Clinical Rheumatology (2022) 41:3675–3686
https://doi.org/10.1007/s10067-022-06349-y

ORIGINAL ARTICLE

# The comparison of cardiovascular disease risk prediction scores and evaluation of subclinical atherosclerosis in rheumatoid arthritis: a cross-sectional study

**Hafis Muhammed[1] · Durga Prasanna Misra[1] · Neeraj Jain[2] · Sujata Ganguly[1] · Sarit Sekhar Pattanaik[1] · Mohit K. Rai[1] · Anamika Kumari Anuja[1] · Namita Mohindra[2] · Sudeep Kumar[3] · Vikas Agarwal[1]**

Received: 26 June 2022 / Revised: 28 July 2022 / Accepted: 20 August 2022 / Published online: 25 August 2022


## Abstract

**Objectives** Primary objectives estimated prevalence of traditional cardiovascular disease (CVD) risk factors and compared different CVD risk prediction algorithms in an Indian rheumatoid arthritis (RA) population. Secondary objectives evaluated associations between carotid intima-media thickness (CIMT) and subclinical atherosclerosis (SCA) with CVD risk factors and CVD risk scores.

**Methods** The presence of CVD risk factors were recorded, and 10-year CVD risk was predicted using Framingham risk scoring (FRS) using lipids (FRS-Lipids), FRS using body mass index (FRS-BMI), QRISK-2, SCORE, and the algorithm recommended by ACC/AHA (ASCVD). CIMT was measured on the far-wall of the common carotid artery. Subclinical atherosclerosis was defined as CIMT > 0.9 mm or the presence of carotid plaque.

**Results** A total of 332 patents were enrolled, 12% had diabetes mellitus, 21.4% hypertension, and 6.9% were current/past smokers. Proportions of RA with predicted 10-year CVD risk > 10% varied from 16.2 to 41.9% between scores. Highest magnitude of risk was predicted by FRS-BMI. Agreement between scores in predicting risk was moderate in general. Mean CIMT was 0.70 ± 0.15 mm. Age, male sex, and extra-articular manifestations associated with greater CIMT. All risk scores except SCORE moderately correlated with CIMT. About one-seventh had SCA defined as CIMT > 0.9 mm or the presence of carotid plaques, associated with increasing age, male gender, or higher ratio of total cholesterol to high-density lipoprotein cholesterol. ASCVD and QRISK-2 scores had maximum area under curve for distinguishing SCA.

**Conclusion** Individual CVD risk scores predict 10-year CVD risk differently in Indian patients with RA, and require validation for predicting hard end points (CVD events, mortality).

**Key Points**

- *Diabetes mellitus and hypertension are the most prevalent cardiovascular disease risk factors in Indian patients with RA.*
- *Individual cardiovascular risk prediction scores predict risk differently in Indian patients with RA, highest risk being predicted by the FRS-BMI.*
- *Carotid intima-media thickness in RA associated with increasing age, male sex and extra-articular manifestations.*
- *14% RA had subclinical atherosclerosis, associated with increasing age, male sex, and higher total cholesterol to HDL-C ratio, best distinguished by ASCVD and QRISK-2 scores.*

**Keywords** Cardiovascular risk · Carotid intima-media thickness · Risk scores · Rheumatoid arthritis

## Introduction

Patients with rheumatoid arthritis (RA) have increased cardiovascular disease (CVD) morbidity and mortality. The risk of mortality in RA is up to 60% higher than in the general population, contributed in large by CVD [1, 2]. There is conflicting data regarding prevalence of

✉ Durga Prasanna Misra
durgapmisra@gmail.com; dpmisra@sgpgi.ac.in

Extended author information available on the last page of the article

traditional CVD risk factors such as age, diabetes mellitus, hypertension, smoking, dyslipidemia, and obesity. While some studies have shown a higher prevalence of these risk factors in RA patients when compared with general population, other have failed to detect a significant difference [3]. There is a paucity of data on the prevalence of CVD risk factors in Indian patients with RA.

Various algorithms have been developed to predict the risk of CVD events. Commonly used algorithms include Framingham Risk scoring using lipids (FRS-Lipids), Framingham risk scoring using body mass index (FRS-BMI), QRISK cardiovascular disease risk algorithm (QRISK-2), Systemic coronary risk evaluation score (SCORE), and the algorithm recommended by the American College of Cardiology/American Heart Association (ACC/AHA) for atherosclerotic cardiovascular disease (ASCVD) [4–7]. Even though these risk scores are validated in many populations, none have been prospectively validated in the Indian population [8]. Various risk scores are used in clinical practice without homogeneity among clinicians. Understanding the performance of these algorithms is important, as it influences CVD risk mitigation strategies. Among these algorithms, only QRISK-2 considers RA as a predictive variable for CVD risk [6]. In this context, the European Alliance of Associations for Rheumatology (EULAR) has recommended the adaptation of risk prediction models for patients with RA by using a multiplication factor of 1.5 for the calculated CVD risk, if such a correction has not already been included in the said algorithm [9]. Currently, there are no recommendations regarding the preferred CVD risk algorithm in the Indian population. Performance of CVD risk algorithms after modification recommended by EULAR in an Indian population has also not yet been evaluated. The EULAR recommends the use of SCORE to predict 10-year risk in a population where a cardiovascular risk algorithm has not yet been validated [9].

Carotid intima media thickness (CIMT) measured at distal common carotid artery using B-mode ultrasonography is a non-invasive marker of subclinical atherosclerosis (SCA) [10]. CIMT also predicts asymptomatic coronary artery disease [11]. Various studies have identified CIMT as an independent predictor of future CVD events [10]. CIMT has been proposed as an aid to improve CVD risk stratification along with multivariate prediction algorithms [12].

The primary objective of this study was to assess the prevalence of traditional CVD risk factors in Indian patients with RA population, and to compare various CVD risk prediction algorithms (selected based on previous literature adapted to the feasibility in our scenario) [9, 13, 14] after adaptation of EULAR recommendations related to adjustment of calculated risk in patients with RA [9]. As a secondary objective, we also evaluated associations between CIMT and CVD risk scores predicted by various algorithms, as well as associations of CIMT and of SCA with various CVD risk factors.

## Methods

This was a cross-sectional study. The study was approved by the Institute Ethics Committee, SGPGIMS [ethics submission number 2018–5-DM-EXP, letter number PGI/BE/52/2018, date of approval 19 February 2018]. Patients fulfilling the 2010 American College of Rheumatology (ACR)/EULAR criteria for RA [15] attending the hospital out-patient clinic at the Department of Clinical Immunology and Rheumatology at Sanjay Gandhi Post Graduate Institute of Medical Sciences (a tertiary-care teaching referral hospital in North India) were included after seeking written informed consent for participation between March 2018 and December 2019. Those patients who consented to participate were included consecutively. Patients who had pre-existing CVD were excluded. Demographic details, anthropometric measurements, and clinical characteristics were recorded. All patients were screened for the presence of traditional CVD risk factors, i.e., a prevalent diagnosis of diabetes mellitus or hypertension, smoking, family history of CVD, and chronic kidney disease. Lipid profile [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG)] was estimated on fasting serum sample. Serum cytokines IL-6 (R&D Systems, USA), TNF-α (R&D Systems, USA), and IL-1β (R&D Systems, USA) were measured using commercially-procured enzyme-linked immunosorbent assay (ELISA).

