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Original Article

Higher non-HDL-cholesterol to HDL-cholesterol ratio is linked to increase in non-alcoholic fatty liver disease: secondary analysis based on a longitudinal study

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Abstract: Background: Non-high-density lipoprotein cholesterol (non-HDLc) to HDLc ratio (non-HDLc/HDLc), is a viable predictor of metabolic syndrome, insulin resistance, and other cardiac diseases. The study aimed to assess whether non-HDLC/HDLc ratio is an independent predictor of NAFLD. Methods: The present study was a longitudinal study, involving 16173 Chinese men and women, aging 14-95 years old, who received a medical check-up program in a health examination Center in China. A total of 16173 initially NAFLD-free non-obese individuals were included, who completed a 5-year follow-up examination in the longitudinal study. NAFLD was defined by ultrasonographic detection of steatosis in the absence of other liver disease. Univariate and multivariate Cox proportional hazards analyses were used to assess the association between nonHDLC/HDLc and NAFLD. ROC curve analysis was performed to compare the predictive value between the nonHDLc/HDLc and the nonHDLc for NAFLD. Results: During the five-year follow-up period, a total of 2322 participants (14.4%) developed NAFLD. The HRs for NAFLD in the longitudinal population were 1.3 (95% CI 1.1 to 1.7) and 1.5 (95% CI 1.1 to 2.0) compared with Q1. AUC values for nonHDLc/HDLc ratios (0.705) were significantly higher than nonHDLc (0.656) ($P<0.05$), while the cut-off value for the detection of NAFLD was 2.26. Individuals with higher nonHDLc/HDLc ratio had an increased cumulative incidence rate of NAFLD in non-obese individuals. Conclusion: The Non-HDLc ratio/HDLc is an independent predictor of NAFLD. This may help with early identification of high-risk individuals.

Keywords: Non-HDLc/HDLc ratio, prospective study, fatty liver disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) is an intricate multi-pronged disease covering a spectrum of liver pathologies, including non-alcoholic steatohepatitis (NASH), and hepatic steatosis [1, 2]. NAFLD, a common liver disease, with a prevalence of ~20%-30% in the general population and ~35.1-58.3% in Western countries, is also often associated with cardiovascular diseases (such as coronary heart disease [CHD]), dyslipidemia, and diabetes [3-6]. NAFLD not only appears to be a marker of metabolic disorders, but also appears to be actively involved in the formation of endothelial dysfunction and atherosclerosis [7, 8]. It is therefore important to determine the future development of NAFLD. Early intervention in these high-risk patients may prevent the occurrence of NAFLD. Interventions include education about healthy diet, physical exercise, and weight loss [9, 10].

NAFLD is closely associated withdyslipidemia [11]. The primary features of NAFLD patients are dyslipidemia in atherosclerotic lipid mass spectrum, low high-density lipoprotein cholesterol (low-HDLc), high triglyceride (TG) levels, low-density lipoprotein (LDL) particles, and an increase in TG-rich lipoproteins (including very-LDL [VLDL] and intermediate-density lipoprotein [IDL]) [11, 12]. Non-HDLc, defined as total cholesterol minus HDLc, includes IDL, VLDL, and LDL particles total cholesterol content. According to previous research, HDLc level was increased in patients with NAFLD in Africa [13, 14]. A recent study shows that nonHDLc is better than other indicators in predicting the occurrence of NAFLD [14].

