Association of the Non-HDL-cholesterol to HDL-cholesterol Rate and the Risk of Non-alcoholic Fatty Liver Disease Among Children and Adolescence: A Retrospective Cohort Study

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Research

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Abstract

Background: The non-HDL-cholesterol to HDL-cholesterol (non-HDL-c/HDL-c) rate shows a close relationship to multiple dyslipidemia related disease. This paper aims at investigating the association of the non-HDL-c/HDL-c rate and the risk of NAFLD among children and adolescence in China.

Methods: In this retrospective cohort study, a total of 7759 eligible children and adolescence (5692 boys, 2067 girls) having received regular medical examination were recruited. We collected anthropometric measurements and laboratory tests data of subjects. The binary logistics regression was employed for the assessment of the associations of the non-HDL-c/HDL-c rate with NAFLD. Sex-specific ROC curve analysis was conducted for comparing the predictive value of non-HDL-c/HDL-c rate, non-HDL-c and HDL-c for NAFLD.

Results: The total NAFLD prevalence was 4.36%, higher in boys than that in girls (5.61% vs. 1.9%, P<0.001). It is noteworthy that NAFLD prevalence displayed positive correlation with the non-HDL-c/HDL-c rate（Chi-square test, P<0.001). The binary logistics regression analysis shows that the OR were 8.61 (95% CI = 5.90-12.57, P< 0.001) in the maximum tertiles (maximum non-HDLc/HDLc ratio) compared with the minimum tertiles. When potential confounders were regulated, compared with the minimum tertiles, the OR for the maximum tertiles (OR=3.94, 95%CI=2.33-6.66, P< 0.001) was still significantly higher. AUC values of the non-HDL-c/HDL-c rate (0.787 in boys and 0.763in girls) noticeably reached over non-HDL-c (0.719 in boys and 0.661 in girls) and HDL-c (0.726 in boys and 0.732 in girls). Furthermore, the optimal cutoff value of the non-HDL-c/HDL-c rate for NAFLD was 2.475 in boys and 2.695 in girls.

Conclusions: The present study indicate that a higher non-HDL-c/ HDL-c rate caused a higher risk of NAFLD among children and adolescence. Moreover, the non-HDL-c/HDL-c rate showed a better predictive value for NAFLD than the non-HDL-c and HDL-c in both boys and girls.

Background

Non-alcoholic fatty liver disease (NAFLD) refers to a chronic liver disease, involving fatty liver or hepatic steatosis, as well as nonalcoholic steatohepatitis (NASH)[1]. Nowadays, NAFLD is shifting to the most frequent reason for chronic liver disease in pediatric population. Given epidemiological data, NAFLD prevalence is 2.6–7.1% of all children and about 27.8–41.2% of obese children. Furthermore, the incidence rate of NAFLD is on the rise[2] [3].

NAFLD is now recognized as a metabolic syndrome manifested in hepatic area, and its progressive form NASH elevating the risk of liver cancer, end-stage liver disease and cirrhosis[4]. Furthermore, Pediatric NAFLD is considered to be related to the pathogenesis of cardiovascular disease, metabolic syndrome and diabetes mellitus[5]. Since children with NAFLD are usually symptomless, it is challenging to diagnosis of NAFLD among pediatric population. Liver biopsy is known as the gold standard for NAFLD diagnosis, whereas it is not readily accepted by children as its invasive nature. Liver ultrasonography refers to a feasible and noninvasive mean to diagnose NAFLD, whereas not all children undergo liver

ultrasonography since their parents may be reluctant to let them receive medical examination for a clinically silent disease[6]. Thus, valuable predictors for NAFLD should be identified for early detection and prevention of later progression.

