Research Article

# Comparison of Cardiovascular Risk Classification by Established Risk Scores Across Glycemic Status in an Indian Population

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**Keywords**

Cardiovascular risk, Framingham Risk Score, ASCVD Risk Estimator Plus, QRISK3, WHO non-laboratory risk charts, Clinical Utility Index, Classification concordance, India

**Abstract**

**Background**: Cardiovascular disease (CVD) risk estimation is central to preventive care, particularly in populations with a high burden of diabetes and prediabetes. Most widely used cardiovascular risk prediction models were developed in Western populations and may show variable risk classification when applied to Indian cohorts.

**Objectives**: To compare cardiovascular risk classification using four established 10-year risk prediction models - Framingham Risk Score (FRS), ASCVD Risk Estimator Plus, QRISK3, and WHO non-laboratory risk charts - across different glycemic statuses in an Indian population.

**Methods**: This cross-sectional analytical study included 257 adults classified as normoglycemic controls (n = 76), prediabetics (n = 49), and diabetics (n = 132). Ten-year cardiovascular risk was estimated using FRS, ASCVD, QRISK3, and WHO non-laboratory charts. Risk category distributions were compared using chi-square analysis. Comparative classification behaviour across models was assessed using ROC curves, comparative classification metrics, and Clinical Utility Index (CUI), interpreted solely as measures of comparative classification behaviour rather than predictive validation.

**Results**: Substantial heterogeneity in cardiovascular risk classification was observed across models. QRISK3 classified the highest proportion of diabetic individuals as high cardiovascular risk (40.9%), whereas FRS classified only 6.8% into the high-risk category. WHO non-laboratory charts did not identify any participant as high risk at the ≥30% threshold. Significant differences across glycemic groups were observed for FRS, ASCVD, and QRISK3 ($p < 0.05$). QRISK3 demonstrated a greater tendency to classify participants into higher cardiovascular risk categories, whereas FRS and WHO non-laboratory charts showed a more conservative classification pattern.

**Conclusion:** Cardiovascular risk classification varies substantially across commonly used prediction models when applied to Indian individuals across different glycemic states. These findings reflect differences in classification behaviour rather than predictive performance and highlight the need for population-specific validation using longitudinal cardiovascular outcome studies.

**Key Message**

- Existing cardiovascular risk models developed in Western populations may not accurately reflect risk in Indian populations.
- This study found marked variability in risk classification across FRS, ASCVD, QRISK3, and WHO models, particularly among diabetics.
- The findings highlight the need for cautious interpretation and population-specific validation of cardiovascular risk assessment tools in India.

## Introduction

Cardiovascular disease (CVD) remains the leading cause of global mortality, accounting for nearly one-third of all deaths worldwide, with a disproportionate burden in low- and middle-income countries such as India [1]. Diabetes mellitus accelerates atherosclerosis through endothelial dysfunction, chronic inflammation, oxidative stress, dyslipidemia, and prothrombotic mechanisms, substantially increasing cardiovascular morbidity and mortality [2]. Prediabetes is now recognized as an independent cardiovascular risk state, with evidence of early vascular dysfunction and subclinical atherosclerosis preceding overt diabetes [3].

Indian populations exhibit a distinctive cardiometabolic phenotype characterized by higher visceral adiposity, insulin resistance, low high-density lipoprotein cholesterol, elevated triglycerides, and earlier onset of cardiovascular events at lower body mass indices compared with Western populations [4]. This "South Asian phenotype" contributes to premature coronary artery disease and higher case-fatality rates, underscoring the need for accurate cardiovascular risk stratification in Indian settings [5]. Despite this vulnerability, cardiovascular risk assessment in India largely relies on prediction models developed in Western cohorts, which may inadequately capture ethnicity-specific risk patterns [6].

Estimation of 10-year cardiovascular risk is central to preventive cardiology and informs decisions regarding lifestyle modification and pharmacological therapy [7]. The Framingham Risk Score (FRS) and ASCVD Risk Estimator Plus are widely used but are primarily validated in Western populations and may underestimate cardiovascular risk in South Asians [8,9].QRISK3 incorporates a broader range of variables, including ethnicity and comorbid conditions, potentially improving risk classification in diverse populations, although it was developed using United Kingdom data and remains inadequately evaluated in resident Indian populations [10,11]. The World Health Organization (WHO) non-laboratory cardiovascular risk charts facilitate risk estimation in low-resource settings but may underestimate risk among high-risk individuals [12].

Previous Indian studies have demonstrated substantial discordance among cardiovascular risk prediction models, with some tools classifying individuals with established cardiovascular disease as low risk, raising concerns regarding their clinical applicability [13,14].

However, there is limited comparative evidence evaluating cardiovascular risk classification and clinical utility of multiple risk prediction models across different glycemic states - diabetes, prediabetes, and normoglycemia - in Indian populations [15]. Clinical Utility Index (CUI) and receiver operating characteristic (ROC) curve analysis provide complementary approaches for evaluating the practical and discriminatory characteristics of risk prediction models beyond conventional statistical measures [16–18].

Therefore, the present study was undertaken to compare cardiovascular risk classification using FRS, ASCVD Risk Estimator Plus, QRISK3, and WHO non-laboratory risk charts among diabetic, prediabetic, and normoglycemic individuals in an Indian population, with the aim of informing appropriate cardiovascular risk assessment in Indian clinical practice.

## Methods

### Study Setting and Design

This was a cross-sectional analytical study conducted at a tertiary-care teaching hospital in South India. The hospital serves a heterogeneous population from both urban and rural backgrounds, making it suitable for evaluating cardiovascular risk stratification across different glycemic states. The study was designed to compare cardiovascular risk classification patterns generated by multiple established 10-year cardiovascular risk prediction models within the same cohort.

