**Title: COVID-19 Susceptibility and Clinical Outcomes in Autoimmune Inflammatory Rheumatic Diseases (AIRDs): A Systematic Review and Meta-Analysis**

*Running Title: COVID-19 susceptibility and clinical outcomes in AIRD*

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**Keywords:** Autoimmune inflammatory rheumatic disease; COVID-19; SARS-CoV-2; Steroid; connective tissue disease; Inflammatory arthritis; Disease-modifying antirheumatic drugs

**Abstract**

**OBJECTIVE:** This meta-analysis aims to assess the susceptibility to and clinical outcomes of COVID-19 in autoimmune inflammatory rheumatic disease (AIRD) and following AIRD drug use.

**MATERIALS AND METHODS:** We included observational and case-controlled studies assessing susceptibility and clinical outcomes of COVID-19 in patients with AIRD as well as the clinical outcomes of COVID-19 with or without use of steroids and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

**RESULTS:** Meta-analysis including three studies showed that patients with AIRD are not more susceptible to COVID-19 compared to patients without AIRD or the general population (OR: 1.11, 95% CI: 0.58 to 2.14). Incidence of severe outcomes of COVID-19 (OR: 1.34, 95% CI: 0.76 to 2.35) and COVID-19 related death (OR: 1.21, 95% CI: 0.68 to 2.16) also did not show significant difference. The clinical outcomes of COVID-19 among AIRD patients with and without csDMARD or steroid showed that both use of steroid (OR: 1.69, 95% CI: 0.96 to 2.98) or csDMARD (OR: 1.35, 95% CI: 0.63 to 3.08) had no effect on clinical outcomes of COVID-19.

**CONCLUSIONS:** AIRD does not increase susceptibility to COVID-19, not affecting the clinical outcome of COVID-19. Similarly, the use of steroids or csDMARDs for AIRD does not worsen the clinical outcome.

**Introduction**

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged. Since then, SARS-CoV-2, now more commonly known as coronavirus disease of 2019 (COVID-19), has caused a rapidly spreading pandemic. Despite the development of several effective vaccines, COVID-19 continues to spread worldwide1. Experts' opinions are emerging that this pandemic will not end soon and will be with humanity for the next few years2. This continued spread of COVID-19 is a particular threat for patients with preexisting medical conditions. Therefore, there has been much research on the correlation between various diseases and COVID-19. Risk factors associated with higher mortality due to COVID-19 that have already been identified include age over 70, obesity, cardiovascular disease, chronic kidney failure under dialysis, cancer under treatment, decreased immunity, cirrhosis, diabetes, pregnancy, and chronic respiratory disease3. However, the association between autoimmune rheumatic disease (AIRD) and COVID-19 is still controversial.

AIRD is a group of diseases characterized by chronic systemic inflammatory diseases involving the musculoskeletal system due to abnormal immune response to autoantigens4. Examples of such diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren’s syndrome (SS), systemic sclerosis (SSc), polymyoitis (PM), dermatomyositis (DM), antiphospholipid syndrome (APS), spondyloarthropathies (SpA), and systemic vasculitis. Some AIRDs, such as RA and SLE, are known to be associated with an increased risk of infection compared to the general population5-7. Moreover, most of the drugs used to treat AIRD are immunosuppressants. Biologic disease-modifying antirheumatic drugs (bDMARDs) such as abatacept and adalimumab are used to treat moderate and severe patients. Some studies have reported that standard-dose and high-dose bDMARDs are associated with an increase in serious infections compared to traditional DMARDs (tDMARDs) in patients with RA8,9. Several studies have reported that glucocorticoid and tDMARDs also increase the risk of infection10-12. However, paradoxically, tocilizumab – a bDMARD - and corticosteroids are used as treatments for COVID-1913-16. As such, there has yet to be a clear conclusion regarding the association between AIRD and the use of DMARD with COVID-19. There are some systemic reviews on this subject, but there are currently no meta-analyses that include only well-conducted studies. Therefore, we employed strict inclusion criteria and excluded confounding variables to establish a more credible rationale for the association between AIRD and DMARD with COVID-19.

