The triglyceride-glucose index (TyG) and Nonalcoholic fatty liver in the Japanese population: a retrospective cross-sectional study

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Research

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Abstract

Background: Evidences regarding the association between triglyceride-glucose index (TyG) and Nonalcoholic fatty liver (NAFLD) are controversial. Therefore, the goals of this research are to evaluate whether TyG is independently associated with NAFLD and the ability of TyG index to detect NAFLD in the Japanese population.

Methods: The present study was a cross-sectional study. The data was downloaded from the DATADRYAD website. A total of 13178 participants was involved in a hospital in Japan from 2004 to 2015. The correlation between TyG and NAFLD was detected by using binary logistic regression and Generalized additive models. The likelihood ration test was used to examine the modification and interaction of subgroups. Furthermore, the ability of TyG to predict NAFLD was evaluated by using receiver operating characteristic (ROC) curves. The formula for the TyG index was ln [fasting triglyceride level (mg / dl) × fasting blood glucose level (mg / dl) / 2]

Results: The average age of the selected participants was 43.36±8.89 years old, and about 51.02% of them were male. In fully-adjusted binary logistic regression model, TyG was positively related with the risk of NAFLD (Odds ratio (OR)=2.45, 95%CI 2.12-2.82). The relationship between TyG and NAFLD was a non-linear relationship, and its inflection point was 8.22. The effect sizes and the confidence intervals of the left and right sides of inflection point were 3.26(2.44 - 4.35) and 2.09 (1.72 - 2.54), respectively. By subgroup analysis, the stronger association was found in females, low GGT, non-obesity, non-visceral fat obesity (P for interaction <0.05). Among the total population, the AUC for TyG [0.810 (0.804 - 0.817)] was worse than ALT [0.829 (0.822 - 0.835)] but better than TG [0.799 (0.792 - 0.805)] and FPG [0.715 (0.707 - 0.722)]. A similar result was found for men. In the women, the AUC for the TyG was superior to ALT, FPG, and TG.

Conclusion: The association between TyG and NAFLD is non-linear. TyG is stronger positively correlated to the risk of NAFLD when TyG is less than 8.22. TyG is helpful to identify individuals with NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by ectopic triglycerides deposition in liver cells that includes steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis[1]. NAFLD is increasingly considered as a clinical syndrome, which is associated with type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), and chronic kidney disease (CKD) [2]. The global prevalence of NAFLD is 25.24%, and it is rising rapidly [3]. It will cause huge health and economic burden for individuals, society, and nation. The gold standard of NAFLD is liver biopsy, which can accurately evaluate the important pathological manifestation of NAFLD, such as hepatic steatosis, inflammation, and fibrosis. Taking the test with high-risk and invasive into account, a non-invasive and convenient screening method is needed to identify patients with NAFLD in the large-scale epidemiological investigations.

The pathogenesis of NAFLD is considered to be insulin resistance(IR) and oxidative stress[4]. The product of fasting triglycerides and glucose levels (TyG), suggested by Simental-Mendía *e*t al.[5], is highly associated with IR[6–8]. Thus, TyG is a cheap and convenient clinical alternative indicator of IR. In recent years, TyG has related to the risks of T2DM[9–12], hypertension[13, 14], metabolic syndrome[15, 16], and cardiovascular disease[17, 18]. Furthermore, several studies showed that TyG is associated with NAFLD in China[19, 20], Korea[21], Japan[22], France[23]. However, Everton Cazzo et al.[24] and Silan Zheng et al.[25] suggested that there was no association between TyG and NAFLD in Brazil and China, respectively. The findings from previous studies regarding the relationship between TyG and NAFLD are controversial. In view of the differences in research design, target population, and data analysis of these studies, more research and exploration is needed to draw reliable conclusions.

Therefore, the purpose of our research was to detect the relationship between TyG and the risk of NAFLD and to assess the predictor power of TyG for NAFLD in the Japanese population.

Methods

Data source and study population

Researchers can use the "DATADRYAD" database (www.Datadryad.org) to download raw data freely. Data was referenced from the Dryad packet (Okamura, Takuro et al. (2019), Data from: Ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study, Dataset, https://doi.org/10.5061/dryad.8q0p192). The database included variables as follows: (age, gender, waist circumference(WC), weight, body mass index (BMI), alanine aminotransferase (ALT), fasting plasma glucose (FPG), aspartate transaminase (AST), γ-glutamyltranspeptidase (GGT), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), smoking status, exercise, fatty liver, ethanol consumption, and triglyceride (TG), hemoglobin A1c (HbA1c), Obesity phenotype, obesity, visceral fat obesity, systolic blood pressure (SBP), diastolic blood pressure (DBP), diabetes mellitus (DM), and follow up duration).

To promote public health, Murakami Memorial Hospital (Gifu City, Japan) performed a population-based cohort research. Okamura et al.[26] analyzed the population who entered the study cohort from 2004 to 2015 and researched the effect of the obese phenotype on the risk of type 2 diabetes. On this basis, we further set the following exclusion criteria to select 13,178 participants (6,723 men and 6,455 women): (1) Participants lacked relevant covariate data such as alcohol, exercise, abdominal ultrasound or height; (2) Participants had hepatitis B or C virus; (3) Participants had alcoholic fatty liver (ethanol consumption > 140g per week for men, > 70g per week for women); (4) Participants had taken medication during baseline examinations; (5) The fasting plasma glucose of the participants was greater than 6.1 mmol/L or had type 2 diabetes at baseline. Murakami Memorial Hospital's Ethics Committee approved Okamura et al. and every subject signed an informed consent form.

Data collection and measurements

Baseline information on all participants was obtained through questionnaires. Okamura et al. estimated the average weekly ethanol intake by investigating participants the type and amount of elcohol consumed each week in the previous month. They categorized participants into four categories: non-alcoholic or minimal drinking, <40 g per week; light drinking, 40-140 g per week; moderate drinking, 140-280 g per week; or heavy drinking, > 280 g per week. Participants were grouped into three categories based on smoking status: non-smokers were participants who had never smoked before, ex-smokers were defined as participants who had previously smoked but had quit smoking before the baseline survey, but current smokers were participants who continued to smoke during the baseline survey. For sports activities, they defined regular athletes as regularly participating in an activity every week. Those who met the following conditions are type 2 diabetes: HbA1c ≥ 6.5%, fasting plasma glucose ≥ 7 mmol / L or self-reported. BMI ≥ 25 kg / m2 was defined as obesity. Waist circumference (WC) ≥90 cm for men and waist circumference ≥80 cm for women were defined as visceral fat obesity. Hypertension was defined as systolic blood pressure (SBP) ≥140mmHg or diastolic blood pressure (DBP) ≥90mmHg. The triglyceride-glucose index (TyG) was calculated as Ln (TAG (mg/dL) × glucose (mg/dL))/2.

