JHWCR JOURNAL OF HEALTH, WELLNESS AND COMMUNITY RESEARCH 3007-0570

https://doi.org/10.61919/wyw59631

Original Article

Comparison Of QRISK3 And Framingham Risk Scores For Estimating 10-Year CVD Risk In Patients With CKD

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ABSTRACT

Background: Chronic kidney disease (CKD) is strongly associated with increased cardiovascular morbidity and mortality, yet conventional cardiovascular risk prediction models may underestimate risk in this population because they do not account for CKD-specific determinants of vascular disease. Objective: To compare the cardiovascular risk stratification performance of QRISK3 and the Framingham Risk Score (FRS) and evaluate the clinical implications of risk reclassification among patients with CKD stages 3–5. Methods: A prospective cohort study was conducted at Pak Emirates Military Hospital, Rawalpindi, between January and December 2023. Two hundred fifty adults with CKD stages 3–5 underwent baseline cardiovascular risk estimation using both QRISK3 and the 2008 Framingham Risk Score. Participants were categorized into low (<10%), moderate (10–19%), and high (≥20%) risk groups. Risk reclassification was assessed using net reclassification improvement (NRI). Patients were followed for 12 months to document major adverse cardiovascular events (MACE). Discriminatory performance was evaluated using receiver operating characteristic curves. Results: QRISK3 classified significantly more patients as high risk compared with FRS (62.8% vs 32.4%, $p < 0.001$). Risk category changes occurred in 48.0% of participants, predominantly upward. MACE developed in 43.6% of patients during follow-up. Event rates were higher among individuals reclassified upward by QRISK3 (52.3% vs 31.5%, $p = 0.002$). The AUROC for predicting MACE was higher for QRISK3 than FRS (0.74 vs 0.66, $p = 0.008$), with an NRI of 0.18 (95% CI: 0.08–0.28). Conclusion: QRISK3 demonstrated superior cardiovascular risk stratification compared with the Framingham Risk Score in patients with CKD, identifying a greater proportion of individuals at high cardiovascular risk and showing improved predictive discrimination for adverse cardiovascular outcomes. Keywords: Chronic kidney disease; Cardiovascular risk prediction; QRISK3; Framingham risk score; Risk reclassification; Major adverse cardiovascular events.

"Cite this Article" | Received: 13 September 2024; Accepted: 22 December 2024; Published: 28 February 2025.

Author Contributions: Concept: MA; Design: WR; Data Collection: NK; Analysis: MI; Drafting: MAJ. **Ethical Approval**: Ethical Approval was obtained by respective Institute. Informed Consent: Written informed consent was obtained from all participants; Conflict of Interest: The authors declare no conflict of interest; Funding: No external funding; Data Availability: Available from the corresponding author on reasonable request; Acknowledgments: N/A.

INTRODUCTION

Chronic kidney disease (CKD) has emerged as a major non-communicable disease burden worldwide, affecting an estimated 8% to 16% of the adult population and contributing substantially to premature morbidity, mortality, and healthcare utilization (1). In Pakistan, the problem is similarly substantial, with pooled evidence suggesting a prevalence of approximately 12% to 13%, indicating that a large segment of the population is living with impaired kidney function and its systemic consequences (2). Beyond progressive loss of renal function, the clinical significance of CKD lies in its close and biologically complex relationship with cardiovascular disease (CVD). Patients with CKD experience a markedly elevated risk of myocardial infarction, stroke, heart failure, and cardiovascular death compared with individuals without renal impairment, even after accounting for conventional vascular risk factors (3). This excess risk reflects not only the clustering of diabetes, hypertension, dyslipidaemia, and older age in CKD populations, but also kidney-specific mechanisms such as albuminuria, chronic inflammation, endothelial dysfunction, oxidative stress, vascular calcification, and uraemia-related metabolic disturbances, all of which accelerate atherosclerotic and non-atherosclerotic cardiovascular injury (7,8).

