Risk factors for acute coronary events in patients with rheumatoid arthritis

Abdulsalam Noorwali[a], Narges Omran[b], Samah H. Elmedany[c], Amal M. El-Barbary[c]

[a]Department of Internal Medicine, Umm Alqura University, [b]Department of Internal Medicine, Alnoor General Hospital, Makkah, Saudi Arabia, [c]Department of Rheumatology and Rehabilitation, Faculty of Medicine, Tanta University, Tanta, Egypt

Correspondence to Amal M. El-Barbary, MD, Department of Rheumatology and Rehabilitation, Faculty of Medicine, Tanta University, El-Geish Street, Tanta, Gharbia, 31511, Egypt; Tel: 0403352236; e-mail: ml_barbary@yahoo.com

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Objectives
The aim of this study was to assess the role of disease activity, line of treatment, and carotid atherosclerosis in the risk for acute coronary syndrome (ACS) in rheumatoid arthritis (RA) patients.
Patients and methods
In this prospective study, we ascertained ACS on 124 patients with RA. Disease activity score 28 was used for the assessment of RA activity. Insulin resistance was evaluated using homeostasis model assessment-insulin resistance. Carotid atherosclerosis was measured using high-resolution ultrasound. We used Cox's proportional hazards models to estimate the association between ACS and atherosclerosis, cardiovascular (CV) risk factors, and RA line of treatment.
Results
Among the 124 RA patients without a history of previous ACS, 16 incident ACS events occurred over 30 months. Old age, long RA disease duration, high BMI, and 10-year cardiovascular disease risk were associated with an increased risk for ACS. High mean disease activity score 28, rheumatoid factor, and anticitrullinated peptide antibodies (ACPA) levels were significantly associated with ACS risk. Treatment with disease-modifying antirheumatic drugs or biological disease-modifying antirheumatic drugs (DMARDs) did not alter the ACS risk. Logistic regression analysis showed that carotid plaques were a good predictor for ACS in RA patients.
Conclusion
The main finding of this study was a general tendency toward an association of disease activity, rheumatoid factor, and ACPA with the risk for ACS. In addition, subclinical atherosclerosis detected by means of carotid intima-media thickness and the presence of carotid plaques were good predictors for RA patients with ACS. Treatment with any DMARD or biologic DMARDs was not linked to an altered risk for ACS.

Keywords:
acute coronary syndrome, atherosclerosis, rheumatoid arthritis

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Introduction

Cardiovascular disease (CVD) is considered the chief cause of death in rheumatoid arthritis (RA) patients. RA increases the risk for cardiovascular (CV) mortality by up to 50% when compared with general population [1–3]. Traditional CV risk factors (hypertension, smoking, and diabetes mellitus) failed to explain the increased risk for mortality in RA [4].

Systemic inflammation associated with RA appears to be a key factor of increased CV risk [1]. Chronic inflammatory state in RA is related to accelerated atherosclerosis, exacerbating adverse changes in both proven and novel CV risk factors [5,6].

Atherosclerosis of the carotid vasculature has a direct link with high CVD rates [7]. Measurement of the intima-media thickness (IMT) of the carotid artery is a noninvasive useful index for detecting preclinical atherosclerosis and predictor of coronary artery diseases [8].

Furthermore, histological evidence of inflammation and plaque instability in the coronary arteries of patients with RA was detected in a postmortem series compared with non-RA controls [9]. This supports the theory that the mechanisms responsible for CV events in RA may vary from those in the general population.

The aim of this study was to assess the role of clinical and laboratory measures of disease activity, line of treatment, multiple CV risk factors, and carotid

atherosclerosis on the risk for acute coronary syndrome (ACS) in a relatively large cohort of RA patients.

Patients and methods

Study design

Between 1 January 2014 and 30 June 2016, the present cross-sectional study was conducted on 124 RA patients who fulfilled the 2010 RA classification criteria [10]. The sample size for the present study originated from a group of 230 consecutive RA patients (28 patients were excluded due to overlap with other rheumatic diseases, 32 patients were excluded because of a history of ischemic heart disease before the diagnosis of RA, 40 patients were excluded due to severe comorbid condition, and six patients were unwilling to participate in the study).