### Sample Size

The sample size was selected to support a comparative evaluation of cardiovascular risk classification across multiple prediction models in a cross-sectional design. A total of 257 participants is comparable to prior Indian studies assessing inter-model variability in cardiovascular risk scores and is adequate for detecting differences in risk category distribution using chi-square analysis and estimating relative discriminatory behaviour through ROC analysis. No formal a priori sample size calculation was performed because this exploratory cross-sectional study included all eligible participants meeting the predefined inclusion criteria during the study period. Therefore, the available sample of 257 participants was considered appropriate for hypothesis-generating comparison of cardiovascular risk classification patterns rather than formal model validation [6,11].

**Study Population and Sampling Strategy**

Adult participants attending outpatient departments and inpatient services of the hospital during the study period were screened for eligibility. A consecutive sampling strategy was employed to recruit eligible participants who met the inclusion criteria. Individuals were enrolled after obtaining informed written consent. Participants were categorized into three groups based on glycemic status: healthy controls, prediabetics, and diabetics.

**Inclusion Criteria**

1. Adults aged ≥18 years
2. Willingness to provide informed consent
3. Availability of clinical and biochemical data required for cardiovascular risk calculation

**Exclusion Criteria**

Known history of established cardiovascular disease (e.g., myocardial infarction, stroke, coronary revascularization)

**Operational Definitions**

Diabetes mellitus was defined according to the American Diabetes Association (ADA) criteria, based on fasting plasma glucose, HbA1c values, or documented medical history. Prediabetes was defined as impaired fasting glucose and/or HbA1c values within the prediabetic range as per ADA guidelines. Cardiovascular risk categorization was performed using four established risk prediction models. High cardiovascular risk was defined as a 10-year risk ≥20% for Framingham Risk Score (FRS), ASCVD Risk Estimator Plus, and QRISK3, while a threshold of ≥30% was used for the WHO non-laboratory risk charts, in accordance with standard recommendations for each model.

**Study Procedures**

Detailed demographic and clinical information was collected from all participants using a structured proforma. Data recorded included age, sex, smoking status, family history of cardiovascular disease, and relevant medical history. Medication history including antihypertensive therapy, lipid-lowering agents, glucose-lowering medications, and antiplatelet therapy was recorded whenever available and incorporated into the corresponding cardiovascular risk score calculations according to the requirements of each model. Anthropometric measurements such as height and weight were obtained using calibrated instruments, and body mass index (BMI) was calculated. Blood pressure was measured using a standardized protocol after adequate rest. Biochemical parameters, including fasting plasma glucose and lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) were obtained from laboratory records of the Department of Biochemistry at the study institution. All biochemical analyses were performed in the same laboratory using standardized analytical procedures and calibrated automated analyzers according to institutional quality control protocols. Fasting plasma glucose and lipid parameters were measured using routine enzymatic methods employed in the clinical laboratory.

The baseline demographic, anthropometric, clinical, and biochemical characteristics of the study participants according to glycemic status are summarized in Table 1.

**Table 1:** Baseline demographic, anthropometric, clinical, and biochemical characteristics of study participants according to glycemic status.

| Variable | Control (n=76) | Prediabetes (n=49) | Diabetes (n=132) | p-value |
|---|---|---|---|---|
| Age (years) | 38.48 ± 11.72 | 52.33 ± 13.47 | 55.90 ± 12.39 | <0.0001 |
| Males n (%) | 32 (42.1) | 24 (49.0) | 63 (47.7) | 0.86 |
| Female n (%) | 44 (57.9) | 25 (51.0) | 69 (52.3) | |
| Current smokers n (%) | 4 (5.3) | 7 (14.3) | 15 (11.4) | 0.21 |
| Non-smokers n (%) | 72 (94.7) | 42 (85.7) | 117 (88.6) | |
| Height (cm) | 164.1 ± 10.13 | 159.7 ± 11.04 | 161.8 ± 10.23 | 0.0557 |
| Weight (kg) | 68.28 ± 11.83 | 70.65 ± 13.42 | 70.42 ± 13.33 | 0.4247 |
| BMI (kg/m²) | 25.36 ± 3.74 | 27.87 ± 4.70 | 26.94 ± 4.90 | 0.0039 |
| Waist-Hip Ratio | 1.055 ± 0.22 | 0.9525 ± 0.08 | 0.9455 ± 0.10 | <0.0001 |
| Systolic Blood Pressure (mmHg) | 119.8 ± 16.87 | 133.4 ± 18.13 | 133.1 ± 19.90 | <0.0001 |
| Diastolic Blood Pressure (mmHg) | 79.49 ± 10.99 | 85.0 ± 10.27 | 81.91 ± 10.78 | 0.0161 |
| Fasting Plasma Glucose (mg/dL) | 90.09 ± 24.57 | 98.0 ± 13.68 | 161.7 ± 69.33 | <0.0001 |
| HbA1c (%) | 5.393 ± 0.66 | 5.949 ± 0.20 | 8.49 ± 1.76 | <0.0001 |

| Variable | Control (n=76) | Prediabetes (n=49) | Diabetes (n=132) | p-value |
|---|---|---|---|---|
| Total Cholesterol (mg/dL) | 169.4 ± 36.26 | 176.4 ± 42.06 | 172.7 ± 41.35 | 0.603 |
| Triglycerides (mg/dL) | 124.5 ± 67.56 | 145.7 ± 66.27 | 170.3 ± 101.70 | 0.0007 |
| HDL Cholesterol (mg/dL) | 42.21 ± 8.79 | 42.82 ± 17.08 | 42.72 ± 11.75 | 0.9439 |
| LDL Cholesterol (mg/dL) | 115.9 ± 31.87 | 119.9 ± 39.58 | 116.2 ± 40.41 | 0.8144 |

*Data are presented as mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. P-values were obtained using one-way ANOVA for continuous variables and chi-square test for categorical variables.*

Significant differences were observed across glycemic groups for age, body mass index, blood pressure, fasting plasma glucose, HbA1c, and triglyceride levels, whereas sex distribution, smoking status, and most lipid parameters were comparable between groups. These baseline characteristics provide important context for interpreting differences in cardiovascular risk classification across the evaluated risk prediction models.

