Myeloperoxidase as an important predictor of cardiovascular risk in individuals with rheumatoid arthritis

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Abstract

Background Rheumatoid arthritis is an inflammatory disease with joint manifestations. In the presence of extra-articular manifestations, the morbidity and severity of the disease increase. Glucocorticoid is used as a treatment and may result in side effects related to cardiovascular risk.

Methods This was a cross-sectional study including 59 volunteers with rheumatoid arthritis receiving treatment at a hospital of Campos Gerais that aimed to establish the relation between cardiovascular risk, glucocorticoid treatment and myeloperoxidase in these patients. Subjects were divided into two groups: using (n = 39) and without glucocorticoids (n = 20). They underwent clinical evaluation, physical examination and blood samples were taken. Statistical analysis was performed using Student’s t test and Mann–Whitney test. Logistic regression was performed to assess the cardiovascular risk. The significance level was 5% (α = 0.05). Calculations were performed using the Statistical Package for the Social Science version 21.0.

Results There has been a significant difference between groups in blood glucose values (p = 0.012), which can be explained by the different percentage of diabetic patients in the groups. When assessing cardiovascular risk using the predictors of glucocorticoid dose, time of glucocorticoid use, myeloperoxidase, and C-reactive protein together, these were responsible for significantly predicting this risk (p = 0.015).

Conclusion A significant relation between the predictor myeloperoxidase alone was also demonstrated (p = 0.037), it may be an important predictor of cardiovascular risk among individuals with rheumatoid arthritis.

Graphical abstract

Keywords Cortico therapy · Rheumatoid arthritis · Cardiovascular risk · Myeloperoxidase

Extended author information available on the last page of the article
Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease with great impact on the patient’s life and society health care, whose prevalence rate ranges from 0.55 to 1.0% in the world population. This disease preferentially affects women, with peak incidence between 30 and 50 years (Hunter et al. 2017). It is characterized by peripheral, symmetrical polyarthritis, which leads to deformity and destruction of large and small joints. The severity of this pathology can increase overtime and may result in progressive development of joint destruction, deformity and significant decline in the functional capacity of the individual (Negrei et al. 2016).

The clinical manifestations of RA can be divided into joint and extra joint (Germano et al. 2014) and in the latter situation, morbidity and severity of the disease increase, and may decrease life expectancy by 5–10 years in relation to the general population. This decrease is related to the higher risk of cardiovascular diseases (CVD), which is 2–5 times higher than in the general population (Amaya-Amaya et al. 2013; McInnes and Schett 2011).

The reason why the prevalence of CVD occurs early and more intensely in patients with RA has been the subject of intense research. It is known that RA is related to the increase in the thickness of the intima and media layers of the common and femoral carotid arteries, a fact that correlated with severity and chronicity of rheumatologic disease (Braun et al. 2017).

Studies report that dyslipoproteinemia and inflammation of the endothelium are contributing factors to the most frequent atherosclerosis process in RA (Verhoeven et al. 2016), but further research is needed to shed light on autoimmune participation in atherosclerosis and possible exogenous factors, including the treatment used in the disease (Braun et al. 2017).

The similarity of inflammation of rheumatoid synovitis, with inflammation occurring in atheroma, as well as corticosteroid therapy, makes patients with RA the target of investigations into the complex inflammatory mechanism that occurs in atherosclerosis (Aviña-zubieta et al. 2013). The two processes present common constituents, such as elevated C-reactive protein (CRP), myeloperoxidase (MPO), cytokines and fibrinogen, suggesting that the association of factors present in systemic inflammation of RA may accelerate atherosclerosis (Daugherty et al. 1994; Ferreira et al. 2016).

Despite the important improvement in the diagnosis and available treatments, a high morbidity of CVD still remains. This is due to the combination of different factors, such as: (i) chronic inflammatory features that predispose to the development of comorbidities; (ii) side effects of drugs used in the therapy (for example glucocorticoids —GCS); (iii) the increased prevalence of traditional risk factors; and (iv) persistent disease activity, when this is more aggressive.

Acute myocardial infarction (AMI) is the main cause of death in the Western civilization, as the main consequence of coronary artery disease (CAD) (Braun et al. 2017).

From these data, it is important to evaluate the levels of biological markers importantly related to the increased risk of cardiovascular event, such as ultrasensitive C-reactive protein (us-CRP) and MPO (Amaya-Amaya et al. 2013; Meuwese et al. 2007).

