLD.TLR4, a receptor that detects patterns, is found on immune cells and responds to different molecules like lipopolysaccharides (LPS) from intestinal bacteria [22]. In NAFLD, TLR4 is activated by free fatty acids that are released from hepatocytes, and this leads to the recruitment of immune cells and the production of inflammatory cytokines [23, 24]. TLR4, a receptor located in the cell membrane, plays a role in identifying pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), leading to the initiation of inflammatory reactions. Stimulation of TLR4 is recognized to trigger the generation and discharge of inflammatory cytokines, like IL-6, TNF-α, and IL-1β, leading to the production of hs-CRP [25]. Collectively, these research findings indicate that increased levels of hs-CRP could play a role in the onset and advancement of NAFLD, potentially by promoting inflammation. Additional research is necessary to completely comprehend the mechanisms behind this connection and to ascertain whether lowering hs-CRP levels could serve as a potential predictive and therapeutic approach for NAFLD.

Our research found that non-obese people with non-alcoholic fatty liver disease (NAFLD) had notably higher levels of various health markers, including age, waist size, body weight, blood pressure, cholesterol, liver enzymes, and blood sugar, compared to individuals without NAFLD. This study emphasizes the various metabolic irregularities linked to NAFLD. These results suggest that NAFLD is not just a liver disease but also a systemic metabolic disorder that affects multiple organ systems and functions. According to the study, those who have NAFLD have significantly lower levels of high-density lipoprotein cholesterol, also referred to as "good cholesterol." The severity of NAFLD and HDL-C levels have been shown to be

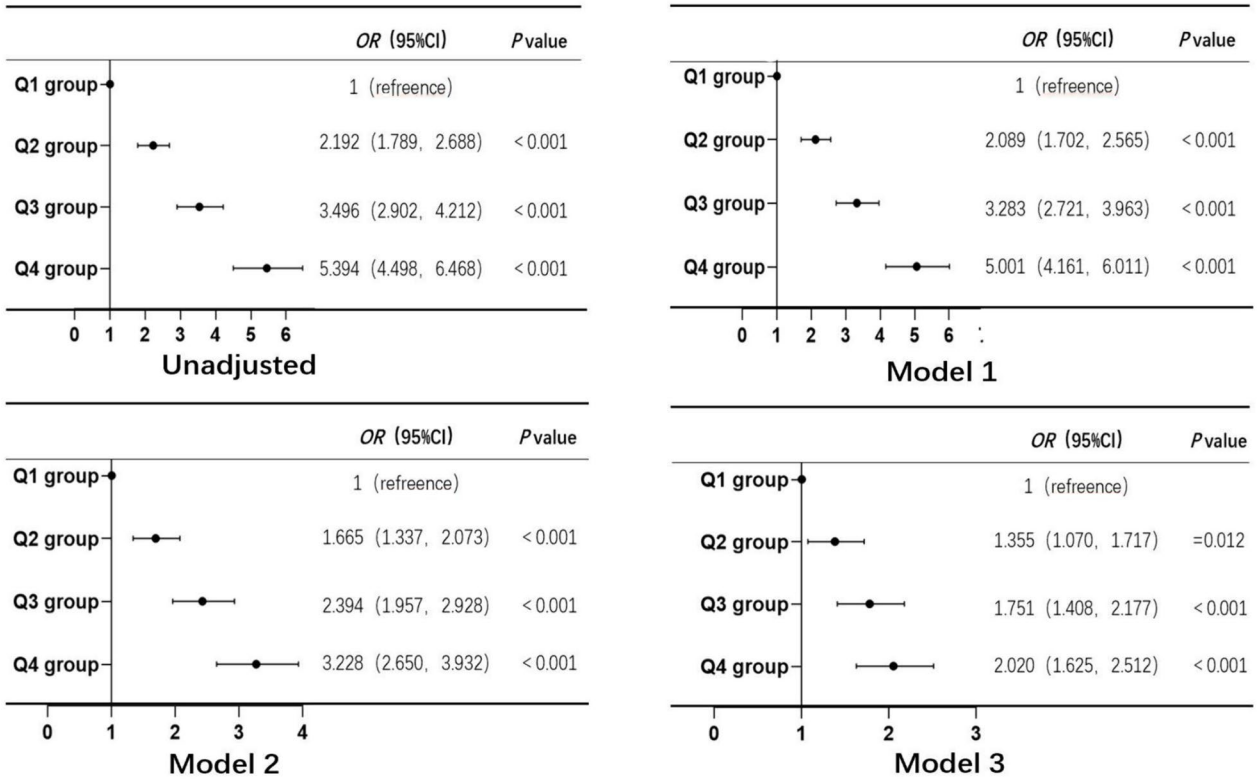

Fig. 2 Risk was determined by the quartile of baseline serum hs-CRP in unadjusted and adjusted models. Model1 accounted for age and gender adjustments; Model2 included adjustments for Model1 as well as waist circumference and BMI; Model3 further adjusted for systolic and diastolic blood pressure, fasting blood sugar, total cholesterol, triglycerides, HDL cholesterol, ALT, AST, GGT, uric acid, and HbA1c

inversely correlated in prior studies, which is consistent with this finding [26]. The study suggests that low levels of HDL-C may promote the accumulation of cholesterol in the liver, potentially leading to the development and advancement of NAFLD. This study also found an association between NAFLD and indicators of insulin resistance and diabetes [27]. According to the study, those with NAFLD have higher fasting blood glucose and glycated hemoglobin levels, both of which are symptoms of impaired glucose metabolism. The data suggest that NAFLD and diabetes share metabolic risk factors like obesity, insulin resistance, and dyslipidemia.

There are some limitations in this study. The sample is from only one hospital, which is not ideal in representativeness. Moreover, this study is a cross-sectional study, which is not enough to infer causality, and the diagnosis of fatty liver is based on B-ultrasound not the gold standard of diagnosis. However, the sample size of this study was large. All the data were strictly reviewed and entered into the database, which provided certain clinical value for the diagnosis and treatment of non-alcoholic fatty liver disease in non-obese patients.

Conclusions

This study provides valuable information for the indicators of systemic metabolic abnormalities and hs-CRP associated with NAFLD in non-obese people. Identifying risk factors can help health care providers target at-risk populations and implement appropriate preventive measures to reduce the Prevalence rate of NAFLD. Further studies are needed to validate these results and investigate the mechanisms that link these risk factors to NAFLD.

Abbreviations

NAFLD Non-alcoholic fatty liver disease
hs-CRP Hypersensitive C-reactive protein

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Author contributions

Conceptualization，Changxi Chen; Data curation,Guitao Xia, Yuemei Xu，Cheng Zhang and Mengting Li; Formal analysis, Changxi Chen and Hongliang Li;Funding acquisition, Changxi Chen and Hongliang Li; Writing–original draft, Guitao Xia, Changxi Chen; Writing–review and editing, All author.

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Data availability
Contact the corresponding author if there is a reasonable request for data.

Declarations

Ethics approval and consent to participate
The study was approved by the ethics committees of Zhenhai Lianhua Hospital. The informed consents were obtained from the objects (decision no. 20120213).

Competing interests
The authors declare no competing financial interests.

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