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Cut-off Values and Clinical Utility of Surrogate Markers for Insulin Resistance and Beta-Cell Function to Identify Metabolic Syndrome and Its Components among Southern Indian Adults

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Background: Insulin resistance (IR) is a collective clinical entity that exacerbates metabolic syndrome (MetS). As the gold-standard test to quantify IR involves intravenous insulin loading and repeated blood glucose monitoring, many indices have been developed for IR assessment for convenience. This study tested the ideal cut-off values and clinical utility of IR indices in identifying MetS.

Methods: We recruited 150 subjects, 75 MetS patients and 75 healthy controls, then obtained written informed consent to participate in this study. We collected fasting blood samples for glucose and lipid profiles and calculated nineteen indices of IR and insulin secretion using validated formulae. We determined the precision of these IR indices using the area under the curve (AUC) in a receiver operating characteristic analysis.

Results: Subjects with MetS have significantly higher IR coupled with lower insulin sensitivity and beta-cell function than controls. Among the surrogate markers of IR tested, the homeostatic model assessment of insulin resistance (HOMA-IR), HOMA-adiponectin (HOMA-AD), triglyceride-glucose (TyG) index, HOMA-1%S (insulin sensitivity), quantitative insulin sensitivity check index (QUICKI), McAuley index, single-point insulin sensitivity estimator (SPISE), and HOMA-2%B (beta-cell function) showed the highest AUC values for detecting MetS.

Conclusion: Our study results suggest that the ideal cut-off and AUC values identified for HOMA-IR, HOMA-AD, the TyG index, HOMA-1%S, QUICKI, the McAuley index, SPISE, and HOMA-2%B offer a clinical approach to the early detection and risk stratification for MetS among people in southern India.

Key words: Beta-cell function, Homeostatic model assessment of insulin resistance, Insulin sensitivity, Homeostatic model assessment-adiponectin, McAuley index, Single-point insulin sensitivity estimator

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INTRODUCTION

During the past decade, technological breakthroughs in health-care and medical technologies have substantially improved the diagnostic approaches to and treatment options for cardiovascular disease (CVD). Nonetheless, CVD is the primary cause of morbidity and mortality globally.¹ Impaired glucose tolerance, atherogenic

dyslipidemia, hypertension (HTN), and central or abdominal obesity are well-known CVD risk factors. Metabolic syndrome (MetS) is the collection of all the CVD risk factors related to vascular and metabolic dysfunctions that precede overt CVD and type 2 diabetes mellitus (T2DM).² The association of MetS and its components with CVD risk is complicated and multifactorial. It ranges from developing resistance to insulin, aggravated glycemic and lipid

profiles, and oxidative stress to low-grade inflammation, and all the factors are interconnected and share underlying mechanisms and pathways.³ In addition to those risk factors, the etiology of MetS can also include smoking and drinking habits, a fatty diet, physical inactivity, and heavy work stress. It is essential to improve our knowledge about the onset and pathogenesis of MetS to facilitate practical therapeutic strategies.⁴ The prevalence of MetS is rising rapidly, which affects public health. According to the evidence, approximately one-fourth of the world's population can be classified as having MetS.⁵ In India, a community-based cross-sectional study in 2017 showed that the prevalence of MetS had increased from 24% to 33%.⁶ Thus, studies on MetS and ways to reduce CVD risk are intended to build better prevention strategies.

Insulin resistance (IR) is a noteworthy risk factor for CVD and T2DM. It appears to be the most predominant of the five clinical risk factors used to diagnose MetS.⁷ IR is a state in which the insulin hormone no longer has sufficient capability to bind to its receptors and signal anticipated functions, which leads the liver, skeletal muscle, and adipose tissue to have reduced sensitivity to the metabolic effects of insulin. In other words, a known dosage of insulin does not increase the glucose disposal of a person with IR as much as it does in a healthy person, and that can contribute to beta-cell dysfunction.⁸ Genetic abnormalities in proteins involved in the insulin pathway and increased visceral fat have been proposed as significant contributors to IR.⁹ In this study, we focus on IR to enhance our understanding of MetS and find diagnostic markers to identify MetS. Among the various methods available for the estimation of IR, the gold standard and validated technique is the hyperinsulinemic-euglycemic clamp test, which directly measures the insulin-mediated glucose disposal rate *in vivo* in a steady-state.¹⁰ It involves continuously loading and adjusting insulin and glucose intravenously and testing blood glucose at regular intervals over a 2-hour period.¹¹ Its application to quantify IR in clinical practice is limited by its dosage, invasiveness, complexity, time-consumption, and expense. Obviously, surrogate IR markers are needed. In recent years, many studies have focused on finding simpler, non-invasive surrogate IR indices that use equations and software to enable the early diagnosis and risk stratification of MetS.

Currently, three categories of surrogate IR markers are available. The first category involves glucose loading, insulin loading, com-

bined glucose and insulin loading, and measuring glucose and insulin at hourly intervals. The second category comprises markers that address IR in a steady state without a glucose or insulin intervention.¹² The third category contains indirect markers that correlate with IR, such as ferritin, insulin-like growth factor binding protein-1, adiponectin, or resistin.¹³ To preserve simplicity and enhance clinical utility, we designed this study to investigate the ideal cut-off values for IR markers in the second category and compare their detectable accuracy in identifying MetS among the people in southern India.

