Risk prediction of the metabolic syndrome using TyG Index and SNPs: a 10-year longitudinal prospective cohort study

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Abstract

TyG (triglyceride and glucose) index using triglyceride and fasting blood glucose is recommended as a useful marker for insulin resistance. To clarify whether the TyG index is a marker for predicting the metabolic syndrome (MetS) and to investigate the importance of single nucleotide polymorphisms (SNPs) in MetS diagnosis. From 2001 to 2014, a longitudinal prospective cohort study of 3,580 adults aged 40 to 70 years was conducted. Area under the receiver operating characteristic curves (AUROC) and Youden index (YI) were calculated to assess the diagnostic value. During the 14 year follow-up, 1270 subjects developed MetS. Five SNPs in four genes (*BUD13* rs10790162, *ZPR1* rs2075290, *APOA5* rs2266788, *APOA5* rs2075291, and *MKL1* rs4507196) significantly correlated with susceptibility to MetS (P<0.00005). The areas under the curve of TyG index and HOMA-IR were 0.854 (95% confidence interval [CI], 0.841–0.867), and 0.702 (95% CI, 0.684–0.721), respectively. Despite no statistical significance, AUROC and YI were increased when MetS was diagnosed using TyG index and the five SNPs. TyG index might be useful for identifying individuals at high risk of developing MetS. The combination of TyG index and SNPs showed better diagnostic accuracy than TyG index alone, indicating the potential value of novel SNPs for MetS diagnosis.

Introduction

The metabolic syndrome (MetS) is a clustering of metabolic risk factors, including central obesity, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL) [1, 2]. MetS is closely related to the development of diabetes, cardiovascular disease, and mortality. The prevalence of MetS has increased due to changes in lifestyle and dietary habits. Therefore, early identification of subjects at high risk of MetS is essential to prevent the occurrence and progression of MetS.

Various predictive models for MetS such as the TyG (triglyceride and glucose) index and homeostasis model assessment-insulin resistance (HOMA-IR) have been suggested [3–5]. The TyG index, defined as the product of fasting plasma glucose (FPG) and triglyceride (TG) levels, is considered a good marker for early identification of IR. Because IR is a key factor in the development of MetS, the TyG index might be a better marker than others for diagnosing individuals with MetS.

Recently, many studies have suggested that gene susceptibility plays a key role in MetS development and that single-nucleotide polymorphisms (SNPs) are associated with MetS development independently or in combination with environmental factors [6–8]. A recent genome-wide association study (GWAS) of MetS in a large population-based cohort study revealed that variants in the BUD13, ZNF259, APOA5, LPL, and CETP genes were associated with MetS. However, few GWAS have been conducted in Asian populations.

It is important to identify parameters that serve as diagnostic and prognostic markers for MetS. Therefore, we have attempted to construct a new index consisting of the TyG index and SNPs, which would exhibit high area under the receiver operating characteristics (AUROC), sensitivity, and specificity.

In this study, we have used 10-year longitudinal prospective cohort data to examine whether the TyG index is a valuable marker for predicting MetS and investigate the value of novel susceptibility genes in combination with the TyG index for predicting MetS.

Patients And Methods

Study population

We analyzed a database from the community-based Korean Genome and Epidemiology Study longitudinal prospective cohort of subjects from the Ansan (urban) and Anseong (rural) areas. The inclusion criteria included age ≥40 years, complete data measurements, and informed consent from subjects. Subjects with mental disorders, malignant tumors, or incomplete recorded information in their medical records were excluded from this study. Among 9,333 participants, a total of 3,580 subjects (1,666 males and 1,914 females) with complete data were included in this study. From 2001 to 2014, these participants have been biennially followed up. We defined the participants with newly diagnosed of MetS by the modified NCEP-ATP III criteria as MetS group, the healthy participants as Non-MetS group. The study protocol was approved by the Institutional Review Board (IRB; KBP-2017-014) of Korea Centers for Disease Control and Prevention. All participants provided written informed consent before the commencement of the study.

Clinical and laboratory assessments

Each subject completed a past medical history questionnaire and underwent anthropometric assessment. Laboratory and radiological tests were conducted on the same day. Waist circumference was measured at the midpoint between the lower costal margin and the level of the anterior superior iliac crest. The laboratory evaluations included serum total cholesterol, triglyceride, low-density lipoprotein cholesterol, HDL cholesterol, fasting glucose, and serum insulin.