Because it is an inflammatory pathology, RA therapy is based on therapeutic drugs with anti-inflammatory action, being the first treatment used for inflammation of the disease based on the use of GCS results in decreased activation, proliferation, differentiation and survival of various inflammatory cells. The higher the dose used in the treatment, the greater the effect (Ferreira et al. 2016). However, long-term use of GCS in patients with RA may result in deleterious side effects, such as hyperglycemia, hepatosteatosis and insulin resistance (IR) (Patel et al. 2017).

The causes related to the association between RA and cardiovascular risk (CVR) have not yet been well studied, thus the present study aims to characterize RA patient’s risk factors for cardiovascular diseases and evaluate possible predictors for CVD in individuals undergoing treatment with GCS.

Methods

This is an uncontrolled single-center cross-sectional study. All participants signed a Free and Informed Consent Form (FICF), approved by the Committee of Research Ethics of the State University of Ponta Grossa (UEPG), number 1.879.373.

From April 2017 to June 2019, 59 patients with RA were selected, defined according to the classification criteria of the American College of Rheumatology (Aletaha et al. 2010), who were evaluated in the rheumatology clinic of the Regional University Hospital of Campos Gerais (HURCG), in the municipality of Ponta Grossa–Paraná, Brazil. The participants were referred to the University Laboratory of Clinical Analysis (ULCA) of UEPG, for blood collection and subsequent laboratory tests.

Pregnant women, individuals with neoplasms, other rheumatological autoimmune diseases, as well as those presenting some infectious process at the time of care were excluded from the study.

The 59 study participants were divided into two experimental groups considering the presence or not of treatment with GCS. Thus, the group with GCS consisted of 39 patients, while the group without GCS had 20 patients.

The volunteers underwent clinical evaluation and a complete physical examination, which included a count...
of swollen and painful joints. Information was obtained through interviews and review of medical records. Each patient’s history in disease-related aspects, such as clinical manifestations (including joint, extra-articular, comorbidities and risk factors for CAD), previous laboratory data, prescribed treatments (current and previous), and diagnostic criteria used, were evaluated.

Interviews and analysis of medical records were evaluated: age, gender, smoking, medications of current and previous use, presence of autoimmune diseases, as well as history of chronic diseases, such as diabetes mellitus (DM), systemic arterial hypertension (SAH) and cardiovascular disease.

Systemic blood pressure of patients in the sitting position after at least five minutes of rest was determined. Two to three measurements were made for each individual and the purposes of analysis, the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were used. The patients were weighed and measured on a mechanical scale with anthropometric ruler, without shoes, to calculate body mass index. The waist and hip dimensions were also measured to calculate the waist–hip ratio.

The activity of RA was evaluated by calculating the Disease Activity Score index in 28 joints (DAS28). For this calculation, the following variables were used: count of 28 joints (right and left side: shoulders, elbows, wrists, metacarpophalangeal, proximal interphalangeal of hands and knees) regarding the presence of pain and edema, C-reactive protein (CRP) and visual scale of general health analog/overall activity of the disease evaluated by the patient, whose values range from zero to one hundred. Patients were classified according to Table 1 after DAS28 calculation as follows:

**Table 1** Classification of the patient regarding the intensity/activity of THE according to DAS28

| DAS28   | Classification               |
|---------|-----------------------------|
| < 2.6   | Remission (inactive disease) |
| 2.6 ≤ 3.2 | Light activity             |
| 3.2 ≤ 5.1 | Moderate activity          |
| > 5.1   | High activity               |

Source: Modified from Source: Van Der Heijde et al. 2010

Blood collection was performed from each patient, and the samples were transferred to different tubes for the analysis: tube 1—containing anticoagulant EDTA K⁺ used to perform glycated hemoglobin fraction A₁c (HBA1c); tube 2—containing sodium fluoride anticoagulant, used for centrifugation and separation of separate plasma, for serum glucose dosage according to the standard procedure of ULCA working routine and tube 3—containing separator gel, being subsequently centrifuged (10 min/300 rpm) and the serum separated for different tests.

