

# Cardiovascular Risk and Subclinical Atherosclerosis in Senegalese Patients with Rheumatoid Arthritis: A Cross-Sectional Study in a Single Centre

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## Abstract

**Introduction:** Rheumatoid arthritis (RA) is associated with increasing of cardiovascular (CV) morbidity and mortality due to accelerated atherosclerosis. Several studies showed also the increasing of the prevalence of subclinical atherosclerosis, but there are little data from sub-Saharan Africa. The aim of our study was to assess the prevalence of cardiovascular risk factors, subclinical carotid atherosclerosis and the ability of the Systematic Coronary Risk Estimation (SCORE) modified by European League Against Rheumatism (EULAR) to predict the high CV risk in our patients. **Patients and Method:** We conducted a cross sectional study in Senegalese patients with RA. The RA was retained according to 2010 American College of Rheumatology (ACR)-European League Against Rheumatism (EULAR) criteria. Patients with RA were assessed in a clinical research consultation. **Results:** We included 50 RA patients. The mean age was 44 years (+/- 12.37) and the sex-ratio was 0.06. The frequency distribution of traditional cardiovascular risk factors was: hypertension (HT) (30%), diabetes-mellitus (6%), smoking (2%), no-exercise (22%), obesity (16%), metabolic syndrome (8%). Fifty-eight percent of patients were classified at low cardiovascular risk according to mSCORE. 51.7% of patients classified as moderate-risk according to mSCORE, were reclassified as high cardiovascular risk according to carotid ultrasound evaluation (gold-standard). The sensitivity of the mSCORE in the prediction of high CV risk was low at 20%. In the present study, the prevalence of carotid subclinical atherosclerosis was 20%. Age (>45 years) and HT

were correlated to subclinical atherosclerosis. **Conclusion:** In the present study, the prevalence of atherosclerosis in RA patients was higher than expected frequency in comparison with the prevalence in Senegalese general population. We showed that CV risk was underestimated by mSCORE which had a low sensitivity in the prediction of high risk. We showed also the importance of carotid ultrasound for an appropriate stratification of the risk.

## Keywords

Rheumatoid Arthritis, Subclinical Atherosclerosis, Africa South of the Sahara

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## 1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by progressive joint destruction associated with extra-articular manifestations affecting different internal organs [1] [2].

RA is the most common chronic inflammatory joint disease and occurs throughout the world, in all ethnic groups, with a prevalence that ranges from 0.3% to 1.2% [2].

RA is associated with increasing of cardiovascular (CV) morbidity and mortality due to accelerated atherosclerosis. Thus, there is evidence of close relationship between RA and CV events such as stroke, congestive heart-failure and myocardial infarction [1] [3]-[16].

Several studies showed also the increasing of the prevalence of subclinical atherosclerosis, using different modalities including carotid ultrasound to detect carotid plaques.

Subclinical atherosclerosis may additionally identify the patients with high risk of CV events [17].

The high incidence of CV morbidity and mortality may due to higher prevalence of traditional cardiovascular risk factors and the role of systemic inflammation [11].

However, there are paucity data about CV risk and RA in sub-Saharan Africa [10] [18].

We conducted a cross sectional study in Senegalese patients with RA to assess the prevalence of cardiovascular risk factors, subclinical carotid atherosclerosis and the ability of the Systematic Coronary Risk Estimation (SCORE) modified by European League Against Rheumatism (EULAR) to predict the high CV risk in our patients.

## 2. Patients and Methods

### 2.1. Study Population

We conducted a cross sectional study in the Department of Internal Medicine of our institution during the period from July 03, 2017 to December 31, 2018.

We included patients followed for RA that met the 2010 American College of Rheumatology (ACR)-European League Against Rheumatism (EULAR) criteria [19].

RA patients with other autoimmune diseases or a history of clinical cardiovascular events (such as myocardial infarction, stroke, or peripheral arterial disease) were not included.

## 2.2. Clinical and Laboratory Assessment

Patients with RA were assessed in a clinical research consultation.