**Cardiovascular Risk Prediction Models**

For each participant, 10-year cardiovascular risk was independently calculated using the Framingham Risk Score, ASCVD Risk Estimator Plus, QRISK3, and WHO non-laboratory risk charts, following the input variables and cut-off thresholds specified for each model.The Framingham Risk Score (FRS), ASCVD Risk Estimator Plus, QRISK3, and WHO non-laboratory cardiovascular risk charts differ in the clinical and metabolic variables incorporated for cardiovascular risk estimation. All four models include age, sex, systolic blood pressure, smoking status, and diabetes status. Ethnicity is incorporated in ASCVD and QRISK3, while body mass index is included only in QRISK3 and WHO non-laboratory models. Lipid parameters such as total cholesterol and high-density lipoprotein cholesterol are used in FRS and ASCVD, whereas QRISK3 employs the cholesterol-to-HDL ratio and WHO non-laboratory charts do not include biochemical lipid variables. QRISK3 uniquely incorporates additional clinical comorbidities and treatment-related variables, including family history of premature cardiovascular disease, chronic kidney disease, atrial fibrillation, inflammatory disorders, medication use, and socioeconomic deprivation indices (Table 2). Variables unique to QRISK3 including ethnicity, family history, chronic kidney disease, medication use, and comorbid conditions were operationalized using available clinical records. Variables unavailable in the study cohort were handled according to model guidance and documented assumptions.

**Table 2:** Comparative distribution of clinical and metabolic parameters included in major cardiovascular risk prediction models (FRS, ASCVD, QRISK3, and WHO non-laboratory charts).

| Parameter | FRS | ASCVD | QRISK3 | WHO Non-Lab |
|---|---|---|---|---|
| Age | ✓ | ✓ | ✓ | ✓ |
| Sex | ✓ | ✓ | ✓ | ✓ |
| Ethnicity / Race | X | ✓ (race) | ✓ | X |
| Total Cholesterol | ✓ | ✓ | X | X |
| HDL Cholesterol | ✓ | ✓ | X (uses ratio) | X |
| Chol/HDL Ratio | X | X | ✓ | X |
| LDL Cholesterol | X | ✓ | X | X |
| Systolic Blood Pressure | ✓ | ✓ | ✓ | ✓ |
| Hypertension Treatment | ✓ | ✓ | X | X |
| Smoking Status | ✓ | ✓ | ✓ | ✓ |
| Diabetes Status | ✓ | ✓ | ✓ (Type 1 / 2) | ✓ |
| BMI | X | X | ✓ | ✓ |

| Parameter | FRS | ASCVD | QRISK3 | WHO Non-Lab |
|---|---|---|---|---|
| Family History of CVD | X | X | ✓ (<60 yrs) | X |
| Chronic Kidney Disease | X | X | ✓ | X |
| Atrial Fibrillation | X | X | ✓ | X |
| Rheumatoid Arthritis | X | X | ✓ | X |
| Migraine | X | X | ✓ | X |
| Severe Mental Illness | X | X | ✓ | X |
| Systemic Lupus Erythematosus | X | X | ✓ | X |
| Corticosteroid Use | X | X | ✓ | X |
| Antipsychotic Use | X | X | ✓ | X |
| Socioeconomic / Deprivation Index | X | X | ✓ | X |

✓- *Clinical and Metabolic Parameters Included Under Each Risk Score*

*X- Clinical and Metabolic Parameters Not Included Under Each Risk Score*

**Data Management and Statistical Analysis**

**Data were entered into a structured database and analyzed** using SPSS and GraphPad Prism software. Categorical variables were summarized as frequencies and percentages. Differences in cardiovascular risk category distribution across glycemic groups were assessed using the chi-square test.

To compare the relative classification behaviour of the risk models within the cohort, Relative High-Risk Classification Concordance, Relative Low-Risk Classification Concordance, Positive Classification Concordance, Negative Classification Concordance, the area under the receiver operating characteristic (ROC) curve (AUC), and the Clinical Utility Index (CUI) were calculated using binary high-risk versus non-high-risk classification. For comparative classification analyses, diabetes mellitus status was used as the reference classification state because longitudinal cardiovascular outcome data were unavailable. Diabetes mellitus was selected as the surrogate reference classification because it represents one of the strongest established determinants of future cardiovascular disease and is incorporated as a major predictor in all evaluated cardiovascular risk models. In the absence of longitudinal cardiovascular outcome data, diabetes status provided a clinically relevant comparator for evaluating relative differences in cardiovascular risk classification across the models rather than true prediction of cardiovascular events. Accordingly, ROC analysis was used solely to compare relative classification behaviour across models and should not be interpreted as validation against future cardiovascular events. These measures were interpreted as comparative classification metrics, rather than as validation against clinical cardiovascular outcomes, as no longitudinal event data were available.