The C-reactive protein (CRP) dosage was performed by the ultrasensitive immunoturbidimetric method-Wiener® and the rheumatic factor (RF) dosage was performed by semi-quantitative technique by Wiener®. The dosages of total cholesterol, HDL cholesterol, LDL cholesterol and glucose were performed by the enzymatic method in the CT300i Wiener®. The measurements of insulin, troponin, Creatine Kinase Myocardial Band- mass (CKMB-mass) and homocysteine were performed by electrochemiluminescence in the COBAS e411® 5th generation. Hba1c was dosed using the High-Performance Liquid Chromatography (HPLC) methodology in the D-10® Biorad.

Part of the serum sample of each patient was separated into aliquots of 300 μl in microtubes, and then they were taken to the freezer at a temperature of – 80 °C, for subsequent measurement of MPO; interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).

IL-1β and IL-6 dosages were performed through enzyme immunoassay (ELISA) methodology, using immune-reactive tools®, following the manufacturer’s guidelines. For TNF-α, the reactive agent from Sigma-Aldrich brand® the ELISA methodology was used, following the manufacturer’s guidelines. For the evaluation of MPO levels, reactive Immunology Consultants Laboratory, Inc® was used via ELISA methodology, following the manufacturer’s guidelines. The absorbances of these tests were read in an H1 microplate reader with control and Biotek® Gen5® data reading software (BioTek Instruments, Inc., Winooski, Vermont, USA).

The calculation for cardiac risk assessment was applied to the patient’s data, according to the 2013 American College of Cardiology (ACC)/American Heart Association (AHA), Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (Stone et al. 2014) using the Heart Risk Calculator, taking into account: gender, age, smoking, ethnicity, diabetes, total cholesterol and HDL cholesterol values in mg/dL, SBP and DBP (mm Hg) and use of antihypertensive therapy.

For the evaluation of IR, the calculation of the HOMA-IR index was used according to the following formula:

\[
\text{HOMA} = \frac{\text{glucose (nmol/L) } \times \text{insulin (μg/mL)}}{22.5}
\]
The results were analyzed with student $t$ tests for unpaired samples and Mann–Whitney nonparametric test. The nonparametric model was used only for the variables that even after transformation (logarithmic) did not present normal distribution (Kolmogorov–Smirnov test, $p < 0.05$). The significance level adopted was 5% ($\alpha = 0.05$). All calculations were performed with the statistical package SPSS® (Statistical Package for the Social Sciences) version 21.0 (SPSS Inc Chicago Illinois USA).

A predictive model for CVR was constructed through a logistic regression that included the following predictor variables: GCS dose, time of GCS use, serum MPO and serum $\text{us}$-CRP. After normality analysis performed with the Kolmogorov–Smirnov test, the variables did not present normal distribution ($p < 0.0001$), so they were dichotomized according to the reference values. GCS dose: $\leq 7.5$ mg/day of prednisone (safe) and $> 7.5$ mg/day (cardiovascular risk); time of GCS use: $\leq 3$ months (safe) and $> 3$ months (cardiovascular risk); MPO: $\leq 350$ ng/mL (normal) and $> 350$ ng/mL (high) and CRP: $\leq 0.3$ mg/dL (low/medium risk) and $> 0.3$ mg/dL (high risk). The dependent variable CVR was also dichotomized: low risk ($< 7.5$) and high risk ($> 7.5$). The values of the odds ratio ($\text{Odds Ratio}$ (OR)) with a 95% confidence interval are presented. For the statistical model, the relationships were considered significant when $p < 0.05$.

The equation of logistic regression was:

$$\text{Logit} \left( p_i \right) = \beta_0 + \beta_1 x_{1,i} + \ldots + \beta_k x_{k,i}$$

The probability for the dependent binary variable, considering the predictor variables was, (equation):

$$p_i = \frac{1}{1 + \exp\left(-\left( \beta_0 + \beta_1 x_{1,i} + \ldots + \beta_k x_{k,i} \right) \right)}$$

Where:
- Logit ($\text{PI}_i$) is the linear logistic function;
- $\beta_0$ is the constant;
- $\beta_i$ is the angular coefficient;
- $x_i$ is the predictor variable;
- $p$ is the probability;
- $\exp$ is the basis of the Neperian logarithm.

All calculations were performed with the IBM-SPSS version 21 program (IBM Corp.®Released 2012. IBM SPSS Statistics for Mac OS®. Armonk, NY: IBM Corp.).

### Results

The study included 59 patients diagnosed with RA, of whom 51 were women and 8 were men. Patients were categorized as to the use of GCS and CVR factors, such as smoking, DM and SAH were evaluated. No significant differences were found between the groups when these variables were evaluated. The results obtained are expressed in Table 2.

