Effect of anti-rheumatic drugs on the clinical outcome of autoimmune rheumatic diseases patients infected with COVID-19: A systemic review and meta-analysis

Qin-Yi Su¹, Sheng-Xiao Zhang¹, Jing Luo¹, Ting Cheng¹, He-Yi Zhang², Yan Zhang², Bing-Ru Zhao², Chong Gao³, and Cai-Hong Wang¹

¹Second Hospital of Shanxi Medical University
²Shanxi Medical University Jinci College
³Brigham and Women’s Hospital Department of Pathology

March 28, 2023

Abstract

The immune deregulation and disease-modifying anti-rheumatic drugs (DMARDs) make patients with autoimmune rheumatic diseases (ARD) more susceptible to infection. We aimed to investigate the prevalence and clinical outcome of COVID-19 in ARD patients with different treatments. PubMed, Embase, Medline, Cochrane Library, Web of Science were searched to identify the relevant evidence up to March 20, 2023. The overall prevalence of COVID-19 in ARD patients was 0.061. The ARD patients with glucocorticoids (GC) treatment had the highest prevalence [0.088(95%CI:0.065-0.110)] compared to biological (b) DMARDs [0.041(95%CI:0.031-0.051)], conventional synthetic (cs) DMARDs [0.055(95%CI:0.043-0.067)], and anti-TNF therapy [0.029(95%CI:0.003-0.056)]. In contrast, those receiving anti-TNF therapy had the lowest prevalence. The overall hospitalization rate, ICU admission rate, and mortality of ARD patients due to COVID-19 were 0.402(95%CI:0.330-0.476), 0.077(95%CI:0.051-0.107), and 0.073(95%CI:0.046-0.104). Using bDMARDs had lower hospitalization rates [0.216(95%CI:0.147-0.286)], ICU admission rates [0.010(95%CI:0.000-0.037)], and mortality [0.039(95%CI:0.007-0.087)]. Regression analysis showed a significant negative relationship between bDMARDs monotherapy and ICU admission rates (regression coefficient: -0.156, 95%CI: -0.260 - -0.051, P=0.006). Patients using csDMARDs had higher hospitalization rates [0.607(95%CI:0.450-0.755)], ICU admission rates [0.055(95%CI:0.037-0.075)], and mortality [0.074(95%CI:0.041-0.114)]. Patients using GC had a higher hospitalization rate [0.703(95%CI:0.449-0.910)], higher ICU admission rate [0.094(95%CI:0.046-0.152)], and lower mortality [0.070(95%CI:0.033-0.114)]. Regression analysis showed a significant positive correlation between GC monotherapy and hospitalization (regression coefficient: 0.484, 95%CI:0.146-0.822, P=0.006). For ARD patients, csDMARDs were associated with disease severity in COVID-19, bDMARDs were associated with a reduced risk of severe disease, and GC was effective in patients with severe COVID-19-related respiratory failure.
# Qin-Yi Su and Sheng-Xiao Zhang contributed to the work equally and should be regarded as co-first authors.

* Cai-Hong Wang is corresponding authors.

* Cai-Hong Wang: Phone number: +8613603515399; E-mail address: snwch@sina.com; Present address: 382, Wuyi Road, Taiyuan, Shanxi

**Data availability statement**

All data relevant to the study are included in the article or uploaded as Supporting Information. The data are available by accessing the published studies listed in supplementary material S2.

**Funding statement**

This work was supported by the National Science Foundation of China (No.82001740), the National Social Science Fund of China (21BTQ050), the National Natural Science Foundation of China (No. 81971543), Natural Science Foundation of China (No. 81471618), Key Research and Development (R&D) Projects of Shanxi Province (201803D31119), and Four “Batches” Innovation Project of Invigorating Medical through Science and Technology of Shanxi Province(NO 2022XM05).

**Conflict of interest disclosure**

The authors declare they have no competing interests.

**Ethics approval statement**

Not Applicable.

**Patient consent statement**

Not Applicable.

