Triglycerides to Total Cholesterol Ratio: An Early Screening Tool for NAFLD in Chinese Populations

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Research

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Abstract

Background: Non-alcoholic fatty liver disease(NAFLD) has a high prevalence in the general population worldwide. Both triglycerides (TG) and total cholesterol (TC) are correlated with the prevalence of NAFLD. The study purpose is to determine whether TG/TC is an effective method to screen NAFLD in the general Chinese population.

Methods: 93,449 subjects with average age of 43.7 ± 14.3 years were included in this cross-sectional study. Multiple logistic regressions and receiver operator characteristic curve (ROC) analyses were performed.

Results: Among these subjects, 16,138 (42.7%) men and 9,591 (17.2%) women were diagnosed with NAFLD. Subjects in the higher quartiles of TG/TC had a higher prevalence of NAFLD. After adjusting multiple confounding factors, the odds ratio (OR) for NAFLD in the highest compared with the lowest quartile was 4.08 (95%CI 3.64, 4.57) in men and 4.65 (95%CI 4.14, 5.21) in women. Moreover, ROC analyses suggested TG/TC showed high diagnostic ability for detecting NAFLD, and the areas under the curves (AUC) in men and women were 0.920 (95%CI 0.917, 0.923) and 0.863 (95%CI 0.859, 0.867), respectively. Furthermore, the diagnostic ability was significantly higher in younger age groups. The AUC in 18–34 and 35–44 years group were 0.943 (95%CI 0.939, 0.946) and 0.921 (95%CI 0.917, 0.925), respectively. Besides, the women and the young people had a greater negative predictive values (90.84% for women, 93.13% for aged 18–34).

Conclusion: TG/TC shows a high diagnostic accuracy for identifying NAFLD in young women, providing an important clue to establish a new tool to screen NAFLD particularly in Chinese young females.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is an expanding global health problem, with a high prevalence in the general population. Worldwide, the prevalence of NAFLD diagnosed by imaging varies between 14% and 32% [1]. In China, NAFLD influences over 25% of the population, and its prevalence is rapidly increasing because of the considerable alteration in lifestyle and population age structure[2, 3]. NAFLD can increased the risk of cirrhosis, hepatocellular carcinoma, and death[4, 5]. Furthermore, considering the growing burden of NAFLD, early detection or screening of the disease are of utmost importance. Currently, liver biopsy is the gold standard for the diagnosis of NAFLD, but there are well-known limitations including sampling errors, invasiveness, high cost and severe complications, such as mortality, bleeding, and pain[6]. The imaging diagnosis of NAFLD, such as ultrasonography and magnetic resonance elastography, is more safe but still expensive and highly dependent on experienced imaging doctors[7]. Therefore, simple, inexpensive and noninvasive methods are urgently needed to be used for diagnosing NAFLD.

Numerous epidemiological studies suggest that dyslipidemia is closely related to NAFLD[8, 9]. Previous studies demonstrated that triglycerides (TG) and cholesterol were important risk factors of NAFLD and associated with its pathogenesis in animal experiments[10–14]. It's well established that the accumulation of TG within hepatocytes could lead to NAFLD[10]. Besides, among NAFLD patients, cholesterol metabolism was significantly altered reflected by increased cholesterol synthesis and diminished absorption[11]. In animal experiments, high cholesterol diets and free cholesterol accumulation in hepatic stellate cells were toxic to livers of rats and mice[12–14]. However, the diagnostic ability based on a single lipid parameter was not enough[15]. Recent studies based on ratio, as such triglyceride to high-density lipoprotein cholesterol (TG/HDL-C)[15], total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C)[16], and apolipoprotein B/AI (ApoB/A I)[17], explored the diagnostic value for NAFLD, and the AUC of TG/HDL-C is significantly higher than that based on a single lipid parameter.

To date, there are limited evidence of the indexes on the ability of identifying NAFLD. Furthermore, among these indexes, the highest AUC of those was only 0.85[15, 16, 17]. It is utmost important to set a new index for accurately identifying individuals at high risk of NAFLD in clinical practice. As triglycerides and total cholesterol are both available on traditional lipid panels and requires no additional cost, we performed a large scale of cross-sectional analysis to investigate the association between triglycerides to total cholesterol ratio (TG/TC) and prevalence of NAFLD and evaluate the accuracy of TG/TC as a marker for NAFLD.