A 10-year CVD risk was predicted with FRS-Lipids, FRS-BMI, QRISK-2, SCORE, and ASCVD using online calculators available. Since literature regarding CVD risk scores was unavailable for patients with RA from India, we compared the magnitude of predicted 10-year CVD risk with different risk scores. The choice of FRS-Lipids, FRS-BMI, QRISK-2, and ASCVD scores was based on previous literature which had used these scores in other populations to calculate the predicted 10-year risk of CVD events [13, 14]. The SCORE algorithm was chosen as it was recommended by the EULAR recommendations in vogue at the time the study was planned [9]. Whenever the age of a patient was lesser than the least permissible for calculations using a risk score (ASCVD and SCORE: ≥ 40 years; FRS-Lipids and FRS-BMI: ≥ 30 years, QRISK-2: ≥ 25 years), the lowest age group permissible for calculating that risk score was assumed. All scores except QRISK-2 were multiplied by 1.5 as recommended by the EULAR. If a patients' calculated value exceeded the maximum possible value for the risk score, then the maximum

score that could be predicted by the algorithm was taken as the risk estimate. Patients were classified to "low risk" (< 10% risk of CVD event in 10 years), "intermediate risk" (10–20% risk of CVD event in 10 years), and "high risk" (> 20% risk of CVD event in 10 years) for each score [16]. It must be noted that SCORE assesses the 10-year risk of cardiovascular death, whereas, the other risk scores used calculate the 10-year risk of cardiovascular events [14]. Therefore, discrepancy between SCORE and other cardiovascular risk prediction scores was expected.

CIMT was measured during diastole (identified by electrocardiographic gating) [17] on the far-wall of the common carotid artery at least 5 mm proximal to carotid bulb using B-mode ultrasonography (Esaote MyLab Xvision) equipped with linear array transducer. Six separate readings were taken each on left side and right side. Mean of left and right average intima media thickness was taken as the CIMT. The presence of plaques were recorded. Carotid plaques were defined as protrusion of the vascular wall into the lumen exceeding 1.5 mm or greater than 50% of the CIMT in the adjacent vessel wall [18]. Since heterogenous definitions of SCA exist in the literature, three definitions of SCA were used in exploratory analyses. SCA was defined as a CIMT value greater than 0.9 mm or the presence of carotid plaque [19], or, greater than 75$^{th}$ percentile of CIMT for that age and sex in the Indian population [20] or the presence of carotid plaque (defined as protrusion of the vascular wall into the lumen exceeding 1.5 mm or greater than 50% of the CIMT in the adjacent vessel wall) [18]. However, since the absolute values of CIMT are small, a cutoff of 75th percentile for CIMT might misclassify women as having SCA with this CIMT cutoff [21]. Therefore, keeping in mind that a majority of our patients with RA are women, we chose a third, more stringent definition of SCA as CIMT greater than mean + 2 standard deviations of the age- and sex-specific mean value for the Indian population [20] or the presence of carotid plaques. All carotid intima medial thickness measurements were carried out by a single trained observer (HM). Reliability of measurements of CIMT was assessed by randomly selecting 20 scans and re-scoring by an expert in vascular ultrasound (DPM), and assessing intraclass correlation coefficient (ICC) by two-way mixed effects model using STATA 16.1 I/C. Further, all scans were confirmed by two experts in vascular ultrasound (DPM, NJ).

### Statistical analysis

Assuming a prevalence ($P$) of cardiovascular risk factors of 30% (prevalence of various risk factors varies from 15 to 40% in various studies) among patients with RA patients, for a precision d = 0.05, the sample size n was calculated to be 323 [22]. Sample size was calculated using the formula $n = [Z^2 \times P(1-P)]/d^2$. Z is the statistic for level of confidence of 95%. A p value of < 0.05 was considered as statistically significant. Categorical variables were expressed as number (percentage), and compared between groups using Chi squared test or Fisher's exact test. Normality was assessed using Kolmogorov–Smirnov test. Normally distributed continuous variables were expressed as mean ± standard devation (SD). Student $t$-test was used for inter-group comparisons between continuous variables. Bland Altman plots were generated to estimate systematic differences between each of the risk scores. Linear correlation between CIMT and cardiovascular risk scores was assessed using Pearson's correlation coefficient. These analyses were performed using Graphpad v8 and Graphpad Prism v9.3.1. Weighted kappa analysis was performed to see agreement between various cardiovascular risk score in predicting low, intermediate and high risk (using SPSS software, v23.0, IBM 2010). Since the ASCVD and SCORE CVD risk scoring algorithms are validated only in age ≥ 40 years, receiver operating characteristic (ROC) curves for subclinical atherosclerosis with cardiovascular risk scores were generated using STATA 16.1 I/C (using the command roccomp) for those patients with RA whose age was at least 40 years. For associations of carotid intima medial thickness with different covariates, linear regression models were developed using STATA 16.1 I/C. To identify associations of subclinical atherosclerosis (yes or no) with different covariates, logistic regression models were developed using STATA 16.1 I/C.

## Results

### Demographics and clinical details

A total of 332 patients with RA were recruited (282 females). Mean age of patients was 47.16 ± 12.57 years; male patients were older than female patients. About one-fourth (23.3%) were seronegative for both rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA), whereas 44.9% had an erosive joint disease. Extra-articular manifestations were seen in 5.4% of patients, most commonly being Sjogren's (4.5%). Most patients were on methotrexate and hydroxychloroquine. Only four patients were on biologics. Disease characteristics of patients are shown in Table 1.

### Prevalence of traditional CVD risk factors

Smoking was reported by 23 (6.9%) patients; 4.8% were current smokers. Forty (12.0%) patients had diabetes mellitus and 71 (21.4%) had hypertension. A family history of CVD was obtained in 8.7% of patients. Diabetes

**Table 1** Demographics, disease characteristics, and the prevalence of traditional cardiovascular risk factors in study subjects

| Variable | All ($n=332$) | Male ($n=50$) | Female ($n=282$) | $p$ value |
|---|---|---|---|---|
| Age (years) | 47.2 ± 12.6 | 52.9 ± 12.4 | 46.2 ± 12.4 | **< 0.001** |
| Disease duration (years) | 7.3 ± 5.9 | 6.08 ± 4.83 | 7.44 ± 6.07 | 0.135 |
| Body mass index | 24.17 ± 4.73 | 22.56 ± 3.52 | 24.46 ± 4.86 | **0.009** |
| Positive ACPA ($n=270$)[#] | 246 (74.1%) | 34 (68.0%) | 212 (75.2%) | 0.286[a] |
| Positive RF ($n=298$)[#] | 286 (86.1%) | 44 (88.0%) | 242 (85.8%) | 0.680[a] |
| DAS 28 ESR | 3.54 ± 1.15 | 3.04 ± 1.16 | 3.62 ± 1.14 | **0.001** |
| Erosions ($n=327$)[#] | 149 (44.9%) | 17 (34%) | 132 (46.8%) | 0.093[a] |
| Secondary Sjogren's syndrome | 15 (4.5%) | 1 (2.0%) | 14 (5.0%) | 0.709[b] |
| ILD | 5 (1.5%) | 1 (2.0%) | 4 (1.4%) | 0.560[b] |
| EAM | 18 (5.4%) | 2 (4.0%) | 16 (5.7%) | > 0.999[b] |
| ESR (mm/hr) | 40.8 ± 27.5 | 31.6 ± 22.8 | 42.4 ± 27.9 | **0.010** |
| Glucocorticoids | 168 (50.6%) | 17 (34.0%) | 151 (53.5%) | **0.011**[a] |
| Methotrexate | 252 (75.9%) | 40 (80.0%) | 212 (75.2%) | 0.462[a] |
| Leflunomide | 24 (7.2%) | 2 (4.0%) | 22 (7.8%) | 0.552[b] |
| Sulfasalazine | 21 (6.3%) | 3 (6.0%) | 18 (6.4%) | > 0.999[b] |
| Hydroxychloroquine | 214 (64.5%) | 34 (68.0%) | 180 (63.8%) | 0.570[a] |
| NSAIDs | 128 (38.6%) | 18 (36.0%) | 110 (39.0%) | 0.687[a] |
| Biologics | 4 (0.3%) | 3 (6%) | 1 (0.4%) | **0.012**[b] |
| Smoking ever | 23 (6.9%) | 14 (28.0%) | 9 (3.2%) | **< 0.001**[a] |
| Active smoker | 16 (4.8%) | 9 (18.0%) | 7 (2.5%) | **< 0.001**[a] |
| Type 2 diabetes mellitus | 40 (12.0%) | 13 (26.0%) | 27 (9.6%) | **0.001**[a] |
| Hypertension | 71 (21.4%) | 13 (26.0%) | 59 (20.9%) | 0.422[a] |
| Family history of CVD | 29 (8.7%) | 6 (12.0%) | 23 (8.2%) | 0.375[a] |
| Chronic kidney disease | 4 (1.2%) | 2 (4.0%) | 2 (0.7%) | 0.109[b] |
| Systolic BP, mm Hg | 131.9 ± 19.2 | 137.7 ± 15.4 | 130.9 ± 19.6 | **0.021** |
| Diastolic BP, mm Hg | 79.5 ± 9.2 | 81.8 ± 8.5 | 79.1 ± 9.2 | 0.054 |
| TC, mg/dL | 163.2 ± 38.3 | 153.0 ± 42.8 | 165.0 ± 37.2 | 0.041 |
| LDL-C, mg/dL | 97.6 ± 26.5 | 93.4 ± 26.6 | 98.4 ± 26.4 | 0.219 |
| Triglyceride, mg/dL | 126.6 ± 56.3 | 120.8 ± 44.0 | 127.6 ± 58.3 | 0.433 |
| VLDL-C, mg/dL | 25.1 ± 11.3 | 24.8 ± 10.2 | 25.2 ± 11.5 | 0.818 |
| HDL-C, mg/dL | 47.1 ± 9.9 | 44.7 ± 9.2 | 47.5 ± 9.9 | 0.063 |