METHODS

Study participants

Our subjects, aged 18 to 65 years, participated in this cross-sectional study from November 2018 to February 2020. This study has ethical clearance from the Institutional Ethics Committee (Human research), Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India (JIP/IEC/2018/0301). All participants provided signed and dated written informed consent before their enrollment. Seventy-five adults diagnosed with MetS were recruited from the Endocrine outpatient department (Fig. 1). Based on the National Cholesterol Education Program Adult Treatment Panel III guidelines, MetS was defined as having any three of the following five conditions^{3,4}: waist circumference (WC) ≥ 90 cm in Asian males, ≥ 80 cm in Asian females; fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L) or receiving medication for T2DM; serum triglycerides (TG) ≥ 150 mg/dL (1.7 mmol/L) or receiving specific treatment for dyslipidemia; high-density-lipoprotein cholesterol (HDL-C) ≤ 40 mg/dL (1.03 mmol/L) in males, ≤ 50 mg/dL (1.29 mmol/L) in females or receiving specific treatment for dyslipidemia; systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or receiving antihypertensive medication. Among the 75 subjects in the MetS group, 34 were receiving oral hypoglycemic agents (metformin, daonil), 20 were receiving lipid-lowering agents (atorvastatin), and 15 were taking antihypertensive agents (envas). Seventy-five healthy volunteers who did not have MetS were included in the study as age and sex-matched controls. Potential subjects with a medical history of ischemic heart disease; cancer; thyroid disorders; neurological,

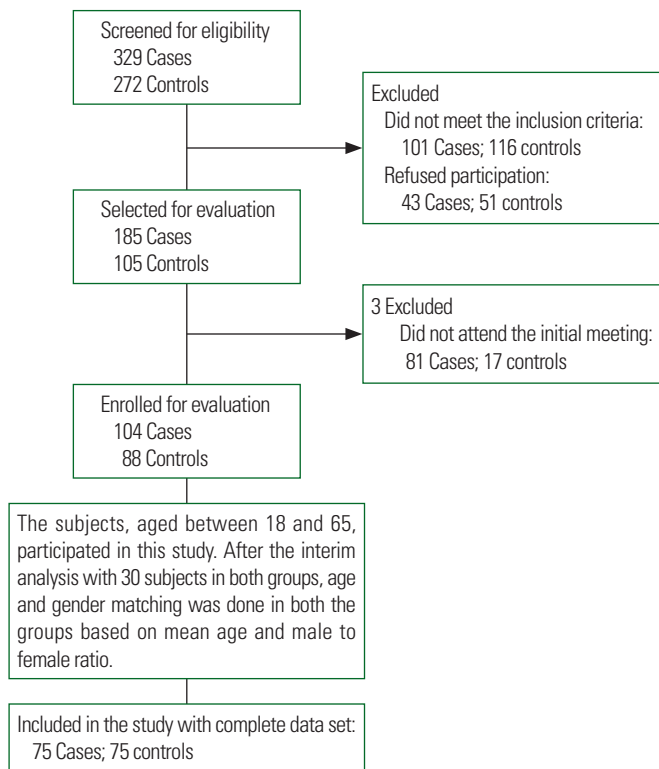


Figure 1. Flow diagram of the selection and continuity of study participants.

psychological, or other endocrinology disorders; or drug intake for any chronic illness were excluded.

Sample size calculation

We used the OpenEpi version 3 (Andrew G. Dean and Kevin M. Sullivan, Atlanta, GA, USA), online calculator to estimate the sample size. Based on a previous report,¹⁴ the recommended sample size was 108, with 54 subjects in each group, to determine differences of 1.7 between two independent medians with an interquartile range of homeostatic model assessment of insulin resistance (HOMA-IR) values (1.6 [1.1–2.4] vs. 3.3 [2.0–4.8]) with a power of 80% and an alpha error of 0.05. We recruited 150 participants, with 75 in each group, to enable broader and wider coverage of the population, provide more information, and reduce uncertainty.

Brief procedures

Assessment of traditional anthropometric measures

We evaluated subject standing height and weight using a wall-mounted stadiometer and digital weight balance while the subjects were wearing light clothing and barefoot. Body mass index (BMI)

was calculated as weight in kg divided by height in m². WC was measured using a stretchable measuring tape at the narrowest point around the abdomen between the inferior border of the last costal rib and the upper portion of the iliac crest. Hip circumference (HC) was taken around the most comprehensive part of the buttocks. The waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) of the subjects were calculated. Brachial artery blood pressure (BP) was measured thrice in the subject's left arm in a sitting position after a rest of five minutes using an Omron (SEM-1; Kyoto, Japan).

Assessment of biochemical profile

We assayed glucose and lipid profiles using an AU680 Analyzer (Beckman Coulter, Atlanta, GA, USA). Serum low-density lipoprotein cholesterol (LDL-C) was calculated based on the Friedewald formula [LDL-C = total cholesterol – (HDL-C + TG/5)]. The Friedewald formula is not valid when the serum TG of an individual is < 400 mg/dL.¹⁵ The atherogenic index of plasma (AIP) was calculated using the formula [AIP = log₁₀(TG/ HDL-C)]. Insulin and adiponectin levels were quantified using a commercially available enzyme-linked immunosorbent assay kit (Calbiotech, El Cajon, CA, USA).