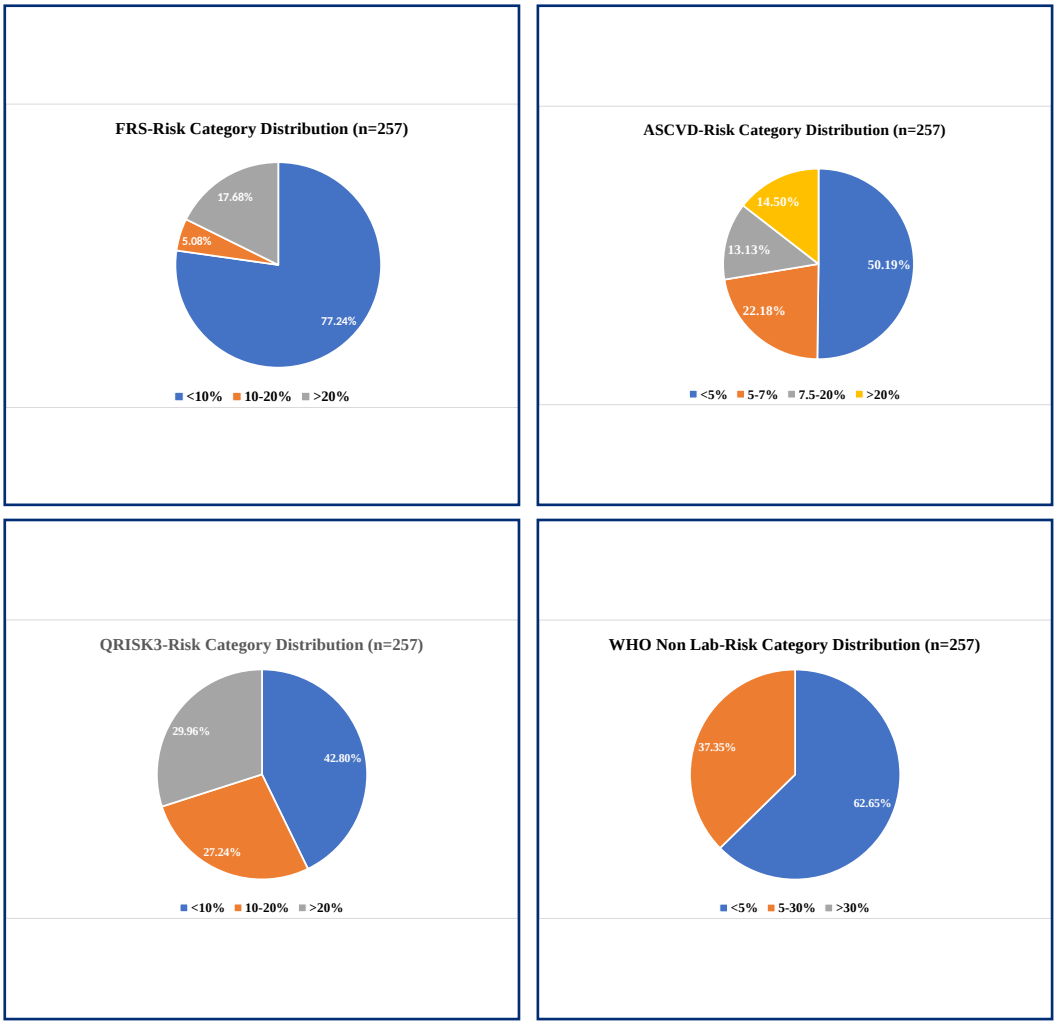
Clinical Utility Index for positive ($CUI^+$) and negative ($CUI^-$) outcomes was calculated to assess the practical implications of risk classification in identifying individuals more likely to be classified as high or low risk by each model. A p-value $<0.05$ was considered statistically significant for all analyses. As longitudinal cardiovascular outcomes were unavailable, Relative High-Risk Classification Concordance, Relative Low-Risk Classification Concordance, Positive Classification Concordance, Negative Classification Concordance, ROC analysis, and Clinical Utility Index were used only as comparative measures describing differences in classification behaviour across models and should not be interpreted as measures of predictive accuracy. Participants with incomplete data required for risk score calculation were excluded from model-specific analyses. No imputation procedure was applied.

**Results**

Risk Category Distribution Across Cardiovascular Risk Scores

Marked variability was observed in cardiovascular risk classification across the four models (Figure 1). According to the Framingham Risk Score (FRS), only 5.08% of participants were classified as having high cardiovascular risk (>20%), with most participants categorized as low or intermediate risk. The ASCVD Risk Estimator Plus classified 14.5% of participants as high risk (>20%). QRISK3 demonstrated a greater tendency to classify participants into higher risk categories; however, percentages presented in Figure 1 represent distribution across the entire study cohort (n = 257). WHO non-laboratory risk charts did not classify any participant as having a 10-year cardiovascular risk ≥30%.

**Figure 1:** Distribution of 10-year cardiovascular risk categories across the entire study population (n = 257) using Framingham Risk Score (FRS), ASCVD Risk Estimator Plus, QRISK3, and WHO non-laboratory risk charts.




**Comparison of Cardiovascular Risk Classification Across Glycemic States**

Comparison of cardiovascular risk classification across normoglycemic controls, prediabetic individuals, and diabetic individuals demonstrated statistically significant differences for multiple cardiovascular risk prediction models (Table 3). The Framingham Risk Score (FRS) showed a significant variation in risk category distribution across the three glycemic groups ($\chi^2 = 8.852$; $p = 0.012$), with a higher proportion of participants in the prediabetic and diabetic groups classified as high risk compared with controls. Similarly, the ASCVD Risk Estimator Plus demonstrated highly significant differences in cardiovascular risk classification across glycemic states ($\chi^2 = 19.12$; $p < 0.0001$). The QRISK3 model also showed significant variation in cardiovascular risk distribution among controls, prediabetics, and diabetics ($\chi^2 = 28.98$; $p < 0.0001$), with a greater proportion of diabetic individuals categorized into the high-risk group. In contrast, WHO non-laboratory cardiovascular risk charts did not demonstrate variation across glycemic groups, as no participant exceeded the predefined ≥30% cardiovascular risk threshold.