Non-high-density lipoprotein cholesterol (non-HDL-c), which refers to total cholesterol (TC) minus high-density lipoprotein cholesterol (HDL-c), is regarded as secondary target of lipid-lowering therapeutic method. Several studies reported that the non-HDL-c/HDL-c rate displays close relationships to multiple dyslipidemia-related disease. A Prospective study form UK reported the non-HDL-c/HDL-c rate can more significantly predict coronary heart disease in type 2 diabetes than non-HDL-c[7]. Moreover, The non-HDL-c/HDL-c rate is an independent risk factor of chronic kidney disease and gallbladder polyp, and it is an ideal marker for insulin resistance and metabolic syndrome[8–10]. As revealed from a perspective cohort study, non-HDL-c/HDL-c rate can more noticeably predict new-onset NAFLD than Non-HDL-c among adults[11]. However, the association between the non-HDL-c/HDL-c ratio and NAFLD among pediatric population remians unknown. Therefore, this retrospective study aims at exploring the association of the non-HDL-c/HDL-c rate and the risk of NAFLD among Chinese children and adolescence.

Materials And Methods

Subject

7759 children and adolescence (age 2–18 years) having received regular medical examination from January 2015 to January 2020 in the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University were retrospectively reviewed. Exclusion criteria were metabolic liver disease, hepatitis B virus or hepatitis c virus infection, Wilson's disease, medication use in the past 1 months, hereditary hyperlipidemia and alcohol consumption.

Anthropometric measurements and laboratory tests

The clinical and anthropometric measurements assessed were age, gender, weight and height. Height and weight were tested on the same day, which were nearest 0.01 kg and 0.01 m. BMI was weight (kg) divided by height squared (m^2). Children referred to obesity if their BMI above 95th percentile[12]. As for laboratory test, under standard laboratory procedures, this study employed fasting blood samples to delve into metabolic variables. This study collected the parameters, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG), total cholesterol (TC), albumin(ALB), uric acid (UA), glycosylated hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG). By the Homeostasis Model Assessment of IR (HOMA-IR), insulin resistance (IR) was determined. By the Quantitative Insulin-sensitivity Check Index (QUICKI), this study conducted the evaluation of insulin-sensitivity (IS). HOMA-IR index and QUICKI were calculated by: HOMA-IR = fasting insulin (U/mL) × fasting glucose (mg/dL)/405, QUICKI = 1/[log fasting insulin(U/ml) + log fasting glucose (mg/dl)][13].

Ultrasonography

Liver ultrasonography was performed by an experienced expert with a Philips En2visor26 type ultrasonic diagnostic instrument (probe frequency 3.5-5.0 MHz). The NAFLD was diagnosed based on the following radiologic parameters: deep attenuation of ultrasound signal, vascular blurring, and diffusely increased echogenicity (bright) liver exhibiting liver echogenicity over kidney or spleen[14].

Statistical analysis

All data were analyzed by SAS version 9.3 (SAS Institute, Cary, NC). Means ± standard deviations denoted continuous data, and categorical variables were expressed as percentages. For the assessment of the difference in groups, this study performed independent sample t-test for continuous variables with normal distribution and Chi-square test for categorical data. The binary logistics regression was applied to assess odds rates (OR) and 95% confidence intervals (CI) in terms of the relationships of the non-HDL-c/HDL-c rate and NAFLD. For the assessment of the utility of different lipid levels as predictors for NAFLD, sex-specific receiver operating characteristic (ROC) curve was plotted for the cut-off level of the non-HDL-c/HDL-c rate to predict NAFLD. $P < 0.05$ was considered exhibiting statistical significance. Figures here were generated by Graphpad prism 6 project.

Results

Baseline characteristics

This study recruited a total of 7759 eligible children and adolescence (5692 boys, 2067 girls). Table 1 draws the comparison of the baseline characteristics of participants by tertiles of the non-HDL-c/HDL-c rate. Significant differences were identified in the three groups. In contrast to subjects in the maximum tertile of the non-HDL-c/HDL-c rate, those in the minimum tertile were had lower ALT, UA, ALB, TC, TG, LDL, HBA1C(%), FBG, HOMA-IR and higher HDL and QUICKI ($P < 0.001$). The incidence of obesity noticeably rose across non-HDL-c/HDL-c tertiles (4.81% vs. 9.22% vs. 21.18%, for tertile 1 vs. tertile 2 vs. tertile 3, respectively, $P < 0.001$).