Values expressed as mean ± SD for continuous variables and n (percentage) for discrete variables. Compared between males and females using t test for continuous variables and chi squared test[a]/Fisher's exact test[b] for categorical variables. *ACPA* anti-cyclic citrullinated peptide antibody, *BP* blood pressure, *CVD* cardiovascular disease, *DAS28 ESR* disease activity score using 28 joint count and ESR, *EAM* extra-articular manifestations, *ESR* erythrocyte sedimentation rate, *HCQ* hydroxychloroquine, *HDL-C* high-density lipoprotein cholesterol, *ILD* Interstitial lung disease, *LDL-C* low-density lipoprotein cholesterol, *NSAID* non-steroidal anti-inflammatory drugs, *RF* rheumatoid factor, *TC* total cholesterol, *VLDL-C* very low-density lipoprotein cholesterol

[#]These variables were available only for the number of patients mentioned in brackets

mellitus and smoking were more prevalent in males than in females. Details of traditional CVD risk factors in the study subjects are given in Table 1.

## Comparison of various CVD risk scores

CVD risk scoring was performed in 272 patients for whom concurrent carotid ultrasonography was also performed. Percentage of patients with predicted CVD risk of > 10% in 10 years varied from 16.2% with SCORE to 41.9% with FRS-BMI. Agreement between scores in predicting low, high and intermediate risk was moderate in general with maximum agreement between QRISK-2 and FRS-Lipids (weighted kappa: 0.790). Agreement was least for SCORE with any other algorithm (Table 2). Overall, ASCVD scores were lower than scores predicted by algorithms other than SCORE (Fig. 1). SCORE, even though calculated a lower risk than all other algorithms since it calculates the risk

of cardiovascular death (as opposed to other scores which calculate risk of cardiovascular events), behaved erratically beyond 15% 10-year CVD risk estimate. No systematic biases could be identified between QRISK-2 and either Framingham score, although discrepancies between scores occurred in general at higher scores (Fig. 1). According to ACC/AHA guidelines, 24.8% of our patients should have been on at least moderate intensity statin therapy (whereas none of them were on statins).

## Predictors of CIMT and SCA

There was excellent inter-rater reliability of CIMT measurements (ICC was 0.95, 95% CI 0.87–0.98). CIMT was performed in 270 patients (two carotid ultrasound images were rejected for technical reasons). Mean CIMT was $0.70 \pm 0.15$ mm, significantly higher in males, those with diabetes mellitus or hypertension and those with extra-articular manifestations of RA when compared with those without (Supplementary table 1). Mean CIMT of patients with and without family history of cardiovascular disease were comparable. Amongst disease characteristics, the presence of extra-articular manifestations associated with higher mean CIMT. Also mean CIMT did not differ in accordance to RF or ACPA seropositivity (Supplementary table 1). Serum cytokines could be analyzed in 235 (IL-1β), 217 (IL-6), and 232 patients (TNF-α) due to the limitation of available ELISA kits.

Linear regression models for carotid intima media thickness were developed using the covariates which had an association with CIMT on univariable linear regression with $p < 0.2$ (age, gender, disease duration, the presence of extra-articular manifestations, waist-hip ratio, triglycerides, diabetes mellitus, hypertension, smoking, TNF-α) (Supplementary table 2). The model was adequately powered assuming at least the requirement of eight observations per covariate (17 covariates, 206 observations) [23]. A model including these variables had similar performance when compared

**Table 2** Estimate of risks with different cardiovascular disease risk scores in patients with rheumatoid arthritis and agreement between them

| Risk score | ASCVD | FRS-LIPIDS | SCORE | QRISK2 | FRS-BMI |
|---|---|---|---|---|---|
| ***Cardiovascular risk*** | | | | | |
| Low (< 10%) | 224(82.4%) | 171(62.9%) | 228(83.8%) | 185(68.0%) | 158(58.1%) |
| Intermediate (10–20%) | 27(9.9%) | 57(21.0%) | 7(2.6%) | 39(14.3%) | 55(20.2%) |
| High (> 20%) | 21(7.7%) | 44(16.2%) | 37(13.6%) | 48(17.6%) | 59(21.7%) |
| ***Agreement between risk scores**** | | | | | |
| | ASCVD | FRS-LIPIDS | SCORE | QRISK2 | FRS-BMI |
| ASCVD | – | 0.545 (0.454–0.636) | 0.472 (0.339–0.604) | 0.602 (0.515–0.689) | 0.450 (0.361–0.538) |
| FRS-LIPIDS | – | – | 0.460 (0.359–0.561) | 0.790 (0.729–0.851) | 0.776 (0.717–0.835) |
| SCORE | – | – | – | 0.485 (0.378–0.593) | 0.403 (0.306–0.500) |
| QRISK2 | – | – | – | – | 0.720 (0.652–0.788) |

*Weighted kappa (95% confidence intervals)

