Comparing Cardiovascular Event Risk Prediction Tools in Nigerians with Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease with increased cardiovascular event risk. The Framingham risk calculator is considered less accurate for RA patients. The QRISK and ERS-RA calculators were developed in response to these issues but have never been used by Nigerians. This study compared all three calculators to determine which one best estimates the 10-year cardiovascular event risk of patients with rheumatoid arthritis attending the rheumatology clinic of Jos University Teaching Hospital.

Methods: This was a hospital-based cross-sectional study carried out between 2019 and 2022 in the rheumatology clinic of Jos University Teaching Hospital (JUTH). Eighty-five RA patients aged 30 years and above who met the inclusion criteria were recruited consecutively. Framingham risk, QRISK3 and the ERS-RA scores were calculated for each patient, and their level of agreement was determined using Kappa statistics. Data was analysed using STATA version 14; a P value < 0.05 was considered statistically significant.

Result: There were 60 females and 25 males, with a mean age of 52.5±12.5 years. The median (IQR) scores for Framingham and QRISK3 were 6.3% (2.8-11.7%) and 4.8% (1.9-12.7%) respectively. Agreement between Framingham and QRISK3 was 93% (low-risk), 73.3% (intermediate risk) and 92.3% (high-risk) estimates. The ERS-RA calculator had the highest prediction in fair to moderate agreement with the Framingham and the QRISK calculators.

Conclusion: The RA-specific ERS-RA calculator predicted more CVD risk than the general population's QRISK3 and Framingham risk scores. We therefore recommend the ERS-RA calculator for use in our RA population.

Keywords: Rheumatoid Arthritis, cardiovascular risk, Framingham, QRISK3, ERS-RA, Nigeria.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease predominantly affecting the joint, with varied extra-articular manifestations. It has a global prevalence of 0.5 – 1%[1] and a prevalence of 0.3% in Nigeria.[2] Cardiovascular disease is the most common cause of death in patients with rheumatoid arthritis, accounting for more than half of such mortality.[3-5] The increased cardiovascular mortality seen in RA is mainly due to ischemic heart diseases, including acute coronary syndromes, myocardial infarction and congestive cardiac failure, compared to other forms of cardiac deaths.[4] The risk of cardiac disease in RA patients is said to be two-fold higher compared to the general population, and traditional risk factors like cigarette smoking, obesity, hypertension, insulin resistance and dyslipidaemia cannot fully explain the excess risk.[3,5,6] Chronic inflammation, physical inactivity resulting from joint pain and swelling, depression, stress, and side effects of drugs like Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and glucocorticoids worsen the risk of cardiovascular diseases in RA patients.[3,6] The European Alliance for Rheumatology (EULAR) recommends that cardiovascular risk scores adapted for RA patients should be multiplied by a factor of 1.5 to account for these additional factors when at least two of the following: RA duration >10 years, rheumatoid factor and/or Anti-Cyclic Citrullinated Protein (ACCP) positivity and severe extra-articular manifestations are present.[6,7]

In Nigeria, the burden of traditional modifiable risk factors for cardiovascular diseases, including obesity, pre-diabetes, diabetes and hypertension, has been on the increase mainly due to increasing urbanisation and changing lifestyles.[8-11] Over 22% of Nigerians are estimated to have a moderate to high risk of developing a cardiovascular event in the next ten years using the Framingham risk calculator.[12,13] However, the Framingham calculator is considered unreliable for rheumatoid arthritis patients because it focuses on traditional cardiovascular risk factors like age, gender, smoking, hypertension and dyslipidaemia without accounting for the additional risk factors identified in RA patients. This resulted in the development of the QRESEARCH cardiovascular risk algorithm (QRISK3) calculator, which takes cognisance of additional risk factors such as ethnicity, body mass index (BMI), family history of CVD, and comorbidities and incorporates RA as an independent risk factor for CVD events. More recently, the Expanded Cardiovascular Risk Score for RA (ERS-RA) criteria was developed as RA - specific CVD risk calculator because it includes specific RA variables like RA duration, clinical disease activity index (CDAI), disability index (HAQ-DI), and prednisolone use in its estimates.[14]

