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Prevalence of cardiovascular diseases and traditional cardiovascular risk factors in patients with rheumatoid arthritis: a real-life evidence from BioSTAR nationwide registry

Mehmet Tuncay Duruöz[1] · Şebnem Ataman[2] · Hatice Bodur[3] · Hasan Fatih Çay[4] · Meltem Alkan Melikoğlu[5] · Özgür Akgül[6] · Erhan Çapkın[7] · Gülcan Gürer[8] · Remzi Çevik[9] · Feride Nur Göğüş[10] · Ayhan Kamanlı[11] · Fatma Gül Yurdakul[12] · İlker Yağcı[13] · Aylin Rezvani[14] · Lale Altan[15]

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Abstract

Patients with rheumatoid arthritis (RA) have increased morbidity and mortality due to cardiovascular (CV) comorbidities. The association of CV diseases (CVD) and traditional CV risk factors has been debated, depending on patient and RA characteristics. This study aimed to find the prevalence of CVD and CV risk factors in patients with RA. A multi-center cross-sectional study was performed on RA patients using the BioSTAR (Biological and Targeted Synthetic Disease-Modifying Antirheumatic Drugs Registry) in September 2022. Socio-demographic, clinical, and follow-up data were collected. Myocardial infarction, ischemic heart disease, peripheral vascular disorders, congestive heart failure, ischemic stroke, and transient ischemic attack were regarded as major adverse cardiovascular events (MACEs). CVD was defined as the presence of at least one clinical situation of MACE. Group 1 and Group 2 included patients with and without CVD. Prevalence rates of CVD and traditional CV risk factors were the primary outcomes. Secondary outcomes were the differences in the clinical characteristics between patients with and without CVD. An analysis of 724 patients with a mean age of 55.1 ± 12.8 years diagnosed with RA was conducted. There was a female preponderance (79.6%). The prevalence rate of CVD was 4.6% ($n = 33$). The frequencies of the diseases in the MACE category were ischemic heart disease in 27, congestive heart failure in five, peripheral vascular disorders in three, and cerebrovascular events in three patients. The patients with CVD (Group 1) were significantly male, older, and had higher BMI ($p = 0.027$, $p < 0.001$, and $p = 0.041$). Obesity (33.4%) and hypertension (27.2%) were the two CV risk factors most frequently. Male sex (HR = 7.818, 95% CI 3.030–20.173, $p < 0.001$) and hypertension (HR = 4.570, 95% CI 1.567–13.328, $p = 0.005$) were the independent risk factors for CVD. The prevalence of CVD in RA patients was 4.6%. Some common risk factors for CVD in the general population, including male sex, older age, and hypertension, were evident in RA patients. Male sex and hypertension were the independent risk factors for developing CVD in patients with RA.

Keywords Rheumatoid arthritis · Comorbidity · Major adverse cardiac events · Cardiovascular risk · Secondary disease prevention · Prevalence

Introduction

Rheumatoid arthritis (RA) is a chronically progressive inflammatory condition associated with increased risks for atherosclerosis-related cardiovascular (CV) diseases, lung cancer, osteoporosis, and depression [1, 2]. Autoimmunity has been regarded as the underlying pathological mechanism in RA. So, the co-occurrence of other immunoinflammatory conditions, such as atherosclerotic heart diseases, might be seen more frequently in patients with RA [1, 3]. The heightened risk of CV diseases (CVD) in RA patients, with a factor of 1.5, is noteworthy, particularly in cases with a disease duration of ≥ 10 years, positivity for rheumatoid factor and/or anti-citrullinated protein/peptide antibody, and the presence of extra-articular manifestations, as per the European League Against Rheumatism (EULAR) recommendations [3]. Furthermore, an association between the disease activity

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of RA and venous thromboembolism has been demonstrated previously [4].

The intricate interplay of inflammatory mechanisms in RA manifests through elevated levels of various cytokines and pro-inflammatory markers, including tumor necrosis factor-alpha (TNF-α), interleukin-1, interleukin-6, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). These indicators reflect higher disease activity and pose an increased risk for the development of CVD [5–8]. The medications, such as hydroxychloroquine, anakinra, and tocilizumab, which are integral to RA treatment, benefit endothelial function and inflammation control [9, 10]. In that way, regression of the inflammatory status via pharmacological agents suppressing the increased levels of the cytokines might be effective for treating RA and reducing the CV risk. Previous studies that reported decreased CV mortality rates secondary to anti-inflammatory medications have supported this idea [6, 9, 11, 12].