Methods

Study population

The cross-sectional study population comprised individuals who visited the Health Management Center in the Third Xiangya Hospital of Central South University (Changsha), the largest medical institution in central China, between 2012 and 2018. A total of 686,264 individuals aged ≥ 18 years, who performed abdominal ultrasonography examination agreed to be included in this cross-sectional study. The study protocol was approved by the Medical Ethics Committee of the Third Xiangya Hospital., and were conducted according to the guidelines from the Helsinki Declaration. All the subjects has signed an informed written consent. Subjects who met the following criteria were excluded (Fig. 1): 1) excessive alcohol consumption, which was defined as an average consumption of alcohol ≥ 140 g/week for males and ≥ 70 g/week for females,[18, 19] and no available data on alcohol drinking (n = 332,014) ; 2) viral hepatitis, schistosomiasis liver disease or other chronic liver diseases(n = 87,609); 3) a history of taking lipid-lowering medications (n = 2,393);4) no available data on TC or TG, (n = 546); 5)no available data on liver ultrasonography examination(n = 170,253).

Data collection and measurements

All participants underwent an interview by trained interviewers and complete questionnaires. Age, sex, alcohol drinking, smoking history, exercise, and medical history. For the analyses, cigarette smoking was recorded as smoking (smoking currently and smoking before)or never smoking. Participants were considered physically active when reporting every-day exercise.

Waist circumference (WC) was measured at the umbilical level using an un-stretched tape without applying pressure to the body surface. Blood pressure (BP) was measured on the right arm in the sitting position using a corrected mercury sphygmomanometer after at least 10 min rest. Systolic BP and diastolic BP were each measured twice with a 30 s interval, and the mean of the two readings was considered the participant's BP. If the two readings differed by > 5 mmHg, a third measurement was performed and the average of all three readings was applied.

All measurement methods of blood samples collected from the antecubital vein, including fasting blood glucose (FBG), alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin(TBIL), serum uric acid, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and creatinine, were described in previous study[19].

Assessment of non-alcoholic fatty liver disease

The Assessment of non-alcoholic fatty liver disease has been described previously[19]. The diagnosis of NAFLD was based on liver ultrasound for the presence of liver steatosis, excluding acute or chronic liver disease and secondary

hepatic fat accumulation, including excessive alcohol drinking and taking steatogenic medication[20, 21]. Experienced and trained radiologists performed the liver ultrasonography, who were blinded to the subjects' clinical diagnosis and biochemical tests. The ultrasonographic criteria of hepatic steatosis included: diffusely increased liver near field ultrasound echo ('bright liver'), liver echo greater than kidney, vascular blurring and the gradual attenuation of far field ultrasound echo. Participants with Two or more of the abnormal findings listed above were diagnosed with hepatic steatosis.

Statistical analysis

Basic features of the study participants were presented as the mean ± standard deviation (SD) for continuous variables and as numbers with percentages for categorical variables. Comparisons of basic characteristics between the NAFLD and non-NAFLD groups were tested by using Student t tests for continuous variables and Pearson's $\chi 2$ test for categorical variables. To explore the association between the levels of TG/TC and the prevalence of NAFLD, The study subjects was divided into 4 groups according to TG/TC quartiles (Q1,Q2,Q3,Q4). Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression analysis to determine the risk of NAFLD in each TG/TC quartile and using the lowest quartile as the reference. The area under the receiver operating characteristic curve (AUROC) was used to describe the diagnostic accuracy of TG/TC. The AUROCs were tested using a nonparametric approach. The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) for relevant cut-offs were also displayed. All statistical analyses were conducted using Stata version 16.0 (Stata Corp, College Station, TX) and P values of < 0.05 were considered statistically significant.

Results

Characteristics of the study subjects

Totally 93,449 subjects, 37,752 men and 55,697 women with average age of 43.7 ± 14.3years, were included. Among these subjects, 16,138 (42.7%) men and 9,591 (17.2%) women were diagnosed with NAFLD. Characteristics of the NAFLD and non-NAFLD groups were shown in Table 1.The NAFLD group had a higher level of TG, TC, and LDL-C. Meanwhile, the patients with NAFLD had higher WC, SBP, DBP, FBG, ALT, AST, uric acid, creatinine and reduced TBIL, HDL-C levels than those without NAFLD. Besides, the subjects with no-smoking and exercising every day had a lower prevalence of NAFLD .

