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COHORT STUDIES

Increased short-term risk of cardiovascular events in inflammatory rheumatic diseases: results from a population-based cohort

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Abstract

Cardiovascular diseases represent the first cause of death globally. Inflammatory rheumatic disease (IRMD) patients, due to their lifelong inflammatory status, are at increased risk of developing premature cardiovascular disease. We aimed to assess the risk for cardiovascular events (CVE) in a population-based study. We followed 10,153 adults from the EpiDoC Cohort, a large Portuguese population-based prospective study (2011–2016). IRMD patients were identified at baseline and followed during 5 years. CVE were defined as a composite of self-reported myocardial infarction or angina pectoris, arrhythmias, valvular disease, stroke or transient ischemic attack and peripheral artery disease. Statistical analysis was performed by utilizing multivariate logistic regression and goodness-of-fit and area under ROC curve. At baseline, IRMD patients had similar age as the non-IRMD participants (mean age 55 vs 53 years-old; 72.1% female); dyslipidaemia and sedentary lifestyle were more common (40.7% vs 31.4%, $p=0.033$; 87.3% vs 67%, $p=0.016$, respectively). During an average follow-up of 2.6 years, 26 CVE were reported among IRMD patients. IRMD patients had higher odd of CVE (OR 1.64, 95% CI 1.04–2.58; $p=0.03$), despite comparable mortality rates (1.7% vs 0.7%, $p=0.806$). A stepwise approach attained that gender, age, history of hypertension, body mass index, IRMD and follow-up time are the most important predictive variables of CVE (AUC 0.80). IRMD patients, at community level, have an increased short-term risk of major CVE when compared to non-IRMD, and that highlights the potential benefit of a systematic screening and more aggressive cardiovascular risk assessment and management of these patients.

Keywords Rheumatic diseases · Inflammation · Cardiovascular diseases · Prospective study · Risk assessment

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Key messages

Inflammatory rheumatic disease (IRMD) patients have an increased short-term risk of cardiovascular (CV) events compared with those without IRMD.

IRMD is an independent risk factor of major cardiovascular events.

These results suggest that proactive and targeted CV risk assessment and modifying approaches in IRMD patients´ management are warranted.

Introduction

Cardiovascular events (CVE) account for a major health burden and increased mortality rates in all societies [1, 2]. Prediction of absolute risk of cardiovascular (CV) diseases has important clinical significance as it can greatly guide clinicians in preventing and managing these disorders [3, 4]. It is important to improve risk communication, motivate changes in lifestyle and behaviours, treat modifiable risk factors, and promote adherence to therapy [3, 4].

The Framingham tool has been a cornerstone for CVE long-term risk prediction for many years, establishing a 10-year CV risk score, based on defined risk factors (age, sex, smoking status, blood pressure, and cholesterol levels) [5–7]. Nevertheless, it has notable limitations [8]. Although it is a widely validated long-term CVE risk prediction tool, the Framingham tool was not designed for short-term risk prediction [9]. Also, it does not account for several documented long-term risk factors such as metabolic syndrome, lifestyle choices of activities, family history, or other chronic comorbidities [10, 11]. Inflammatory rheumatic diseases (IRMD) [12–14], due to their lifelong inflammatory status, are by themselves a load to the overall CV risk [15–18]. Disease flares in the case of IRMD also hinder the prediction of CVE, especially if we apply long-term prediction risk scores that do not account for its contribution as an independent risk factor [12, 19, 20]. Recognizing this increased risk, the European League Against Rheumatism (EULAR) recommends applying a multiplication factor of 1.5 to determine CV risk in rheumatoid arthritis (RA) if the patient fulfils specific criteria [15]. Nonetheless, recent studies show that this factor does not significantly improve risk prediction [12, 21–23].

The ability to forecast the short-term risk of cardiovascular events would represent an important advance in cardiovascular medicine because it would clarify which individuals are in the most urgent need for intervention. It is unknown whether having an IRMD is a short-term risk factor for CVE. Acknowledging these facts and aiming at a more realistic assessment of the CV disease risk in the IRMD population, we sought to evaluate short-term (5-year) risk for CVE independently of traditional risk factors and to identify other risk factors that may forecast a short-term risk of CVE in this population-based study.