Definition of MetS

MetS was diagnosed as the presence of three or more of the following parameters according to the modified NCEP-ATP III criteria: (i) waist circumference: ≥90 cm in men and ≥80 cm in women (in accordance with the International Obesity Task Force criteria for Asian-Pacific population); (ii) triglycerides: ≥150 mg/dL; (iii) HDL-cholesterol: <40 mg/dL in men and <50 mg/dL in women; (iv) blood pressure: ≥130/85 mmHg or antihypertensive medications; and (v) fasting blood glucose: ≥110 mg/dL (fasting blood glucose ≥100 mg/dL was revised in 2005) or antidiabetic medications.

Clinical surrogate markers

The TyG index was calculated as ln [fasting triglycerides (mg/dL) × FPG (mg/dL)/2]. HOMA-IR was calculated as FPG (mmol/L) × fasting insulin (mIU/L)/22.5.

Genotyping

In this study, genotyping of the HumanCoreExome 12v1 chip (Illumina, Inc., San Diego, CA, USA) was performed and the data was analyzed. First, all genetic variants were examined for Hardy–Weinberg equilibrium. From the 77,421 SNPs in the HumanCoreExome 12v1 chip data, we excluded SNPs based on the Hardy-Weinberg equilibrium test for quality control, SNPs in sex chromosomes and the mitochondria, and monomorphic SNPs. After filtering the SNPs, 1,284 SNPs remained.

Statistical analysis

Data are presented as the mean ± standard deviation. The patient characteristics were compared using the $\chi 2$ test for categorical variables and Student's t-test and Mann–Whitney U-Test for continuous variables. A logistic regression analysis was performed to examine the association between the development of MetS and genetic polymorphisms using the SNP & Variation Suite (Golden Helix, Bozeman, MT, USA). PolyPhen-2, SIFT, and PROVEAN software were used for predicting protein damage caused by SNPs. AUROC, sensitivity, and specificity were assessed using the "ROC curve analysis" function of MedCalc. The Youden index (YI) was calculated as: (sensitivity + specificity) - 1. AUROC was defined as excellent (AUC 0.9–1), good (AUC 0.8–0.89), fair (AUC 0.7–0.79), poor (AUC 0.6–0.69), or fail/no discriminatory capacity (AUC 0.5–0.59).

Results

Demographics and clinical characteristics

Among 3,580 participants, the prevalence rate of MetS during the 14-year period was 35.4% (n=1,270). As shown in Table 1, the participants were divided into 2 subgroups according to modified NCEP-ATP III criteria: MetS group (n=1,270, 35.4%) and healthy group (n=2,310, 64.5%). The average age was higher than MetS. (p value <0.05). The prevalence rates of MetS in women and men were 42.4% and 27.4%, respectively. Subjects diagnosed with MetS showed higher WC, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, TG, HOMA-IR, and TyG index and lower HDL-C than those without MetS (P<0.05). All MetS components (hyperglycemia, elevated blood pressure, elevated TG, low HDL-C and central obesity) were higher in patients with MetS than in those without MetS (P<0.05).

Table 1
Characteristics of the participants according to presence of metabolic syndrome

Variable	Non-MetS	MetS	*P*-value
	(N=2310)	(N=1270)	
Age (yr)	49.33±7.90	53.79±8.11	0.000
Men (%)	1208(52.3)	458(36.1)	0.000
Height (cm)	161.1±8.2	158.6±8.9	0.000
Weight (Kg)	60.7±9	67.5±10.4	0.000
BMI (Kg/m^2)	23.3±2.6	26.8±2.8	0.000
Waist curcumferecnce (cm)	78.05±7.50	89.25±7.06	0.000
Systolic blood pressure (mmHg)	115.99±15.14	134.38±17.28	0.000
Diastolic blood pressure (mmHg)	77.90±10.15	88.88±10.54	0.000
Total cholesterol (mg/dL)	186.8±32.5	198.2±36.4	0.000
HDL cholesterol (mg/dL)	48.32±10.12	39.00±6.92	0.000
Triglyceride (mg/dL)	122.30±59.71	227.58±136.89	0.000
Fasting glucose (mg/dL)	83.05±13.23	93±26.39	0.000
HOMA-IR	1.38±0.78	2.10±1.36	0.000
TyG index	8.44±0.42	9.12±0.54	0.000
Metabolic syndrome component			
High blood pressure	571(24.7)	989(77.9)	0.000
Imparied fasting glucose	92(4.0)	281(22.1)	0.000
High triglyceride (mg/dL)	428(18.5)	983(77.4)	0.000
Low HDL cholesterol (mg/dL)	934(40.4)	1141(89.8)	0.000
Abdominal obesity	321(13.9)	1032(81.3)	0.000
Values are presented as mean ± SD			
Abbreviations: MetS, metabolic syndrome; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; Tyg index, triglyceride-glucose index			

