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COVID-19 susceptibility and clinical outcomes in autoimmune inflammatory rheumatic diseases (AIRDs): a systematic review and meta-analysis

J.I. SHIN[1], S.E. KIM[2], M.H. LEE[2], M.S. KIM[3], S.W. LEE[4,5], S. PARK[2], Y.H. SHIN[6], J.W. YANG[7], J.M. SONG[8], S.Y. MOON[4], S.Y. KIM[9], Y. PARK[2], D.I. SUH[10], J.M. YANG[11,12], S.H. CHO[13], H.Y. JIN[4], S.H. HONG[2], H.-H. WON[14], A. KRONBICHLER[15], A. KOYANAGI[16,17], L. JACOB[16,18], J. HWANG[19], K. TIZAOUI[20], K.H. LEE[1], J.H. KIM[1,21], D.K. YON[4,22], L. SMITH[23]

[1]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea
[2]Yonsei University College of Medicine, Seoul, Republic of Korea
[3]Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, Republic of Korea
[4]Department of Data Science, Sejong University College of Software Convergence, Seoul, Republic of Korea
[5]Sungkyunkwan University School of Medicine, Suwon, Republic of Korea
[6]Department of Pediatrics, CHA Gangnam Medical Center, CHA University School of Medicine, Seoul, Republic of Korea
[7]Department of Nephrology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea
[8]Keimyung University School of Medicine, Daegu, Republic of Korea
[9]Department of Otorhinolaryngology-Head and Neck Surgery, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea
[10]Department of Pediatrics, Seoul National University College of Medicine, Seoul, South Korea
[11]Department of Ophthalmology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[12]Department of Ophthalmology, Dongguk University Ilsan Hospital, Goyang, Republic of Korea
[13]Division of Allergy-Immunology, University of South Florida Morsani College of Medicine, Tampa, FL, USA
[14]Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Samsung Medical Center, Seoul, Republic of Korea
[15]Department of Medicine, University of Cambridge, Cambridge, UK
[16]Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Barcelona, Spain
[17]ICREA (Catalan Institution for Research and Advanced Studies), Barcelona, Spain
[18]Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France
[19]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
[20]Department of Basic Sciences, Medicine Faculty of Tunis, Tunis El Manar University, Tunis, Tunisia
[21]Department of Pediatrics, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[22]Center for Digital Health, Medical Science Research Institute, Kyung Hee University College of Medicine, Seoul, Republic of Korea
[23]Centre for Health, Performance and Wellbeing, Anglia Ruskin University, Cambridge, UK

Jae Il Shin, Sung Eun Kim, Min Ho Lee, Seung Won Lee, Seoyeon Park, Youn Ho Shin, Jae Won Yang and Jun Min Song contributed equally to this work

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 with-

Corresponding Authors: Dong Keon Yon, MD; e-mail: yonkkang@gmail.com
Ji Hong Kim, MD, Ph.D; e-mail: kkkjhd@yuhs.ac

out 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.

Key Words:

Autoimmune inflammatory rheumatic disease, COVID-19, SARS-CoV-2, Steroid, Connective tissue disease, Inflammatory arthritis, Disease-modifying antirheumatic drugs.

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 worldwide[1]. Experts' opinions are emerging that this pandemic will not end soon and will be with humanity for the next few years[2]. 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 disease[3]. 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 autoantigens[4]. 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 population[5-7]. 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 RA[8,9]. Several studies have reported that glucocorticoid and tDMARDs also increase the risk of infection[10-12]. However, paradoxically, tocilizumab – a bDMARD - and corticosteroids are used as treatments for COVID-19[13-16]. 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) guideline[17]. 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 I^2 statistic. A I^2 value of less than 50% was assumed to represent a low level of heterogeneity, 50%-74% a moderate level, and $\geq$ 75% a high level[20]. 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.