Surrogate markers of IR and insulin secretion

IR indices

We used these indices, calculated as follows: HOMA-IR¹⁶: fasting plasma insulin (μU/mL) × FPG (mmol/L)/22.5; HOMA2-IR¹⁷: the online HOMA Calculator v2.2.2; HOMA-adiponectin (HOMA-AD)¹⁸: fasting plasma insulin (μU/mL) × FPG (mmol/L)/adiponectin (μg/mL); HOMA-triglycerides (HOMA-TG)¹⁹: fasting plasma insulin (μU/mL) × FPG (mmol/L)/TG (mg/dL); triglyceride-glucose (TyG) index²⁰: FPG (mmol/L)/TG (mmol/L); fasting insulin to glucose ratio (FIGR)²¹: fasting plasma insulin (μU/mL)/FPG (mg/dL); fasting insulin resistance index (FIRI)¹⁰: fasting plasma insulin (μU/mL) × FPG (mmol/L)/25.

Insulin sensitivity indices

We used these indices, calculated as follows: HOMA-1%S (insulin sensitivity)¹⁶: 1/HOMA-IR × 100; HOMA-2%S¹⁷: the online HOMA calculator v2.2.2; quantitative insulin sensitivity check index (QUICKI)²²: 1/[log (fasting insulin in μU/mL) + log (FPG in

mg/dL)]; Bennet index²³: $1/[\log(\text{fasting insulin in } \mu\text{U/mL}) \times \log(\text{FPG in mmol/L})]$; McAuley index²⁴: $\exp[2.63 - 0.28 \ln(\text{insulin in } \mu\text{U/L}) - 0.31 \ln(\text{TG in mmol/L})]$; Raynaud index²⁵: $40/\text{fasting insulin } (\mu\text{U/mL})$; Reciprocal insulin²⁶: $1/\text{fasting insulin } (\mu\text{U/mL})$; glucose to insulin (GI) ratio²⁶: $\text{FPG (mg/dL)}/\text{fasting plasma insulin } (\mu\text{U/mL})$; fasting insulin sensitivity index (FISI)²⁷: $10^4/[\text{fasting plasma insulin } (\mu\text{U/mL}) \times \text{FPG (mmol/L)}]$; single-point insulin sensitivity estimator (SPISE)²⁸: $600 \times \text{HDL-C} / 0.185 / (\text{TG} \times 0.2 \times \text{BMI}^{1.338})$.

Beta cell function indices

HOMA-1%B (beta-cell function)¹⁶: $[20 \times \text{fasting insulin } (\mu\text{U/mL})] / [\text{FPG (mmol/L)} - 3.5]$; HOMA-2%B¹⁷: the online HOMA calculator v2.2.2.

Statistical analysis

Statistical analyses were carried out using IBM SPSS ver. 20.00 (IBM Corp., Armonk, NY, USA). We use the mean $\pm$ standard deviation and median with interquartile range to represent continuous variables, depending on the normality of the data, which was tested by the Kolmogorov-Smirnov test. The Student independent t-test (two-tailed) and Mann-Whitney U-test were used to compare the continuous variables. Categorical findings are presented as percentages, and chi-square test was used to detect differences between the groups. By observing the area under the curve (AUC) in a receiver operating characteristic (ROC) analysis, we calculated the detectable accuracy of the IR indices to identify MetS and its components. MedCalc 11.4.2.0 (Ostend, Belgium) was used for the AUC comparisons. A logistic regression analysis was done using MedCalc software to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) that surrogate IR markers have for MetS and its components. A *P*-value was considered statistically significant at less than 0.05.

RESULTS

Table 1 depicts the demographic and anthropometric data for the healthy control subjects and MetS subjects. We observed no significant differences in age, sex, smoking, family history of HTN, T2DM, and CVD between the control and MetS group subjects

Table 1. Comparison of demographic and anthropometric data between healthy control subjects and patients with MetS

Variable	Control group (n=75)	MetS group (n=75)	<i>P</i>
Age (yr)	44.18 $\pm$ 8.32	46.13 $\pm$ 6.12	0.105
Sex (male:female)	37:38	43:32	0.326
Smoking	11 (14.7)	15 (20)	0.388
Alcohol intake	21 (28)	33 (44)	0.041
Family H/O HTN	27 (36)	36 (48)	0.317
Family H/O T2DM	38 (50.7)	40 (53.3)	0.744
Family H/O CVD	8 (10.7)	12 (16)	0.337
High WC	9 (12)	34 (45.3)	0.001
Hyperglycemia	18 (24)	69 (92)	0.001
High TG	14 (18.7)	40 (53.3)	0.001
Low HDL-C	7 (9)	51 (68)	0.001
High BP	15 (20)	32 (42.7)	0.003
Height (cm)	164.04 $\pm$ 8.05	160.73 $\pm$ 9.48	0.022
Weight (kg)	69.17 $\pm$ 10.73	73.60 $\pm$ 7.28	0.004
BMI (kg/m ²)	26.25 $\pm$ 3.23	27.50 $\pm$ 3.61	0.027
WC (cm)	90.94 $\pm$ 8.9	98.63 $\pm$ 9.68	0.001
HC (cm)	100.05 $\pm$ 9.44	102.20 $\pm$ 9.36	0.164
WHR	0.90 $\pm$ 0.04	0.96 $\pm$ 0.05	0.001
WHtR	0.55 $\pm$ 0.05	0.62 $\pm$ 0.07	0.001

Values are presented as mean $\pm$ standard deviation or number (%). BMI, WHR, and WHtR should be lower to be healthy.