When comparing the anthropometric and metabolic profile of patients with and without GCS, no statistically significant differences were found between the groups considering Body Mass Index (BMI), waist-hip ratio, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, homocysteine, troponin, HBA1c, insulin, HOMA-IR, CKMB-mass, SBP, DBP, RF, DAS28-PCR, IL-1β, TNF-α, IL-6 and MPO. However, the mean blood glucose was higher in patients who did not use corticosteroids, and this result was statistically significant ($p = 0.012$). The results obtained are presented in Table 3.

In relation to the cardiovascular risk assessment, using ACC/AHA, Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, when we used four predictors (GCS dose, time of GCS use, MPO and PCR-$\text{us}$), considered together, these were responsible for predicting CVR significantly ($n = 59$, $\chi^2 \text{MPO} = 12.36$, $p = 0.015$).

Logistic regression analysis after adjustment showed a significant relationship with the predictor variable (Ratio of changes = 10.0 CI 95% = 1.14–87.2; $p = 0.037$), these results and CVR are expressed in Table 4.
Table 3: Anthropometric and metabolic data compared between users and non-users of glucocorticoids. Average ± SD and Median (interquartile range)

| Variables                        | No GCS (No. 20) | GCS (No. 39) | p value  |
|----------------------------------|----------------|-------------|----------|
| **IMC (kg/m²)**                  | 28.9 ± 5.1     | 26.7 ± 7.1  | 0.230 ns |
|                                  | 27.4 (24.1–32.6)| 25.0 (21.6–29.3) |          |
| Waist ratio                      | 0.9 ± 0.1*     | 0.9 ± 0.1***| 0.521 ns |
|                                  | 0.9 (0.9–1.0)  | 0.9 (0.8–1.0) |          |
| Total Cholesterol (mg/dL)        | 189.0 ± 48.9   | 203.6 ± 46.3| 0.267 ns |
|                                  | 181.0 (148.5–238.3)| 216.0 (183.0–234.0) |         |
| HDL Cholesterol (mg/dL)          | 52.2 ± 13.7    | 54.8 ± 15.3 | 0.530 ns |
|                                  | 51.5 (40.4–62.0)| 54.0 (45.5–59.0) |          |
| LDL Cholesterol (mg/dL)          | 111.6 ± 40.2   | 124.5 ± 38.0| 0.230 ns |
|                                  | 93.8 (79.8–153.4)| 126.0 (106.0–149.0) |        |
| Triglycerides (mg/dL)            | 126.4 ± 63.9   | 129.4 ± 55.7| 0.855 ns |
|                                  | 105.3 (82.0–172.5)| 116.0 (90.0–116.4) |        |
| Blood glucose (mg/dL)            | 122.6 ± 56.0   | 99.0 ± 40.4 | 0.012 s  |
|                                  | 103.5 (87.5–122.0)| 90.0 (83.0–98.0) |          |
| Homocysteine (μMOL/L)            | 12.2 ± 4.6     | 11.8 ± 4.1  | 0.710 ns |
|                                  | 12.4 (8.6–15.8)| 11.3 (8.2–14.6) |          |
|Troponin (ng/L)*                  | 6.9 ± 6.1      | 6.0 ± 3.9   | 0.534 ns |
|                                  | 5.0 (3.0–7.8)  | 5.0 (3.0–7.0) |          |
| ws-PCR (mg/dL)*                  | 9.6 ± 15.0     | 9.7 ± 13.2  | 0.985 ns |
|                                  | 4.2 (1.3–12.4) | 3.6 (1.6–11.2)|          |
|HBA1C (%)*                       | 6.3 ± 1.9      | 5.8 ± 1.1   | 0.271 ns |
|                                  | 5.8 (5.0–6.4)  | 5.6 (5.2–6.1) |          |
|Insulin (μUI/mL)*                 | 16.6 ± 13.2    | 15.0 ± 10.5 | 0.604 ns |
|                                  | 11.0 (6.2–23.0)| 11.0 (8.0–22.0)|         |
|HOMA-IR*                         | 6.0 ± 7.8      | 3.6 ± 3.0   | 0.197 ns |
|                                  | 3.3 (1.5–7.6)  | 2.6 (1.7–4.5) |          |
|CKMB mass*                       | 2.7 ± 3.2      | 2.1 ± 1.5   | 0.434 ns |
|                                  | 1.5 (1.0–3.0)  | 2.0 (1.0–2.0) |          |
|SBP (mm Hg)*                     | 132.5 ± 20.0   | 127.3 ± 17.5| 0.304 ns |
|                                  | 130.0 (120.0–147.5)| 130.0 (110.0–140.0) |      |
|DBP (mm Hg)*                     | 74.0 ± 8.2     | 74.6 ± 9.9  | 0.805 ns |
|                                  | 70.0 (70.0–80.0)| 80.0 (70.0–80.0) |          |
|RF (UI/mL)*                      | 96.8 ± 153.6   | 297.9 ± 561.5| 0.250 ns |
|                                  | 32.0 (4.0–112.0)| 64.0 (8.0–256.0) |          |
|DAS 28-PCR*                      | 4.1 ± 1.4**    | 4.4 ± 1.5** | 0.372 ns |
|                                  | 3.7 (3.2–5.1)  | 4.3 (3.2–5.4) |          |
|IL-1β*                           | 7.4 ± 1.4      | 11.1 ± 10.8 | 0.290 ns |
|                                  | 7.0 (6.4–8.6)  | 8.4 (6.0–10.6) |          |
|TNF-α*                           | 52.3 ± 23.4    | 71.6 ± 57.6 | 0.608 ns |
|                                  | 42.8 (41.6–57.7)| 50.2 (37.2–97.0) |          |
|IL-6*                            | 67.9 ± 67.6    | 94.6 ± 107.3| 0.248 ns |
|                                  | 55.4 (12.5–113.7)| 37.6 (7.1–185.5) |        |
|MPO*                             | 198.1 ± 100.6  | 200.0 ± 124.4| 0.954 ns |
|                                  | 164.5 (114.6–271.7)| 139.6 (115.3–262.0) |      |

