CLINICAL SCIENCE

Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis

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ABSTRACT

Objectives The prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases who are frequently treated with disease modifying therapies remains poorly understood. This meta-analysis aims to assess the prevalence and clinical outcomes of COVID-19 in autoimmune diseases.

Methods Electronic databases were searched for observational and case–controlled studies. We sorted medications into glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologic or targeted synthetic DMARDs (b/tsDMARDs), which was also divided into monotherapy and b/tsDMARDs–csDMARDs combination therapy.

Results We analysed 62 observational studies with a total of 319 025 patients with autoimmune diseases. The prevalence of COVID-19 was 0.011 (95% CI: 0.005 to 0.025). Meta-analysis of seven case–controlled studies demonstrated that the risk of COVID-19 in autoimmune diseases was significantly higher than in control patients (OR: 2.19, 95% CI: 1.05 to 4.58, p=0.038). Meta-regression analysis showed glucocorticoids were significantly associated with the risk of COVID-19. For clinical outcomes, we assessed 65 studies with 2766 patients with autoimmune diseases diagnosed with COVID-19. The rates of hospitalisation and mortality were 0.35 (95% CI: 0.23 to 0.50) and 0.066 (95% CI: 0.036 to 0.12), respectively. Glucocorticoids, csDMARDs and b/tsDMARDs–csDMARDs combination therapy increased the risk of these outcomes, whereas b/tsDMARDs monotherapy, particularly antitumour necrosis factor agents, were associated with a lower risk of hospitalisation and death.

Conclusions Our meta-analysis demonstrated that patients with autoimmune diseases had an increased risk of COVID-19, primarily attributed to glucocorticoid use. b/tsDMARDs monotherapy was associated with a lower risk of severe COVID-19 suggesting its safety in the COVID-19 pandemic.

Key messages

What is already known about this subject?

- The prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases who are frequently treated with immunosuppressive or anticytokine drugs remains poorly understood.

What does this study add?

- The prevalence of COVID-19 in autoimmune diseases was 0.011 (95% CI: 0.005 to 0.025) which was significantly higher than in the comparator population.
- Glucocorticoids increased the risk of COVID-19 and its severe outcomes.
- Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologic or targeted synthetic DMARDs (b/tsDMARDs)–csDMARDs combination therapy significantly increased the risk of severe outcomes, whereas b/tsDMARDs monotherapy, in particular anti-tumour necrosis factor therapy, reduced the risk of severe COVID-19.

How might this impact on clinical practice or future developments?

- Unlike glucocorticoids, csDMARDs and b/tsDMARDs–csDMARDs combination therapy, b/tsDMARDs monotherapy can be safely used during COVID-19 pandemic.

INTRODUCTION

The outbreak of COVID-19 caused by the novel SARS-CoV-2 has spread worldwide leading to large number of infections and deaths.[1] Patients with autoimmune diseases (ADs) are frequently treated with immunosuppressive or anticytokine drugs, which raises concern for infectious complications, placing patients and physicians at a crossroads with respect to continuation or cessation of these disease modifying therapies.

To understand the incidence and prognosis of COVID-19 in ADs, international registries of patients with inflammatory bowel disease (SECURE-IBD registry[2]) or rheumatic diseases (C19-GRA[3]) diagnosed with COVID-19 have been developed and analysed their COVID-19 outcomes. These data have demonstrated that similar to the general population, age and underlying comorbidities are poor prognostic factors of COVID-19 in ADs.[4] In terms of treatments, both registries demonstrated that patients treated with glucocorticoids (GCs) had poor clinical outcomes of COVID-19, whereas those treated with antitumour necrosis factor (TNF) therapies, particularly when used as a monotherapy, had a decreased risk of hospitalisation due to COVID-19.[2 3] These findings suggest that anti-TNF monotherapy may be protective against severe COVID-19. However, each study or registry has a limited sample size. Therefore, there

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is a need to integrate findings across studies to better understand the risk of COVID-19 in ADs.

This systematic review and meta-analysis aimed to determine the prevalence of COVID-19 and investigate its clinical outcomes in ADs. We also assessed how individual risk factors, including comorbidities and medical therapies, influence the prevalence and clinical outcomes in ADs.

METHODS

Search strategy and study selection

This meta-analysis was conducted according to a priori defined protocol that is in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.[5] The protocol of this meta-analysis has been submitted to the International Prospective Register of Systematic Reviews.[6] We searched PubMed/MEDLINE, Scopus, EMBASE, medRxiv (https://www.medrxiv.org/) from inception to 31 July 2020 to identify studies assessing the prevalence and clinical outcomes of COVID-19 in ADs.

As for inclusion criteria, we considered observational or case–controlled studies reporting the prevalence and clinical outcomes of COVID-19 in ADs. There were no restrictions regarding age, sex or duration of the study. We imposed no geographic or language restrictions. Three authors (SA, SH and AS) independently screened each of the potential studies to determine whether they were eligible for inclusion. Areas of disagreement or uncertainty were resolved by consensus among the authors. Studies were identified with the following terms: 'COVID-19', 'inflammatory bowel disease', 'psoriasis', 'rheumatic diseases', 'systemic lupus erythematosus' and 'autoimmune diseases'.

Single case reports were excluded. Given several studies used initial data from C19-GRA registry, we included a study with data of the first 600 patients submitted to C19-GRA registry[3] and excluded other studies with preliminary data.[7–9] For an analysis for the prevalence of COVID-19, studies in which all of included patients were COVID-19 were excluded. As for clinical outcomes of COVID-19, studies that included only hospitalised or deceased patients were excluded. The search strategy is described in figure 1.

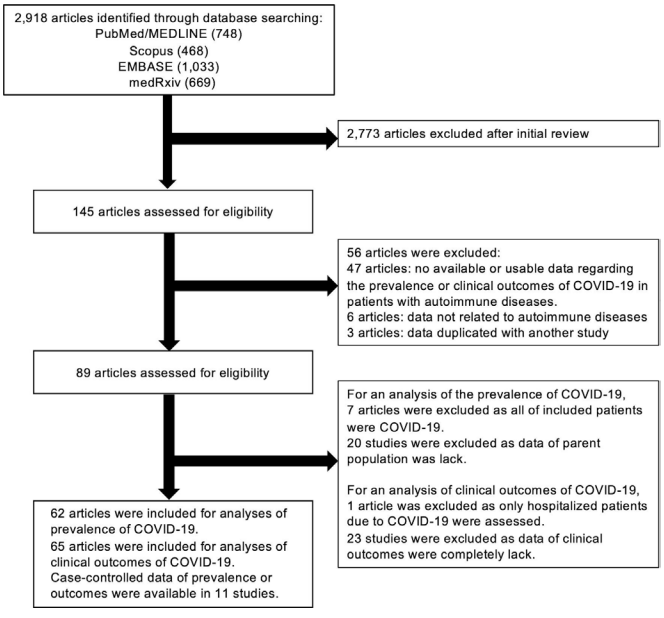

Figure 1 Flow chart of the assessment of the studies identified in the meta-analysis.

Data extraction and quality assessment

All data were independently abstracted in duplicate by two authors (SA and AS) by using a data extraction form. Data on the study characteristics, such as author name, year of publication, study design, duration, study location, sample size, diagnosis of ADs, type of medications, age and gender of patients, comorbidities including hypertension, diabetes and obesity, prevalence and clinical outcomes of COVID-19 were collected. We rated the quality of evidence according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence obtained from the present meta-analysis.[10]

Outcome assessment

The primary outcome was the prevalence of suspected or confirmed COVID-19 with a positive PCR test for SARS-CoV-2 in ADs. The numbers of patients with COVID-19 and confirmed cases in each of studies are shown in online supplemental table S1. To conduct subgroup analyses with each diagnosis, we classified ADs based on the digestive, musculoskeletal and integumentary systems. Diseases of the digestive system were categorised into IBD and autoimmune hepatic diseases (AHD). Rheumatic diseases (RD) included rheumatoid arthritis, systemic lupus erythematosus (SLE), psoriatic arthritis, spondyloarthritis, ankylosing spondylitis, vasculitis, polymyalgia rheumatica, Sjögren's syndrome (SjS), systemic sclerosis (SSc) and other autoimmune-mediated diseases (including Behcet's syndrome, sarcoidosis and inflammatory myopathies). Given that several studies of RD focused only on patients with SLE, SjS or SSc, these studies were categorised into 'SLE/SjS/SSc'. Diseases of the skin were categorised as 'psoriasis/autoimmune skin diseases (AISD)'. Two studies included various ADs and were classified as 'immune-mediated inflammatory disease (IMID)'.[11 12]

Secondary outcomes included the following COVID-19 clinical outcomes: (1) hospitalisation, (2) intensive care unit (ICU) admission, (3) mechanical or non-invasive ventilation and (4) death. Subgroup analyses evaluating individual comorbidities[13] and medication use prior to COVID-19 diagnosis were conducted. We divided medication use into the following three categories: (1) GCs, (2) conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), (3) biologic or targeted synthetic DMARDs (b/tsDMARDs). Budesonide, which is used as an ileal release form in IBD, was not included in the GCs when data were available. csDMARDs included hydroxychloroquine, chloroquine, thiopurines, cyclophosphamide, cyclosporine, tacrolimus, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid and sulfasalazine. b/tsDMARDs included abatacept, belimumab, CD-20, interleukin (IL)-1, IL-6, IL-12/23, IL-23, IL-17, TNF, α4β7 integrin and Janus kinase inhibitors.[3] We also divided b/tsDMARDs into monotherapy and b/tsDMARDs–csDMARDs combination therapy if studies separately presented the data. If not, we considered b/tsDMARDs as utilised as a monotherapy.

Statistical analysis

We undertook a meta-analysis of the prevalence and clinical outcomes of COVID-19 among individuals with ADs from observational or case–control studies by using a random effects model. We evaluated the presence of heterogeneity across studies by using the I^2 statistic. An I^2 value of <25% indicates

low heterogeneity, 25%–75% as moderate heterogeneity and >75% as considerable heterogeneity.[14] Heterogeneity was evaluated by using Cochran's Q-statistics with a significance level of p<0.10.[15] Begg's and Egger's tests were performed to access publication bias and funnel plots were constructed to visualise possible asymmetry when three or more studies were available.[16 17] A random effects meta-regression model was used to assess the contributions of each of potential risk factors and medication class to the prevalence and adverse clinical outcomes. If the number of available studies for each analysis was less than 10, we did not perform meta-regression analysis due to its low reliability.

Statistical analyses were performed using the Comprehensive Meta Analysis Software (V.3.0; Biostat, Englewood, NJ, USA). All statistical tests except for the Q-statistics used a two-sided p-value of 0.05 for significance.

RESULTS

Study characteristics

We identified 2918 citations through the literature search, excluded 2773 titles and abstracts after initial screening and assessed 145 studies for eligibility. A final number 89 full-text articles met all eligibility criteria. For the analysis of COVID-19 prevalence, we included 62 observational studies with a total of 319 025 patients with ADs. For clinical outcomes, we included 65 studies with 2766 patients with ADs diagnosed with COVID-19. Among these studies, we identified 11 studies with case–controlled data which compared the prevalence or clinical outcomes of COVID-19 in patients with ADs to those without ADs or the general population (figure 1). The characteristics and outcomes of the included studies are summarised in online supplemental table S1.

Prevalence of COVID-19 in autoimmune diseases

Meta-analysis of 62 observational studies including 319 025 patients with ADs from 15 countries showed that the prevalence of COVID-19 was 0.011 (95% CI: 0.005 to 0.025) (figure 2A). In the subgroup analyses, the prevalence of COVID-19 in AHD, IBD, psoriasis/AISD, RD and SLE/SjS/SSc were 0.036 (95% CI: 0.004 to 0.258), 0.003 (95% CI: 0.001 to 0.006), 0.011 (95% CI: 0.006 to 0.021), 0.009 (95% CI: 0.005 to 0.014), 0.034 (95% CI: 0.014 to 0.080), respectively, with IBD having the lowest prevalence (figure 2A). SLE/SjS/SSc showed a higher prevalence (0.034) when compared with the other disease groups, which is likely due to a higher proportion of GC use (60.3%) in the SLE/SjS/SSc subgroup (online supplemental table S1). Heterogeneity was considerable in overall (I^2=96.8%) and most subgroup analyses, which was primarily due to the difference in study sizes. The funnel plot was not asymmetric, indicating no publication bias, which was supported by Egger's test (p=0.083) but not Begg's test (p=0.002) (online supplemental figure S1). The subgroup analysis according to country showed that the prevalence range of COVID-19 was 0.002–0.012, with European countries having the highest prevalence (online supplemental figure S2).

Meta-analysis of seven case–controlled studies showed that the risk of COVID-19 in ADs was significantly higher than in control patients (OR: 2.19, 95% CI: 1.05 to 4.58, p=0.038). These studies only included individuals with psoriasis and RD, and both diseases demonstrated an elevated risk of COVID-19 as compared with controls (OR: 3.43, 95% CI: 1.68 to 7.01, p=0.001, OR: 1.60, 95% CI: 1.13 to 2.25, p=0.008, respectively) (figure 2B). There was low to considerable heterogeneity in overall (I^2=78.0%) and in each subgroup analysis (I^2=0% with psoriasis, and I^2=53.1% with RD). No publication bias was detected by Begg's and Egger's tests (Begg: p=1.00, Egger: p=0.25) (online supplemental figure S3).

Meta-regression analysis of the variables potentially associated with the risk of COVID-19 showed that studies with a higher proportion of GC use in patients with ADs had a higher prevalence of COVID-19 (regression coefficient: 0.020, 95% CI: 0.001 to 0.040, p=0.042). Meanwhile, age, proportion of males, hypertension, diabetes or therapies including csDMARDs and b/tsDMARDs did not contribute to the risk of COVID-19 (table 1).