Definition of fatty liver

According to Asia-Pacific Working Party guidelines[27], people with excessive drinking (> 140 g / week for men, > 70 g / week for women) or liver virus were excluded. The experienced operator performed abdominal ultrasound tests, and then, without knowing other data from the participants, the gastroenterologists diagnosed fatty liver which was based on liver contrast and liver brightness[28].

Statistical analysis

The presentation of continuous variables was divided according to their distribution status:(1) normal distribution (mean ± standard deviation) and skewed distribution (median (quartile)). Categorical variables were presented as frequency or as percentage. Whether the differences between groups were statistically different was tested by One-way analysis of variance (normal distribution), Kruskal Wallis H test (skewed distribution), and Chi-square test (categorical variable). We used univariate and multivariate binary logistic regression to assess the correlation between TyG and NAFLD. According to the STROBE statement, three models were used to evaluate the relationship: unadjusted, minimally adjusted, and fully adjusted models. We selected potential covariates if they changed the estimates of TyG on NAFLD by at least 10% or were significantly correlated with NAFLD. Thus, potential covariates involved in this study included age, BMI, WC, ALT, AST, GGT, HDL-C, TC, TG, HbA1C, FPG, SBP, DBP, and ethanol consumption, gender, regular exercise, Smoking status. For sensitivity analysis, we treated TyG as a continuous and categorical variable to evaluate its relationship to NAFLD. Besides, the nonlinear relationship between TyG and NAFLD was estimated using the Generalized Additive Model (GAM). If there was a non-linear relationship, we used the recursive method to calculate the inflection point, performed a two-piecewise linear regression, and used the maximum model likelihood test. To find modifications and interactions, we used a stratified linear regression model and a likelihood ratio test in the different subgroups. For the evaluation of diagnostic ability, we performed the receiver operating characteristic (ROC) curve analysis

and compared the areas under the ROC curve (AUC) to find the strongest predictor of NAFLD. We performed statistical analyses with the statistical software packages R (http://www.R-project.org, The R Foundation), MedCalc software programs (Version 19.0.7), and Empower-Stats (http://www.empowerstats.com, X&Y Solutions,Inc., Boston, MA). Statistically different was defined as P values less than 0.05.

Results

Baseline characteristics of selected participants

13,178 participants in total were selected for the present research through strict selection criteria. Table 1, grouped by TyG quartiles, shows the baseline characteristics of these selected participants. In general, the average age of those selected was 43.36 ± 8.89 years old, and 51.02% of those were male. A total of 2361 had NAFLD and the prevalence was 17.92%. No statistically significant differences were detected among different TyG groups (all p values < 0.05). Compared to that of other three groups (Q 1-3), Participants in the highest group of TyG (Q 4) had the higher values in age, BMI, WC, ALT, AST, GGT, TC, TG, HbA1C, FPG, SBP, DBP and consisted of more male, past and current smoker, NAFLD than those of the other groups. The contrary results were detectd in HDL-C, female, regular exercise, non -smoker, non-NAFLD.

Univariate analysis

The results of the univariate analysis were showed in Table 2. We performed univariate binary logistic regression and found that HDL-C and regular exercise were negatively correlated with NAFLD. To the contrary, the univariate analysis displayed that age, BMI, WC, ALT, AST, GGT, TC, TG, HbA1C, FPG, SBP, DBP, TyG, ethanol consumption, male, smoking status (past and current) were positively correlated with Nonalcoholic fatty liver.

Results of unadjusted and adjusted binary logistic regression

In this study, we used univariate and multivariate binary logistic regression to construct three models through to analyze to assess the independent effect of TyG on NAFLD. Table 3 shows the effect sizes (Odds ratio (OR)) and 95% confidence intervals. In the unadjusted model, TyG showed positive correlation with NAFLD (OR=7.79, 95% confidence interval (CI): 7.08 - 8.56, P <0.0001). In the minimum-adjusted model, the result did not change significantly after adjusting for age and gender (OR=6.18, 95% CI 5.59 - 6.83, P <0.0001). In fully adjusted model (adjusted age, gender, ALT, AST, GGT, SP, BMI, WC, regular exercise, HDL-C, TC, HbA1C, Ethanol consumption, Smoking status), the association between TyG and NAFLD could also be detected (OR=2.45, 95% CI 2.12-2.82, P <0.0001). For the stability of our results, TyG was treated as categorical variable (Quartile of TyG) and the P for trend in the fully adjusted model was agreed with the result when TyG was a continuous variable.

The results of the nonlinearity of TyG and NAFLD

In the present study, the non-linear correlation between TyG and NAFLD was analyzed by the Smooth curve and the Generalized additive model (Figure 1 and Table 4). After adjusting for age, gender, BMI, WC, ALT, AST, GGT, HDL-C, TC, TG, HbA1C, FPG, SBP, DBP, ethanol consumption, regular exercise, and smoking status, we detected that the correlation between TyG and NAFLD was non-linear. Using two-piecewise binary logistic regression and recursive algorithm, the inflection point of curve was calculated to be 8.22 (log-likelihood ratio test P 0.023). When TyG was less than 8.22, the effect size and 95% CI were 3.26, 2.44 - 4.35, respectively. When TyG was greater than or equal to 8.22, the effect size and 95% CI were 2.09, 1.72 - 2.54, respectively.

The results of subgroup analyses

The stratification variables (age, gender, ALT, AST, GGT, HDL-C, TC, HbA1c, obesity, visceral fat obesity, hypertension, smoking status, ethanol consumption, regular exercise) were used to assess the trend of effect sizes (Table 5). The tests of interaction were statistically significant for these variables including gender, GGT, Obesity, visceral fat obesity. For men, one unit increase of TyG was correlated with 3.20 times higher risk of NAFLD. For women, an increase of the TyG by one unit was associated with 2.24 times higher risk of NAFLD. The change in gender is significant (P for interaction = 0,0076). The stronger association was also detected in low GGT (3.73 with low GGT vs 2.25 with middle GGT, and vs 2.12 with high GGT), non-obesity (2.72 with non-obesity vs 1.99 with obesity), non-visceral fat obesity (2.65 with non-visceral fat obesity vs 1.88 with visceral fat obesity).