Student’s t test for unpaired samples
Mann–Whitney Test

*1 volunteer excluded
**2 excluded volunteers
***3 excluded volunteers

* Significant difference (p < 0.05)
** Significant difference (p > 0.05)
ns Not significant difference (p ≥ 0.05)
In the present study, the mean blood glucose of patients who did not use GCS was higher when compared to those who used this therapy. These data can be conflicting because it is known that the use of GCS can cause hyperinsulinemia, IR and an inhibiting effect on beta cell functions, which can lead to the development of DM (Cansu et al. 2019; Mills and Devendra 2015). However, these undesirable effects of using GCS may be dependent on dose and time of use. Some studies also point out that IR caused by the inflammatory process of RA is improved with low levels of GCS as inflammation is resolved, while moderate- to high-dose therapy can lead to hyperglycemia and overt DM (Cansu et al. 2019; Ferreira et al. 2016; Ogawa et al. 2005).

Another factor to be taken into account is that the glucose dosages of this study were performed fasting. It is known that fasting glucose concentrations are commonly normal in patients with hyperglycemia induced by GCS. However, it is generally accepted that GCS causes an increase in postprandial glucose concentrations (Gulliford et al. 2006; Lillegraven et al. 2019). The onset of hyperglycemia should also be evaluated and the best time of day to sample blood glucose concentrations for appropriate early treatment in patients who are treated with moderate- to high-dose therapy can lead to hyperglycemia and overt DM (Cansu et al. 2019; Ferreira et al. 2016; Ogawa et al. 2005).

It is also known that glucose metabolism is often impaired in patients with active and early RA, probably, at least in part, related to inflammation. Thus, short-term treatment with high doses of prednisone would not further deteriorate glycemic control, as determined in the fasting state and after an oral glucose load, in some patients. Studies show that there may be great variability among individuals, some of which may improve and others show deterioration in glucose tolerance. The use of GCS by patients with chronic inflammatory conditions may improve glucose tolerance via anti-inflammatory and disease-modifying effects, as it has been demonstrated in several short-term studies (Den Uyl et al. 2012).

Despite the various hypotheses raised and which may be related to the difference in blood glucose between the groups, it should be taken into account that the prevalence of individuals previously diagnosed with DM in the group that did not use GCS (25%) was higher than that found in the group using this treatment (10%). Although there was not a significant difference in this research, this may be a contributing factor for the differences in blood glucose values between groups.