Table 1
Baseline characteristics by tertiles of the non-HDL-c/HDL-c rate

characteristics	non-HDL-c/HDL-c ratio			*P* value
	Tertile 1	Tertile 2	Tertile 3	
	(≤ 1.79)	(1.80–2.36)	(≥ 2.37)	
Sample size	2577	2580	2602	
Age (year)	9.24 ± 3.11	9.00 ± 3.31	9.03 ± 3.47	0.017
Sex, n (%)				< 0.001
Girl	771 (29.92)	950 (36.82)	906 (34.82)	
Boy	1806(70.08)	1630(63.18)	1696(65.18)	
ALT (U/L)	15.12 ± 8.49	15.93 ± 17.55	19.27 ± 19.88	< 0.001
AST (U/L)	26.51 ± 6.75	26.64 ± 13.29	27.09 ± 13.62	0.175
Uric acid (umol/L)	300.55 ± 69.92	305.06 ± 73.84	327.42 ± 85.44	< 0.001
Albumin (g/L)	45.36 ± 2.22	45.48 ± 2.17	45.78 ± 2.33	< 0.001
Total cholesterol (mmol/L)	4.09 ± 0.63	4.27 ± 0.65	4.62 ± 0.82	< 0.001
Triglycerides (mmol/L)	0.77 ± 0.30	0.89 ± 0.36	1.21 ± 0.64	< 0.001
HDL-c (mmol/L)	1.67 ± 0.29	1.39 ± 0.22	1.17 ± 0.21	< 0.001
LDL-c (mmol/L)	1.90 ± 0.45	2.31 ± 0.46	2.79 ± 0.67	< 0.001
HBA1C (%)	5.43 ± 0.29	5.43 ± 0.27	5.46 ± 0.29	0.001
Fasting plasma glucose (mmol/L)	4.68 ± 0.39	4.70 ± 0.38	4.73 ± 0.37	< 0.001
HOMA-IR	1.42 ± 1.28	1.67 ± 1.93	2.16 ± 2.07	< 0.001
QUICK	0.76 ± 0.18	0.73 ± 0.17	0.68 ± 0.17	< 0.001
Percentage of obesity(N[%])	124 (4.81%)	238 (9.22%)	551 (21.18%)	< 0.001
Data are expressed as the mean ± SD or percentage				
ALT Alanine aminotransferase; AST Aspartate aminotransferase; IDL-c low-density lipoprotein cholesterol; HDL-c High-density lipoprotein cholesterol; HbA1c Glycosylated hemoglobin A1c; HOMA-IR Homeostasis Model Assessment of IR; QUICKI Quantitative Insulin-sensitivity Check Index				
Children referred to obesity if their BMI above 95th percentile				

NAFLD prevalence and the rise of the non-HDL-c/HDL-c rate

NAFLD prevalence showed positively correlation with the non-HDL-c/HDL-c rate. The proportion of subjects who had NAFLD in tertile 2 (2.33%, $P < 0.001$) and tertile 3 (9.49%, $P < 0.001$) was significantly

higher than that in tertile 1 (1.2%). NAFLD prevalence in tertile 3 was nearly eight time larger compared with that of tertile 1. (Fig. 1)

Gender specific differences on the prevalence of pediatric NAFLD

The overall NAFLD prevalence was 4.36%. It is noteworthy that NAFLD prevalence in boy was higher than that in girl. (5.61% vs. 1.9%, $P < 0.001$) (Fig. 2).

Association between the non-HDL-c/HDL-c rate and the incidence of NAFLD in children and adolescence

Table 2 lists the results of the binary logistics regression analysis. The OR for NAFLD was significantly elevated as the tertiles of non-HDL-c/HDL-c rate arose. For a function of the tertiles of non-HDL-c/HDL-c rate, the OR for NAFLD was 8.61 (95% CI = 5.90-12.57, $P < 0.001$) in children and adolescence, in the maximum tertiles compared with the minimum tertiles. Further adjustment of age, sex, ALT, UA, ALB, FBG, HOMA-IR exerted no effect on this association. In comparison with tertile 1, the OR for tertile 3 (OR = 3.94, 95%CI = 2.33–6.66, $P < 0.001$) was still significantly higher. Moreover, 0.9 μmol/L increase in the non-HDL-c/HDL-c rate showed associations with 2.70 fold larger danger of getting NAFLD (OR = 2.70, 95%CI = 2.19–3.34, $P < 0.001$). As revealed from the mentioned findings, higher non-HDL-c/HDL-c ratio was highly positively associated with an increased risk of NAFLD among children and adolescence.