**Abstract:**

The immune deregulation and disease-modifying anti-rheumatic drugs (DMARDs) make patients autoimmune rheumatic diseases (ARD) more susceptible to infection. We aimed to investigate the prevalence and clinical outcome of COVID-19 in ARD patients with different treatments. PubMed, Embase, Medline, Cochrane Library, Web of Science were searched to identify the relevant evidence up to March 20, 2023. The overall prevalence of COVID-19 in ARD patients was 0.061. The ARD patients with glucocorticoids (GC) treatment had the highest prevalence [0.088(95%CI:0.065-0.110)] compared to biological (b) DMARDs [0.041(95%CI:0.031-0.051)], conventional synthetic (cs) DMARDs [0.055(95%CI:0.043-0.067)], and anti-TNF therapy [0.029(95%CI:0.003-0.056)]. In contrast, those receiving anti-TNF therapy had the lowest prevalence. The overall hospitalization rate, ICU admission rate, and mortality of ARD patients due to COVID-19 were 0.402(95%CI:0.330-0.476), 0.077(95%CI:0.051-0.107), and 0.073(95%CI:0.046-0.104). Using bDMARDs had lower hospitalization rates [0.216(95%CI:0.147-0.286)], ICU admission rates [0.010(95%CI:0.000-0.037)], and mortality [0.039(95%CI:0.007-0.087)]. Regression analysis showed a significant negative relationship between bDMARDs monotherapy and ICU admission rates (regression coefficient:-0.156, 95%CI:-0.260 - -0.051, P=0.006). Patients using csDMARDs had higher hospitalization rates [0.607(95%CI:0.450-0.755)], ICU admission rates [0.055(95%CI:0.037-0.075)], and mortality [0.074(95%CI:0.041-0.114)]. Patients using GC had a higher hospitalization rate [0.703(95%CI:0.449-0.910)], higher ICU admission rate [0.094(95%CI:0.046-0.152)], and lower mortality [0.070(95%CI:0.033-0.114)]. Regression analysis showed a significant positive correlation between GC monotherapy and hospitalization (regression coefficient:0.484, 95%CI:0.146-0.822, P=0.006). For ARD patients, csDMARDs were associated with disease severity in COVID-19, bDMARDs were associated with a reduced risk of severe disease, and GC was effective in patients with severe COVID-19-related respiratory failure.

**Keywords:** Coronavirus; Epidemiology; Immunity/Immunization
1 Introduction

The pandemic of novel coronavirus disease 2019 (COVID-19) caused by the emerging severe acute respiratory syndrome coronavirus 2 (sars-cov-2) has become a global health crisis (WHO, 2020b), leading to a large number of infections and deaths. By March 20, 2023, over 608 million confirmed cases, including 6.50 million deaths, were reported. Patients with autoimmune rheumatic diseases (ARD) are frequently treated with immunosuppressive drugs, which raises concern for infectious complications, placing patients and physicians at a crossroads concerning the continuation or cessation of these disease-modifying therapies.

Nowadays, more attention has been paid to the impact of disease-modifying antirheumatic drugs (DMARDs) on the prevalence of COVID-19 and clinical outcomes in ARD patients. Some studies reported fewer patients on low-or-medium-dose glucocorticoid (GC) therapy had severe COVID-19 conditions compared to those without GC before the COVID-19 diagnosis. Other studies found the use of systemic glucocorticoids (sGC) (> 5 mg/day of prednisone) was significantly associated with hospital admission caused by sars-cov-2 infection. In some registry studies, patients with baseline TNF inhibitor therapy had lower odds of severe COVID-19 outcomes. Still, the risk of infection observed in rheumatoid arthritis (RA) patients treated with biologic DMARDs (bDMARDs), including TNF inhibitor therapy, was generally considered slightly higher (from 1.5- up to 2-fold) compared with conventional synthetic DMARDs (csDMARDs). Each study or registry has a limited sample size, and the analysis is not comprehensive. Therefore, there is a need to integrate findings across studies to better understand the risk of COVID-19 in patients with ARD.

This study aimed to determine the prevalence of COVID-19 in ARD patients and investigate the effect of anti-rheumatic therapy on the clinical outcome of ARD patients with COVID-19 to guide clinical treatment better.