While previous documentation of Nigerians' cardiovascular risk has been made, attention has not been paid to special groups like those with rheumatic diseases who suffer from chronic inflammatory disorders. Therefore, rheumatologists in Nigeria and sub-Saharan Africa have relied on studies from Europe that indicate patients with rheumatoid arthritis have excess cardiovascular disease risk compared to the general population. That assumption has been guiding the way Nigerians with rheumatoid arthritis are assessed and managed for cardiovascular risk without any local data. We compared the Framingham criteria, Q-RISK3 and the ERS-RA calculators in estimating the 10-year cardiovascular event risk of patients with rheumatoid arthritis attending the rheumatology clinic of Jos University Teaching Hospital to determine which one is most likely to better estimate CVD risk in our population.

Patients and methods

Study design and setting

This was a hospital-based cross-sectional study carried out between 2019 and 2022 in the rheumatology clinic of Jos University Teaching Hospital (JUTH). Jos University Teaching Hospital is the only accredited postgraduate rheumatology training institution in north-central Nigeria, receiving referrals from all six regional and neighbouring states.

Study population

The target population was all rheumatoid arthritis patients aged 30 years and above attending the rheumatology clinic of JUTH, fulfilling the revised 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) criteria for the classification of rheumatoid arthritis.[15] The inclusion was limited to those 30 years or older because the Framingham risk calculator is only valid for persons aged 30 years and above. Patients with other autoimmune diseases, rheumatoid arthritis overlap syndromes, and other comorbidities that have a direct impact on the cardiovascular system, such as chronic liver disease and hyper or hypothyroidism, were excluded. The estimated minimum sample size for the study was 80, using the sample size calculation for an infinite population with a finite correction.[16] A convenience sampling method was used to recruit 85 subjects who met the inclusion criteria to participate in the study.

Ethical considerations

Ethical approval with clearance number JUTH/DCS/ADM/127/XXVII/800 was obtained from the Human Research Ethics Committee of the Jos University Teaching Hospital. Written informed consent was also obtained from the participants. The study was carried out in full compliance with the principles of the Helsinki Declaration.

Study Procedure

A proforma was designed to obtain information on socio-demographic and relevant RA data. while the Stanford Health Assessment Questionnaire (HAQ) was used to assess the activities of daily living and graded from 0 (no disability) to 3 (severe disability) and a functional disability index (FDI) was calculated from the HAQ scores. Both questionnaires were administered by a trained research assistant, who also ensured that patients carried out the appropriate investigations. Weight was recorded in kilograms to the nearest 0.1kg using a flat scale on a firm horizontal surface with participants wearing only light clothes and without shoes and headgear. Height was measured without shoes, caps or headgear with subjects standing erect on a stadiometer. Measurements were taken to the nearest 0.01-meter. The body mass index (BMI) was calculated from weight in kilograms (kg) divided by the height in meter squared (m^2). Pulse rate and blood pressure were measured after five minutes of rest. The blood pressure was measured using a mercury sphygmomanometer in a sitting position with the arm at the level of the heart. Systolic blood pressure was recorded at phase one of the Korotkoff sound and diastolic blood pressure was recorded at phase five. Three readings were taken and the average of the best two readings was recorded. All peripheral and central pulses were assessed; the cardiac apex and heart sounds were also documented.