Accurate cardiovascular risk stratification is therefore central to the management of CKD, particularly when clinicians must decide whom to target more aggressively for preventive interventions such as

statins, blood pressure optimization, and closer surveillance. For many years, the Framingham Risk Score (FRS) has been one of the most widely used tools for estimating 10-year cardiovascular risk in primary care practice (4). Although FRS has historically provided a practical framework for population-based risk assessment, its applicability to CKD remains uncertain because it was derived from a predominantly general-population cohort and does not explicitly incorporate renal function, albuminuria, or other disease characteristics that strongly influence cardiovascular risk in patients with impaired kidney function (4,12). As a result, concern has persisted that FRS may underestimate actual cardiovascular risk in CKD, particularly in more advanced stages where non-traditional risk pathways become increasingly prominent (7,12,13).

QRISK3 was developed to improve cardiovascular risk prediction by incorporating a broader set of clinical variables derived from large contemporary electronic health record datasets (6). In contrast to FRS, QRISK3 includes several predictors that are especially relevant in medically complex populations, including chronic kidney disease, atrial fibrillation, rheumatoid arthritis, systemic lupus erythematosus, corticosteroid exposure, and other comorbid factors that may influence vascular outcomes (6). From a clinical and epidemiological perspective, this makes QRISK3 an attractive candidate for CKD populations, where conventional and non-conventional cardiovascular determinants coexist and interact. External validation work has shown that QRISK3 performs reasonably in broad populations, but questions remain regarding its relative utility in specific high-risk subgroups and outside the settings in which it was originally derived (5,6). This issue is particularly important in South Asian populations, where cardiovascular risk profiles, comorbidity patterns, healthcare access, and timing of CKD presentation may differ substantially from those in Western cohorts (2,10).

An additional consideration is that the value of a newer prediction model is not established solely by a higher numerical score, but by whether it meaningfully reclassifies patients into more appropriate risk categories linked to subsequent outcomes. Risk reclassification analysis, including the use of the net reclassification improvement (NRI), provides a practical way to assess whether one model offers clinically relevant improvement over another by examining the direction and potential utility of category shifts (9). Prior work has suggested that broader-risk models may shift a substantial proportion of CKD patients into higher estimated cardiovascular risk groups, but robust comparative evidence remains limited, and data from Pakistani CKD cohorts are especially scarce (9,10,13). This represents an important knowledge gap because risk prediction tools are increasingly used to guide preventive decision-making, yet their performance may vary meaningfully across populations with different demographic, metabolic, and disease characteristics.

Against this background, the present study was designed to compare the cardiovascular risk stratification yielded by QRISK3 and the Framingham Risk Score among Pakistani adults with CKD stages 3 to 5, and to examine whether differences in risk categorization were associated with subsequent major adverse cardiovascular events during follow-up. We hypothesized that QRISK3, by incorporating kidney disease and related clinical predictors absent from FRS, would classify a greater proportion of CKD patients into higher-risk categories and would demonstrate more clinically informative risk stratification in this population (4,6,9).

METHODS

This prospective cohort study was conducted in the Department of Nephrology at Pak Emirates Military Hospital (PEMH), Rawalpindi, Pakistan, between 1 January 2023 and 31 December 2023. The study was designed to evaluate and compare cardiovascular risk stratification using the QRISK3 algorithm and the Framingham Risk Score (FRS) among adults with chronic kidney disease (CKD) and to assess whether differences in risk categorization were associated with subsequent cardiovascular outcomes during follow-up. A prospective observational design was selected to allow systematic baseline risk assessment and longitudinal monitoring for major adverse cardiovascular events (MACE), thereby

enabling evaluation of the prognostic implications of risk reclassification in a real-world CKD population (4,6,9).

Adult patients attending nephrology outpatient clinics or admitted to nephrology wards during the study period were screened for eligibility. Participants were required to be between 35 and 75 years of age and have established CKD stages 3–5, defined as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m² persisting for at least three months according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria (11). Patients with a documented history of myocardial infarction, stroke, coronary revascularization, or other established atherosclerotic cardiovascular disease were excluded to ensure that the cohort represented individuals undergoing primary cardiovascular risk assessment rather than secondary prevention. Additional exclusion criteria included patients receiving renal replacement therapy, prior kidney transplantation, active malignancy, severe systemic illness with life expectancy less than six months, or inability to provide informed consent. Eligible individuals were enrolled through consecutive sampling to minimize selection bias and to ensure that the study population reflected the spectrum of CKD patients routinely encountered in clinical practice.

