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ORIGINAL ARTICLE

Predictive Value of Hemoglobin Glycation Index Combined with TyG-WHtR for Metabolic Syndrome in Middle-Aged and Older Adults

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ABSTRACT

Background: **The aim is to evaluate the predictive performance of the Hemoglobin Glycation Index (HGI) and the triglyceride glucose-waist-to-height ratio (TyG-WHtR), both alone and combined, for Metabolic Syndrome (MetS) in a middle-aged and elderly population.**

Methods: **A total of 560 subjects aged ≥ 45 years were enrolled from the health examination center and endocrinology outpatient department. MetS was diagnosed using the Adult Treatment Panel III (ATP III) criteria. HGI was calculated based on the linear regression equation of glycated hemoglobin (HbA1c) on fasting plasma glucose (FPG). TyG-WHtR was calculated as the product of the TyG index and waist-to-height ratio (WHtR). Receiver operating characteristic (ROC) curve analysis, the DeLong test, calibration curves, and decision curve analysis (DCA) were used to evaluate the discriminatory ability, calibration, and clinical net benefit of the individual indicators and the combined model.**

Results: **Among the 560 participants, 45.9% were female, and the prevalence of MetS was 38.9%. Multivariate logistic regression identified both HGI and TyG-WHtR as independent predictors of MetS. The areas under the curve (AUC) for predicting MetS were 0.718 for HGI, 0.758 for TyG-WHtR, and 0.826 for the combined model. The combined model demonstrated significantly superior discriminatory ability compared to either single indicator (DeLong test, $p < 0.05$). The combined model was well-calibrated, and DCA indicated the highest net benefit across a wide range of clinically relevant threshold probabilities.**

Conclusions: **The combination of HGI and TyG-WHtR significantly improves the predictive performance for MetS in a middle-aged and elderly population. The combined model is well-calibrated and provides high clinical net benefit, offering a practical supplementary tool for the early identification of MetS in health check-up and outpatient settings.**

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KEYWORDS

metabolic syndrome, glycated hemoglobin index, TyG-WHtR, middle-aged and elderly population, prediction model, receiver operating characteristic curve

INTRODUCTION

Metabolic syndrome (MetS) is a clinical syndrome characterized by a cluster of metabolic disorders, including central obesity, dyslipidemia, elevated blood pressure, and elevated fasting blood glucose. It is a significant risk factor for type 2 diabetes and cardiovascu-

lar disease [1]. In China, the prevalence of MetS continues to rise due to population aging and lifestyle changes. Based on data from the 2015 - 2017 National Nutrition and Health Surveillance, the prevalence of MetS among adults aged ≥ 20 years has increased significantly, particularly among women, individuals aged ≥ 45 years, and urban residents [2,3]. MetS is not only a precursor to chronic diseases but is also closely associated with adverse outcomes such as frailty and premature death, making early identification and risk stratification crucial for chronic disease prevention and control [4]. Traditional metabolic risk assessment relies on insulin resistance indices (such as HOMA-IR) or single obesity indicators (such as BMI or waist circumference). However, the former requires insulin testing and is relatively costly, while the latter fails to fully reflect metabolic heterogeneity [5]. Therefore, there is a practical need to develop simple screening tools based on routine laboratory tests.

The Hemoglobin Glycation Index (HGI) is calculated as the difference between the measured glycated hemoglobin (HbA1c) and the HbA1c predicted by a regression equation based on fasting plasma glucose (FPG), reflecting interindividual differences in glycation susceptibility [6,7]. HGI offers an additional dimension of individualized risk assessment beyond single glucose or HbA1c measures and is particularly sensitive in cases of significant discrepancies between average glucose levels and HbA1c [8]. Numerous studies have confirmed that a high HGI is independently associated with the risk of major adverse cardiovascular events, coronary heart disease, stroke, and all-cause mortality, indicating its potential value in metabolic disease risk assessment [7,9-11].