ROC analyses for TyG, ALT, FPG, and TG to predict the risk of NAFLD

For predicting the risk of NAFLD, we performed ROC analyses by using TyG, ALT, FPG, and TG in Figure 2 and Table 6. Among the total population, the areas under the ROC curve (AUC) of TyG was 0.810（95 % CI 0.804 - 0.817）, which was worse than ALT [0.829 (95 % CI 0.822 - 0.835), P < 0.0001] but better than TG [0.799 (95 % CI 0.792 - 0.805), P < 0.0001] and FPG [0.715 (95 % CI 0.707 - 0.722), P < 0.0001]. Among the men, the ROC AUCs (95% CI) were 0.748 (0.737 - 0.758), 0.797 (0.788 - 0.807), 0.635 (0.624 - 0.647) and 0.739 (0.728 - 0.749) for TyG, ALT, FPG, and TG, respectively. Among the women, AUCs of ROC (95% CI) for TyG, ALT, FPG, and TG were 0.818 (0.809 - 0.828), 0.765 (0.755 - 0.776), 0.719 (0.708 - 0.730), and 0.804 (0.794 - 0.814), respectively. For men, the AUC was worse for TyG than ALT but better than TG and FPG (P <0.0001). For women, the AUC for the TyG was superior to ALT, FPG, and TG (P<0.0001).

Discussion

The present study indicated TyG, both as continuous and categorical variables, was positively correlated with NAFLD after adjusting relative covariates. We firstly detected that the non-linear relation between TyG and NAFLD showed a threshold effect. When the inflection point is 8.22, the relationships between TyG and NAFLD showed significant differences [left (OR 3.26, 95% CI 2.44–4.35) VS right (OR 2.09, 95% CI 1.72–2.54), P < 0.05]. Besides, the results of this research found the stronger relationships were observed in male, low GGT, non-obesity, non-visceral fat obesity by conducted subgroup analysis. Furthermore, comparing the AUC, the predictive value of ALT was superior to TG, FPG, and TyG in the

males and the total population, however, TyG had the strongest predictive power on NAFLD in the females.

IR is characterized by decreasing sensitivity of tissues to insulin which can inhibit lipolysis of adipose tissue. Excessed free fatty acids, caused by IR, are deposed in the liver and results in the formation of hepatic steatosis[4, 29]. Lipotoxicity of FFAs presents as increasing oxidative stress and mitochondrial dysfunction in hepatocytes[4]. For reducing lipotoxicity, the FFAs are resynthesized into triglycerides which can be stored in hepatocytes or transported as very low density lipoprotein (VLDL) into blood[4]. IR most often presents with hyperglycemia and hypertriglyceridemia. Simental-Mendia et al.[5]proposed that TyG expressed as Ln (fasting triglycerides (mg/dl) × fasting blood glucose (mg/dl)/2), was highly correlated with euglycemic-hyperinsulinemic clamp test and HOMA-IR[6–8]. Thus, many studies have explored the association between TyG and NAFLD. In a retrospective cohort study that selected 16,093 apparently healthy Japanese participants, Kitae, A et al.[22] demonstrated that the higher TyG at baseline indicated a higher probability of NAFLD both in men and women. Similar findings were also reported in the researches of Zhang, S et al.[19], Zheng, R et al.[20], Petta, S et al.[30], Lee, S.B et al.[21], Fedchuk, L et al.[23], and Luis E. Simental-Mendía et al.[31]. Their conclusions were agreed with our findings. However, some other studies were not consistent with our findings. Selecting 89 patients with morbid obesity, Cazzo, E et al.[24] did not detect a significant correlation between TyG and NAFLD in a cross-sectional study. The cross-sectional study found that LAP, rather than TyG, was independently associated with hepatic steatosis which was assessed by controlled attenuation parameter (CAP) among 101 women with polycystic ovary syndrome[25]. Previous studies are controversial due to different study designs, population ethnicity, sample size, and statistical method.

In the subgroup analysis, we found that BMI, WC, GGT, and gender affect the association between TyG and NAFLD after adjusting other covariates. Zhang, S et al.[19] also detected that the stronger association between TyG and NAFLD were detected in BMI < 25 kg/m^2 (OR 4.1 with BMI < 25 kg/m^2 vs OR 2.8 with BMI > = 25 kg/m^2) after adjusting related covariates, however, the association was not found in different gender. A meta-analysis showed that the prevalence of NAFLD was different in gender and men were more likely than women to suffer from NAFLD[32]. The potential mechanism is the sex hormone difference between men and women. Similar results have not been reported before, we are unable to explain why the associations between TyG and NAFLD are stronger in low GGT, non-visceral fat obesity.

To the best of our knowledge, Petta, S et al. [30]first showed that TyG index, whose AUC is 0.682, predicted the severity of liver steatosis in 340 Italian patients with Genotype 1 Chronic Hepatitis C. Then, TyG, which was correlated with IR, could be used to diagnose liver steatosis but had deficiency quantitative evaluation for the severity of fatty liver, which was proposed by Fedchuk, L et al.[23]. In addition, Simental-Mendia et al.[31] observed that TyG is better than SteatoTest, NashTest, and Fatty liver index for detecting hepatic steatosis in 50 asymptomatic women. Among 10,761 healthy Chinese subjects, Zhang, S et al.[19] reported that TyG is a potential diagnostic indicator of NAFLD by a cross-sectional study. When the cut-

off value of TyG is 8.5, the sensitivity and specificity is 72.2% and 70.5%, respectively. The population-based cohort study performed by Zheng R et al. showed that TyG independently correlates with NAFLD and is a reliable indicator for predicting NAFLD which comparing with ALT, TG, and FPG. Compared with HOMA-IR, TyG has a stronger ability to predict the risk of NAFLD in 4,986 Korean population, which conducted by Lee, S.B et al.[21]. However, our study displayed that TyG was better than ALT, TG, and FPG in diagnosing NAFLD only in women and ALT, rather than TyG, is the strongest indicator in men and total population. The previous studies have not compared TyG to ALT in different gender, thus, more research is needed to find the stronger predictors for identifying NAFLD.

