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COVID-19 in Autoimmune Rheumatic Diseases: Lessons Learned and Emerging Risk Stratification Approaches

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ABSTRACT

The coronavirus disease (COVID-19) pandemic has posed unique challenges for individuals with autoimmune and autoinflammatory rheumatic diseases (AARDs), raising critical concerns about susceptibility, disease severity, treatment outcomes, and vaccine response. This mini-review draws on data from a national Greek cohort and global studies. It summarizes current evidence on disease course and risk stratification in AARD patients with COVID-19. Most patients experienced mild disease; however, those with advanced age, interstitial lung disease (ILD), and treatment with rituximab, mycophenolate mofetil, or corticosteroids demonstrated increased risk for hospitalization and mortality. In contrast, biologics targeting pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin 6 (IL-6) were not associated with worse outcomes and, in some analyses, correlated with reduced hospitalization rates. Notably, long-term sequelae, particularly persistent fatigue, emerged as a common burden, underscoring the overlap between post-viral symptoms and underlying autoimmune dysfunction. The serologic response to SARS-CoV-2 infection and vaccination was attenuated in some AARD subgroups, especially in patients receiving B-cell depleting therapies, emphasizing the need for tailored immunization and preventive strategies. Additionally, anosmia was inversely associated with hospitalization and may represent a biomarker of milder disease and more effective early immune responses. This review highlights key predictors of adverse outcomes and discusses implications for immunosuppression management, vaccination timing, and long-term care. As the pandemic evolves, identifying high-risk AARD patients and implementing precision prevention and treatment strategies remain vital priorities.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has introduced profound challenges to healthcare systems worldwide, particularly in the management of immunocompromised populations[1].

Individuals with autoimmune and autoinflammatory rheumatic diseases (AARDs) form a distinct clinical subgroup. Their underlying immune dysregulation and frequent use of immunosuppressive therapies make them particularly vulnerable. Since the start of the pandemic, there have been concerns about their increased susceptibility to SARS-CoV-2 infection, more severe disease, and weaker immune responses to both infection and vaccination[1-3].

A growing body of observational studies and international registries has sought to delineate the outcomes of COVID-19 in patients with AARDs, generating a complex and often heterogeneous picture. While some reports suggested an elevated risk of hospitalization and

death[3,4], others have pointed to more favorable outcomes, particularly among younger patients or those on specific biologic therapies[5,6]. Importantly, emerging evidence indicates that not all immunosuppressive agents confer equal risk, with B-cell depleting therapies and systemic corticosteroids consistently associated with poorer prognoses[2,7], whereas agents targeting cytokines such as tumor necrosis factor (TNF) and interleukin 6 (IL-6) may not increase—and may even attenuate—disease severity[6].

The study by Bakasis et al.[1] contributes valuable data from Greece, presenting clinical outcomes from a real-world cohort of AARD patients infected with SARS-CoV-2. The findings from this study offer an opportunity to contextualize national data within the broader framework of international literature and help identify consistent risk factors such as age, pulmonary comorbidities (e.g., interstitial lung disease), and specific immunomodulatory regimens[8,9].

Furthermore, the pandemic has underscored the complex interplay between viral infection, immune dysregulation, and long-term sequelae such as post-COVID fatigue. Patients with rheumatic diseases may be particularly vulnerable to prolonged immune perturbations and symptom persistence, as evidenced by several prospective studies[10,11]. The attenuated antibody responses observed in immunosuppressed patients[11,12], especially those treated with rituximab or mycophenolate, further complicate management and necessitate tailored preventive strategies[13].

This review aims to critically examine the current evidence on COVID-19 outcomes in patients with AARDs, focusing on susceptibility, clinical course, treatment-related risks, and post-acute sequelae. Drawing on data from both the Greek cohort and international studies, it highlights key predictors of severe disease, immunologic response variability, and implications for clinical management. Through this synthesis, we seek to clarify patient subgroups at heightened risk, inform vaccination and treatment strategies, and identify knowledge gaps to be addressed in future research.

Clinical Course of COVID-19 in AARD Patients

The clinical presentation and outcomes of COVID-19 in patients with AARDs have been explored across national cohorts and large international registries, revealing both convergent and context-dependent findings.