2 Materials and Methods

This systematic meta-analysis was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines and registered on the International Prospective Register of Systematic Reviews (PROSPERO) trial registry (CRD42021292364).  

2.1 Data sources and search strategy

We searched for relevant studies published from inception to March 20, 2023, on CBM, CNKI, China Science and Technology Journal Database, WanFang Data, PubMed, Embase, Web of Science, Cochrane Library, and Medline, with no restrictions on publication language or primary outcome. The articles were retrieved using a combination of subject terms and free words. The relevant papers were identified using Medical Subject Headings (MeSH) terms: “COVID-19” and related free words. To conduct subgroup analyses with each diagnosis, we also used the MeSH terms for each specific disease, including “ARDs”, “Arthritis, Rheumatoid”, “Lupus Erythematosus, Systemic”, “Sjogren’s Syndrome”, “Antiphospholipid Syndrome”, “Spondylitis, Ankylosing”, “Arthritis, Psoriatic”, “Vasculitis”, “Gout”, “Connective Tissue Diseases”, “Scleroderma, Systemic”. In addition, we manually searched the reference lists of published systematic reviews and original articles. The search strategy were described in Supplementary Material p1.

2.2 Study selection and data extraction

The meta-analysis of the results in original studies conducted on humans that had the following MeSH terms and free words in the title or abstract: ‘COVID-19’ AND ‘ARDs’ or ‘Arthritis, Rheumatoid’ or ‘Lupus Erythematosus, Systemic’ or ‘Sjogren’s Syndrome’ or ‘Antiphospholipid Syndrome’ or ‘Spondylitis, Ankylosing’ or ‘Arthritis, Psoriatic’ or ‘Vasculitis’ or ‘Gout’ or ‘Connective Tissue Diseases’ or ‘Scleroderma, Systemic’.

The meta-analysis excluded studies that were non-original, multiple reports of the same or overlapping data, or conducted without a control group. Single case reports were excluded. As for the clinical outcomes of COVID-19, studies including only hospitalized or dead patients were excluded. In addition, we excluded studies with missing data that could not be obtained even after contacting the authors.
Two investigators independently assessed the studies based on the eligibility criteria; a third investigator resolved disagreements. A data collection sheet was used to record information related to the first author's name, publication year, study design, study location, numbers of patients diagnosed with COVID-19, type of medications, age, gender, 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. Evidence was graded according to the Newcastle–Ottawa Quality Assessment Scale (NOS). The quality of studies was assessed using Stata 12.0.

2.3 Statistical analysis
We used Stata 12.0 software (Stata Corp, College Station, TX, USA) for the meta-analysis. We undertook a meta-analysis of the prevalence and clinical outcomes of COVID-19 among individuals with ARDs from observational by using a random effects model. We evaluated the presence of heterogeneity across studies by using the I² statistic. An I² value of <25% indicates low heterogeneity, 25%–75% as moderate heterogeneity, and >75% as considerable heterogeneity. A random effects regression model was used to assess the contributions of each potential risk factor and medication class to the prevalence and adverse clinical outcomes. Since the medication regimen of each patient in the included studies could not be obtained, we regarded the drugs used by the patients as the drugs used by all patients in the studies, regardless of the proportion of the number of people who have used the drugs in the studies. Besides, we regarded the drugs used by more than 50% of the patients in this study as the primary drugs used by all patients.

3 Results
3.1 Study characteristics
We identified 14169 citations through the literature search, excluded 1706 titles and abstracts after initial screening. The final 146 full-text articles met all eligibility criteria(Figure 1). To analyze COVID-19 prevalence, we included 68 observational studies totaling 384582 patients with ARD. For clinical outcomes, we included 85 studies with 167554 patients with ARD diagnosed with COVID-19. Among these studies, 56 were included with data from 127984 ARD patients diagnosed with COVID-19 who have used anti-rheumatic drugs to explore the effect of anti-rheumatic drugs on clinical outcomes of COVID-19 in autoimmune diseases. We divided the anti-rheumatic medications used by patients into three classes:GC, csDMARDs, and bDMARDs, and we also analyzed the anti-TNF therapy separately. The characteristics and outcomes of the included studies are summarized in Supplementary Material p2.
3.2 Prevalence of COVID-19 in autoimmune rheumatic diseases