**Table 3:** Distribution of 10-year cardiovascular risk categories across normoglycemic, prediabetic, and diabetic individuals using FRS, ASCVD, QRISK3, and WHO non-laboratory risk prediction models, with chi-square comparison.

| RISK SCORES | | CONTROL | | PREDIABETIC | | DIABETES | | CHI SQUARE | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | | Frequency | % | Frequency | % | Frequency | % | | |
| FRS | <20 | 76 | 100.0 | 43 | 87.8 | 123 | 93.2 | 8.852 | 0.012 |
| | >20 | 0 | 0.0 | 6 | 12.2 | 9 | 6.8 | | |
| ASCVD | <20 | 75 | 98.7 | 43 | 87.8 | 101 | 76.5 | 19.12 | <0.0001 |
| | >20 | 1 | 1.3 | 6 | 12.2 | 31 | 23.5 | | |
| QRISK3 | <20 | 70 | 92.1 | 40 | 81.6 | 78 | 59.1 | 28.98 | <0.0001 |
| | >20 | 6 | 7.9 | 9 | 18.4 | 54 | 40.9 | | |
| WHO NONLAB | <30 | 76 | 100.0 | 49 | 100.0 | 132 | 100.0 | 0 | – |
| | >30 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | | |

*FRS: Framingham Risk Score; ASCVD: ASCVD Risk Estimator Plus; QRISK3: QRISK3; WHO NONLAB: WHO non-laboratory risk charts. Percentages are calculated within each glycemic status group (column percentages).*

**Table 4:** Comparative Classification Concordance Metrics of FRS, ASCVD, QRISK3, and WHO Non-Laboratory Cardiovascular Risk Prediction Models.

| COMPARATIVE CLASSIFICATION MEASURES | FRS >20% | | ASCVD >20% | | QRISK3 >20% | | WHO NONLAB >30% | |
|---|---|---|---|---|---|---|---|---|
| | VALUE | 95%CI | VALUE | 95%CI | VALUE | 95%CI | VALUE | 95%CI |
| Relative High-Risk Classification Concordance | 6.82 | 3.16–12.65 | 23.48 | 16.62–31.50 | 40.91 | 32.37–49.87 | 0.00 | 0.00–2.76 |
| Relative Low-Risk Classification Concordance | 95.20 | 88.15–98.69 | 93.60 | 85.86–97.44 | 85.60 | 76.57–91.68 | 100.00 | 94.20–100.0 |
| Positive Classification Concordance | 60.00 | 31.32–83.16 | 81.58 | 64.98–92.04 | 78.26 | 63.75–88.90 | – | – |
| Negative Classification Concordance | 43.07 | 34.41–51.99 | 50.43 | 41.59–59.20 | 53.73 | 44.68–62.61 | 41.25 | 33.20–49.72 |

*FRS: Framingham Risk Score; ASCVD: ASCVD Risk Estimator Plus; QRISK3: QRISK3; WHO NONLAB: WHO non-laboratory risk charts; CI: Confidence Interval.*

*Note: Positive clinical state = Diabetes mellitus; Positive test = High cardiovascular risk category as per model thresholds. Diabetes mellitus was used as the surrogate reference classification state because longitudinal cardiovascular outcome data were unavailable. Relative High-Risk Classification Concordance, Relative Low-Risk Classification Concordance, Positive Classification Concordance, and Negative Classification Concordance describe the comparative classification behaviour of the evaluated cardiovascular risk models and should not be interpreted as measures of diagnostic accuracy or predictive performance.*

### Comparative Classification Behaviour Across Cardiovascular Risk Prediction Models

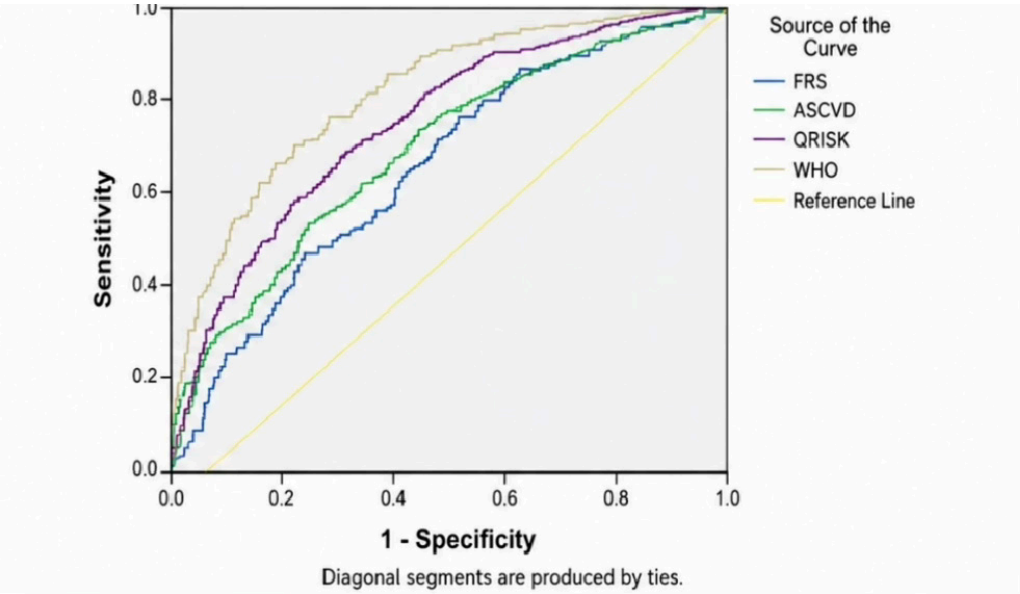
The comparative classification characteristics of the four cardiovascular risk prediction models varied considerably with respect to relative classification concordance for higher- and lower-risk categorization (Table 4). When diabetes mellitus was used as the surrogate reference classification state, QRISK3 demonstrated the greatest concordance for identifying participants classified into higher cardiovascular risk categories, whereas FRS demonstrated greater concordance for classifying participants into lower-risk categories. ASCVD showed intermediate classification concordance, while WHO non-laboratory charts demonstrated no concordance for high-risk classification at the ≥30% threshold because no participant exceeded this cut-off. These findings should be interpreted solely as comparative classification behaviour rather than diagnostic accuracy or predictive performance.

