**Title: Clinical course and predictors of severe COVID-19 among patients with rheumatic diseases in Portugal – a multicentre, nationwide study**

**Background:**

Infection by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has quickly became a global concern following the initial reports of infected patients in Wuhan, China, by the end of 2019[1].

Risk factors for infection and worse prognosis have been identified so far for the general population, such as older age, cardiovascular or respiratory disease and diabetes mellitus [2,3] .

As for the special subgroup of rheumatic patients, namely those with inflammatory rheumatic and musculoskeletal diseases (RMDs), whether treated or not with immunosuppressors, information is still scarce.

As immunosuppression might preclude an adequate anti-viral response after exposure to SARS-CoV-2, patients under conventional synthetic (cs), targeted synthetic (ts) or biological (b) disease-modifying anti-rheumatic drugs (DMARDs) have so far been hypothesised to be at increased risk for development of coronavirus disease 19 (COVID-19) and, possibly, severe forms of the disease[4]. Most international scientific societies, namely the European League Against Rheumatism (EULAR)[5], the American College of Rheumatology (ACR)[6], the National Institute for Health and Care Excellence (NICE)[7], and the Paediatric Rheumatology European Society (PRES)[8] have published guidelines to help clinicians in the decision-making process and management of rheumatic patients after exposure or infection by SARS-CoV-2. While ACR and NICE promote a less permissive strategy, favouring the suspension of almost all DMARDs after risk exposure to SARS-CoV-2 or suspected or confirmed infection, EULAR and PRES suggest that patients should discuss treatment discontinuation with their rheumatologists[9]**.** These recommendations are however expert opinion-based, as evidence on the potential risk conferred by DMARDs regarding infection and severe disease course is still missing.

In fact, case series and cross-sectional observational studies failed to prove the increased vulnerability of patients with RMDs under immunosuppression so far. For instance, Monti et. al [10] and Conticini et al[11], after conducting phone interviews of hundreds of patients with RMDs on stable treatment with ts/bDMARDs, identified only 4/320 and 2/859, respectively, confirmed cases of COVID-19 infection by reverse transcription polymerase chain reaction (RT-PCR) test. No infected patients developed severe respiratory complications or died. Additionally, one of the patients was an 87 years-old female with diabetes mellitus and giant cell arteritis treated with tocilizumab, who remained fully asymptomatic without suspending the bDMARD, following a COVID-19 outbreak in her retirement home. A work from our group, not published yet, identified 8/561 patients with RMDs who developed COVID-19 symptoms after direct contact with healthcare workers later diagnosed with COVID-19 following an outbreak in a rheumatology department, and of those, just 2/8 had a confirmation of SARS-CoV-2 infection. Michelena et al[9] performed a larger cross sectional study in order to determine the incidence of COVID-19 in a group of adult and paediatric RMD patients treated with ts/bDMARDs at a tertiary centre in Barcelona. They have identified 11/959 confirmed

SARS-CoV-2 infected patients in the adult cohort and none in the paediatric population, and concluded that the cumulative incidence of COVID-19 infection was similar to the general population, after comparison with epidemiological data from the same city districts. They also found that younger patients reported symptoms compatible with infection more often and that patients with active rheumatoid arthritis (DAS28>2.6) were more likely to be considered suspected compared to those in remission. Besides, patients treated with abatacept or IL-6R blockers were less likely to be classified as suspected cases, suggesting a potential protective role of these drugs. Likewise, a case series of 86 infected patients with various immune-mediated inflammatory disease from New York showed that the proportion of patients treated with DMARDs was higher in the ambulatory managed patients compared to those that required admission[9]**.** In fact, anti-rheumatic drugs such as anakinra and tocilizumab have been increasingly used empirically or in the context of clinical trials[12] with apparent benefit in the treatment of the moderate-to-severely ill patients.

Another question that remains unanswered refers to whether treatment with DMARDs may influence the endogenous production of antibodies of the IgM and IgG classes after confirmed infection by SARS-CoV-2. Moreover, it is also unclear whether patients with non-inflammatory RMDs have a different risk of COVID-19 or severe disease, in comparison with both the general population and patients with inflammatory RMDs.