The following data were refined:

- General data such as age, gender, existence of smoking, alcohol consumption, family history of early cardiovascular disease among 1st degree relatives.
- The existence of a cardiovascular risk factor: smoking, overweight (defined by body mass index  $> 25 \text{ kg/m}^2$ ) or obesity (defined by a body mass index  $> 30 \text{ kg/m}^2$ ), waist circumference measurement, high blood pressure (HBP), diabetes-mellitus (DM), dyslipidemia according to their standard definitions.
- The disease duration, the diagnosis delay of RA, the clinical pattern, the disease activity by the disease activity score 28 with CRP (DAS-28 CRP) at the inclusion of this study, the duration of corticosteroid therapy, the daily dose and background therapy RA [20]. Active disease was defined by  $\text{DAS-28} \geq 2.6$  [20].
- The following biological investigations were carried out (CRP, creatinine and calculation of glomerular filtration rate, fasting blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, LDL cholesterol, LDL cholesterol, Uricemia).
- SCORE: We calculated the SCORE and we also applied a multiplier factor of 1.5 for the modified SCORE (mSCORE) according to EULAR guidelines [21]. We defined the different groups of risk: low risk ( $<1\%$ ), moderate risk ( $1\% - 5\%$ ), high risk ( $5\% - 10\%$ ), very high risk of CV mortality ( $>10\%$ ).
- The immunological patterns such as the results of rheumatoid factor (RF) or anti-cyclic citrullinated peptides (CCP) were specified from the observation files.

## 2.3. Carotid Ultrasound

The vascular ultrasound was performed by a device Esaotemylab alpha with a 3 - 13 MHz linear probe. The measurement of the carotid intima-media thickness (cIMT) was performed at the common carotid artery 1.5 cm from the carotid bulb by a trained ultrasonographer and an automated measurement software (<sup>RF</sup>QIMT). Carotid atherosclerosis was defined by the existence of plaques or  $\text{cIMT} \geq 0.9 \text{ mm}$  [22].

## 2.4. Statistical Analysis

The data were recorded and analyzed using SPSS 23.0 software.

The results were expressed as a mean (+/- standard deviation) for the continuous variables and as percentages for the categorical variables.

Means were compared using t Student test, and comparisons between categorical measures were made using chi2 test. The p-value < 0.05 was considered statistically significant.

The gold standard for the definition of high-cardiovascular risk was cIMT  $\geq$  0.90 mm or atherosclerosis plaques. We used this definition for the derivation of sensitivity of mSCORE to the prediction of the high cardiovascular risk.

## 2.5. Ethics

The study was conducted in accordance with the Helsinki Declaration. An informed written consent has been obtained for of all investigations on patients of the study.

## 3. Results

We included 50 patients followed for RA. These were 47 women and 03 men with a sex ratio of 0.06. The mean age was 44 years (+/- 12.37).

The mean duration of disease progression was 76.49 months (+/- 87.2) and the mean diagnostic delay was 38.27 (+/- 78.2).

Clinically, the mean number of painful joints was 5.6 (+/- 7.9) and the mean number of swollen joints was 5.02 (+/- 5.4). Joint deformities were noted in 66% of patients and extra-articular manifestations in 64% of cases.

The mean DAS-28 was 3.8 (+/- 1.2).

Anti-CCP was positive in 96.6% of patients and RF in 66.6% of cases. Clinical, immunological and therapeutic data are summarized in **Table 1**.

The frequency distribution of traditional cardiovascular risk factors was: hypertension (HT) (30%), diabetes-mellitus (6%), smoking (2%), no-exercise (22%), obesity (16%), metabolic syndrome (8%) (**Table 2**).

The distribution of the cardiovascular risk level by SCORE and mSCORE has been presented in **Table 3**. Fifty-eight percent had a low risk according to SCORE and mSCORE. Twenty-eight percent had moderate risk and eight percent had high risk according to mSCORE.

The mean cIMT was 0.63 mm (+/- 1.36). 10 patients (20%) had carotid atherosclerosis.

Eight patients (out of 14% or 51.7%) classified as moderate-risk according to mSCORE, were reclassified as high cardiovascular risk according to carotid ultrasound evaluation (gold-standard).

The sensitivity of the mSCORE equation in cardiovascular high-risk prediction was 20%, similar to the SCORE.

In the present study, only age (>45 years, p-value: 0.01) and hypertension (0.009) were correlated with carotid atherosclerosis (**Table 4**).