MetS, metabolic syndrome; H/O, history of; HTN, hypertension; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; WC, waist circumference; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; BMI, body mass index; HC, hip circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

(Table 1). Anthropometric measurements (weight, BMI, WC, WHR, and WHtR) were significantly higher in the MetS group than in the control group (*P* < 0.001).

The impaired glycemic state in the MetS group was observed as significantly increased FPG and insulin levels (Table 2). In contrast, adiponectin levels in the MetS group were significantly decreased. Atherogenic dyslipidemia in the MetS group was evident as significantly increased lipid parameters (TC, TG) and lipid ratios (LDL/HDL-C, TG/HDL-C, TC/HDL-C, non-HDL/HDL-C, AIP), except for HDL-C (*P* < 0.001), which was significantly decreased (Table 2). MetS subjects had higher LDL-C levels than controls, but that difference was not statistically significant. Based on the estimated cardiovascular parameters, the MetS group exhibited pre-hypertension status, with significantly increased systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) (Table 2).

Among the IR indices, the HOMA-IR, HOMA2-IR, HOMA-AD, HOMA-TG, TyG index, and FIRI values were significantly higher

Table 2. Comparison of biochemical and cardiometabolic parameters between healthy control subjects and patients with MetS

Variable	Control group (n=75)	MetS group (n=75)	P
FPG (mg/dL)	93.00 (86–100)	129 (118–145)	0.001
Insulin (μ U/mL)	11.7 (8.8–14.9)	14.9 (12.9–18.6)	0.001
Adiponectin (μ g/mL)	17.36 (13.26–23.08)	12.1 (9.13–18.23)	0.001
BHR (/min)	72.90 $\pm$ 8.73	76.37 $\pm$ 11.55	0.039
SBP (mmHg)	119.05 $\pm$ 12.59	127.33 $\pm$ 13.79	0.001
DBP (mmHg)	77.29 $\pm$ 11.06	80.93 $\pm$ 7.23	0.018
MAP (mmHg)	91.21 $\pm$ 10.81	96.39 $\pm$ 8.56	0.001
TC (mg/dL)	174.87 $\pm$ 22.53	187.17 $\pm$ 28.89	0.004
TG (mg/dL)	129 (100–147)	154 (116–180)	0.001
HDL-C (mg/dL)	46.05 $\pm$ 4.95	37.73 $\pm$ 6.28	0.001
LDL-C (mg/dL)	105.20 $\pm$ 22.78	109.81 $\pm$ 27.18	0.350
VLDL-C (mg/dL)	24 (16–30)	27 (19–37)	0.050
LDL-C/HDL-C	2.34 $\pm$ 0.60	2.83 $\pm$ 0.91	0.001
TG/HDL	2.78 (2.18–3.17)	4.17 (3.14–5.08)	0.001
TC/HDL	3.82 $\pm$ 0.54	4.99 $\pm$ 1.15	0.001
Non-HDL-C/HDL-C	2.82 $\pm$ 0.54	3.99 $\pm$ 1.15	0.001
AIP	0.431 $\pm$ 0.12	0.602 $\pm$ 0.16	0.001

Values are presented as median (interquartile range) or mean $\pm$ standard deviation. FPG, insulin, BHR, SBP, DBP, MAP, and all the lipid parameters except HDL-C should be lower to be healthy; HDL-C and adiponectin should be higher.

MetS, metabolic syndrome; FPG, fasting plasma glucose; BHR, basal heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; AIP, atherogenic index of plasma.

($P < 0.001$) in the MetS subjects than in the controls (Table 3). In contrast, the values for the insulin-sensitivity indices and beta-cell function indices (HOMA-1%S, HOMA-2%S, QUICKI, Bennet index, McAuley index, Raynaud index, reciprocal insulin, FISI, SPISE, HOMA-1%B, and HOMA-2%B) were significantly lower in the MetS group than the control group.

Table 4 explains the detectable accuracy of all the surrogate markers of IR and insulin secretion in identifying MetS among the south-Indian subjects in our study population. Among the IR and insulin secretion markers, HOMA-IR, HOMA-AD, the TyG index, HOMA-1%S, QUICKI, the McAuley index, SPISE, and HOMA-2%B yielded an AUC above 0.8, showing the best detectable accuracy for the identification of MetS. Most of the other indices tested (HOMA2-IR, HOMA-TG, FIRI, HOMA-2%S, the Bennet index, Raynaud index, reciprocal insulin, FISI, and HOMA-1%B) reported an AUC between 0.6 and 0.8. In our results, FIGR and the GI ratio were the least effective, with the lowest AUC in the ROC analysis.