Table 1. Baseline characteristics

nonHDLc/HDLc	Q1	Q2	Q3	*P*-value
Number	5324	5412	5437	
Age (years)	42.5 ± 14.8	43.1 ± 14.9	44.1 ± 15.1	<0.001
BMI	20.6 ± 2.0	21.4 ± 2.0	22.1 ± 1.9	<0.001
ALT	17.8 ± 17.9	19.4 ± 13.6	22.9 ± 17.3	<0.001
AST	22.4 ± 10.1	22.7 ± 8.7	24.0 ± 9.7	<0.001
Albumin	44.3 ± 2.8	44.4 ± 2.7	44.6 ± 2.6	<0.001
BUN	4.5 ± 1.4	4.6 ± 1.3	4.8 ± 1.4	<0.001
Cr	75.5 ± 26.3	78.9 ± 22.5	81.0 ± 27.7	<0.001
UA	249.6 ± 78.4	279.2 ± 82.9	310.0 ± 85.4	<0.001
FPG	5.0 ± 0.7	5.1 ± 0.8	5.3 ± 0.9	<0.001
TC	4.3 ± 0.7	4.6 ± 0.7	4.9 ± 0.7	<0.001
TG	0.9 ± 0.4	1.2 ± 0.5	1.8 ± 1.3	<0.001
HDLc	1.8 ± 0.3	1.5 ± 0.2	1.1 ± 0.2	<0.001
LDLc	2.0 ± 0.4	2.3 ± 0.4	2.5 ± 0.4	<0.001
nonHDLc	2.6 ± 0.5	3.2 ± 0.5	3.7 ± 0.6	<0.001
SBP	117.1 ± 16.4	120.7 ± 16.5	124.2 ± 16.5	<0.001
DBP	70.6 ± 9.9	72.7 ± 10.2	75.0 ± 10.5	<0.001
Sex (n, %)				<0.001
Male	2670 (50.2%)	2580 (47.7%)	2440 (44.9%)	
Female	2654 (49.8%)	2832 (52.3%)	2997 (55.1%)	
NAFLD (n, %)				<0.001
None	5043 (94.7%)	4740 (87.6%)	4068 (74.8%)	
Yes	281 (5.3%)	672 (12.4%)	1369 (25.2%)	

ALT, alanine aminotransferase; SBP, Systolic blood pressure; AST, BUN, TC, total cholesterol; blood urea nitrogen; BMI, body mass index; FPG, fasting plasma glucose; aspartate aminotransferase; TG, triglycerides; UA, uric acid; HDLc, high-density lipoprotein cholesterol; DBP, diastolic blood pressure; LDLc, low-density lipoprotein cholesterol; NAFLD, Cr, creatinine; non-alcoholic fatty liver disease. Values are presented as number (%) or mean ± standard deviation, U/L, mmol/L, kg/m^2, umol/L, and mmHg.

Prospective diabetes studies in the UK have found that non-HDLc/HDLc ratio is a more useful predictor of CHD in patients with type 2 diabetes than non-HDLc [15]. In addition, the ratio proved to be an effective predictor of the incidence of coronary heart disease in patients with chronic kidney disease (CKD) and the best predictor of insulin resistance [16].

This study aimed to assess whether non-HDLC/HDLc ratio is an independent predictor of NAFLD.

Methods

Study population

The methods and the study population presented here are an extension of a previously reported prospective study [17], carried out at the Wenzhou People's Hospital, Wenzhou city, China, between January 2010 and December 2014. The study comprised of a total of 33153 patients, which were initially NAFLD-free. However, only a total of 16173 NAFLD-free participants were included in the study. The 16173 participants finally included in the study completed the five-year follow-up examination. The inclusion and exclusion criteria are as previously reported in the literature [17]. The ethics committee of Wenzhou People's Hospital approved the research protocol. Informed consent was obtained before the study, as previously reported in the literature [17].

Data source

We retrieved our information from the 'DATADRYAD' database. Dryad data package of Wang et al, 2016 was cited in the study. The variables analyzed were: sex, age, low and HDLc, alanine aminotransferase (ALT), BMI, systolic and diastolic blood pressure (SBP/DBP), TG, albumin, fasting plasma glucose (FPG), uric acid (UA), aspartate transaminase (AST), fasting total cholesterol (TC), creatinine, TC, and blood urea nitrogen.

Ultrasonographic diagnosis of NAFLD

The NAFLD diagnosis was based on the diagnostic criterion of the Chinese Liver Disease Association [18].