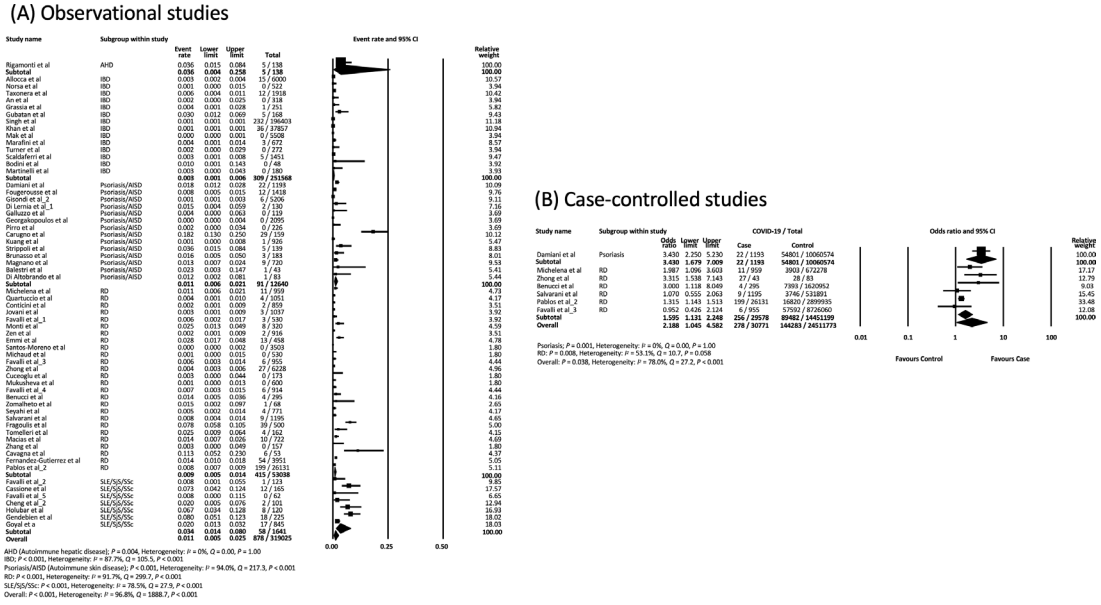

Figure 2 (A) Meta-analysis of observational studies to determine the prevalence of COVID-19 in patients with autoimmune diseases. (B) Meta-analysis of case–controlled studies to compare the prevalence of COVID-19 in autoimmune diseases with those without autoimmune diseases or general population.

Table 1 Meta-regression of the variables potentially associated with the prevalence of COVID-19

Variables	Number of studies	Coefficient	SE	Lower 95% CI	Upper 95% CI	Z value	P value
Age (mean/median)	42	0.043	0.024	−0.003	0.089	1.82	0.069
Male (%)	44	−0.018	0.011	−0.040	0.004	−1.64	0.101
HTN (%)	12	0.025	0.029	−0.031	0.081	0.88	0.377
DM (%)	13	0.060	0.099	−0.134	0.253	0.60	0.546
Obesity (%)	<10	NA	NA	NA	NA	NA	NA
Comorbidities (≥1) (%)	<10	NA	NA	NA	NA	NA	NA
Glucocorticoids (%)	26	0.020	0.010	0.001	0.040	2.04	**0.042**
csDMARDs (%)	24	0.005	0.010	−0.015	0.025	0.47	0.637
b/tsDMARDs (%, mono)	31	−0.006	0.008	−0.021	0.010	−0.72	0.469
b/tsDMARDs (%, combo)	<10	NA	NA	NA	NA	NA	NA
b/tsDMARDs (%, mono/combo)	34	−0.004	0.007	−0.019	0.010	−0.56	0.574
TNF antagonists (%, mono/combo)	30	−0.020	0.013	−0.045	0.004	−1.63	0.104
Non-TNF antagonists (% mono/combo)	29	−0.006	0.012	−0.029	0.018	−0.47	0.641

b/tsDMARDs, biologic or targeted synthetic DMARDs (abatacept, belimumab, CD-20, IL-1, IL-6, IL-12/23, IL-23, IL-17, α4β7 integrin, TNF and Janus kinase (JAK) inhibitors); combo, combination therapy with csDMARDs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs (hydroxychloroquine, chloroquine, thiopurines, cyclophosphamide, cyclosporine, tacrolimus, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid and sulfasalazine); DM, diabetes; HTN, hypertension; mono, monotherapy; NA, not available; TNF, tumour necrosis factor.

Clinical outcomes of COVID-19 in autoimmune diseases

Meta-analysis of 65 observational studies including 2766 patients with ADs diagnosed with COVID-19 showed that the hospitalisation rate due to COVID-19 was 0.35 (95% CI: 0.23 to 0.50) (figure 3A). Hospitalisation rates of AHD, IBD, IMID, psoriasis/AISD, RD and SLE/SjS/SSc were 0.52 (95% CI: 0.23 to 0.80), 0.29 (95% CI: 0.21 to 0.38), 0.24 (95% CI: 0.12 to 0.43), 0.26 (95% CI: 0.15 to 0.41), 0.54 (95% CI: 0.46 to 0.63) and 0.33 (95% CI: 0.20 to 0.49), respectively, with RD having the highest hospitalisation rate. Studies of RD included more elderly patients and patients with comorbidities (online supplemental table S1). Heterogeneity was considerable in overall (I^2=81.8%) and moderate to considerable in subgroup analyses (I^2=28.1%–79.9%) except for AHD (I^2=0%). Funnel plot demonstrated no asymmetry, therefore suggesting there was no small-study effects or publication bias, which was supported by Begg's and Egger's tests (online supplemental figure S4A).

The mortality due to COVID-19 in patients with ADs was 0.066 (95% CI: 0.036 to 0.12) (figure 3B). Mortality of AHD, IBD, IMID, psoriasis/AISD, RD and SLE/SjS/SSc were 0.094 (95% CI: 0.019 to 0.36), 0.045 (95% CI: 0.032 to 0.063), 0.017 (95% CI: 0.004 to 0.065), 0.097 (95% CI: 0.042 to 0.21), 0.113 (95% CI: 0.098 to 0.13) and 0.069 (95% CI: 0.032 to 0.14), respectively. Patients with RD had the highest mortality rate, which was consistent with the analysis of the hospitalisation rate. Heterogeneity was moderate in overall (I^2=26.6%) and absent in subgroup analyses (I^2=0%) except for IBD (I^2=49%). Begg's (p=0.003), but not Egger's (p=0.093), test was suggestive of

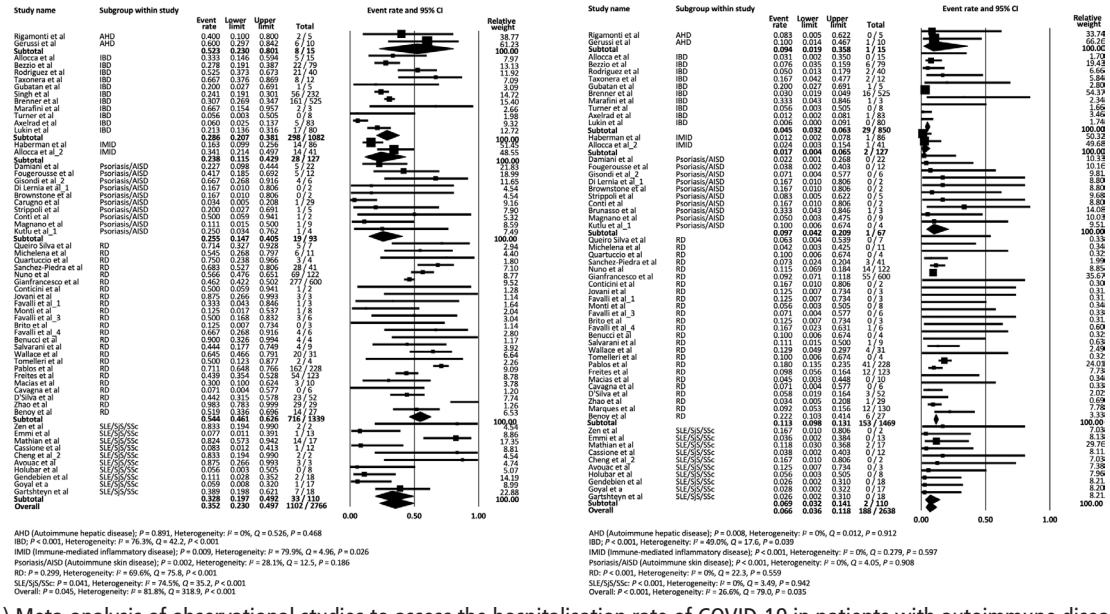

Figure 3 (A) Meta-analysis of observational studies to assess the hospitalisation rate of COVID-19 in patients with autoimmune diseases. (B) Meta-analysis of observational studies to assess the mortality rate of COVID-19 in patients with autoimmune diseases.

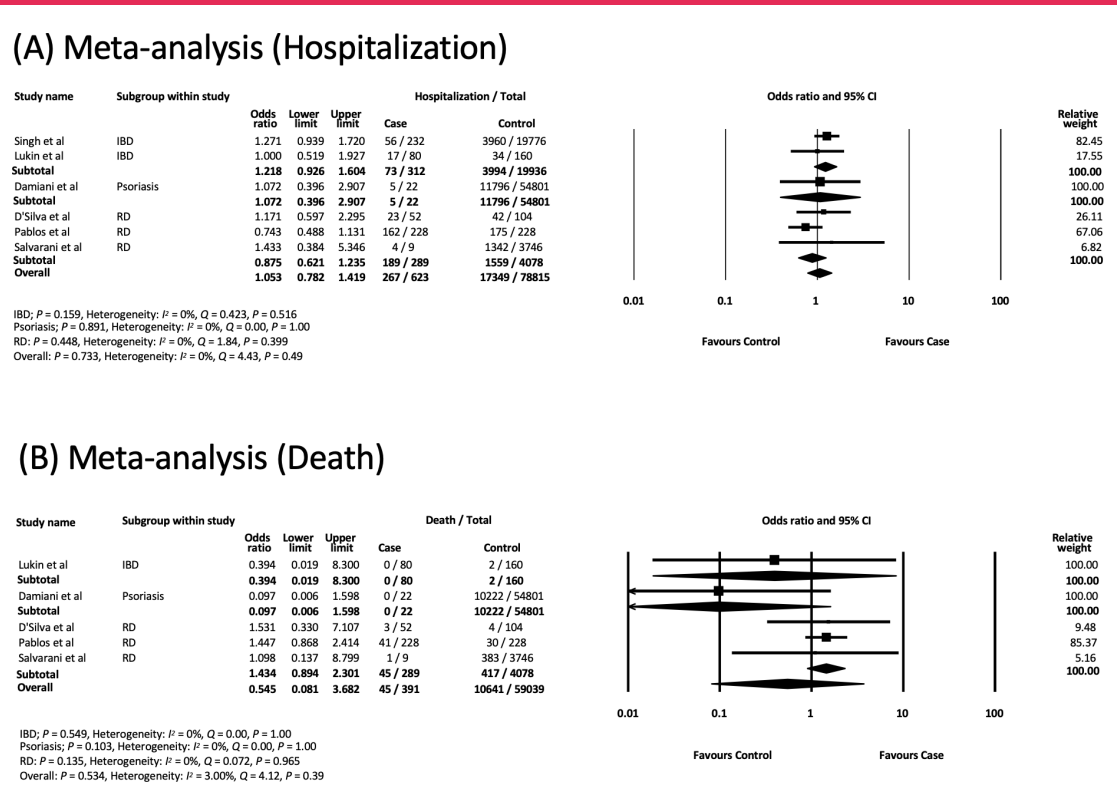

Figure 4 (A) Meta-analysis of case–controlled studies to assess the hospitalisation rate of COVID-19 in patients with autoimmune diseases. (B) Meta-analysis of case–controlled studies to assess the mortality rate of COVID-19 in patients with autoimmune diseases.

publication bias, but the funnel plot was not asymmetric (online supplemental figure S4B). Overall rates of ICU admission and mechanical or non-invasive ventilation were 0.087 (95% CI: 0.045 to 0.16) (online supplemental figure S5A) and 0.11 (95% CI: 0.063 to 0.18) (online supplemental figure S5B), respectively.

Meta-analysis of six case–controlled studies showed no differences in hospitalisations (OR: 1.05, 95% CI: 0.78 to 1.42, p=0.73) (figure 4A), death (OR: 0.55, 95% CI: 0.081 to 3.68, p=0.53) (figure 4B), ICU admission (OR: 1.22, 95% CI: 0.42 to 3.60, p=0.72) (online supplemental figure S6A) or mechanical/non-invasive ventilation (OR: 1.03, 95% CI: 0.22 to 4.81, p=0.97) when compared with the control population (online supplemental figure S6B). Each disease subgroup did not show any remarkable differences in these clinical outcomes. All analyses showed low to moderate heterogeneity (I^2=0%–73.5%) and no publication bias (online supplemental figure S6C,D and S7).

Subgroup analyses according to comorbidities showed that patients with age ≥64 years old, male gender, hypertension, diabetes, BMI ≥30 and at least one comorbidity had higher rates of hospitalisation, ICU admission, ventilation and death due to COVID-19 when compared with those without these comorbidities (online supplemental table S2). Subgroup analyses according to medical therapies showed that patients treated with GCs, csDMARDs or b/tsDMARDs–csDMARDs combination therapy had a 2–3 times higher event rate of each clinical outcome when compared with those treated with b/tsDMARDs monotherapy (online supplemental table S3). Importantly, patients with anti-TNF monotherapy use tended to have a lower rate of hospitalisation and mortality when compared with those with non-TNF-targeted monotherapy (online supplemental table S3). Analysis of hospitalisation rates showed moderate heterogeneity, but most other analyses had low heterogeneity (online supplemental tables S2 and S3).