Genome-wide Association Analysis Of Mets

As shown in Table 2, we selected the most significant SNPs from the HumanCoreExome 12v1 chip data of the MetS and healthy groups using the logistic regression test and p-values. Significant SNPs in the genes were sorted by their p-values. Of the 1,284 SNPs detected in the HumanCoreExome 12v1 chip data, five SNPs of four genes (*BUD13* rs10790162, *ZPR1* rs2075290, *APOA5* rs2266788, *APOA5* rs2075291, and *MKL1* rs4507196) were significantly correlated with MetS susceptibility ($p<0.00005$).

Table 2
SNPs associated with MetS

rs ID	Gene(s)	Chromosome	Position	Minor Allele	Major Allele	Mutation	P	FDR	SIFT	PROVEAN	PolyPhen
rs10790162	*BUD13*	11	116639104	A	G	intron	0.00001	0.128	-	-	-
rs2075290	*ZPR1*	11	116653296	G	A	intron	0.00003	0.165	-	-	-
rs2266788	*APOA5*	11	116660686	G	A	upstream	0.00003	0.158	-	-	-
rs2075291	*APOA5*	11	116661392	A	C	missense	0.00000	0.000	deleterious	deleterious	probably damaging
rs4507196	*MKL1*	22	40849704	A	C	intron	0.00004	0.192	-	-	-

The Comparison Between Tyg Index And Homa-ir

The incidence of MetS increased proportionally with the TyG index quartiles (Q1, 2.1%; Q2, 8.0%; Q3, 22.4%; and Q4, 41.8%). Similar results were observed for HOMA-IR (Q1, 16.5%; Q2, 15.8%; Q3, 19.6%; and Q4, 32.8%) (Fig. 1). Figure 2 shows the calculated fitted value using logistic regression analysis. The dependent variable is MetS and the independent variables are TyG index and HOMA-IR, respectively. The linear relationship between the fitted value of MetS and the independent variables means a strong predictive power and gray area means 95% CI. In HOMA-IR, the fitted value was increased up to a certain extent in the lower values but decreased in the higher values. However, TyG index reveals a linear relationship and area of 95 % CI is narrower than HOMA-IR.

The Comparison Of Parameters For Predicting Mets

The ROC curves for each parameter to predict MetS are shown in Fig. 3. The AUCs, optimal cut-off values, sensitivity, specificity, and YI of each parameter for predicting MetS are shown in Table 3. The TyG index showed higher AUROC (0.854) than HOMA-IR (0.702), and the difference between the two groups was significant, suggesting higher accuracy and reliability of TyG for MetS diagnosis than HOMA-IR. The sensitivities of TyG and HOMA-IR were 79.7 and 52.7, respectively, and the specificities were 79.3 and 78.3, respectively. A combination of the TyG index with each of the five SNPs resulted in an identical AUROC of 0.861. Although the difference was not statistically significant, it was higher than that obtained by the TyG alone. The combination of the TyG index with each of the five SNPs also showed higher sensitivity than TyG alone; however, the specificities for both conditions were low.