Statistical analysis

Analyses in the study were all performed with EmpowerStats, and the statistical software package R. Categorical and continuous variables were, respectively, expressed as percentage or frequency, and normal distribution (mean ± standard deviation) or skewed distribution (median/quartile). Statistical differences were determined using chi-square tests, One-Way Anova, and Kruskal Wallis H test. The associa-

Table 2. Results of univariate analysis

	Statistics	Hazard ratio (95% CI)	*P*-value
Sex			
Male	7690 (47.5%)	1.0	
Female	8483 (52.5%)	1.2 (1.1, 1.3)	<0.001
Age	43.2 ± 15.0	1.0 (1.0, 1.0)	<0.001
BMI	21.4 ± 2.0	2.0 (1.9, 2.1)	<0.001
ALT	20.1 ± 16.5	1.0 (1.0, 1.0)	<0.001
AST	23.0 ± 9.5	1.0 (1.0, 1.0)	<0.001
Albumin	44.4 ± 2.7	1.0 (1.0, 1.0)	0.096
BUN	4.6 ± 1.4	1.0 (1.0, 1.0)	0.333
Cr	78.5 ± 25.7	1.0 (1.0, 1.0)	<0.001
UA	279.8 ± 85.9	1.0 (1.0, 1.0)	<0.001
FPG	5.1 ± 0.8	1.6 (1.5, 1.7)	<0.001
TC	4.6 ± 0.7	1.5 (1.4, 1.5)	<0.001
TG	1.3 ± 0.9	2.5 (2.3, 2.6)	<0.001
HDLc	1.5 ± 0.4	0.2 (0.2, 0.2)	<0.001
LDLc	2.3 ± 0.5	2.1 (1.9, 2.4)	<0.001
nonHDLc	3.2 ± 0.7	2.2 (2.0, 2.3)	<0.001
nonHDLc/HDLc	2.3 ± 0.9	2.1 (2.0, 2.2)	<0.001
SBP	120.7 ± 16.7	1.0 (1.0, 1.0)	<0.001
DBP	72.8 ± 10.4	1.1 (1.0, 1.1)	<0.001

tions between baPWV and TG/HDL were evaluated using a Univariate linear regression model (ULR), whereas a stratified regression model was used to determine the subgroups. A *P* value of <0.05 was considered significant.

Results

Baseline characteristics

A total of 16 173 initially NAFLD-free non-obese individuals were included in the final analysis (**Table 1**). After 33.65 months of observation, 2322 (14.36%) non-obese individuals developed NAFLD. The non-HDLc/HDLc ratios stratification groups defined by tertiles were group Q1: ≤1.83, group Q2: 1.83-2.57, and group Q3: ≥2.57. Compared with subjects in the lowest tertile of the non-HDLc/HDLc ratio, the following indicators are elevated: Age; BMI; AST; ALT; uric UA; FPG; TC; TG; LDLc; SBP; DBP. The NAFLD incidence significantly increased across the non-HDLc/HDLc tertiles (5.3% vs. 12.4% vs. 25.2% for tertile 1, 2, and 3, respectively).

Univariate analysis

The results of the univariate analysis (UA) showed that ALT, Cr, FPG, UA, age, TC, TG, HDLc, SBP, LDL-C, non-HDLc, BMI, AST, sex, DBP, and non-HDLc/HDLc were correlated with NAFLD. We found that albumin and BUN were not associated with NAFLD. The UA also indicated that female sex values were positively correlated, while the HDLc valueshowed negative correlation with the risk of NAFLD (**Table 2**).

The results of the relationship between non-HDLc/HDLc and NAFLD

We used the ULR model to evaluate non-HDLc/HDLc and NAFLD relationship (**Table 3**). Compared with patients in the lowest tertile, non-HDLc/HDLc ratios in the highest tertile had a 5-and a 0.5-fold increased risk of new-onset NAFLD) in both the minimally, and fully adjusted model (adjusted age, sex) (HR=6.0; 95% CI, 5.2-6.8; P<0.001, and HR=1.5; 95% CI, 1.1-2.0; *P*=0.011, respectively).

The non-linear relationship analyses (NLR)

Since the non-HDLc/HDLc is a continuous variable, NLR analysis is essential. In the present study (**Figure 1**), we found non-HDLc/HDLc and NAFLD relationship to be non-linear after adjusting Cr, AST, FPG, UA, ALT, sex, TC, TG, BMI, HDLc, SBP, LDLc, age, and DBP. By the two-piecewise regression model, the inflection point was 3.34. Hence, we calculated the left inflection point *p*-value, 95% CI, and the effect size to be 1.6, 1.3, and 1.4, <0.01, respectively. However, on the right of the inflection point, we found the non-HDLc/HDLc and the NAFLD relationship to be 0.8, 0.7 to 1.0, 0.034 respectively (**Table 5**).