The Triglyceride-Glucose Index (TyG), calculated from FPG and triglyceride levels, is a surrogate marker of insulin resistance known for its stability and practicality. The TyG index correlates strongly with HOMA-IR and has demonstrated superior discriminative ability for predicting MetS [12,13]. In recent years, composite indices combining the TyG index with obesity measures such as the Waist-to-Height Ratio (WHtR), including triglyceride glucose-waist-to-height ratio (TyG-WHtR), have been developed. These indices simultaneously reflect glucolipid metabolic burden and body fat distribution, showing better predictive performance for type 2 diabetes, cardiovascular and cerebrovascular diseases, and MetS compared to traditional single indicators [14-16]. Although HGI and TyG-WHtR have each demonstrated predictive value in their respective contexts, studies exploring their combined use for predicting MetS are still limited. HGI reflects chronic glycemic exposure and individual glycation susceptibility, whereas TyG-WHtR reflects insulin resistance and central fat accumulation, suggesting they represent complementary pathways in metabolism. Furthermore, both indices are derived from routine fasting blood tests and simple anthropometric measurements, offering advantages such as low cost, operational simplicity, and good reproducibility, making them suitable for community screening and primary care chronic disease management. This study aims to investigate the predictive efficacy of a combined HGI and TyG-WHtR model for MetS in a middle-aged and elderly population, to provide an evidence base for the development of early screening tools.

MATERIALS AND METHODS

Study subjects and data source

This study consecutively enrolled middle-aged and elderly individuals from the Health Examination Center and the Endocrinology and Metabolism outpatient department of The People's Hospital of Longhua, Shenzhen between February 2024 and February 2025. The inclusion criteria were: 1) patients aged ≥ 45 years; 2) patients who completed the questionnaire, physical measurements, and fasting blood draw during the same visit. The exclusion criteria were: 1) patients with acute inflammation or infection; 2) patients with active malignant tumors; 3) pregnant patients; 4) patients with severe hepatic or renal dysfunction; 5) patients with significant thyroid dysfunction; 6) patients with miss-ing data for key variables (including FPG, HbA1c, tri-glycerides (TG), high-density lipoprotein cholesterol (HDL-C), blood pressure, waist circumference, or height). All eligible participants were included after providing written informed consent. The study protocol was approved by Ethics Committee of The People's Hospital of Longhua, Shenzhen.

Laboratory measurements and index calculations

Blood collection was performed after an overnight fast (≥ 8 - 10 hours). Peripheral venipuncture or indwelling venous catheters were used according to the hospital's standard operating procedures, with all samples managed using a barcode system. A 2 mL sample of dipotassium EDTA (K_2EDTA) anticoagulated whole blood was collected for HbA1c measurement. Tubes were gently inverted for mixing after collection. HbA1c was measured using a Beckman Coulter platform following the manufacturer's instructions, using a method standardized by the National Glycohemoglobin Standardization Program (NGSP) and aligned with the Diabetes Control and Complications Trial (DCCT) reference. For routine biochemical tests - including FPG, TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and uric acid (UA) - blood was collected in a 3 - 5 mL serum separation tube (SST). After complete clotting, SST samples were centrifuged at 1,500 - 2,000 x g for 10 minutes at room temperature to separate serum. All analyses were completed within 2 hours of collection using a Beckman Coulter fully automated biochemistry/immunoassay platform, with internal quality control and external national quality assessment performed according to established protocols. Trained personnel conducted physical measurements, including height, weight, waist circumference, and seated blood

pressure (with the average of at least two readings recorded). Body mass index (BMI) was calculated as weight (kg)/height (m)², and the WHtR was calculated as waist circumference divided by height.

Insulin resistance-related indices were calculated using standard formulas: TyG index = ln [TG (mg/dL) x FPG (mg/dL)]/2 (unit conversion: TG [mmol/L] x 88.57, FPG [mmol/L] x 18.02). TyG-WHtR was subsequently calculated as TyG index x WHtR. The HGI was determined using the within-sample regression residual method: a linear regression of HbA1c on FPG was fitted to obtain individualized predicted HbA1c values, and HGI was calculated as measured HbA1c - predicted HbA1c. Smoking and alcohol consumption history were obtained from patient interviews and electronic medical records.

Definition of MetS

MetS was defined according to the Adult Treatment Panel III (ATP III) criteria. Diagnosis was established when at least three of the following five components were present: 1) Waist circumference: ≥ 90 cm for men or ≥ 80 cm for women; 2) TG ≥ 1.70 mmol/L; 3) HDL-C: < 1.04 mmol/L for men or < 1.29 mmol/L for women; 4) Blood pressure: systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg, or current use of antihypertensive medication; 5) FPG ≥ 5.6 mmol/L, or current use of glucose-lowering medication [17].