Material and methods

Study design

Our study was based on the EpiDoC cohort, which was created to address gaps that exist in Portuguese epidemiological information, valid and useful to support public health decision-making. This was an epidemiological, observational and longitudinal population-based study up to 5 years follow-up [24]. The EpiDoC (Epidemiology of Chronic Diseases) cohort study constitutes a large population database for medical and health-related research. So far, three health surveys of the general adult population in Portugal had been completed: EpiDoC 1 (September 2011 until December 2013), EpiDoC 2 (March 2013 until July 2015) and EpiDoC 3 (September 2015 until July 2016).

EpiDoC 1 was performed in 2 phases. The first phase was a face to face interview and the second one was a detailed clinical evaluation in all subjects who screened positive for at least one rheumatic and musculoskeletal disease during the initial interview (sensitivity 98% and specificity 22%), plus a random 20% sample of individuals without positive screening for rheumatic complaints to address rheumatic and musculoskeletal diseases prevalence and its burden in Portugal. The sample was stratified according to the Portuguese Nomenclature of Territorial Units for Statistics (NUTS II; seven territorial units: Norte, Centro, Alentejo, Algarve, Lisboa e Vale do Tejo, Madeira, and Azores) and the size of the population (< 2000; 2000–9999; 10,000–19,999; 20,000–99,999; and ≥ 100 000 inhabitants). In EpiDoC 2 and 3, data were collected through a phone interview, to address lifestyles and their determinants and identify innovative solutions. In each follow-up interview, research assistants applied a nuclear questionnaire (including questions on new cardiovascular events or risk factors).

Study population

The study population was composed of adults (≥ 18 years old) who were non-institutionalised and living in private households in Mainland Portugal and Islands (Azores and Madeira). Exclusion criteria were: residents in hospitals, nursing homes and military institutions or prisons, and individuals unable to speak Portuguese or unable to complete

the questionnaires [25]. Participants were included through a process of multistage random sampling, as described above. In each phase, participants were asked about their sociodemographic data, socioeconomic profile, and lifestyle habits. Anthropometric data (self-reported weight and height) and self-reported chronic diseases (high cholesterol, high blood pressure, mental disease, cardiac disease, diabetes, hyperuricemia, neurological disease) were also assessed.

Exposure definition

The presence of an IRMD was considered if a subject, after the clinical appointment of the second phase of EpiDoC1, had an adjudicated event by the rheumatologist combined with the fulfilment of validated classification criteria to establish a diagnosis of Systemic Lupus Erythematosus [26], RA [27], Ankylosing Spondylitis [28] or Polymyalgia Rheumatica [29].

Outcome definition: Incident major CVE was defined by the composite outcome of self-reported events of myocardial infarction, unstable angina or angina pectoris (ischemic heart disease), arrhythmias, valvular disease, stroke or transient ischemic attack, peripheral artery disease, and death due to CV disease. Only the first event during follow-up time was considered. CV risk assessment was characterized by analysing the self-report CV risk at baseline, including the dichotomous variables (gender, history of diabetes, history of dyslipidaemia, history of hypertension, history of hyperuricemia, smoking status, alcohol consumption, exercise practise) and the continuous variables (age, body mass index (BMI), years of schooling and follow-up time). Smokers were considered if they smoked at baseline and former smokers if they had quit. Obesity was defined as a $BMI \geq 30 Kg/m^2$. Follow-up time was accounted in years from the first interview until the last contact.

Covariates of interest: All covariates of interest were determined prior to the index case (cohort entry).

Statistical analysis

Covariate distribution among the groups was examined using descriptive statistics (t-test for continuous variables and chi-square for dichotomous variables). Continuous variables were summarised as mean (SD) or median (IQR) when their distribution departed from normal, and categorical variables as proportions. To assess the association between IRMD and major CVE, after univariable analysis, we adjusted by logistic regression for possible confounders. Hypothesised effect modifiers and traditional CV factors were tested in the model and the likelihood ratio test was used to determine the significance of the interactions which, when present, were taken into consideration in the multivariate analysis. To find the best-fit predictive variables model, a stepwise increase approach was used with a probability threshold of 0.05. Calibration was checked by goodness-of-fit test and discrimination by the area under the receiver operating characteristic (ROC) curve. Statistical analysis was performed using Stata 14.0 (StataCorp, College Station, Texas, USA) and significance value was defined as $p < 0.05$ throughout.

Sample size determination

Power calculations prior to the start of the study revealed that 2% of 7591 individuals represents the projected population, according to the national CVE prevalence [30]. The national cumulative incidence of CV comorbidities is 0.6% and other studies reported a hazard ratio (HR) above 1.5 [31]. With 172 patients with IRMD and 7417 non-IRMD, we assumed to have a power > 0.9 to detect a HR as small as 1.3.