Regarding the CVS score, ACC/AHA, there was no significant difference between the groups regarding the use or not of GCS, when evaluated in isolation. However, after adjustment, when the variables “GCS dose”, “time of GCS use”, “PCR-us dosage” and “MPO” were evaluated together, it was observed that significantly, they can be predictors of CVR when related to the score. However, when the variables were analyzed alone, serum MPO is significantly shown as a predictor of CVR, different from the other variables analyzed in the set, which in isolation do not present themselves as predictors of CVR in patients with RA.

MPO has the ability to activate metalloproteinases of the latent matrix, in active forms, and may play an important role in sites of plate fissure. This includes the oxidation of LDL, turning it pro-atherogenic (Daugherty et al. 1994; Meuwese et al. 2007; Podrez et al. 1999) as well as oxidative modification of apolipoprotein AI, attenuating its ability to promote cholesterol efflux (Malle et al. 2006; Memon et al. 2020). Studies indicate that MPO has been identified

| Variables         | β    | S.E  | Wald | Gl  | p    | Odds ratio | C.I. 95% Lower | C.I. 95% Superior |
|-------------------|------|------|------|-----|------|------------|----------------|------------------|
| GCS dose          | 0.60 | 0.68 | 0.76 | 1   | 0.382 | 1.82       | 0.48           | 6.93             |
| GCS time          | 0.82 | 0.71 | 1.33 | 1   | 0.249 | 2.27       | 0.56           | 9.12             |
| MPO               | 2.30 | 1.11 | 4.34 | 1   | 0.037*| 10.00     | 1.14           | 87.21            |
| us-CRP            | 0.80 | 0.80 | 1.01 | 1   | 0.315 | 2.23       | 0.47           | 10.57            |
| Constant          | − 3.71 | 1.20 | 9.59 | −   | 0.115 | 0.002     | −              | −                |

*Significant difference (p < 0.05)
in human plaques and exerts potent pro-atherogenic effects, as well as evidence that its systemic levels serve as a strong and independent predictor of endothelial dysfunction in individuals. MPO activity also decreases the bioavailability of nitric oxide, which leads to endothelial dysfunction. This combination of harmful effects culminated in the concept that MPO can be an active mediator of atherogenesis, and high levels of MPO may be associated with increased CVR in apparently healthy individuals (Khan et al. 2019; Nicholls & Hazen 2005).

It is clear that the elevation of inflammatory markers, such as MPO and us-CRP, and the interaction between them precedes the coronary artery disease in years. These biomarkers have potential relevance in the exploration of strategies for the prevention and treatment of CVD in these patients, because they are responsible for approximately half of the deaths. Some studies have shown that cardiovascular events occur a decade earlier than in population controls (Bacon et al. 2002). Several publications have addressed the effects of risk factors related to RA on accelerated atherosclerosis, but most studies were cross-sectional, finding associations, but not necessarily causality (Pope et al. 2016). Thus, the use of biomarkers that could serve as an aid tool in the preventive diagnosis of such complications would be relevant.

In our study, it is not observed that the dose or time of use of GCS influence the CVR score when evaluated in isolation. Despite a few studies, little is known about the long-term effects of corticosteroid therapy on the development of CVD. Most studies evaluated exposure to GCS only as a single variable, for example, in initial, current or cumulative use (Davis et al. 2007; Wei et al. 2004). Thus, cumulative measures of exposure to GCS, such as total duration of use or total cumulative dose, vary over time, which may have an influence on the risk of AMI. Efficient modeling of time-dependent GCS exposure measures is especially important, as knowledge about how CVR changes with increasing cumulative dose and/or duration of GCS is necessary to find an optimal balance between the anti-inflammatory benefits of GCS and increased CVR.

**Conclusion**

Our findings indicate that MPO is an important predictor of CVR in patients with RA, when associated with scores commonly used to assess this risk. This relationship seems to be present independently of the GCS dose or time of its usage. Based on these findings, there is a need for other prospective clinical trials to determine whether MPO is a reliable biomarker for predicting CVD in RA.

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**Availability of data and materials** All data are available for publication.

**Declarations**

**Conflict of interest** The authors declare no competing interests.

**Ethical approval** The study was approved by the Committee of Research Ethics of the State University of Ponta Grossa (UEPG) through the Brazilian Platform, number 1.879.373, in accordance with the Helsinki declaration of 1975, as revised in 1983.

**Consent for publication** The informed consent was obtained from all individual participants included in the study and for its publication.

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