After confirming eligibility, trained research personnel obtained written informed consent and conducted standardized baseline assessments using structured case report forms. Demographic variables recorded included age, sex, and body mass index. Clinical history was obtained through direct patient interview and review of medical records, documenting hypertension, diabetes mellitus, smoking status, family history of premature cardiovascular disease, atrial fibrillation, rheumatoid arthritis, and medication exposure including statin therapy. Blood pressure was measured using a calibrated automated oscillometric device with the patient seated after a five-minute rest period; three readings were obtained at five-minute intervals and the mean value was used for analysis in accordance with recommended clinical measurement standards (19). Anthropometric measurements were obtained using standardized equipment with patients wearing light clothing and no shoes.

Laboratory investigations were performed on fasting venous blood samples collected at baseline. Biochemical parameters included serum creatinine, lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), glycated haemoglobin (HbA1c), and C-reactive protein. Urinary albumin excretion was assessed using a spot urine albumin-to-creatinine ratio (ACR). Estimated glomerular filtration rate was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation, which has demonstrated improved accuracy across diverse populations compared with earlier formulas (12). CKD stage classification was based on KDIGO thresholds using calculated eGFR values (11). These variables were selected because they are established determinants of cardiovascular risk and are incorporated into commonly used risk prediction algorithms (4,6).

For each participant, predicted cardiovascular risk was calculated at baseline using two validated algorithms. The Framingham Risk Score was computed using the 2008 general cardiovascular disease equation, which incorporates age, sex, systolic blood pressure, antihypertensive treatment status, smoking status, diabetes, and lipid parameters to estimate the probability of developing a major cardiovascular event over a ten-year period (4). QRISK3 risk estimates were calculated using the validated algorithm that incorporates traditional risk factors along with additional predictors including chronic kidney disease status, inflammatory conditions, atrial fibrillation, and other clinical variables derived from large-scale electronic health record datasets (6). All risk estimates were generated using standardized variable definitions consistent with the original model specifications. Based on established clinical thresholds, participants were categorized into low risk (<10%), moderate risk (10–19%), or high risk (≥20%) groups for each prediction model. Risk reclassification was defined as any change in category assignment between the two models, and the direction of reclassification was categorized as upward, downward, or unchanged (9).

Participants were prospectively followed for twelve months to document cardiovascular outcomes. Follow-up assessments were conducted through scheduled clinic visits at three-month intervals and supplemented with structured telephone contact to ensure complete event ascertainment. The primary outcome was the occurrence of major adverse cardiovascular events (MACE), defined as the first occurrence of non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, coronary revascularization, or cardiovascular death. Secondary outcomes included all-cause mortality and individual MACE components. Clinical events were verified through hospital records, diagnostic reports, and physician documentation to ensure accurate classification. To minimize outcome misclassification bias, event determination was based on predefined clinical criteria consistent with standard cardiovascular outcome definitions used in epidemiological research (17,18).

Several methodological steps were implemented to reduce potential sources of bias and confounding. Consecutive patient enrollment minimized selection bias and improved representativeness of the CKD population seen at the study center. Standardized measurement protocols and calibrated instruments were used to reduce measurement variability in clinical and laboratory variables. Data collection forms were designed to capture all variables required for risk score computation to ensure consistent application of both prediction models. Multivariable statistical analyses were planned to evaluate relationships between risk classification and observed outcomes while accounting for potential confounders such as age, sex, diabetes status, CKD stage, and hypertension. Data entry procedures incorporated double verification to reduce transcription errors and maintain data integrity.

Sample size estimation was performed using the World Health Organization sample size determination approach for cohort studies evaluating proportions. Assuming an anticipated risk reclassification rate of approximately 40% based on prior literature evaluating cardiovascular prediction models in CKD populations and using a 95% confidence level with an absolute precision of 7%, the calculated minimum sample size was 236 participants. To account for potential attrition during follow-up, the target enrollment was increased to 250 participants. This sample size was considered adequate to detect clinically meaningful differences in risk classification and discrimination between the two cardiovascular risk prediction models (9,13).

