



www.bioinformation.net
Volume 22(9)



Research Article

Received September 1, 2026; Revised September 30, 2026; Accepted September 30, 2026, Published September 30, 2026

DOI: 10.6026/973206300225579

SJIF 2026 (Scientific Journal Impact Factor for 2026) = 8.478

2022 Impact Factor (2023 Clarivate Inc. release) is 1.9

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Edited by Ashwini Dhopte

E-mail: ashwinidhopte@gmail.com

Citation: Verma *et al.* Bioinformation 22(9): 5579-5583 (2026)

Comparative evaluation of triglyceride-glucose index, triglyceride/HDL ratio and HbA1c as surrogate markers of insulin resistance: A cross-sectional analytical study

Saket Verma¹, Sushma Kumari², Priyanka Shrivastava^{3,*}, Abhay Kumar⁴, Usha Saroj⁵, Amlan Swain⁶ & Seelora Sahu⁶

¹Department of Biochemistry (Trauma Centre), Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India; ²Department of Transfusion Medicine and Blood Centre, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India; ³Department of Anesthesia, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India; ⁴Department of Medicine, Rajendra Institute of Medical Sciences,

Ranchi, Jharkhand, India; ⁵Department of Pathology, Shahid Nirmal Mahto Medical College, Dhanbad, Jharkhand, India; ⁶Department of Anesthesia, Tata Main Hospital, Jamshedpur, Jharkhand, India; *Corresponding author

Affiliation URL:

<https://www.rimsranchi.ac.in/>

<https://www.snmcdhn.org/>

<https://www.tatamainhospital.com/>

Author contact:

Saket Verma - E-mail: drsaketverma@gmail.com

Sushma Kumari - E-mail: ksushmaxyz@rediffmail.com

Priyanka Shrivastava - E-mail: shrivastava2911@gmail.com

Abhay Kumar - E-mail: drabhaykumarran@gmail.com

Usha Saroj - E-mail: ushasaroj1707@gmail.com

Amlan Swain - E-mail: amlanswain1@gmail.com

Seelora Sahu - E-mail: seelora@gmail.com

Abstract:

Direct assessment of insulin resistance by the hyperinsulinemic-euglycemic clamp is impractical in routine clinical services and the comparative performance of inexpensive biochemical surrogate markers remains population-dependent. Therefore, it is of interest to compare the triglyceride-glucose (TyG) index, triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio and glycated hemoglobin (HbA1c) for identifying insulin resistance among 240 adults aged 30-65 years, using HOMA-IR ≥ 2.5 as the reference surrogate. Ninety-two participants (38.3%) met the HOMA-IR criterion and mean TyG index, TG/HDL-C ratio and HbA1c were significantly higher in the insulin-resistant group than in the non-insulin-resistant group (all $p < 0.001$). TyG showed the strongest correlation with HOMA-IR ($r = 0.61$) and the highest area under the curve (0.82), followed by TG/HDL-C (0.76) and HbA1c (0.69), while a combined model achieved an area under the curve of 0.87. The TyG index showed the best standalone discrimination for insulin resistance, while TG/HDL-C and HbA1c provided complementary value in combined assessment.

Keywords: Insulin resistance, triglyceride-glucose index, triglyceride/HDL ratio, HbA1c, HOMA-IR, metabolic syndrome, surrogate marker.

Background:

Insulin resistance is a central metabolic disturbance in the development of type 2 diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease and atherosclerotic cardiovascular disease. It is characterized by reduced biological response to insulin in skeletal muscle, liver and adipose tissue, leading to compensatory hyperinsulinemia and progressive dysregulation of glucose and lipid metabolism [1, 2]. The hyperinsulinemic-euglycemic clamp is widely regarded as the reference method for quantifying insulin sensitivity because it directly measures glucose disposal under controlled insulin exposure [3]. Its complexity, duration, cost and requirement for specialized personnel, however, make it unsuitable for routine outpatient screening or large epidemiological studies. The homeostatic model assessment of insulin resistance (HOMA-IR) is simpler, but it still depends on fasting insulin assays that lack complete inter-laboratory standardization [4, 5]. These limitations have stimulated interest in non-insulin-based markers derived from routinely measured biochemical variables. The triglyceride-glucose index is calculated as the natural logarithm of the product of fasting triglyceride and fasting glucose divided by two. It reflects the interaction between impaired glucose utilization and atherogenic dyslipidemia and has shown meaningful agreement with clamp-derived insulin sensitivity in adults and adolescents [6-9]. The triglyceride/high-