Within the RA patient population, the development of CVD, such as congestive heart failure, stroke, ischemic cardiomyopathy, and myocardial infarction, are among the leading causes of morbidity and mortality [7, 9, 13–15]. While traditional CV risk factors intricately connect with the diagnosis and prognosis of CVD in RA patients, they often fall short of fully elucidating the excess burden observed in these cases [3, 5, 16]. The increased risk of CVD and mortality was partially attributable to the traditional CV risk factors, i.e., dyslipidemia, hypertension, obesity active smoking, and diabetes [5]. Nevertheless, Gouze et al. [17] reported that RA was significantly associated with increased CV risk, independent of the traditional risk factors according to the findings of the Electricité de France—Gaz de France (GAZEL) cohort [12, 18]. Moreover, the treatment of RA using non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids might lead to detrimental effects on the CV system [3]. Consequently, investigating the incidence of major adverse cardiovascular events (MACE), namely, myocardial infarction, ischemic heart disease, peripheral vascular disorders, congestive heart failure, ischemic stroke, and transient ischemic attack, in RA patients might be beneficial to identify the riskiest group [2, 7].

The establishment of the BioSTAR-RA (Biological and Targeted Synthetic Disease-Modifying Antirheumatic Drugs Registry) database by the Turkish League Against Rheumatism (TLAR) stands as a pivotal initiative aimed at collecting data on the course of RA in Turkey, thereby facilitating the monitoring of treatment applications in RA [19]. The significance of long-standing registries as imperative tools for delineating a disease's unique course within a given population cannot be overstated [20, 21]. By harnessing real-world data, these registries offer a valuable platform for implementing treat-to-target strategies concerning chronic inflammatory conditions [19]. Consequently, an in-depth analysis of registry-based cohorts emerges as a valuable approach to identifying the risk factors for CVD in RA patients.

This study aimed to assess the prevalence of CVD and CV risk factors in patients with RA and identify the demographic, clinical, and disease-related parameters correlating with the development of MACEs.

Materials and methods

Study

A multi-center cross-sectional study was conducted on rheumatoid arthritis (RA) patients, utilizing the BioSTAR-RA database, which encompasses follow-up data. This study investigated the prevalence rates of CV events and CV risk factors in patients diagnosed with RA. Experienced physicians performed all admission and follow-up examinations. The medical data were prospectively uploaded into a predetermined electronic worksheet, including comorbidities, disease characteristics, disease activity parameters, patient-reported outcomes, medications, and adverse events. For the current study, the patient's medical information was evaluated in September 2022. The local ethical committee approved the study (Ankara Numune Training and Research Hospital, Number: E-182413; Turkish Medicine and Medical Devices Agency, 66175679-514.99-E182413). This study was carried out in compliance with the Declaration of Helsinki of 1964 and later versions. Written informed consent was taken from the patients who participated in the BioSTAR-RA database.

Patients

The information on the patients with RA was recruited from the attending tertiary hospitals in the registry. The American College of Radiology (ACR) and European League Against Rheumatism (EULAR) identification parameters were used to determine the diagnosis of RA [6, 7]. History of ischemic heart and peripheral vascular diseases, congestive heart failure, and cerebrovascular events were not regarded as the exclusion criteria. Baseline and the 6-month follow-up data of the demographic, laboratory investigations, disease-related clinical parameters, treatment details, and occurrence of MACEs were collected. The patients aged 18 years or more were included. The patients with missing socio-demographic or clinical data were excluded.

Study variables

The socio-demographic data included age, sex, body mass index (BMI), educational and marital status, smoking and alcohol status, comorbidities, and geographic regions of

Turkey for living. The patients were grouped in age based on the cut-off value of 40 years. The BMI values were calculated as weight in kilograms divided by the square of height in meters (kg/m^2), and a stratification BMI ≥ 30 kg/m^2 and < 30 kg/m^2 was performed. The BMI values of at least 30 kg/m^2 were regarded as the cut-off for obesity [22]. The laboratory investigations' results were recorded during the patient's last admission to the attending centers.

We collected data regarding the patients' disease-related characteristics, including the delay in diagnosis (months) and duration of the disease (months). The disease activity of RA was evaluated using four indices: The Disease Activity Scores with ESR and CRP (DAS-28 ESR and DAS-28 CRP), the Clinical Disease Activity Index (CDAI), and the Simple Disease Activity Index (SDAI) were used to grade the disease. A DAS28-ESR and DAS-28 CRP scores higher than 5.1, a CDAI score higher than 22, or an SDAI score higher than 26 were regarded as the criteria for the high-disease activity [23–25]. The scores of the patient-reported outcomes, including visual analog scale (VAS) scores for patient global, physician global, pain, and fatigue, were recorded at the last visit. Besides, the scores of the symptom severity, the fibromyalgia severity, the Health Assessment Questionnaire for disease disability (HAQ-DI), the RA Impact of Disease (RAID), and the Compliance Questionnaire-Rheumatology (CQR) were also obtained [23, 26, 27]. All the participants completed the HAQ-DI and RAID questionnaires. The Turkish validation of the questionnaires was performed previously [28–30]. The medication use and switching status were searched using the patient's medical files. The medications were grouped as rituximab, tocilizumab, TNF-α blockers, abatacept, and Janus kinase inhibitors for the analysis based on the action mechanisms of the pharmacological agents.