Table 1
Clinical and biochemical characteristics of the study subjects with or without NAFLD

	ALL	Non-NAFLD	NAFLD	P value
N	93449	67720	25729	
Age (years)	43.7 ± 14.3	41.6 ± 14.0	49.0 ± 13.8	<0.001
gender				<0.001
Male,%	37,752	21614(57.3)	16138(42.7)	
Female,%	55,697	46106(82.8)	9591(17.2)	
waist(cm)	79.1 ± 10.0	75.6 ± 7.9	88.3 ± 9.3	<0.001
Physical activity				<0.001
Occasionally,%	55697	42147(72.3)	16969(28.7)	
Everyday,%	34333	25573(74.5)	8760(25.5)	
smoke				<0.001
Yes,%	64452	45854(71.1)	18598(28.9)	
No,%	28997	21866(75.4)	7131(24.6)	
SBP (mmHg)	119.6 ± 16.2	116.5 ± 15.1	128.0 ± 15.9	<0.001
DBP (mmHg)	72.9 ± 10.4	70.9 ± 9.7	78.3 ± 10.5	<0.001
FBG (mmol/L)	5.3 ± 1.1	5.2 ± 0.8	5.8 ± 1.5	<0.001
ALT (U/L)	25.3 ± 21.0	21.3 ± 16.8	35.9 ± 26.6	<0.001
AST(U/L)	22.2 ± 10.4	21.2 ± 10.2	24.1 ± 10.4	<0.001
TBIL (μmol/L)	16.1 ± 5.9	16.3 ± 5.9	15.7 ± 5.8	<0.001
Uric acid (μmol/L)	308.9 ± 85.2	288.7 ± 76.2	362.1 ± 84.8	<0.001
TG (mmol/L)	1.5 ± 1.2	1.2 ± 0.8	2.3 ± 1.7	<0.001
TC (mmol/L)	5.0 ± 1.0	4.9 ± 0.9	5.3 ± 1.0	<0.001
HDL-C (mmol/L)	1.4 ± 0.3	1.5 ± 0.3	1.3 ± 0.3	<0.001
LDL-C(mmol/L)	2.8 ± 0.8	2.8 ± 0.8	3.0 ± 0.9	<0.001
Creatinine (μmol/L)	84.6 ± 429.8	80.3 ± 389.5	95.7 ± 521.3	<0.001

Abbreviations: WC waist circumference, SBP systolic blood pressure, DBP diastolic blood pressure, FBG fasting blood glucose, ALT alanine transaminase, AST: aspartate aminotransferase, TBIL total bilirubin, TG triglyceride, TC total cholesterol, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol

Continuous variables were presented as means ± SD

Association between TG/TC and the prevalence of non-alcoholic fatty liver disease

As was shown in Table 2, higher quartiles of TG/TC was more associated with the increased risk of NAFLD in both men and women. In men, After adjusting for age and waist (Model2), the OR for NAFLD in the comparison between the highest and lowest quartiles of TG/TC was 5.14(95% CI 4.64, 5.69). After further adjusting smoking, physical activity, SBP, DBP, FBG, TBIL, UA, LDLC, HDLC (Model4), the OR (4.08,95%CI 3.64,4.57) in the highest compared with the lowest quartile of TG/TC was still significant. Furthermore, subgroup analysis indicated that the association between TG/TC and NAFLD was more stronger in women. In adjusted Model4, the OR (4.65, 95% CI 4.14, 5.21) in the highest compared with the lowest quartile of TG/TC was higher than that in men. When TG/TC is considered as a continuous exposure variable, the results was (per SD increment, Table 2).