In this systematic review and meta-analysis, we investigated the susceptibility of AIRD patients to SARS-CoV-2 infection, and the association between AIRD and use of DMARDs with clinical outcomes of COVID-19.

**Materials and Methods**

**Search strategy and study selection**

This meta-analysis was completed in accordance with a pre-defined protocol which follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline17. The protocol we followed has been registered in PROSPERO (ID: CRD42020216281). We conducted literature search in PubMed/MEDLINE, Embase Ovid, and Google Scholar for published studies and in MedRxiv for pre-printed studies. We searched all database from their inception to 14 February 2021 to identify studies assessing susceptibility and clinical outcomes of COVID-19 in patients with Autoimmune Inflammatory Rheumatic Diseases (AIRDs).

We searched for observational or case-controlled studies and we also included unpublished studies and grey literatures. There were no restrictions regarding age, sex, duration, or publication status of study. However, literature search was limited only to studies written in English and studies published between 2019 and 2021 to limit our scope to COVID-19. Search terms included: ‘COVID-19’, ‘SARS-CoV-2’, ‘Coronavirus’, ‘rheumatoid’, ‘connective tissue disease’, ‘rheumatic disease’, ‘severe acute respiratory syndrome’, ‘mortality’ and their variants. In PubMed, search strategy ((rheumatoid) OR (rheumatic) OR 'connective tissue disease' OR 'gout' OR lupus OR (arthritis) OR 'autoimmune inflammatory rheumatic diseases') AND COVID-19 AND (feature OR outcome OR severity OR 'risk factor' OR mortality OR death OR ICU OR ventilator OR ventilation) were used. In MedRxiv, search strategy "(rheumatoid OR rheumatic OR lupus OR arthritis OR 'autoimmune') AND COVID-19 AND (mortality OR outcome OR severity OR severe)" and full text or abstract or title "COVID-19 OR severe OR death OR ICU OR "OR"" (match whole all) and posted between "01 Dec, 2019 and 14 Feb, 2021" were used. Similar searching strategies were implemented in Google Scholar and Embase Ovid. To differentiate our study from previous studies, we excluded observational studies presenting crude (unadjusted) results or derived conclusions from uncontrolled populations. We only considered studies that adjusted for relevant confounding variables through methods such as propensity score matching (PSM), inverse probability treatment weighting (IPTW), or regression model adjustment. Also, we only considered studies providing evidence that the risk for such confounding was low by establishing baseline similarity between the groups, usually in matched cohort studies. Two authors (ML, SK) independently identified eligible studies, and reached a consensus on which to include. Any disagreement was adjudicated by a third reviewer (MSK).

**Data extraction and quality assessment**

Three authors (MH, SE, and MSK) independently extracted data using a standardized data extraction sheet. Any discrepancies were resolved though discussion. We extracted data including author name, year of publication, the journal in which the study was published, demographics, study design, sample size, diagnosed disease of patients, incidence and clinical outcomes of COVID-19. The risk of bias was assessed using Risk of Bias in Non-randomized Studies of intervention (ROBINS-I) tool whereas the quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS)18,19.

**Outcome assessment**

The primary outcomes were susceptibility of COVID-19, incidence of severe COVID-19, and COVID-19-related death in patients with AIRD compared to those without this condition. Severe COVID-19 was defined as COVID-19 infection necessitating intensive care unit (ICU) admission, invasive ventilation, or death due to COVID-19. The secondary outcomes were clinical outcomes of COVID-19 exclusively in steroid or conventional synthetic disease-modifying antirheumatic drugs (csDMARD) users with AIRD compared with non-users with AIRD. Outcomes were estimated as adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