Table 3. Comparison of surrogate markers of IR and insulin secretion between healthy control subjects and patients with MetS

Variable	Control group (n=75)	MetS group (n=75)	P
HOMA-IR	2.67 (1.98–3.53)	4.63 (3.69–6.82)	0.001
HOMA2-IR	1.51 (1.13–1.96)	2.06 (1.77–2.72)	0.001
HOMA-AD	3.85 (1.82–5.24)	8.11 (5.24–9.86)	0.001
HOMA-TG	0.47 (0.33–0.64)	0.81 (0.53–1.01)	0.001
TyG index	7.55 (5.54–8.92)	12.26 (9.95–14.44)	0.001
FIGR	2.05 (1.89–2.30)	2.31 (1.73–2.64)	0.307
FIRI	2.41 (1.78–3.18)	4.17 (3.33–6.14)	0.001
HOMA-1%S	37.40 (28.30–50.56)	21.58 (14.65–27.06)	0.001
HOMA-2%S	66.10 (51–88.7)	49 (37.4–56.7)	0.001
QUICKI	0.33 (0.31–0.34)	0.30 (0.29–0.31)	0.001
Bennet index	1.32 (1.19–1.52)	1.01 (0.86–1.11)	0.001
McAuley index	7.43 $\pm$ 2.70	6.01 $\pm$ 1.90	0.001
Raynaud index	3.41 (2.68–4.54)	2.68 (2.15–3.10)	0.001
1/Insulin	0.085 (0.067–0.114)	0.066 (0.054–0.078)	0.001
GI ratio	8.76 (7.81–9.53)	7.77 (6.81–10.43)	0.316
FISI	9.23 (6.98–12.48)	5.32 (3.61–6.68)	0.001
SPISE	6.01 (4.65–7.20)	3.53 (2.80–5.11)	0.001
HOMA-1%B	130.82 (108–164.25)	80.57 (65.90–96.01)	0.001
HOMA-2%B	110.20 (97.30–129.10)	73.80 (61.30–87.03)	0.001

Values are presented as median (interquartile range) or mean $\pm$ standard deviation. All the IR indices should be lower to be healthy, and the insulin sensitivity and beta-cell function indices should be higher.

IR, insulin resistance; MetS, metabolic syndrome; HOMA, homeostatic model assessment; AD, adiponectin; TG, triglycerides; TyG, triglyceride-glucose; FIGR, fasting insulin to glucose ratio; FIRI, fasting insulin resistance; %S, insulin sensitivity; QUICKI, quantitative insulin sensitivity check index; 1/Insulin, reciprocal insulin; GI, glucose to insulin; FISI, fasting insulin sensitivity index; SPISE, single-point insulin sensitivity estimator; %B, beta-cell function.

Table 5 provides information about the proportion of subjects with values higher than the cut-off for each index. Compared with the control group, the MetS group had a higher proportion of subjects with higher cut-off values for HOMA-IR and QUICKI (93.3%), indicating increased IR and decreased insulin sensitivity, respectively.

The AUC values for HOMA-IR, HOMA-AD, the TyG index, HOMA-1%S, QUICKI, the McAuley index, SPISE, and HOMA-2%B in identifying MetS and its components are shown in Supplementary Table 1. Among those markers of IR and insulin secretion, HOMA-IR has the largest AUC for identifying MetS (AUC, 0.851; 95% CI, 0.784–0.904). SPISE has the highest AUC for predicting central obesity, and HOMA-IR, HOMA-AD, the TyG index, HOMA-1%S, QUICKI, and the McAuley index showed similar AUCs for predicting central obesity. An elevated FPG was best predicted by HOMA-IR, HOMA-AD, the TyG index, HOMA-1%S, QUICKI,

Table 4. AUCs, ideal cut-offs, sensitivity, and specificity of surrogate markers for IR and insulin secretion for identifying MetS in the ROC analysis

Variable	AUC (95% CI)	P	Cut-off value	Sensitivity	Specificity	Youden index
HOMA-IR	0.851 (0.784–0.904)	0.001	≥ 2.86	86.67	70.67	0.5733
HOMA2-IR	0.787 (0.712–0.849)	0.001	≥ 1.69	80.01	65.33	0.4533
HOMA-AD	0.846 (0.778–0.899)	0.001	≥ 6.26	68.14	85.33	0.5333
HOMA-TG	0.755 (0.678–0.822)	0.001	≥ 0.72	53.33	81.35	0.3467
TyG index	0.836 (0.767–0.891)	0.001	≥ 9.88	76.00	88.00	0.6400
FIGR	0.548 (0.465–0.630)	0.335	≥ 2.41	85.33	46.67	0.3200
FIRI	0.768 (0.669–0.850)	0.001	≥ 2.96	83.67	70.47	0.4414
HOMA-1%S	0.850 (0.783–0.903)	0.001	≤ 28.2	82.74	77.33	0.5731
HOMA-2%S	0.779 (0.704–0.843)	0.001	≤ 53.9	69.33	74.67	0.4400
QUICKI	0.844 (0.776–0.898)	0.001	≤ 0.32	93.33	61.33	0.5467
Bennet index	0.795 (0.721–0.856)	0.001	≤ 1.2	89.30	74.62	0.4534
McAuley index	0.815 (0.743–0.874)	0.001	≤ 6.05	78.76	92.12	0.4937
Raynaud index	0.742 (0.664–0.810)	0.001	≤ 3.10	76.01	62.67	0.3867
1/Insulin	0.735 (0.657–0.804)	0.001	≤ 0.08	86.67	50.15	0.3733
GI ratio	0.547 (0.464–0.629)	0.343	≤ 7.45	85.33	55.81	0.2928
FISI	0.797 (0.724–0.858)	0.001	≤ 6.96	83.67	70.37	0.4414
SPISE	0.822 (0.751–0.880)	0.001	≤ 3.79	73.47	90.70	0.5067
HOMA-1%B	0.784 (0.680–0.875)	0.001	≤ 94.74	71.43	74.42	0.4585
HOMA-2%B	0.842 (0.773–0.896)	0.001	≤ 87.12	93.62	76.74	0.6800