## 4. Discussion

RA is the first chronic rheumatism in the general population [2] [23] [24]. This

**Table 1.** Rheumatoid arthritis-related factors at inclusion.

Variables	Results: Mean (+/- SD) or %.
Mean disease duration (months)	76.49 (+/- 87.2)
Mean diagnostic delay (months)	38.27 (+/- 78.2)
Number of painful joints	5.6 (+/- 7.9)
Number of swollen joints	5.02 (+/- 5.4)
Clinical tenosynovitis (%)	27.7%
Number of night awakening	0.86 (+/- 1.8)
Morning stiffness duration (minutes)	30.4 (+/- 37.7)
Joints deformities (%)	66 %
DAS 28 CRP (mean value)	3.8 (+/- 1.2)
Extra-articulaire manifestations (%)	64%
Positivity of Rheumatoid Factor	20/30 (66.6%)
Positivity of anti-CCP	29/30 (96.6%)
Prednisone	98%
Methotrexate	70%
Sulfasalazine	28%
Hydroxychloroquine	50%
Patients followed by up to 1 DMARD	34%

DAS 28-CRP: disease activity score 28 with C-reactive protein; anti-CCP: anti-cyclic citrullinated peptides antibodies; DMARD: disease modifying anti-rheumatic drug.

**Table 2.** Cardiovascular risk factors at the inclusion.

Variables	Results (%)
Patients with prior history of DM	4
Patients with prior history of HT	14
HT (at the inclusion)	32
Abnormal serum glucose	4
DM	6
Dyslipidemia	30
Tobacco Smoking	2
Alcohol consumption	0
No exercise	22
Obesity	16
High waist circumference, men (>102)	0
High waist circumference, women (>88 cm)	21.2
Metabolic syndrome	8

DM: diabetes-mellitus; HT: Hypertension.

**Table 3.** Cardiovascular risk stratification.

Cardiovascular Risk	SCORE (%)*	mSCORE (%)*
Low (<1%)	58	58
Moderate ( $\geq 1\%$ et <5%)	30	28
High-risk ( $\geq 5\%$ et <10%)	6	8
Very high-risk ( $\geq 10\%$ )	0	0
Not applicable*	6	6

SCORE: Systematic coronary risk estimation; mSCORE: Systematic Coronary risk estimation modified by European league against rheumatism. \*Diabetes-mellitus.

**Table 4.** Correlation between carotid atherosclerosis and disease-related or cardiovascular-risk factors.

Variables	p-value
Age (<45 ans/ $\geq 45$ ans)	<b>0.01</b>
Sex	0.43
Diagnostic delay (<12 mois/ $\geq 12$ mois)	0.35
No-exercice	0.44
Hypertension	<b>0.009</b>
Obesity	0.68
Dyslipidémie	0.84
Metabolic syndrome	0.36
Disease activity	0.14
Extra-articulaire manifestations	0.28
Joints-deformities	0.72
Corticosteroid duration (<24 mois/ $\geq 24$ mois)	0.13
Corticosteroid dose, daily (<10 mg/j/ $\geq 10$ mg/j)*	0.87
Rheumatoid factor	0.53
Anti-CCP	0.17

anti-CCP: anti-cyclic citrullinated peptides antibodies.

chronic inflammatory disease is associated with an increased risk of mortality, as compared with general population, mainly due to cardiovascular events [1] [3]-[16].

The mechanisms leading to accelerated atherosclerosis and increased rate of CV events are complex including traditional CV factors, systemic chronic inflammation; genetic compound; RA therapies such as corticosteroids [16] [25].

In the present study, we assessed the prevalence of carotid subclinical atherosclerosis and we found a lower prevalence when compared with other series. Ambrosino *et al.*, reported a meta-analysis of 59 observational studies and showed an increased prevalence of atherosclerosis in RA patients with a prevalence of 32.7% [26]. Two studies were also especially conducted in sub-Saharan

Africa about RA and subclinical atherosclerosis [9] [18]. They found also a high prevalence when compared with our study, 35.5% in black patients in South Africa and 32% in Kinshasa (Democratic Republic of Congo) [9] [18]. However, in Italia and India, the prevalence of subclinical atherosclerosis was slightly lower to this present study, respectively 16% and 15.2% [16] [17]. This could suggest differences due to environmental and genetic factors. Indeed, several studies have confirmed the role of genetic factors in the development of atherosclerosis in RA. Thus, alleles from the *HLA-DRB1* genes especially the *HLA-DRB1\*0404* allele were associated with dysfunctional endothelial and presence of atheroma plaques [25] [27]. Other genes variants were also associated with cIMT in RA patients [4].