Our study offers several advantages. (1) the sample size of our study is relatively large; (2) In the observational study, we fully adjust potentially confounding factors such as ethanol consumption, regular exercise, and smoking status. (3) For sensitivity analysis, we explore the relationship between TyG and NAFLD by treating TyG as continuous and categorical variables; (4) In contrast to previous studies, GAM is used to explore the nonlinear relationship between TyG and NAFLD; (5) In the subgroup analysis, we use stratified linear regression models and likelihood ration tests to find the modifications and interactions and to get a stable result in different subgroups.

Some limitations in the present study should be listed. (1) Our study is a retrospective study that cannot draw a conclusion on the direction of causality. However, it can provide direction for future research; (2) Our study has strict criteria for inclusion and exclusion, the extrapolation of our results may exist limitations. However, this can enhance the accuracy of the result; (3) The gold standard of NAFLD is liver biopsy, however, cheap and convenient ultrasonography is frequently used in large epidemiological studies; (4) Raw data does not offer other laboratory results, such as insulin concentration, inflammatory factors, which may correlations with TyG and NAFLD.

Conclusion

The association between TyG and NAFLD is non-linear. TyG is stronger positively correlated to the risk of NAFLD when TyG is less than 8.22. TyG is helpful to identify individuals with NAFLD.

Abbreviations

BMI, body mass index; WC, Waist circumference; HDL-C, high-density lipoprotein cholesterol; TC, Total cholesterol; TG, Triglycerides; HbA1c, hemoglobin A1c; FPG, Fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; GAM, Generalized additive models; TyG, Triglyceride-glucose index; NAFLD, Nonalcoholic fatty liver.

Declarations

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Authors' contributions

En-qian Liu performed the analysis and interpretation of the data and drafted the manuscript. Ya-ping Weng and Ai-ming Zhou contributed to the discussion and reviewed the manuscript. Chun-lai Zeng helped to supervise the study. Finally, the final manuscript was read and approved by all authors.

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Availability of data and materials

Data can be downloaded from 'DATADRYAD' database (www.Datadryad.org).

Ethics approval and consent to participate

Murakami Memorial Hospital's Ethics Committee approved Okamura et al.[26] and every subject signed an informed consent form.

Consent for publication

Not applicable.

Competing interests

All the authors reported that they have no conflicts of interest.

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References

1. Andronescu CI, Purcarea MR, Babes PA. Nonalcoholic fatty liver disease: epidemiology, pathogenesis and therapeutic implications. *J Med Life.* 2018;11(1):20-23.
2. Byrne CD, Targher G. NAFLD: A multisystem disease. *J Hepatol.* 2014;62(1):S47-S64. doi:10.1016/j.jhep.2014.12.012
3. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 2016;64(1):73-84. doi:10.1002/hep.28431
4. JK D, JW T, PN N. Pathogenesis of non-alcoholic fatty liver disease. *QJM : monthly journal of the Association of Physicians.* 2010;103(2):71-83. doi:10.1093/qjmed/hcp158
5. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The Product of Fasting Glucose and Triglycerides As Surrogate for Identifying Insulin Resistance in Apparently Healthy Subjects. *Metab Syndr Relat D.* 2008;6(4):299-304. doi:10.1089/met.2008.0034
6. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO, Jacques-Camarena O, Rodríguez-Morán M. The Product of Triglycerides and Glucose, a Simple Measure of Insulin Sensitivity. Comparison with the Euglycemic-Hyperinsulinemic Clamp. *The Journal of Clinical Endocrinology & Metabolism.* 2010;95(7):3347-3351. doi:10.1210/jc.2010-0288
7. Du T, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovasc Diabetol.* 2014;13:146. doi:10.1186/s12933-014-0146-3
8. Vasques ACJ, Novaes FS, de Oliveira MDS, Matos Souza JR, Yamanaka A, Pareja JC, Tambascia MA, Saad MJA, Geloneze B. TyG index performs better than HOMA in a Brazilian population: A hyperglycemic clamp validated study. *Diabetes Res Clin Pr.* 2011;93(3):e98-e100. doi:10.1016/j.diabres.2011.05.030
9. Zhang M, Wang B, Liu Y, Sun X, Luo X, Wang C, Li L, Zhang L, Ren Y, Zhao Y, Zhou J, Han C, Zhao J, Hu D. Cumulative increased risk of incident type 2 diabetes mellitus with increasing triglyceride glucose index in normal-weight people: The Rural Chinese Cohort Study. *Cardiovasc Diabetol.* 2017;16(1):30. doi:10.1186/s12933-017-0514-x
10. Navarro-Gonzalez D, Sanchez-Inigo L, Pastrana-Delgado J, Fernandez-Montero A, Martinez JA. Triglyceride-glucose index (TyG index) in comparison with fasting plasma glucose improved diabetes prediction in patients with normal fasting glucose: The Vascular-Metabolic CUN cohort. *Prev Med.* 2016;86:99-105. doi:10.1016/j.ypmed.2016.01.022