Statistical analysis

All data processing and analysis were performed using R (version 4.4.3). Descriptive statistics were calculated for the overall cohort and stratified by the presence or absence of MetS. Continuous variables with an approximately normal distribution were presented as mean ± standard deviation and were compared using the independent samples *t*-test; variables with a non-normal distribution were presented as median (interquartile range) and were compared using the Wilcoxon rank-sum test. Categorical variables were presented as number (percentage) and were compared using the chi-squared test or Fisher's exact test, as appropriate. For regression modeling, the individual defining components of MetS and the raw measurements used to calculate key indices were not included in the same model to avoid data leakage and mitigate multicollinearity. Other candidate variables were first screened using univariable logistic regression (two-sided test, $p < 0.05$ for entry). Variables were subsequently incorporated into the multivariable logistic regression model based on a combination of statistical significance and clinical plausibility. Multicollinearity was assessed using the variance inflation factor (VIF), with a VIF < 5 considered acceptable. Discriminatory ability was evaluated using receiver operating characteristic (ROC) curve analysis, reporting the area under the curve (AUC) with its 95% confidence interval (CI). Pairwise comparisons of AUCs were performed using the DeLong test. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test with 10 groups and by plotting calibration curves based on 1,000 bootstrap samples. The calibration-in-the-large (intercept), calibration slope, Brier score, and scaled Brier score were also reported. Clinical utility was evaluated using decision curve analysis (DCA) across a threshold probability range of 0.05 to 0.95, with the net benefit of the model compared against the "Treat-all" and "Treat-none" strategies. All tests were two-sided, and a p-value < 0.05 was considered statistically significant. No artificial intelligence-assisted technologies were used in the manuscript.

RESULTS

Baseline characteristics and intergroup comparisons

A total of 560 middle-aged and elderly participants were included in this study, including 257 (45.9%) females. MetS was identified in 218 participants (38.9%) (Table 1). The overall mean age was 59.46 ± 9.01 years. Compared with the non-MetS group, the MetS group exhibited significantly higher values for obesity-related indices and blood pressure, including BMI (23.57 ± 3.62 vs. 22.85 ± 3.44), waist circumference (84.44 ± 7.85 vs. 80.41 ± 7.68 cm), WHtR (0.53 ± 0.05 vs. 0.50 ± 0.05), SBP, and DBP (all $p < 0.001$). Regarding glucose metabolism, the MetS group demonstrated higher FPG and HbA1c levels (FPG: 6.02 ± 1.65 vs. 5.12 ± 1.83 mmol/L; HbA1c: 5.81 ± 0.75 vs. 5.13 ± 0.79%). In the overall sample, HbA1c showed a significant linear correlation with FPG, described by the regression equation: HbA1c = 3.25 + 0.392 x FPG ($R^2 = 0.717$, $p < 0.001$). This equation was used to obtain the individualized predicted HbA1c, and the HGI was calculated as measured HbA1c - predicted HbA1c. HGI was also significantly elevated in the MetS group (0.47 [0.18, 0.78] vs. 0.13 [-0.15, 0.40], $p < 0.001$). In the lipid profile, the MetS group had higher TG, LDL-C, and TC levels, but lower HDL-C levels (all $p \leq 0.006$). UA levels were also higher in the MetS group ($p = 0.004$). Markers of insulin resistance burden, namely the TyG index and TyG-WHtR, were significantly elevated in the MetS group (both $p < 0.001$). The distribution of sex, smoking status, and alcohol consumption did not differ significantly between the two groups ($p > 0.05$). Overall, the MetS group presented a composite phenotype characterized by central obesity, elevated blood pressure, and dysregulation of glucose and lipid metabolism.

Univariable and multivariable logistic regression

Prior to modeling, the defining components of MetS (waist circumference, TG, HDL-C, blood pressure, FPG) and the raw measurements used to calculate key indices (e.g., TG, FPG, HbA1c, WHtR) were excluded. Remaining variables were screened using univariable analysis (two-sided $p < 0.05$ for entry into the model). Univariable analysis indicated that both HGI (odds ratio [OR] = 2.47, 95% CI: 2.01 - 3.07, $p < 0.001$) and TyG-

Table 1. Baseline characteristics of middle-aged and older adults overall and stratified by MetS.