### ROC Analysis and Clinical Utility of Cardiovascular Risk Scores

Receiver operating characteristic (ROC) curve analysis was performed to assess the relative discriminatory behaviour of the

cardiovascular risk prediction models in classifying individuals as high versus non-high cardiovascular risk (Figure 2). All four models demonstrated discriminatory ability above the reference line, with QRISK3 showing the highest area under the curve (AUC), followed by ASCVD, WHO non-laboratory charts, and FRS. As the study lacked longitudinal cardiovascular outcome data, ROC analysis was interpreted as a comparative measure of classification behaviour rather than as an assessment of predictive accuracy for incident cardiovascular events.

**Figure 2:** Receiver operating characteristic (ROC) curves illustrating the comparative classification behaviour of FRS, ASCVD, QRISK3, and WHO non-laboratory cardiovascular risk models for classification of high versus non-high cardiovascular risk, together with corresponding area under the curve (AUC) values and 95% confidence intervals.



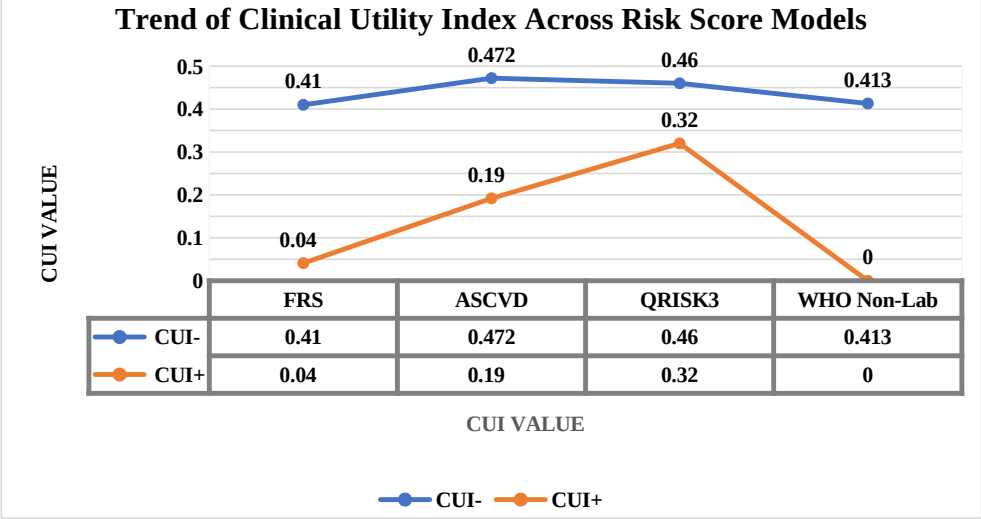

| Risk Score | AUC | Standard Error | 95% CI | | p-value |
|---|---|---|---|---|---|
| | | | Lower Bound | Upper Bound | |
| FRS | 0.733 | 0.035 | 0.664 | 0.801 | <0.001 |
| ASCVD | 0.729 | 0.033 | 0.664 | 0.794 | <0.001 |
| QRISK | 0.780 | 0.031 | 0.720 | 0.840 | <0.001 |
| WHO | 0.787 | 0.031 | 0.727 | 0.847 | <0.001 |

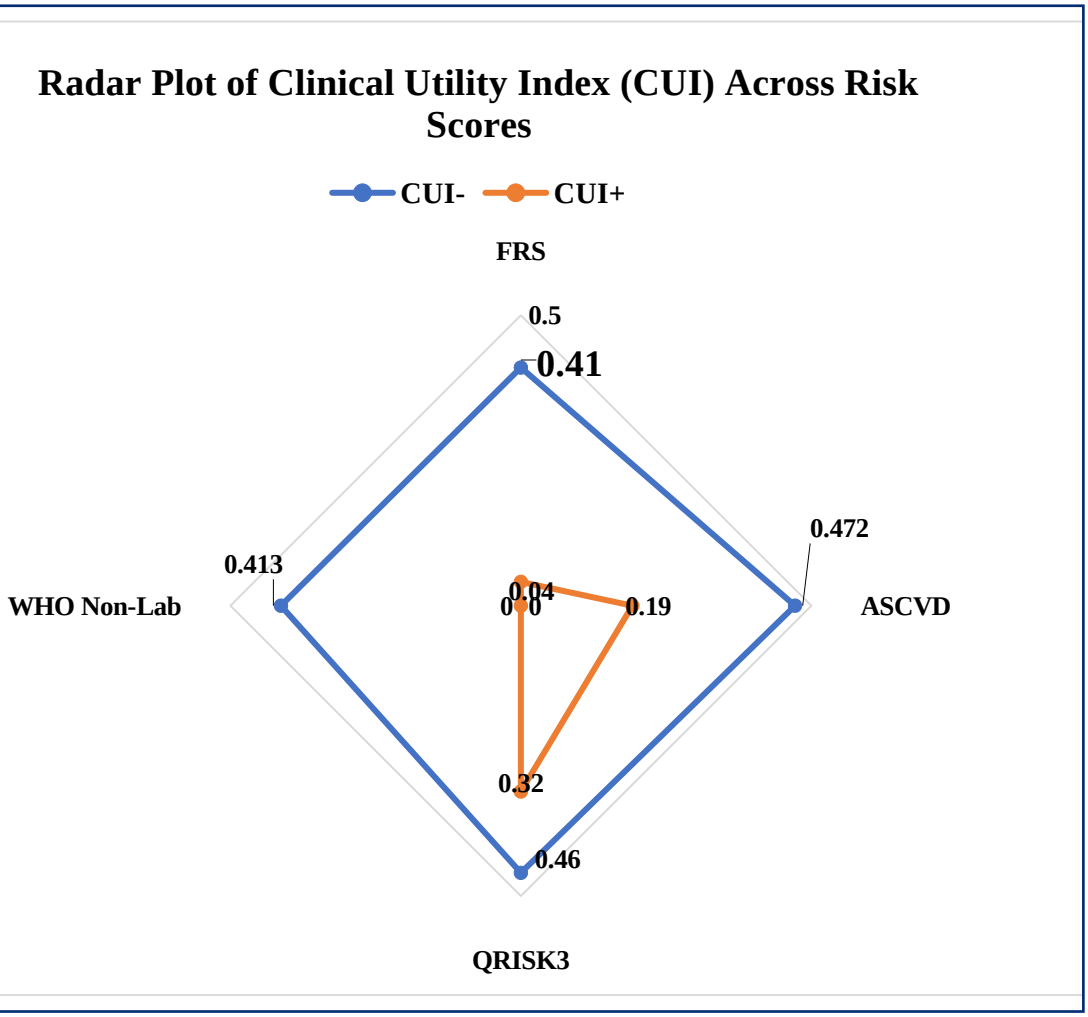
*Note: AUC values were estimated using nonparametric ROC analysis.*
*p-values indicate comparison against the null hypothesis of AUC = 0.5.*