Table 2
Odds ratios and 95% confidence intervals for non-alcoholic fatty liver disease according to quartiles of TG/TC

	Quartiles of TG/TC					
	Q1	Q2	Q3	Q4	per SD increment	P for trend
MAN						
N	14698	10535	7666	4853		
Model1	1(Ref)	2.15(1.95,2.36)	4.19(3.83,4.59)	11.51(10.53,12.58)	69.42(60.43,79.74)	< 0.001
Model2	1(Ref)	1.53(1.37,1.72)	2.43(2.19,2.70)	5.14(4.64,5.69)	15.77(13.65,18.21)	< 0.001
Model3	1(Ref)	1.53(1.37,1.71)	2.43(2.19,2.70)	5.13(4.64,5.68)	15.73(13.62,18.10)	< 0.001
Model4	1(Ref)	1.40(1.25,1.57)	2.07(1.86,2.31)	4.08(3.64,4.57)	14.49(12.19,17.20)	< 0.001
WOMAN						
N	8667	12827	15693	18510		
Model1	1(Ref)	2.46(2.25,2.69)	5.52(5.07, 6.01)	13.70(12.57, 14.94)	139.70(117.30,166.30)	< 0.001
Model2	1(Ref)	1.91(1.72,2.11)	3.30(3.00, 3.64)	7.09(6.43, 7.81)	32.28(26.85,38.80)	< 0.001
Model3	1(Ref)	1.91(1.73,2.11)	3.31(3.01, 3.64)	7.10(6.44, 7.83)	32.34(26.90,38.80)	< 0.001
Model4	1(Ref)	1.63(1.47,1.81)	2.50(2.25,2.77)	4.65(4.14,5.21)	15.20(12.22,18.90)	< 0.001
Model1:adjusted for age						
Model2:further adjusted for waist						
Model3:further for adjusted for smoke ,physical activity						
Model4:further adjusted for SBP,DBP,FBG,TBIL,UA,LDLC,HDLC						
Per SD increment: per SD increment of log TG/TC						

Accuracy of TG/TC for diagnosing non-alcoholic fatty liver disease

To investigate the accuracy of TG/TC for detecting NAFLD, the ROC of TG/TC was analyzed. As shown in Fig. 2, the area under the curve (AUC) of TG/TC was 0.920 (0.917,0.923) in women and 0.863(0.859,0.867) in men, after adjusting multiple confounding factors. The sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) for both gender were shown in Table S1.

Assessment of the diagnosing accuracy of TG/TC in different age groups

The AUC for TG/TC as a diagnosing index of NAFLD in different age groups was showed in Table 3. The diagnostic ability of TG/TC was significantly better in young age groups, and the AUC of TG/TC in 18–34 years group and 35–44 years group were 0.943(95%CI 0.939,0.946) and 0.921(95%CI 0.917,0.925), with NPV 0f 93.13% and 89.27%, respectively. The sensitivity, specificity, PPVs and NPVs of each age groups were shown in Table 3.

Table 3
Comparison of areas under the ROC curves of TG/TC in different ages groups

Age,years	N	AUC(95%CI)	P value	sensitivity	specificity	PPV	NPV
18–34	29470	0.943(0.939,0.946)	< 0.001	59.53%	96.45%	74.64%	93.13%
35–44	21249	0.921(0.917,0.925)	< 0.001	66.14%	92.77%	75.08%	89.27%
45–54	19731	0.876(0.871,0.880)	< 0.001	67.60%	87.10%	75.05%	82.41%
55–64	10401	0.848(0.840,0.855)	< 0.001	69.99%	82.32%	74.76%	78.57%
65–75	5690	0.830(0.820,0.841)	< 0.001	67.43%	80.56%	71.86%	77.06%
75+	3134	0.824(0.810,0.838)	< 0.001	60.85%	84.07%	69.62%	78.17%
Abbreviations: PPV positive predictive values;NPV negative predictive value							

Discussion

It is already established that dyslipidaemia played the important role in NAFLD. However, the diagnostic ability of current indexes based lipids was limited. Surprisingly, in our study, the TG/TC ratio had a high diagnostic ability for identifying NAFLD than before, especially in young females. Furthermore, TG/TC had a high NPV(> 90%) in women and aged 18–34 groups, which means it could be used to exclude subjects with NAFLD for these population in clinical settings. The characteristics of TG/TC made it become a strong surrogate for screening NAFLD particularly in Chinese young females.