Data protection and ethics

The study was performed according to the principles established by the Declaration of Helsinki and the Portuguese law at the beginning of the study (Law n. 46/2004, of 24th August). The study proposal was reviewed and approved by the competent Portuguese authorities: the National Committee for Data Protection and the NOVA Medical School Ethics Committee, registration number 05-2012-CEFCM.

Results

Of 10,153 EpiDoC participants, 172 had a confirmed diagnosis of IRMD (Fig. 1). During an average follow-up of 2.6 years (interquartile range [2.02; 3.32]), 26 CVE were reported among IRMD patients. Baseline characteristics are found in Table 1. Age was similar in both groups, with a predominance of female gender ($p = 0.004$), dyslipidaemia diagnosis ($p = 0.033$), and sedentary lifestyle ($p = 0.016$). At least 1/3 of the controls practiced regular exercise, compared with 23% of the IRMD population. BMI, hypertension, diabetes, hyperuricemia, current tobacco use status, and current alcohol consumption prevalence were comparable at baseline between the 2 groups. The level of education did not differ between groups at baseline. IRMD group had a higher prevalence of CVE during follow-up time (15.1%; 26 events vs 792 events in non-IRMD; $p < 0.01$). However, all-cause mortality was not statistically different between the 2 groups ($p = 0.806$) (Table 2).

The loss to follow-up time diverges between both groups, with a median follow-up of 2.6 years in the IRMD population, compared with 2.4 years in the non-IRMD group ($p < 0.01$) (Table 2). Furthermore, specific CVE prevalence was similar in both populations, with ischemic heart disease and arrhythmias being the most common Table 2.

The odds of major CVE are reported in Table 3. In comparison to the general population, the multivariate models showed that the relative probability of a major CVE was 1.64 times higher in IRMD patients, independently of traditional risk factors and other potential confounders, as follow-up time and exercise practice Table 3.

After a stepwise approach to find the best predictive model, gender, age, history of hypertension, BMI, IRMD, and follow-up time were found to be the most important predictive variables of CVE, with an area under ROC of 0.80 Fig. 2.

Discussion

Our results show that having an IRMD is an independent risk factor for CVE and is associated with 64% higher odds of developing a short-term cardiovascular disease, compared to the general population. Other identified predictors include gender, age, history of hypertension, BMI, and follow-up time. In line with previous studies [32–34], our results highlight the potential benefit for more aggressive and targeted CV risk approaches in these patients.

Several international societies developed guidelines for the management of CV comorbidities based on CV risk scores [3, 4]. However, it is recognized that these CV risk calculators, developed for the general population, do not accurately predict CV risk in IRMD patients [12]. This happens because CV risk factors do not fully explain the increased risk in IRMD, thus underestimating the actual risk [14]. New specific risk calculators have been proposed, such as QRISK2, Expanded CV risk score for RA (ERS_SA), and EULAR 1.5 multiplier, yet they are not superior to the general population CV risk calculators [23].

Previous studies already reported an increased risk of CV diseases in chronic IRMD populations from different countries and with different lifestyles [35–37], with a similar magnitude to that observed in patients with diabetes [38]. In addition to the increased prevalence of traditional CV risk factors, such as dyslipidaemia, hypertension, smoking, obesity and diabetes, the inflammatory status of IRMD, as well as genetic factors and medication effects, might contribute to this increased overall CV disease risk [18]. Markers of active inflammation, including erythrocyte sedimentation rate, C reactive protein levels, and disease activity scores have all been associated with an increased CV risk [18]. Even low-grade disease activity seems to be associated with CV system changes [17]. The results of our study, composed by community patients, expectedly under a better disease control and with a lower inflammatory burden than those on specialized care, are in line with this evidence. Carotid ultrasonography, coronary calcium score, and anti-Apo A-I have also been suggested as markers to aid in a more accurate CV risk stratification [14, 39, 40].

In this population-based study, we tested the hypothesis of whether IRMD participants are at an increased short-term risk for CVE. Testing for such a short-term period could have concealed the high risk of the IRMD group. Nonetheless, we could still demonstrate 1.64 higher odds of developing a cardiovascular event under 5 years, indicating an increased absolute risk or this population. We may speculate that by reducing the period of analysis, we can mitigate the impact of different grades of inflammation over the years on the assessment of global CV risk, namely disease flares, and different therapeutical options.