The patients were recruited from the rheumatology outpatient clinic and rheumatology Inpatient Department of Alnoor Specialist Hospital, a tertiary care teaching institute in Makkah, Saudi Arabia. Patients with the following conditions were excluded from the study: (i) age under 18 years; (ii) RA overlap with other rheumatic diseases; (iii) individuals with a history of ischemic heart disease before the diagnosis of RA; (iv) cases of ACS that began before the baseline visit were not counted in this study; (v) severe comorbid cases such as patients with end-stage renal failure, respiratory failure, and liver failure, which is likely to compromise survival or study participation; and (vi) unwillingness to cooperate with study procedures, or other inabilities.

Approval was obtained from the Local Research Ethics Committee of Alnoor Specialist Hospital, and written informed consent was obtained from each participant (N:11237).

Clinical assessment

Patients were subjected to the following procedures: full medical history; thorough clinical examination including general and systemic (especially blood pressure measurement and BMI calculation) and information on all systemic treatments with antiplatelet usage (asprin), lipid-lowering medication (statin), disease-modifying antirheumatic drugs (DMARDs), glucocorticoid treatment, and its dose and biological DMARDs.

RA disease activity was assessed using the disease activity score 28 (DAS28) [11] and classified as low, moderate, or high disease activity according to the European League against Rheumatism definition, with low disease activity defined as DAS28 less than or equal to 3.2, moderate defined as DAS28 between 3.2 and less than or equal to 5.1, and high defined as DAS28 greater than 5.1. Remission is defined as DAS28 less than 2.6 [12]. Health Assessment Questionnaire results were also collected [13].

Medical chart data including all visits at rheumatology clinics or cardiology clinic from the time of RA diagnosis to the end of the study were collected. Patients were evaluated until completion of the study, or the initial occurrence of ACS, the one that occurred first. In the event of multiple occurrences of ACS, only the first was counted.

ACS outcome was defined as the first episode of ACS and/or intervention for ACS registered (myocardial infarction, unstable angina, cardiac arrest, or death with ischemic heart disease listed as the first or first underlying cause of death on the death certificate) after RA diagnosis until the end of the study. Medical charts were retrieved to ensure that the diagnostic criteria for ACS, as defined by the Joint European Society of Cardiology/American College of Cardiology Committee [14], were fulfilled. Conventional CVD risk factors such as age, sex, smoking status, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and the Systematic Coronary Evaluation Score (SCORE) [15] were calculated to determine the 10-year risk for fatal CVD.

Laboratory evaluation

The following laboratory investigations were carried out: complete blood count, fasting venous plasma glucose, fasting serum insulin level (enzyme-linked immunosorbent assay method), serum lipid profile, rheumatoid factor (RF), and anticyclic citrullinated protein antibody. Insulin resistance (IR), which is the main outcome of the metabolic syndrome, was evaluated using the homeostasis model assessment (HOMA) (calculator available from www. OCDEM. ox.ac.uk), which is based on fasting plasma glucose and serum insulin concentrations [16]. Values were considered abnormal when HOMA-IR was more than 2 [17].

Carotid ultrasound

After a baseline evaluation at the recruitment site, we invited all patients for an additional visit to undergo a high-resolution B-mode carotid ultrasound evaluation; Mylab 70 Esaote (Genoa, Italy) equipped with a 7–12 MHz linear transducer and the automated software-guided technique radio frequency-quality IMT in real-time (Esaote, Maastricht, the Netherlands) was used.

The patients were placed in supine position with the chin extended, turning the head away from the side being examined. Measurements were made bilaterally at the carotid bulb, at 1 cm distal to common carotid artery far wall proximal to the bulb and in the proximal most portion of the internal carotid artery near its origin. The mean of the six readings so obtained was used to calculate the carotid intima-media thickness (CIMT) [18]. A cutoff value of 0.72 mm was taken for IMT; patients who had IMT above this value were considered to have atherosclerosis [19]. Carotid artery plaques were identified bilaterally as recommended in the Mannheim consensus – that is, when a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness of greater than 1.5 mm as measured from the media–adventitia interface of the intima–lumen interface [20].

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using statistical package for social science SPSS version 17.0 (SPSS, Chicago, IL, USA). Quantitative variables were described as mean and SD. Qualitative variables were described as number and percentage. The unpaired *t*-test was used to compare two groups as regards quantitative variables. The χ^2-test was used to compare qualitative variables between groups. The one-way analysis of variance test was used to compare more than two groups. The Spearman correlation test was used to rank different variables against each other positively or inversely. Logistic regression analysis was used to discover the effect of qualitative parameters in another parameter. A *P*-value less than or equal to 0.05 was considered statistically significant. Cox proportional hazard models were used to evaluate associations between risk factors and development of ACS. Associations were expressed in the form of hazard ratios, and 95% confidence intervals represented the uncertainty of the estimation. The hazard ratio was interpreted as a multiplier of the risk for ACS, corresponding to a 1-U increase in the predictor.