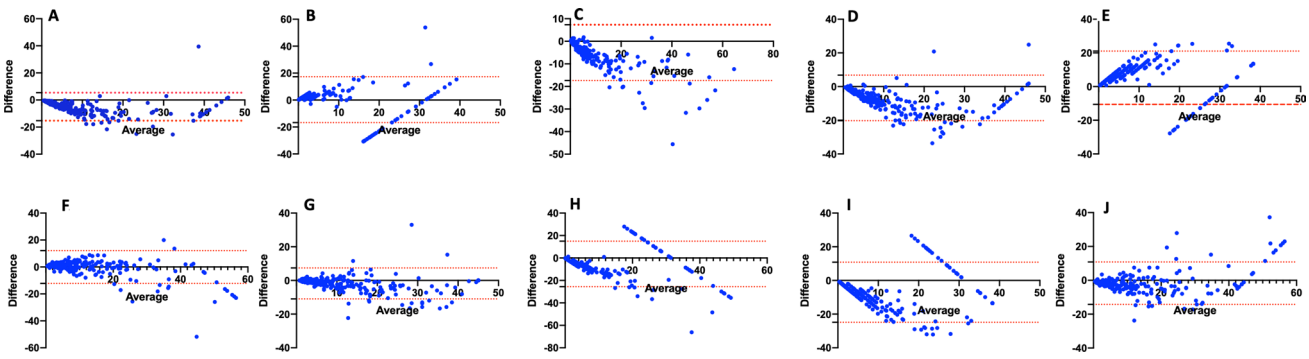


**Fig. 1** Bland Altman plots depicting agreement between different pairs of cardiovascular risk scores in patients with rheumatoid arthritis. **A** ASCVD vs FRS-LIPIDS. **B** ASCVD vs SCORE. **C** ASCVD vs QRISK-2. **D** ASCVD vs FRS-BMI. **E** FRS-LIPIDS vs SCORE. **F** FRS-LIPIDS vs QRISK-2. **G** FRS-LIPIDS vs BMI. **H** SCORE vs QRISK-2. **I** SCORE vs FRS-BMI. **J** QRISK-2 vs FRS-BMI

with a model including all the covariates from the univariable analyses (likelihood ratio test $p$ value 0.518). After multivariable adjustment, age ($p < 0.001$), gender ($p = 0.013$), and extra-articular manifestations ($p = 0.002$) were significantly associated with CIMT (Table 3). The linear regression model had moderate fit ($R^2$ 0.446).

Based on a definition of CIMT > 0.9 mm or carotid plaques, 14.07% (38/270) had SCA [in those ≥ 40 years, 17.68% (35/198) had SCA]. When defined as CIMT > 75th percentile for age and sex or carotid plaques, 206/270 (76.30%) had SCA [in those ≥ 40 years, 77.78% (154/198) had SCA]. Using the third definition of CIMT > mean + 2standard deviations for age and sex or carotid plaques, 78/270 (28.89%) had SCA [in those ≥ 40 years, 27.27% (54/198) had SCA]. Logistic regression models for SCA were developed after first delineating continuous variables into categorical groups (decades for age, tertiles for disease duration, body mass index, waist-hip ratio, total cholesterol:HDL-C ratio, triglycerides, LDL-C, serum IL-1, IL-6, and TNF-α). Thereafter, those covariates which had an association with subclinical atherosclerosis on univariable linear regression with $p < 0.2$ were used as covariates in the logistic regression model (Supplementary tables 3, 4 and 5). The models were adequately powered assuming at least the requirement of eight observations per covariate (17 covariates, 206 observations or 194 observations) [23]. A model including covariates with a $p$ value < 0.2 for the association on univariable analysis had similar performance when compared with a model including all the covariates from the univariable analyses (likelihood ratio test $p$ value 0.643 for SCA defined as CIMT > 0.9 mm or carotid plaques; likelihood ratio test $p$ value 0.592 for SCA defined as CIMT > 75th percentile for age and sex or carotid plaques; likelihood ratio test $p$ value 0.801 for SCA defined as CIMT > mean + 2standard deviations for age and sex or carotid plaques). For SCA defined as CIMT > 0.9 mm or carotid plaques, after multivariable-adjusted logistic regression analyses, age ($p < 0.001$), male gender ($p = 0.018$), and higher total cholesterol:HDL-C ratio ($p = 0.032$) remained significant associations of SCA (Table 4). No variables were significantly associated with SCA after multivariable adjustment based on the other two definitions (Supplementary table 6).

## Comparison of CVD risk scores with CIMT and their discriminative ability to predict SCA

All risk scores except SCORE (due to limitations of SCORE detailed earlier) had moderate correlation with CIMT (Supplementary table 7). QRISK-2 had the greatest magnitude

**Table 4** Multivariable-adjusted logistic regression analyses between subclinical atherosclerosis[#] and risk factors for atherosclerosis in patients with rheumatoid arthritis

| Covariate | Odds ratio | 95% confidence interval | $p$ value |
|---|---|---|---|
| Age (per decade) | 2.31 | 1.45–3.68 | **< 0.001** |
| Gender (male vs female) | 3.79 | 1.25–11.49 | **0.018** |
| Total cholesterol:HDL-C ratio (tertiles) | 2.00 | 1.06–3.76 | **0.032** |
| Diabetes mellitus | 1.34 | 0.39–4.63 | 0.644 |
| Hypertension | 1.34 | 0.44–4.04 | 0.605 |
| Current or past smoking | 0.61 | 0.12 – 3.20 | 0.555 |
| IL-1β (pg/mL) (tertiles) | 1.34 | 0.74–2.44 | 0.338 |
| TNF-α (pg/mL) (tertiles) | 0.65 | 0.36–1.16 | 0.147 |

$n = 206$ for the model, pseudo $R^2 = 0.227$. *CVD* cardiovascular disease, *HDL-C* high-density lipoprotein cholesterol, *IL* interleukin, *LDL-C* low-density lipoprotein cholesterol, *TNF-α* tumor necrosis factor alpha

[#]Subclinical atherosclerosis defined as carotid intima medial thickness > 0.9 mm or the presence of carotid plaques

**Table 3** Multivariable-adjusted linear regression analyses between carotid intima-medial thickness (mm) and risk factors for atherosclerosis in patients with rheumatoid arthritis

| Covariate | Regression coefficient | 95% confidence interval | p value |
|---|---|---|---|
| Age (years) | +0.0064 | +0.0049, +0.0078 | **< 0.001** |
| Gender (male vs female) | +0.0613 | +0.0143, +0.1082 | **0.013** |
| Disease duration (years) | +0.0017 | −0.0009, +0.0043 | 0.203 |
| Presence of extra-articular manifestations | +0.1098 | +0.0430, +0.1767 | **0.001** |
| Waist-hip ratio | +0.1416 | −0.0527, +0.3360 | 0.152 |
| Triglycerides (mg/dL) | +0.00003 | −0.0002, +0.0003 | 0.834 |
| Diabetes mellitus | +0.0253 | −0.0251, +0.0756 | 0.324 |
| Hypertension | +0.0022 | −0.0396, +0.0440 | 0.901 |
| Current or past smoking | −0.0192 | −0.0863, +0.0479 | 0.573 |
| TNF-α | −0.0001 | −0.0003, +0.0001 | 0.340 |

$n = 206$ for the model, $R^2 = 0.446$. *CVD* cardiovascular disease, *HDL-C* high-density lipoprotein cholesterol, *IL* interleukin, *LDL-C* low-density lipoprotein cholesterol, *TNF-α* tumor necrosis factor alpha

of correlation with CIMT ($r = 0.570$). When ROC curves were plotted with SCA defined by CIMT > 0.9 mm or carotid plaques, highest area under curve (AUC) were obtained (between 0.695–0.772 for all CVD risk scores); ASCVD (0.772) and QRISK-2 (0.756) had maximum AUC (Fig. 2, Supplementary table 8). Using this definition, patients with SCA were more likely to be of older age, males, having erosive rheumatoid arthritis, and with lower levels of HDL-C (Supplementary table 9). When SCA was either defined as CIMT > 75th percentile for age and sex or carotid plaques or as CIMT > mean + 2 standard deviations for age and sex or carotid plaques, all the risk scores had poorer performance to discriminate SCA than with the previous definition (Supplementary Fig. 1, Supplementary table 8).

## Discussion

The present study identified hypertension, diabetes mellitus, family history of CVD and smoking as the most prevalent CVD risk factors in patients with RA. Smoking and diabetes mellitus were more prevalent in male subjects with RA. Different CVD risk scores performed differently in our population, with greatest magnitude of CVD risk denoted by FRS-BMI and least risk with the SCORE algorithm. Age, male sex, and the presence of extra-articular manifestations associated with greater CIMT. About one-seventh of our patients had SCA defined as CIMT > 0.9 mm or the presence of carotid plaques, a definition which associated with increasing age, male gender, and higher ratio of total cholesterol to HDL-C.