**Statistical Analysis**

We calculated ORs with 95% CI to assess all outcomes in the study. We performed a meta-analysis using random effect model. Heterogeneity of studies was investigated using the *I²* statistic. An *I²* value of less than 50% was assumed to represent a low level of heterogeneity, 50%–74% a moderate level, and ≥ 75% a high level20. Heterogeneity was further evaluated by using Cochrane’s Q-statistics with a significance level of *p* < 0.10. Publication bias was evaluated by Egger’s test and funnel plots to detect possible asymmetry when three or more studies were used. Egger’s linear regression test was used to evaluate asymmetry, and *p* < 0.10 was set as the level of significance. All statistical analyses were performed using the R (version 3.6.1) software.

**Results**

**Study characteristics**

We identified 1,024 records after duplicates were removed. Through the initial screening with titles and abstracts, 279 were assessed for eligibility. After reviewing the full-text, 12 records met the eligibility criteria and were included in our analyses (**Figure 1**)21-32. The characteristics of included studies are displayed in **Table I**. Among these studies, 10 studies were included to compare severe outcomes and 3 studies were included to compare susceptibility to COVID-19 in patients with AIRD with those without AIRD. For subgroup analysis, 3 and 5 studies were included to evaluate severe outcomes and use of csDMARDs and glucocorticoids, respectively. The risk of bias for all included studies was assessed and the majority of the studies (50%) were with moderate risk. The quality assessment was also conducted with all included studies (**Table II**). Studies that scored more than 6 out of 8 were considered high quality studies, and 10 out of 12 studies (83%) were of high quality.

**Susceptibility to COVID-19 in AIRD**

Three studies and 13,771 patients were included in the meta-analysis of susceptibility to COVID-19 (**Figure 2**). The results showed that patients with AIRD are not more susceptible to COVID-19 compared to patients without AIRD or the general population (OR: 1.11, 95% CI: 0.58 to 2.14). Heterogeneity was moderate overall. (*I²* = 70%) No evidence of publication bias was indicated with the funnel plot, as well as with Egger’s test (*p* = 0.763).

**Incidence of severe outcomes of COVID-19 in AIRD**

A meta-analysis of severe COVID-19 outcomes in AIRD patients was performed (**Figure 3**). Meta-analysis with 4 studies including 6,640 patients showed that the incidence of any severe outcome of COVID-19 was not significantly different between patients with AIRD and those without (OR: 1.34, 95% CI: 0.76 to 2.35). Heterogeneity was moderate (*I²* = 70%). Publication bias was found in the funnel plot and Egger’s test (*p* =0.038).

**COVID-19 related death in AIRD**

Three studies and 6,350 patients were included to analyze COVID-19 related death in patients with AIRD compared to those without AIRD. (**Figure 3**) COVID-19-related death was not found to be higher in patients with AIRD (OR: 1.21, 95% CI: 0.68 to 2.16). No evident heterogeneity was found (*I²* = 0%). The funnel plots and Egger’s tests showed no evidence of publication bias in all meta-analyses (*p* = 0.508).

**Use of medications in patients with AIRD and COVID-19 outcome**

In a subgroup analysis, we compared the clinical outcome of COVID-19 among AIRD patients with and without csDMARD and steroid use. (**Figure 4**) The results showed that both use of steroid (OR: 1.69, 95% CI: 0.96 to 2.98) and csDMARD (OR: 1.35, 95% CI: 0.63 to 3.08) had no effect on clinical outcomes of COVID-19. There was moderate heterogeneity in both meta-analyses (*I²* = 64% and *I²* = 62%). No publication bias was found in funnel plots and Egger’s tests (*p* = 0.052 and *p* = 0.975).

**Discussion**

In the present study, we report the susceptibility of AIRD patients to SARS-CoV-2 infection, and the association between the use of steroids/DMARDs and the clinical outcomes of COVID-19 in AIRD patients. Our results show that susceptibility to COVID-19, severe outcomes of COVID-19, and COVID-19 related death are all not significantly different between AIRD patients and patients without this condition. Also, both use of steroid and csDMARD had no effect on clinical outcomes of COVID-19 in AIRD patients.