In the Greek cohort by Bakasis et al.[1], the majority of 77 patients experienced a mild course, with hospitalization required in 23.3% of the patients and mortality reported in only 1.3%. Fatigue, low-grade fever, and upper respiratory symptoms were the most common clinical manifestations. However, while valuable as a real-world snapshot, the small sample size and lack of multivariable analyses limit the ability to draw definitive conclusions about risk stratification.

By contrast, the COVID-19 Global Rheumatology Alliance (C19-GRA) registry, encompassing over 6,000 patients across diverse regions, reported higher rates of hospitalization (~46%) and mortality (~9%)[2, 3]. Similarly, the French RMD COVID-19 cohort (FAI2R) of 694 patients found a hospitalization rate of 37% and mortality of 8.3%[4]. Both registries offer more robust estimates due to larger sample sizes, multicenter designs, and adjustment for key confounders, such as age, comorbidities, and immunosuppressive treatment.

These differences underscore regional and methodological variability. For example, the relatively younger mean age (49.5 years) and lower use of high-risk immunosuppressants in the Greek cohort may partly explain its favorable outcomes. The FAI2R and C19-GRA registries[2,4], in contrast, included older patients with more comorbidities, a higher proportion of systemic diseases and greater use of corticosteroids or rituximab—factors associated with worse prognosis.

Despite such disparities, common themes emerge across cohorts: advancing age, comorbidities (especially interstitial lung disease), and use of certain immunosuppressive agents consistently predict poorer outcomes, while cytokine-targeting biologics (e.g., TNF inhibitors) appear relatively safe.

Thus, while the Greek study provides context-specific insights, particularly regarding early infection waves and local treatment practices, its findings are best interpreted alongside the larger, more generalizable datasets from international consortia. Synthesizing these sources allows for a more balanced and comprehensive risk stratification framework for AARD patients affected by COVID-19.

Impact of Immunosuppressive Therapy on COVID-19 Outcomes

One of the central concerns in the management of AARDs during the COVID-19 pandemic has been the potential impact of immunosuppressive therapy on infection severity and clinical outcomes. In the Greek cohort by Bakasis et al.[1], corticosteroids, mycophenolate mofetil, and rituximab were more frequently used among hospitalized and critically ill patients. While this observation aligns with international datasets, it is important to interpret these associations within the methodological context of the studies.

In the C19-GRA registry—a large multinational physician-reported database including over 6,000 patients—use of prednisone at doses ≥10 mg/day was independently associated with increased odds of hospitalization (OR 2.05) and mortality (OR 2.14)[2].

Importantly, this registry controlled for disease activity and comorbidities, strengthening the inference that corticosteroids per se contribute to adverse outcomes. In contrast, smaller observational studies like the Greek study (n=77) lacked formal multivariate adjustment for confounding variables such as disease activity, concomitant immunosuppression, and vaccination status, which may limit the generalizability of their findings.

Rituximab, a B-cell depleting agent, has consistently emerged as a high-risk therapy. A cohort study by Avouac et al. (FAI2R Consortium) involving 109 patients treated with rituximab demonstrated a significantly higher mortality rate (11.9%) compared to matched AARD patients not receiving rituximab[7]. Notably, this French multicenter cohort employed multivariable models adjusting for age, sex, comorbidities, and disease activity, enhancing internal validity. However, the population included primarily Western European patients, potentially limiting external applicability to other regions with different healthcare infrastructure or SARS-CoV-2 variant predominance.

In contrast, anti-TNF and IL-6 inhibitors were not associated with worse outcomes across multiple datasets. The C19-GRA registry[2] and the Spanish BIOBADASER cohort[14], which included biologics and targeted synthetic agents, both indicated that these agents did not increase the risk of hospitalization or death. These findings suggest a possible immunomodulatory role that mitigates cytokine storm without impairing antiviral responses. Nonetheless, most evidence stems from observational data prone to indication bias (e.g., TNF inhibitors often used in less systemically ill patients), and randomized controlled trials in this context are lacking.

Importantly, only a few studies—such as Deepak et al.[15]—integrated immunologic endpoints such as antibody titers post-infection or vaccination, providing mechanistic insights that support clinical findings. Their analysis, though limited by its preprint status and geographic concentration in the U.S., highlights the functional implications of immunosuppressive regimens on SARS-CoV-2 immunity.