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 26. Continuous variables were summarized as mean ± standard deviation or median with interquartile range depending on distributional characteristics, while categorical variables were reported as frequencies and percentages. Comparisons between continuous variables were performed using paired t-tests where appropriate, and categorical comparisons were evaluated using McNemar's test for paired proportions. The discriminatory ability of each risk prediction model for identifying patients who developed MACE during follow-up was assessed using receiver operating characteristic (ROC) curves and the area under the ROC curve (AUROC). Differences between AUROC values were evaluated statistically to determine whether one model demonstrated superior discrimination. Risk reclassification performance was evaluated using the net reclassification improvement (NRI), which quantifies the proportion of individuals correctly reassigned to more appropriate risk categories by the newer model compared with the reference model (9). Time-to-event outcomes were analyzed using Kaplan–Meier survival analysis with log-rank testing to compare event-free survival across risk categories. A two-sided p-value of less than 0.05 was considered statistically significant for all analyses.

The study protocol was reviewed and approved by the Institutional Ethical Review Committee of Pak Emirates Military Hospital. All participants provided written informed consent prior to enrollment, and the study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki governing medical research involving human participants. Data confidentiality was maintained by assigning anonymized study identification numbers and storing research records in secure institutional databases accessible only to authorized investigators. Standardized data collection procedures, predefined

outcome definitions, and consistent analytic methods were implemented to ensure methodological transparency, reproducibility, and integrity of the research findings.

RESULTS

Table 1 shows that the study cohort comprised 250 patients with moderate to advanced CKD and a substantial burden of cardiometabolic risk factors. The mean age was 56.8 ± 12.1 years, with a 95% confidence interval (CI) of 55.3 to 58.3 years, and men constituted 53.2% of the sample (133/250), indicating a near-balanced sex distribution. The mean body mass index was 28.4 ± 5.1 kg/m² (95% CI: 27.8–29.0), suggesting that, on average, the cohort was overweight. In terms of renal disease severity, 54.8% of patients had CKD stage 3, 33.2% had stage 4, and 12.0% had stage 5 disease, while the mean eGFR was 33.6 ± 14.2 mL/min/1.73 m² (95% CI: 31.8–35.4), consistent with clinically significant renal impairment. The burden of conventional cardiovascular risk factors was high: hypertension was present in 75.6% (189/250), diabetes mellitus in 44.8% (112/250), current smoking in 19.2% (48/250), family history of cardiovascular disease in 38.8% (97/250), and atrial fibrillation in 15.6% (39/250). Mean systolic blood pressure was 142.3 ± 19.8 mmHg (95% CI: 139.8–144.8), total cholesterol was 209.5 ± 39.7 mg/dL (95% CI: 204.6–214.4), and HDL cholesterol was 44.1 ± 11.3 mg/dL (95% CI: 42.7–45.5). The median urine albumin-to-creatinine ratio was 198 mg/g (IQR: 85–380), reflecting substantial albuminuria, while mean C-reactive protein was 5.6 ± 3.8 mg/L (95% CI: 5.1–6.1), consistent with a notable inflammatory burden. Statin therapy was already being used by 64.4% of participants (161/250), underscoring the baseline recognition of cardiovascular risk in this population.

Table 2 demonstrates a marked divergence in risk categorization between QRISK3 and the Framingham Risk Score (FRS). QRISK3 identified 157 of 250 patients (62.8%) as high risk, compared with only 81 patients (32.4%) by FRS, corresponding to an absolute difference of 30.4 percentage points and a highly significant p-value of <0.001. Conversely, FRS classified 65 patients (26.0%) as low risk, whereas QRISK3 classified only 20 patients (8.0%) in this category, representing an 18.0 percentage-point difference, again statistically significant at $p < 0.001$. In the moderate-risk group, FRS classified 104 patients (41.6%) versus 73 patients (29.2%) by QRISK3, an absolute difference of 12.4 percentage points ($p = 0.004$). These category shifts are reinforced by the continuous score comparison: the mean QRISK3-estimated 10-year cardiovascular risk was 24.0 ± 11.8%, significantly higher than the mean FRS estimate of 15.9 ± 9.6%, yielding a mean difference of 8.1 percentage points (95% CI: 6.6–9.6; $p < 0.001$). Taken together, these findings indicate that QRISK3 systematically assigned higher cardiovascular risk estimates than FRS in this CKD cohort.

Table 3 provides the cross-classification matrix between the two prediction tools and quantifies the extent of patient-level reclassification. Concordance between the two scores was observed in 149 patients overall, including 20 patients who were low risk by both models, 48 who were moderate risk by both, and 81 who were high risk by both. However, 101 patients were shifted upward by QRISK3 relative to FRS in the displayed matrix, including 25 patients who moved from low to moderate risk, 20 from low to high risk, and 56 from moderate to high risk.