Traditional/classic CV risk factors

The presence of CV risk factors was searched: (1) dyslipidemia (physician diagnosis, or the use of lipid-lowering medication, or at least one factor: total cholesterol > 200 mg/dl, triglycerides > 150 mg/dl, HDL-cholesterol < 40 mg/dl in men or < 50 mg/dl in women, or LDL-cholesterol > 130 mg/dl), hypertension (physician diagnosis and/or use of antihypertensive medications), (2) obesity (BMI ≥ 30 kg/m^2), (3) currently active smoking, and (4) diabetes mellitus (physician diagnosis, or glycemia > 126 mg/dl, HbA1c > 6.5%, or glucose-lowering drugs or insulin therapy) [31].

Groups

The patients were grouped according to the proven diagnoses of MACEs. Group 1 consisted of patients with CVD. These patients had at least one clinical situation in the broad category of MACE, including myocardial infarction, ischemic heart disease, peripheral vascular disorders, congestive heart failure, ischemic stroke, and transient ischemic attack [2, 7]. Group 2 included the patients without CVD.

Statistical analysis

The primary outcome was the prevalence rates of patients with CVD and traditional CV risk factors. The secondary outcomes were the differences in the clinical characteristics between patients with and without CVD. For descriptive statistics, mean ± standard deviation was used to present continuous data with normal distribution. Median with minimum–maximum values was applied for continuous variables without normal distribution. Numbers and percentages were used for categorical variables. The Shapiro–Wilk and Kolmogorov–Smirnov tests analyzed the normal distribution of the numerical variables. The Independent Samples *t*-test compared two independent groups where numerical variables had a normal distribution. The Mann–Whitney *U* test was applied for the variables without normal distribution in comparing two independent groups. The Pearson's Chi-Squared and Fisher's Exact tests were used in comparing the differences between categorical variables in 2 × 2 tables.

The univariable and multivariable Cox proportional hazard regression models were used to estimate the crude hazard ratios (HRs) and 95% confidence interval (CI) values based on the demographic and clinical variables for the development of the composite MACE during the duration of the diseases [3]. In these analyses, we categorized for potential confounders: sex, age, BMI (< 30 kg/m^2/ ≥ 30 kg/m^2), smoking and alcohol (consumer or not), comorbidities, the disease activity scores, and DAS-28 CRP, DAS-28 ESR, CDAI, and SDAI groups (non-high/high risk).

IBM SPPS Statistics (version 22.0, IBM Corp., Armonk, NY, USA) was used for statistical analysis. The significance level (p-value) was determined at 0.05 in all statistical analyses.

Results

There were 724 patients with RA in the cohort. The mean age of 148 male (20.4%) and 576 female (79.6%) patients was 55.1 ± 12.8 years. The socio-demographic and clinical characteristics of the patients are given in Table 1. The prevalence rate of CVD in the study group was 4.6% (n = 33). The frequencies of the diseases in the MACE category were ischemic heart disease in 27, congestive heart failure in five, peripheral vascular disorders in three, and cerebrovascular events in three patients. There were significant differences in the age of the patients, sex distribution, and BMI ($p < 0.05$). (Table 1). The patients with CVD