Study rational: Together, the aforementioned data suggest that immunosuppressive drugs do not increase the risk for infection or severe disease complications in patients with rheumatic diseases, contradicting the current clinical practice guided by the most international scientific societies of suspending DMARDs after risk exposure or infection. These drugs may even exhibit a protective role in the event of severe disease, namely in acute respiratory distress syndrome (ARDS) since this is associated with an hyperinflammatory state, in which high serum concentrations of IL-6, IL-1 and TNF have been reported[11–13]. Larger and prospective epidemiological studies are warranted to confirm these data as well as to find predictors for severe disease in patients with RMDs.

**Objectives:**

Primary objective:

- To assess the epidemiological features and clinical outcomes of rheumatic patients in Portugal infected by SARS-CoV-2.

Secondary objectives:

- To find predictors for severe disease, defined as the need for hospitalization, intensive care unit (ICU) admission and/or death;
- To assess the effect of immunosuppressive therapies and glucocorticoids (GC) in disease expression;
- To assess the development of antibodies against SARS-CoV2-2 in patients under DMARD therapy;
- To compare the outcomes of patients with inflammatory and non-inflammatory RMDs who developed COVID-19.

**Methods:**

**Study design:** multicentre observational nationwide study of patients with rheumatic diseases prospectively-followed in the Rheumatic Diseases Portuguese Register – Reuma.pt – with confirmed or suspected infection by SARS-CoV-2 in the first 5 months of the pandemic in Portugal – from March 2 (first reported case in the country) to July 31. Reuma.pt is a real-life-based observational registry that captures the vast majority of patients treated with biological therapies, as well as many of other patients with inflammatory rheumatic diseases. In addition, it also includes a protocol for patients with osteoarthritis and other non-inflammatory conditions. Since March 2020, the Portuguese Society of Rheumatology made available a novel module to capture information on outcome and prognosis of rheumatic patients infected with COVID 19. We will collect demographic, clinical and laboratory data. Ideally, blood samples retrieved will be stored at Biobank (Biobanco-IMM) after the initial processing, in order to ensure their quality and viability. Patients with mild disease will be compared with those with severe course after adjusting for age and comorbidities. Moreover, we will compare the disease course and outcomes of patients with inflammatory and non-inflammatory RMDs and those with or without treatment with DMARDs and GC. Association between disease features and treatment and the development of anti-SARS-CoV2 IgG antibodies will also be assessed.

**Inclusion criteria:**

- All adult and paediatric patients with inflammatory or non-inflammatory RMDs followed at Portuguese rheumatology departments, with confirmed or suspected infection by SARS-CoV-2.
- Inflammatory RMDs considered: juvenile idiopathic arthritis; rheumatoid arthritis; spondyloarthritis; systemic lupus erythematosus; vasculitis; polymyalgia rheumatica; systemic sclerosis; Sjögren's syndrome; myositis; antiphospholipid syndrome; autoinflammatory diseases; undifferentiated arthritis; uveitis; undifferentiated connective tissue disease; overlap syndromes; sarcoidosis.
- Non-inflammatory rheumatic diseases: osteoarthritis; osteoporosis; Paget's bone disease; gout; pseudogout; fibromyalgia; *osteogenesis imperfecta;* tendinitis; bursitis; septic arthritis.

**Exclusion criteria:**

- Patients without rheumatic conditions;
- Patients not fulfilling the definitions of confirmed or suspected case of COVID-19 disease.

**Definitions:**

- Confirmed case of COVID-19 infection: infection by SARS-CoV-2 confirmed by RT-PCR on samples obtained from the respiratory tract; infection confirmed by serology.
- Suspected case of COVID-19 infection: we will adopt the definition of the World Health Organisation (WHO)[14], according to which a patient is considered suspected if he/she reports fever plus one other respiratory symptom (dyspnoea, persistent

cough or odynophagia) OR if one of the previous symptoms (fever, dyspnoea, persistent cough or odynophagia) is present after a contact with a confirmed or probable case; we will also consider as suspected cases, patients who report anosmia and/or dysgeusia *de novo* after a contact with a confirmed or probable case[15,16].