11. Wang B, Zhang M, Liu Y, Sun X, Zhang L, Wang C, Li L, Ren Y, Han C, Zhao Y, Zhou J, Pang C, Yin L, Feng T, Zhao J, Hu D. Utility of three novel insulin resistance-related lipid indices for predicting type 2 diabetes mellitus among people with normal fasting glucose in rural China. *J Diabetes.* 2018;10(8):641-652. doi:10.1111/1753-0407.12642
12. Low S, Khoo K, Irwan B, Sum CF, Subramaniam T, Lim SC, Wong T. The role of triglyceride glucose index in development of Type 2 diabetes mellitus. *Diabetes Res Clin Pract.* 2018;143:43-49. doi:10.1016/j.diabres.2018.06.006
13. Jian S, Su-Mei N, Xue C, Jie Z, Xue-sen W. Association and interaction between triglyceride-glucose index and obesity on risk of hypertension in middle-aged and elderly adults. *Clin Exp Hypertens.* 2017;39(8):732-739. doi:10.1080/10641963.2017.1324477
14. Wang K, He G, Zhang Y, Yin J, Yan Y, Zhang Y, Wang K. Association of triglyceride-glucose index and its interaction with obesity on hypertension risk in Chinese: a population-based study. *J Hum Hypertens.* 2020. doi:10.1038/s41371-020-0326-4
15. Moon S, Park JS, Ahn Y. The Cut-off Values of Triglycerides and Glucose Index for Metabolic Syndrome in American and Korean Adolescents. *J Korean Med Sci.* 2017;32(3):427-433. doi:10.3346/jkms.2017.32.3.427
16. Angoorani P, Heshmat R, Ejtahed H, Motlagh ME, Ziaodini H, Taheri M, Aminaee T, Goodarzi A, Qorbani M, Kelishadi R. Validity of triglyceride–glucose index as an indicator for metabolic syndrome in children and adolescents: the CASPIAN-V study. *Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity.* 2018;23(6):877-883. doi:10.1007/s40519-018-0488-z
17. Li S, Guo B, Chen H, Shi Z, Li Y, Tian Q, Shi S. The role of the triglyceride (triacylglycerol) glucose index in the development of cardiovascular events: a retrospective cohort analysis. *Sci Rep-Uk.* 2019;9(1). doi:10.1038/s41598-019-43776-5
18. Sánchez-Íñigo L, Navarro-González D, Fernández-Montero A, Pastrana-Delgado J, Martínez JA. The TyG index may predict the development of cardiovascular events. *Eur J Clin Invest.* 2016;46(2):189-197. doi:10.1111/eci.12583
19. Zhang S, Du T, Zhang J, Lu H, Lin X, Xie J, Yang Y, Yu X. The triglyceride and glucose index (TyG) is an effective biomarker to identify nonalcoholic fatty liver disease. *Lipids Health Dis.* 2017;16(1). doi:10.1186/s12944-017-0409-6
20. Zheng R, Du Z, Wang M, Mao Y, Mao W. A longitudinal epidemiological study on the triglyceride and glucose index and the incident nonalcoholic fatty liver disease. *Lipids Health Dis.* 2018;17(1):262. doi:10.1186/s12944-018-0913-3
21. Lee SB, Kim MK, Kang S, Park K, Kim JH, Baik SJ, Nam JS, Ahn CW, Park JS. Triglyceride Glucose Index Is Superior to the Homeostasis Model Assessment of Insulin Resistance for Predicting Nonalcoholic Fatty Liver Disease in Korean Adults. *Endocrinol Metab (Seoul).* 2019;34(2):179-186. doi:10.3803/EnM.2019.34.2.179
22. Kitae A, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. The Triglyceride and Glucose Index Is a Predictor of Incident Nonalcoholic Fatty Liver Disease: A Population-Based Cohort Study. *Can J*

Gastroenterol Hepatol. 2019;2019:5121574. doi:10.1155/2019/5121574

23. Fedchuk L, Nascimbeni F, Pais R, Charlotte F, Housset C, Ratziu V. Performance and limitations of steatosis biomarkers in patients with nonalcoholic fatty liver disease. *Aliment Pharmacol Ther.* 2014;40(10):1209-1222. doi:10.1111/apt.12963
24. Cazzo E, Jimenez LS, Gestic MA, Utrini MP, Chaim F, Chaim F, Pareja JC, Chaim EA. Type 2 Diabetes Mellitus and Simple Glucose Metabolism Parameters may Reliably Predict Nonalcoholic Fatty Liver Disease Features. *Obes Surg.* 2018;28(1):187-194. doi:10.1007/s11695-017-2829-9
25. Zheng S, Tong M, Dong L, Du C, Zheng X, Wang L, Huang P, Liu W, Lin M, Liu C. Lipid accumulation product independently correlate with hepatic steatosis quantified by controlled attenuation parameter in women with polycystic ovary syndrome. *Endocr Connect.* 2020;9(2):154-162. doi:10.1530/EC-19-0559
26. Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study. *Int J Obes (Lond).* 2019;43(1):139-148. doi:10.1038/s41366-018-0076-3
27. Chitturi S, Farrell GC, Hashimoto E, Saibara T, Lau GK, Sollano JD, Asia-Pacific WPON, The APWP. Non-alcoholic fatty liver disease in the Asia–Pacific region: Definitions and overview of proposed guidelines. *J Gastroen Hepatol.* 2007;22(6):778-787. doi:10.1111/j.1440-1746.2007.05001.x
28. Hashimoto Y, Hamaguchi M, Kojima T, Ohshima Y, Ohbora A, Kato T, Nakamura N, Fukui M. The modest alcohol consumption reduces the incidence of fatty liver in men: a population-based large-scale cohort study. *J Gastroen Hepatol.* 2015;30(3):546-552. doi:10.1111/jgh.12786
29. VT S, ZX L, X Q, BD E, S B, D B, AJ R, GI S. Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. *The Journal of biological chemistry.* 2004;279(31):32345-32353. doi:10.1074/jbc.M313478200
30. Petta S, Di Marco V, Di Stefano R, Cabibi D, Cammà C, Marchesini G, Craxì A. TyG index, HOMA score and viral load in patients with chronic hepatitis C due to genotype 1. *J Viral Hepatitis.* 2011;18(7):e372-e380. doi:10.1111/j.1365-2893.2011.01439.x
31. Simental-Mendia LE, Simental-Mendia E, Rodriguez-Hernandez H, Rodriguez-Moran M, Guerrero-Romero F. The product of triglycerides and glucose as biomarker for screening simple steatosis and NASH in asymptomatic women. *Ann Hepatol.* 2016;15(5):715-720. doi:10.5604/16652681.1212431
32. Li Z, Xue J, Chen P, Chen L, Yan S, Liu L. Prevalence of nonalcoholic fatty liver disease in mainland of China: A meta-analysis of published studies. *J Gastroen Hepatol.* 2014;29(1):42-51. doi:10.1111/jgh.12428