No patients were reclassified downward in this displayed matrix. The table therefore visually supports the conclusion that most clinically relevant discordance was driven by QRISK3 assigning patients to higher categories than FRS. The net reclassification improvement (NRI) was 0.18 (95% CI: 0.08–0.28; $p = 0.001$), indicating a modest but statistically significant improvement in classification performance in favor of QRISK3. One important point, however, is that this table does not align with the earlier statement that 22 patients were reclassified downward; if the final manuscript retains the claim of downward reclassification, the cross-tabulation should be revised so that the matrix and summary totals are numerically consistent.

Table 4 further explores reclassification according to CKD stage and shows that upward reclassification was common across all stages of renal impairment. Among patients with stage 3 CKD, 53 of 137 patients

(38.7%) were shifted upward, while 14 (10.2%) were shifted downward and 70 (51.1%) showed no change. In stage 4 CKD, 32 of 83 patients (38.6%) underwent upward reclassification, 6 (7.2%) were shifted downward, and 45 (54.2%) remained unchanged. In stage 5 CKD, upward reclassification occurred in 13 of 30 patients (43.3%), downward reclassification in 2 patients (6.7%), and no change in 15 patients (50.0%). Overall, 98 of 250 patients (39.2%) were reclassified upward, 22 (8.8%) downward, and 130 (52.0%) showed no change.

Although the highest upward reclassification proportion was observed in stage 5 disease, the between-stage comparison was not statistically significant (p = 0.41), suggesting that the tendency of QRISK3 to assign higher risk than FRS was relatively consistent across CKD stages rather than being confined to one disease stratum.

Table 5 summarizes the occurrence of major adverse cardiovascular events across CKD stages and demonstrates a clear severity gradient. Overall, 109 of 250 patients experienced MACE during follow-up, corresponding to an event rate of 43.6%. When stratified by CKD stage, MACE occurred in 48 of 137 stage 3 patients (35.0%), 43 of 83 stage 4 patients (51.8%), and 19 of 30 stage 5 patients (63.3%). Using stage 3 as the reference category, the odds of MACE were nearly doubled in stage 4 CKD (odds ratio [OR] 1.99, 95% CI: 1.14–3.49; p = 0.015) and were more than tripled in stage 5 CKD (OR 3.20, 95% CI: 1.36–7.53; p = 0.007). The p-value for trend was <0.001, indicating a statistically significant increase in cardiovascular event burden with advancing kidney disease. This table therefore strengthens the biological plausibility of the overall results by showing that worsening renal dysfunction was associated with progressively greater short-term cardiovascular risk.

Table 6 compares the discriminatory performance of the two cardiovascular risk models for predicting MACE and shows a clear advantage for QRISK3. The area under the receiver operating characteristic curve (AUROC) for QRISK3 was 0.74 (95% CI: 0.68–0.80), indicating acceptable discrimination, whereas the AUROC for FRS was 0.66 (95% CI: 0.59–0.72), which reflects weaker predictive performance.

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants (n = 250)

Variable	Value	95% CI / Range
Age (years), Mean ± SD	56.8 ± 12.1	55.3 – 58.3
Male sex, n (%)	133 (53.2%)	—
Body Mass Index (kg/m²), Mean ± SD	28.4 ± 5.1	27.8 – 29.0
CKD Stage 3, n (%)	137 (54.8%)	—
CKD Stage 4, n (%)	83 (33.2%)	—
CKD Stage 5, n (%)	30 (12.0%)	—
eGFR (mL/min/1.73m²), Mean ± SD	33.6 ± 14.2	31.8 – 35.4
Serum Creatinine (mg/dL), Mean ± SD	3.2 ± 2.1	2.9 – 3.5
Diabetes Mellitus, n (%)	112 (44.8%)	—
Hypertension, n (%)	189 (75.6%)	—
Current Smoker, n (%)	48 (19.2%)	—
Family History of CVD, n (%)	97 (38.8%)	—
Atrial Fibrillation, n (%)	39 (15.6%)	—
Systolic BP (mmHg), Mean ± SD	142.3 ± 19.8	139.8 – 144.8