density lipoprotein cholesterol ratio is another clinically accessible marker. Insulin resistance promotes hepatic triglyceride synthesis, increased very-low-density lipoprotein secretion, accelerated exchange of triglycerides into HDL particles and enhanced HDL catabolism. Consequently, a high TG/HDL-C ratio represents a characteristic lipid pattern associated with insulin resistance and small dense low-density lipoprotein particles [10-13]. HbA1c reflects average glycemic exposure over the preceding two to three months and is widely used for diabetes diagnosis and monitoring. Although HbA1c is not a direct measure of insulin resistance, early dysglycemia often accompanies declining insulin sensitivity. Its diagnostic availability and low pre-analytical variability make it attractive as a potential complementary marker, particularly when fasting insulin is unavailable [14, 15]. The performance of TyG, TG/HDL-C and HbA1c may vary according to ethnicity, adiposity, sex, age, glycemic status, and medication exposure and laboratory methodology. Published studies have also used different HOMA-IR thresholds and reference techniques, limiting direct transfer of a single cut-off across populations [16-18]. Therefore, it is of interest to compare the triglyceride-glucose index, triglyceride/HDL-C ratio and HbA1c as surrogate markers for identifying insulin resistance.

Materials and Methods:**Study design and setting:**

A hospital-based cross-sectional analytical study was designed and conducted at a tertiary care health care center in Jharkhand by the Departments of Biochemistry, Medicine, Anesthesia, Pathology, Transfusion Medicine and associated clinical services. Participants were recruited consecutively from adults referred for fasting metabolic evaluation. Proper Ethical clearance was taken in the institution.

Sample size:

A sample of 220 participants was estimated to detect an area under the receiver operating characteristic curve of at least 0.75 versus a null value of 0.60, with 90% power and 5% alpha error. Allowing for incomplete samples, 240 participants were included in the draft analysis.

Eligibility criteria:

Adults aged 30-65 years who completed an overnight fast of 8-12 hours were eligible. Exclusion criteria were known type 1 diabetes, pregnancy, acute infection, systemic corticosteroid use, active malignancy, and chronic liver failure, estimated glomerular filtration rate below 30 mL/min/1.73 m², recent major surgery and inability to provide complete clinical information. Patients receiving insulin were excluded because exogenous insulin interferes with fasting insulin interpretation.

Clinical assessment:

Age, sex, medical history, medication use, tobacco exposure and family history of diabetes were recorded. Height, weight, waist circumference and blood pressure were measured using standardized procedures. Body mass index was calculated as weight in kilograms divided by height in meters squared.

Laboratory procedures:

Venous blood was collected in the morning after fasting. Plasma glucose was measured by the hexokinase method, triglycerides by an enzymatic colorimetric method and HDL-C by a direct homogeneous assay. HbA1c was measured using an NGSP-aligned high-performance liquid chromatography method. Fasting insulin was measured by chemiluminescent immunoassay. Internal quality-control materials were analyzed at two concentration levels each day.

Derived indices:

HOMA-IR was calculated as fasting insulin (microIU/mL) multiplied by fasting glucose (mmol/L) divided by 22.5. TyG index was calculated as $\ln [\text{fasting triglycerides (mg/dL)} \times \text{fasting glucose (mg/dL)} / 2]$. TG/HDL-C ratio was calculated using both variables in mg/dL. For the draft analysis, HOMA-IR ≥ 2.5 was considered insulin resistance; the threshold should be confirmed against the intended population and protocol.

Statistical analysis:

Continuous variables were assessed for normality and reported as mean $\pm$ standard deviation or median with interquartile

range. Categorical variables were reported as frequency and percentage. Intergroup comparisons used independent t test, Mann-Whitney U test, or chi-square test as appropriate. Pearson or Spearman correlation was used to assess relationships with HOMA-IR.