Our results are in line with some previous results but inconsistent with others. When we analyzed 13,771 patients included in three studies, we did not find any difference in terms of susceptibility to COVID-19 between AIRD patients and patients without AIRD (OR: 1.11, 95% CI: 0.58 to 2.14). Also, when analyzing the 6,640 patients included in four studies, we did not find any difference in severe outcomes of COVID-19 between AIRD patients and patients without AIRD (OR: 1.34, 95% CI: 0.76 to 2.35). According to the 6,350 patients included in three studies, there were no significant differences in COVID-19 mortality between patients with and without AIRD (OR: 1.21, 95% CI: 0.68 to 2.16). In contrast to our results, according to data from 123 patients attending a rheumatology outpatient clinic of a tertiary hospital in Madrid, Spain, having a systemic autoimmune condition increased the risk of hospital admission due to COVID-1923. However similar results to our study have been found in another study on 62 patients with COVID-19 and underlying rheumatic and musculoskeletal diseases (RMD) that no specific RMD diagnoses was associated with increased odds of hospitalization due to COVID-1933.

Regarding impacts of steroids and csDMARD on clinical outcomes of COVID-19 in AIRD patients, our results are in line with most of the previous studies on this topic. We compared the clinical outcome of COVID-19 within AIRD patients with and without csDMARD and steroid use and found that both use of steroids (OR: 1.69, 95% CI: 0.96 to 2.98) and csDMARD (OR: 1.35, 95% CI: 0.63 to 3.08) had no effect on clinical outcomes of COVID-19. According to data from 456 patients, a retrospective observational matched cohort study from the databases of five reference centers in Spain pertaining to a public research network for the investigation of inflammation and rheumatic diseases showed similar results, i.e., previous immunosuppressive therapies were not associated with severe COVID-19 (Glucocorticoids: OR: 2.20, 95% CI: 1.36 to 3.54, csDMARDs: OR: 1.04, 95% CI: 0.64 to 1.72)27.

Most of the systematic studies on COVID-19 and AIRD in the past included limitations of meta-analysis studies, which have been described in many other papers34-36. We tried to get rid of those limitations. Thus, it is an initial approach to meta-analysis including only well-conducted studies with strict inclusion criteria and excluding confounding variables to establish more credible evidence on the association between AIRD and DMARD with COVID-19. Unlike the previous meta-analysis study of 26 articles37, we excluded observational studies presenting unadjusted results or conclusions. We only considered studies that adjusted for relevant confounding variables through methods such as PSM, IPTW, or regression model adjustment. Also, we only included studies providing evidence that the risk for such confounding was low by establishing baseline similarity between the groups, usually in matched cohort studies. We used ROBINS-I tool to assess risk of bias and in addition, the quality of included studies was assessed using the NOS. Furthermore, we performed a meta-analysis using random effect model, while heterogeneity between studies was investigated using the *I²* statistic. Therefore, we were able to present far more accurate data.

**Conclusions**

Susceptibility to COVID-19, severe outcomes of COVID-19 and COVID-19 related death are all not significantly different between patients with AIRD and those without AIRD. Also, steroid and csDMARD therapy in AIRD patients were not associated with severe COVID-19. More research is needed to find out specific risk factors in AIRD patients with severe COVID-19 outcomes, but according to our data, AIRD patients do not need discontinuation of steroid or csDMARD therapy because of COVID-19.

**Declarations**

**Ethics approval and consent to participate**: Not applicable  
**Consent for publication**: All the authors checked and gave their approval of this version to be published.  
**Availability of data and material**: No datasets were generated or analyzed during this study.  
**Conflict of interest**: all authors confirm to have no actual or potential conflict of interests.  
**Funding**: No financial support was provided for research conduct and/or preparation of the article.  
**Authors' contributions**: All authors made substantial contributions to all of the following; (1) conception and design of the study, data acquisition, or analysis and interpretation of data; (2) drafting or critical revision of the article for intellectual content; and (3) final approval of version to be submitted.