A meta-analysis of 68 observational studies, including 384582 patients with ARDs, showed that the prevalence of COVID-19 was 0.061 (95% CI: 0.056-0.066) (Figure 2). In the subgroup analyses, the prevalences of COVID-19 in RA, systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), connective tissue disease (CTD) and psoriatic arthritis (PsA) were 0.028 (95% CI: 0.019-0.037), 0.047 (95% CI: 0.033-0.061), 0.074 (95% CI: 0.039-0.108), 0.058 (95% CI: 0.046-0.070) and 0.194 (95% CI: 0.090-0.297), respectively. RA patients had the lowest prevalence, and PsA patients had the highest. The prevalence of COVID-19 in vasculitis and systemic sclerosis (SSc) was not statistically significant (Figure p3). Heterogeneity was considerable overall ($I^2 = 99.5\%$), and in most subgroup analyses, primarily due to the use of drugs for different diseases and differences in study sizes.
Figure 2: The prevalence of COVID-19 in autoimmune rheumatic diseases.

3.3 Impact of drugs on the prevalence of COVID-19

Drugs used by patients with ARDs impact the infection of COVID-19 (Figure p4). The regression analysis showed that anti-rheumatic medication did not contribute to the risk of COVID-19 (Figure p5 and p6). From the perspective of the primary drugs, the prevalence of ARD patients mainly using GC, bDMARDs, csDMARDs, and anti-TNF therapy was 0.088(95%CI:0.065-0.110), 0.041(95%CI:0.031-0.051), 0.055(95%CI:0.043-0.067) and 0.029(95%CI:0.003-0.056), respectively (Figure 3). Patients mainly using GC had the highest prevalence, and those using anti-TNF therapy had the lowest prevalence.
Figure 3: The prevalence of ARD patients after using anti-rheumatic drugs from the perspective of the main drugs. (A) GC, (B) bDMARDs, (C) csDMARDs, (D) anti-TNF therapy.

From the perspective of the primary drugs, the prevalences of SLE patients mainly using GC and csDMARDs were 0.101 (95% CI: 0.035-0.166) and 0.095 (95% CI: 0.041-0.149), respectively, using GC had a higher prevalence and using csDMARDs had a lower prevalence. The prevalence of vasculitis patients using GC was 0.081 (95% CI: 0.005-0.157), and using bDMARDs and csDMARDs were both 0.047 (95% CI: -0.021 to 0.114), respectively, using GC have the highest prevalence. The prevalence of AS patients using bDMARDs was 0.074 (95% CI: 0.039-0.108). Due to the small number of studies and the limitations of statistical methods, the prevalences of RA patients using bDMARDs and csDMARDs were both 0.028 (95% CI: 0.019-0.037). Besides, The prevalence of PsA patients using bDMARDs was 0.289 (95% CI: -0.099 to 0.677), suggesting the prevalence in PsA was not statistically significant (Figure p7).

3.4 Clinical outcomes of COVID-19 in autoimmune rheumatic diseases

A meta-analysis of 85 observational studies, including 167,554 patients with ARDs diagnosed with COVID-19, showed that the hospitalization rate due to COVID-19 was 0.402 (95% CI: 0.330-0.476) (Figure 4). Hospitalization rates of AS, PsA, CTD, SLE, RA, SSc and vasculitis were 0.095 (95% CI: 0.042-0.160), 0.148 (95% CI: 0.021-0.331), 0.364 (95% CI: 0.155-0.603), 0.325 (95% CI: 0.125-0.566), 0.321 (95% CI: 0.154-0.487), 0.535 (95% CI: 0.171-0.884) and 0.627 (95% CI: 0.576-0.678) (Figure p8). Notably, patients with vasculitis had the highest hospitalization rate, and those with AS had the lowest hospitalization rate. Heterogeneity was considerable overall ($I^2=99.8\%$) and subgroup analyses ($I^2=42.3\%-99.9\%$).
Figure 4: Clinical outcomes of COVID-19 in autoimmune rheumatic diseases. (A) Hospitalization rates. (B) Mortality. (C) ICU admission rate.