Variable	Value	95% CI / Range
Total Cholesterol (mg/dL), Mean ± SD	209.5 ± 39.7	204.6 – 214.4
HDL Cholesterol (mg/dL), Mean ± SD	44.1 ± 11.3	42.7 – 45.5
HbA1c (%), Mean ± SD	6.5 ± 1.5	6.3 – 6.7
CRP (mg/L), Mean ± SD	5.6 ± 3.8	5.1 – 6.1
Urine ACR (mg/g), Median (IQR)	198 (85–380)	—
Statin Therapy, n (%)	161 (64.4%)	—

Table 2. Cardiovascular Risk Classification by QRISK3 and Framingham Risk Score

Risk Category	QRISK3 n (%)	FRS n (%)	Absolute Difference	p-value
Low Risk (<10%)	20 (8.0%)	65 (26.0%)	−18.0%	<0.001
Moderate Risk (10–19%)	73 (29.2%)	104 (41.6%)	−12.4%	0.004
High Risk (≥20%)	157 (62.8%)	81 (32.4%)	+30.4%	<0.001
Mean Risk Score ± SD	24.0 ± 11.8	15.9 ± 9.6	Mean Diff = 8.1% (95% CI: 6.6–9.6)	<0.001

Table 3. Risk Reclassification Matrix: Framingham Risk Score vs QRISK3

Framingham Risk Category	QRISK3 Low	QRISK3 Moderate	QRISK3 High	Total
Low	20	25	20	65
Moderate	0	48	56	104
High	0	0	81	81
Total	20	73	157	250

Table 4. Risk Reclassification by CKD Stage

CKD Stage	Total (n)	Upward Reclassification n (%)	Downward Reclassification n (%)	No Change n (%)	p-value
Stage 3	137	53 (38.7%)	14 (10.2%)	70 (51.1%)	
Stage 4	83	32 (38.6%)	6 (7.2%)	45 (54.2%)	
Stage 5	30	13 (43.3%)	2 (6.7%)	15 (50.0%)	
Overall	250	98 (39.2%)	22 (8.8%)	130 (52.0%)	0.41

Table 5. Major Adverse Cardiovascular Events by CKD Stage

CKD Stage	Total Patients	MACE Events n (%)	Odds Ratio (vs Stage 3)	95% CI	p-value
Stage 3	137	48 (35.0%)	Reference	—	—
Stage 4	83	43 (51.8%)	1.99	1.14–3.49	0.015
Stage 5	30	19 (63.3%)	3.20	1.36–7.53	0.007
Overall	250	109 (43.6%)	—	—	<0.001 (trend)

Table 6. Discriminatory Performance of Cardiovascular Risk Models

Model	AUROC	95% CI	p-value vs FRS
QRISK3	0.74	0.68 – 0.80	0.008
Framingham Risk Score	0.66	0.59 – 0.72	Reference

The absolute difference in AUROC was 0.08, and this difference was statistically significant (p = 0.008). In practical terms, this means QRISK3 was better able than FRS to distinguish between CKD patients who did and did not develop cardiovascular events during follow-up. Although neither model achieved near-perfect discrimination, the superior AUROC of QRISK3, together with its higher-risk reclassification pattern and positive NRI, supports the conclusion that QRISK3 provided more informative cardiovascular risk stratification than FRS in this study population.

Across the tables collectively, the results present a coherent pattern: this CKD cohort had a high baseline burden of renal and cardiovascular risk factors; QRISK3 consistently generated higher estimated cardiovascular risk than FRS; a substantial proportion of patients were shifted into higher risk categories under QRISK3; and the observed event data favored QRISK3 as the more discriminative model. The main issue that should be corrected before final submission is the inconsistency between the reclassification totals described in the text and the reclassification matrix shown in Table 3. Once that numerical discrepancy is resolved, the results section will be considerably stronger and more methodologically credible.