Meta-regression analysis showed that older age (regression coefficient: 0.070, 95% CI: 0.046 to 0.095, p<0.001), a higher proportion of patients with hypertension (regression coefficient: 0.017, 95% CI: 0.002 to 0.032, p=0.024), or at least one comorbidity (regression coefficient: 0.024, 95% CI: 0.007 to 0.040, p=0.004) in patients with ADs and COVID-19 had a higher risk of hospitalisation due to COVID-19. Older age (regression coefficient: 0.068, 95% CI: 0.048 to 0.089, p<0.001), a higher proportion of hypertension (regression coefficient: 0.034, 95% CI: 0.022 to 0.045, p<0.001) and diabetes (regression coefficient: 0.038, 95% CI: 0.012 to 0.064, p=0.004) were associated with a higher mortality rate due to COVID-19 (table 2). In terms of treatments, studies with a greater proportion of patients on csDMARDs or b/tsDMARDs–csDMARDs combination therapy showing a higher rate of hospitalisation or death and conversely, studies with a higher proportion of patients on b/tsDMARDs monotherapy, particularly anti-TNF monotherapy, had a lower rate of hospitalisation and mortality due to COVID-19. A higher proportion of GC use tended to be associated with a higher rate of hospitalisation and death, although this result was not statistically significant (table 2).

Grading the quality of evidence

Based on the GRADE approach, an overall quality of evidence for this analysis was moderate as the heterogeneity was considerable (online supplemental table S4).

DISCUSSION

Our meta-analysis showed that although patients with ADs have a higher prevalence of COVID-19, their clinical outcomes were not considerably worse when compared with individuals without ADs. Meta-regression analysis demonstrated that prior GC use was associated with the increased risk of SARS-CoV-2 infection.

Table 2 Meta-regression of the variables potentially associated with clinical outcomes of COVID-19

Variables	Number of studies	Coefficient	SE	Lower 95% CI	Upper 95% CI	Z value	P value
Hospitalisation							
Age (mean/median)	50	0.070	0.013	0.046	0.095	5.61	**<0.001**
Male (%)	50	−0.012	0.008	−0.028	0.004	−1.52	0.129
HTN (%)	38	0.017	0.008	0.002	0.032	2.26	**0.024**
DM (%)	36	0.024	0.014	−0.004	0.052	1.67	0.095
Obesity (%)	24	0.012	0.009	−0.006	0.030	1.32	0.187
Comorbidities (≥1) (%)	27	0.024	0.008	0.007	0.040	2.85	**0.004**
Glucocorticoids (%)	44	0.011	0.006	−0.0003	0.022	1.91	0.056
csDMARDs (%)	40	0.014	0.005	0.005	0.023	2.94	**0.003**
b/tsDMARDs (%, mono)	49	−0.014	0.004	−0.022	−0.005	−3.13	**0.002**
b/tsDMARDs (%, combo)	26	0.016	0.007	0.001	0.030	2.11	**0.035**
b/tsDMARDs (%, mono/combo)	49	−0.005	0.004	−0.013	0.003	−1.18	0.237
TNF antagonists (%, mono)	44	−0.019	0.007	−0.032	−0.005	−2.66	**0.008**
TNF antagonists (%, combo)	22	0.028	0.017	−0.006	0.062	1.59	0.111
TNF antagonists (%, mono/combo)	46	−0.015	0.007	−0.027	−0.002	−2.24	**0.025**
Non-TNF antagonists (%, mono)	44	−0.012	0.008	−0.027	0.002	−1.64	0.102
Non-TNF antagonists (%, combo)	21	0.039	0.019	0.003	0.076	2.09	**0.036**
Non-TNF antagonists (%, mono/combo)	47	−0.002	0.007	−0.015	0.011	−0.33	0.739
Death							
Age (mean/median)	48	0.068	0.010	0.048	0.089	6.54	**<0.001**
Male (%)	48	−0.006	0.008	−0.023	0.010	−0.76	0.449
HTN (%)	37	0.034	0.006	0.022	0.045	5.84	**<0.001**
DM (%)	35	0.038	0.013	0.012	0.064	2.86	**0.004**
Obesity (%)	24	0.013	0.007	−0.001	0.027	1.87	0.062
Comorbidities (≥1) (%)	26	0.013	0.008	−0.004	0.029	1.53	0.127
Glucocorticoids (%)	43	0.011	0.006	−0.001	0.022	1.78	0.075
csDMARDs (%)	40	0.012	0.004	0.004	0.020	2.99	**0.003**
b/tsDMARDs (%, mono)	49	−0.011	0.005	−0.020	−0.002	−2.31	**0.021**
b/tsDMARDs (%, combo)	26	0.013	0.009	−0.004	0.030	1.52	0.128
b/tsDMARDs (%, mono/combo)	49	−0.010	0.004	−0.018	−0.002	−2.48	**0.013**
TNF antagonists (%, mono)	44	−0.018	0.008	−0.033	−0.003	−2.29	**0.022**
TNF antagonists (%, combo)	22	0.009	0.019	−0.029	0.047	0.47	0.642
TNF antagonists (%, mono/combo)	46	−0.017	0.007	−0.030	−0.004	−2.55	**0.011**
Non-TNF antagonists (%, mono)	45	−0.006	0.008	−0.022	0.010	−0.78	0.438
Non-TNF antagonists (%, combo)	21	0.030	0.019	−0.007	0.066	1.57	0.115
Non-TNF antagonists (%, mono/combo)	48	−0.006	0.007	−0.019	0.007	−0.87	0.387

b/tsDMARDs, biologic or targeted synthetic DMARDs (abatacept, belimumab, CD-20, IL-1, IL-6, IL-12/23, IL-23, IL-17, TNF, α4β7 integrin and Janus kinase (JAK) inhibitors); combo, combination therapy with csDMARDs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs (hydroxychloroquine, chloroquine, thiopurines, cyclophosphamide, cyclosporine, tacrolimus, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid and sulfasalazine); DM, diabetes; HTN, hypertension; mono, monotherapy; TNF, tumour necrosis factor.

We also found that the following factors associated with severe COVID-19 outcomes: (1) GC use, (2) older age, (3) comorbidities such as hypertension or diabetes, (4) csDMARDs and (5) b/tsDMARDs–csDMARDs combination therapy. However, b/tsDMARDs monotherapy, particularly anti-TNF therapy, was associated with reduced risk of hospitalisation and mortality due to COVID-19.

Our data showed that the prevalence of COVID-19 in ADs was 0.011 (95% CI: 0.005 to 0.025) and subgroup analysis revealed the prevalence in IBD was lower than that in RD or

SLE/SjS/SSc. Previous studies have also reported differences in the prevalence of COVID-19 in patients with IBD (0.4%[18]) and RD (0.76%).[19] Our meta-regression analysis demonstrated that GC use prior to COVID-19 significantly contributed to the disease prevalence. Indeed, the mean percentage of GC use in studies of IBD (12.6%) was lower than in RD (37.8%) and SLE/SjS/SSc (60.3%), suggesting that the differential infectious risk among diseases might be attributed to GC use prior to developing COVID-19. Recent studies showed that active disease and GC use were associated with higher risk of SARS-CoV-2 infection[20] or severe COVID-19[21] in patients with ADs. Another study reported on the beneficial effect of dexamethasone in reducing mortality among those hospitalised with COVID-19.[22] Further investigations into the use of GCs in patients with ADs and the risk of COVID-19 in patients with active disease requiring GCs are needed.

In terms of the clinical outcomes, we found that the subgroup of RD had the highest rate of hospitalisation and mortality due to COVID-19. Our meta-regression analysis demonstrated that older age, comorbidities, csDMARDs and b/tsDMARDs–csDMARDs combination therapy contributed to severe COVID-19 outcomes. Supporting this result, the mean age (58.3 years), proportion of individuals with underlying comorbidities (71.8%) and b/tsDMARDs–csDMARDs combination therapy use (33.1%) was highest in the RD subgroup when compared with all other disease subgroups. Meanwhile, our data showed that b/tsDMARDs monotherapy, particularly anti-TNF therapy, might be protective against severe COVID-19. This finding was consistent with the C19-GRA registry which reported that the hospitalisation rate of RD patients treated with csDMARDs and b/tsDMARDs–csDMARDs combination therapy was 55% and 36%, respectively, whereas those with b/tsDMARDs monotherapy had a lower hospitalisation rate (29%).[3] A recent study which assessed associations between serum levels of cytokines including IL-1β, IL-6 and TNF and COVID-19 outcomes demonstrated that an increased level of TNF can be a predictor of poor outcomes in patients under 70 years.[23] These findings suggested that anti-TNF therapies might prevent severe COVID-19, however, further investigations are needed because anti-TNF drugs are associated with increased risk of serious infections in ADs.[24 25]

Limitations

Meta-analyses of observational studies regarding the prevalence of COVID-19 and hospitalisation rate had considerable heterogeneities. The cause of this heterogeneity could be potentially explained by the differences in study size, inclusion of different diseases and study location. Thus, we undertook subgroup analyses and performed meta-regression to assess the effect of each potential risk factor on the individual outcomes. Subgroup analyses regarding the hospitalisation outcome revealed low-moderate heterogeneities, which suggested that the difference among subgroups contributed to the initial heterogeneity. Second, although we assessed the effect of b/tsDMARDs monotherapy and b/tsDMARDs–csDMARDs combination therapy on the outcomes separately, not all studies presented data in these two groups. In a situation where csDMARDs were stopped for fear of COVID-19 in patients on combination therapies, washout periods of csDMARDs could not be considered. Third, the sensitivity of RT-PCR for SARS-CoV-2 from nasopharyngeal swab is roughly 70%.[26 27] Meanwhile, although there was no guideline regarding COVID-19 testing in patients starting immunosuppressants,[28] patients with ADs might have been tested earlier and more frequently compared with the general population due to their concern of infectious risk of SARS-CoV-2. Hence, these issues might affect the result of the prevalence data in our meta-analysis.

CONCLUSION

This study is the first comprehensive meta-analysis which determined the prevalence and clinical outcomes of COVID-19 in ADs. Our study suggests that GC use increases the risk of SARS-CoV2 infection and might contribute to the higher prevalence of COVID-19 in ADs. Although GCs, csDMARDs and b/tsDMARDs–csDMARDs combination therapy contributed to disease severity in COVID-19, b/tsDMARDs monotherapy, especially anti-TNF monotherapy, was associated with reduced risk of severe disease. Our meta-analysis provides evidence that b/tsDMARDs monotherapy can be safely used during the pandemic.

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Table S1. Characteristics of studies included in the meta-analysis