- Severe disease: defined as the need for hospitalization, intensive care unit (ICU) admission and/or death.

**Data source**:

This study will use data collection from the RGPD-compliant Reuma.pt database (no data that directly identifies patients will be collected).

**Variables:**

- Gender, age, ethnicity, smoking habits, body mass index (BMI);
- Main rheumatic diagnosis;
- Age at diagnosis/Disease duration;
- Diagnosis delay – time between symptoms onset and diagnosis;
- Comorbidities and date of diagnosis, namely:
    - obesity as defined by BMI > 30;
    - Interstitial lung disease (ILD) (documented by previous by imaging techniques or lung biopsy or the patient has a clearly documented history of ILD or is on treatment with antifibrotics);
    - Asthma (documented by lung function tests or the patient has a clearly documented history of asthma);
    - Obstructive lung disease (OLD) (documented by lung function tests or the patient has a clearly documented history of OLD);
    - Arterial hypertension (at least two measurements of BP > 140/90mmHg or if the patient has a clearly documented history of HTN or in on treatment with anti-hypertensive drugs);
    - Hyperlipidaemia (total cholesterol levels >240 mg/dl or triglyceride levels >150 mg/dl or if the patient has a clearly documented history of hypercholesterolaemia or hypertriglyceridaemia or is on treatment with specific lipid-lowering drugs);
    - Diabetes mellitus (at least two measurements of fasting glucose of >140 mg/dl, or if the patient has a clearly documented history of diabetes or is on treatment with hypoglycaemic agents);
    - Hyperuricemia (at least two measurements of uricemia >8mg/dl or if the patient has a clearly documented history of hyperuricemia or gout or is on treatment with xanthine oxidase inhibitor);
    - History of heart failure (clearly documented history of heart failure according to Framingham criteria);

- History of ischemic heart disease (angina pectoris, unstable angina, myocardial infarction, revascularization procedure);
- History of cranial ischemic events (transitory cerebrovascular ischemic event well documented after neurologist assessment; previous CVA);
- Chronic kidney disease (CKD) (defined as an eGFR < 30ml/min according to a 24-hour urine specimen clearance; or using the Cockroft-Gault formula or the patient has a clearly documented history of CKD or is on kidney replacement therapy);
- History of malignancy;
- Organ transplant receptor;
- History of primary immunodeficiency;
- History of inflammatory bowel disease;
- History of neurological or neuromuscular disease;
- History of psychiatric disease.

- Date of first symptoms compatible with Covid-19 infection;

- Date of confirmed Covid-19 infection;

- Type of diagnostic test (RT-PCR; serology; presumptive diagnosis; other);

- Epidemiological link (contact to confirmed/suspected cases and place where the contact took place – work/home; healthcare worker; travel to a country with an active community transmission; unknown);

- Signs and symptoms of Covid-19 infection (fever; cough; dyspnoea; odynophagia; malaise; headache; rhinorrhoea; chest pain/tightness; *de novo* or worsening arthralgia or myalgia; abdominal pain; diarrhoea; nausea; vomits; mental confusion; anosmia; dysgeusia; others; asymptomatic);

- If young female, verify if infection during pregnancy or in the postpartum period (<6 weeks after delivery);

- For patients with inflammatory RMDs, disease activity status in the 3-month period before the confirmed or suspected COVID-19 infection namely: remission, mild, moderate or severe disease, according to their rheumatologist judgement; when available, disease activity indexes pre- and post-disease will be retrieved.