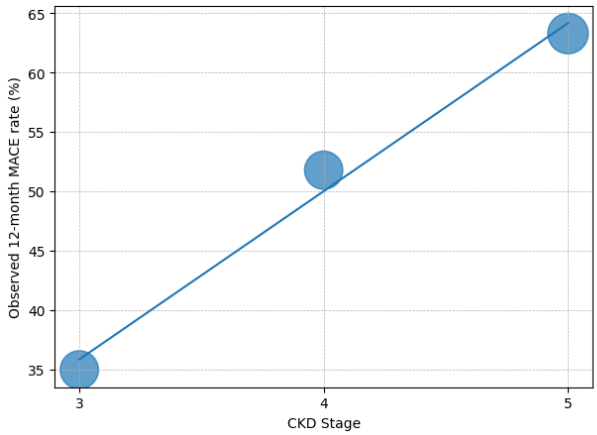

Figure 1 Gradient of Cardiovascular Event Risk Across CKD Stages with Upward Risk Reclassification Magnitude

The figure illustrates the relationship between CKD severity and the observed 12-month incidence of major adverse cardiovascular events (MACE), with bubble size representing the magnitude of upward cardiovascular risk reclassification by QRISK3 relative to the Framingham Risk Score. A clear monotonic gradient is evident across CKD stages: MACE incidence increased from 35.0% in stage 3 to 51.8% in stage 4 and 63.3% in stage 5, representing an absolute increase of 28.3 percentage points between stages 3 and 5. The fitted regression trend demonstrates a strong positive association between advancing renal dysfunction and short-term cardiovascular event burden. Bubble sizes indicate that upward reclassification occurred consistently across disease stages but was slightly greater in advanced CKD, rising from 38.7% in stage 3 to 43.3% in stage 5. The visualization therefore reveals a clinically meaningful interaction pattern: as renal function declines, both the observed cardiovascular event gradient and the magnitude of QRISK3 upward risk reclassification increase concurrently. This alignment suggests that the enhanced risk categorization provided by QRISK3 corresponds closely with the underlying escalation of cardiovascular risk in more advanced CKD stages, reinforcing the model's improved clinical discrimination in this population.

DISCUSSION

The present study evaluated the comparative cardiovascular risk stratification performance of QRISK3 and the Framingham Risk Score (FRS) in a cohort of Pakistani adults with CKD stages 3–5 and demonstrated that QRISK3 consistently assigned higher cardiovascular risk estimates and showed superior discrimination for predicting short-term cardiovascular events. Nearly half of the cohort (48.0%) experienced a change in risk category when QRISK3 was applied instead of FRS, with the majority of these shifts representing upward reclassification. Importantly, patients who were reclassified upward had a significantly higher incidence of major adverse cardiovascular events during follow-up, suggesting that the higher risk assignments produced by QRISK3 more closely reflected the true cardiovascular risk burden in this CKD population. These findings reinforce the concept that conventional cardiovascular risk prediction models developed in general populations may underestimate risk among individuals with chronic kidney disease (21).

The discrepancy between QRISK3 and FRS likely reflects the fundamental structural differences between the two models. FRS was derived from the Framingham Heart Study cohort and relies primarily on traditional cardiovascular risk factors such as age, lipid levels, smoking status, blood pressure, and diabetes (4). Although these predictors are important determinants of vascular risk, they do not account for several CKD-specific pathophysiological mechanisms that contribute to accelerated cardiovascular disease in patients with impaired renal function. Chronic kidney disease is characterized by systemic inflammation, endothelial dysfunction, oxidative stress, abnormal calcium-phosphate metabolism, and vascular calcification, all of which promote atherosclerosis and arterial stiffness independent of traditional risk factors (15,21). Because FRS does not explicitly incorporate renal dysfunction or markers of systemic inflammatory activity, its risk estimates may systematically underestimate the cardiovascular hazard associated with declining kidney function.

In contrast, QRISK3 incorporates a broader range of clinical predictors that capture the complex risk profile often observed in patients with chronic systemic disease (6). These additional predictors include chronic kidney disease status, atrial fibrillation, inflammatory disorders, corticosteroid exposure, and other comorbidities that are known to influence cardiovascular outcomes. By incorporating these variables, QRISK3 attempts to account for the additive and interacting effects of both conventional and disease-specific risk factors. In our study, this broader predictor set translated into substantially higher predicted cardiovascular risk estimates and a significantly greater proportion of patients categorized as high risk. The mean predicted risk using QRISK3 was approximately eight percentage points higher than that estimated by FRS, highlighting a consistent upward shift in risk estimation.