Table 3
The AUROC, optimal cut-off values, sensitivity, and specificity of the clinical parameters for predicting MetS

	Gene	AUROC	SE.AUC	Lower limit	Upper limit	z	Sensitivity	specificity	cut-off	p-value	
HOMA-IR		0.702	0.009	0.684	0.721	21.682	52.7	78.3	1.783	0.000	fair
TyG		0.854	0.007	0.841	0.867	53.866	79.7	79.3	8.719	0.000	good
rs10790162	*BUD13*	0.861	0.006	0.848	0.873	57.513	84.1	74.7	19.548	0.000	good
rs2075290	*ZNF259*	0.861	0.006	0.848	0.873	57.482	83.9	74.9	19.548	0.000	good
rs2266788	*APOA5*	0.861	0.006	0.848	0.873	57.461	83.9	74.9	19.548	0.000	good
rs2075291	*APOA5*	0.861	0.006	0.848	0.873	57.459	83.5	75.4	19.548	0.000	good
rs4507196	*MKL1*	0.861	0.006	0.848	0.873	57.398	84.3	73.9	19.563	0.000	good

Discussion

In this study, we investigated the possibility for diagnosing MetS using the TyG index in a longitudinal prospective cohort study. And we firstly suggested the diagnostic value of the five SNPs—*BUD13* rs10790162, *ZPR1* rs2075290, *APOA5* rs2266788, *APOA5* rs2075291, and *MKL1* rs4507196—in MetS.

The TyG index—defined as the product of FPG and TG levels—was proposed by Guerrero-Romero et al. as a marker of insulin resistance [3]. Several reports have investigated the diagnostic value of the TyG index for MetS across different ethnic groups. Khan et al. have demonstrated that the TyG index is a good marker for diagnosing individuals with MetS with the highest area under cover [9] In addition, similar results were also obtained in Caucasian populations. Unger et al. have demonstrated the TyG index as an ideal marker of MetS in 525 adults [10]. Therefore, we demonstrated a more economical and convenient predictive method of MetS in large populations by determining the TyG index in this study. Our analysis showed that TyG index showed higher AUROC as well better sensitivity and specificity than HOMA-IR., which is currently used as a non-invasive method for diagnosing MetS. HOMA–IR had a nonlinear relationship with the fitted value of MetS. However, TyG index showed a linear relationship in our study. This result implies that TyG index is more valuable than HOMA-IR in predicting the development of MetS

Although an increasing number of researches have suggested the role of SNPs in the occurrence and development of MetS, only a few studies have investigated the role of genotyping for MetS diagnosis. In this study, we found a strong correlation between MetS and five SNPs—BUD13 rs10790162, ZPR1 rs2075290, APOA5 rs2266788, APOA5 rs2075291, and MKL1 rs4507196.

BUD13 is located on chromosome 11q23 and plays a critical role in regulating lipid metabolism [7, 11]. Interestingly, rs10790162 in the *BUD13* gene was recently found to be associated with MetS. *ZPR1*, also known as *ZNF259*, is an essential regulatory protein for normal nuclear function in cell proliferation and signal transduction. *ZPR1* plays an important role in insulin sensitivity; obesity; and glucose, fatty acid, and cholesterol metabolism [7, 12]. The *BUD13* and *ZNF259* genes are located downstream of the *APOA5* gene, which is located on chromosome 11q23. *APOA5* encodes an apolipoprotein that plays an important role in regulating plasma triglyceride levels, a major risk factor for coronary artery disease [7, 13, 14]. Rs2266788 in the *APOA5* gene was recently found to be associated with MetS. Moreover, the *MKL1* gene is significantly associated with lipid and glucose metabolism [15].

To determine the role of SNPs in the pathogenesis of MetS, we combined the SNPs with the TyG index to diagnose MetS. Of note, the combination of the TyG index with the five SNPs exhibited higher sensitivity and AUROC than the TyG index alone, for diagnosing MetS. These data support the potential value of combining the TyG index with SNPs for screening MetS.

The strengths of this study are that the subjects were from a large cohort that was subjected to long-term follow-up and there were sufficient cases for rigorous analysis. To our knowledge, this is the first report on the TyG index and novel SNPs in an Asian population that examined their ability as a predictive marker for MetS. However, there were some limitations to this study. As our subjects were Korean rural adults, it is unclear whether our results can be applied to different regional populations and ethnic groups. Further studies with multi-centers, a larger sample size, and more detailed information are required to assess the predictive value of MetS.

Our results show the possibility for diagnosing MetS using the TyG index. Moreover, we explored genetic polymorphisms associated with MetS using a genome-wide approach. The combination of the TyG index with five SNPs also showed better diagnostic value than the TyG index alone. Future studies are required to validate our results and define the functional effects of these SNPs on MetS to optimize tailored therapies and individualize MetS patient care.