Over the last decades, the prevalence has risen in young adults, which was often unrecognized[22]. A recent cross-sectional analysis, which evaluated the prevalence of NAFLD in subjects aged 18–35 years, suggest that the prevalence in young adults has increased almost 2.5 times over three decades, ranging from 9.6% in 1988–1994 to 24% in 2005–2010, and over one half of morbidly obese young adults had NAFLD (57.4%)[23]. Besides, some risk factors, such as obesities, type 2 diabetes, smoking, and unhealthy diets, were increasingly prevalent among young adults, which led to a higher risk for NAFLD[24–27]. This trend of NAFLD prompted us to explore the diagnostic ability of TG/TC in different age groups. Interestingly, our study showed that the diagnostic accuracy of TG/TC was

significantly better in young age groups, in which we found an AUC of 0.943 in 18–34 years group and 0.921 in 35–44 years group. Our results supported that TG/TC was a powerful index that could be applied to screen NAFLD, especially in young population.

Furthermore, the diagnostic ability of TG/TC was significantly higher than other indexes based on lipid parameters, with AUROC of 0.920 in women and 0.863 in men. Fan and his colleague analyzed the association between different serum lipids (TG, TC, LDL-C, HDL-C,) and NAFLD in a cross-sectional study, with AUROC of 0.84,0.65,0.65,0.77 respectively. Meanwhile, they found the AUC of TG/HDL-C in women and men was 0.85 (0.84–0.86) and 0.79 (0.78–0.80), respectively.[15]. A perspective cohort study including 3374 Chinese adults investigated the association between nonHDL-C/HDL-C with NAFLD, with AUROC of 0.717 in women and 0.682 in men[28]. The Jinchang Cohort study consisting of 32,121 subjects, evaluated the ability of TC/HDL-C for identifying NAFLD, and the results suggested the AUC of TC/HDL-C was 0.645[16]. Therefore, TG/TC was more powerful for identifying NAFLD.

The underlying mechanism about the association between TG/TC and NAFLD has not been clarified. The association between TG/TC could be partly explained by elevated plasma triglycerides. Our study showed people with NAFLD had a higher triglycerides levels, which is consistent with previous study [8, 29]. Triglyceride molecules represent the major form of storage and transport of fatty acids within cells and in the plasma[10]. Steatosis develops when fatty acid (FA) input rate (uptake and synthesis and subsequent esterification to TG) was greater than fatty acid output rate (oxidation and secretion), steatosis develops [30]. Besides, insulin resistance may play a role in the association between TG/TC and NAFLD. Insulin resistance accelerates NAFLD by inducing lipolysis of TG in adipose tissue and de novo synthesis of TG in the liver[31]. Furthermore, IR could be accompanied by systemic inflammation, which played an important role in hepatic steatosis[32]. Some inflammation cells activation, such as Kupfer cells[33], stellate cells [34] and circulating mononuclear cells that infiltrate the liver[35], could trigger TG accumulation in the liver. However, because of the lack data of serum insulin level, our study couldn't investigate the relationship between TG/TC and insulin resistance.

The advantages of our study included that it was a large-scale cross-sectional study and first investigated the association between TG/TC and NAFLD. Furthermore, as a novel index for diagnosing NAFLD, TG/TC was radiation-free, simple, cheap, and easy to perform, compared with CT and MRI. However, some limitations of our study were existed. First, our study was cross-sectional, and the effects of TG/TC for identifying NAFLD should be test in prospective observational studies. Second, the diagnosis of NAFLD in our study was based on ultrasonic examination. The diagnosis of ultrasonography examination could also be influenced by interobserver variation, even if the radiologist were very experienced. However, the gold standard for diagnosis of NAFLD was liver biopsy, which was not appropriate as a screening tool for a population-based epidemiological study[36].

Conclusion

In conclusion, TG/TC ratio is significantly associated with the prevalence of NAFLD, and the diagnostic accuracy of TG/TC is especially high among young woman. TG/TC ratio may be a potential early screening tool for NAFLD in Chinese young females.

Abbreviations

ALT: alanine transaminase, AST: aspartate aminotransferase, AUC: area under the curves, DBP: diastolic blood pressure, FBG: fasting blood glucose, HDL-C high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol , NAFLD: Non-alcoholic fatty liver disease, NPV: negative predictive value, PPV: positive predictive value,

ROC: receiver operator characteristic curve, SBP: systolic blood pressure, TC: total cholesterol, TG: triglycerides, WC: waist circumference

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Medical Ethics Committee of the Third Xiangya Hospital and all participants signed a written consent form.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

There are no potential conflicts of interest relevant to this article reported.