Metabolic profiles, including fasting blood sugar, electrolytes, creatinine, uric acid, urea, lipid profile, complete blood count, and erythrocyte sedimentation rate (ESR), were performed in JUTH laboratory. Hyperlipidaemia was defined as LDL cholesterol $\geq$ 3.4mmol/l and/or the use of lipid-lowering medications; hypertension was defined as a blood pressure measurement of $\geq$40/90mmhg or the use of antihypertensive medications; diabetes mellitus was defined as fasting blood sugar $\geq$ 7.0 mmol/l and/or the use of antidiabetic agents and other CVD risk factors reported were defined according to standard definitions.[17-21] Serostatus indicated whether a participant was seropositive or seronegative. Seropositivity meant positive rheumatoid factor and/or anticcp, and seronegative meant both were negative. DAS28ESR and CDAI were calculated using an online calculator from MD+CALC[22]. Framingham risk score was calculated using the Medscape reference calculator based on Framingham risk score 2008. [23] QRISK3 was calculated at the QRISK website [24] and the ERS-RA scores were calculated using the online calculator tool available at the verity research website. [25]

Data management

Data collected in the proforma and the HAQ questionnaire were entered into a Microsoft Excel sheet and subsequently imported into STATA for analysis. STATA IC 14.2 by Stata Corp LLC, Texas, USA, for Macintosh Operating Systems was used to analyse the data. The sociodemographic and clinical characteristics of the study population and the prevalence of cardiovascular risk factors were expressed as frequencies and proportions. Kappa statistics was used to assess the level of agreement between each of the RA-related calculators with the Framingham calculator as the gold standard, and Spearman's correlation coefficient was used to test the relationship between these RA-related risk scores and Framingham risk scores given that the Shapiro-wilk test showed that our data were not normally distributed. A p value < 0.05 was considered statistically significant in all instances.

Results

Eighty-five individuals with a diagnosis of RA participated in the study, the majority of whom were females, 60 (70.5%) with a mean age of 52.5±12.5 years and the mean duration of RA was 2.2±0.6 years. Most participants, 34 (40.0%), had moderate disease activity by DAS28ESR and low disease activity, 30 (35.3%) by CDAI estimation (Kappa 0.53, P<0.0001). Table 1.

Twelve (75.0 %) of the men in the study were 45 years or older, while 31 (44.9%) of the women were 55 years or older. Fifty-one (60.0 %) of the participants had a diagnosis of hypertension and dyslipidemia, while 7 (8.2%) had diabetes. Table 2.

Both the Framingham and the QRISK calculators predicted an almost equal proportion of patients across all categories of cardiovascular event risk with significant agreement, kappa = 0.85, P<0.0001. Figure 1. The median (IQR) Framingham score was 6.3% (2.8-11.7%), while that of QRISK3 was 4.8% (1.9-12.7%). QRISK3 agreed with Framingham in 93.0 % of the low-risk estimates, 73.3% at intermediate risk and 92.3% at high-risk estimates. Table 3. When compared to the Framingham calculator as the gold standard, the QRISK3 calculator had a sensitivity and specificity of 87.5%, respectively, with a Receiver Operating Characteristics (ROC) curve of 0.875 and a confidence interval of 0.79 – 0.95.

Sixty-one (71.8%) of the participants met the criteria for a 1.5 multiplier applied to their Framingham score, leading to the re-categorisation of 7 (8.2%) of them from low-risk to the intermediate risk group and 2 (2.4%) from intermediate to high risk. Table 4

The ERS-RA calculator predicted 36 (42.4%) patients to have a high 10-year CVD risk, in fair to moderate agreement with the Framingham and the QRISK calculators. Table 5.

Table 1. Socio-demographic and clinical characteristics of the study participants