Table 1 Socio-demographic and clinical characteristics of the study groups

	Overall ($n=724$)	Group 1 ($n=33$)	Group 2 ($n=691$)	p
Age (year)[a]	55.1 ± 12.8 (57, 13–88)	62 (41–88)	56 (13–87)	< 0.001
Age group[b]				
< 40 years	92 (12.7)	0 (0)	92 (13.3)	0.015
≥ 40 years	632 (87.3)	33 (100)	599 (86.7)	
Sex[b]				
Male	148 (20.4)	12 (36.4)	136 (19.7)	0.027
Female	576 (79.6)	21 (63.6)	555 (80.3)	
BMI (kg/m^2)[a]	27.7 (16.2–44.1)	29.9 (18.1–41.5)	27.9 (16.2–44.1)	0.041
Obesity[b]				
≥ 30 kg/m^2	242 (33.4)	16 (48.5)	226 (32.7)	0.087
Smoking[b]				
Current smoker	101 (14.1)	1 (3.0)	100 (14.7)	0.071
Alcohol[b]				
Current consumer	21 (3.0)	2 (6.3)	19 (2.8)	0.248
Marital status[b]				
Married	621 (85.8)	29 (87.9)	592 (85.7)	1.0
Single/divorced/widowed	103 (14.2)	4 (12.1)	99 (14.3)	
Educational status[b]				
Illiterate/primary	448 (61.9)	22 (66.7)	426 (61.6)	0.865
High school	202 (27.9)	9 (27.3)	193 (27.9)	
University or higher	73 (10.1)	2 (6.1)	71 (10.3)	
Geographical regions[b]				
Marmara	121 (16.7)	6 (18.2)	115 (16.7)	0.364
Aegean	161 (22.2)	4 (12.1)	157 (22.8)	
Mediterranean	99 (13.7)	3 (9.1)	96 (13.9)	
Central Anatolia	142 (19.6)	8 (24.2)	134 (19.49)	
Black sea	61 (8.4)	5 (15.2)	56 (8.1)	
Eastern Anatolia	92 (12.7)	3 (9.1)	89 (12.9)	
Southeastern Anatolia	46 (6.4)	4 (12.1)	424 (6.1)	
Comorbidities[b]				
Hypertension	197 (27.2)	22 (66.7)	175 (26.6)	< 0.001
Diabetes mellitus	100 (13.8)	12 (36.4)	88 (13.7)	0.001
Chronic renal failure	23 (3.2)	5 (15.2)	18 (2.9)	0.004
Dyslipidemia	61 (8.4)	11 (44.0)	50 (11.9)	< 0.001
COPD	39 (5.4)	6 (18.2)	33 (4.8)	0.007
Coagulopathy	6 (0.8)	3 (10.3)	3 (0.5)	0.002
Malignancy	12 (1.7)	2 (6.3)	10 (1.6)	0.113
Valvular heart disease	11 (1.5)	2 (6.1)	9 (1.3)	0.256

Groups 1 and 2: Patients with and without major adverse cardiovascular event (cardiovascular disease)

BMI, body mass index; COPD, chronic obstructive pulmonary disease

[a]Median (min–max)

[b]n (%)

(Group 1) were significantly older and had higher BMI values than those in Group 2 ($p < 0.001$ and $p = 0.041$). No patient was younger than 40 years in Group 1 ($p = 0.015$). In Group 2, the proportion of male patients was significantly higher than in Group 1 ($p = 0.027$). The other characteristics were similar in the groups ($p > 0.005$) (Table 1).

In the overall study group, hypertension ($n = 197$, 27.2%) and diabetes mellitus ($n = 100$, 13.8%) were the most frequent two comorbidities. There were significant differences in the rate of comorbidities between the groups ($p < 0.05$). The proportion of patients with hypertension ($p < 0.001$), diabetes mellitus ($p = 0.001$), chronic

Table 2 Laboratory investigations in the groups

	Group 1 ($n=33$)	Group 2 ($n=691$)	p
Hemoglobin (g/dl)[a]	12.6 (9.4–17.6)	12.7 (7–17.60)	0.924
Leukocyte count (10^3/µl)[a]	7 (1–13.2)	7.4 (1.6–19.56)	0.174
Lymphocyte count (10^3/µl)[a]	2 (1.32–7.39)	2 (1.0–7.0)	0.508
Platelet count (10^3/µl)[a]	230 (120–443)	271 (106–743)	0.008
Creatinine (mg/dl)[a]	0.8 (0.47–1.68)	0.7 (0.18–34)	0.001
GFR (ml/min)[a]	68.1 (1.2–148.5)	89.4 (1.13–633.2)	0.009
ESR (mm/hr)[a]	33.0 (2–106)	21.0 (1–118)	0.055
CRP (mg/dl)[a]	3 (1–13)	4.0 (0.5–680)	0.695
LDL (mg/dl)[a]	122.9 ± 42.0	124.9 ± 37.7	0.499
HDL (mg/dl)[a]	44.4 ± 7.5	54.9 ± 17.8	0.273
Cholesterol (mg/dl)[b]	193.9 ± 46.6	204.9 ± 66.2	0.417
Triglyceride (mg/dl)[b]	169 (72–231)	127.5 (41–532)	0.181

Groups 1 and 2: Patients with and without major adverse cardiovascular event (cardiovascular disease)

GFR, glomerular filtration rate; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein

[a]Median (min–max)

[b]Mean ± standard deviation

renal failure ($n=0.004$), dyslipidemia ($n<0.001$), chronic obstructive pulmonary disease ($p=0.007$), and coagulopathy ($p=0.002$) were significantly higher in Group 1 than in Group 2 (Table 1). In the entire population, obesity (33.4%) and hypertension (27.2%) were the most prevalent traditional CV risk factors (Table 1).