Results

One hundred and twenty-four RA patients were included in this study [110 (88.7%) female and 14 (11.3%) male]. Patients were subdivided according to the presence or absence of ACS into two groups (Table 1). Patients with ACS were in their fifth decade of life (mean±SD: 58.31±12.16) years with a significant difference between them and patients without ACS as regards the age (Table 1). There was no association between hypertension, diabetes mellitus, or smoking and ACS. Patients with high BMI were significantly associated with a risk for ACS (P=0.025). RA patients with ACS were significantly associated with the 10-year CVD risk (P<0.05). The mean RA disease duration among patients with ACS was 10.11 years with a significant difference between them and patients without ACS.

The high DAS28 was associated with an increased risk for ACS. Among the other DAS28 components (number of tender joints and number of swollen joints), there were generally negative associations except for patient global health assessment, which was significantly associated with ACS (P=0.05). Almost 60% of the patients with ACS (62.5%) had moderate DAS28 score (3.2–5.1); 12.5% had severe disease activity. Only four (12%) patients had mild disease activity.

On comparison of serum lipid profile among patients with and those without ACS, there was no significant difference in the mean serum total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein levels between the two groups. In the present study, serum insulin levels and IR determined using the HOMA-IR were found to be significantly higher in patients in the ACS group compared with the other group.

Univariate analysis demonstrated a statistically significantly increased risk for ACS in patients with high C-reactive protein (CRP), positive RF, and high level of anticyclic citrullinated protein antibody.

The mean IMT at various points of measurement and the mean of the six-readings, CIMT, are shown in Table 1. RA patients with ACS had a higher mean CIMT compared with RA patients without ACS (P=0.001). Carotid plaque was found more frequently among the cases with ACS compared with cases without ACS (P=0.034).

Figure 1 showed that for a cutoff value of CIMT greater than or equal to 0.72 mm, the sensitivity and specificity were 75.0 and 70.4%, respectively, with an accuracy of 76.9%. In addition, logistic regression analysis showed that plaques were a strong predictor for ACS in RA patients (the sensitivity and specificity were 62.5 and 84.259%, respectively, with an accuracy of 81.452%).

Table 2 shows the recorded characteristics that were independently significantly related to ACS patients in a multivariable logistic regression model. Of the 14

Table 1 Comparison between the two groups of rheumatoid arthritis patients as regards demographic, cardiovascular risk, clinical, laboratory, and radiological parameters

	Patients without ACS (*n*=108)	Patients with ACS (*n*=16)	*P*-value	Odd (95% CI)
Demographics				
Age (years)	48.44±12.83	58.31±12.16	0.005*	1.072 (1.019–1.127)
Sex				
Male	11 (10.19)	3 (18.75)	0.344	0.491 (0.121–1.996)
Female	97 (89.81)	13 (81.25)		
CVR factor				
Hypertensive[a]	53 (49.07)	10(62.50)	0.320	1.730 (0.587–5.094)
Diabetes mellitus	31 (28.70)	6(37.50)	0.481	1.490 (0.499–4.453)
BMI (kg/m^2)	28.194±6.604	30.507±5.154	0.025*	1.11 (1.013–1.219)
Current smoker	9 (8.33)	3 (18.75)	0.201	2.54 (0.608–10.595)
10 years CVR	2.73±3.85	6.88±7.36	0.042*	1.146 (1.046–1.255)
Disease status				
Duration of RA (years)	5.462±4.767	10.113±7.114	<0.001**	1.253 (1.107–1.418)
DAS28	3.343±1.193	3.796±1.059	0.028*	1.285 (0.801–2.062)
EULAR disease activity score				
≤3.1 (low)	40 (37.04)	4(25)	0.290	1.602 (0.669–3.836)
3.2–5.1 (moderate)	60 (55.56)	10(62.50)		
≥5.2 (high)	8 (7.41)	2 (12.50)		
Disease disability index	0.93±1.14	1.06±0.68	0.505	1.102 (0.732–1.659)
Laboratory values				
Total cholesterol (mg/dl)	187.66±42.25	184.19±53.26	0.806	0.998 (0.986–1.010)
Triglycerides (mg/dl)	114.32±59.26	116.31±56.76	0.900	1.001 (0.992–1.009)
HDL cholesterol (mg/dl)	53.57±11.63	54.50±15.96	0.826	1.006 (0.964–1.050)
LDL cholesterol (mg/dl)	119.92±41.81	124.44±49.93	0.734	1.002 (0.990–1.015)
Serum insulin (uIU/ml)	9.349±6.129	13.745±7.664	0.002*	1.119 (1.042–1.201)
HOMA-IR	2.100±1.386	4.564±4.301	0.000*	1.605 (1.249–2.062)
C-reactive protein (mg/dl)	1.04±1.68	2.25±5.38	0.025*	1.136 (1.165–1.336)
ESR (mm/h)	36.99±24.62	37.00±24.71	0.999	1 (0.979–1.022)
RF positive	77 (71.30)	14 (87.5)	0.017*	0.264 (0.089–0.787)
ACCP antibody positive	75 (69.44)	14 (87.5)	0.048*	4.631 (1.002–21.40)
ACCP antibody level				
Low positive	43 (39.81)	4(25)	0.012*	2.589 (1.238–5.415)
Strong positive	32(29.63)	10(62.5)		
Radiological parameters				
CIMT (mm)	0.68±0.16	0.81±0.15	0.006*	109.6 (3.8–3136.13)
Plaques positive	17 (15.74)	10 (62.5)	0.034*	0.313 (0.107–0.915)