**Figure legends**

**Figure 1.** PRISMA flow chart showing selection process of the studies

**Figure 2.** Susceptibility to COVID-19 in patients with AIRD compared to general population

**Figure 3.** All severe COVID-19 outcomes in patients with AIRD compared to non-AIRD

**Figure 4.** Forest plots and funnel plots showing clinical outcomes of COVID-19 according

**Table legends**

**Table I.** Characteristics of studies included in the meta-analysis

**Table II.** Quality assessment

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**Table I. Characteristics of studies included in the meta-analysis**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Susceptibility** | | | | | | | | | | |
| **Author,**  **Year** | **Country** | **Population** | **Race/**  **Ethnicity** | **Study design** | **No. of**  **Population** | **Outcome** | | | | **Adjustment of outcome** |
| Zhong et al., 2020 | China | AIRD | N/A | Cohort  (Multi center) | Total: 126 | PCR positive COVID-19 | | | | Age, Sex |
| Gu et al., 2020 | USA | AIRD | Whites: 3374  Black: 981  Other: 486 | Cohort  (Single Center) | Total: 5698 | PCR positive COVID-19 | | | | Age, Sex, SES, Comorbidities |
| Salvarani et al., 2020 | Italy | N/A | N/A | Cohort  (Multi center) | Total: 7947 | PCR positive COVID-19 | | | | Age, Sex |
| **Clinical outcomes** | | | | | | | | | | |
| **Author,**  **Year** | **Country** | **Population** | **Race/**  **Ethnicity** | **Study design** | **No. of**  **Population** | **Outcome** | | | | **Adjustment of outcome** |
| **Hospitalization** | **ICU** | **Ventilation** | **Death** |
| D’Silva et al., 2020 | USA | AIRD | White: 77  Black: 29  Asian: 8  Other: 42 | Cohort  (Multi center) | Total: 156  AIRD: 52  Non-AIRD: 104 | ● | ●\* | | ● | Age, BMI, Smoking,  Comorbidities |
| Pablos et al., 2020 | Spain | AIRD | N/A | Case control  (Multi center) | Total: 456  AIRD: 228  Non-AIRD: 228 | ● | ● | ● | ● | Age, Sex, Obesity, Diabetes, Heart failure, GC |
| Brenner et al., 2020 | Nationwide | AIRD | White: 442  Black: 26  Asian: 14  Other: 61 | Cohort  (Multi center) | Total: 525  GC: 12  Non-GC:513 | ●\*§ | - | - | ● | Age, Sex, Disease, Severity, BMI, Smoking, Comorbidity, TNF antagonist, 5-ASA/SSA |
| ●\*§ | | |
| Gu et al., 2020 | USA | AIRD | Whites: 3374  Black: 981  Other: 486 | Cohort  (Single Center) | Total: 5698 | ● | ● | - | ● | Age, Sex, SES, Comorbidities |
| Siso´-Almirall et al., 2020 | Spain | AIRD | N/A | Cohort  (Multi Center) | Total: 322  AIRD: 21  Non- AIRD: 301 | ●\* | ●\* | - | ●\* | Age, Sex, Co Age, Sex morbidities |
| Scirè et al., 2020 | Italy | AIRD | N/A | Cohort  (Multi center) | Total: 232 | - | ● ‡§ | | | Sex, Age >65, Comorbidities |
| Singh et al., 2020 | Nationwide | AIRD | White 177  Black: 29 | Cohort  (Multi Center) | Total: 464  AIRD: 232  Non AIRD: 232 | ●§\* | - | - | ● | Propensity score matching  (age, sex, race, BMI, comorbidities) |
| Freites et al., 2020 | Spain | AIRD [[1]](#footnote-1) | N/A | Cohort  (Single Center) | Total: 123 | ●‡§ | - | - | - | Age, Sex, Comorbidity, disease |
| Gianfrancesco et al., 2020 | Nationwide | AIRD | N. America: 340  S, America: 16  Europe: 218,  SE Asia: 5  Other: 29 | Cohort  (Multi center) | Total: 600  Non-DMARD: 97  csDMARD: 272 | ●\* | - | - | - | Age, Disease, Comorbidities, Smoking history, NSAIDs, GC |
| Total: 600  Non-GC: 403 GC: 189 | ●\* | - | - | - | Age, Disease, Comorbidities, Smoking history, NSAIDs DMARDs |
| Gupta et al., 2021 | USA | AIRD | Black: 424  Others: 57 | Cohort  (Single Center) | Total: 496  AIRD: 38  Non- AIRD: 444 | - | - | - | ● | Race, Age, Sex, Comorbidities |