The EULAR recommends CVD risk assessment every 5 years in patients with inflammatory arthritis [9, 24]. There

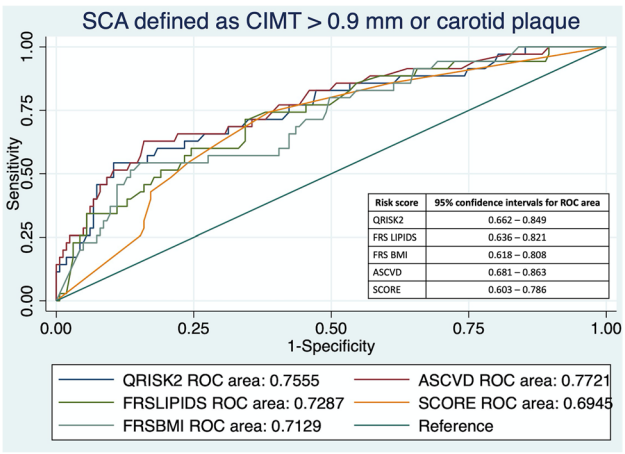


**Fig. 2** Receiver operating characteristics curve for subclinical atherosclerosis [(SCA), defined as carotid intima-media thickness (CIMT) > 0.9 mm or carotid plaques] and different cardiovascular disease risk prediction scores

are widespread variations in prevalence of each of risk factors across studies. These variations can be explained by differences in cutoffs taken for diseases and difference of study population. Prevalence of hypertension varies from 4 to 73% across studies [25]. In our study, nearly one-fifth of patients had hypertension. Prevalence of diabetes mellitus in the present study was 12%. There is considerable heterogeneity in the prevalence data of diabetes mellitus in RA across populations which is varying from 1.3% to 16.6% [26–30]. A systematic review and meta-analysis of seven studies including 1230 patients with RA and 1597 controls showed a higher prevalence of diabetes mellitus in RA than in the general population (odds ratio 1.74, 95% confidence intervals 1.22–2.50) [25]. Despite the higher risk, screening and management of CVD risk factors remains suboptimal in RA patients, more so in developing nations [31]. Evidence from a recent multicentric study of > 14,000 patients with RA worldwide (the Survey of Cardiovascular Disease Risk Factors in patients with Rheumatoid Arthritis – SURF-RA study) suggests that patients with RA who concomitantly have diabetes mellitus have a greater prevalence of hypertension and hyperlipidemia than those RA without diabetes mellitus [32]. In the present study, a significantly higher proportion of male patients with RA had diabetes mellitus than females. Prevalence of smoking was also higher in males. However, smoking prevalence could possibly be under reported in cross-sectional studies like ours. There is a scarcity of published literature on prevalence of CVD risk factors in Indian population. A study from Southern India identified diabetes mellitus (14.4%) and hypertension (20.7%) as the most common comorbidities in RA patients, akin to our observations [33]. The prevalence of diabetes mellitus in our RA patients was higher than the reported prevalence of diabetes mellitus (7.2%) in the general adult population of India [34]. Prevalence of hypertension in the general adult Indian population varies from 16 to 34% across studies [35], similar to that observed by us. The recent SURF-RA study revealed that only one-half of patients with RA who have hypertension attain a target blood pressure of < 140/90 mm Hg [36].

Our study also identified a practice gap in CVD risk monitoring and primary prevention in an Indian RA population. At least 24.8% of our study population should have been on moderate intensity statin therapy if ACC/AHA guidelines [37] were practiced, whereas none of them were. Of note, the present study excluded patients with prior or incident CVD at the index visit. In the recently published SURF-RA study (which also included patients with CVD), 52% patients with RA merited statin therapy, and 84.6% of those needing statin therapy were receiving the same. However, on stratifying by risk group as per SCORE, 58% of those with 10-year CVD risk between 5–10% and 37% of those with 10-year CVD risk ≥ 10% had actually attained the LDL-C target goals

recommended despite being on statins [36]. Therefore, the use of statins as well as the attainment of lipid targets with statin therapy both remain suboptimal in patients with RA. These findings highlight the importance of sensitizing rheumatologists to the need for screening and adopting measures to decrease cardiovascular risk in RA.

Various algorithms are available for predicting CVD risk in general population. Most of these algorithms do not factor in RA as a risk factor for CVD. It has been shown that these algorithms systematically under estimate CVD risk in RA [3]. The choice of the cardiovascular risk scores in our study was based on previous studies which had used these scores [13, 14] as well as the prevalent EULAR recommendations at that time [9]. We did not use the Reynolds risk score used in other studies since it requires highly-sensitive C-reactive protein (CRP), which we anticipated might not be available for all of our patients as erythrocyte sedimentation rate rather than CRP is more commonly used in our setting due to cost constraints. The QRISK-2 algorithm considers RA as a risk factor when predicting 10-year CVD risk. Recently, a RA-specific risk algorithm (the Expanded Risk Score in Rheumatoid Arthritis or ERS-RA) was developed by a consortium of Rheumatologists from North America [38]. However, the better performance of RA-specific scores in comparison to other scores is yet to be established. Also, this score has been developed predominantly in a North American population and is not validated in our population, therefore, we did not utilize this score [14]. We compared various risk algorithms after adapting the multiplication factor of 1.5 as suggested by EULAR. There was considerable variation between different CVD risk scores in predicting 10-year CVD risk. Proportion of patients with a predicted risk of > 10% varied from 16.2 to 41.9% when different algorithms were used. Agreement between scores in predicting low, intermediate and high risk was moderate in general. There was a reasonable degree of agreement between QRISK-2, FRS-BMI and FRS-Lipids. Agreement was least for SCORE with any other CVD risk score. Even though SCORE in general predicted a lower risk than other algorithms (as it calculates the risk of cardiovascular death as opposed to the other scores used which calculate the risk of cardiovascular events), this bias was not systematic when the predicted risk was higher. The limitations of SCORE have now been addressed with the SCORE2 (for age group of 40–69 years) and the SCOPE2-OP (for age group ≥ 70 years) [39]. These scores calculate the 10-year risk of cardiovascular events and death, however were published in 2021 and were not available at the time our study was conducted [39]. Our findings suggest that the prediction algorithms after adapting EULAR modifications behave differently in Indian RA patients and each estimates CVD risk to a different degree. Similar disparities between CVD risk scores have also been identified in other populations. In a study of 116 patients with RA from Mexico, six CVD risk scores (FRS-BMI, FRS-Lipids, QRISK-2, ASCVD, Reynolds risk score, and Extended Risk Score—Rheumatoid Arthritis) identified cardiovascular risk to differing extents [13]. Similar to our study, the FRS-Lipids predicted the highest magnitude of CVD risk in this study also [13]. The onset of rheumatoid arthritis as well as of cardiovascular disease both occur at an earlier age in the Indian population. Therefore, the development of specific cardiovascular risk scores for Indian patients might be an important agenda for future research [40–44].