Table 2
Odds ratios (95% CI) for NAFLD by non-HDL-c/HDL-c ratio

Non-HDL-c/HDL-c ratio	N	Cases (%)	Crude		Adjusted*	
			OR(95%CI)	*P*	OR(95%CI)	*P*
Category variable						
Tertile 1 (≤ 1.79)	2577	31 (1.20)	1.0(1.0,1.0)	Ref.	1.0(1.0,1.0)	Ref.
Tertile 2(1.80–2.36)	2580	60 (2.33)	1.96(1.16,3.03)	0.002	1.56(0.85,2.85)	0.014
Tertile 3 (≥ 2.37)	2602	247 (9.49)	8.61 (5.90,12.57)	0.000	3.94 (2.33,6.66)	0.000
Continuous variable						
Per IQR(= 0.9)	7759	338(4.34)	3.24(2.87,3.66)	0.000	2.70(2.19,3.34)	0.000
Data are odds rates (OR) and 95% confidence intervals (CI), *P* value						
HDL-c High-density lipoprotein cholesterol						
Adjusted* for age, sex, alanine aminotransferase, uric acid, albumin, fasting plasma glucose, HOMA-IR						

The predictive value of the non-HDL-c/HDL-c rate for NAFLD risk

To compare the predictive value of non-HDL-c/HDL-c rate, non-HDL-c and HDL-c for NAFLD, this study conducted the sex-specific receiver operating characteristic (ROC) curve analyses (Fig. 3). The area under the curves (AUCs) of the non-HDL-c/HDL-c rate (AUC = 0.787, 95% CI = 0.758–0.816 in boys and AUC = 0.763, 95% CI = 0.688–0.837 in girls) noticeably reached over those of non-HDL-c (AUC = 0.719, 95% CI = 0.687–0.751 in boys and AUC = 0.661, 95% CI = 0.580–0.743 in girls) and those of HDL-c (AUC = 0.726, 95% CI = 0.698–0.755 in boys and AUC = 0.732, 95% CI = 0.663–0.802 in girls). Furthermore, the optimal cutoff value of the non-HDL-c/HDL-c rate for NAFLD in boys was 2.475, exhibiting a sensitivity of 71.18% and a specificity of 74.46%; besides, the cutoff value in girls was 2.695, exhibiting a sensitivity of 66% as well as a specificity of 80.09%.

Discussion

In the present retrospective cohort study, we found for first time that a higher non-HDL-c/ HDL-c rate had a higher risk of NAFLD among children and adolescence. It is noteworthy that the mentioned relationship lasted when potential confounders were regulated. Moreover, the non-HDL-c/HDL-c rate a better predictive value for NAFLD than the non-HDL-c and HDL-c in both boys and girls. The findings of this study suggested that the non-HDL-c/HDL-c ratio may help early identify NALFD among children and adolescents.

Previous studies had confirmed that metabolic syndrome(MetS) and obesity are the major risk factors for paediatric NAFLD and dyslipidemia play a pivotal role in NAFLD pathogenesis[4, 15]. Recent clinical trials suggest that statin-based therapies (lipid-lowing drug statin treatment) could improve liver tests and live ultrasonographic evidence of NAFLD patients[16]. The dyslipidemia in NAFLD is characterized by elevated conditions of TG and dense low-density lipoprotein (LDL) particles and decreased conditions of low high-density lipoprotein (HDL) cholesterol[17]. In NAFLD, as driven by lipid metabolism abnormalities, excess fat undergoes accumulation in the hepatocytes. The mentioned intrahepatic lipid accumulating was attributed to decreased triglycerides (TG) export and significantly low density lipoprotein (VLDL) synthesis as well as liver free fatty acid (FFA) uptake [18, 19]. Ectopic lipid overloading in hepatocytes are associated with an induction of inflammation and oxidative stress, and the secreting of several cytokines (including adiponectin, interleukins (ILs) and tumor necrosis factor (TNF))[20]. Moreover, excess of FFAs form to fatty acyl-CoAs catalyzed by acetyl coenzyme A (acyl-CoA), thereby probably inducing β-oxidation pathways. The above inflammation, oxidative stress are involved in NAFLD initiation and progression [21, 22].