Variable	Frequency (%), n = 85
Age group, years	
30-60	60 (70.6)
>60	25 (29.4)
Mean age (SD) = 52.5±12.5years	
Duration of RA in years	
<1	8 (9.4)
1-5	49 (57.7)
5-10	28 (32.9)
Mean RA duration = 2.2±0.6years	
Sex	
Females	69.0 (81.2)
Males	16.0 (18.8)
Marital status	
Single	7 (8.2)
Married	68 (80.0)
Divorced	1 (1.2)
Widowed	9 (10.6)
Occupation	
Formal	33 (38.8)
Informal	15 (17.7)
Unemployed	26 (30.6)
Retired	11 (12.9)
Erythrocyte Sedimentation Rate (ESR)	
Normal (0-20mm in the first hour)	11 (12.9)
Abnormal (>20mm in the first hour)	74 (87.1)
Serostatus	
Negative	24 (28.2)
Low positive	8 (9.4)
High Positive	53 (62.4)
Disease Activity Score 28 (DAS28)	
Remission	12 (14.2)
Low disease activity	11 (12.9)
Moderate disease activity	34 (40.0)
High disease activity	28 (32.9)
Clinical Disease Activity Index	
Remission	13 (15.3)
Low disease activity	30 (35.3)
Moderate disease activity	23 (27.1)
High disease activity	19 (22.3)
HAQ-DI categories	
Mild-moderate	53 (62.4)
Moderate-severe	26 (30.5)
Severe-very severe	6 (7.1)
Deformity	
Yes	35 (41.2)
No	50 (58.8)
Rheumatoid Nodules	
Yes	6 (7.1)
No	79 (92.9)
Radiological abnormality	
Yes	20 (23.5)
No	65 (76.5)

SD = Standard Deviation, CI = Confidence interval, RA = Rheumatoid Arthritis,
HAQ-DI = Health Assessment Questionnaire Disability index

Table 2. Prevalence of traditional cardiovascular risk factors in RA patients

Variable	Frequency, n (%) n=85	
Age	Yes	No
Male≥45years	12 (75.0)	4 (25.0)
Female ≥55years	31 (44.9)	38 (55.1)
Smoking	6 (7.1)	79 (92.9)
Obesity	26 (30.6)	59 (69.4)
Diabetes	7 (8.2)	78 (91.8)
Hypertension	51 (60.0)	34 (40.0)
Dyslipidemia	51 (60.0)	34 (40.0)
Total cholesterol ≥5.2mmol/l	26 (30.6)	59 (69.4)
LDL cholesterol ≥3.4mmol/l	18 (21.2)	67 (78.8)
HDL cholesterol ≤1mmo/l (Male)	7 (43.7)	9 (56.3)
HDL cholesterol ≤1.3mmo/l (female)	31 (44.9)	38 (55.1)
Chronic Kidney Disease	7 (8.2)	78 (91.8)
Family history of cardiovascular disease	24 (28.2)	61 (71.8)