Other recent studies have evaluated CVD risk scores in patients with RA, spondyloarthritis (SpA) and systemic lupus erythematosus (SLE). Wah-Suarez et al. evaluated the performance of different CVD risk scores in 97 patients with RA of Mexican Mestizo ethnicity in relation to carotid plaques or CIMT > 0.9 mm. In this study, QRISK2 (AUC 0.727), SCORE (0.723), and ASCVD (AUC 0.703) algorithms had the greatest association with carotid plaques. QRISK2 (AUC 0.818), FRS-Lipids (AUC 0.811), ASCVD (AUC 0.791), FRS-BMI (0.786), SCORE (AUC 0.723), and RRS (AUC 0.703) best associated with CIMT > 0.9 mm [45]. Jafri et al. assessed concordance between classification as high or low predicted CVD risk using FRS and ASCVD scores in 96 patients with RA and 157 patients with SLE from North America. There was 88.5% concordance in RA and 93% concordance in SLE, suggesting that both these scores performed similarly in their population of RA or SLE [46]. Sivakumaran et al. evaluated the performance of different CVD risk scores in 1887 patients with SLE from North America [47]. A SLE-specific CVD risk score (the SLE cardiovascular risk equation) and a modified FRS (where predicted risk was doubled due to SLE) predicted the highest magnitude of 10-year CVD risk in those with or without CVD [47]. Unlike in RA [14], the SLE-specific CVD risk score predicted higher risk in patients with SLE than other conventionally used CVD risk scores [47]. Galarza-Delgado and colleagues evaluated the reclassification of CVD risk after carotid ultrasonography in 81 Mexican Mestizo patients with psoriatic arthritis (PsA), 44.4% of whom had carotid plaques and 51.9% had SCA. Each of the FRS-BMI, FRS-Lipids, ASCVD, SCORE, QRISK3, or RRS algorithms reclassified CVD risk with an increase of 2–threefold after incorporating findings from carotid ultrasonography [48]. Liew et al. evaluated predicted 10-year CVD risk using the ASCVD algorithm in 211 patients with ankylosing spondylitis (AS) or axial SpA from North America. The observed mean 10-year CVD risk in patients with AS or axial SpA was 6.7%, similar to that observed in healthy controls of similar age, sex and ethnicity [49]. Navarini et al. evaluated the performance of various CVD risk scores in a retrospective cohort of 133 patients with AS, eighteen of who had experienced CVD events. They reported highest concordance

with CVD events for RRS (c-statistic 0.72) and SCORE (c-statistic 0.71) [50].

Mean CIMT in our patients with RA was 0.70 mm, similar to other studies including one from the Indian subcontinent [51]. Increasing age, male gender, and the presence of extra-articular manifestations associated with higher CIMT after multivariable-adjusted analyses. Age and male gender have been associated previously with increased CVD risk in RA [52]. Extra-articular manifestations of RA are also recognized to portend a greater risk of CVD, including incident CVD events, in RA [53, 54]. Since there is no single validated definition of SCA, we used three different definitions of SCA in exploratory analyses. The prevalence of SCA varied with each definition (14.07% with CIMT > 0.9 mm or plaques, 76.30% with CIMT > 75th percentile for age and sex or plaques, 28.89% with CIMT > mean + 2SD for age and sex or plaques). Of note, these were patients with RA without overt CVD. Age and male gender as well as increased ratio of total cholesterol to HDL-C independently associated with the definition of SCA as CIMT > 0.9 mm or plaques after multivariable adjustment (but no significant adjusted associations with the other two definitions of SCA were observed). A Turkish study identified age, smoking, C-reactive protein and erythrocyte sedimentation rate as independent predictors of SCA [55]. CVD risk mitigation strategies have successfully used inflammatory cytokine blockade to reduce future CVD events [56]. Use of tumor necrosis factor alpha inhibitors (TNFi) biologics has been noted to be protective against SCA [55, 57]. However, we could not identify an association between inflammatory cytokines IL-1β, IL-6, TNF-α with CIMT or SCA after multivariable adjustment. Since most of our patients were on DMARDs, this might have dampened the levels of these inflammatory markers, thereby making it difficult to identify such an association in a cross-sectional study. Use of biologics was very less in our study population which also highlights special socioeconomic considerations in developing countries in RA management. As discussed earlier, RA-specific cardiovascular risk scores such as the ERS-RA have not been proven to better predict CVD risk than those risk scores already used in the general population [14]. Future attempts to develop a RA-specific CVD risk scoring algorithm might consider including potential disease-specific risk factors such as extra-articular manifestations of RA.

The various CVD risk scores also best distinguished SCA with the definition of CIMT > 0.9 mm or plaques. Our study identified a better association of QRISK-2 and ASCVD than SCORE with SCA. In a study from Turkey, when risk scores were compared with CIMT, ASCVD performed better than SCORE [55]. Another recent study from Switzerland reported that all CVD risk scores have good discriminative ability in predicting CIMT [58]. There was no improvement is discriminative ability when RA-specific risk algorithm (ERS-RA) was used [58]. We did not use ERS-RA algorithm in our study. EULAR had previously recommended the use of SCORE for predicting risk in RA patients in populations where a validated risk score is not available [9]. Our analysis showed that SCORE poorly correlated with SCA when compared with other CVD risk scores and had more discrepancies with other algorithms, likely due to the fact that SCORE estimates the 10-year risk of cardiovascular death alone. In the aforementioned study from Switzerland, all risk scores other than the ERS-RA (viz., FRS-BMI, ASCVD, modified SCORE, and QRISK-3) had good discriminative ability to predict subclinical atherosclerosis.

Some limitations of the present study need to be considered. The study was cross-sectional in nature; therefore, we could not use the real-life incidence of cardiovascular events as an outcome which would have been possible in a long-term cohort study. We used a proxy measure of CVD risk, viz., subclinical atherosclerosis assessed using carotid ultrasound for CIMT and carotid plaques, as well as assessed the prediction of such subclinical atherosclerosis with estimated 10-year CVD risk using different risk scores. We did not screen for non-traditional novel CVD risk factors other than inflammatory cytokines. We also did not account for the lipid paradox that can occur in RA. Furthermore, only 4% of our patients were on biologics with none of them on anti-TNF agents. This is in striking contrast to western population where about one-fourth of patients are on biologic therapy [59]. This highlights the special scenario of resource limited countries but also limits the generalizability of our observations to situations where biologic DMARDs are more accessible. We have not performed comparisons between CVD risk scores in our patients with RA with other inflammatory rheumatic diseases. Strengths of our study were the evaluation of the performance of different CVD risk scores in RA and the use of carotid ultrasonography to further delineate subclinical atherosclerosis (using already available age- and sex-specific cut-offs for CIMT as defined in the Indian population).

## Conclusion

Identifying prevalence of risk factors and subclinical atherosclerosis in Indian RA patients might enable the formulation of CVD risk reduction strategies in this population. The results from our study reveal that hypertension, diabetes mellitus and smoking were the most prevalent cardiovascular risk factors in our patients with RA. Rheumatologists should be aware of such CVD risk factors and suitably address them during routine clinical care of patients with RA. The study findings also highlight the heterogeneity of risk prediction models when applied to non-derivation cohorts without validation. FRS-BMI and FRS-Lipids reported the highest

magnitude of predicted 10-year CVD risk. However, long-term prospective studies should be conducted to validate these algorithms in an Indian RA population in terms of hard clinical end points such as CVD events or CVD mortality. There is also a compelling need for improving the evidence base related to the use of CVD risk scores in an Indian population.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10067-022-06349-y.

**Author contribution** The conception and design of the study – DPM, VA, SK; acquisition of data, analysis and interpretation of data – HM, DPM, NJ, SG, SSP, MKR, AKA, NM. Drafting the article – HM, DPM, NJ; revising it critically for important intellectual content – SG, SSP, MKR, AKA, NM, SK, VA. Final approval of the version to be submitted – DPM, HM, NJ, SG, SSP, MKR, AKA, NM, SK, VA. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved – DPM, HM, NJ, SG, SSP, MKR, AKA, NM, SK, VA.

**Data availability** Data pertaining to this article shall be shared on reasonable request to the corresponding author (Durga Prasanna Misra, durgapmisra@gmail.com).