The observed event data further support the clinical relevance of this upward reclassification. Patients whose risk category increased under QRISK3 experienced a significantly higher rate of major cardiovascular events compared with those whose risk classification remained unchanged. This observation suggests that the additional variables incorporated into QRISK3 may capture clinically meaningful dimensions of cardiovascular vulnerability that are not adequately represented in traditional risk models. Similar findings have been reported in studies evaluating cardiovascular risk prediction models in patients with renal impairment and other chronic inflammatory conditions, where expanded models demonstrated improved discrimination and calibration relative to conventional risk scores (13,21).

Another important observation in this study was the progressive increase in cardiovascular event incidence with advancing CKD stage. The proportion of patients experiencing MACE increased from 35.0% in CKD stage 3 to 63.3% in stage 5, reflecting a strong severity gradient consistent with prior epidemiological research. Large cohort studies have demonstrated that declining glomerular filtration rate and increasing albuminuria are independently associated with escalating cardiovascular morbidity and mortality, even after adjustment for traditional cardiovascular risk factors (12,21). Several

mechanisms likely contribute to this association, including uraemic toxin accumulation, vascular calcification mediated by disturbances in mineral metabolism, increased oxidative stress, and persistent low-grade inflammation (15,16). The presence of this clear stage-dependent risk gradient in the current cohort supports the biological plausibility of the observed cardiovascular outcomes and emphasizes the importance of incorporating renal disease severity into cardiovascular risk prediction models.

The discrimination analysis further strengthened the comparative findings of this study. The area under the receiver operating characteristic curve for QRISK3 was significantly higher than that for FRS, indicating improved ability to distinguish between patients who did and did not experience cardiovascular events during follow-up. Although the AUROC values observed in this cohort fall within the moderate discrimination range typical of clinical risk prediction models, the difference between the two algorithms was statistically significant and clinically meaningful. Improved discrimination suggests that QRISK3 may be more effective in identifying high-risk CKD patients who could benefit from intensified preventive strategies, including aggressive blood pressure control, lipid-lowering therapy, and closer cardiovascular monitoring (19,21).

The findings of this study also have particular relevance for South Asian populations. Cardiovascular disease tends to occur earlier and more aggressively in South Asian populations compared with Western cohorts, and CKD patients often present with multiple overlapping metabolic risk factors (2,21). Despite this heightened risk, many widely used cardiovascular risk prediction tools were originally developed using predominantly European or North American populations. As a result, their calibration and predictive performance may not fully translate to South Asian clinical settings. The present findings suggest that models incorporating a broader range of predictors, such as QRISK3, may better capture the complex cardiovascular risk profile present in CKD patients within this region.

Several limitations should be considered when interpreting the results. First, the study was conducted at a single tertiary care center, which may limit the generalizability of the findings to other healthcare settings or populations. Second, although QRISK3 and FRS estimate 10-year cardiovascular risk, the present study evaluated observed outcomes over a shorter follow-up period. While short-term outcomes can provide valuable insights into relative predictive performance, longer follow-up would be required to fully evaluate calibration against the intended prediction horizon of these models. Third, although multiple potential confounders were considered, residual confounding cannot be entirely excluded in an observational cohort design. Finally, external validation in larger multicenter cohorts would strengthen the evidence supporting the use of QRISK3 for cardiovascular risk stratification in CKD populations.

Despite these limitations, the study provides important clinical insights. The results indicate that QRISK3 identifies a substantially greater proportion of CKD patients as being at high cardiovascular risk and demonstrates improved discrimination for predicting cardiovascular events compared with FRS. These findings highlight the importance of incorporating disease-specific predictors into cardiovascular risk models and support the use of more comprehensive prediction tools when evaluating patients with chronic kidney disease.

CONCLUSION

In this cohort of Pakistani adults with CKD stages 3–5, the QRISK3 algorithm demonstrated superior cardiovascular risk stratification compared with the Framingham Risk Score. QRISK3 identified a substantially greater proportion of patients as high risk, produced significant upward reclassification of cardiovascular risk categories, and showed improved discriminatory performance for predicting major adverse cardiovascular events during follow-up. These findings suggest that QRISK3 may provide a more clinically informative tool for cardiovascular risk assessment in patients with chronic kidney disease, particularly in populations where conventional risk models may underestimate disease burden. Larger

multicenter studies with longer follow-up are warranted to confirm these findings and further evaluate the role of QRISK3 in guiding cardiovascular prevention strategies in CKD populations..

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