The ICU admission rate of COVID-19 patients with ARDs was 0.077 (95% CI: 0.051-0.107) (Figure 4). ICU admission rates of RA, SLE and CTD, PsA were 0.117 (95% CI: 0.066-0.168), 0.218 (95% CI: 0.099-0.361) and 0.054 (95% CI: 0.028-0.081), 0.046 (95% CI: 0.007-0.084) (Figure p9). The mortality due to COVID-19 in ARD patients was 0.073 (95% CI: 0.046-0.104) (Figure 4). Mortality rates of RA, SLE, CTD and vasculitis were 0.049 (95% CI: 0.025-0.079), 0.146 (95% CI: 0.051-0.241), 0.058 (95% CI: 0.016-0.120), and 0.224 (95% CI: 0.179-0.269). The mortality rates in AS, SSC, and gout were 0.000 (95% CI: 0.000-0.018), 0.007 (95% CI: 0.000-0.018), and 0.099 (95% CI: -0.138 to 0.336), which were all not statistically significant (Figure p10). SLE patients had the highest ICU admission rate, and vasculitis patients had the highest mortality. In contrast, PsA patients had the lowest ICU admission rate, and RA patients had the lowest mortality.

3.5 Impact of drugs on clinical outcomes

Considering the impact of treatment after infection with sars-cov-2 in patients with ARDs on clinical outcomes, we conducted a subgroup analysis. Without considering the proportion of patients using drugs, regression analysis showed that ARD patients using GC had a higher hospitalization rate of COVID-19 (regression coefficient: 0.484, 95% confidence interval: 0.146-0.822, P = 0.006), and using bDMARDs had a lower ICU admission rate of COVID-19 (regression coefficient: -0.156, 95% confidence interval: -0.260 - -0.051, P = 0.006). The clinical outcomes of ARD patients infected with COVID-19 who have used anti-rheumatic drugs are shown in Supplementary Material Figure p11 and Figure p12.
From the perspective of major drugs, the hospitalization rates of ARD patients using GC, bDMARDs, csDMARDs, and anti-TNF therapy were 0.703 (95% CI: 0.449-0.910), 0.216 (95% CI: 0.147-0.286), 0.607 (95% CI: 0.450-0.755) and 0.271 (95% CI: 0.132-0.409) (Figure 5). Interestingly, the hospitalization rates of GC and csDMARD patients were higher than the total rate, and patients with bDMARDs and anti-TNF therapy were lower hospitalization than total cases. However, regression analysis showed that regardless of whether the patients mainly used GC or bDMARDs or csDMARDs or anti-TNF treatment, these treatment regimens had no effect on the hospitalization rate of patients with COVID-19 (Figure p13).

Figure 5: The effect of anti-rheumatic drugs on the clinical outcomes of autoimmune rheumatic diseases from the perspective of the main drugs. (1) The hospitalization rates of ARD patients after using anti-rheumatic drugs. (A) GC, (B) bDMARDs, (C) csDMARDs, (D) anti-TNF therapy. (2) The ICU admission rates of ARD patients after using anti-rheumatic drugs. (E) GC, (F) bDMARDs, (G) csDMARDs, (H) anti-TNF therapy. (3) The mortality of ARD patients after using anti-rheumatic drugs. (I) GC, (J) bDMARDs, (K) csDMARDs, (L) anti-TNF therapy.