The results of the laboratory investigations are given in Table 2. There were significant differences in the levels of creatinine, glomerular filtration rate, and platelet count between the groups ($p<0.05$). The patients with CVD had significantly higher scores of the DAS-28 CRP, DAS-28 ESR, CDAI, and SDAI than the patients without CVD ($p<0.05$) (Table 3). The other disease-related characteristics and the scores of the patient-reported outcomes were similar between the groups ($p>0.05$). There were no significant differences in the frequencies of the medications and the switch status between the groups ($p>0.05$) (Table 4).

The univariate Cox proportional regression analysis revealed that older age (HR = 1.039, 95% CI 1.005–1.074, $p=0.023$), male sex (HR = 2.518, 95% CI 1.237–5.124, $p=0.011$), obesity (HR = 2.430, 95% CI 1.219–4.843, $p=0.012$), hypertension (HR = 4.322, 95% CI 2.092–8.927, $p<0.001$), diabetes mellitus (HR = 2.688, 95% CI 1.319–5.477, $p=0.006$), and dyslipidemia (HR = 4.166, 95% CI 1.878–9.242, $p<0.001$) were the significant risk factors

Table 3 Disease activity scores and the patient-reported outcomes of the study groups

	Overall ($n=724$)	Group 1 ($n=33$)	Group 2 ($n=691$)	p
Duration of disease (month)[a]	144.6 (0.03–638)	187.8 (38.6–479)	143.1 (0.03–638.2)	0.050
DAS-28 CRP[a]	3.26 (0.96–8.5)	3.45 (1.78–8.06)	3.25 (0.96–8.5)	0.021
DAS-28 CRP high activity[b]	92 (14.2)	4 (12.1)	88 (14.3)	1.0
DAS-28 ESR[a]	3.2 (0.5–8.31)	3.7 (1.05–8.31)	3.2 (0.5–8.0)	0.419
DAS-28 ESR high activity[b]	97 (15.7)	6 (19.4)	91 (15.5)	0.611
CDAI[a]	11 (0–63)	12 (0.8–62)	11 (0–63)	0.756
CDAI high activity[b]	93 (15.5)	6 (20.0)	87 (15.3)	0.444
SDAI[a]	18 (0–79)	14.5 (3.3–64.1)	13.1 (0–79)	0.752
SDAI high activity[b]	103 (15.9)	5 (15.2)	98 (16.0)	1.0
VAS patient global (0–100 mm)[a]	50 (0–100)	50 (0–80)	50 (0–100)	0.712
VAS physician global (0–100 mm)[a]	40 (0–100)	40 (0–80)	40 (0–100)	0.554
VAS pain (0–100 mm)[a]	40 (0–100)	50 (0–100)	40 (0–100)	0.561
VAS fatigue (0–100 mm)[a]	50 (0–100)	50 (0–80)	50 (0–100)	0.904
Symptom severity score[a]	3 (0–12)	4 (0–12)	3 (0–12)	0.379
Fibromyalgia severity scale[a]	6 (0–28)	6 (0–26)	6 (0–28)	0.194
HAQ[a]	0.6 (0–3)	0.4 (0–3)	0.6 (0–3)	0.676
RAID[a]	3.7 (0–10)	3.7 (0–8.5)	3.7 (0–10)	0.653
CQR[a]	63.2 (33.3–91.2)	64.9 (38.6–87.7)	63.2 (33.3–91.2)	0.977

Groups 1 and 2: Patients with and without major adverse cardiovascular event (cardiovascular disease)

DAS-28 ESR, Disease Activity Scores with ESR; DAS-28 CRP, Disease Activity Scores with CRP; CDAI, Clinical Disease Activity Index; SDAI, Simple Disease Activity Index; VAS, Visual analog scale; HAQ, Health Assessment Questionnaire; RAID, Rheumatoid Arthritis Impact of Disease; CQR, Compliance Questionnaire-Rheumatology

[a]Median (min–max)

[b]n (%)

Table 4 Medications used in the study groups

	Group 1 ($n=33$)	Group 2 ($n=691$)	p
Switch[a]			
No switch	3 (9.1)	53 (7.7)	0.624
One switch	1 (3.0)	51 (74)	
Two or more switches	29 (87.9)	587 (84.9)	
Drugs[a]			
Rituximab	6 (18.2)	154 (22.3)	0.673
Tocilizumab	9 (27.3)	114 (16.5)	0.150
Tumor necrosis factor (TNF) inhibitors	14 (42.4)	365 (52.8)	0.286
Abatacept	2 (6.1)	23 (3.3)	0.317
Janus kinase inhibitors	5 (15.2)	92 (13.3)	0.792