The subgroup results analyses

The interactions test results were statistically significant for AST, BUN, Age, Cr, UA, TC, SBP and DBP (*P*-values for interaction <0.05), whereas the interactions test results showed no statistical significance for ALT, albumin, Sex, FPG, TG, and BMI (*P*-values for interactions >0.05) (**Table 4**).

The non-HDLc and the non-HDLc/HDLc ratio predictive value for the risk of NAFLD

A ROC curve analysis was used to compare the predictive values (**Figure 2**), It showed that the AUCs for non-HDLc/HDLc ratio were significantly higher than those for the non-HDLc value (0.705; 95% CI, 0.694-0.716, and 0.656; 95%

Table 3. Relationship between nonHDLc/HDLc and NAFLD in different models

Variable	Crude model	Model 1 (HR, 95% CI, *P*)	Model 2 (HR, 95% CI, *P*)
nonHDLc/HDLc (quartile)			
Q1	1.0	1.0	1.0
Q2	2.5 (2.2, 2.9) <0.001	2.5 (2.2, 2.9) <0.001	1.3 (1.1, 1.7) 0.014
Q3	6.0 (5.3, 6.9) <0.001	6.0 (5.2, 6.8) <0.001	1.5 (1.1, 2.0) 0.011

Model 1 is adjusted for sex and age. Model 2 is adjusted for ALT; AST; Sex; Albumin; BUN; Age; CR; UA; GLU; TG; HDLc; LDLc; BMI; SBP; DBP.

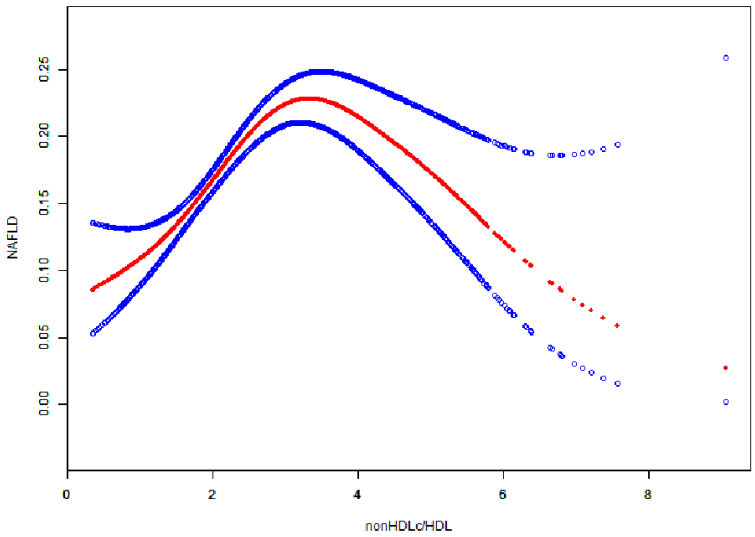

Figure 1. Relationship between nonHDLc/HDLc and NAFLD. A nonlinear relationship between them was detected after adjusting for ALT, AST, Albumin, BUN, CR, Age, UA, GLU, TG, HDLc, sex, LDLc, BMI, SBP and DBP.

CI, 0.644-0.667, P<0.01, respectively). The optimal non-HDLc/HDLc ratio cut-off value for the identification of NAFLD was 2.26, with a specificity of 58.2% and a sensitivity of 72.9%.

Discussion

It has been determined that dyslipidemia in NAFLD patients is characterized by increased serum triglyceride levels and reduced HDL levels [11]. However, in recent years, there has been increasing evidence of the role of cholesterol in the pathogenesis of NAFLD. However, it is unclear whether lipoprotein abnormalities may cause NAFLD attacks. In this study, we proved that non-HDLc/HDLc is an independent predictor of NAFLD occurrence. In this study, we demonstrated for the first time that the non-HDLc/HDLc ratio is an independent predictor of NAFLD and is more useful than nonHDLc in the non-obese Chinese population.