Study	Study location	Total number of patients[#]	Diagnosis	Demographics of patients with autoimmune diseases							COVID-19		Demographics of patients with autoimmune diseases and COVID-19							COVID-19 outcomes[##]			
				Mean/ Median Age (y/o)	Male (%)	Comorbidities (%)	GCs (%)	csDMARDs (%)	b/tsDMARDs monotherapy (%)	b/tsDMARDs –csDMARDs combination therapy (%)	Number of COVID19 (n)	Number of Confirmed COVID-19 with positive PCR (n)	Mean/ Median Age (y/o)	Male (%)	Comorbidities (%)	GCs (%)	csDMARDs (%)	b/tsDMARDs monotherapy (%)	b/tsDMARDs –csDMARDs combination therapy (%)	Hospitalization (n)	ICU admission (n)	Ventilation (n)	Death (n)
Rigamonti et al[1]	Italy	138	AHD	63.5	8.7	NA	NA	NA	NA	NA	5	5	51.8	20.0	60.0	100.0	60.0	0.0	0.0	2	NA	NA	0
Gerussi et al[2]	Italy	NA	AHD	NA	NA	NA	NA	NA	NA	NA	10	10	56.4	30.0	NA	60.0	30.0	0.0	0.0	6	NA	3	1
Average per study			**AHD**	**63.5**	**8.7**	**NA**	**NA**	**NA**	**NA**	**NA**			**54.1**	**25.0**	**60.0**	**80.0**	**45.0**	**0.0**	**0.0**				
Allocca et al[3]	France/Italy	6000	IBD	NA	NA	NA	NA	NA	NA	NA	15	15	39.1	26.7	60.0	13.3	20.0	60.0	13.3	5	0	NA	0
Norsa et al[4]	Italy	522	IBD	46	58.0	NA	3.1	19.2	15.7	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Taxonera et al[5]	Spain	1918	IBD	NA	NA	NA	NA	NA	NA	NA	12	12	52.3	25.0	41.7	0.0	50.0	8.3	33.3	8	1	1	2
An et al[6]	China	318	IBD	39.2	NA	15.4	NA	NA	NA	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Grassia et al[7]	Italy	251	IBD	NA	NA	NA	NA	NA	16.3	NA	1	NA	NA	NA	NA	NA	100.0	0.0	0.0	NA	NA	NA	NA
Gubatan et al[8]	USA	168	IBD	47.7	47.6	NA	20.2	8.9	28.6	NA	5	5	70.6	40.0	NA	20.0	20.0	20.0	NA	1	1	1	1
Singh et al[9]	USA	196403	IBD	NA	NA	NA	NA	NA	NA	NA	232	232	51.2	36.6	NA	47.8	14.7	15.9	NA	56	NA	NA	NA
Khan et al[10]	USA	37857	IBD	NA	NA	NA	NA	NA	NA	NA	36	NA	63	NA	NA	NA	5.6	8.3	NA	NA	NA	NA	NA
Mak et al[11]	Hong Kong/Taiwan	5508	IBD	46.9	67.8	NA	30.6	43.4	19.2	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Marafini et al[12]	Italy	672	IBD	46	53.7	NA	4.3	6.4	35.9	NA	3	3	NA	NA	NA	NA	NA	NA	NA	2	NA	NA	1
Turner et al[13]	China/South Korea	272	IBD	NA	NA	NA	NA	NA	NA	NA	8	6	16.1	62.5	NA	12.5	50.0	37.5	25.0	0	0	0	0
Scaldaferri et al[14]	Italy	1451	IBD	44	58.0	NA	NA	NA	85.1	NA	5	5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bodini et al[15]	Italy	48	IBD	NA	NA	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Martinelli et al[16]	Italy	180	IBD	15.3	53.3	NA	5.0	33.3	12.2	11.1	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lukin et al*[17]	USA	1386	IBD	NA	NA	NA	NA	NA	NA	NA	80	NA	48.3	56.3	NA	12.5	NA	47.5	NA	17	3	2	0
Bezzio et al[18]	Italy	NA	IBD	NA	NA	NA	NA	NA	NA	NA	79	49	47	55.7	38.0	11.4	NA	59.5	NA	22	11	11	6
Rodriguez et al[19]	Spain	NA	IBD	NA	NA	NA	NA	NA	NA	NA	40	40	58.5	60.0	62.5	10.0	32.5	17.5	5.0	21	0	0	2
Brenner et al[20]	International registry	NA	IBD	NA	NA	NA	NA	NA	NA	NA	525	525	42.9	52.6	33.1	7.0	NA	55.0	9.9	161	24	21	16
Axelrad et al[21]	USA	NA	IBD	NA	NA	NA	NA	NA	NA	NA	83	45	35	53.0	NA	7.2	7.2	74.7	NA	5	1	1	1
Average per study			**IBD**	**40.7**	**56.4**	**15.4**	**12.6**	**22.2**	**30.4**	**11.1**			**47.6**	**46.8**	**47.1**	**14.2**	**33.3**	**33.7**	**14.4**				
Haberman et al[22]	USA	NA	IMID	NA	NA	NA	NA	NA	NA	NA	86	59	46	43.0	NA	9.3	32.6	72.1	NA	14	1	1	1
Allocca et al_2[23]	Italy	NA	IMID	NA	NA	NA	NA	NA	NA	NA	41	25	48	41.5	31.7	17.1	24.4	65.9	NA	14	0	10	1
Average per study			**IMID**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**			**47.0**	**42.2**	**31.7**	**13.2**	**28.5**	**69.0**	**NA**				
Damiani et al[24]	Italy	1193	Psoriasis/ AISD	55	68.0	NA	0.0	0.0	NA	NA	22	22	59	72.7	40.9	0.0	0.0	100.0	0.0	5	0	NA	0
Fougerousse et al[25]	France	1418	Psoriasis/ AISD	NA	56.2	35.1	NA	23.0	70.9	2.5	12	12	NA	NA	NA	NA	NA	66.7	8.3	5	2	NA	0
Gisondi et al_2[26]	Italy	5206	Psoriasis/ AISD	53.2	54.2	NA	NA	NA	100.0	NA	6	NA	56.3	50.0	50.0	NA	NA	100.0	NA	4	1	0	0
Di Lernia et al_1[27]	Italy	130	Psoriasis/ AISD	48.4	54.6	NA	NA	NA	NA	NA	2	2	52	0.0	50.0	NA	100.0	NA	NA	0	0	0	0
Galluzzo et al[28]	Italy	119	Psoriasis/ AISD	NA	NA	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Georgakopoulos et al[29]	Canada	2095	Psoriasis/ AISD	NA	NA	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Pirro et al[30]	Italy	226	Psoriasis/ AISD	53	61.1	NA	NA	NA	100.0	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Carugno et al[31]	Italy	159	Psoriasis/ AISD	51.5	71.7	NA	NA	NA	100.0	NA	29	0	46.6	62.1	13.8	NA	NA	NA	NA	1	NA	NA	NA
Kuang et al[32]	China	926	Psoriasis/ AISD	33.1	63.1	NA	NA	NA	NA	NA	1	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Strippoli et al[33]	Italy	139	Psoriasis/ AISD	NA	NA	NA	NA	NA	NA	NA	5	3	51.8	40.0	60.0	NA	NA	100.0	NA	1	NA	0	0
Brunasso et al[34]	Italy	183	Psoriasis/ AISD	48.3	51.9	NA	7.1	31.7	36.1	NA	3	NA	NA	NA	NA	NA	33.3	66.7	NA	NA	NA	NA	1
Magnano et al[35]	Italy	720	Psoriasis/ AISD	NA	NA	NA	NA	NA	NA	NA	9	9	53.9	55.6	55.6	NA	NA	100.0	NA	1	1	NA	0
Balestri et al[36]	Italy	43	Psoriasis/ AISD	NA	NA	NA	NA	NA	NA	NA	1	1	65	0.0	0.0	0.0	100.0	0.0	0.0	0	0	0	0
Di Altobrando et al[37]	Italy	83	Psoriasis/ AISD	58.6	36.1	NA	NA	NA	NA	NA	1	1	53	100.0	NA	100.0	100.0	0.0	0.0	0	0	0	0
Kutlu et al_1*[38]	Turkey	93	Psoriasis/ AISD	NA	NA	NA	NA	NA	NA	NA	4	NA	59	50.0	NA	NA	50.0	NA	NA	1	NA	NA	0
Brownstone et al[39]	USA	NA	Psoriasis/ AISD	NA	NA	NA	NA	NA	NA	NA	2	2	35	NA	NA	NA	NA	100.0	NA	0	0	0	0
Conti et al[40]	Italy	NA	Psoriasis/ AISD	NA	NA	NA	NA	NA	NA	NA	2	2	64	100.0	100.0	0.0	0.0	100.0	0.0	1	1	NA	0
Average per study			**Psoriasis/ AISD**	**50.1**	**57.4**	**35.1**	**3.6**	**18.2**	**81.4**	**2.5**			**54.1**	**53.0**	**46.3**	**25.0**	**54.8**	**73.3**	**1.7**				
Michelena et al[41]	Spain	959	RD	NA	NA	NA	NA	NA	NA	NA	11	11	46.2	54.5	45.5	45.5	45.5	54.5	45.5	6	1	NA	0
Quartuccio et al[42]	Italy	1051	RD	58.4	33.1	NA	13.9	40.6	86.4	NA	4	4	60.3	50.0	100.0	50.0	50.0	50.0	50.0	3	0	0	0
Conticini et al[43]	Italy	859	RD	NA	NA	NA	NA	NA	NA	NA	2	2	69	0.0	50.0	0.0	0.0	100.0	0.0	1	0	0	0
Jovani et al[44]	Spain	1037	RD	NA	NA	NA	NA	NA	NA	NA	3	NA	65	33.3	66.7	0.0	33.3	66.7	33.3	3	0	0	0
Favalli et al_1[45]	Italy	530	RD	50.1	29.8	NA	NA	NA	100.0	NA	3	3	55	66.7	NA	0.0	0.0	100.0	0.0	1	0	0	0
Monti et al[46]	Italy	320	RD	55	31.9	NA	NA	NA	100.0	NA	8	4	57	12.5	100.0	25.0	100.0	100.0	NA	1	0	0	0
Santos-Moreno et al[47]	USA	3503	RD	NA	17.8	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Michaud et al[48]	USA	530	RD	65	15.7	NA	18.1	52.6	46.0	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Favalli et al_3[49]	Italy	955	RD	52.8	32.7	NA	28.3	52.7	97.1	NA	6	6	NA	NA	66.7	0.0	66.7	33.3	66.7	3	0	0	0
Zhong et al[50]	China	6228	RD	45.9	13.0	NA	19.2	42.2	1.5	NA	27	20	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cuceoglu et al[51]	Turkey	173	RD	13.3	53.2	NA	NA	20.8	100.0	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mukusheva et al[52]	Kazakhstan	600	RD	NA	NA	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Favalli et al_4[53]	Italy	914	RD	55.9	31.7	NA	35.3	NA	71.7	NA	6	6	NA	NA	NA	NA	NA	NA	NA	4	NA	NA	1
Benucci et al[54]	Italy	295	RD	NA	NA	NA	NA	NA	NA	NA	4	4	60	0.0	50.0	50.0	75.0	25.0	75.0	4	1	NA	0
Zomalheto et al[55]	Benin	68	RD	49.9	4.4	NA	75.0	NA	NA	NA	1	1	NA	NA	NA	NA	100.0	NA	NA	0	0	0	0
Seyahi et al[56]	Turkey	771	RD	42	31.8	NA	44.1	NA	39.6	NA	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Salvarani et al[57]	Italy	1195	RD	NA	43.8	NA	NA	NA	NA	NA	9	9	NA	NA	NA	NA	NA	100.0	NA	4	NA	NA	1
Fragoulis et al[58]	Greece	500	RD	53.7	26.8	NA	46.6	73.4	NA	NA	39	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tomelleri et al[59]	Italy	162	RD	61	27.2	NA	62.3	42.6	54.9	4.9	4	4	57.3	50.0	100.0	100.0	50.0	0.0	50.0	2	NA	0	0
Macias et al[60]	Spain	722	RD	57	17.2	NA	NA	NA	NA	NA	10	3	NA	NA	NA	NA	NA	NA	NA	3	0	NA	0
Zhang et al[61]	China	157	RD	38.4	33.1	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cavagna et al[62]	Italy	53	RD	61	28.3	NA	NA	NA	NA	NA	6	0	57	33.3	NA	NA	NA	NA	NA	0	0	0	0
Emmi et al***[63]	Italy	458	RD	56	26.0	NA	55.5	49.1	41.3	NA	13	1	42	15.4	NA	69.2	69.2	53.8	NA	1	1	0	0
Zen et al***[64]	Italy	916	RD	53.6	21.4	NA	9.9	83.3	18.7	NA	2	2	NA	0.0	NA	0.0	100.0	0.0	0.0	2	0	0	0
Fernandez-Gutierrez et al**[65]	Spain	3951	RD	61.8	27.7	NA	45.7	75.2	20.3	NA	54	41	NA	NA	NA	59.3	75.9	14.8	NA	54	NA	NA	NA

Pablos et al_2[66]	Spain	26131	RD	65	44.0	NA	NA	NA	NA	NA	199	199	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
D'Silva et al*[67]	USA	2154	RD	NA	NA	NA	NA	NA	NA	NA	52	52	62.5	30.8	NA	36.5	48.1	36.5	NA	23	11	11	3
Zhao et al*[68]	China	3059	RD	NA	NA	NA	NA	NA	NA	NA	29	NA	61	13.8	100.0	24.1	NA	3.4	NA	29	1	2	1
So et al*[69]	Hong Kong	1016	RD	NA	NA	NA	NA	NA	NA	NA	5	5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Benoy et al*[70]	Italy	7600	RD	NA	NA	NA	NA	NA	NA	NA	27	19	68	63.0	44.4	22.2	88.9	18.5	NA	14	2	2	6
Queiro Silva et al[71]	Spain	NA	RD	NA	NA	NA	NA	NA	NA	NA	7	NA	49.3	57.1	NA	0.0	0.0	57.1	0.0	5	2	NA	0
Sanchez-Piedra et al[72]	Spain	NA	RD	NA	NA	NA	NA	NA	NA	NA	41	31	59.4	39.0	NA	48.8	56.1	53.7	56.1	28	6	NA	3
Nuno et al[73]	Spain	NA	RD	NA	NA	NA	NA	NA	NA	NA	122	100	58.3	34.4	NA	39.3	86.9	34.4	NA	69	6	NA	14
Gianfrancesco et al[74]	International registry	NA	RD	NA	NA	NA	NA	NA	NA	NA	600	548	57.5	29.5	NA	31.5	45.3	17.8	20.7	277	NA	NA	55
Brito et al[75]	Brazil	NA	RD	NA	NA	NA	NA	NA	NA	NA	3	3	55	33.3	66.7	0.0	0.0	100.0	NA	0	0	0	0
Wallace et al[76]	USA	NA	RD	NA	NA	NA	NA	NA	NA	NA	31	NA	61	29.0	NA	38.7	77.4	NA	NA	20	NA	6	4
Pablos et al[77]	Spain	NA	RD	NA	NA	NA	NA	NA	NA	NA	228	228	63	38.2	NA	39.9	68.9	23.2	NA	162	15	19	41
Freites et al[78]	Spain	NA	RD	NA	NA	NA	NA	NA	NA	NA	123	58	59.9	30.1	NA	49.6	84.6	22.0	NA	54	2	2	12
Marques et al[79]	Brazil	NA	RD	NA	NA	NA	NA	NA	NA	NA	130	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	12
Average per study			**RD**	**52.4**	**28.1**	**NA**	**37.8**	**53.3**	**59.8**	**4.9**			**58.3**	**32.5**	**71.8**	**31.7**	**57.5**	**46.3**	**33.1**				
Favalli et al_2[80]	Italy	123	SLE/SjS/SSc	49.3	10.6	NA	64.2	59.3	20.3	NA	1	1	32	0.0	NA	0.0	100.0	0.0	100.0	1	1	1	1
Cassione et al[81]	Italy	165	SLE/SjS/SSc	52.5	32.1	NA	56.4	NA	0.0	0.0	12	4	43.3	8.3	NA	33.3	NA	0.0	0.0	1	1	1	0
Favalli et al_5[82]	Italy	62	SLE/SjS/SSc	44.1	9.7	NA	74.2	80.6	51.6	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cheng et al_2[83]	China	101	SLE/SjS/SSc	42	11.9	NA	94.1	83.2	0.0	0.0	2	2	24	0.0	NA	100.0	100.0	0.0	0.0	2	0	0	0
Holubar et al[84]	France	120	SLE/SjS/SSc	47.1	8.3	NA	41.7	52.5	0.0	0.0	8	0	NA	NA	25.0	NA	NA	NA	NA	0	0	0	0
Gendebien et al[85]	Belgium	225	SLE/SjS/SSc	51.7	7.1	NA	25.3	30.7	3.6	NA	18	5	NA	NA	NA	NA	NA	NA	NA	2	0	0	0
Goyal et al [86]	India	845	SLE/SjS/SSc	34.8	8.0	NA	66.2	96.2	NA	NA	17	2	29.3	0.0	NA	82.4	100.0	17.6	NA	1	NA	NA	0
Gartshteyn et al*[87]	USA	1285	SLE/SjS/SSc	NA	NA	NA	NA	NA	NA	NA	18	10	44.3	11.1	NA	38.9	NA	16.7	NA	7	NA	3	0
Mathian et al[88]	France	NA	SLE/SjS/SSc	NA	NA	NA	NA	NA	NA	NA	17	17	53.5	23.5	NA	70.6	100.0	0.0	0.0	14	7	5	2
Avouac et al[89]	Italy/France	NA	SLE/SjS/SSc	NA	NA	NA	NA	NA	NA	NA	3	2	66.3	33.3	100.0	100.0	66.7	33.3	66.7	3	2	2	0
Average per study			**SLE/SjS/SSc**	**45.9**	**12.5**	**NA**	**60.3**	**67.1**	**12.6**	**0.0**			**41.8**	**10.9**	**62.5**	**60.7**	**93.3**	**9.7**	**33.3**				

If the parent population of autoimmune diseases was not available, an analysis for the prevalence of COVID-19 was not conducted. ## If all of clinical outcomes regarding COVID-19 were not available, we declined an analysis of COVID-19 outcomes. * These studies were excluded for an analysis of the prevalence as all of included patients were COVID-19. ** This study was excluded for an analysis of COVID-19 outcomes as only hospitalized patients of COVID-19 were included. *** In these studies, the parent populations were categorized into RD but patients with COVID-19 were in the subgroup of SLE/SjS/SSc.