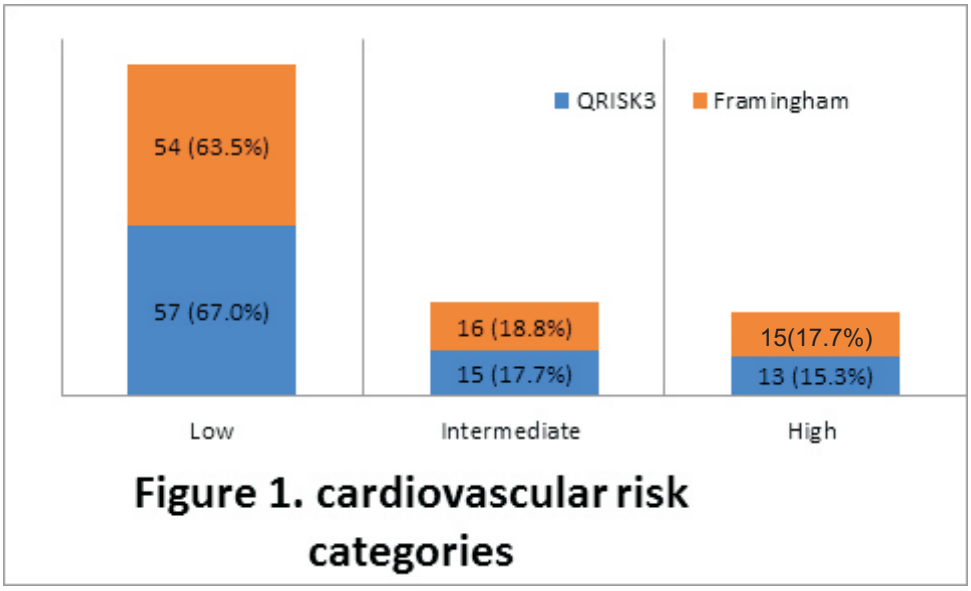

Figure 1. cardiovascular risk categories

Table 3. Kappa agreement of Framingham criteria with QRISK assessment

	QRISK Categories			
Framingham Categories	**Low, n (%)**	**Intermediate, n (%)**	**High, n (%)**	**Total**
Low	53 (93.0)	1 (6.7)	0 (0.0)	54
Intermediate	4 (7.0)	11 (73.3)	1 (7.7)	16
High	0 (0.0)	3 (20.0)	12 (92.3)	15
Total	57(100.0)	15 (100.0)	13 (100.0)	85
Agreement =94.7%, expected agreement = 63.5%, kappa = 0.85, P<0.0001				

n = number, % = percentage

Table 4. Application of the 1.5 multiplier factor to Framingham risk categories

	1.5 Multiplier			
Framingham	**Low, n (%)**	**Intermediate, n (%)**	**High, n (%)**	**Total**
Low	47 (100.0)	7 (33.3)	0 (0.0)	54
Intermediate	0 (0.0)	14 (66.7)	2 (11.8)	16
High	0 (0.0)	0 (0.0)	15 (88.2)	15
Total	47(100.0)	21 (100.0)	17 (100.0)	85

n = number, %=Percentage

Table 5. Comparison between ERS-RA with the general population risk calculators

	ERS-RA		
Framingham	**<7.5, n (%)**	**>7.5, n (%)**	
Low	46 (93.9)	8 (22.2)	Kappa -0.67, P = 1.000
Intermediate	3 (6.1)	13 (36.1)	Kappa 0.32, P = 0.0002
High	0 (0.0)	15 (41.7))	Kappa 0.45, P<0.0001
Total	49 (100.0)	36 (100.0)	
QRISK 2			
Low	49 (100.0)	8 (22.2)	Kappa -0.72, P = 1.000
Intermediate	0 (0.0)	15 (41.7)	Kappa 0.45, P<0.0001
High	0 (0.0)	13 (36.1)	Kappa 0.39, P<0.0001
Total	49 (100.0)	36 (100.0)	

n = number, % = percentage

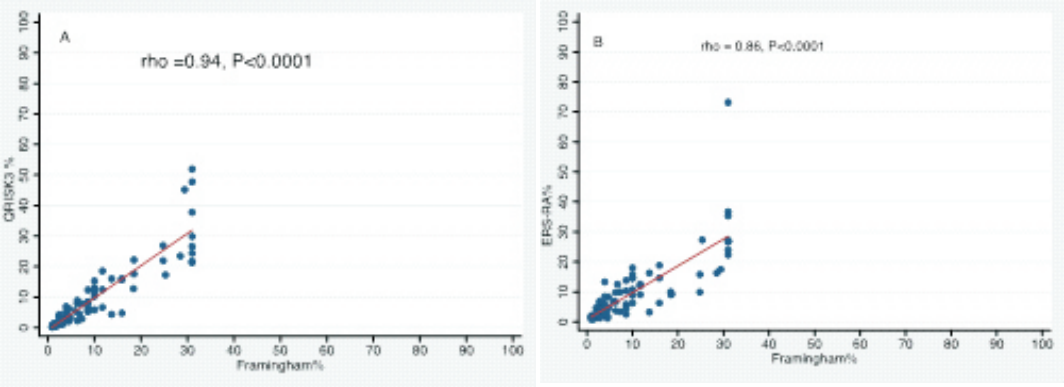

Figure 2: Spearman's correlation of QRISK3 (A) and ERS-RA (B) to the Framingham risk calculator

Discussion

The question of the most appropriate calculator predicting the 10-year cardiovascular event risk in patients with rheumatoid arthritis is still unsettled. While several prediction calculators have been developed in Europe and America, these calculators are mostly designed for the originating populations. In Nigeria, the Framingham risk calculator has long been used to predict cardiovascular events in the general population. However, this is considered less accurate for RA patients as it does not account for it as an independent risk factor. [3,4] Other general population prediction calculators that account for RA as an independent risk factor, such as the QRISK calculator and those that are specific to the RA population, like the ERS-RA calculator, have been developed in response to these issues but have never been used in Nigerians.