**Comparison of Clinical Utility Index ($CUI^+$ and $CUI^-$) Across Cardiovascular Risk Prediction Models**

Clinical Utility Index (CUI) analysis was used to evaluate the practical implications of cardiovascular risk classification by integrating the comparative classification concordance measures. QRISK3 demonstrated the highest positive clinical utility ($CUI^+ = 0.320$), indicating a greater tendency to classify individuals into higher cardiovascular risk categories. In contrast, ASCVD demonstrated the highest negative clinical utility ($CUI^- = 0.472$), indicating a greater tendency to classify participants into lower-risk categories. FRS showed comparatively low positive clinical utility ($CUI^+ = 0.041$) but moderate negative clinical utility ($CUI^- = 0.410$), reflecting a conservative classification profile. WHO non-laboratory cardiovascular risk charts demonstrated no positive clinical utility at the predefined threshold ($CUI^+ = 0.000$), although negative clinical utility remained moderate ($CUI^- = 0.413$). (Figure 3) These findings reflect differences in classification behaviour rather than predictive accuracy for future cardiovascular outcomes.

**Figure 3:** Trend and radar plot illustrating the comparative clinical utility index for positive ($CUI^+$) and negative ($CUI^-$) outcomes across FRS, ASCVD, QRISK3, and WHO non-laboratory cardiovascular risk prediction models.



## Discussion

The present study provides a comparative evaluation of four widely used 10-year cardiovascular risk prediction models - Framingham Risk Score (FRS), ASCVD Risk Estimator Plus, QRISK3, and WHO non-laboratory risk charts - across normoglycemic, prediabetic, and diabetic individuals in an Indian population. The principal finding is the substantial heterogeneity in risk classification across models, with marked discordance in the proportion of individuals categorized as high cardiovascular risk, particularly among those with diabetes mellitus. Differences in cardiovascular risk classification may influence how individuals are categorized by commonly used risk assessment tools. In high-burden settings such as India, understanding these classification differences is important when interpreting estimated cardiovascular risk.

### Interpretation of Risk Classification Differences

The observed variability across risk scores highlights the challenges of applying cardiovascular risk algorithms developed in Western populations to Indian settings. In the present cohort, QRISK3 classified a considerably higher proportion of diabetic individuals as high risk compared with FRS and ASCVD, while the WHO non-laboratory charts failed to identify any participant as high risk at the recommended ≥30% threshold. These findings underscore that different models emphasize distinct combinations of demographic, metabolic, and clinical variables, leading to divergent risk stratification even within the same population.

QRISK3 incorporates a broader range of variables, including ethnicity, body mass index, family history of premature cardiovascular disease, chronic kidney disease, and selected comorbid conditions. This broader clinical scope may explain its tendency to classify a larger proportion of individuals—particularly diabetics—as higher risk in the present study.

In contrast, FRS and ASCVD rely more heavily on age and traditional lipid parameters, which may lead to relative under-classification of risk in younger individuals with adverse metabolic profiles, a pattern commonly observed in South Asian populations.

### Diagnostic Metrics and Methodological Considerations

The classification concordance measures reported in this study (formerly corresponding to sensitivity, specificity, positive predictive value, and negative predictive value), together with the area under the receiver operating characteristic (ROC) curve (AUC) and the Clinical Utility Index (CUI), were used solely for comparative classification analysis within the study cohort and should not be interpreted as measures of diagnostic or prognostic performance. However, it is important to emphasize that this was a cross-sectional study without longitudinal cardiovascular outcomes, and therefore these metrics should not be interpreted as true diagnostic accuracy against a gold-standard clinical endpoint. Rather, they reflect how differently each model classifies individuals as higher or lower risk relative to the others.

Within this context, QRISK3 demonstrated greater relative classification concordance for identifying participants categorized as high cardiovascular risk, whereas FRS and WHO non-laboratory models demonstrated greater concordance for classifying participants into lower-risk categories. These patterns illustrate the trade-off between broader risk capture and conservative classification inherent to different algorithms and should be interpreted as classification tendencies rather than predictive superiority.