Non-HDL-c contains multiple lipoproteins(lipoprotein A, intermediate-density lipoprotein (IDL), low density lipoprotein (LDL) and very-low-density lipoprotein (VLDL)) and was demonstrated as a secondary targets for lipid-lowering therapy[23]. In comparison with the non-HDL-c, the non-HDL-c/HDL-c rate can cover more comprehensive abilities of lipid dysregulation and better for assessing lipid-related disease risk.

Existing studies reported that non-HDL-c/HDL-c rate more effectively predicts CVD in type 2 diabetes than non-HDL-c[11], and the ratio exhibits higher predictive value than the apoB/apoA1 rate in terms of insulin resistance and MS[8]. Moreover, as revealed from a perspective cohort study, non-HDL-c/HDL-c rate outperforms non-HDL-c in predicting new-onset NAFLD in Chinese adult population[11]. Thus, the associations of the non-HDL-c/HDL-c rate and the risk of NAFLD among children and adolescence should be explored.

Dividing the baseline characteristical data of 7759 participants into tertiles according to non-HDL-c/HDL-c ratio, we found anthropometric variables such as ALT, TG, LDL, HBA1C(%), FBG were higher in the highest tertile than the lowest one, The similar results can be found in previous studies[24]. As expected, the incidence of obesity significantly increased across non-HDL-c/HDL-c tertiles. In addition, the prevalence of NAFLD increased as the tertiles of the non-HDL-c/HDL-c ratio rose. The binary logistics regression analysis suggested that higher non-HDL-c/HDL-c ratio was highly positively associated with an increased risk of NAFLD. In terms of gender distribution, Our study found the prevalence of NAFLD by gender was significant higher in boys compared to girls. The result of this study complies with Brunt EM et al.[25] and Welsh JA et al.[26], demonstrating that boys are more likely to develop NAFLD than girls. It has been indicated this phenomenon may be attributed to the potential protective role of estrogen against hepatic steatosis[27, 28].

The findings here are of certain clinical implications. We performed ROC curve analyses to explore the predictive value of the non-HDL-c/HDL-c ratio for NAFLD risk. Our findings suggest that the non-HDL-c/HDL-c ratio may serve as a more effective predictor for pediatric NAFLD than non-HDL-c and HDL-c. The optimal cutoff values of the non-HDL-c/HDL-c rate to identify NAFLD was 2.475 in boys and 2.695 in girls. Besides, the non-HDL-c/HDL-c rate exhibits simplicity and feasibility to determine. Accordingly, the non-HDL-c/HDL-c rate might feasibly achieve prediction and be used for screening for NALFD among children and adolescents.

Some limits are worth noting here. First, the diagnosis of NAFLD was performed using ultrasonography instead of liver biopsy (gold standard for diagnosing NAFLD) which is limited for its complications and invasiveness. However, the sensitivity of ultrasonography is low when NAFLD with fat contents less than 30%, thereby probably causing misdiagnosis[29]. Second, since this was a single center cohort study, largescale and multiple center studies should be conducted to confirm our conclusions of the present study. Third, this study had a retrospectively designing process, so the causality between non-HDL-c/HDL-c rate and NAFLD is not able to be overall set. The association requires confirmation by prospective retrospective study.

Conclusions

To sum up, as proved by the results of this study, a higher non-HDL-c/ HDL-c rate had a higher risk of NAFLD among children and adolescence for the first time. Moreover, the non-HDL-c/HDL-c rate showed a better predictive value for NAFLD than the non-HDL-c and HDL-c borth in boys and girls, which is simple

and feasible to get by calculating from traditional lipid measures. For the mentioned reason, the non-HDL-c/HDL-c rate may be an effective predictor to detect individuals at risk of NAFLD and facilitate the prevention of the disease progression and favor long-term outcomes.