Our study brings a new contribution to the field addressing the risk of developing CVE in a specific group of diseases that have been out of the scope of the main prediction scores. It determines the risk based on the collection of

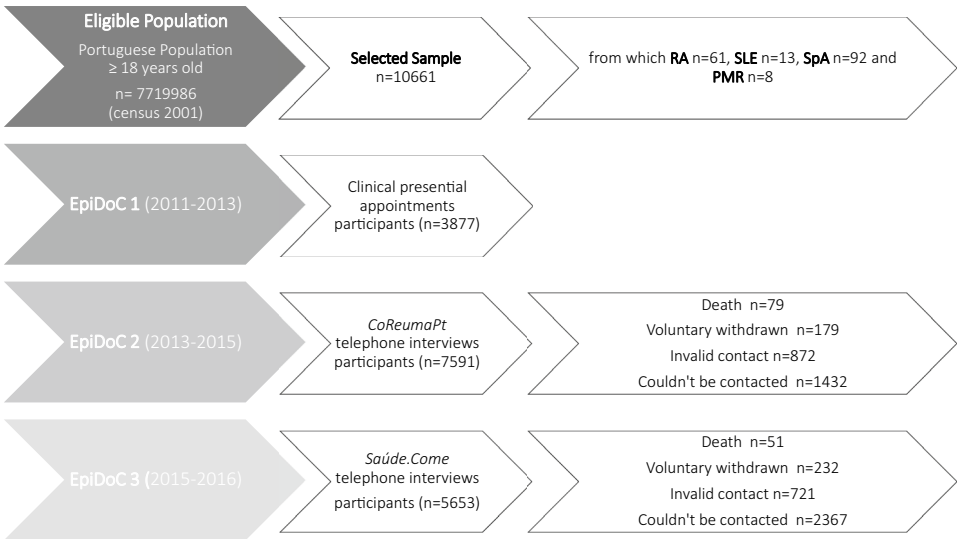

Fig. 1 Flowchart of follow-up in EpiDoC studies. Total voluntary withdrawn or could not be contacted in the inflammatory rheumatic disease population equals two and in non-IRMD equals 5903. IRMD donates inflammatory rheumatic diseases that include *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *SpA* Ankylosing Spondylitis, *PMR* polymyalgia rheumatica

Table 1 Comparison of baseline characteristics between patients and controls

	IRMD $n=172$	Non-IRMD $n=10,489$	p value
Age (years)	55 [25; 66.5]	53 [39; 67]	0.13
Male, *n* (%)	48 (27.9%)	4062 (38.7%)	0.004
BMI, *n* (%)	25.9 [23.5; 29.3]	25.9 [23.2; 29.1]	0.66
Hypertension, *n* (%)	61 (31.6%)	3308 (31.5%)	0.538
Diabetes, *n* (%)	13 (7.56%)	1204 (11.5%)	0.269
Dyslipidaemia, *n* (%)	70 (40.7%)	3290 (31.4%)	0.033
Hyperuricemia, *n* (%)	4 (3.1%)	126 (2.3%)	0.156
Smoker, *n* (%)	24 (14%)	2076 (19.8%)	0.152
Alcohol consumption, *n* (%)	87 (50.6%)	5930 (56.5%)	0.241
Exercise practice, *n* (%)	39 (22.7%)	3460 (33%)	0.016
Previous cardiovascular event, *n* (%)	28 (16.3%)	340 (3.24%)	0.358
Education (years) [IQR]	6 [4; 12]	6 [4; 12]	0.626

BMI body mass index, *IRMD* inflammatory rheumatic diseases, *n* number, *[IQR]* interquartile range

Table 2 Comparison of general outcomes and cardiovascular events between inflammatory rheumatic disease subjects and controls

Follow-up General Outcomes			
	IRMD $n=172$	Non-IRMD $n=10,489$	p value
Follow-up time (years)	2.6 [2.02; 3.32]	2.41 [0; 3.1]	<0.01
Follow-up rates, *n* (%)	154 (89.5%)	9498 (90.5%)	0.660
Cardiovascular event, *n* (%)	26 (15.1%)	792 (7.6%)	<0.01
Death, *n* (%)	3 (1.74%)	78 (0.7%)	0.806
Cardiovascular events			
	IRMD $n=26$	Non-IRMD $n=792$	p value
Ischemic Heart Disease, *n* (%)	9 (34.62%)	186 (23.48%)	0.376
Arrhythmias, *n* (%)	6 (23.08%)	233 (29.42%)	0.646
Valvular disease, *n* (%)	2 (7.69%)	71 (8.96%)	0.744
Peripheral arterial disease, *n* (%)	4 (15.38%)	95 (11.99%)	0.763
Transient Ischemic Attack or Stroke, *n* (%)	5 (19.23%)	207 (26.14%)	0.793

IRMD inflammatory rheumatic diseases

community self-reported data from a large cohort of patients representative of national data and longitudinally followed, contrary to the most studied registries and cohorts of rheumatic diseases that are hospital-based [15].