Cut-off values correspond to the highest Youden index.

AUC, area under the curve; IR, insulin resistance; MetS, metabolic syndrome; ROC, receiver operating characteristic; HOMA, homeostatic model assessment; AD, adiponectin; TG, triglycerides; TyG, triglyceride-glucose; FIGR, fasting insulin to glucose ratio; FIRI, fasting insulin resistance; %S, insulin sensitivity; QUICKI, quantitative insulin sensitivity check index; 1/Insulin, reciprocal insulin; GI, glucose to insulin; FISI, fasting insulin sensitivity index; SPISE, single-point insulin sensitivity estimator; %B, beta-cell function.

and HOMA-2%B. The TyG index, McAuley index, and SPISE showed the largest AUCs for predicting elevated TG and reduced HDL-C. None of the indices tested showed good predictive ability in identifying high BP.

Among the markers of IR, insulin sensitivity and beta-cell function tested, HOMA-IR, HOMA-AD, the TyG index, HOMA-1%S, QUICKI, the McAuley index, SPISE, and HOMA-2%B were associated with increased odds of having MetS and its components after adjustment for age, sex, BMI, smoking, and alcohol status (Supplementary Table 2). The binomial logistic regression analysis showed that subjects with higher HOMA-IR levels were more likely to have MetS and hyperglycemia than those with lower HOMA-IR levels (OR, 2.24; 95% CI, 1.60–3.13 and OR, 16.47; 95% CI, 6.12–28.44, respectively). Subjects with higher TyG index and lower McAuley index values were more likely to have dyslipidemia (elevated TG) and hyperglycemia (OR, 3.46; 95% CI, 2.32–4.83 and OR, 3.34; 95% CI, 2.84–4.16, respectively).

DISCUSSION

The quantification of IR is of utmost importance, because it is the root factor associated with the clinical and metabolic abnormalities in MetS. It predicts the future risk of developing T2DM and CVD, can remain undiagnosed for a long time, and is established before any signs of disease appear. It is crucial to address IR as soon as possible to reduce the risk of developing life-threatening illnesses. Therefore, in this pioneering regional study, we have focused on understanding the ideal cut-off values and clinical utility of surrogate IR and insulin secretion markers for detecting MetS and its components among subjects near a tertiary care teaching hospital in southern India.

Matthews et al.¹⁶ developed the homeostatic model assessment concept in 1985 to quantify IR, insulin sensitivity, and beta-cell functions. In this study, we found that HOMA-IR was significantly higher in the MetS group than in the controls. The World Health Organization²⁹ has defined IR as a HOMA-IR of ≥ 1.8. In the current study, a HOMA-IR cut-off of ≥ 2.86 provided adequate pre-

Table 5. Proportion of subjects with values higher than the cut-off for the IR, insulin sensitivity, and beta-cell function indices

Variable	Cut-off value	Control group (n=75)	MetS group (n=75)	P
HOMA-IR	≥ 2.86	34 (45.3)	70 (93.3)	0.001
HOMA2-IR	≥ 1.69	27 (36)	60 (80)	0.001
HOMA-AD	≥ 6.26	12 (16)	52 (69.3)	0.001
HOMA-TG	≥ 0.72	15 (20)	43 (57.3)	0.001
TyG index	≥ 9.88	9 (12)	57 (76)	0.001
FIGR	≥ 2.41	12 (16)	35 (46.7)	0.001
FIRI	≥ 2.96	22 (29.3)	65 (86.7)	0.001
HOMA-1%S	≤ 28.2	18 (24)	59 (78.7)	0.001
HOMA-2%S	≤ 53.9	19 (25.3)	52 (69.3)	0.001
QUICKI	≤ 0.32	29 (38.7)	70 (93.3)	0.001
Bennet index	≤ 1.2	19 (25.3)	67 (89.3)	0.001
McAuley index	≤ 6.05	11 (14.7)	46 (61.3)	0.001
Raynaud index	≤ 3.10	28 (37.3)	57 (76)	0.001
1/Insulin	≤ 0.08	37 (49.3)	65 (86.7)	0.001
GI ratio	≤ 7.45	11 (14.7)	36 (48)	0.001
FISI	≤ 6.96	17 (22.7)	60 (80)	0.001
SPISE	≤ 3.79	5 (6.7)	43 (57.3)	0.001
HOMA-1%B	≤ 94.74	7 (9.3)	56 (74.7)	0.001
HOMA-2%B	≤ 87.12	6 (8)	57 (76)	0.001

Values are presented as number (%).