Abbreviations

NAFLD: Non-alcoholic fatty liver disease; Non-HDL-c/HDL-c: Non-HDL-cholesterol to HDL-cholesterol; NASH: Nonalcoholic steatohepatitis; Non-HDL-c: Non-high-density lipoprotein cholesterol; TC: Total cholesterol; HDL-c: High-density lipoprotein cholesterol; AST: Aminotransferase; ALT: Alanine aminotransferase; LDL: Low-density; HDL: High-density lipoprotein; TG: Triglycerides; ALB: Albumin; UA: Uric acid; FPG: Fast plasma glucose; HOMA-IR: Homeostasis Model Assessment of IR; QUICKI: Quantitative Insulin-sensitivity Check Index; OR: Odds rate; CI: Confidence intervals; ROC: Receiver operating characteristic; AUC: Area under the curve

Declarations

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Authors’ contributions

SXY and XHZ designed the study and and wrote the manuscript; MSY, GRL, LM and JWZ collected anthropometric measurements and laboratory tests data, XZX analysed the data. All authors approved the final manuscript.

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Availability of data and materials

All data used in this study are available from the corresponding Author.

Ethics approval and consent to participate

This retrospective study protocol obtained the approving documents from the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. All children’s parents provided informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

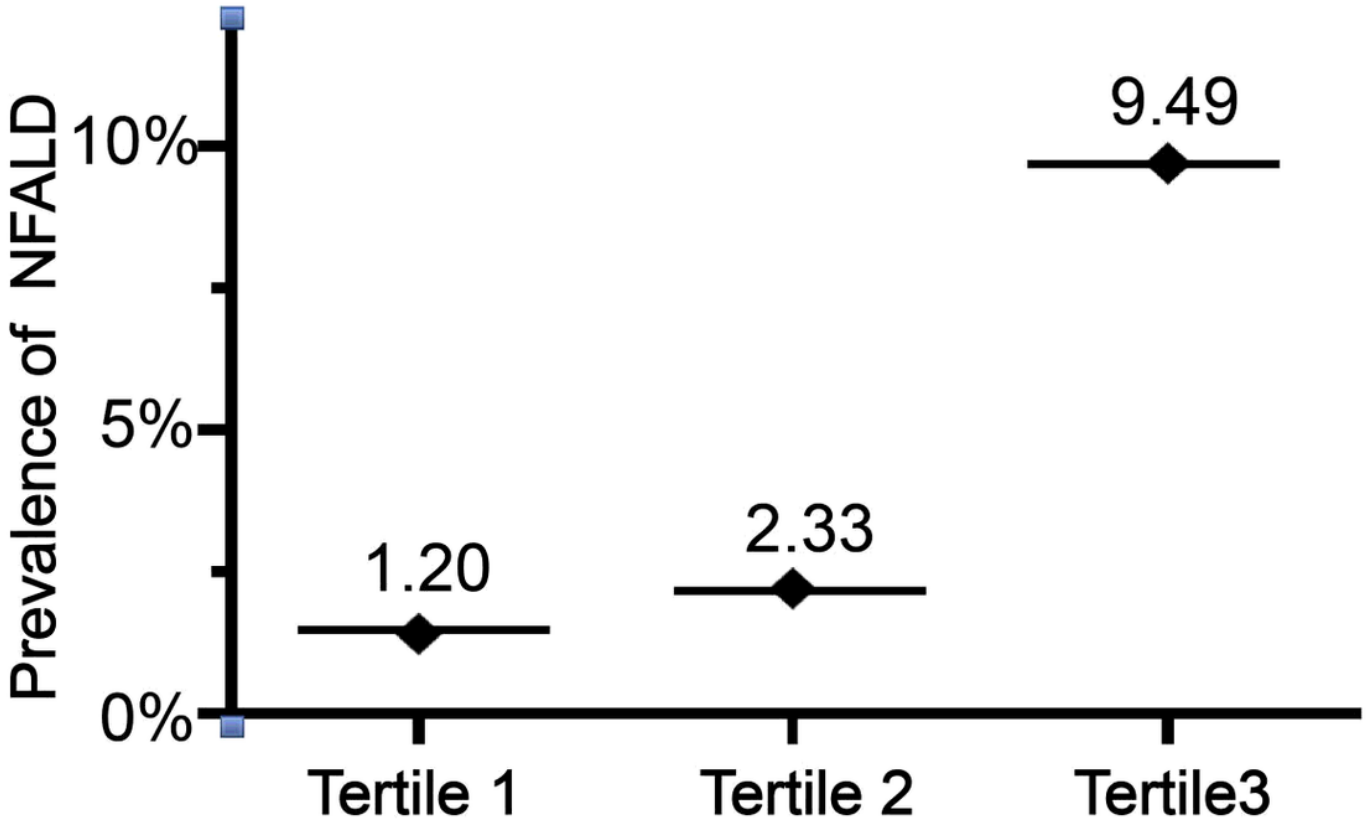

Figure 1

The prevalence of NAFLD according to the non-HDL-c/HDL-c ratio tertiles

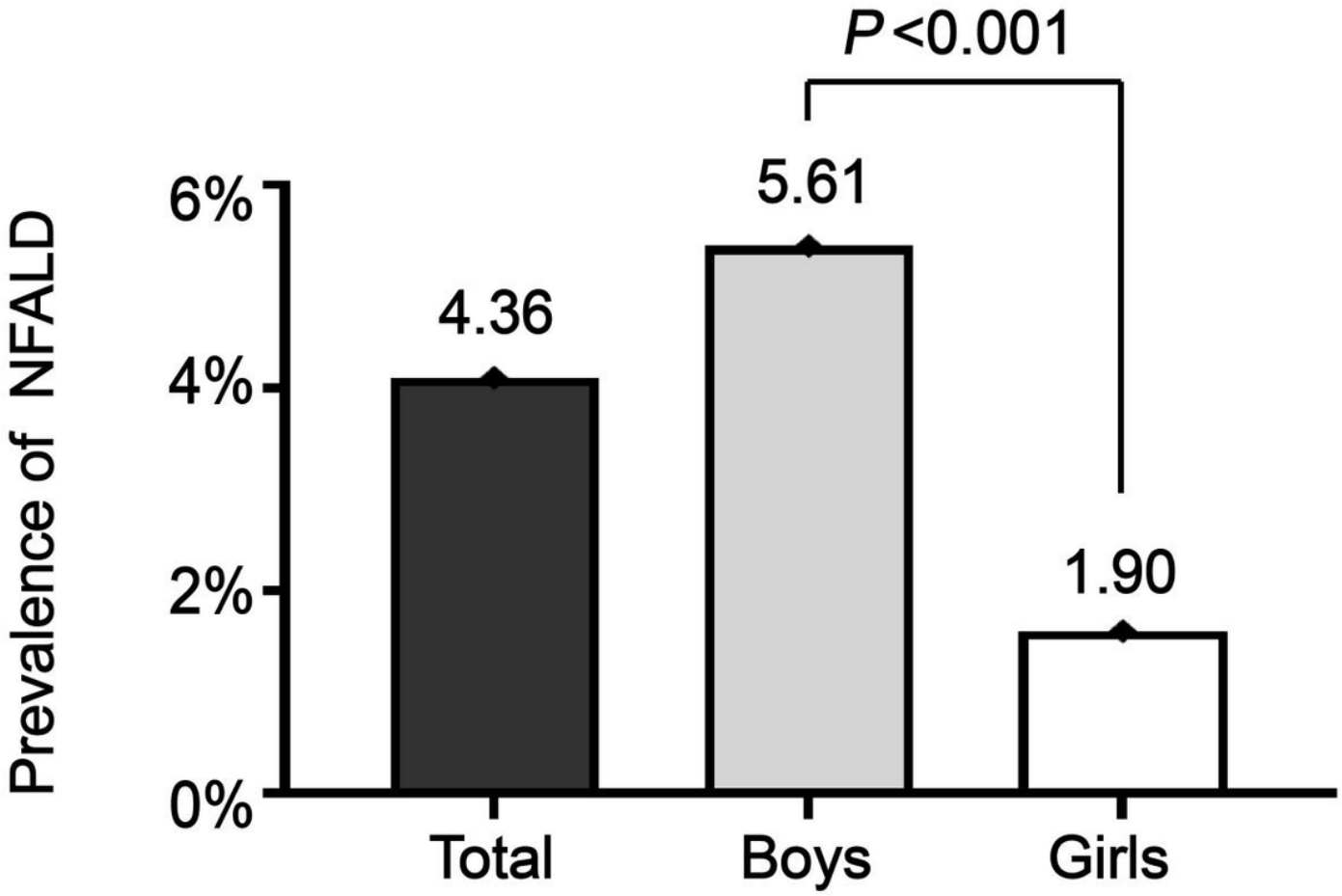

Figure 2

Gender specific differences on the prevalence of pediatric NAFLD

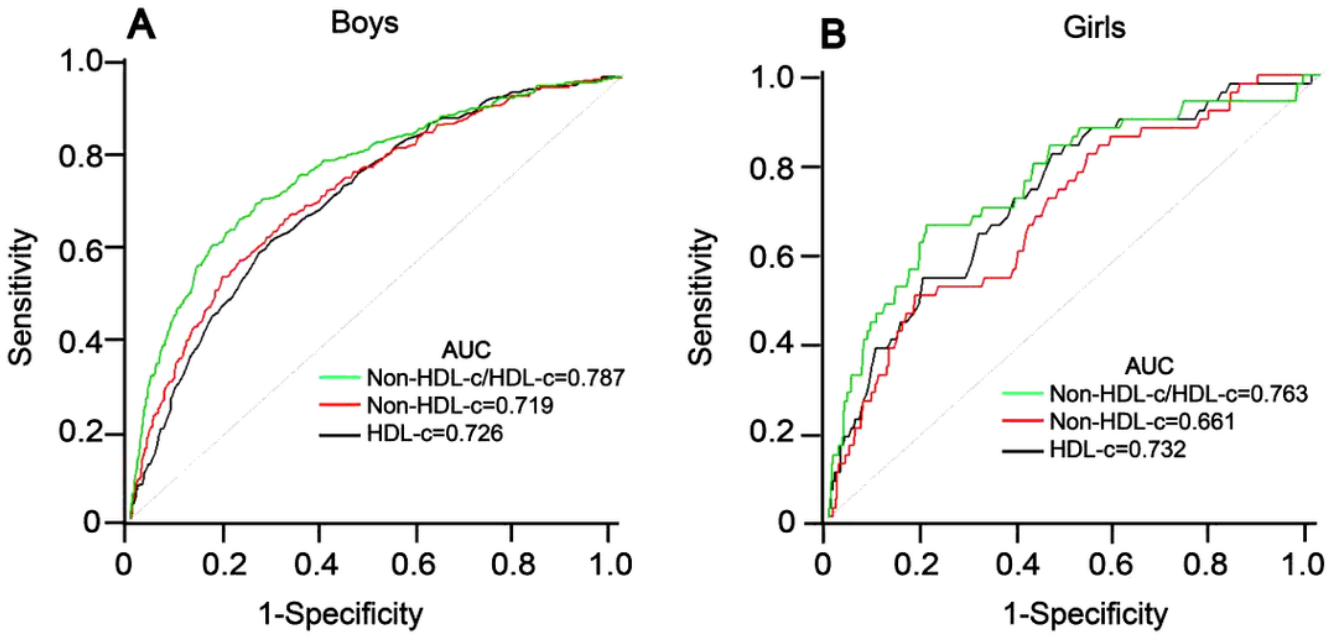

Figure 3

Receiver operating characteristic curve of non-HDL-c/HDL-c ratio, HDL-c and non-HDL-c for NAFLD in boys (A) and girls (B)