Variable	Total (n = 560)	With MetS (n = 218)	Without MetS (n = 342)	p-value
Gender (female)	257 (45.9%)	113 (51.8%)	144 (42.1%)	0.030
Age (years)	59.46 ± 9.01	59.70 ± 8.63	59.31 ± 9.26	0.613
BMI (kg/m^2)	23.13 ± 3.53	23.57 ± 3.62	22.85 ± 3.44	0.020
Waist (cm)	81.98 ± 7.98	84.44 ± 7.85	80.41 ± 7.68	< 0.001
WHtR	0.51 ± 0.06	0.53 ± 0.05	0.50 ± 0.05	< 0.001
SBP (mmHg)	127.85 ± 14.19	132.12 ± 14.48	125.13 ± 13.32	< 0.001
DBP (mmHg)	80.06 ± 9.12	82.75 ± 9.46	78.35 ± 8.48	< 0.001
FPG (mmol/L)	5.47 ± 1.82	6.02 ± 1.65	5.12 ± 1.83	< 0.001
HbA1c (%)	5.39 ± 0.84	5.81 ± 0.75	5.13 ± 0.79	< 0.001
HGI	0.25 (-0.03, 0.56)	0.47 (0.18, 0.78)	0.13 (-0.15, 0.40)	< 0.001
TG (mmol/L)	1.42 (0.95, 2.07)	1.93 (1.26, 2.37)	1.26 (0.81, 1.65)	< 0.001
HDL-C (mmol/L)	1.25 ± 0.29	1.12 ± 0.28	1.33 ± 0.27	< 0.001
LDL-C (mmol/L)	2.91 ± 0.85	3.04 ± 0.89	2.84 ± 0.81	0.006
TC (mmol/L)	4.97 ± 0.98	5.14 ± 0.92	4.87 ± 1.00	0.001
Uric acid (μmol/L)	329.66 ± 95.62	344.43 ± 99.11	320.25 ± 92.25	0.004
Current smoking	203 (36.3%)	71 (32.6%)	132 (38.6%)	0.175
Current drinking	149 (26.6%)	53 (24.3%)	96 (28.1%)	0.377
TyG index	8.66 (8.11, 9.15)	9.07 (8.56, 9.41)	8.46 (7.92, 8.83)	< 0.001
TyG-WHtR	4.35 ± 0.62	4.69 ± 0.58	4.13 ± 0.55	< 0.001

Approximately normally distributed continuous variables are presented as mean ± SD; skewed variables as median (IQR); categorical variables as n (%). p-values were derived from independent-samples *t*-test (normal data), Wilcoxon rank-sum test (skewed data), and χ^2 test or Fisher's exact test for categorical data, as appropriate. Statistical significance set at $p < 0.05$.
BMI: body mass index, WHtR: waist-to-height ratio, SBP/DBP: systolic/diastolic blood pressure, FPG: fasting plasma glucose, TG: triglycerides, HDL-C/LDL-C: high-/low-density lipoprotein cholesterol, TC: total cholesterol, UA: uric acid, TyG: triglyceride-glucose index, TyG-WHtR: TyG multiplied by WHtR, HGI: hemoglobin glycation index, calculated as HGI = observed HbA1c - predicted HbA1c, where the predicted HbA1c is obtained from a sample-level linear regression of HbA1c on FPG.

Table 2. Univariable and multivariable logistic regression analyses for metabolic syndrome (MetS).

Variable	Univariate analysis			Multivariate analysis		
	Unit	OR (95% CI)	p	Unit	OR (95% CI)	p
HGI	per 1 SD	2.47 (2.01 - 3.07)	< 0.001	per 1 SD	10.20 (6.45 - 16.74)	< 0.001
TyG-WHtR	per 1 SD	3.00 (2.41 - 3.80)	< 0.001	per 1 SD	3.49 (2.68 - 4.65)	< 0.001
Age (years)	per 1 SD	1.04 (0.88 - 1.24)	0.618			
Sex	female vs. male	1.48 (1.05 - 2.08)	0.026	female vs. male	1.35 (0.86 - 2.15)	0.196
BMI (kg/m^2)	per 1 SD	1.23 (1.04 - 1.46)	0.019	per 1 SD	0.97 (0.77 - 1.21)	0.759
LDL-C (mmol/L)	per 1 SD	1.28 (1.08 - 1.52)	0.006	per 1 SD	0.51 (0.38 - 0.66)	< 0.001
TC (mmol/L)	per 1 SD	1.33 (1.12 - 1.59)	0.001	per 1 SD	1.40 (1.11 - 1.76)	0.004
Uric acid (μmol/L)	per 1 SD	1.29 (1.09 - 1.54)	0.004	per 1 SD	0.29 (0.19 - 0.41)	< 0.001
Current smoking	yes vs. no	0.77 (0.54 - 1.10)	0.148			
Current drinking	yes vs. no	0.82 (0.56 - 1.21)	0.327			