Values are given as mean±SD or *n* (%). ACCP, anticyclic citrullinated protein antibody; ACS, acute coronary syndrome; CVR, cardiovascular risk; DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; EULAR, European League against Rheumatism; HAQ, Health Assessment Questionnaire; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; CI, confidence interval; CIMT, carotid intima-media thickness; LDL, low-density lipoprotein; RA, rheumatoid arthritis; RF, rheumatoid factor. [a]Systolic pressure>150 mmHg or diastolic pressure>90 mmHg. *P<0.05. **P<0.001.

characteristics entered into the model, three (RF, presence of anticyclic citrullinated protein antibodies, and carotid plaques) were significantly associated with ACS.

Pharmacologic therapies used in the treatment of RA patients are presented in Table 3. As expected, among the vast majority of RA patients with and those without ACS under DMARDs treatment, there was no statistically significant difference between the two groups with regard to line of treatment. More than 90% of patients were under DMARDs and approximately one-third in each group received corticosteroids. No significant difference emerged between the two groups either in antiplatelet usage (aspirin), lipid-lowering agent (statin), cumulative steroid dose, anti-tumor necrosis factor (anti-TNF) therapy (adalimumab, etanrecept, and infliximab), interleukins-6 receptors inhibitor (tocilizumab), abatacept, and rituximab.

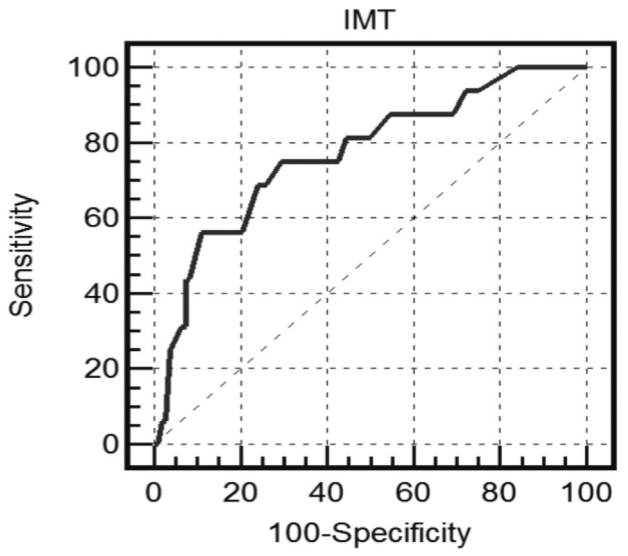
Discussion

The focus of this study was to examine factors associated with the presence of ACS in RA patients. Inflammation is a key feature during all stages of atherosclerotic pathogenesis [21]. Inflammation affects the composition and stability of atherosclerotic lesions

and also promotes clotting [22], and hence induces permissive conditions for atherothrombotic events. Our findings of an association between indices of high average clinical disease activity, based on DAS28, patient global health assessment questioner score, and the risk for ACS is consistent with previous reports [2,23,24].