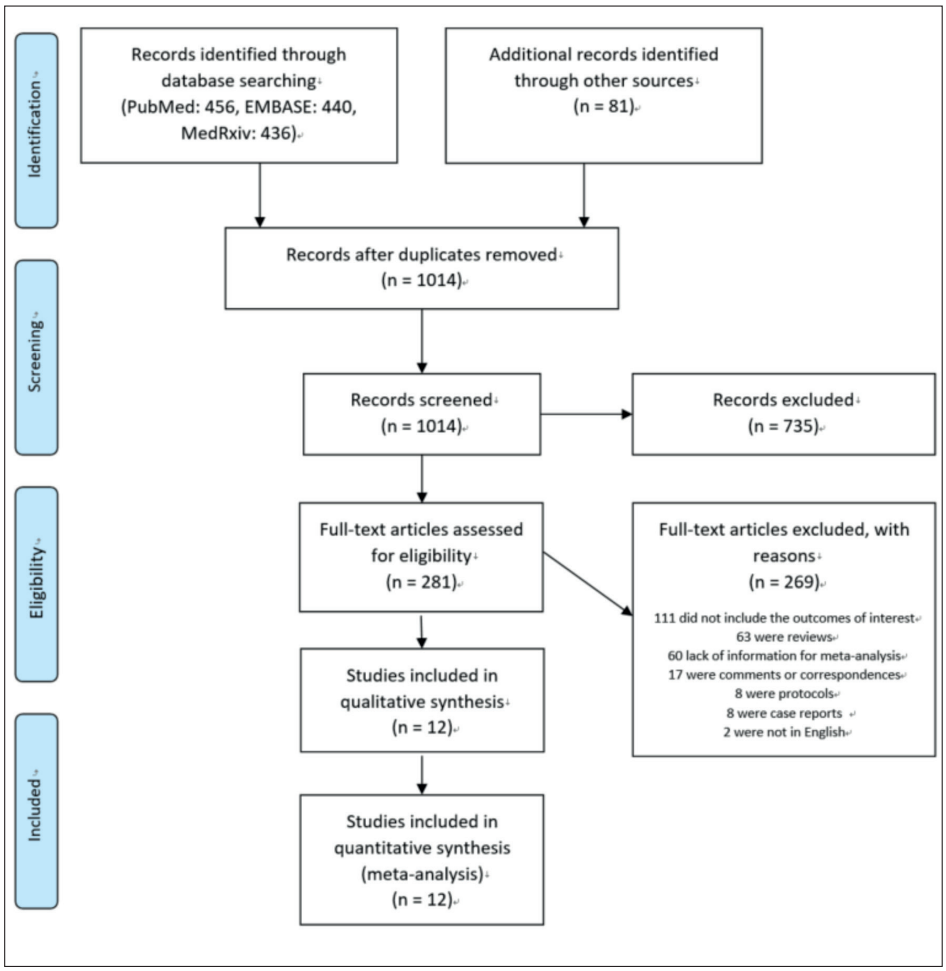

Figure 1. PRISMA flow chart showing selection process of the studies.

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. (I^2 = 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 (I^2 = 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

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

Susceptibility									
Author, Year	**Country**	**Population**	**Race/ Ethnicity**	**Study design**	**No. of Population**	**Outcome**			**Adjustment of outcome**
Zhong et al[32], 2020	China	AIRD	N/A	Cohort (Multi center)	Total: 126	PCR positive COVID-19			Age, Sex
Gu et al[25] 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[28] 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[22]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[27] 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[21] 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[25] 2020	USA	AIRD	Whites: 3374 Black: 981 Other: 486	Cohort (Single Center)	Total: 5698	•	•	-	•	Age, Sex, SES, Comorbidities
Siso´-Almirall et al[31] 2020	Spain	AIRD	N/A	Cohort (Multi Center)	Total: 322 AIRD: 21 Non- AIRD: 301	•*	•*	-	•*	Age, Sex, Co Age, Sex morbidities
Scirè et al[29] 2020	Italy	AIRD	N/A	Cohort (Multi center)	Total: 232	-	• ‡§			Sex, Age >65, Comorbidities
Singh et al[30] 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[23] 2020	Spain	AIRD [1]	N/A	Cohort (Single Center)	Total: 123	•‡§	-	-	-	Age, Sex, Comorbidity, disease
Gianfrancesco et al[24] 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[26] 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			
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 fo outcomes to occur	Adequacy of follow up of cohorts of cohorts	Total quality score
D'Silva et al[22] 2020		*	*	*	**	*			6
Pablos et al[27] 2020		*	*	*	**	*			6
Gianfrancesco et al[24] 2020	*	*	*	*	**	*		*	8
Scirè et al[29] 2020	*	*	*	*		*			5
Zhong et al[32], 2020	*	*	*	*	**			*	7
Salvarani et al[28] 2020		*	*	*	**	*			6
Freites et al[23] 2020		*	*	*	**	*			6
Singh et al[30] 2020	*	*	*	*	**	*			7
Brenner et al[21] 2020	*	*	*	*	**	*		*	8
Gupta et al[26] 2021		*	*	*		*			4
Gu et al[25] 2020		*	*	*	**	*			6
Siso´-Almirall et al[31] 2020		*	*	*	**	*			6