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Authors' contributions

Study design: Hong Yuan, Yao Lu Acquisition of the data: Jiangang Wang, Zhiheng Chen Data analysis and interpretation of the data: Yiping Yang, Jingyuan Chen, Drafting the manuscript or revising it critically for important intellectual content: Jingyuan Chen. All authors read and approved the final manuscript

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Figures

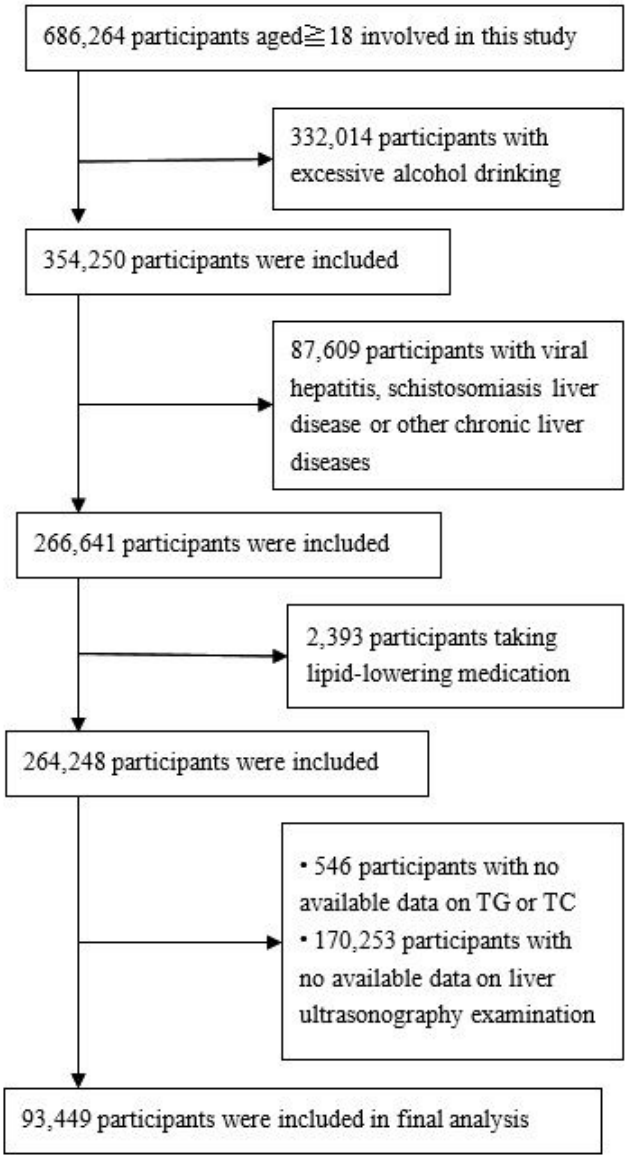

Figure 1

Flowchart of participants

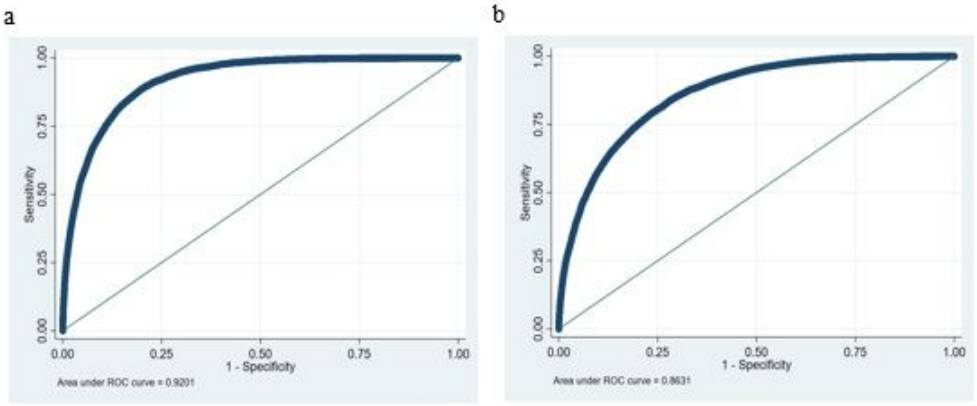

Figure 2

ROC curve of TG/TC in women (a) and men (b). Footnote: a. The areas under the ROC curve for the TG/TC ratio in women was 0.9201. b. The areas under the ROC curve for the TG/TC ratio in men was 0.8630.

Supplementary Files

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