There are several limitations in our study, mostly driven by the study design and the available data in the EpiDoC cohort [24], which was not originally created for this goal. Disease activity and acuity measurement, chronic disease duration, medication records, and grading of some variables are lacking [41]. Other predictors, e.g. measures of ethnicity and socioeconomic status, are also desirable to avoid undertreatment of vulnerable groups [42]. Additionally, only self-reported events were considered, including death, which may have led to a lower risk attribution. Being a population-based study, IRMD patients are in lower number when compared to hospital cohorts, due to the rarity of these diseases at a community level (~3% [43],). Loss to follow-up is a frequent problem in cohort studies than can lead to bias; however, follow-up rates in this study are considered acceptable [44].

In perspective, CV risk in IRMD is still underestimated in clinical practice and the management of CV risk remains deficient [18]. The development of disease-specific scores that accurately reflect the CV risk is necessary, as is the enrolment in prospective trials assessing the role of several strategies in the reduction of CV risk. Likewise, more

Table 3 Odds for major adverse cardiovascular events in the IRMD population

	OR	CI (95%)	*p* value
Unadjusted	2.18	1.42–3.33	< 0.01
Age-gender adjusted	2.1	1.36–3.22	0.001
Traditional risk factors adjusted	2.11	1.37–3.26	0.001
Traditional risk factors-follow-up time adjusted	1.73	1.1–2.72	0.02
Risk factors adjusted	2.06	1.33–3.18	0.001
Fully adjusted	1.64	1.04–2.58	0.033

Traditional risk factors: age, gender, history of hypertension, diabetes, dyslipidaemia, smoking status and body mass index

Risk factors: traditional risk factors plus exercise practice, and alcohol consumption

Fully adjusted: risk factors plus follow-up time

OR Odds-ratio, *CI* confidence intervals

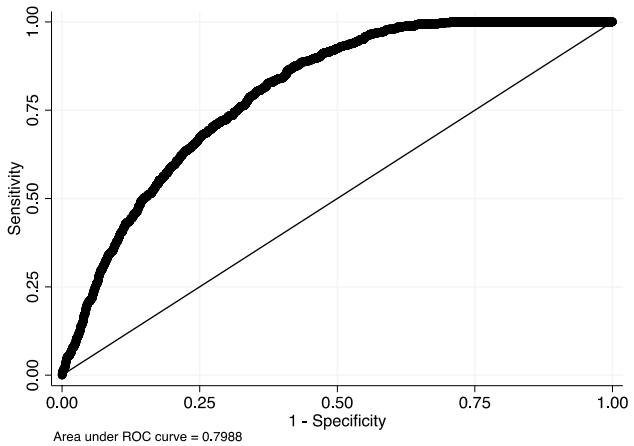

Fig. 2 ROC curve of the model for identifying the most important predictive variables of cardiovascular event. Included variables: gender, age, history of hypertension, body mass index, inflammatory rheumatic disease and follow-up time. *ROC* receiver operating characteristic

evidence on the effects of rheumatological and cardiovascular disease treatments on CV risk is lacking.

In conclusion, patients with inflammatory rheumatic diseases are at an increased short-term risk of major cardiovascular events at the community level when compared to the general population beyond traditional risk factors. The findings highlight the potential benefit of a systematic screening and aggressive targeted cardiovascular risk management.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by VSD, AMR and SSD. The first draft of the manuscript was written by VSD and all authors commented on previous versions of the manuscript. All authors read, approved and take full responsibility for the integrity of the study and the final manuscript.

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Compliance with ethical standards

Conflict of interest Dr. Barkoudah reports research support from National Institutes of Health/National Heart, Lung, and Blood Institute, Bristol Myers Squibb and Janssen, payments made to Brigham and Women's Hospital for performing clinical endpoints and Advisory Board fees from Bristol Myers Squibb, Janssen, Novartis, Pfizer and Portola, and travel expenses from Alexion; all outside he presented work. No other conflict of interest was identified.

Ethical approval Approved by NOVA Medical School Ethics Committee and the National Committee for Data Protection.

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