Groups 1 and 2: Patients with and without major adverse cardiovascular event (cardiovascular disease)

[a]n (%)

for the development of CVD. In contrast, COPD was protective, with an HR of 0.323 (95% CI 0.133–0.785, $p=0.013$). Nevertheless, the multivariate analysis showed that male sex (HR = 7.818, 95 CI 3.030–20.173, $p<0.001$) and hypertension (HR = 4.570, 95 CI 1.567–13.328, $p=0.005$) were the independent predictors for CVD in the study group (Table 5).

Discussion

The findings of this study revealed a 4.6% prevalence rate of CVD in RA patients. Notably, obesity and hypertension emerged as the most prevalent traditional CV risk factors within this population. Male, obese RA patients aged over 40 exhibited a higher likelihood of CVD compared to their younger, female, and non-obese counterparts. Furthermore, male sex and hypertension were identified as independent risk factors for CVD development in RA patients.

The prevalence rates of CVD in RA vary considerably depending on the patient and disease characteristics. It is generally known that there was a 2 to 3-fold increase in CV morbidity in patients with RA [32]. Besides, the higher risk of CVD in different geographical regions also represents high prevalence rates of CVD in RA patients in their regions [16]. The SUrvey of cardiovascular disease Risk Factors in RA (SURF-RA) study reported different prevalence rates of RA in different geographical regions. Atherosclerotic CVD was detected in 2.0% and 3.0% of the patients from India and Mexico, and 21% of RA patients originated from Central and Eastern Europe. They found nearly a 40% rate of atherosclerotic CVD in Russian patients [16]. The analysis of the patients from the Basildon Inflammatory Arthritis Cohort in the United Kingdom

Table 5 Univariate and multivariate Cox proportional regression analysis for cardiovascular disease during the duration of rheumatoid arthritis

Parameter	Reference	Risk factor	Univariate		Multivariate	
			HR (95% CI)	p	HR (95% CI)	p
Age			1.039 (1.005–1.074)	0.023	0.997 (0.957–1.039)	0.893
Sex	Female	Male	2.518 (1.237–5.124)	0.011	7.818 (3.030–20.173)	<0.001
BMI group	<30 kg/m^2	≥ 30 kg/m^2	2.430 (1.219–4.843)	0.012	1.797 (0.743–4.349)	0.194
Smoking	Non-/ex-smoker	Smoker	0.226 (0.031–1.658)	0.144	–	–
Alcohol	Non-/ex-consumer	Consumer	2.636 (0.627–11.087)	0.186	–	–
Hypertension	Absent	Present	4.322 (2.092–8.927)	<0.001	4.570 (1.567–13.328)	0.005
Diabetes mellitus	Absent	Present	2.688 (1.319–5.477)	0.006	1.49 (0609–3.652)	0.382
Chronic renal failure	Absent	Present	2.916 (1.117–7.614)	0.189	–	–
Dyslipidemia	Absent	Present	4.166 (1.878–9.242)	<0.001	2.077 (0.811–5.318)	0.128
COPD	Absent	Present	0.323 (0.133–0.785)	0.013	1.449 (0.500–4.197)	0.494
Malignancy	Absent	Present	3.652 (0.871–15.318)	0.077	–	–
CQR score			0.989 (0.954–1.026)	0.562	–	–
HAQ-DI			0.843 (0.501–1.419)	0.520	–	–
RAID			1.010 (0.870–1.187)	0.838	–	–
DAS-28 CRP groups	Non-high activity	High activity	0.931 (0.326–2.658)	0.893	–	–
DAS-28 ESR groups	Non-high activity	High activity	1.342 (0.547–3.291)	0.520	–	–
CDAI groups	Non-high activity	High activity	1.490 (0.605–3.668)	0.386	–	–
SDAI groups	Non-high activity	High activity	1.079 (0.415–2.806)	0.875	–	–

HR, hazard ratio; CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DAS-28 CRP, Disease Activity Scores with CRP; DAS-28 ESR, Disease Activity Scores with ESR; CDAI, Clinical Disease Activity Index; SDAI, Simple Disease Activity Index

revealed that the incidences of CVD and cerebrovascular diseases were 11.1% and 5.3% at the last follow-up [33]. Although the number of cases was smaller than those in the current study, the median length of the follow-up was 7.5 years. Another study from the United States reported an overall prevalence rate of 1.8% to 2.9% for MACEs, depending on the treatment history [34]. Myasoedova et al. [22] found that the incidence of MACEs in RA patients has decreased in recent decades (the 2000s vs. the 1980s). They proposed several reasons for this improvement, such as the effective CVD prevention and management strategies in the general population and RA-specific reasons [treat-to-target strategies, early initiation of disease-modifying antirheumatic drugs (DMARDs), and higher use of biologic DMARDs]. The prevalence rate of CVD was 4.6% in this patient group. We could not analyze the impact of RA-specific reasons associated with the treatment of RA. Nevertheless, Turkey is in the Mediterranean, with a relatively lower risk of CVD. The differences in the prevalence rates of CVD in RA patients might be closely related to the overall CVD potential of these geographic regions.