Declarations

Author contributions SWK, SKK, YSK and MSP designed research; SWK and MSP. conducted review and editing; SWK, SKK, YSK and MSP preformed the experimental work and analysis; and SWK, SKK and MSP wrote the paper. All authors approved the manuscript.

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Availability of data and material The data used to support the findings of this study are included within the article. All data generated or analysed during this study are included in this published article and its supplementary information.

Conflict of interest The authors declare that there are no conficts of interest..

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. The present study was approved by the Institutional Review Board (IRB; KBP-2017-014) of Korea Centers for Disease Control and Prevention.

Consent to participate Written informed consent was obtained from all enrolled patients.

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Figures

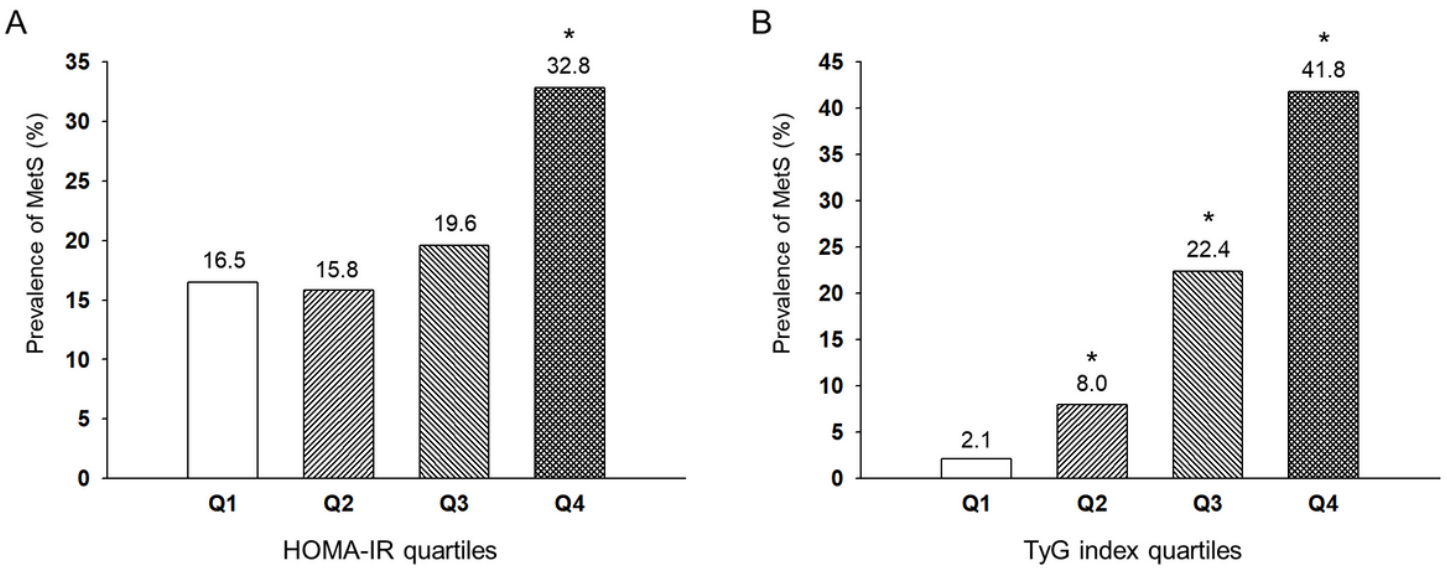

Figure 1

Prevalence of metabolic syndrome according to HOMA-IR and TyG index quartile

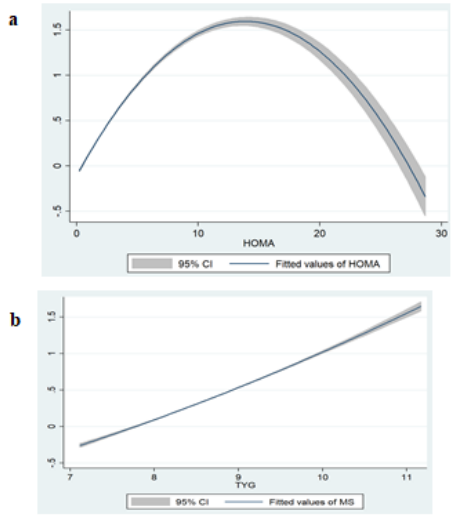

Figure 2

(a) HOMA-IR has a nonlinear relationship with the fitted value of MetS. (b) TyG index has a linear relationship with the fitted value of MetS and area of 95 % CI is narrower than HOMA-IR.