AHD, autoimmune hepatic diseases; AISD, autoimmune skin diseases; b/tsDMARDs, biologic or targeted synthetic DMARDs (abatacept, belimumab, CD-20, IL-1, IL-6, IL-12/23, IL-23, IL-17, $\alpha4\beta7$ integrin, TNF, and Janus kinase (JAK) inhibitors); csDMARDs, conventional synthetic disease-modifying antirheumatic drugs (hydroxychloroquine, chloroquine, thiopurines, cyclophosphamide, cyclosporine, tacrolimus, leflunomide, methotrexate, mycophenolate mofetil,/mycophenolic acid, and sulfasalazine); GCs, glucocorticoids; IBD, inflammatory bowel disease; ICU, intensive care unit; IMID, immune-mediated inflammatory disease; NA, not available; RD, rheumatic diseases; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Table S2. Subgroup meta-analysis according to comorbidities in patients with autoimmune diseases diagnosed with COVID-19

Subgroup	Outcomes	Number of studies	Event (n)	Total (n)	Event rate	95% CI	I^2 (%)	Q	P-value
Age ≥ 64	Hospitalization	11	193	300	0.632	0.506-0.742	39.6	16.6	0.085
	ICU	8	13	124	0.128	0.078-0.201	0	4.74	0.692
	Ventilation	8	13	118	0.135	0.082-0.213	0	6.39	0.495
	Death	10	14	130	0.134	0.084-0.207	0	6.18	0.722
Age < 64	Hospitalization	22	300	959	0.339	0.271-0.414	34.5	32.1	0.057
	ICU	16	17	509	0.059	0.038-0.092	2.58	15.4	0.423
	Ventilation	14	13	474	0.049	0.031-0.076	0	12.9	0.452
	Death	21	5	529	0.045	0.027-0.074	0	17.8	0.600
Male	Hospitalization	24	272	680	0.405	0.306-0.513	66.0	67.6	< 0.001
	ICU	19	22	491	0.094	0.053-0.161	31.6	26.3	0.092
	Ventilation	15	14	444	0.061	0.035-0.102	9.0	15.4	0.353
	Death	25	28	524	0.101	0.066-0.150	18.7	29.5	0.201
Female	Hospitalization	34	382	1074	0.338	0.267-0.417	58.2	79.0	<0.001
	ICU	27	17	560	0.063	0.044-0.091	0	18.5	0.855
	Ventilation	23	17	515	0.067	0.046-0.098	0	20.5	0.55
	Death	35	16	615	0.067	0.047-0.094	0	20.7	0.964
HTN	Hospitalization	15	224	368	0.579	0.488-0.664	31.0	20.3	0.121
	ICU	12	4	45	0.173	0.086-0.317	0	4.5	0.952
	Ventilation	9	1	32	0.127	0.054-0.272	0	0.26	1.00
	Death	16	14	108	0.188	0.125-0.273	0	4.96	0.992
No HTN	Hospitalization	21	268	834	0.313	0.235-0.403	65.6	58.2	<0.001
	ICU	15	4	268	0.066	0.034-0.127	7.75	15.2	0.366
	Ventilation	11	3	188	0.080	0.036-0.168	8.97	11.0	0.359
	Death	22	5	386	0.058	0.034-0.095	0	14.9	0.827
DM	Hospitalization	8	88	125	0.698	0.611-0.773	0	4.78	0.687
	ICU	4	1	12	0.191	0.052-0.502	0	1.58	0.664
	Ventilation	3	0	9	0.131	0.026-0.459	0	0.18	0.912
	Death	5	2	26	0.139	0.047-0.345	0	2.35	0.672
No DM	Hospitalization	27	445	1195	0.351	0.274-0.437	73.9	99.6	<0.001
	ICU	18	25	364	0.101	0.054-0.180	46.2	31.6	0.017
	Ventilation	16	25	335	0.116	0.069-0.190	30.8	21.7	0.117
	Death	24	24	519	0.081	0.058-0.112	0	14.0	0.927
BMI ≥ 30	Hospitalization	4	28	51	0.486	0.229-0.751	33.9	4.54	0.209
	ICU	3	1	9	0.182	0.046-0.508	0	0.020	0.99
	Ventilation	0	0	4	NA	NA	NA	NA	NA
	Death	5	9	65	0.156	0.087-0.264	0	0.29	0.99

BMI < 30	Hospitalization	19	108	267	0.418	0.305-0.542	50.6	36.4	0.006
	ICU	15	19	175	0.141	0.094-0.206	0	10.1	0.752
	Ventilation	11	15	129	0.140	0.089-0.212	0	5.16	0.881
	Death	20	19	280	0.104	0.072-0.148	0	9.66	0.961
Comorbidity (≥ 1)	Hospitalization	19	145	274	0.518	0.370-0.662	40.8	30.4	0.034
	ICU	19	21	306	0.105	0.069-0.158	3.50	18.7	0.413
	Ventilation	14	17	268	0.087	0.058-0.13	0	8.82	0.786
	Death	23	23	328	0.105	0.074-0.147	0	19.8	0.596
No comorbidity	Hospitalization	11	93	402	0.237	0.192-0.289	1.03	10.1	0.431
	ICU	12	12	443	0.043	0.027-0.068	0	6.34	0.850
	Ventilation	7	9	386	0.048	0.022-0.102	14.7	7.04	0.318
	Death	15	5	462	0.041	0.023-0.074	2.33	14.3	0.425

BMI, body mass index; DM, diabetes; HTN, hypertension; ICU, intensive care unit.

Table S3. Subgroup meta-analysis according to medical therapies in patients with autoimmune diseases diagnosed with COVID-19

Subgroup	Outcomes	Number of studies	Event (n)	Total (n)	Event rate	95% CI	I^2 (%)	Q	P-value
Glucocorticoids	Hospitalization	20	241	421	0.560	0.462-0.653	43.4	33.5	0.021
	ICU	16	13	161	0.143	0.089-0.221	0	13.3	0.578
	Ventilation	14	11	155	0.126	0.076-0.202	0	11.1	0.603
	Death	22	19	190	0.147	0.102-0.206	0	6.89	0.998
csDMARDs	Hospitalization	23	297	616	0.440	0.351-0.533	49.2	43.3	0.004
	ICU	18	8	213	0.101	0.057-0.171	1.18	17.2	0.441
	Ventilation	16	6	197	0.097	0.051-0.179	10.0	16.7	0.339
	Death	24	20	266	0.120	0.085-0.168	0	8.96	0.996
b/tsDMARDs (Monotherapy)	Hospitalization	28	153	755	0.249	0.186-0.325	54.7	59.6	<0.001
	ICU	24	12	574	0.058	0.037-0.091	3.20	23.8	0.417
	Ventilation	18	5	495	0.041	0.024-0.070	0	15.2	0.583
	Death	30	5	645	0.054	0.034-0.085	0	27.5	0.544
b/tsDMARDs + csDMARDs (Combination)	Hospitalization	10	78	198	0.409	0.309-0.518	15.5	10.6	0.301
	ICU	10	8	78	0.141	0.076-0.245	0	7.73	0.561
	Ventilation	8	4	70	0.130	0.051-0.295	18.1	8.55	0.287
	Death	11	2	80	0.093	0.045-0.184	0	2.88	0.984
b/tsDMARDs (Monotherapy or Combination)	Hospitalization	32	237	958	0.291	0.223-0.370	61.4	80.2	<0.001
	ICU	27	22	657	0.085	0.053-0.133	22.2	33.4	0.151
	Ventilation	21	10	568	0.060	0.035-0.102	13.0	23.0	0.290
	Death	34	8	730	0.048	0.032-0.073	0	27.5	0.736
Anti-TNF drugs (Monotherapy)	Hospitalization	18	53	362	0.191	0.126-0.278	33.8	25.7	0.080
	ICU	19	5	340	0.060	0.034-0.102	0	17.0	0.523
	Ventilation	14	1	306	0.053	0.026-0.105	0	11.8	0.542
	Death	22	2	374	0.062	0.035-0.108	0	15.7	0.785
Anti-TNF drugs + csDMARDs (Combination)	Hospitalization	5	25	61	0.408	0.291-0.536	0	3.22	0.522
	ICU	4	5	59	0.108	0.049-0.222	0	2.07	0.559
	Ventilation	3	2	56	0.061	0.020-0.175	0	1.51	0.471
	Death	5	2	61	0.075	0.028-0.186	0	2.12	0.714
Anti-TNF drugs (Monotherapy or combination)	Hospitalization	22	83	429	0.246	0.166-0.349	44.6	37.9	0.013
	ICU	22	10	406	0.062	0.039-0.096	0	16.8	0.724
	Ventilation	17	3	368	0.049	0.027-0.087	0	13.8	0.617
	Death	26	5	442	0.057	0.035-0.091	0	17.9	0.847
Non-TNF drugs (Monotherapy)	Hospitalization	18	56	246	0.284	0.181-0.415	49.1	33.4	0.010
	ICU	16	6	224	0.069	0.039-0.118	0	11.0	0.752

	Ventilation	11	4	187	0.055	0.028-0.102	0	4.20	0.938
	Death	21	3	260	0.074	0.042-0.127	0	13.7	0.846
Non-TNF drugs + csDMARDs (Combination)	Hospitalization	3	4	6	0.631	0.173-0.933	30.5	2.88	0.237
	ICU	3	2	6	0.369	0.067-0.827	30.5	2.88	0.237
	Ventilation	2	2	4	0.500	0.041-0.959	53.7	2.16	0.142
	Death	3	0	6	0.167	0.033-0.536	0	0.00	1.000
Non-TNF drugs (Monotherapy or combination)	Hospitalization	21	64	256	0.331	0.218-0.467	51.7	41.4	0.003
	ICU	19	10	235	0.102	0.059-0.172	11.0	20.2	0.320
	Ventilation	13	7	193	0.078	0.043-0.139	2.26	12.3	0.424
	Death	24	3	271	0.077	0.045-0.129	0	14.0	0.928

b/tsDMARDs, biologic or targeted synthetic DMARDs (abatacept, belimumab, CD-20, IL-1, IL-6, IL-12/23, IL-23, IL-17, $\alpha 4\beta 7$ integrin, TNF, and Janus kinase (JAK) inhibitors); csDMARDs, conventional synthetic disease-modifying antirheumatic drugs (hydroxychloroquine, chloroquine, thiopurines, cyclophosphamide, cyclosporine, tacrolimus, leflunomide, methotrexate, mycophenolate mofetil,/mycophenolic acid, and sulfasalazine); HTN, hypertension; ICU, intensive care unit; TNF, tumor necrosis factor.

Table S4. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria for studies included in the meta-analysis

(A) Meta-analysis of observational studies

Number of participants	**Starting Level of Evidence**	**Quality assessment**					**Reasons to increase level of evidence** (Large magnitude of effect; Dose-response gradient; Potential confounding)	**Overall quality of evidence**
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias		
319,025	High	Not serious	Serious[1]	Not serious	Not serious	Not serious	N/A	Moderate

1. due to heterogeneity

(B) Meta-analysis of case-controlled studies

Number of participants	**Starting Level of Evidence**	**Quality assessment**					**Reasons to increase level of evidence** (Large magnitude of effect; Dose-response gradient; Potential confounding)	**Overall quality of evidence**
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias		
30,771 (case) and 24,511,773 (control)	High	Not serious	Serious[1]	Not serious	Not serious	Not serious	N/A	Moderate

1. due to heterogeneity

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Figure S1. Funnel plots for meta-analysis regarding the prevalence of COVID-19 in patients with autoimmune diseases