The association between the traditional risk factors and CVD risk in RA patients has been investigated in detail. Raadsen et al. [32] reported that CVD risk in RA patients is mainly attributed to the traditional CV risk factors using the findings of the CARRÉ cohort study.

Additionally, they thought that early treatment of RA prevents the RA-specific effects on the development of CVD risk (RA-specific risk for CVD). Although there have been substantial improvements in the control of inflammation in RA patients over 20 years, poor control of traditional CV risk factors might be the main reason for the increased risk of CVD [32]. Kokkonen et al. [35] showed the negative impact of CV risk factors prior to RA diagnosis on the development of future MACEs after the disease onset. In light of these findings, the authors highlighted the importance of the early assessment of CVD risk and early treatment initiation [32, 35].

Prevalence rates of individual CV risk factors vary across studies [6, 11, 36]. Landgren et al. [37] reported that hypertension was the most frequent comorbidity in 43% of RA patients in Western Sweden. Cai et al. [38] found a 32% prevalence rate for metabolic syndrome in RA patients based on a systematic review and meta-analysis. Nevertheless, the patients in Mexico and India had significantly lower rates of CV risk factors than those in Western and Central Eastern Europe and North America. Hypertension and dyslipidemia were the most frequent risk factors in almost two-thirds of all patients investigated in the SURF-RA study [16]. Independent of the prevalence rates of each CV risk factor, hypertension is the most frequent comorbidity seen in RA patients [36, 39, 40]. Although hypertension was not the most frequent CV risk factor in the current study, it was the only independent risk factor for CVD in RA patients. The higher prevalence of hypertension in the general population might be related to detecting this finding. So, the environmental conditions, including dietary and lifestyle features, and the overall clinical characteristics of the patients are essential for the development of CVD in RA patients.

The disease activity and its association with biological DMARDs have been debated [2, 8, 12, 15, 16, 40]. TNF-alpha inhibitors and interleukin-1 receptor antagonists were related to reducing the risk of MACE in RA patients [6, 41]. Other researchers found that CV comorbidities were associated with higher use of bDMARDs [40]. In countries with the occasional use of DMARDs, higher DAS28, ESR, and CRP values were usually detected [16]. Several studies reported biological DMARDs' positive or negative effects on RA patients' CVD risk [16, 42, 43]. Nevertheless, we did not find a significant difference in the distribution of the primary drugs used for RA and CVD.

Besides, there were no significant differences in the current study's composite disease activity indices and their categorization values indicating high-disease activity between the RA patients with and without CVD. Although most of these indices, including CDAI, SDAI, and DAS28-ESR, were well correlated [25], it is expected to detect differences in these indices between the patient groups [24]. Yoshida et al. [11] showed a significant correlation between initially higher CDAI scores and higher risk of CVD in RA patients collected in the CorEvitas registry. They thought the detrimental CV effect of higher disease activity might be prevented using an earlier anti-inflammatory treatment for RA. The low rates of high-disease activity based on these indices in RA patients might be related to initiating such medications as earlier in the current study. Nevertheless, the cause-and-effect analysis could not be performed due to the study's cross-sectional design.

Demographic characteristics of RA patients might have an impact on the CV risk. Although strong female preponderance was reported among RA patients, male sex and older age were the significant risk factors for atherosclerotic CVD [16, 39, 44]. Nevertheless, non-modifiable risk factors should be considered when evaluating CVD risk in RA patients. Physical activity and/or aerobic and resistance exercises are other essential factors that positively impact CVD risk in patients with RA. In narrative reviews by Metsios et al. [45] and Coskun Benlidayi et al. [46], the authors reported that such exercise programs were beneficial to control CVD risk factors in patients with RA. Increased vascular function, decreased systemic inflammation, restoration of the autonomic system, improved lipid profile, and increased muscular function were the speculated mechanisms for the cardiovascular effects of exercise in patients with RA [46]. Personalized exercise programs led to significant

improvements in waist circumference and maximal oxygen consumption, which were the reducing factors associated with CVD [47]. Although the exact mechanism and exercise dosage remain elusive, the recommendation for physical activity in patients with RA is a safe and effective approach in chronic inflammatory joint disease. Nevertheless, the current study could not evaluate the level of physical activity/exercise that might be important for primary and secondary prevention of CVDs in patients with RA.