Tables

Table1 Baseline characteristics of study participants by quartiles of TyG

	Q1 (≤7.59)	Q2 (7.59 to ≤8.01)	Q3 (8.01 to ≤ 8.46)	Q4 (10.73)	P-value	P-value*
	3493	3336	3269	3080		
s	40.28 ± 8.11	43.20 ± 8.85	44.69 ± 8.89	45.60 ± 8.76	<0.001	<0.001
m2	20.34 ± 2.37	21.36 ± 2.68	22.56 ± 3.07	24.23 ± 3.14	<0.001	<0.001
	70.62 ± 7.02	73.94 ± 7.95	77.73 ± 8.50	82.83 ± 8.31	<0.001	<0.001
L	14.00 (11.00-17.00)	15.00 (12.00-19.00)	18.00 (13.00-23.00)	23.00 (17.00-32.00)	<0.001	<0.001
L	16.00 (13.00-19.00)	16.00 (13.00-20.00)	17.00 (14.00-21.00)	19.00 (15.00-24.00)	<0.001	<0.001
L	12.00 (10.00-15.00)	13.00 (10.00-17.00)	15.00 (12.00-21.00)	21.00 (15.00-31.00)	<0.001	<0.001
ng/dL	65.25 ± 14.52	60.02 ± 14.51	53.61 ± 13.09	44.62 ± 10.68	<0.001	<0.001
lL	181.74 ± 29.94	193.85 ± 30.58	203.30 ± 31.10	215.81 ± 33.57	<0.001	<0.001
lL	32.50 ± 8.42	54.32 ± 7.29	80.27 ± 11.37	154.71 ± 65.17	<0.001	<0.001
%	5.12 ± 0.30	5.16 ± 0.31	5.20 ± 0.33	5.26 ± 0.34	<0.001	<0.001
'dL	88.24 ± 6.71	91.67 ± 6.79	94.10 ± 6.63	96.99 ± 6.54	<0.001	<0.001
Hg	107.33 ± 12.60	111.64 ± 13.88	115.86 ± 14.44	120.90 ± 14.69	<0.001	<0.001
Hg	66.31 ± 8.89	69.35 ± 9.64	72.47 ± 9.97	76.24 ± 10.17	<0.001	<0.001
onsumption	0.69 (0.00-2.31)	0.69 (0.00-2.94)	0.69 (0.00-3.58)	0.69 (0.00-3.81)	<0.001	<0.001
	7.22 ± 0.31	7.81 ± 0.12	8.22 ± 0.13	8.86 ± 0.34	<0.001	<0.001
%					<0.001	-
	2689 (76.98%)	1866 (55.94%)	1276 (39.03%)	624 (20.26%)		
	804 (23.02%)	1470 (44.06%)	1993 (60.97%)	2456 (79.74%)		
exercise, %					0.009	-
	2877 (82.36%)	2707 (81.15%)	2736 (83.70%)	2586 (83.96%)		
	616 (17.64%)	629 (18.85%)	533 (16.30%)	494 (16.04%)		
status, %					<0.001	-
	2804 (80.27%)	2262 (67.81%)	1864 (57.02%)	1375 (44.64%)		
	377 (10.79%)	520 (15.59%)	635 (19.42%)	743 (24.12%)		
t	312 (8.93%)	554 (16.61%)	770 (23.55%)	962 (31.23%)		
ısion, %					<0.001	-
	3440 (98.48%)	3222 (96.58%)	3057 (93.51%)	2741 (88.99%)		
	53 (1.52%)	114 (3.42%)	212 (6.49%)	339 (11.01%)		
%					<0.001	-
	3407 (97.54%)	3079 (92.30%)	2633 (80.54%)	1698 (55.13%)		
	86 (2.46%)	257 (7.70%)	636 (19.46%)	1382 (44.87%)		

Values are means ±SDs, Median (Q1-Q3), or n (%). Differences in baseline characteristics were compared with the use of chi-square tests for categorical variables and ANOVA for continuous variables.

BMI, body mass index; WC, Waist circumference; HDL-C, high-density lipoprotein cholesterol; TC, Total cholesterol; TG, Triglycerides; HbA1C, hemoglobin A1c; FPG, Fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; TyG, Triglyceride-glucose index; NAFLD, Nonalcoholic fatty liver.

Table 2 Univariate analysis for NAFLD

	Statistics	OR(95% CI) P-value
Age, years	43.36 ± 8.89	1.02 (1.01, 1.02) <0.0001
BMI, kg/m2	22.06 ± 3.16	1.65 (1.61, 1.68) <0.0001
WC, cm	76.08 ± 9.14	1.21 (1.20, 1.22) <0.0001
ALT, IU/L	16.00 (12.00-23.00)	1.10 (1.10, 1.11) <0.0001
AST, IU/L	17.00 (14.00-21.00)	1.09 (1.08, 1.10) <0.0001
GGT, IU/L	14.00 (11.00-20.00)	1.05 (1.04, 1.05) <0.0001
HDL-C, mg/dL	56.22 ± 15.39	0.93 (0.92, 0.93) <0.0001
TC, mg/dL	198.12 ± 33.66	1.01 (1.01, 1.01) <0.0001
TG, mg/dL	78.43 ± 55.89	1.02 (1.02, 1.02) <0.0001
HbA1C, %	5.18 ± 0.32	4.40 (3.80, 5.08) <0.0001
FPG, mg/dL	92.60 ± 7.40	1.12 (1.11, 1.12) <0.0001
SBP, mmHg	113.71 ± 14.77	1.05 (1.05, 1.06) <0.0001
DBP, mmHg	70.93 ± 10.33	1.08 (1.08, 1.09) <0.0001
TyG	8.00 ± 0.64	7.79 (7.08, 8.56) <0.0001
Ethanol consumption (g/week)	1.00 (0.00-18.00)	1.00 (1.00, 1.00) 0.0039
Gender, %		
female	6455 (48.98%)	Ref
male	6723 (51.02%)	5.06 (4.54, 5.64) <0.0001
Visceral fat obesity, %		
non	11439 (86.80%)	Ref
yes	1739 (13.20%)	6.48 (5.81, 7.22) <0.0001
Obesity, %		
non	11061 (83.94%)	Ref
yes	2117 (16.06%)	11.76 (10.58, 13.07) <0.0001
Regular exercise, %		
non	10906 (82.76%)	Ref
yes	2272 (17.24%)	0.81 (0.72, 0.92) 0.0009
Smoking status, %		
never	8305 (63.02%)	Ref
past	2275 (17.26%)	2.17 (1.94, 2.43) <0.0001
current	2598 (19.71%)	2.05 (1.84, 2.29) <0.0001
Hypertension, %		
non	12460 (94.55%)	Ref
yes	718 (5.45%)	4.45 (3.81, 5.19) <0.0001