Observational studies

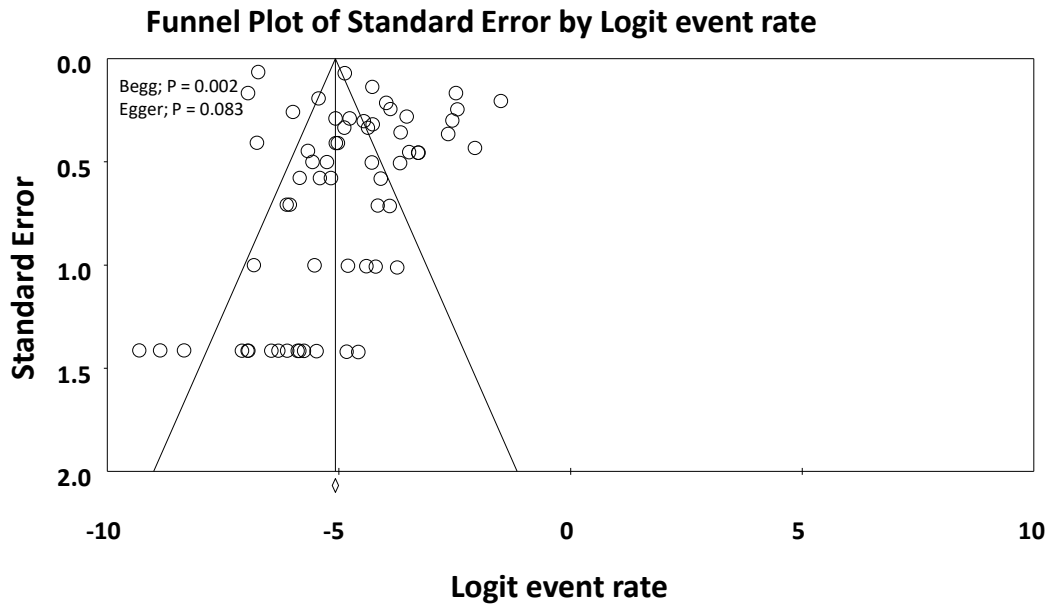
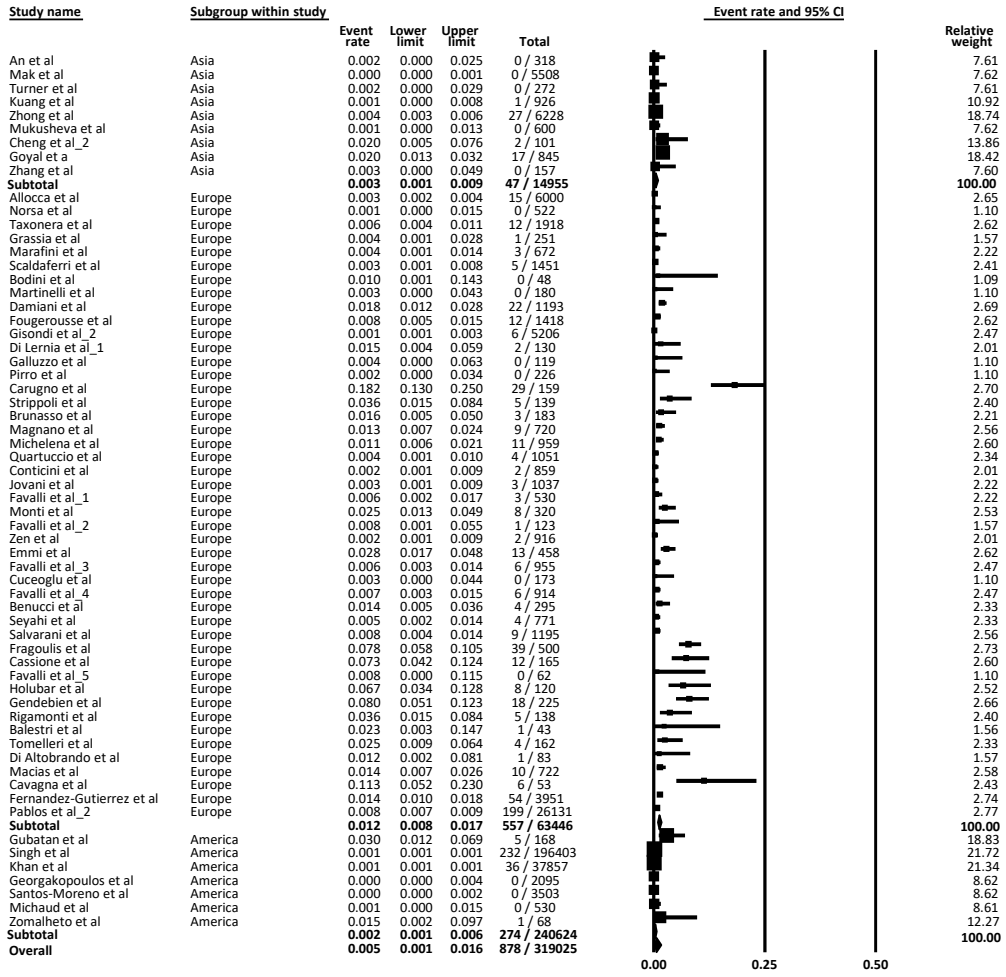


Figure S2. Meta-analysis regarding the prevalence of COVID-19 in patients with autoimmune diseases (by country)



Study name	Subgroup within study	Event rate	Lower limit	Upper limit	Total	Relative weight
An et al	Asia	0.002	0.000	0.025	0 / 318	7.61
Mak et al	Asia	0.000	0.000	0.001	0 / 5508	7.62
Turner et al	Asia	0.002	0.000	0.029	0 / 272	7.61
Kuang et al	Asia	0.001	0.000	0.008	1 / 926	10.92
Zhong et al	Asia	0.004	0.003	0.006	27 / 6228	18.74
Mukusheva et al	Asia	0.001	0.000	0.013	0 / 600	7.62
Cheng et al_2	Asia	0.020	0.005	0.076	2 / 101	13.86
Goyal et a	Asia	0.020	0.013	0.032	17 / 845	18.42
Zhang et al	Asia	0.003	0.000	0.049	0 / 157	7.60
Subtotal		**0.003**	**0.001**	**0.009**	**47 / 14955**	**100.00**
Allocca et al	Europe	0.003	0.002	0.004	15 / 6000	2.65
Norsa et al	Europe	0.001	0.000	0.015	0 / 522	1.10
Taxonera et al	Europe	0.006	0.004	0.011	12 / 1918	2.62
Grassia et al	Europe	0.004	0.001	0.028	1 / 251	1.57
Marafini et al	Europe	0.004	0.001	0.014	3 / 672	2.22
Scaldaferri et al	Europe	0.003	0.001	0.008	5 / 1451	2.41
Bodini et al	Europe	0.010	0.001	0.143	0 / 48	1.09
Martinelli et al	Europe	0.003	0.000	0.043	0 / 180	1.10
Damiani et al	Europe	0.018	0.012	0.028	22 / 1193	2.69
Fougerousse et al	Europe	0.008	0.005	0.015	12 / 1418	2.62
Gisondi et al_2	Europe	0.001	0.001	0.003	6 / 5206	2.47
Di Lernia et al_1	Europe	0.015	0.004	0.059	2 / 130	2.01
Galluzzo et al	Europe	0.004	0.000	0.063	0 / 119	1.10
Pirro et al	Europe	0.002	0.000	0.034	0 / 226	1.10
Carugno et al	Europe	0.182	0.130	0.250	29 / 159	2.70
Strippoli et al	Europe	0.036	0.015	0.084	5 / 139	2.40
Brunasso et al	Europe	0.016	0.005	0.050	3 / 183	2.21
Magnano et al	Europe	0.013	0.007	0.024	9 / 720	2.56
Michelena et al	Europe	0.011	0.006	0.021	11 / 959	2.60
Quartuccio et al	Europe	0.004	0.001	0.010	4 / 1051	2.34
Conticini et al	Europe	0.002	0.001	0.009	2 / 859	2.01
Jovani et al	Europe	0.003	0.001	0.009	3 / 1037	2.22
Favalli et al_1	Europe	0.006	0.002	0.017	3 / 530	2.22
Monti et al	Europe	0.025	0.013	0.049	8 / 320	2.53
Favalli et al_2	Europe	0.008	0.001	0.055	1 / 123	1.57
Zen et al	Europe	0.002	0.001	0.009	2 / 916	2.01
Emmi et al	Europe	0.028	0.017	0.048	13 / 458	2.62
Favalli et al_3	Europe	0.006	0.003	0.014	6 / 955	2.47
Cuceoglu et al	Europe	0.003	0.000	0.044	0 / 173	1.10
Favalli et al_4	Europe	0.007	0.003	0.015	6 / 914	2.47
Benucci et al	Europe	0.014	0.005	0.036	4 / 295	2.33
Seyahi et al	Europe	0.005	0.002	0.014	4 / 771	2.33
Salvarani et al	Europe	0.008	0.004	0.014	9 / 1195	2.56
Fragoulis et al	Europe	0.078	0.058	0.105	39 / 500	2.73
Cassione et al	Europe	0.073	0.042	0.124	12 / 165	2.60
Favalli et al_5	Europe	0.008	0.000	0.115	0 / 62	1.10
Holubar et al	Europe	0.067	0.034	0.128	8 / 120	2.52
Gendebien et al	Europe	0.080	0.051	0.123	18 / 225	2.66
Rigamonti et al	Europe	0.036	0.015	0.084	5 / 138	2.40
Balestri et al	Europe	0.023	0.003	0.147	1 / 43	1.56
Tomelleri et al	Europe	0.025	0.009	0.064	4 / 162	2.33
Di Altobrando et al	Europe	0.012	0.002	0.081	1 / 83	1.57
Macias et al	Europe	0.014	0.007	0.026	10 / 722	2.58
Cavagna et al	Europe	0.113	0.052	0.230	6 / 53	2.43
Fernandez-Gutierrez et al	Europe	0.014	0.010	0.018	54 / 3951	2.74
Pablos et al_2	Europe	0.008	0.007	0.009	199 / 26131	2.77
Subtotal		**0.012**	**0.008**	**0.017**	**557 / 63446**	**100.00**
Gubatan et al	America	0.030	0.012	0.069	5 / 168	18.83
Singh et al	America	0.001	0.001	0.001	232 / 196403	21.72
Khan et al	America	0.001	0.001	0.001	36 / 37857	21.34
Georgakopoulos et al	America	0.000	0.000	0.004	0 / 2095	8.62
Santos-Moreno et al	America	0.000	0.000	0.002	0 / 3503	8.62
Michaud et al	America	0.001	0.000	0.015	0 / 530	8.61
Zomalheto et al	America	0.015	0.002	0.097	1 / 68	12.27
Subtotal		**0.002**	**0.001**	**0.006**	**274 / 240624**	**100.00**
Overall		**0.005**	**0.001**	**0.016**	**878 / 319025**	

Asia; $P < 0.001$, Heterogeneity: $I^2 = 82.2\%$, $Q = 45.1$, $P < 0.001$
Europe; $P < 0.001$, Heterogeneity: $I^2 = 93.5\%$, $Q = 687.3$, $P < 0.001$
America; $P < 0.001$, Heterogeneity: $I^2 = 90.4\%$, $Q = 62.7$, $P < 0.001$
Overall: $P < 0.001$, Heterogeneity: $I^2 = 96.8\%$, $Q = 1888.7$, $P < 0.001$

Figure S3. Funnel plots for meta-analysis regarding the prevalence of COVID-19 in patients with autoimmune diseases

Case-controlled studies

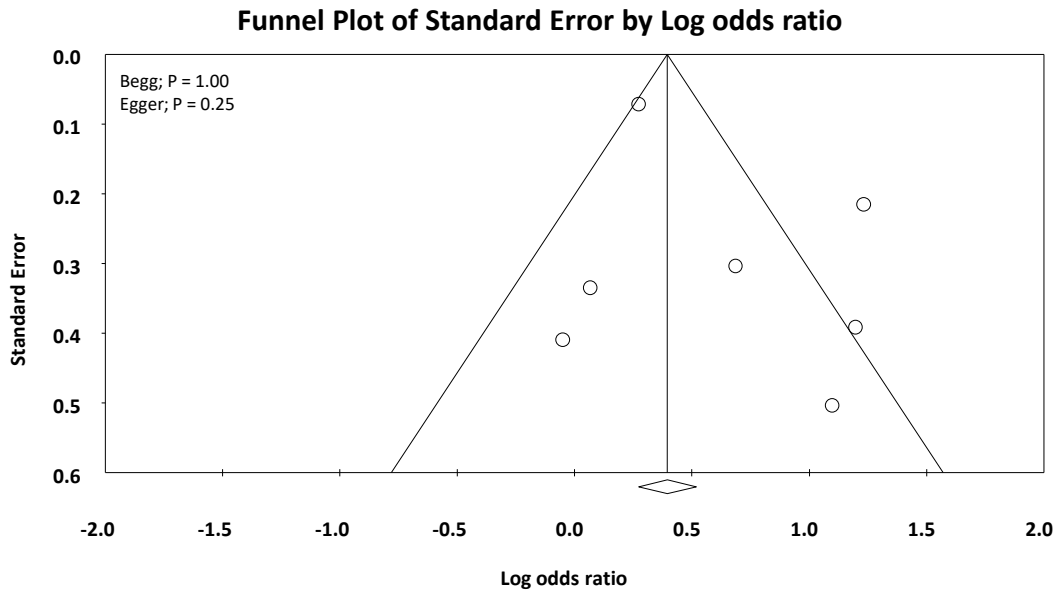
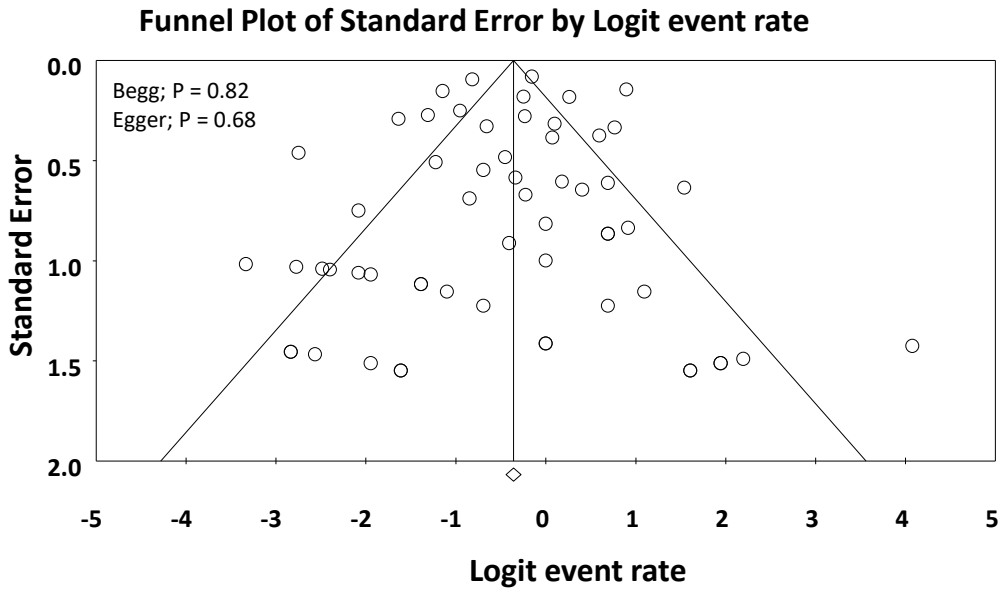


Figure S4. Funnel plots for meta-analysis regarding clinical outcomes of COVID-19 in patients with autoimmune diseases (Observational studies)