Studies have shown that cholesterol homeostasis of metabolic disorders is a critical factor in the pathogenesis of NAFLD [19]. Several experimental and observational studies have shown that changes in the release and synthesis of LDL, IDL, and VLDL might play an essential role in the pathogenesis of NAFLD [20]. Increasing evidence suggests that cholesterol-lowering therapies can effectively reduce cardiovascular disease and improve liver damage in patients with NAFLD [21]. Excessive intracellular cholesterol leads to activation of liver X receptors (LXRs), which induces liver steatosis [22]. Furthermore, LXRs may facilitate very low density lipoprotein (a VLDL) secretion. Accompanying hypertriglyceridemia and increased VLDLs underlie the synthesis of LDL with a weak affinity for its receptor. Oxidized LDLs could promote inflammatory responses by binding to scavenger receptors. However overexpression of inflammatory cytokines caninhibits cholesterol elimination through bile acids and activates cholesterol synthesis. This consequentially, leads to an increase in LDLc and a reduction in HDLc.

It is reported in the literature that the non-HDLc/HDLc ratio can adequately represent the balance between pro-atherosclerotic and anti-atherosclerotic lipoproteins as well as identify comprehensive lipid disorders [XX]. Studies have shown that the ratio of non-HDLc/HDLc is better at predicting cardiovascular disease than non-HDLc [23], as well as a better predictor for metabolic syndrome and insulin resis-

Table 4. Effect size of nonHDLc/HDLc on NAFLD in prespecified and exploratory subgroups

Characteristic	No. of participants	Effect Size (95% CI)	*P* for interaction
Sex			0.974
Male	7690	2.1 (1.9, 2.2)	
Female	8483	2.1 (1.9, 2.2)	
Age (year)			0.004
14-33	5079	2.2 (2.0, 2.5)	
34-46	5391	2.2 (2.0, 2.4)	
47-95	5703	1.9 (1.7, 2.0)	
ALT			0.532
1-13	3977	1.9 (1.7, 2.2)	
14-19	3786	2.0 (1.8, 2.2)	
20-674	4365	1.9 (1.8, 2.0)	
AST			0.004
5-18	3197	2.5 (2.2, 2.8)	
19-23	4816	2.1 (2.0, 2.3)	
24-311	4115	1.9 (1.7, 2.0)	
Albumin			0.736
11-42	3289	2.0 (1.8, 2.2)	
43-45	6264	2.0 (1.9, 2.2)	
46-55	5241	2.0 (1.8, 2.1)	
BUN			<0.001
1-3	3133	2.6 (2.3, 2.9)	
4-4	5342	2.3 (2.2, 2.6)	
5-31	7697	1.8 (1.7, 1.9)	
Cr			<0.001
10-67	5282	1.7 (1.5, 1.9)	
68-84	5300	2.1 (1.9, 2.3)	
85-1004	5590	2.2 (2.0, 2.3)	
UA			0.018
17-232	5336	2.2 (1.9, 2.5)	
233-310	5406	1.8 (1.6, 1.9)	
311-706	5430	1.8 (1.7, 1.9)	
FPG			0.067
2.54-4.83	5278	2.1 (1.9, 2.4)	
4.84-5.2	5401	2.1 (2.0, 2.3)	
5.21-20.87	5493	1.9 (1.7, 2.0)	
TC			0.044
2-4.29	5384	2.3 (2.1, 2.6)	
4.3-4.93	5361	2.0 (1.8, 2.2)	
4.94-15.92	5428	2.0 (1.8, 2.1)	
TG			0.636
0.23-0.88	5295	1.5 (1.3, 1.9)	
0.89-1.32	5402	1.4 (1.2, 1.6)	
1.33-30.39	5476	1.5 (1.4, 1.6)	
BMI			0.538
14.53-20.42	5353	1.9 (1.5, 2.3)	
20.43-22.46	5424	1.8 (1.6, 2.0)	

tance [16]. The results of this study shows clinical significance in several practical ways. Compared with traditional lipid parameters, nonHDLc/HDLc ratio can be used as a more effective biomarker to predict and treat NAFLD. Best nonHDLc/HDLc ratio may play an important role in the high-risk groups as a screening test for NAFLD. In addition, nonHDLc values can be easily obtained from conventional fasting blood lipid profiles regardless of TG levels, reducing the need for other and more expensive apolipoprotein B diagnostic tests.