From the perspective of major drugs, the ICU admission rates of ARD patients using GC, bDMARDs, csDMARDs, and anti-TNF therapy were 0.094 (95% CI: 0.046-0.152), 0.010 (95% CI: 0.000-0.037), 0.055 (95% CI: 0.037-0.075) and 0.022 (95% CI: 0.000-0.081) (Figure 5). The ICU admission rates of patients using bDMARDs, csDMARDs, and anti-TNF therapy was lower than the total ICU rate. The mortalities in ARD patients mainly using GC, bDMARDs, csDMARDs, and anti-TNF therapy were 0.070 (95% CI: 0.033-0.114), 0.039 (95% CI: 0.007-0.087), 0.074 (95% CI: 0.041-0.114) and 0.068 (95% CI: 0.034-0.111) (Figure 5). Regression analysis showed that the main use of major drugs was not associated with the ICU admission and mortality (Figure p14 and p15).

Since the effect of drugs on clinical outcomes is different in different diseases, we performed a more detailed stratification. We only selected the studies in which patients using a certain drug exceeded 50% of the total cases. In SLE, the hospitalization rates of patients mainly using GC and csDMARDs were 0.670 (95% CI: 0.406-0.933) and 0.575 (95% CI: 0.434-0.716). The mortality due to COVID-19 in these patients mainly using GC was 0.055 (95% CI: 0.045-0.065). The hospitalization rate of SLE patients using GC was higher than those using DMARDs. The hospitalization rates of RA patients mainly using GC and csDMARDs were both 0.563 (95% CI: 0.192-0.934). The mortality of these patients mainly using GC and csDMARDs were 0.077 (95% CI: 0.035-0.120) and 0.059 (95% CI: 0.022-0.109), respectively, the mortality of RA patients using GC was higher than those of csDMARDs. The hospitalization rates of CTD patients mainly using csDMARDs was 0.466 (95% CI: 0.007-0.974) (Figure p16).

4 Discussion
COVID-19, a pandemic respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), could lead to autoimmune and autoinflammatory diseases. Patients with ARD are associated with immune dysfunction, and often treated with immunosuppressive drugs, making them more susceptible to infection. However, our meta-analysis showed relatively little difference between the prevalence of SARS-CoV-2 infections in ARD patients (0.061) and the global prevalence of SARS-CoV-2 infections (0.077) and the prevalence of ARD patients even lower.

Among ARDs, the prevalence of PsA was the highest. The mucosal immune system is the largest constituent of the immune system, protecting against infectious threats at the primary internal surface. SARS-CoV-2 infection occurs predominantly at the respiratory mucosal surfaces, and decreased mucosal immunity must be beneficial for virus infection. The highest prevalence of PsA with red patches of skin topped with silvery scales suggests that PsA patients may have some defects in mucosal immunity, which is more prone to COVID-19 infections.

Vasculitis patients infected with COVID-19 had the highest mortality and hospitalization rates. COVID-19 made a life-threatening escalation from Th2 immune response to type 3 hypersensitivity with the subsequent deposition of antigen-antibody complexes, particularly inside the walls of blood vessels, to such an extent as to generate a systemic vasculitis in the context of complex immune disease. According to Gell and Coombs classification, type 3 hypersensitivity occurs when excess or slight excess of soluble antigen leads to the accumulation of immune complexes, and the innate immune system cannot fully clear from the circulation. These antigen-antibody complexes precipitate in tissues, especially in blood vessels, and induce a severe inflammatory state through the action of complement anaphylaxis toxins (C3a and C5a), which in turn stimulates the release of histamine by mast cells and the recruitment of phagocytes. Histopathologically, the result of this process in the vascular wall is acute necrotizing vasculitis, accompanied by neutrophil infiltration, karyorrhexis, and fibrinoid necrosis. Platelet aggregation is associated with hypercoagulability and thrombosis described during COVID-19. To prevent C3 activation, anaphylatoxin in this process through specific inhibitors, like compstatin-based AMY-101, provides effective therapeutic results.

Among the ARD patients with COVID-19 infection, SLE patients had the highest ICU admission rate. They had higher rates of hypertension, diabetes mellitus, obesity, and sedentary lifestyle, which were significant risk factors for hospitalization and mortality in COVID-19. Besides, data from the C19-GRA registry suggested that long-term use of GC was associated with poorer outcomes. GC is frequently used to treat SLE, potentially making these patients vulnerable to a more severe COVID-19 disease course.