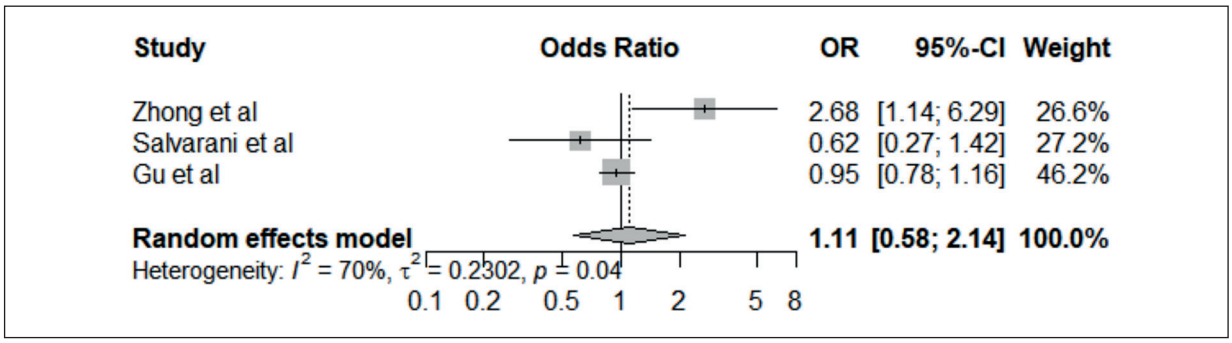

Figure 2. Susceptibility to COVID-19 in patients with AIRD compared to general population.

found to be higher in patients with AIRD (OR: 1.21, 95% CI: 0.68 to 2.16). No evident heterogeneity was found (I^2 = 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 (I^2 = 64% and I^2 = 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