AIRD: autoimmune inflammatory rheumatic disease, RD: rheumatic disease, RA: rheumatic arthritis, SLE: systemic lupus erythematous, Ps: psoriasis, GC: use of glucocorticoid, IBD: inflammatory bowel disease, AID: autoimmune disease, b/tsDMARD: biological DMARDs or targeted synthetic DMARDs, csDMARD: conventional synthetic DMARDs, DMARD: Disease-modifying antirheumatic drugs, SES: social economic status, NSAID: non-steroidal anti-inflammatory drug, TNF: tumor necrosis factor, AZA: azathioprine, SSZ: sulfasalazine, BP: blood pressure ICU: intensive care unit, BMI: body mass index, N/A: not applicable

\*: *p*-value < 0.05

†: c: csDMARD, b/ts: b/tsDMARD

‡: Compared between patients with and without DMARD treatment

§: Compared between patients with and without glucocorticoid treatment

**Table II. Quality assessment**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cohort studies** | **Selection** | | | | **Comparability** | **Outcome** | | | **Total quality score** |
| **Author, year** | **Representativeness of the exposed cohort** | **Selection of the non-exposed cohort** | **Ascertainment of exposure** | **Demonstration that the current outcome of interest was not present at start of study** | **Comparability of cohorts on the basis of the design or analysis** | **Assessment of outcome** | **Was follow-up long enough for outcomes to occur** | **Adequacy of follow up of cohorts** |  |
| D’Silva et al., 2020 |  | **\*** | **\*** | **\*** | **\*\*** | **\*** |  |  | 6 |
| Pablos et al., 2020 |  | **\*** | **\*** | **\*** | **\*\*** | **\*** |  |  | 6 |
| Gianfrancesco et al., 2020 | **\*** | **\*** | **\*** | **\*** | **\*\*** | **\*** |  | **\*** | 8 |
| Scirè et al., 2020 | **\*** | **\*** | **\*** | **\*** |  | **\*** |  |  | 5 |
| Zhong et al., 2020 | **\*** | **\*** | **\*** | **\*** | **\*\*** |  |  | **\*** | 7 |
| Salvarani et al., 2020 |  | **\*** | **\*** | **\*** | **\*\*** | **\*** |  |  | 6 |
| Freites et al., 2020 |  | **\*** | **\*** | **\*** | **\*\*** | **\*** |  |  | 6 |
| Singh et al., 2020 | **\*** | **\*** | **\*** | **\*** | **\*\*** | **\*** |  |  | 7 |
| Brenner et al., 2020 | **\*** | **\*** | **\*** | **\*** | **\*\*** | **\*** |  | **\*** | 8 |
| Gupta et al., 2020 |  | **\*** | **\*** | **\*** |  | **\*** |  |  | 4 |
| Gu et al., 2020 |  | **\*** | **\*** | **\*** | **\*\*** | **\*** |  |  | 6 |
| Siso´-Almirall et al., 2020 |  | **\*** | **\*** | **\*** | **\*\*** | **\*** |  |  | 6 |

1. [↑](#footnote-ref-1)