High inflammatory activity worsens clinical symptoms and general well-being, leading to poorer general health, and hence DAS28 score. High overall disease activity reduces the level of physical function. Furthermore, implementation of adequate physical activity levels has been associated with a better CV profile in RA [25]. Importantly, the general health score does not reflect merely RA disease activity but can also be affected by the presence of other comorbidities and by general well-being. We also documented a positive association between ACS and RA disease duration. This suggests a role for chronic inflammation in the development of CV event.

Figure 1



Receiver operating characteristic (ROC) curves between acute coronary syndrome outcome (positive and negative) and carotid intima-media thickness.

The increased risk for CVD in RA is associated with, although not entirely attributed to, traditional risk factors already established in the general population [9]. Similarly, we found that there was no association between hypertension, diabetes mellitus, or smoking as independent parameters and ACS. Even diabetes and hypertension remained independently associated with ACS that served to refocus attention on their importance in determining the existence of CV events in RA.

Ljung *et al.* [26] documented that the risk for ischemic heart disease in patients with RA was elevated compared with general population and was less manifest in TNF-exposed patients. This risk has been linked to the degree of activity and severity of the disease.

Patients with high BMI and high 10-year CVD risk score were significantly associated with a risk for ACS. In recent years, there has been an increased appreciation that adipose tissue should be viewed as an active endocrine organ. Adipocytokines, in particular adiponectin, are known to have antidiabetic, insulin sensitizing, anti-inflammatory,

Table 2 Multivariable logistic regression model for acute coronary syndrome

	B	SE	Wald	*P*-value	Odd	95% CI for odd	
						Lower	Upper
Age (years)	0.117	0.111	1.125	0.289	1.124	0.905	1.396
BMI (kg/m^2)	0.198	0.128	2.379	0.123	1.219	0.948	1.567
Duration (years)	0.417	0.237	3.093	0.079	1.518	0.953	2.417
DAS28	0.574	0.794	0.523	0.470	1.776	0.374	8.424
HAQ	–0.017	0.049	0.126	0.723	0.983	0.893	1.082
Serum insulin (μIU/ml)	–0.013	0.133	0.010	0.922	0.987	0.761	1.281
HOMA-IR	0.751	0.442	2.888	0.089	2.120	0.891	5.041
RF Positivity	–9.472	3.870	5.990	0.014*	0.000	0.000	0.152
ACCP Positivity	11.713	5.088	5.299	0.021*	122 139.153	5.701	2 616 927 866.53
ACCP level	–0.708	1.329	0.283	0.594	0.493	0.036	6.670
10 years CVR	0.160	0.190	0.711	0.399	1.174	0.809	1.703
C-reactive protein (mg/dl)	0.200	0.160	1.564	0.211	1.221	0.893	1.670
CIMT (mm)	–3.571	7.531	0.225	0.635	0.028	0.000	72 376.604
Plaques	1.967	0.702	7.854	0.005*	7.150	1.807	28.299

ACCP, anticyclic citrullinated protein antibody; *B*, coefficient; CIMT, carotid intima-media thickness; CVR, cardiovascular risk; DAS28, disease activity score 28; HAQ, Health Assessment Questionnaire; HOMA-IR, homeostasis model assessment-insulin resistance; OR, odds ratio; RF, rheumatoid factor. *$P<0.05$. **$P<0.001$.

Table 3 Comparisons between two groups as regards line of treatment

	Patients without ACS (*n*=108) [*n* (%)]	Patients with ACS (*n*=16) [*n* (%)]	*P*-value	Odd (95% CI)
Line of treatment				
Statin usage	50 (46.30)	11 (68.75)	0.094	3.353 (1.017–11.05)4
Asprin usage	51 (47.22)	11(68.75)	0.179	0.4067 (0.132–1.249)
DMARDs				
MTX	99 (91.67)	15 (93.75)	0.768	1.364 (0.161–11.546)
Other than MTX	98 (90.74)	16 (100.00)	0.999	–
Corticosteroid	42 (38.89)	5 (31.25)	0.557	0.714 (0.232–2.202)
Corticosteroid dose (mg)	2.07±2.75	1.56±2.39	0.447	0.928 (0.752–1.145)
bDMARDs				
Adalimumab	12(11.11)	1(6.25)	0.662	0.776 (0.372–1.621)
Etanrecept	13 (12.04)	2 (12.50)		
Infleximab	4 (3.70)	0 (0.00)		
Tocilizumab	14 (12.96)	1 (6.25)	0.453	0.448 (0.055–3.658)
Abatacebt	14 (12.96)	4 (25)	0.211	2.238 (0.633–7.916)
Rutoximab	2 (1.85)	0 (0.00)	0.455	–

ACS, acute coronary syndrome; bDMARDs, biologic disease-modifying antirheumatic drugs; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrxate.

and vasculature protective properties [25]. Circulating adiponectin reduced with increasing adiposity (BMI), IR, atherogenic lipid profile, increased inflammatory markers (CRP, TNF, and interleukin-6), which lead to increased risk for CVD and possibly coronary plaque susceptibility [27–30].