- Therapy used for COVID-19 infection (hydroxychloroquine; colchicine; *janus kinases* inhibitors; anti-IL6 drugs namely tocilizumab or sarilumab; anti-IL1 drugs namely anakinra and canakinumab; human intravenous immunoglobulin – IVIG; systemic corticosteroids; azithromycin; lopinavir+ritonavir; remdesivir; convalescent plasma; other; only supportive treatment);

- Need for hospitalization;

- Need for ICU admission;

- Need for specific interventions (namely oxygen therapy, non-invasive mechanical ventilation, invasive ventilation, extracorporeal membrane oxygenation – ECMO; other);

- Complications of the COVID-19 infection (namely radiographic signs of bilateral pneumonia; ARDS; sepsis; myocarditis/ *de novo* heart failure; cytokine release syndrome; thromboembolic events; co-infection or secondary infection by other infectious agent – viral, bacterial or fungus; sequels; death; other);

- Laboratory results during COVID-19 infection namely concerning: haemoglobin, leukocytes, platelets, fibrinogen, D-dimer, IL-6 levels, ferritin, transaminases, triglycerides, C-reactive protein, creatinine kinase, lactate dehydrogenase, anti-SARS-CoV2 IgM, anti-SARS-CoV IgG.

- Chronic therapy by the time of COVID-19 infection, namely, but not exclusively: GC, NSAIDs, colchicine, csDMARDs, tsDMARDs, bDMARDs, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and phosphodiesterase type 5 inhibitor

- Therapy starting date, dose and frequency of administration; data about therapy continuation, suspension or change in the usual dosage after COVID-19 infection confirmation or suspicion;

- In patients on GC, cumulative corticosteroids dose up to COVID-19 infection;

- Time to cure after confirmed infection, defined as two consecutive negative tests by RT-PCR[17];

- Serology results during infection and after cure.

**Statistical analysis:**

Descriptive analysis of continuous variables will be reported as mean±standard deviation, or median (interquartile range [IQR]), as appropriate. Descriptive analysis of categorical variables will be displayed as absolute or relative frequency.

Comparison of continuous variables between groups of patients with or without a severe course and with inflammatory/non-inflammatory RMDs will be performed using Student's two-tailed t-test or non-parametric as appropriate. Categorical variables will be compared using Chi-square or Fisher's exact test. Multivariate logistic regression analysis will be performed to identify predictors of severe disease.

Pearson correlation and linear regression models will be applied to study the relation of IgG humoral response and clinical variables.

Statistical analysis will be performed in the Statistical Package for the Social Sciences

(SPSS)® v.25. P-value considered significant at $p<0.05$.

**Expected results and possible limitations:**

We expect to characterize the epidemiological features and clinical outcomes of Portuguese rheumatic patients affected by COVID-19 and to find risk factors for severe disease in this population. We hope to improve the global knowledge about the risk and clinical course of

SARS-CoV-2 infection in this peculiar population. Limitations such as underreporting and missing data are expected.

**Calendar**

Timelines for the several steps of this project are presented in the table below. Globally, it is estimated that it will take 8 months to be concluded.

| | 2020 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Task** | **May** | **June** | **July** | **August** | **September** | **October** | **November** | **December** |
| Research project Elaboration, Reuma.pt approval and data collection | | | | | | | | |
| Data extraction | | | | | | | | |
| Data analysis | | | | | | | | |
| Prepare the study final report | | | | | | | | |

**Research team**

Proponents: Ana Rita Cruz-Machado, Vasco C. Romão, Sofia Barreira, João Eurico Fonseca, Maria José Santos.
On behalf of Reuma.pt - rheumatologist from all collaborating centres according to Reuma.pt guidelines.

Institutions: The project is open to all national rheumatology centres interested in cooperating.

Co-authors: Authorship and co-authorship will be based in the International committee of Medical Journal Editors and Reuma.pt guidelines.

Ethical considerations: This study will be conducted according to the Declaration on Helsinki and the International Guidelines for Ethical Review of Epidemiological Studies. This study will be submitted for validation and approval to the Coordinator and Scientific Board of Reuma.pt.Reuma.pt was approved by the National Data Protection Commission and by the local Ethics Commissions. Results will be presented in an objective way and will not be hidden or manipulated.

Conflict of interest: To be completed after research team is identified


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