Outcome was MetS (yes = 1/no = 0). Odds ratios (ORs) for continuous variables are expressed per 1 standard deviation increase; categorical variables are shown as "Yes vs. No" or "Female vs. Male". The multivariable model included variables with univariable $p < 0.05$ with HGI and TyG-WHtR forced in. Statistical significance set at $p < 0.05$.
HGI: hemoglobin glycation index, TyG-WHtR: TyG multiplied by waist-to-height ratio, OR: odds ratio, CI: confidence interval, VIF: variance inflation factor.

Table 3. Diagnostic performance at the Youden-optimal threshold for metabolic syndrome (MetS): HGI, TyG-WHtR, and the combined model (HGI + TyG-WHtR).

Model	AUC	Cutoff	Sensitivity	Specificity	Accuracy	PPV	NPV	Youden	p-value
HGI	0.718	0.485	0.495	0.825	0.696	0.643	0.719	0.320	< 0.001
TyG-WHtR	0.758	4.437	0.697	0.725	0.714	0.618	0.790	0.422	< 0.001
HGI + TyG-WHtR	0.826	0.437	0.702	0.787	0.754	0.677	0.805	0.488	-

Cutoffs correspond to the Youden-optimal threshold (for the combined model, the cutoff is the predicted probability). AUCs are reported with DeLong pairwise comparisons of the combined model versus HGI and versus TyG-WHtR. Statistical significance set at p < 0.05.

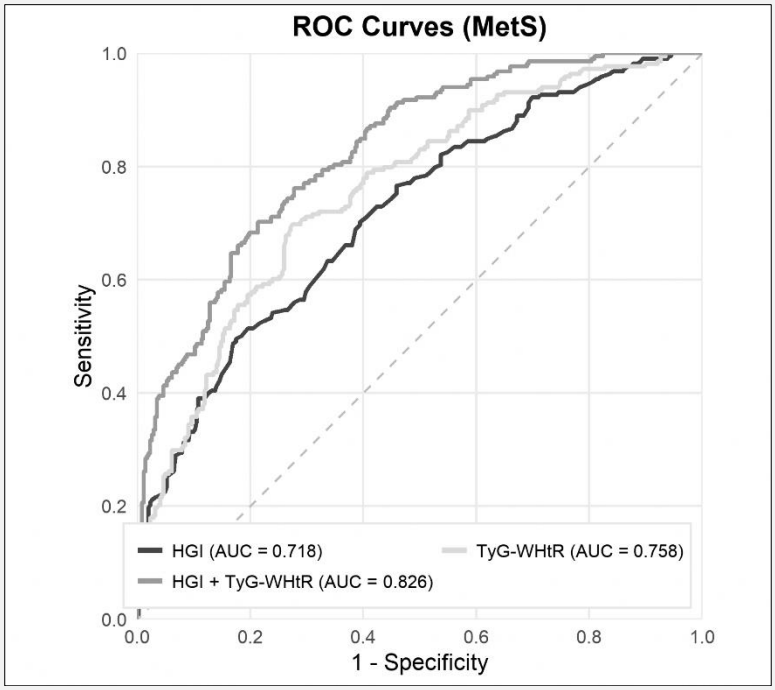


Figure 1. ROC curves for predicting MetS in middle-aged and older adults: HGI, TyG-WHtR, and the combined model.

AUCs with 95% CIs are shown. The combined curve uses the predicted probability from logistic regression including HGI and TyG-WHtR. DeLong tests compare the combined model versus each single index.