(A) Hospitalization



(B) Death

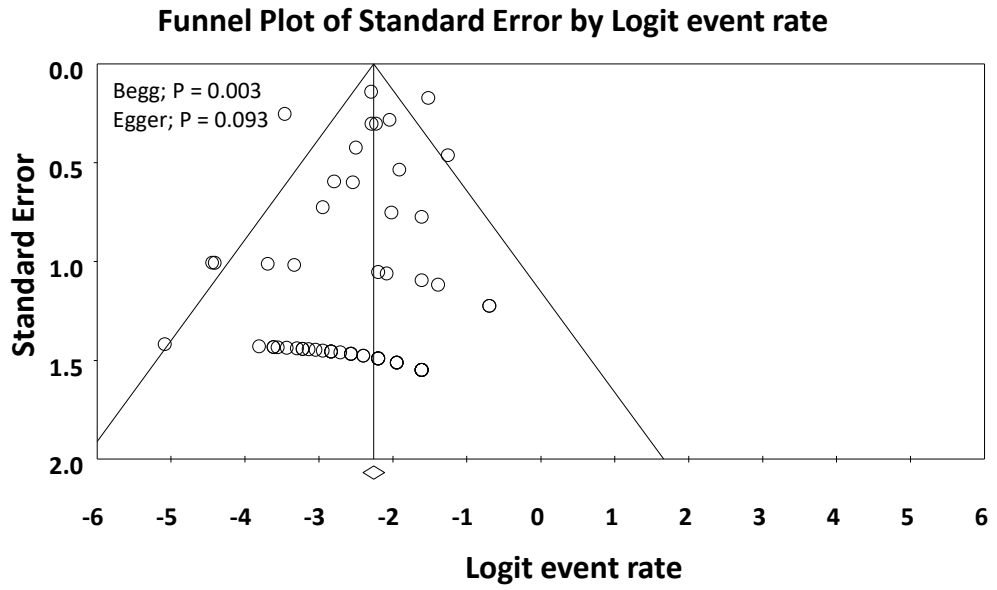
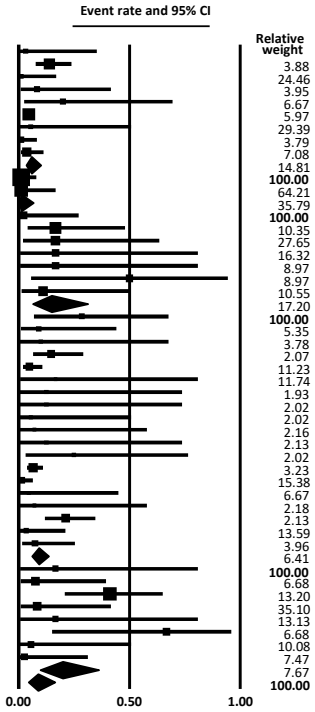


Figure S5. Meta-analysis regarding severe COVID-19 in patients with autoimmune diseases (observational studies)

(A) ICU admission

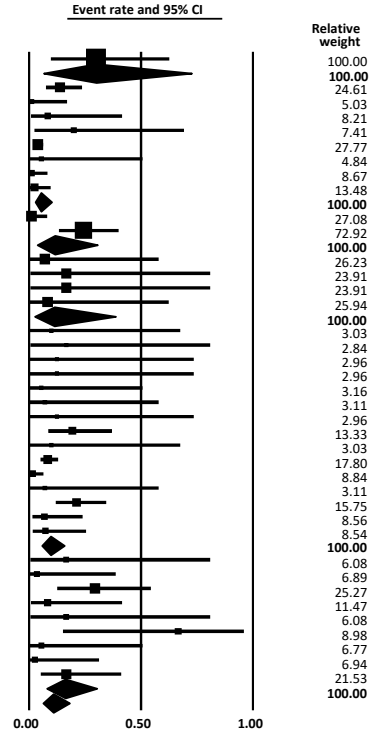
Study name	Subgroup within study	Event rate	Lower limit	Upper limit	Total	Relative weight
Allocca et al	IBD	0.031	0.002	0.350	0 / 15	3.88
Bezzio et al	IBD	0.139	0.079	0.234	11 / 79	24.46
Rodriguez et al	IBD	0.012	0.001	0.167	0 / 40	3.95
Taxonera et al	IBD	0.083	0.012	0.413	1 / 12	6.67
Gubatan et al	IBD	0.200	0.027	0.691	1 / 5	5.97
Brenner et al	IBD	0.046	0.031	0.067	24 / 525	29.39
Turner et al	IBD	0.056	0.003	0.505	0 / 8	3.79
Axelrad et al	IBD	0.012	0.002	0.081	1 / 83	7.08
Lukin et al	IBD	0.038	0.012	0.110	3 / 80	14.81
Subtotal		**0.058**	**0.033**	**0.100**	**41 / 847**	**100.00**
Haberman et al	IMID	0.012	0.002	0.078	1 / 86	64.21
Allocca et al_2	IMID	0.012	0.001	0.164	0 / 41	35.79
Subtotal		**0.012**	**0.002**	**0.065**	**1 / 127**	**100.00**
Damiani et al	Psoriasis/AISD	0.022	0.001	0.268	0 / 22	10.35
Fougerousse et al	Psoriasis/AISD	0.167	0.042	0.477	2 / 12	27.65
Gisondi et al_2	Psoriasis/AISD	0.167	0.023	0.631	1 / 6	16.32
Di Lernia et al_1	Psoriasis/AISD	0.167	0.010	0.806	0 / 2	8.97
Brownstone et al	Psoriasis/AISD	0.167	0.010	0.806	0 / 2	8.97
Conti et al	Psoriasis/AISD	0.500	0.059	0.941	1 / 2	10.55
Magnano et al	Psoriasis/AISD	0.111	0.015	0.500	1 / 9	17.20
Subtotal		**0.148**	**0.063**	**0.312**	**5 / 55**	**100.00**
Queiro Silva et al	RD	0.286	0.072	0.673	2 / 7	5.35
Michelena et al	RD	0.091	0.013	0.439	1 / 11	3.78
Quartuccio et al	RD	0.100	0.006	0.674	0 / 4	2.07
Sanchez-Piedra et al	RD	0.146	0.067	0.290	6 / 41	11.23
Nuno et al	RD	0.049	0.022	0.105	6 / 122	11.74
Conticini et al	RD	0.167	0.010	0.806	0 / 2	1.93
Jovani et al	RD	0.125	0.007	0.734	0 / 3	2.02
Favalli et al_1	RD	0.125	0.007	0.734	0 / 3	2.02
Monti et al	RD	0.056	0.003	0.505	0 / 8	2.16
Favalli et al_3	RD	0.071	0.004	0.577	0 / 6	2.13
Brito et al	RD	0.125	0.007	0.734	0 / 3	2.02
Benucci et al	RD	0.250	0.034	0.762	1 / 4	3.23
Pablos et al	RD	0.066	0.040	0.106	15 / 228	15.38
Freites et al	RD	0.016	0.004	0.063	2 / 123	6.67
Macias et al	RD	0.045	0.003	0.448	0 / 10	2.18
Cavagna et al	RD	0.071	0.004	0.577	0 / 6	2.13
D'Silva et al	RD	0.212	0.121	0.343	11 / 52	13.59
Zhao et al	RD	0.034	0.005	0.208	1 / 29	3.96
Benoy et al	RD	0.074	0.019	0.252	2 / 27	6.41
Subtotal		**0.091**	**0.060**	**0.135**	**47 / 689**	**100.00**
Zen et al	SLE/SjS/SSc	0.167	0.010	0.806	0 / 2	6.68
Emmi et al	SLE/SjS/SSc	0.077	0.011	0.391	1 / 13	13.20
Mathian et al	SLE/SjS/SSc	0.412	0.210	0.648	7 / 17	35.10
Cassione et al	SLE/SjS/SSc	0.083	0.012	0.413	1 / 12	13.13
Cheng et al_2	SLE/SjS/SSc	0.167	0.010	0.806	0 / 2	6.68
Avouac et al	SLE/SjS/SSc	0.667	0.154	0.957	2 / 3	10.08
Holubar et al	SLE/SjS/SSc	0.056	0.003	0.505	0 / 8	7.47
Gendebien et al	SLE/SjS/SSc	0.026	0.002	0.310	0 / 18	7.67
Subtotal		**0.198**	**0.097**	**0.360**	**11 / 75**	**100.00**
Overall		**0.087**	**0.045**	**0.163**	**105 / 1793**	



IBD; $P < 0.001$, Heterogeneity: $I^2 = 51.9\%$, $Q = 16.6$, $P = 0.034$
IMID (Immune-mediated inflammatory disease); $P < 0.001$, Heterogeneity: $I^2 = 0\%$, $Q = 0.00$, $P = 0.989$
Psoriasis/AISD (Autoimmune skin disease); $P < 0.001$, Heterogeneity: $I^2 = 0\%$, $Q = 3.76$, $P = 0.709$
RD: $P < 0.001$, Heterogeneity: $I^2 = 31.5\%$, $Q = 26.3$, $P = 0.093$
SLE/SjS/SSc: $P = 0.001$, Heterogeneity: $I^2 = 43.5\%$, $Q = 12.4$, $P = 0.089$
Overall: $P < 0.001$, Heterogeneity: $I^2 = 48.7\%$, $Q = 85.8$, $P < 0.001$

(B) Mechanical/non-invasive ventilation

Study name	Subgroup within study	Event rate	Lower limit	Upper limit	Total	Relative weight
Gerussi et al	AHD	0.300	0.100	0.624	3 / 10	100.00
Subtotal		**0.300**	**0.065**	**0.726**	**3 / 10**	**100.00**
Bezzio et al	IBD	0.139	0.079	0.234	11 / 79	24.61
Rodriguez et al	IBD	0.012	0.001	0.167	0 / 40	5.03
Taxonera et al	IBD	0.083	0.012	0.413	1 / 12	8.21
Gubatan et al	IBD	0.200	0.027	0.691	1 / 5	7.41
Brenner et al	IBD	0.040	0.026	0.061	21 / 525	27.77
Turner et al	IBD	0.056	0.003	0.505	0 / 8	4.84
Axelrad et al	IBD	0.012	0.002	0.081	1 / 83	8.67
Lukin et al	IBD	0.025	0.006	0.094	2 / 80	13.48
Subtotal		**0.054**	**0.028**	**0.101**	**37 / 832**	**100.00**
Haberman et al	IMID	0.012	0.002	0.078	1 / 86	27.08
Allocca et al_2	IMID	0.244	0.137	0.397	10 / 41	72.92
Subtotal		**0.116**	**0.038**	**0.305**	**11 / 127**	**100.00**
Gisondi et al_2	Psoriasis/AISD	0.071	0.004	0.577	0 / 6	26.23
Di Lernia et al_1	Psoriasis/AISD	0.167	0.010	0.806	0 / 2	23.91
Brownstone et al	Psoriasis/AISD	0.167	0.010	0.806	0 / 2	23.91
Strippoli et al	Psoriasis/AISD	0.083	0.005	0.622	0 / 5	25.94
Subtotal		**0.113**	**0.025**	**0.386**	**0 / 15**	**100.00**
Quartuccio et al	RD	0.100	0.006	0.674	0 / 4	3.03
Conticini et al	RD	0.167	0.010	0.806	0 / 2	2.84
Jovani et al	RD	0.125	0.007	0.734	0 / 3	2.96
Favalli et al_1	RD	0.125	0.007	0.734	0 / 3	2.96
Monti et al	RD	0.056	0.003	0.505	0 / 8	3.16
Favalli et al_3	RD	0.071	0.004	0.577	0 / 6	3.11
Brito et al	RD	0.125	0.007	0.734	0 / 3	2.96
Wallace et al	RD	0.194	0.090	0.369	6 / 31	13.33
Tomelleri et al	RD	0.100	0.006	0.674	0 / 4	3.03
Pablos et al	RD	0.083	0.054	0.127	19 / 228	17.80
Freites et al	RD	0.016	0.004	0.063	2 / 123	8.84
Cavagna et al	RD	0.071	0.004	0.577	0 / 6	3.11
D'Silva et al	RD	0.212	0.121	0.343	11 / 52	15.75
Zhao et al	RD	0.069	0.017	0.238	2 / 29	8.56
Benoy et al	RD	0.074	0.019	0.252	2 / 27	8.54
Subtotal		**0.097**	**0.059**	**0.158**	**42 / 529**	**100.00**
Zen et al	SLE/SjS/SSc	0.167	0.010	0.806	0 / 2	6.08
Emmi et al	SLE/SjS/SSc	0.036	0.002	0.384	0 / 13	6.89
Mathian et al	SLE/SjS/SSc	0.294	0.128	0.542	5 / 17	25.27
Cassione et al	SLE/SjS/SSc	0.083	0.012	0.413	1 / 12	11.47
Cheng et al_2	SLE/SjS/SSc	0.167	0.010	0.806	0 / 2	6.08
Avouac et al	SLE/SjS/SSc	0.667	0.154	0.957	2 / 3	8.98
Holubar et al	SLE/SjS/SSc	0.056	0.003	0.505	0 / 8	6.77
Gendebien et al	SLE/SjS/SSc	0.026	0.002	0.310	0 / 18	6.94
Gartshteyn et al	SLE/SjS/SSc	0.167	0.055	0.409	3 / 18	21.53
Subtotal		**0.162**	**0.079**	**0.302**	**11 / 93**	**100.00**
Overall		**0.109**	**0.063**	**0.182**	**104 / 1606**	



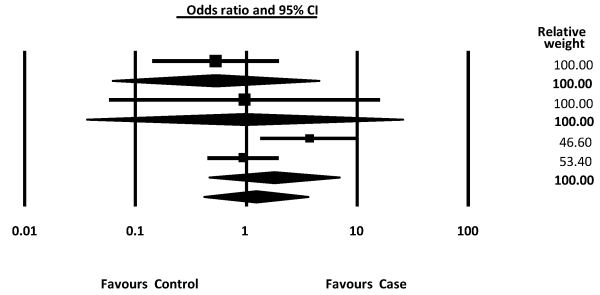
AHD (Autoimmune hepatic disease); $P = 0.362$, Heterogeneity: $I^2 = 0\%$, $Q = 0.00$, $P = 1.00$
IBD; $P < 0.001$, Heterogeneity: $I^2 = 63.0\%$, $Q = 18.9$, $P = 0.008$
IMID (Immune-mediated inflammatory disease); $P = 0.001$, Heterogeneity: $I^2 = 89.6\%$, $Q = 9.58$, $P = 0.002$
Psoriasis/AISD (Autoimmune skin disease); $P = 0.011$, Heterogeneity: $I^2 = 0\%$, $Q = 0.34$, $P = 0.952$
RD: $P < 0.001$, Heterogeneity: $I^2 = 23.6\%$, $Q = 18.3$, $P = 0.192$
SLE/SjS/SSc: $P < 0.001$, Heterogeneity: $I^2 = 19.4\%$, $Q = 9.93$, $P = 0.270$
Overall: $P < 0.001$, Heterogeneity: $I^2 = 54.6\%$, $Q = 83.7$, $P < 0.001$