## Declarations

**Ethics approval** The study was approved by the Institute Ethics Committee, SGPGIMS, Lucknow [ethics submission number 2018–5-DM-EXP, letter number PGI/BE/52/2018, date of approval 19 February 2018]. All participants were recruited into the study after obtaining written informed consent for participation.

**Disclosures** None.

## References


1. Sokka T, Abelson B, Pincus T (2008) Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol 26:S35-61
2. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D (2008) Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 59:1690–1697. https://doi.org/10.1002/art.24092
3. Ferguson LD, Siebert S, McInnes IB, Sattar N (2019) Cardiometabolic comorbidities in RA and PsA: lessons learned and future directions. Nat Rev Rheumatol 15:461–474. https://doi.org/10.1038/s41584-019-0256-0
4. D'Agostino RB Sr, Vasan RS, Pencina MJ et al (2008) General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 117:743–753. https://doi.org/10.1161/circulationaha.107.699579
5. Conroy RM, Pyörälä K, Fitzgerald AP et al (2003) Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 24:987–1003. https://doi.org/10.1016/s0195-668x(03)00114-3
6. Hippisley-Cox J, Coupland C, Vinogradova Y et al (2008) Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 336:1475–1482. https://doi.org/10.1136/bmj.39609.449676.25
7. Goff DC Jr, Lloyd-Jones DM, Bennett G et al (2014) 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129:S49-73. https://doi.org/10.1161/01.cir.0000437741.48606.98
8. Garg N, Muduli SK, Kapoor A et al (2017) Comparison of different cardiovascular risk score calculators for cardiovascular risk prediction and guideline recommended statin uses. Indian Heart J 69:458–463. https://doi.org/10.1016/j.ihj.2017.01.015
9. Agca R, Heslinga SC, Rollefstad S et al (2017) EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 76:17–28. https://doi.org/10.1136/annrheumdis-2016-209775
10. Naqvi TZ, Lee MS (2014) Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC Cardiovasc Imaging 7:1025–1038. https://doi.org/10.1016/j.jcmg.2013.11.014
11. Holland Z, Ntyintyane L, Gill G, Raal F (2009) Carotid intima-media thickness is a predictor of coronary artery disease in South African black patients. Cardiovasc J Afr 20:237–239
12. Baldassarre D, Hamsten A, Veglia F et al (2012) Measurements of carotid intima-media thickness and of interadventitia common carotid diameter improve prediction of cardiovascular events: results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as predictors of vascular events in a high risk European population) study. J Am Coll Cardiol 60:1489–1499. https://doi.org/10.1016/j.jacc.2012.06.034
13. Galarza-Delgado DA, Azpiri-Lopez JR, Colunga-Pedraza IJ et al (2017) Assessment of six cardiovascular risk calculators in Mexican mestizo patients with rheumatoid arthritis according to the EULAR 2015/2016 recommendations for cardiovascular risk management. Clin Rheumatol 36:1387–1393. https://doi.org/10.1007/s10067-017-3551-7
14. Crowson CS, Gabriel SE, Semb AG et al (2017) Rheumatoid arthritis-specific cardiovascular risk scores are not superior to general risk scores: a validation analysis of patients from seven countries. Rheumatology (Oxford) 56:1102–1110. https://doi.org/10.1093/rheumatology/kex038
15. Aletaha D, Neogi T, Silman AJ et al (2010) 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 62:2569–2581. https://doi.org/10.1002/art.27584
16. Sohn C, Kim J, Bae W (2012) The framingham risk score, diet, and inflammatory markers in Korean men with metabolic syndrome. Nutr Res Pract 6:246–253. https://doi.org/10.4162/nrp.2012.6.3.246
17. Wang TJ, Nam BH, D'Agostino RB et al (2003) Carotid intima-media thickness is associated with premature parental coronary heart disease: the Framingham Heart Study. Circulation 108:572–576. https://doi.org/10.1161/01.Cir.0000081764.35431.De
18. Casadei A, Floreani M, Catalini R, Serra C, Assanti AP, Conci P (2012) Sonographic characteristics of carotid artery plaques: implications for follow-up planning? J Ultrasound 15:151–157. https://doi.org/10.1016/j.jus.2012.06.002
19. Mancia G, De Backer G, Dominiczak A et al (2007) 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 28:1462–1536. https://doi.org/10.1093/eurheartj/ehm236
20. Kasliwal RR, Bansal M, Desai N et al (2016) A Study to derive distribution of carotid intima media thickness and to determine its correlation with cardiovascular Risk factors in asymptomatic