The influence of drugs on the COVID-19 infection rate of patients with ARDs is one of the biggest concerns of medical care. We were surprised that the prevalence of SARS-CoV-2 infection in patients with ARDs using GC or csDMARDs or bDMARDs was lower than the global prevalence of COVID-19 infection, indicating that these treatments did not necessarily increase this infection rate. Among all ARD patients infected with COVID-19, patients mainly treated with GC had the highest prevalence. GCs have strong anti-inflammatory effects and induce the apoptosis of lymphocytes. These immune inhibitory effects prevent lethality by excessive inflammation, but simultaneously increase the susceptibility to infection.

Compared with the clinical outcomes of all COVID-19 patients with ARDs treated with several therapies, we found patients using bDMARDs or anti-TNF therapy had lower hospitalization rates, ICU admission rates, and mortality. Besides, bDMARD monotherapy was associated with a lower odds of hospitalization regression coefficient, and largely driven by anti-TNF therapies. Mechanistic studies have suggested that upregulated TNF-α may lead to inflammatory cell death, aberrant germinal center formation, and less robust humoral immune responses in fatal COVID-19, providing a potential biologic rationale for the protective effect of TNF inhibitors. In vitro studies have demonstrated that IL-6 and TNF-α have been regulated by the recombinant protein S of SARS-CoV 2002, indicating that TNF-α inhibitors or the IL-6 inhibitors could decrease the cytokine storm in COVID-19 patients. Anti-TNF therapy has been proposed as a potential treatment for the hyperinflammatory phase of severe COVID-19. We found that GC monotherapy was associated with higher odds of the hospitalization regression coeffi-
cient. Patients using csDMARDs had higher hospitalization rates, ICU admission rates, and mortality, but patients using GC had a higher hospitalization rate, higher ICU admission rate, and lower mortality. In the included studies, the csDMARDs drug used by most patients was hydroxychloroquine (HCQ). The World Health Organization SOLIDARITY trial reported no clinical benefit from HCQ for hospitalized patients with COVID-19\textsuperscript{34}. Abundant evidence from numerous RCTs revealed HCQ does not prevent SARS-CoV-2 infection or improve outcomes in mild, moderate, or severe COVID-19\textsuperscript{35}. HCQ use may even be associated with lower survival\textsuperscript{36}. Therefore, csDMARDs, especially HCQ, are not suggested in the treatment of COVID-19\textsuperscript{25}. Corticosteroids downregulate the release of cytokines, reducing the damage caused by cytokine storms\textsuperscript{25}. GC is effective in patients with severe COVID-19-related respiratory failure, but may not have a benefit in patients with early or mild disease. The Infectious Diseases Society of America (IDSA) guidelines recommend dexamethasone in patients with COVID-19, hypoxemia, and/or critical illness\textsuperscript{37}.

The effects of drugs used on clinical outcomes varied across ARDs. SARS-CoV-2-infected SLE patients with GC treatment had the highest hospitalization rates. sGC use (prednisone > 5 mg/day) in SLE is a risk factor for severe COVID-19 requiring hospitalization\textsuperscript{38}. SARS-CoV-2-infected RA patients with csDMARDs or GC treatment had higher hospitalization rates, and those using GC had the highest mortality. Continuous GC users, on the one hand, inhibit the immune response and delay the clearance of the pathogen. They suppress the host inflammatory response, which in the case of viral infections of the respiratory tract is the primary responsible for lung damage and ARDs\textsuperscript{39}. Clinic evidence point to a predominantly negative effect of continuous corticosteroids in managing this type of infection\textsuperscript{39}.

Our study had several limitations. Meta-analyses of studies regarding the prevalence and clinical outcomes of COVID-19 had considerable heterogeneities. The cause of this heterogeneity could be explained by the differences in study size, including different diseases and study locations. Thus, we performed a subgroup analysis to assess the prevalence and clinical outcome of COVID-19 for each disease and performed a regression. Second, we could not obtain the specific drug use of each patient, and most patients used multi-drug combination therapy, which led to biases in our analysis of the impact of drugs on the prevalence of COVID-19 and clinical outcomes. Third, the sensitivity of RT-PCR for SARS-CoV-2 from the nasopharyngeal swab is roughly 70\%\textsuperscript{40,41}. Fourth, only published studies were included in the meta-analysis, and unpublished articles were excluded; publication and study selection bias may have affected our results. Therefore, further studies are needed to verify our results.