In this study, no significant difference in the lipid profile was found between the RA patients with and those without ACS. In RA, inflammation is associated with a paradoxical inversion of the relationship between CV risk and lipid levels [31–33]. Importantly, several studies have reported increases in lipid levels with a successful reduction in RA disease activity following anti-inflammatory treatment [34]. These findings suggest that the traditional analysis of lipid profiles for predicting CV risk may be confused with disease activity in RA patients [31,32].

In the present study, IR determined using the HOMA-IR was found to be significantly higher in the ACS patient group compared with the non-ACS group. Our results as well as those obtained from La Montagna *et al.* [17] revealed a significant difference between the two groups as regards HOMA-IR.

In our study, RF and ACPA positivity were associated with an increased risk for ACS. Seropositivity, for either RF or ACPAs, is associated with a more severe clinical prognosis [35,36]. Studies that have identified RF as a risk factor for CVD in RA are typically based on older cohorts [37–39], whereas one study of a contemporary RA cohort failed to identify RF as a CV risk marker [24]. It is possible that the development of more efficient RA treatments has effectively altered and improved the disease course of patients who otherwise would have had more severe disease, and that previously reported associations were a reflection of severe disease. In a Spanish RA cohort enrolled between 1988 and 2003, the presence of ACPA was associated with a 2.5-fold increased risk for ischemic heart disease even after adjustment for erythrocyte sedimentation rate, RF, and treatments [24]. ACPA-positive RA has also been associated with an increased risk for subclinical manifestations of CVD, such as more extensive atherosclerotic lesions and structural myocardial abnormalities [40].

There was a strong confirmation suggesting that chronic inflammation plays a role in atherogenesis and in CV morbidity and mortality [41–44].

In addition to the high-grade inflammation seen in rheumatoid joints, blood from RA patients also demonstrate a high concentration of markers of inflammation, such as interleukin-1 and TNF-α [45].

These markers regulate cell-mediated immunity, promoting inflammatory cell migration through the vascular endothelium, resulting in endothelial dysfunction [46,47].

The CIMT has been linked with the severity and the chronicity of the inflammatory response. Long-standing RA patients with mean CRP levels greater than 15 mg/dl had higher CIMT values than those with lower CRP levels [48]. In agreement with the previous reports [46–49], our findings suggest that atherosclerosis is a good predictor for the CV complications of RA patients. At a cutoff value of

CIMT greater than or equal to 0.72 mm, the sensitivity and specificity were 75.0 and 70.4%, respectively, with an accuracy of 76.9% in the prediction of ACS. The presence of plaque in both internal carotid arteries nearly quadrupled the incidence of new ACS compared with that in patients without carotid plaque. Logistic regression analysis showed that plaques were a good predictor for ACS in RA patients. In the multivariable logistic regression model the presence of carotid plaques remained a strong predictor for ACS. The absence of the residual variables from the predictive model should not be understood to mean that they are not associated with ACS, but rather that more outcome events (i.e. more statistical power) would be needed to detect their weaker signals. Alternatively, their absence from the predictive model could mean that their association with ACS is mediated through atherosclerosis. An example of the latter is shown in Table 3, in which age loses its association with ACS, suggesting that age is associated with ACS through the mechanism of atherosclerosis accrual over time.

Further longitudinal follow-up of these patients over a period of time to look for clinical events that reflect the consequences of atherosclerosis would provide valuable corroboration of the observations from this study. Furthermore, the present study was conducted in a Saudi RA population, reflecting only the Saudi healthcare setting. Studying of ACS risk factors should be generalizable; the observed risks may not be directly applicable to populations with different levels of disease control, other CV risk factors, or underlying ACS risks.

Conclusion

The main finding of this study was a general tendency toward an association between disease activity, RF, and ACPA with the risk for ACS. In addition, subclinical atherosclerosis detected by CIMT and the presence of carotid plaques were good predictors for RA patients with ACS. Treatment with methotrexate or any other DMARD, biologic DMARDs, was not linked to an altered risk of ACS in the time frames under study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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