In the present study, the prevalence of atherosclerosis in RA patients was higher than expected frequency. In the Senegalese general population, the prevalence of subclinical atherosclerosis was estimated at 6.8% [28].

Atherogenesis in RA is mediated by traditional CV risk factors and disease related factors particularly high-grade inflammation, disease duration or RA therapies such as corticosteroids. One of the important finding of our study was the results about relations between subclinical atherosclerosis in RA patients and these traditional CV risk factors and disease specific factors. In the present study, only age (>45 years) and HT was correlated to carotid atherosclerosis. Several studies have demonstrated the impact of age in the genesis and development of atherosclerosis [18]. Age plays a role in the appearance of vascular lesions induced by oxidative stress and inflammation. These lesions can lead to the development of atherosclerosis also other CV risk factors such as HT [18]. HT was the most important CV risk factor associated with RA in our study as well as in South Africa [11]. An increased prevalence of HT was also reported in black patients without RA in sub-Saharan Africa [11]. Mulumba *et al.*, reported also an association with older age and HT [18]. Ruscitti *et al.*, showed also a correlation between atherosclerosis and HT [16]. Despite the well-known implication of other CV risk factors such as diabetes-mellitus, smoking, dyslipidemia, or metabolic syndrome, our study failed to demonstrate the expected association among these factors and subclinical atherosclerosis. Additionally, any RA-related factor was associated with carotid atherosclerosis, including disease-duration, disease-activity or joint-deformities. This suggests that our study had potentially limited power to identify significant statistic association between these factors and subclinical atherosclerosis.

Adequate stratification of CV risk is an important step in the management of RA patients [22]. Therefore, we evaluated the ability of the mSCORE in the prediction of the high-CV risk in comparison with carotid ultrasound. Indeed, previous studies have confirmed that a cIMT > 0.90 mm is indicative of atherosclerosis and increased of CV disease [22]. Carotid plaques are also predictors of coronary artery disease progression and closely associated with coronary artery disease [22]. We showed in this present study that the sensitivity of the mSCORE in the prediction of high risk was low, and the CV risk was underestimated by

mSCORE in patient with RA. These results corroborate those of Corrales *et al.* [22]. However, there are differences in the determination. Corrales *et al.* followed the 2009 EULAR recommendations for CV risk management which suggested a multiplication factor 1.5 to calculated total CV disease risk (SCORE) if the patient fulfilled certain disease-specific criteria (*i.e.* disease duration of >10 years, RF or ACPA positivity and the presence of certain extra-articular manifestations) [22] [29]. In our study, mSCORE was obtained after application of the multiplication factor 1.5 in all RA patients according to the 2015/2016 update EULAR guidelines [21].

The main limitations of our study were the cross-sectional design without controls subjects and his small sample size. We did not perform a power analysis prior to the initiation of the study. The sample size was retained according to the limits of means of explorations. However, it's the first study who described the frequency of subclinical atherosclerosis in Senegalese patients with RA. Carotid ultrasound should be proposed for a best CV risk assessment especially in RA patients with moderate CV risk.

## 5. Conclusions

In conclusion, this study showed a prevalence (20%) of subclinical carotid atherosclerosis in black Senegalese patients with RA higher than expected frequency in comparison with the prevalence in Senegalese general population.

We found also a correlation between HT and age (>45 years) and subclinical atherosclerosis, which highlights the importance of the evaluation of traditional CV risk factors in the management of RA.

We showed also, that CV risk was underestimated by mSCORE and the importance of carotid ultrasound for an appropriate stratification of the risk.

However, further studies are needed in sub-Saharan Africa, to evaluate other potential factors such as disease-specific factors that may be induced premature atherosclerosis in patients with RA.

## Consent for Publication

Written informed consent for publication was obtained from the patients.

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## Conflicts of Interest

The authors declare that they have no competing interests.

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