### WHO Non-Laboratory Risk Charts

A notable finding was the inability of the WHO non-laboratory risk charts to classify any participant as high risk using the recommended ≥30% threshold. This observation raises concerns regarding the suitability of these thresholds in Indian populations, particularly among individuals with diabetes and prediabetes. While WHO charts are designed for low-resource settings and prioritize simplicity, their limited sensitivity in this cohort suggests potential underestimation of cardiovascular risk in high-burden populations. These findings are consistent with previous Indian studies reporting under-classification of cardiovascular risk by WHO risk charts and highlight the need for cautious interpretation during clinical decision-making in high-risk populations [11,14].

The absence of participants classified at the ≥30% threshold may also reflect the relatively conservative threshold recommended for WHO non-laboratory risk charts rather than complete failure of the model itself. Alternative thresholds such as ≥20% were not explored because the objective of the present study was to compare each model using its recommended high-risk threshold. Future studies should evaluate whether lower WHO thresholds improve cardiovascular risk classification in Indian populations.

### Clinical Utility Perspective

The incorporation of the Clinical Utility Index (CUI) allowed assessment of the practical implications of cardiovascular risk classification beyond conventional statistical measures. QRISK3 demonstrated higher positive clinical utility, indicating a greater tendency to classify participants into higher cardiovascular risk categories. Conversely, FRS and WHO non-laboratory models demonstrated a greater tendency to classify participants into lower-risk categories. These findings should be interpreted as differences in classification behaviour rather than evidence of predictive superiority or clinical effectiveness. This complementary interpretation reinforces the concept that no single risk score is universally optimal and that the choice of risk assessment tool may influence cardiovascular risk categorization within the same population.

The findings of this study are consistent with previous Indian and South Asian studies demonstrating discordance among cardiovascular risk prediction models and underestimation of risk by traditional Western-derived tools [6]. Prior

investigations in Indian cohorts, including patients with established coronary artery disease, have reported similar limitations of FRS and WHO charts, while broader algorithms such as QRISK-based models tend to identify a higher proportion of individuals as high risk [10]. The present study extends these observations by demonstrating comparable discrepancies across the glycemic spectrum, including individuals with prediabetes [3]. These findings highlight the importance of careful interpretation of cardiovascular risk estimates in Indian populations and support the need for population-specific validation of commonly used cardiovascular risk prediction models.

**Strengths and Limitations**

A key strength of this study is the inclusion of three distinct glycemic categories, allowing assessment of cardiovascular risk stratification across the continuum from normoglycemia to overt diabetes. The simultaneous application of four widely used cardiovascular risk prediction models within the same cohort minimizes inter-study variability and enables direct comparison [7,10]. Additionally, the Clinical Utility Index provided an additional framework for comparing classification behaviour across risk prediction models.

However, several limitations merit consideration. The single-center, cross-sectional design limits generalizability and precludes validation of predicted risk against observed cardiovascular outcomes. The absence of longitudinal cardiovascular outcomes limits assessment of predictive validity, and findings should be interpreted as comparative classification patterns. The modest sample size, particularly in the prediabetic group, may limit precision of subgroup analyses. These limitations underscore the exploratory nature of the findings.

The absence of a gold-standard cardiovascular outcome measure limited the ability to assess true predictive performance and restricted interpretation to comparative classification behaviour across models.

An additional methodological limitation is that diabetes mellitus was used as the surrogate reference classification state for comparative ROC analysis, while diabetes status also contributes directly to all evaluated cardiovascular risk prediction models. This may introduce partial circularity and overestimate relative classification concordance. Accordingly, ROC-derived measures should be interpreted only as comparative descriptors of classification behaviour rather than independent measures of diagnostic or prognostic performance.

**Future Directions**

The marked discordance observed among cardiovascular risk prediction models highlights the urgent need for population-specific validation and recalibration of existing tools or the development of indigenous risk prediction models tailored to Indian populations. Future studies should adopt prospective, longitudinal designs with hard cardiovascular endpoints to evaluate discrimination, calibration, and clinical impact. Future prospective investigations should additionally evaluate agreement among cardiovascular risk prediction models using pairwise cross-classification tables, Cohen's kappa statistics, weighted agreement coefficients, and reclassification analyses to provide a more comprehensive assessment of inter-model concordance. Incorporation of subclinical atherosclerosis markers and cost-effectiveness analyses may further inform optimal risk assessment strategies for resource-constrained settings.

**Conclusion**

This study demonstrates substantial variability in cardiovascular risk classification across commonly used prediction models when applied to Indian individuals across different glycemic states. These findings reflect differences in classification behaviour rather than predictive performance and highlight the need for population-specific validation using longitudinal cardiovascular outcome studies.

**Competing Interests**

The authors have no competing interests to declare that are relevant to the content of this article.

**Author Contributions (CRediT):**

LG.: Conceptualization, Investigation, Data curation, Formal analysis, Writing – original draft.
PR: Methodology, Data curation,
NT: Methodology, Data curation,
MKP: Methodology, Data curation,
JG: Formal analysis, Methodology, Data curation, Validation.
SNK: Conceptualization, Supervision, Writing – review & editing

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**Conflict of interest**

The authors have no competing interests to declare that are relevant to the content of this article.

**Data availability statement**

The data underlying this article will be made available upon reasonable request to the corresponding author.

**Ethical Clearance**

Ethical Approval: The Institutional Ethics Committee clearance was obtained via letter no. Ref: JSS/MC/PG/16,17/2022-23.
Ethics Committee Name: JSS Medical College and Hospital Institutional Ethics Committee
Institution Name: JSS Medical College and Hospital,
Written informed consent was obtained from all the subjects for participation in the study and for the use of patient data for research and educational purposes. The study procedures

adhered to the guidelines of the Declaration of Helsinki 1964 and its subsequent revisions.

The manuscript has been read and approved by all the authors, and the requirements for authorship as stated earlier in this document have been met, and each author believes that the manuscript represents honest work.

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