nationwidE Indian population (SCORE-India). Indian Heart J 68:821–827. https://doi.org/10.1016/j.ihj.2016.04.009
21. Nambi V, Chambless L, Folsom AR et al (2010) Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol 55:1600–1607. https://doi.org/10.1016/j.jacc.2009.11.075
22. Pourhoseingholi MA, Vahedi M, Rahimzadeh M (2013) Sample size calculation in medical studies. Gastroenterol Hepatol Bed Bench 6:14–17
23. Jenkins DG, Quintana-Ascencio PF (2020) A solution to minimum sample size for regressions. PLoS ONE 15:e0229345. https://doi.org/10.1371/journal.pone.0229345
24. Drosos GC, Vedder D, Houben E et al (2022) EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome. Ann Rheum Dis 81:768–779. https://doi.org/10.1136/annrheumdis-2021-221733
25. Boyer JF, Gourraud PA, Cantagrel A, Davignon JL, Constantin A (2011) Traditional cardiovascular risk factors in rheumatoid arthritis: a meta-analysis. Joint Bone Spine 78:179–183. https://doi.org/10.1016/j.jbspin.2010.07.016
26. Roman MJ, Moeller E, Davis A et al (2006) Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. Ann Intern Med 144:249–256. https://doi.org/10.7326/0003-4819-144-4-200602210-00006
27. McEntegart A, Capell HA, Creran D, Rumley A, Woodward M, Lowe GD (2001) Cardiovascular risk factors, including thrombotic variables, in a population with rheumatoid arthritis. Rheumatology (Oxford) 40:640–644. https://doi.org/10.1093/rheumatology/40.6.640
28. Dessein PH, Stanwix AE, Joffe BI (2002) Cardiovascular risk in rheumatoid arthritis versus osteoarthritis: acute phase response related decreased insulin sensitivity and high-density lipoprotein cholesterol as well as clustering of metabolic syndrome features in rheumatoid arthritis. Arthritis Res 4:R5. https://doi.org/10.1186/ar428
29. Gerli R, Sherer Y, Vaudo G et al (2005) Early atherosclerosis in rheumatoid arthritis: effects of smoking on thickness of the carotid artery intima media. Ann N Y Acad Sci 1051:281–290. https://doi.org/10.1196/annals.1361.069
30. Jonsson SW, Backman C, Johnson O et al (2001) Increased prevalence of atherosclerosis in patients with medium term rheumatoid arthritis. J Rheumatol 28:2597–2602
31. Desai SS, Myles JD, Kaplan MJ (2012) Suboptimal cardiovascular risk factor identification and management in patients with rheumatoid arthritis: a cohort analysis. Arthritis Res Ther 14:R270. https://doi.org/10.1186/ar4118
32. Semb AG, Rollefstad S, Ikdahl E et al (2021) Diabetes mellitus and cardiovascular risk management in patients with rheumatoid arthritis: an international audit. RMD Open 7:e001724. https://doi.org/10.1136/rmdopen-2021-001724
33. Chandrashekara S, Shobha V, Dharmanand BG et al (2017) Comorbidities and related factors in rheumatoid arthritis patients of south India- Karnataka Rheumatoid Arthritis Comorbidity (KRAC) study. Reumatismo 69:47–58. https://doi.org/10.4081/reumatismo.2017.898
34. Little M, Humphries S, Patel K, Dewey C (2017) Decoding the type 2 diabetes epidemic in rural India. Med Anthropol 36:96–110. https://doi.org/10.1080/01459740.2016.1231676
35. Anchala R, Kannuri NK, Pant H et al (2014) Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension. J Hypertens 32:1170–1177. https://doi.org/10.1097/hjh.0000000000000146
36. Rollefstad S, Ikdahl E, Wibetoe G et al (2021) An international audit of the management of dyslipidaemia and hypertension in patients with rheumatoid arthritis-results from 19 countries. Eur Heart J Cardiovasc Pharmacother. https://doi.org/10.1093/ehjcvp/pvab052
37. Arnett DK, Blumenthal RS, Albert MA et al (2019) 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 140:e596–e646. https://doi.org/10.1161/cir.0000000000000678
38. Solomon DH, Greenberg J, Curtis JR et al (2015) Derivation and internal validation of an expanded cardiovascular risk prediction score for rheumatoid arthritis: a Consortium of Rheumatology Researchers of North America Registry Study. Arthritis Rheumatol 67:1995–2003. https://doi.org/10.1002/art.39195
39. SCORE2 working group and ESC Cardiovascular risk collaboration (2021) SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J 42:2439–2454. https://doi.org/10.1093/eurheartj/ehab309
40. Chopra A, Raghunath D, Singh A, Subramanian AR (1988) The pattern of rheumatoid arthritis in the Indian population: a prospective study. Br J Rheumatol 27:454–456. https://doi.org/10.1093/rheumatology/27.6.454
41. Malaviya AN, Kapoor SK, Singh RR, Kumar A, Pande I (1993) Prevalence of rheumatoid arthritis in the adult Indian population. Rheumatol Int 13:131–134. https://doi.org/10.1007/bf00301258
42. Bedi GS, Gupta N, Handa R, Pal H, Pandey RM (2005) Quality of life in Indian patients with rheumatoid arthritis. Qual Life Res 14:1953–1958. https://doi.org/10.1007/s11136-005-4540-x
43. Nag T, Ghosh A (2013) Cardiovascular disease risk factors in Asian Indian population: a systematic review. J Cardiovasc Dis Res 4:222–228. https://doi.org/10.1016/j.jcdr.2014.01.004
44. Prabhakaran D, Jeemon P, Roy A (2016) Cardiovascular diseases in India: Current epidemiology and future directions. Circulation 133:1605–1620. https://doi.org/10.1161/circulationaha.114.008729
45. Wah-Suarez MI, Galarza-Delgado DA, Azpiri-Lopez JR et al (2018) The best cardiovascular risk calculator to predict carotid plaques in rheumatoid arthritis patients. Clin Rheumatol 37:2373–2380. https://doi.org/10.1007/s10067-018-4181-4
46. Jafri K, Ogdie A, Qasim A et al (2018) Discordance of the Framingham cardiovascular risk score and the 2013 American College of Cardiology/American Heart Association risk score in systemic lupus erythematosus and rheumatoid arthritis. Clin Rheumatol 37:467–474. https://doi.org/10.1007/s10067-017-3860-x
47. Sivakumaran J, Harvey P, Omar A et al (2021) Assessment of cardiovascular risk tools as predictors of cardiovascular disease events in systemic lupus erythematosus. Lupus Sci Med 8.https://doi.org/10.1136/lupus-2020-000448
48. Galarza-Delgado DA, Azpiri-Lopez JR, Colunga-Pedraza IJ et al (2022) Cardiovascular risk reclassification according to six cardiovascular risk algorithms and carotid ultrasound in psoriatic arthritis patients. Clin Rheumatol 41:1413–1420. https://doi.org/10.1007/s10067-021-06002-0
49. Liew JW, Reveille JD, Castillo M et al (2021) Cardiovascular risk scores in axial spondyloarthritis versus the general population: a cross-sectional study. J Rheumatol 48:361–366. https://doi.org/10.3899/jrheum.200188
50. Navarini L, Caso F, Costa L et al (2020) Cardiovascular risk prediction in ankylosing spondylitis: from traditional scores to machine learning assessment. Rheumatol Ther 7:867–882. https://doi.org/10.1007/s40744-020-00233-4
51. Shakeri A, Bazzaz MB, Khabbazi A, Fouladi RF (2011) Common carotid intima-media thickness in patients with late rheumatoid arthritis; what is the role of gender? Pak J Biol Sci 14:812–816. https://doi.org/10.3923/pjbs.2011.812.816

52. Semb AG, Ikdahl E, Wibetoe G, Crowson C, Rollefstad S (2020) Atherosclerotic cardiovascular disease prevention in rheumatoid arthritis. Nat Rev Rheumatol 16:361–379. https://doi.org/10.1038/s41584-020-0428-y
53. Turesson C, McClelland RL, Christianson TJ, Matteson EL (2007) Severe extra-articular disease manifestations are associated with an increased risk of first ever cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis 66:70–75. https://doi.org/10.1136/ard.2006.052506
54. Figus FA, Piga M, Azzolin I, McConnell R, Iagnocco A (2021) Rheumatoid arthritis: extra-articular manifestations and comorbidities. Autoimmun Rev 20:102776. https://doi.org/10.1016/j.autrev.2021.102776
55. Ozen G, Sunbul M, Atagunduz P, Direskeneli H, Tigen K, Inanc N (2016) The 2013 ACC/AHA 10-year atherosclerotic cardiovascular disease risk index is better than SCORE and QRisk II in rheumatoid arthritis: is it enough? Rheumatology (Oxford) 55:513–522. https://doi.org/10.1093/rheumatology/kev363
56. Ridker PM, Everett BM, Thuren T et al (2017) Antiinflammatory Therapy with canakinumab for atherosclerotic disease. N Engl J Med 377:1119–1131. https://doi.org/10.1056/NEJMoa1707914
57. Karpouzas GA, Ormseth SR, Hernandez E, Budoff MJ (2020) Biologics may prevent cardiovascular events in rheumatoid arthritis by inhibiting coronary plaque formation and stabilizing high-risk lesions. Arthritis Rheumatol 72:1467–1475. https://doi.org/10.1002/art.41293
58. Salaffi F, Carotti M, Di Carlo M et al (2018) The Expanded Risk Score in Rheumatoid Arthritis (ERS-RA): performance of a disease-specific calculator in comparison with the traditional prediction scores in the assessment of the 10-year risk of cardiovascular disease in patients with rheumatoid arthrit. Swiss Med Wkly 148:w14656. https://doi.org/10.4414/smw.2018.14656
59. Curtis JR, Singh JA (2011) Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. Clin Ther 33:679–707. https://doi.org/10.1016/j.clinthera.2011.05.044



## Authors and Affiliations

**Hafis Muhammed[1] · Durga Prasanna Misra[1] · Neeraj Jain[2] · Sujata Ganguly[1] · Sarit Sekhar Pattanaik[1] · Mohit K. Rai[1] · Anamika Kumari Anuja[1] · Namita Mohindra[2] · Sudeep Kumar[3] · Vikas Agarwal[1]**

Hafis Muhammed
hafispoonoor@gmail.com

Neeraj Jain
neerajdmrd@gmail.com

Sujata Ganguly
sujata.ganguly@gmail.com

Sarit Sekhar Pattanaik
saritsekhar@gmail.com

Mohit K. Rai
mohit1049@gmail.com

Anamika Kumari Anuja
anamika.anuja23@gmail.com

Namita Mohindra
mehrotranamita897@gmail.com

Sudeep Kumar
sudeepkum@yahoo.com

Vikas Agarwal
vikasagr@yahoo.com; vikasagr@sgpgi.ac.in

[1] Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

[2] Department of Radiodiagnosis, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

[3] Department of Cardiology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India