WHtR (OR = 3.00, 95% CI: 2.41 - 3.80, p < 0.001) were significantly associated with MetS. BMI, LDL-C, TC, and UA were also significantly associated, whereas age, smoking, and alcohol consumption were not. In the multivariable model, both HGI (OR = 10.20, 95% CI: 6.45 - 16.74, p < 0.001) and TyG-WHtR (OR = 3.49, 95% CI: 2.68 - 4.65, p < 0.001) retained significant independent associations with MetS. LDL-C (OR = 0.51, 95% CI: 0.38 - 0.66, p < 0.001) and UA (OR = 0.29, 95% CI: 0.19 - 0.41, p < 0.001) showed negative associations, while TC showed a positive association (OR = 1.40, 95% CI: 1.11 - 1.76, p = 0.004). Sex and BMI were not significant (Table 2). No multicollinearity was detected, with all VIF values < 5 (HGI 3.41, UA 2.66, LDL-C 1.46, TyG-WHtR 1.13, sex 1.08, TC 1.04, BMI 1.04). These results indicate that HGI and TyG-WHtR are independent factors associated with MetS.

ROC analysis and discriminatory performance

In the discrimination analysis for MetS, HGI, TyG-WHtR, and the combined logistic regression model (using the predicted probability from HGI + TyG-WHtR as

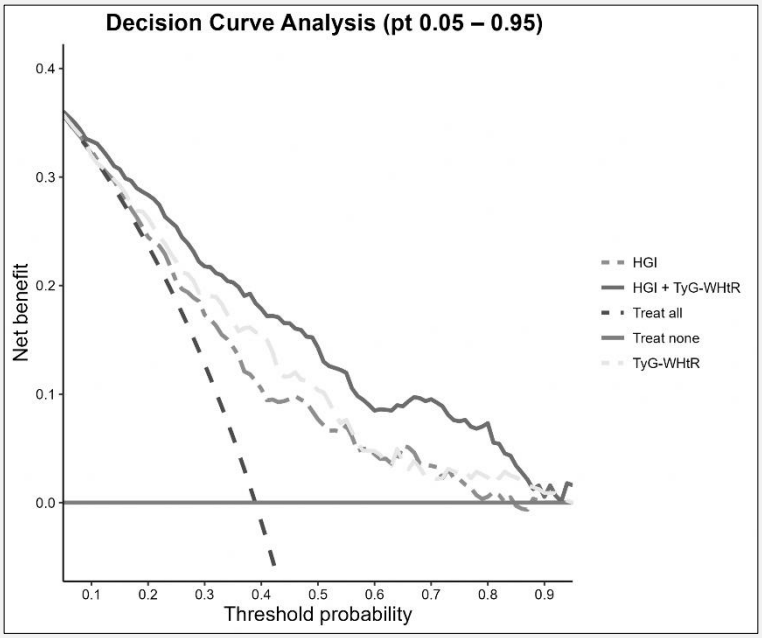


Figure 2. DCA for MetS in middle-aged and older adults (threshold 0.05 - 0.95).

Net benefit for HGI, TyG-WHtR, and their combined logistic model is compared with "treat all/none".

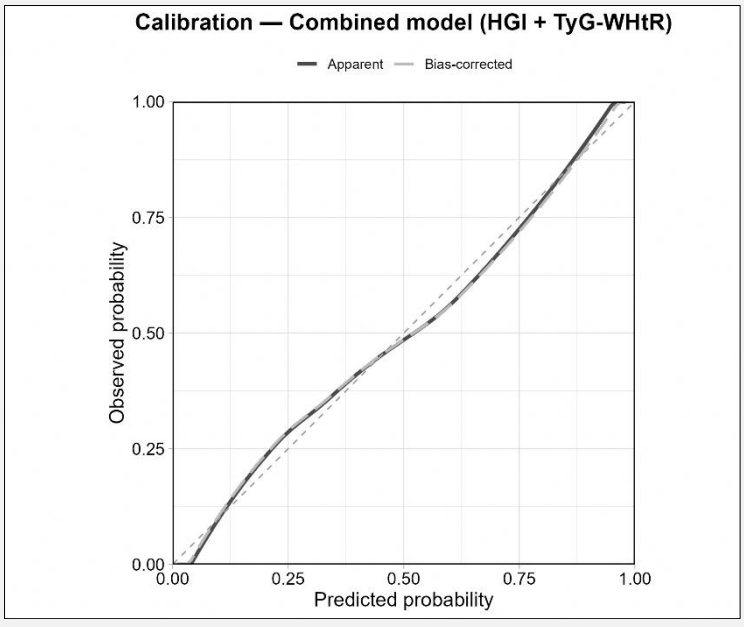


Figure 3. Calibration of the combined model (HGI + TyG-WHtR) for MetS in middle-aged and older adults.