The Framingham criteria estimated that 17.7% of our RA population had a high risk of developing a cardiovascular event in 10 years. This is higher

than the 5.2% and 9.8% estimated in the general population of rural Nigeria using the same risk calculator,[13, 26,] agreeing with the established understanding that CVD risk in RA patients is higher than in the general population.[3-6] It was this understanding that led researchers to believe that these general population calculators were not adequately estimating the CVD risk associated with rheumatoid arthritis, and governing bodies like EULAR to prescribe the use of a 1.5 multiplying factor to absolute CVD risk estimates in patients with rheumatoid arthritis.[27,28] However, applying the 1.5 multiplier to our study population only improved the Framingham risk score by 2.4%.

The QRISK3 calculator also found a higher proportion of our patients with RA in the high-risk category compared to the findings in the general population. However, the proportion of individuals rated as high risk was lower than predicted by the Framingham risk calculator even though the QRISK3 calculator considers RA as an independent risk factor and, as such, applied the EULAR recommended multiplier to all RA patients. [27,29.] Other researchers have similarly reported an underestimation of CVD event risk by the QRISK calculator of as much as 12%. [4, 7, 30]

We assessed the relationship between these two general population calculators and found a significant positive correlation and agreement between the two, especially at the extremes of categories (Kappa =0.85, P<0.0001), higher than the kappa of 0.61 previously reported[4]. Even though the QRISK was primarily developed for the UK and Wales population, it does have a specification for ethnic groups, including black Africans, which makes it useful for Nigerians. Also, the Framingham score has been validated among different populations, including Nigeria. [31] Though the controversies of finding the best risk calculator for CVD in RA persist, [14] our study shows that both are equally useful with no significant difference in their predicted values.

The ERS-RA calculator has been shown to improve CVD risk prediction in RA patients because the RA-specific data augments the contribution of the traditional risk factors to CVD event estimates. [3,7] The ERS-RA calculator more than doubled the proportion of our patients in the high-risk CVD group compared to Framingham or QRISK3. Apart from agreeing with those already estimated as high risk by the other two calculators, the ERS-RA calculator also reclassified 81% of those in the Framingham intermediate category and all of those in the QRISK intermediate category into the high-risk category. This suggests that the ERS-RA is a more effective RA-specific CVD calculator than the Framingham or the QRISK3. Contrary to the findings of another study, where the ERS-RA had the lowest mean estimated 10-year CVD risk of 8.8% compared to Framingham (9.1%) and QRISK (15.5%), the mean score for all three calculators were uniform in our population.[7] This difference may have resulted from the differences in the populations studied. Their study involved a diverse population from Europe to North and South America and South Africa, which may have made their data susceptible to differing responses to each of these calculators; ours was a homogenous population whose response is likely to be similar across the board. Though the RA-specific calculators are not considered superior to the general risk scores, ERS-RA appears to better classify the CVD risk in our population with RA.

Our study may be limited by the lack of hard end-points like ischemic heart diseases, stroke, and CVD death, which are available only in prospective studies. This made it impossible to validate these calculators in our population.

Conclusion

The general risk calculators found a higher risk of CVD in our patients with RA than what is obtainable in the general population, and the RA-specific ERS-RA calculator predicted more CVD risk than both the QRISK3 and the Framingham risk scores in our population.

Even though all the risk calculators are useful in predicting cardiovascular event risk in RA, we recommend the ERS-RA calculator as the most useful for our RA population. However, a validation study may still be required.

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