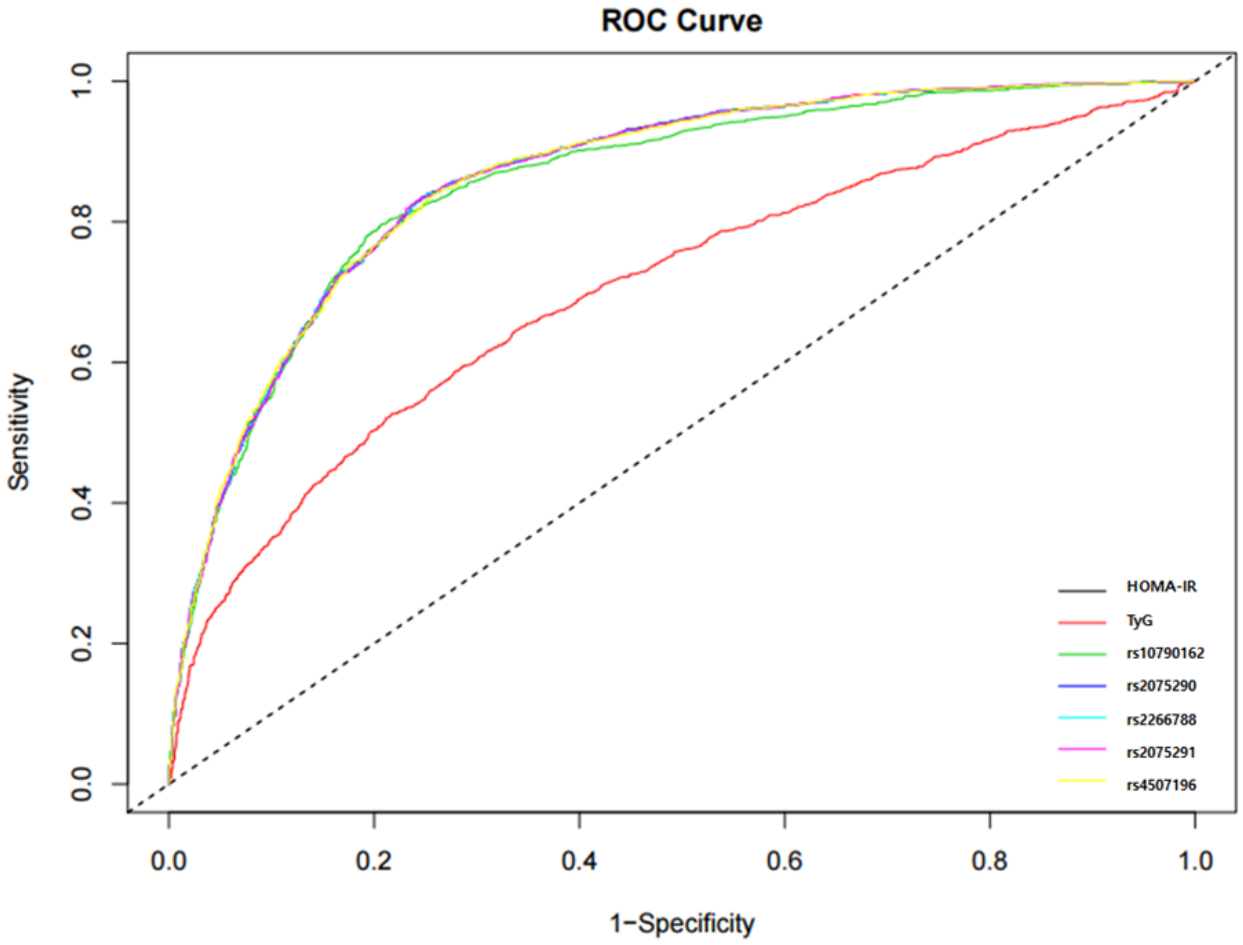

Figure 3

Comparing the area under the receiver-operating characteristic curves between the Tyg index and other indexs to predict Mets.