Apparent and bias-corrected (bootstrap, B = 1,000) curves are plotted against the ideal line. Hosmer-Lemeshow g = 10: χ^2 = 7.99, p = 0.434. Calibration intercept ≈ 0, slope ≈ 1. Brier = 0.165; scaled Brier = 0.307.

the discriminant score) all demonstrated good discriminatory ability. The respective areas under the curve (AUCs) were 0.718 for HGI, 0.758 for TyG-WHtR, and 0.826 for the combined model. At the optimal Youden index threshold, the sensitivity and specificity were 0.495 and 0.825 for HGI (cutoff = 0.485), 0.697 and 0.725 for TyG-WHtR (cutoff = 4.437), and 0.702 and 0.787 for the combined model (probability cutoff = 0.437). The corresponding overall accuracy values were 0.696, 0.714, and 0.754, respectively. Pairwise comparisons using the DeLong test revealed that the AUC of the combined model was significantly higher than that of either single indicator (both $p < 0.05$). The two individual indicators demonstrated comparable and complementary performance, suggesting that information on glycation deviation and insulin resistance/body fat distribution provides additive value for MetS identification (Figure 1, Table 3).

Model calibration and clinical net benefit

In the DCA, all three model curves (HGI, TyG-WHtR, and the combined model) remained above the "treat-none" line. Across a wide range of clinically relevant threshold probabilities (approximately $p_t = 0.10 - 0.60$), the combined model demonstrated a higher net benefit. The two single indicators showed similar net benefit to each other and were superior to the "treat-all" strategy at low to intermediate thresholds (Figure 2). Regarding calibration, the combined model (using the predicted probability from the logistic regression of HGI + TyG-WHtR) performed well. The Hosmer-Lemeshow test (with 10 groups) yielded a χ^2 value of 7.99 ($p = 0.434$). The calibration intercept was close to 0 (95% CI: -0.206 - 0.206), and the calibration slope was close to 1 (95% CI: 0.823 - 1.177). The Brier score was 0.165, and the Scaled Brier score was 0.307. The bias-corrected calibration curve based on bootstrap resampling closely aligned with the apparent calibration curve. Bootstrap confidence intervals further confirmed stable estimates for the intercept (approximately 0) and slope (approximately 1), with a Brier score of 0.164 (95% CI: 0.152 - 0.176) and a Scaled Brier score of 0.309 (95% CI: 0.260 - 0.358) (Figure 3). Overall, the combined model achieved the required standard for application in terms of both net benefit and calibration.

DISCUSSION

Characteristics of MetS in the study population

This study included 560 middle-aged and elderly participants, with a MetS prevalence of 38.9%. Individuals with MetS exhibited a clustering of cardiometabolic risk factors, including central obesity, elevated blood pressure, and abnormal glucose and lipid metabolism, consistent with domestic epidemiological data [18,19]. The MetS group demonstrated significantly higher values for BMI, waist circumference, WHtR, SBP, DBP, FPG, HbA1c, and lipid profile parameters compared to the non-MetS group. This pattern aligns with the typical profile observed in the Chinese population, characterized by the co-occurrence of hypertension, high waist circumference, and low HDL-C [18].

Beyond conventional diagnostic indicators, both TyG-WHtR and HGI were significantly elevated in the MetS group. The combined model of these two indices achieved an AUC of 0.826 in ROC analysis, suggesting their potential value as predictive tools for metabolic risk. The diagnostic criteria, sample composition, and analytical methods employed in this study are consistent with those used in major national cohort studies, ensuring the comparability and regional representativeness of the findings [19,20].

Biological significance and metabolic associations of HGI

The HGI reflects interindividual differences in HbA1c levels under similar blood glucose concentrations, primarily influenced by non-glycemic factors such as erythrocyte lifespan, glycation susceptibility, and hemoglobin variants [21]. Joung et al. verified the consistency and measurement stability between HGI and the glycation gap using continuous glucose monitoring, supporting its reliability as an indicator of individual deviation in HbA1c.