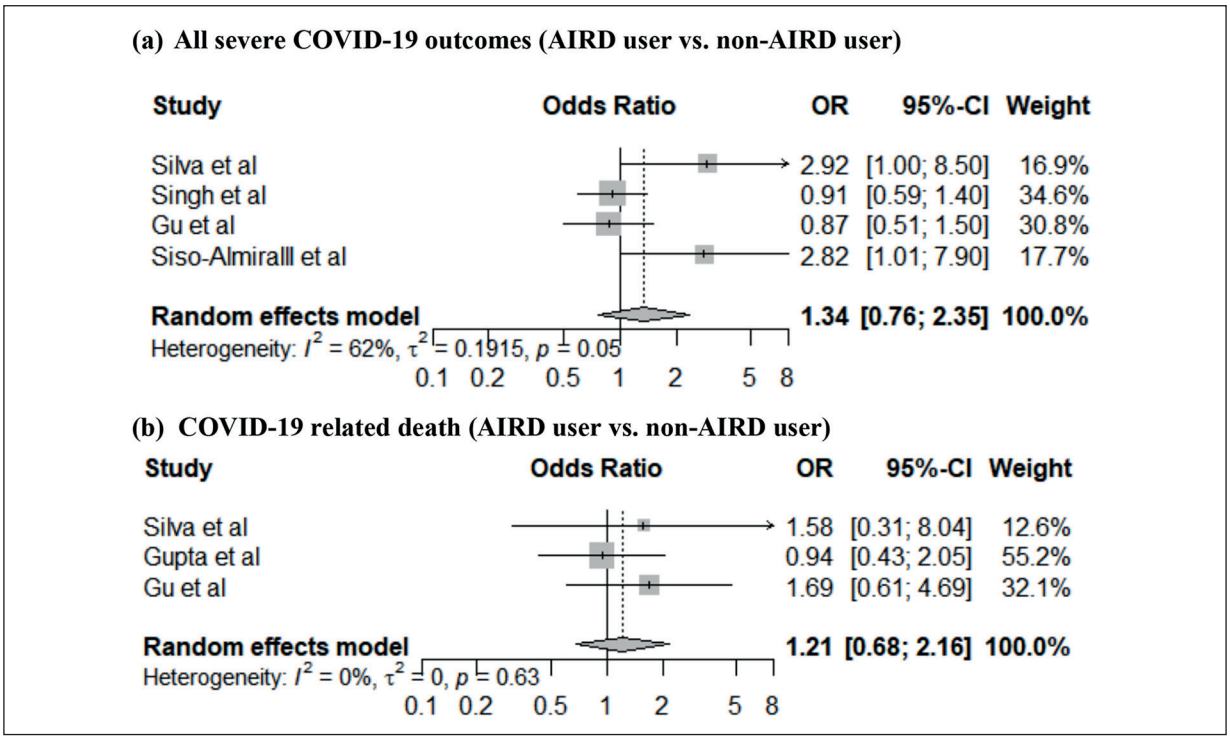

Figure 3. All severe COVID-19 outcomes in patients with AIRD compared to non-AIRD.

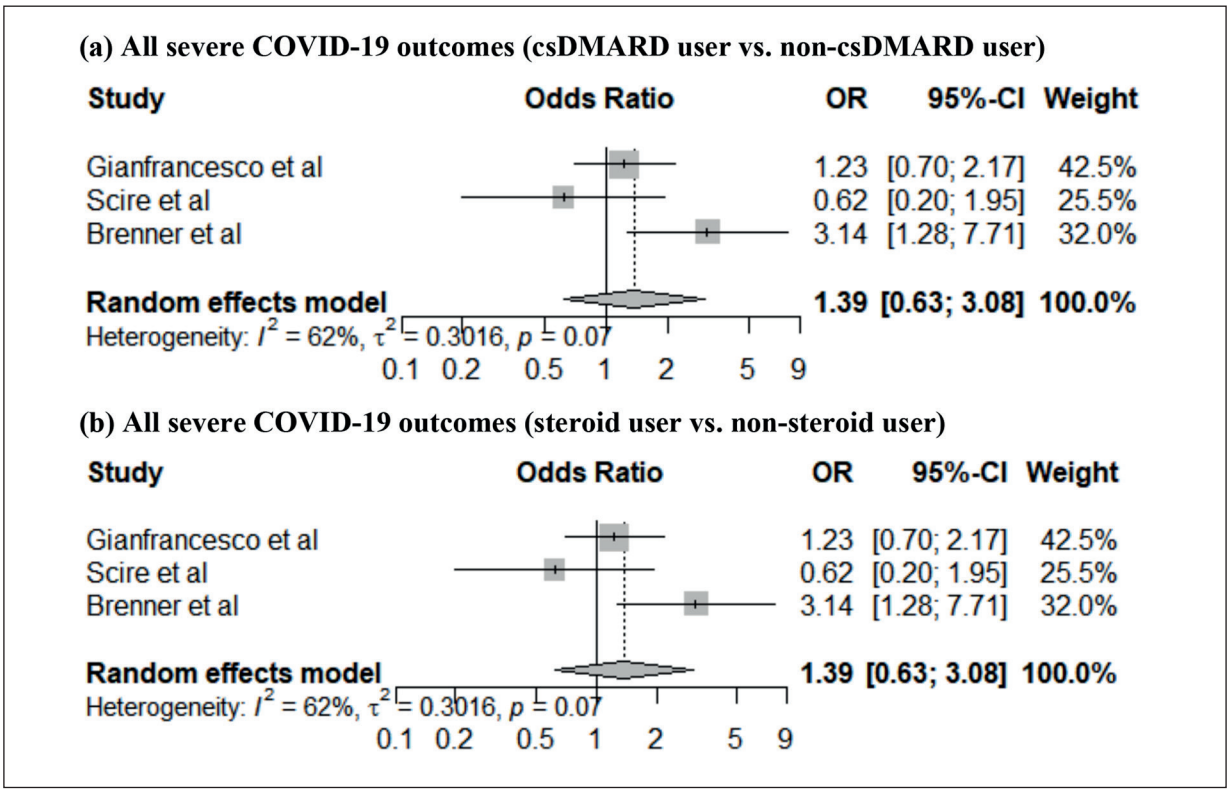

Figure 4. Forest plots and funnel plots showing clinical outcomes of COVID-19 according.

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-19[23]. 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-19[33].

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 papers[34-36]. 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 articles[37], 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 I^2 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.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Consent for Publication

All the authors checked and gave their approval of this version to be published.

Availability of Data and Material

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' Contribution

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.

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