IR, insulin resistance; MetS, metabolic syndrome; HOMA, homeostatic model assessment; AD, adiponectin; TG, triglycerides; TyG, triglyceride-glucose; FIGR, fasting insulin to glucose ratio; FIRI, fasting insulin resistance; %S, insulin sensitivity; QUICKI, quantitative insulin sensitivity check index; 1/Insulin, reciprocal insulin; GI, glucose to insulin; FISI, fasting insulin sensitivity index; SPISE, single-point insulin sensitivity estimator; %B, beta-cell function.

dictive power, sensitivity and specificity in detecting MetS and elevated FPG among the southern Indians (AUC, 0.851; 95% CI, 0.784–0.904 and AUC, 0.963; 95% CI, 0.919–0.987, respectively). Using different criteria to define IR and different approaches to determine cut-off values are the reasons for a notably higher HOMA-IR. Moreover, a high HOMA-IR value correlated strongly with the odds of having MetS and elevated FPG. The HOMA2-IR is a simplified version of HOMA-IR that is calculated using an online calculator.¹⁷ HOMA2-IR displays metabolic processes more precisely than the original HOMA-IR because it highlights the feedback interactions between glucose and insulin in various parts of the body. However, it did not detect MetS more efficiently than HOMA-IR. The differences in the predictive ability of HOMA-IR and HOMA2-IR could reflect a drawback of HOMA2-IR: it accepts only a specific range of values for computation.³⁰ Keskin et al.³¹ observed similar results in the Brazilian Metabolic Syndrome Study; HOMA-IR had a slightly higher AUC than HOMA2-IR in the

ROC analysis. IR is a causative agent of MetS, which could indicate that MetS-related metabolic abnormalities are the end result of long-term IR. Excess weight and obesity in the MetS group could be an essential link between IR and MetS.

Recently, HOMA-AD was introduced as a novel, simple, and adipokine-based IR index that is calculated using serum adiponectin levels as a denominator in the HOMA-IR formula.¹⁸ To date, few studies have addressed the role of the HOMA-AD in IR assessment. Matsuhisa et al.¹⁸ surveyed Japanese respondents and observed that the IR measured by the euglycemic-hyperinsulinemic clamp technique was more significantly associated with HOMA-AD ($r = -0.64$) than with HOMA-IR ($r = -0.59$). In the present study, HOMA-AD has shown higher predictive power in discriminating subjects with MetS and hyperglycemia (AUC, 0.846; 95% CI, 0.778–0.899 and AUC, 0.893; 95% CI, 0.832–0.937, respectively). The ideal cut-off value for identifying MetS with the HOMA-AD index was ≥ 6.26 . Contrary to our findings, Da Silva et al.³² found that the HOMA-AD (AUC, 0.712) had less detectable accuracy than HOMA-IR (AUC, 0.859). However, they also found that HOMA-AD could discriminate patients with and without IR as well as HOMA-IR. The exact mechanisms connecting adiponectin and IR have not been studied extensively. Recent findings show that insulin could specifically affect adiponectin gene expression and *in vitro* adiponectin levels.³³ Thus, it is reasonable to think that the higher insulin levels found in IR subjects could decrease their adiponectin levels. The primary reason for low adiponectin levels in MetS could be central or abdominal obesity because adiponectin levels are determined mainly by the degree of visceral fat.

Another new surrogate marker of IR, the TyG index, was developed by Simental-Mendia et al.³⁴ in 2008 as a product of FPG and TG. Recent studies have found that the TyG index can predict the future risk of diabetes in men and women and is associated with CVD, obesity, fatty liver, and MetS.³⁵ We found the TyG index to be highly predictive of MetS (AUC, 0.836; 95% CI, 0.779–0.928), elevated FPG and TG (AUC, 0.865; 95% CI, 0.799–0.915; and AUC, 0.906; 95% CI, 0.848–0.948, respectively). In other words, the TyG index could precisely identify around 83.6% of individuals with MetS, 86.5% of individuals with elevated FPG, and 90.6% of individuals with high TG. The TyG index is also associated with increased odds of having MetS, elevated FPG and TG. The ideal

cut-off value for the TyG index to detect MetS in our study was ≥ 9.88 . However, certain pathological conditions, such as dyslipidemia and abdominal obesity, might influence the TyG index in ways that affect its ability to identify MetS. These results suggest that both glucose and lipid abnormalities could play a crucial role in the pathogenesis of MetS. Similar results have been reported by Zheng and Mao³⁶ They showed that the TyG index independently predicted incident HTN and suggested that including the TyG index in routine check-ups could help to prevent HTN.