CI confidence interval, Ref reference

Table 3 Relationship between TyG and NAFLD in different models

Variable	Crude model (OR, 95% CI, P)	Minimally adjusted model (OR, 95% CI, P)	Fully adjusted model (OR, 95% CI, P)
TyG	7.79 (7.08, 8.56) <0.0001	6.18 (5.59, 6.83) <0.0001	2.45 (2.12, 2.82) <0.0001
TyG (quartile)			
Q1	Ref	Ref	Ref
Q2	3.31 (2.58, 4.24) <0.0001	2.70 (2.10, 3.48) <0.0001	1.57 (1.19, 2.08) 0.0016
Q3	9.57 (7.60, 12.05) <0.0001	6.89 (5.44, 8.72) <0.0001	2.42 (1.84, 3.18) <0.0001
Q4	32.24 (25.73, 40.40) <0.0001	20.49 (16.21, 25.89) <0.0001	3.95 (2.97, 5.27) <0.0001
P for trend	<0.0001	<0.0001	<0.0001

Crude model: we did not adjust other covariates

Minimally adjusted model: we adjusted age and sex

Fully adjusted model: we adjusted gender; age; ALT; AST; GGT; SP; BMI; WC; regular exercise; HDL-C; TC; HbA1C; Ethanol consumption; Smoking status.

CI confidence interval, Ref reference

Table 4 The result of two-piecewise linear regression model

	OR, 95%CI, P value
Fatting model by standard linear regression	2.45 (2.12, 2.82) <0.0001
Fitting model by two-piecewise linear regression	
Inflection point	8.22
<8.22	3.26 (2.44, 4.35) <0.0001
> 8.22	2.09 (1.72, 2.54) <0.0001
P for log likelihood ratio test	0.023

We adjusted gender; age; ALT; AST; GGT; SP; BMI; WC; regular exercise; HDL-C; TC; HbA1C; Ethanol consumption; Smoking status.

CI confidence interval

Table 5 Effect size of TyG on NAFLD in prespecified and exploratory subgroups

Characteristic	No. of participants	OR (95%CI)	*P*-value	*P* for interaction
Age (year)				0.2561
≤60	429	1.81 (1.04, 3.13)	0.0348	
60	12742	2.50 (2.17, 2.89)	<0.0001	
Gender				
Male	6455	3.20 (2.50, 4.09)	<0.0001	0.0076*
Female	6716	2.24 (1.92, 2.62)	<0.0001	
ALT (tertile)				
Low	4210	3.49 (2.43, 5.01)	<0.0001	0.0571
Middle	4352	2.43 (1.93, 3.07)	<0.0001	
High	4609	2.22 (1.89, 2.61)	<0.0001	
AST (tertile)				0.5125
Low	3895	2.79 (2.13, 3.67)	<0.0001	
Middle	5032	2.37 (1.93, 2.91)	<0.0001	
High	4244	2.37 (1.97, 2.85)	<0.0001	
GGT (tertile)				0.0317*
Low	3793	3.73 (2.48, 5.61)	<0.0001	
Middle	5376	2.25 (1.83, 2.75)	<0.0001	
High	4002	2.12 (1.78, 2.53)	<0.0001	
HDL-C (tertile)				0.1836
Low	4474	2.46 (2.08, 2.90)	<0.0001	
Middle	4383	2.38 (1.88, 3.02)	<0.0001	
High	4314	3.46 (2.40, 4.99)	<0.0001	
TC (tertile)				0.1084
Low	4315	2.22 (1.76, 2.79)	<0.0001	
Middle	4365	2.89 (2.32, 3.59)	<0.0001	
High	4491	2.22 (1.82, 2.71)	<0.0001	
HbA1c (tertile)				0.6258
Low	3080	2.42 (1.84, 3.19)	<0.0001	
Middle	5209	2.61 (2.13, 3.20)	<0.0001	
High	4882	2.32 (1.92, 2.79)	<0.0001	
Obesity				0.0111*
Non	11056	2.72 (2.32, 3.20)	<0.0001	
Yes	2115	1.99 (1.61, 2.47)	<0.0001	
Visceral fat obesity				0.0109
Non	11434	2.65 (2.28, 3.09)	<0.0001	
Yes	1737	1.88 (1.47, 2.41)	<0.0001	
Hypertension				0.8865
Non	12454	2.49 (2.15, 2.88)	<0.0001	
Yes	717	2.42 (1.64, 3.57)	<0.0001	
Smoking status				0.5128
Non	8302	2.60 (2.17, 3.12)	<0.0001	
Past	2272	2.22 (1.73, 2.84)	<0.0001	
Current	2597	2.37 (1.86, 3.02)	<0.0001	
Ethanol consumption				0.4843
<40 (g/week)	10779	2.49 (2.14, 2.91)	<0.0001	
40-140	2392	2.26 (1.76, 2.91)	<0.0001	
Regular exercise				0.9802
Non	10900	2.44 (2.10, 2.84)	<0.0001	
Yes	2271	2.45 (1.87, 3.22)	<0.0001	

Note 1: Above model adjusted for gender; age; ALT; AST; GGT; SP; BMI; WC; regular exercise; HDL-C; TC; HbA1C; Ethanol consumption; Smoking status.

Note 2: In each case, the model is not adjusted for the stratification variable

Table 6 Areas under the receiver operating characteristic curves (AUROC) of TyG for identifying nonalcoholic fatty in different gender.

Variable	AUC	95% CI	P-Value
Men			
TyG	0.748	0.737 to 0.758	--
ALT	0.797	0.788 to 0.807	< 0.0001
FPG	0.635	0.624 to 0.647	< 0.0001
TG	0.739	0.728 to 0.749	< 0.0001
Women			
TyG	0.818	0.809 to 0.828	--
ALT	0.765	0.755 to 0.776	< 0.0001
FPG	0.719	0.708 to 0.730	< 0.0001
TG	0.804	0.794 to 0.814	< 0.0001
Total			
TyG	0.810	0.804 to 0.817	--
ALT	0.829	0.822 to 0.835	0.0020
FPG	0.715	0.707 to 0.722	< 0.0001
TG	0.799	0.792 to 0.805	< 0.0001