5 Conclusion

In conclusion, although our meta-analysis showed little difference between the prevalence of SARS-CoV-2 infections in patients with ARDs and the global prevalence of SARS-CoV-2 infections, the prevalence of COVID-19 in PsA was significantly higher than the global prevalence. The use of DMARDs could reduce the risk of being infected with COVID-19, but the use of GC increased this risk. csDMARDs were associated with disease severity in COVID-19. bDMARDs, especially anti-TNF, were associated with a reduced risk of severe disease. GC is effective in patients with severe COVID-19-related respiratory failure but may not have a benefit in patients with early or mild disease.

6 Supplementary Information

The data underlying this article are available in the article and in its Supplementary material: https://kdocs.cn/l/crOQDUk0Owig.

7 Acknowledgements

We would like to thank all the participants involved in this study. Thanks to the researchers for sharing the original clinical cohort data, which makes this meta-analysis possible. Special thanks to the careful efforts made by reviewers and editors to improve articles.

8 Abbreviations

DMARDs Disease-modifying anti-rheumatic drugs
ARD Atoimmune rheumatic diseases
COVID-19 Coronavirus Disease 2019
GC Glucocorticoids
BDMARDs Biological Disease-modifying anti-rheumatic drugs
CSDMARDs conventional synthetic Disease-modifying anti-rheumatic drugs
Anti-TNF Anti-Tumor Necrosis Factor
ICU Intensive Care Units
Sars-cov-2 Syndrome coronavirus 2
WHO World Health Organisation
PRISMA Preferred Reporting Items for Systematic Reviews
PROSPERO Prospective Register of Systematic Reviews
MeSH Medical Subject Headings
GRADE Grades of Recommendation, Assessment, Development, and Evaluation
NOS Newcastle–Ottawa Quality Assessment Scale
RA Rheumatoid Arthritis
SLE Systemic Lupus Erythematosus
AS Ankylosing Spondylitis
CTD Connective Tissue Disease
PsA Psoriatic Arthritis
SSc Systemic Sclerosis
IL-6 Interleukin-6
TNF-α Tumor Necrosis Factor-alpha
HCQ Hydroxychloroquine
IDSA The Infectious Diseases Society of America

9 Author contributions
QYS and SXZ contributed to the work equally and should be regarded as co-first authors. QYS and SXZ designed the study. SXZ, TC and JL searched the literature. QYS, HYZ and JL selected the data. QYS, SXZ, BRZ and YZ analyzed the data. QYS and SXZ wrote the manuscript. CG and CHW* contributed to manuscript revision, read, and approved the submitted version.

10 Funding Source
This work was supported by the National Science Foundation of China (No.82001740), the National Social Science Fund of China (21BTQ050), the National Natural Science Foundation of China (No. 81971543), Natural Science Foundation of China (No. 81471618), Key Research and Development (R&D) Projects of Shanxi Province (201803D31119), and Four “Batches” Innovation Project of Invigorating Medical through Science and Technology of Shanxi Province(NO 2022XM05).

Data of global prevalence of SARS-CoV-2 infections were obtained from WHO Coronavirus Disease(COVID-19)Dashboard(Data last updated:2023/3/20,9:40am CET).
11 Availability of data and materials
The datasets supporting the conclusions of this article are included within the article and Supplementary material: https://kdocs.cn/l/crOQDUk0Owig.

12 Declarations
Ethics approval and consent to participate
Not Applicable.
Consent for publication
Not Applicable.
Competing interests
The authors declare they have no competing interests.

13 Reference


38. Chen TH, Cheng HT, Yeh CT. Epidemiology changes in peptic ulcer diseases 18 years apart explored from the genetic aspects of Helicobacter pylori. Transl Res. 2021;232:115-120.


null