In addition to the IR indices, we examined insulin sensitivity and beta-cell function indices derived from equations that use glucose and insulin levels. HOMA-1%S and QUICKI indicate insulin sensitivity, and HOMA-2%B is a method for evaluating beta-cell function. In Mexican subjects, Baez-Duarte et al.³⁷ demonstrated a gradual deterioration of beta-cell function and insulin sensitivity in MetS patients as their number of components of MetS increased. We here found that HOMA-1%S, QUICKI, and HOMA-2%B were significantly lower in MetS patients than in controls, confirming the findings of Baez-Duarte et al.³⁷ and indicating that the function or mass of beta cells was significantly reduced in subjects with MetS, along with decreased insulin sensitivity. This can be explained by the fact that a disproportionate accumulation of fat in the abdominal area is related to decreased insulin-mediated glucose disposal in southern-Indian adults. Increased pancreatic beta-cell apoptosis, necrosis, or autophagy could be involved in beta cell dysfunction in MetS. In this study, HOMA-1%S, QUICKI, and HOMA-2%B showed the best predictive power (AUC, 0.850; 95% CI, 0.783–0.903; AUC, 0.844; 95% CI, 0.776–0.898 and AUC, 0.842; 95% CI, 0.773–0.896, respectively), with cut-offs of ≤ 28.2 , ≤ 0.32 , and ≤ 87.12 , respectively, to identify MetS patients from southern India.

In 2001, McAuley et al.²⁴ proposed the McAuley index based on serum insulin and TG, to provide information on the pathophysiology of IR and MetS. Patients with MetS have a significantly lower McAuley index than controls. Thus, the dysregulation of serum lipid metabolism, mainly an increase in TG levels, as the result of hyperinsulinemia can directly cause reduced insulin sensitivity and beta-cell dysfunction through the deposition of TG within cells. We also found that the McAuley index showed good predictive power to identify MetS, elevated FPG and TG, and reduced HDL-C (AUC,

0.815; 95% CI, 0.743–0.874; AUC, 0.796; 95% CI, 0.723–0.857; AUC, 0.895; 95% CI, 0.834–0.939; and AUC, 0.762; 95% CI, 0.680–0.827, respectively). Furthermore, the McAuley index was strongly associated with the odds of having central obesity and elevated FPG. The mean McAuley index in the MetS group was 6.01 ± 1.90 , with a cut-off of ≤ 6.05 . A similar pattern for the McAuley index was reported in a study conducted among Korean adults in 2016 by Kim et al.,³⁸ who concluded that the McAuley index showed the best accuracy in detecting MetS. Contrary to our findings, a 2007 study by Sarafidis et al.³⁹ on a Greek population found that McAuley's index was the worst predictor of insulin sensitivity among the measures examined. This discrepancy in the results could be due to the normal mean TG levels in the Greek study population.

Paulmichl et al.²⁸ introduced SPISE as a reliable tool for estimating IR based on fasting TG, HDL-C, and BMI measurements. They developed the model using computer-assisted mathematical modeling of their study population data. They also compared the reliability of SPISE to that of the gold standard euglycemic-hyperinsulinemic clamp test, HOMA-IR, and other indices for IR. Compared with control subjects, the SPISE value was significantly lower in the MetS group. SPISE showed a high ability to discriminate MetS cases from controls (AUC, 0.822; 95% CI, 0.751–0.880). SPISE can also predict central obesity, elevated FPG and TG, and reduced HDL-C with excellent discriminating power. We observed a cut-off value of ≤ 3.79 for identifying MetS patients in southern India. Paulmichl et al.²⁸ found a SPISE cut-off value of ≤ 6.61 among a European population. The lower cut-off value of SPISE found in this study indicates higher IR and decreased insulin sensitivity among southern Indians. Dudi et al.⁴⁰ demonstrated similar results and found SPISE to be a valuable, low-cost measure with high sensitivity and specificity for IR and insulin sensitivity in MetS among a northern Indian population in 2019.

In conclusion, we found increased IR coupled with decreased insulin sensitivity and beta-cell function in the MetS group compared with the control group. Our study results suggest that HOMA-IR, HOMA-AD, the TyG index, HOMA-1%S, QUICKI, the McAuley index, SPISE, and HOMA-2%B show better detectable accuracy in identifying MetS subjects than the other surrogate markers of IR and insulin secretion we tested. We also obtained ideal cut-off points for the surrogate markers of IR and insulin secretion for the

detection of MetS, and those numbers are not consistent with those in previous studies. The differences in ideal cut-off points could be due to the study design, ethnic differences, sample size, or criteria for MetS diagnosis. Therefore, using these surrogate measures of IR and insulin secretion, in addition to FPG and lipid profiles, could help with the identification and risk stratification of MetS among southern Indians. Our findings suggest that early treatment options to address IR and intervention strategies to improve insulin sensitivity are the best ways to slow disease development and progression.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Study concept and design: CKE, GSG, DY, JS, and BV; acquisition of data: CKE; analysis and interpretation of data: GSG, CKE, and DY; drafting of the manuscript: GSG, CKE, and DY; critical revision of the manuscript: CKE, GSG, DY, JS, and BV; statistical analysis: CKE and DY; obtained funding: CKE; administrative, technical, or material support: GSG; and study supervision: GSG.

SUPPLEMENTARY MATERIALS

Supplementary Tables 1 and 2 can be found via <https://doi.org/10.7570/jomes20071>.

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