Previous studies have shown that a high HGI is associated with insulin resistance, abdominal obesity, dyslipidemia, chronic inflammation, and carotid intima-media thickening [21,22]. Marini et al. identified an independent association between HGI and increased carotid intima-media thickness (IMT) in a non-diabetic population [23]. Consistently, Xie et al. observed an independent relationship between HGI and MetS in a middle-aged and elderly Chinese cohort [22]. The present findings align with these reports: HGI was significantly elevated in the MetS group and remained an independent factor associated with MetS after adjusting for confounders such as BMI and blood lipids.

Mechanistically, a high HGI may represent an increased non-enzymatic glycation burden, promoting the clustering of metabolic abnormalities through pathways involving oxidative stress and chronic inflammation, ultimately leading to vascular endothelial damage [24,25]. Further supporting its potential as an early risk marker, Wang et al., utilizing NHANES data, reported a U-shaped relationship between HGI and cardiovascular disease, with individuals in the high HGI category exhibiting an increased risk of myocardial infarction and heart failure [25].

Predictive value of TyG-WHtR

TyG-WHtR integrates information on glucose-triglyceride metabolic load and abdominal obesity, demonstrating superior performance over single obesity indicators in multiple studies. Analysis of NHANES data by Glasgow et al. showed that TyG-WHtR achieved a significantly higher AUC (0.875) for predicting MetS compared to the TyG index, HOMA-IR, and other com-

monly used indicators [26].
In Chinese populations, Gui et al. found that TyG-WHtR, TyG-BMI, and TyG-WC outperformed traditional obesity measures in middle-aged and elderly adults [27]. Chen et al. confirmed that TyG-WHtR had better predictive efficacy than WHtR and BMI in a high-risk elderly population [28]. Similarly, Li et al., after systematically comparing 13 adiposity/metabolic indices in the CHARLS dataset, concluded that TyG-WHtR demonstrated superior discriminative ability across sex groups.

Predictive performance of the combined indicator
HGI and TyG-WHtR exhibit mechanistic complementarity: HGI reflects processes related to protein glycation and oxidative stress, whereas TyG-WHtR captures information on insulin resistance and central obesity, representing distinct pathological pathways in MetS. The integration of both indices enhanced the model's discriminatory ability, increased net benefit across common risk thresholds, and demonstrated good calibration. This finding is consistent with previous reports on modeling combined variables from different pathways. Li et al., using CHARLS data, found that combined indices achieved higher AUCs than traditional measures with stable performance across sex strata [29]. Wei et al., in an NHANES cohort, confirmed that TyG-WHtR predicts both MetS and future cardiovascular and all-cause mortality risk [30]. Shin et al. demonstrated that integrating genetic, dietary, and clinical features significantly improves MetS identification [31]. The combined strategy in this study exhibits similar advantages, providing empirical support for the refined identification of metabolic risk.

Clinical application prospects and significance
The combination of HGI and TyG-WHtR, derived from routine laboratory tests and simple anthropometric measurements, demonstrates good operability and cost-effectiveness. However, the potential site-specific variability of HGI requires equation recalibration (adjusting the intercept and slope) to maintain longitudinal comparability. Future work should involve multi-center external validation to assess the generalizability and robustness of this combined framework. The optimal decision threshold should also be re-evaluated based on the outcome distribution of the local population. Overall, the HGI and TyG-WHtR combination provides a simple, economical, and widely applicable tool for the early identification and refined management of MetS in middle-aged and elderly populations.

CONCLUSION

In the middle-aged and elderly study population, both HGI and TyG-WHtR exhibited significant associations with MetS and maintained independent effects in the multivariable model, demonstrating complementary information. The combined model based on HGI and TyG-WHtR demonstrated superior discriminatory ability (AUC ≈ 0.826), good calibration (intercept ≈ 0, slope ≈ 1, Brier score ≈ 0.165), and provided higher net benefit across a wide range of threshold probabilities compared to either single indicator. As both indices can be calculated directly from routine health check-up items, the combined model holds promise as a convenient screening and risk stratification tool for MetS in middle-aged and elderly populations, to support early identification and management decisions in outpatient and health check-up settings.

Data Available:
Data is available from the corresponding author on request.

Ethics Statement:
All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All subjects were approved by The People's Hospital of Longhua.

Declaration of Generative AI in Scientific Writing:
No artificial intelligence-assisted technologies were used in the manuscript.

Declaration of Interest:
The authors have no conflicts of interest to declare.

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