Figures

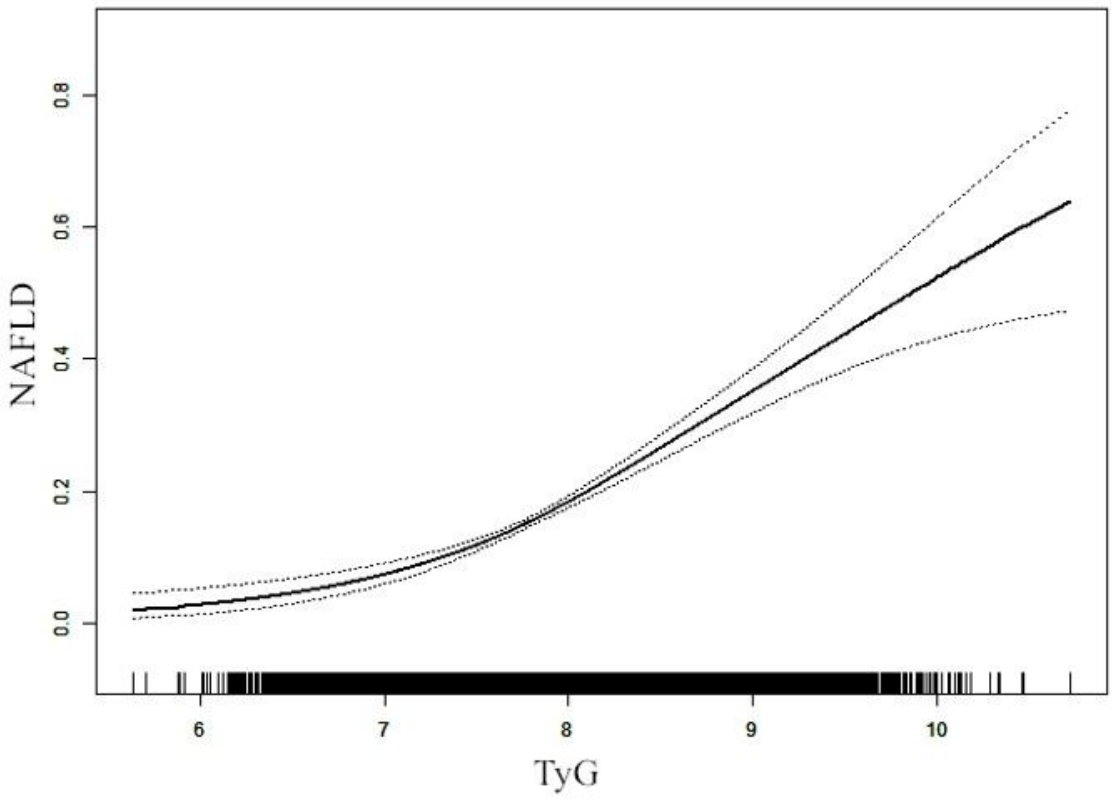

Figure 1

The non-linear relationship between TyG and NAFLD. A non-linear relationship between them was detected after adjusting for gender; age; ALT; AST; GGT; SP; BMI; WC; regular exercise; HDL-C; TC; HbA1C; Ethanol consumption; Smoking status.

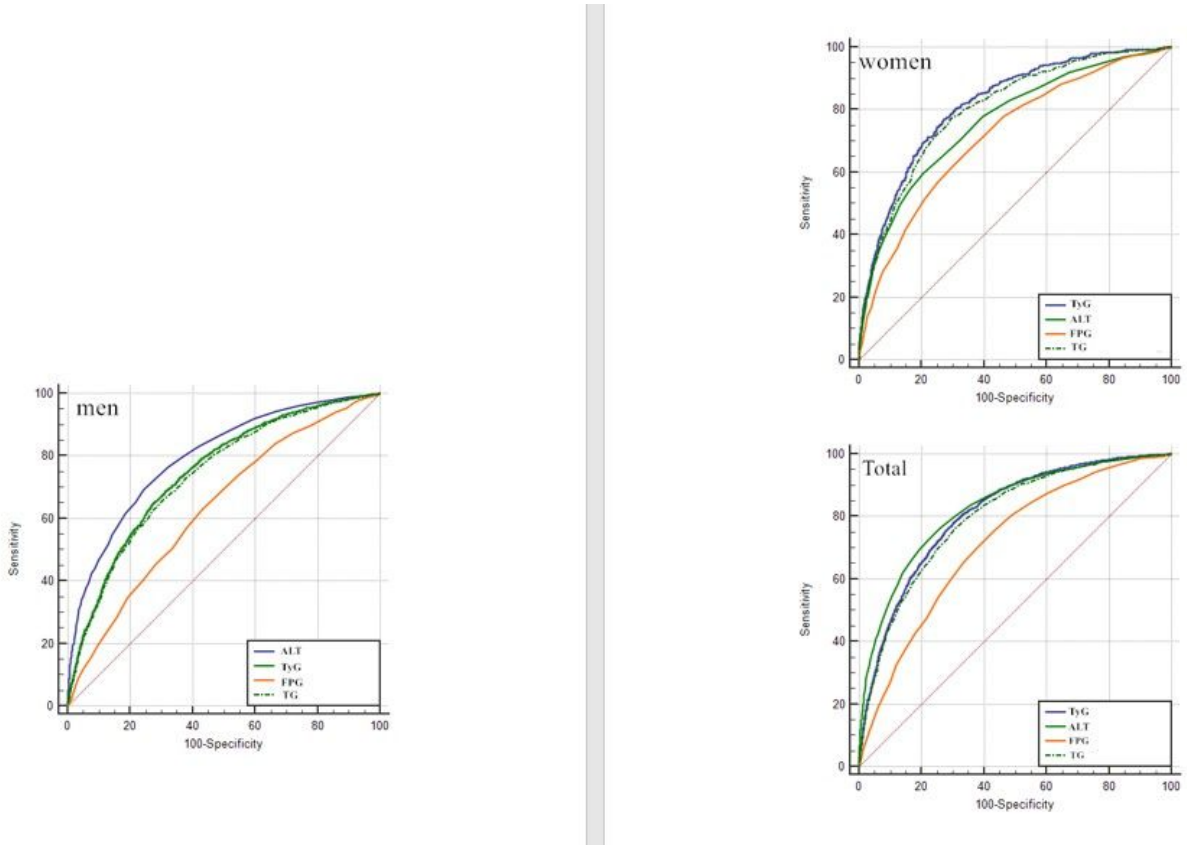

Figure 2

AUROCs for the prediction of NALFD in different gender.