Figure S6. Clinical outcomes of COVID-19 in patients with autoimmune diseases (case-controlled studies)

(A) Meta-analysis (ICU admission)

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	ICU / Total: Cases	ICU / Total: Control	Relative weight
Lukin et al	IBD	0.528	0.143	1.948	3 / 80	11 / 160	100.00
Subtotal		**0.528**	**0.062**	**4.501**	**3 / 80**	**11 / 160**	**100.00**
Damiani et al	Psoriasis	0.963	0.058	15.878	0 / 22	1236 / 54801	100.00
Subtotal		**0.963**	**0.036**	**25.533**	**0 / 22**	**1236 / 54801**	**100.00**
D'Silva et al	RD	3.718	1.347	10.264	11 / 52	7 / 104	46.60
Pablos et al	RD	0.933	0.450	1.936	15 / 228	16 / 228	53.40
Subtotal		**1.777**	**0.460**	**6.866**	**26 / 280**	**23 / 332**	**100.00**
Overall		**1.222**	**0.415**	**3.597**	**29 / 382**	**1270 / 55293**	

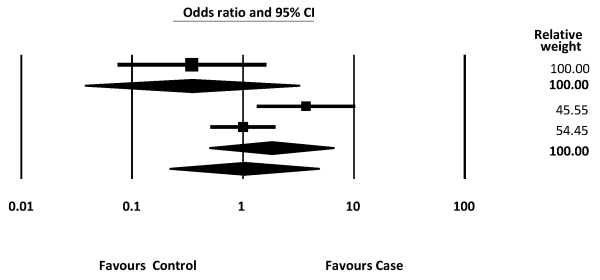
IBD; $P = 0.559$, Heterogeneity: $I^2 = 0\%$, $Q = 0.00$, $P = 1.000$
Psoriasis; $P = 0.982$, Heterogeneity: $I^2 = 0\%$, $Q = 0.00$, $P = 1.000$
RD: $P = 0.404$, Heterogeneity: $I^2 = 78.7\%$, $Q = 4.70$, $P = 0.030$
Overall: $P = 0.716$, Heterogeneity: $I^2 = 55.6\%$, $Q = 6.75$, $P = 0.080$



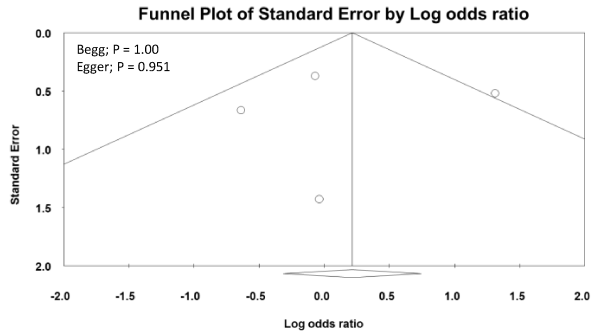
(B) Meta-analysis (Mechanical/non-invasive ventilation)

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Ventilation / Total: Case	Ventilation / Total: Control	Relative weight
Lukin et al	IBD	0.347	0.075	1.606	2 / 80	11 / 160	100.00
Subtotal		**0.347**	**0.038**	**3.192**	**2 / 80**	**11 / 160**	**100.00**
D'Silva et al	RD	3.718	1.347	10.264	11 / 52	7 / 104	45.55
Pablos et al	RD	1.000	0.515	1.943	19 / 228	19 / 228	54.45
Subtotal		**1.819**	**0.505**	**6.552**	**30 / 280**	**26 / 332**	**100.00**
Overall		**1.028**	**0.220**	**4.806**	**32 / 360**	**37 / 492**	

IBD; $P = 0.350$, Heterogeneity: $I^2 = 0\%$, $Q = 0.00$, $P = 1.000$
RD: $P = 0.360$, Heterogeneity: $I^2 = 77.8\%$, $Q = 4.50$, $P = 0.034$
Overall: $P = 0.972$, Heterogeneity: $I^2 = 73.5\%$, $Q = 7.55$, $P = 0.023$



(C) Funnel plot (ICU admission)



(D) Funnel plot (Ventilation)

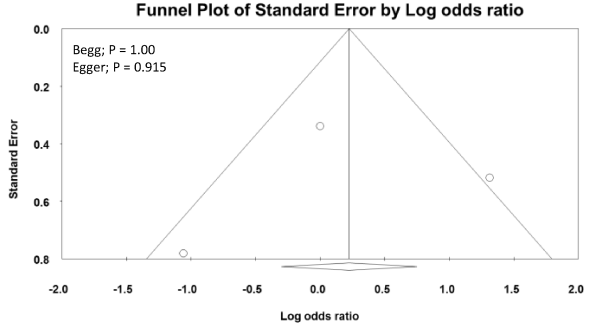
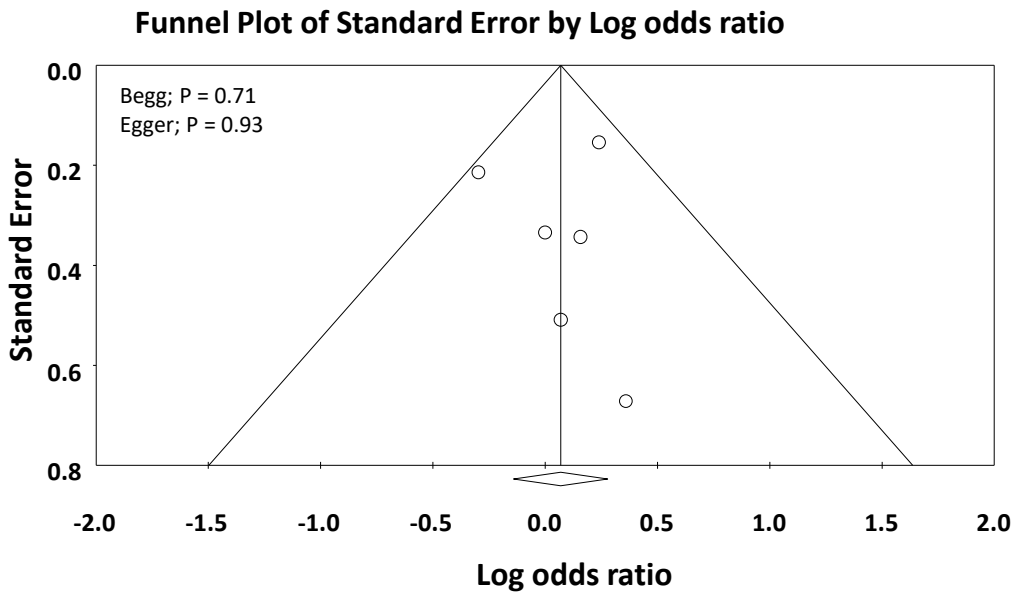
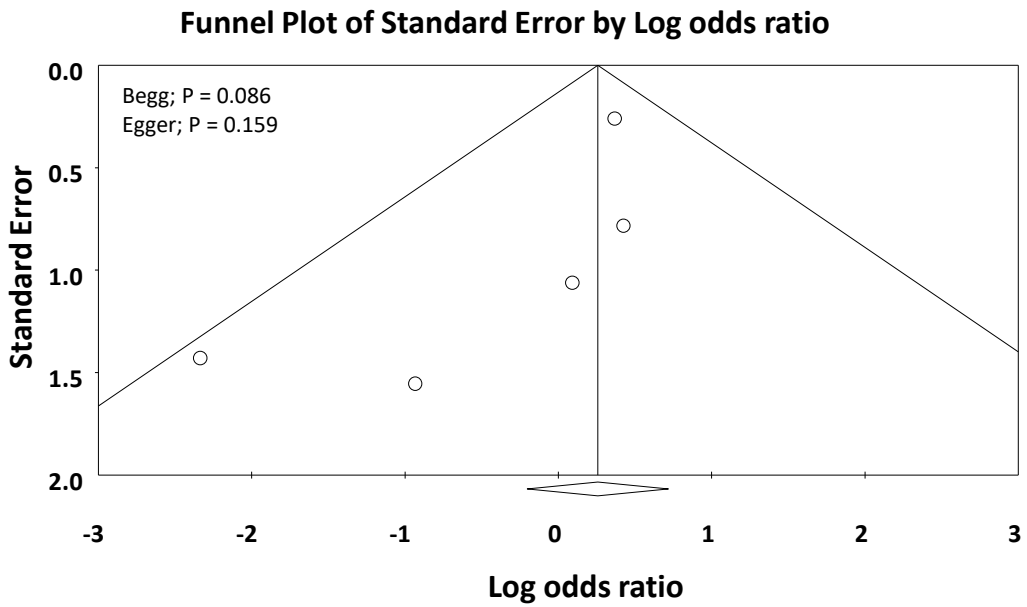


Figure S7. Funnel plots for meta-analysis regarding clinical outcomes of COVID-19 in patients with autoimmune diseases (case-controlled studies)

(A) Hospitalization



(B) Death



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Increased COVID-19 risk in autoimmune disease, but not more severe

People with autoimmune disease have an increased risk of getting infected with COVID-19, especially if they use steroid medicines. However, the risk of severe outcomes of COVID-19 such as hospitalisation or death is not increased.

INTRODUCTION

COVID-19 is the disease caused by a new type of coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It was declared a pandemic by the World Health Organization on 11 March 2020. COVID-19 has forced people to change their behaviours to try to limit the spread of infection.

People with autoimmune diseases such as inflammatory bowel disease, psoriasis, or rheumatic diseases may take drugs that suppress their immune systems. Some of these medicines can increase the risk of infection.

WHAT DID THE AUTHORS HOPE TO FIND?

The authors wanted to see how common COVID-19 is in people with autoimmune diseases. They also hoped to find out more about the outcomes for people with autoimmune diseases when they get COVID-19, such as how severe the infection is, and whether they need to go to hospital.

WHO WAS STUDIED?

The study looked at over 319,000 people from 15 countries to work out how common COVID-19 infection is in people with autoimmune disease. They also looked at over 2700 people with a confirmed diagnosis of COVID-19 to examine the clinical outcomes. The people included had a range of different autoimmune diseases, such as autoimmune hepatic (liver) diseases, inflammatory bowel disease, psoriasis, and lupus. The average age was 42, and just over half of the people included were female.

HOW WAS THE STUDY CONDUCTED?

This was a systematic review and meta-analysis. A systematic review aims to identify all the published evidence on a particular topic and draw it together into one summary. This paper also included a meta-analysis, which uses statistics to be sure that the conclusions are meaningful.

The authors searched databases of journal articles to find studies looking at COVID-19 in people with autoimmune disease. They combined findings from these to see how common COVID-19 was. They also looked at severe outcomes such as needing to be admitted to hospital or intensive care, needing ventilation, and death.

In the analysis, the authors looked at whether any specific factors or medicines contribute to catching COVID-19, and to having worse outcomes. This included seeing if the medicines that people take for their autoimmune disease affect their likelihood of catching COVID-19, or having a more severe infection. Medicines were put into three main groups: 1) glucocorticoids (steroids), 2) conventional synthetic disease-modifying antirheumatic drugs (often shortened to csDMARDs), and 3) biologic or targeted synthetic DMARDs (b/tsDMARDs). This last group was subdivided depending on whether people were taking the b/tsDMARD on its own (monotherapy) or together with a csDMARD (combination therapy).

WHAT WAS THE MAIN FINDING?

The main finding was that COVID-19 was twice as common in people with autoimmune diseases compared to the general population. Taking glucocorticoids increased the risk of getting infected with COVID-19. On the other hand, the risk of severe outcomes of COVID-19 such as hospitalisation or death was not increased in people with autoimmune disease compared to those without, or in the general population.

The authors also found some factors that were associated with having more severe COVID-19. Like in the general population, being older, and having other diseases such as hypertension or diabetes had an impact. Taking steroid medicines was another important factor that increased the risk of having severe COVID-19.

Taking csDMARDs or a combination of b/tsDMARD and csDMARDs also increased the risk of getting a severe infection. However, people with autoimmune disease who were taking a b/tsDMARD as monotherapy – particularly a group of medicines called tumour necrosis factor inhibitors (TNFi) – had a reduced risk of hospitalisation and death due to COVID-19.

ARE THESE FINDINGS NEW?

Yes. This study is the first comprehensive meta-analysis to determine the prevalence and clinical outcomes of COVID-19 in people with autoimmune disease.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

There are some limitations to this type of study. First of all, the observational studies that were combined in the meta-analyses included people with different backgrounds, which reduces how reliable the data are. Secondly, although the authors separately assessed the effect of b/tsDMARD as monotherapy or in combination therapy, not all studies presented information in these two groups. Third, the accuracy of the test for COVID-19 is only 70%, so it is possible people in the studies had false positives or false negatives, which might have affected the results. Lastly, the COVID-19 pandemic is quickly spreading, and the picture continues to change.

WHAT DO THE AUTHORS PLAN TO DO WITH THIS INFORMATION?

The authors are interested in doing a bigger analysis with updated data to understand which specific b/tsDMARDs other than TNFi can contribute to better or worse outcomes of COVID-19 in people with autoimmune disease.

WHAT DOES THIS MEAN FOR ME?

If you have an autoimmune disease, you may be more at risk of catching COVID-19. But this study does not suggest you are more likely to have severe disease or die from it. Some medicines can increase the risk of getting COVID-19 and having worse outcomes. However, it is very important that you do not stop taking medicines for your autoimmune disease without talking to your doctor.

Protect yourself from COVID-19 by following the advice of the government in your country, including wearing masks, washing your hands regularly, avoiding touching your face, and following social distancing rules.

Vaccination programs to slow down the spread of COVID-19 have started. Guidelines recommend that all people with autoimmune disease get vaccinated.

Date prepared: February 2021

Summary based on research article published on: 13 October 2020

From: Akiyama S, *et al*. Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. *Ann Rheum Dis* 2021;80:384–391. doi:10.1136/annrheumdis-2020-218946