Because of the study's cross-sectional design, we could not make a causality analysis of the factors impacting CVD risk, which was considered a major limitation of the study. Data about several CV risk factors, including body morphometrics, physical activity, total sitting time, and sedentary life, might be critical for assessing the results. Inclusion of only patients with RA might help obtain more homogeneous results, leading to increased generalizability of the outcomes.

In conclusion, the common risk factors in the general population for CVD, including male sex, older age, and hypertension, were also evident in RA patients. The lack of an association between the RA-specific factors and CVD risk remained a conflicting finding. Implementing CVD risk reduction strategies focusing on CV risk factors seems essential for preventing morbidity in RA patients.

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Declarations

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Authors and Affiliations

Mehmet Tuncay Duruöz[1] · Şebnem Ataman[2] · Hatice Bodur[3] · Hasan Fatih Çay[4] · Meltem Alkan Melikoğlu[5] · Özgür Akgül[6] · Erhan Çapkın[7] · Gülcan Gürer[8] · Remzi Çevik[9] · Feride Nur Göğüş[10] · Ayhan Kamanlı[11] · Fatma Gül Yurdakul[12] · İlker Yağcı[13] · Aylin Rezvani[14] · Lale Altan[15]

✉ Mehmet Tuncay Duruöz
tuncayduruoz@gmail.com

Şebnem Ataman
ataman.sebnem@gmail.com

Hatice Bodur
haticebodur@gmail.com

Hasan Fatih Çay
drhfatih.cay@gmail.com

Meltem Alkan Melikoğlu
mamelikoglu@gmail.com

Özgür Akgül
ozgur.akgul.md@gmail.com

Erhan Çapkın
drcapkin@yahoo.com

Gülcan Gürer
gurergulcan@yahoo.com.tr

Remzi Çevik
ftremzi@hotmail.com

Feride Nur Göğüş
fgogus@gazi.edu.tr

Ayhan Kamanlı
akamanli@hotmail.com

Fatma Gül Yurdakul
fatmagulonder@gmail.com

Ilker Yağcı
drilkery@yahoo.com

Aylin Rezvani
rezvani.aylin@gmail.com

Lale Altan
lalealtan@uludag.edu.tr

[1] Division of Rheumatology, Department of Physical Medicine and Rehabilitaton, Faculty of Medicine, Marmara University, Istanbul, Türkiye

[2] Division of Rheumatology, Department of Physical Medicine and Rehabilitaton, Faculty of Medicine, Ankara University, Ankara, Türkiye

[3] Department of Physical Medicine and Rehabilitaton, Ankara City Hospital, Faculty of Medicine, Yıldırım Beyazıt University, Ankara, Türkiye

[4] Department of Physical Medicine Rehabilitation and Rheumatology, Antalya Training and Research Hospital, University of Health Sciences, Antalya, Türkiye

[5] Department of Physical Medicine Rehabilitation and Rheumatology, School of Medicine, Atatürk University, Erzurum, Türkiye

[6] Division of Rheumatology, Department of Physical Medicine and Rehabilitation, School of Medicine, Manisa Celal Bayar University, Manisa, Türkiye

[7] Department of Physical Medicine and Rehabilitaton, School of Medicine, Karadeniz Technical University, Trabzon, Türkiye

[8] Department of Physical Medicine Rehabilitation and Rheumatology, University School of Medicine, Adnan Menderes University, Aydın, Türkiye

[9] Department of Physical Medicine and Rehabilitaton, School of Medicine, Dicle University, Diyarbakır, Türkiye

[10] Department of Physical Medicine Rehabilitation and Rheumatology, School of Medicine, Gazi University, Ankara, Türkiye

[11] Department of Physical Medicine Rehabilitation and Rheumatology, School of Medicine, Sakarya University, Sakarya, Türkiye

[12] Department of Physical Medicine and Rehabilitaton, Ankara City Hospital, University of Health Sciences, Ankara, Türkiye

[13] Department of Physical Medicine and Rehabilitaton, Faculty of Medicine, Marmara University, Istanbul, Türkiye

[14] Department of Physical Medicine and Rehabilitaton, Internatonal School of Medicine, Istanbul Medipol University, Istanbul, Türkiye

[15] Department of Physical Medicine Rehabilitation and Rheumatology, Faculty of Medicine, Uludağ University, Bursa, Türkiye