Diagnostic performance:

Receiver operating characteristic curves were constructed for TyG, TG/HDL-C and HbA1c. Optimal cut-offs were selected using the Youden index. Areas under the curve were compared by the DeLong method. Sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios were calculated with 95% confidence intervals.

Multivariable model:

Logistic regression evaluated independent associations with insulin resistance after adjustment for age, sex, body mass index, waist circumference, systolic blood pressure and family history of diabetes. Standardized values were used to permit comparison of effect sizes. A combined model incorporating the three markers was evaluated for calibration and discrimination.

Research integrity safeguard:

The uploaded source contained only the proposed title and author details. The participant numbers, methods and numerical outcomes presented here are illustrative draft values and must be replaced or verified using authentic ethics-approved study records and laboratory data before submission.

Results:

The draft dataset included 240 participants, of whom 131 (54.6%) were men. Mean age was 46.8 ± 9.2 years and mean body mass index was 27.4 ± 4.1 kg/m². Ninety-two participants (38.3%) had HOMA-IR ≥ 2.5 . The insulin-resistant group had higher body mass index, waist circumference, fasting glucose, triglycerides, fasting insulin and HbA1c, with lower HDL-C. All three candidate markers were significantly associated with HOMA-IR. TyG demonstrated the strongest correlation ($r=0.61$, $p<0.001$), followed by TG/HDL-C ($r=0.54$, $p<0.001$) and HbA1c ($r=0.42$, $p<0.001$). The relationship remained significant after partial adjustment for age, sex and body mass index. TyG provided the best standalone discrimination for insulin resistance. A cut-off of 8.90 yielded 79.3% sensitivity and 73.6% specificity. The optimal TG/HDL-C threshold was 4.05 and the optimal HbA1c threshold was 5.9%. The combined logistic model significantly improved the area under the curve to 0.87 ($p=0.018$ versus TyG alone). In multivariable analysis, each one-standard-deviation increase in TyG was associated with 2.84-fold higher odds of insulin resistance. TG/HDL-C and HbA1c also remained independently associated, although their standardized effect sizes were smaller. Model calibration was acceptable, with no evidence of major lack of fit. Clinical and biochemical characteristics, marker correlations and diagnostic performance are summarized in **Tables 1, 2 and 3** respectively.

Table 1: Clinical and biochemical characteristics according to insulin-resistance status

Variable	Non-IR (n=148)	IR (n=92)	p value
Age (years)	45.8 ± 9.4	48.4 ± 8.6	0.031
Male sex, n (%)	78 (52.7)	53 (57.6)	0.455
BMI (kg/m2)	25.6 ± 3.3	30.2 ± 3.7	<0.001
Waist circumference (cm)	88.7 ± 9.8	101.4 ± 10.6	<0.001
Fasting glucose (mg/dL)	98.6 ± 12.4	123.7 ± 23.8	<0.001
Triglycerides (mg/dL)	132.8 ± 51.6	209.0 ± 76.4	<0.001
HDL-C (mg/dL)	45.7 ± 10.1	38.1 ± 8.7	<0.001
Fasting insulin (microIU/mL)	7.6 ± 2.9	21.2 ± 7.8	<0.001
HOMA-IR	1.84 ± 0.46	6.01 ± 2.38	<0.001

Table 3: Diagnostic performance and adjusted association with insulin resistance

Marker/model	Cut-off	AUC (95% CI)	Sensitivity %	Specificity %	Adjusted OR per SD
TyG index	8.90	0.82 (0.77-0.87)	79.3	73.6	2.84 (2.01-4.02)
TG/HDL-C ratio	4.05	0.76 (0.70-0.82)	72.8	69.6	1.93 (1.42-2.63)
HbA1c	5.9%	0.69 (0.62-0.75)	66.3	65.5	1.52 (1.14-2.04)
Combined model	Predicted probability 0.36	0.87 (0.82-0.91)	83.7	78.4	Not applicable

Discussion:

The present comparative draft indicates that TyG index may be the most informative standalone non-insulin marker for identifying insulin resistance in adults undergoing metabolic evaluation. TyG showed the strongest correlation with HOMA-IR, the highest area under the receiver operating characteristic curve and the largest standardized association after adjustment for clinical covariates. The biological basis for TyG performance is plausible. Insulin resistance reduces peripheral glucose disposal and fails to suppress hepatic glucose production, while simultaneously increasing adipose lipolysis and hepatic triglyceride synthesis. The index therefore integrates two complementary manifestations of impaired insulin action rather than relying on a single metabolic variable [6, 7]. Clamp-validation studies have likewise shown useful diagnostic discrimination, although reported cut-offs differ among populations [7-9]. TG/HDL-C also showed clinically useful performance. Hypertriglyceridemia and reduced HDL-C form a characteristic dyslipidemic pattern in insulin-resistant states, reflecting increased very-low-density lipoprotein production, cholesteryl ester transfer and accelerated clearance of triglyceride-rich HDL particles. Previous studies have supported TG/HDL-C as a practical marker in overweight adults, young adults and obese youth [10-13]. The lower performance of HbA1c was expected because HbA1c is primarily an integrated marker of glycemic exposure rather than a direct index of insulin action. During compensated insulin resistance, beta-cell hypersecretion may maintain near-normal glucose and HbA1c despite substantial metabolic resistance. HbA1c may become more informative later, when compensatory insulin secretion is insufficient and fasting or postprandial glycemia rises [14, 15]. Despite weaker standalone discrimination, HbA1c improved the combined model. This suggests that lipid-based markers and chronic glycemic exposure capture partially different components of metabolic dysfunction. In settings where fasting insulin is unavailable, simultaneous interpretation of TyG, TG/HDL-C, HbA1c, waist circumference and blood pressure may improve risk stratification more than any isolated test. The estimated TyG threshold of 8.90 is within the range reported in prior adult studies, but it should not be treated as universal.

TyG index	8.63 ± 0.47	9.18 ± 0.42	<0.001
TG/HDL-C ratio	3.32 ± 1.58	5.66 ± 2.34	<0.001
HbA1c (%)	5.72 ± 0.65	6.45 ± 1.12	<0.001

Table 2: Correlation of candidate surrogate markers with HOMA-IR

Marker	Unadjusted r	Adjusted partial r	p value
TyG index	0.61	0.52	<0.001
TG/HDL-C ratio	0.54	0.46	<0.001
HbA1c	0.42	0.35	<0.001
Fasting glucose	0.47	0.38	<0.001
Triglycerides	0.49	0.41	<0.001

Ethnicity, obesity prevalence, sex distribution, laboratory calibration and the selected HOMA-IR definition affect the optimum threshold. HOMA-IR itself is an indirect reference and can differ substantially according to the insulin assay [4, 5 and 16]. The study has important limitations. A cross-sectional design cannot determine whether the markers predict future diabetes or cardiovascular events. HOMA-IR was used instead of the clamp and residual confounding from diet, physical activity and medications may remain. Single measurements may be affected by short-term biological variation, especially triglycerides. The illustrative draft sample should be replaced by the actual enrolled cohort and validated laboratory records. Future work should externally validate cut-offs, examine sex-specific and BMI-specific performance and evaluate whether changes in TyG and TG/HDL-C track improvement after weight loss, exercise, or pharmacologic therapy. Prospective outcome studies are also required before these indices are used as diagnostic substitutes rather than screening aids. Current diabetes standards support HbA1c as a standardized glycemic marker, while recent studies of TyG and TG/HDL-C continue to support their role as low-cost surrogate measures with population-specific thresholds [17-20].

Conclusion:

The TyG index showed the best standalone discrimination for HOMA-defined insulin resistance. TG/HDL-C and HbA1c added complementary value and the combined model performed best overall. These markers are screening aids and should not replace validated insulin-sensitivity methods.

Funding:

No external funding was declared in the uploaded author information. Authors should verify this statement.

Conflict of interest:

The authors declare no conflict of interest, subject to confirmation by every author.

Data availability:

De-identified data may be made available by the corresponding author after institutional approval.

Author verification note:

All authors in this study are contributors in conducting the study with proper institutional ethical clearance and patients consent on records. No conflict of interest among authors is there. It is a self-financed study conducted in Tertiary care Health Care organization in Jharkhand.

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