The present study has several limitations. Firstly, NAFLD is diagnosed by ultrasound rather than liver histopathology. However, liver ultrasound has been identified as a reliable and accurate tool for detecting fatty liver. Secondly, although we have adjusted for several potential confounding variables, but it may not completely solve the problem of residual and unmeasured confounding variables. Thirdly, as participants of the study were taken from a Chinese population, the results of this study may not apply to people of other races.

Conclusion

Our research provides practical proof for the primary prevention of NAFLD. Through lifestyle interventions (including active exercise, diet adjustments, and weight loss), maintaining the nonHDLc/HDLc ratio within an appropriate range is an effective way to reduce progression of NAFLD.

22.47-25	5396	1.7 (1.6, 1.8)	
SBP			<0.001
77-111	5064	2.7 (2.4, 3.0)	
112-125	5575	2.0 (1.9, 2.2)	
126-208	5514	1.7 (1.6, 1.8)	
DBP			0.002
45-66	4872	2.2 (2.0, 2.5)	
67-76	5824	2.1 (1.9, 2.3)	
77-125	5457	1.8 (1.7, 1.9)	

Table 5. Results of two-piecewise linear regression model

Inflection point of nonHDLc/HDLc	Effect size (HR)	95% CI	*P* value
<3.34	1.4	1.3 to 1.6	<0.01
≥3.34	0.8	0.7 to 1.0	0.034

Effect: NAFLD Cause: nonHDLc/HDLc. Adjusted: Cr, FPG, BMI, UA, age, ALT, TC, sex, TG, DBP, HDLc SBP, LDLc, and AST.

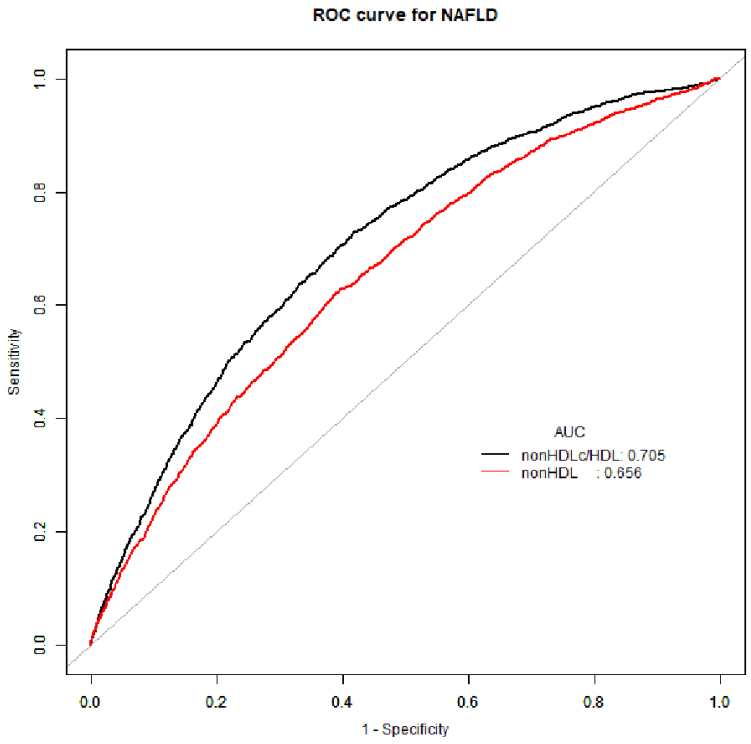

Figure 2. ROC curves of the non-HDLc/HDLc ratio and the non-HDLc for NAFLD. Black line and red line are non-HDLc/HDLc ratio, and non-HDLc value, respectively.

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Disclosure of conflict of interest

None.

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