Comparison across major registries confirms the heightened risk associated with corticosteroids and B-cell depleting therapies. For instance, both the C19-GRA[2] and FAI2R[4] registries found rituximab to be a strong predictor of mortality, with similar adjusted odds ratios despite demographic differences. The BIOBADASER registry supported these findings and further demonstrated that anti-TNF agents are not only safe but may confer a protective effect—particularly in patients with inflammatory arthritis[14]. These consistent patterns across diverse populations reinforce the need to prioritize patients on rituximab or mycophenolate for enhanced preventive strategies.

Table 1 summarizes data of the cohort studies on COVID-19 outcomes in AARD patients.

Figure 1 illustrates the hospitalization odds ratios by therapy in patients with rheumatic disease and COVID-19 based on the study by Strangfeld et al. [2].

Bar chart displaying adjusted odds ratios (ORs) for COVID-19-related hospitalization among patients

Table 1. Summary of Cohort Studies on COVID-19 Outcomes in Patients with Autoimmune and Autoinflammatory Rheumatic Diseases (AARD)

Study / Cohort	Country / Region	N (Patients)	Mean / Median Age	Hospitalization Rate	Mortality Rate	Common Comorbidities	Key Immunosuppressive Treatments
AARD Cohort (Bakasis et al. 2021)	Greece	77	Mean: 49.5 ± 16.8 yrs	23.3%	1.3%	Lung disease (14.2%), Hypothyroidism (16.7%), Dyslipidemia (12.5%)	Corticosteroids (33.8%), Methotrexate (22.1%), Mycophenolate Mofetil (20.8%), Rituximab (5.2%), Anti-TNF agents (19.5%), Hydroxychloroquine (20.8%)
COVID-19 Global Rheumatology Alliance physician-reported registry (Strangfeld et al., 2021)	Global (Europe: 62.1%, North America: 29.6%, others)	3,729	Mean: 57 years	49.0% (1739/3546)	10.5% (390/3729)	Hypertension (35.3%), Chronic lung disease (19.4%), Obesity (16.1%), Diabetes (13.6%), CVD (11.9%), CKD (7.0%)	Glucocorticoids (any) (33%), Glucocorticoids ≥10 mg/day (8.5%), csDMARDs (30%), bDMARDs (33%), TNF inhibitors (19.6%), Rituximab (4.3%), Tocilizumab (2.5%), tsDMARDs (JAKi) (4.6%), Sulfasalazine (2.5%), Other immunosuppressants (AZA, MMF, CYC) (4.5%), No DMARDs (10%)

Study / Cohort	Country / Region	N (Patients)	Mean / Median Age	Hospitalization Rate	Mortality Rate	Common Comorbidities	Key Immunosuppressive Treatments
COVID-19 Global Rheumatology Alliance (C19-GRA) (Gianfrancesco et al. 2020)	Global (over 40 countries, mostly USA, Spain, Italy))	600	Median: 56 years	46%	9%	Hypertension (33%), Lung disease (21%), Diabetes (12%), Cardiovascular disease (11%)	Glucocorticoids (any) (39%), Glucocorticoids ≥10 mg/day (18%), csDMARDs (40%), bDMARDs (42%), TNF inhibitors (25%), Rituximab (7%), Tocilizumab (3%), tsDMARDs (JAKi) (5%), Sulfasalazine (3%), Other immunosuppressants (5%), No DMARDs (11%)
French RMD COVID-19 Cohort (FAI2R) (FAI2R /SFR/SNFMI/ SOFREMIP/CRI/IMIDIATE consortium and contributors, 2021)	France	694	Mean: 56.1 years	37% (256/694) Moderate: 24% Severe: 13%	8.3% overall22.6% in hospitalized subgroup	Hypertension (26.3%), Obesity (21%), Respiratory disease (14.3%), Cardiovascular disease (12.3%), Diabetes (9%), Chronic renal failure (6.1%)	Corticosteroids (any dose) (31.1%), Prednisone ≥10 mg/day (10.5%), Methotrexate (36.4%), Anti-TNF (29.2%), Rituximab (4.9%), IL-6 inhibitors (3.8%), JAK inhibitors (3.0%), Mycophenolate mofetil (2.3%), Hydroxychloroquine (8.2%), Colchicine (3.5%), NSAIDs (10.5%)
French RMD COVID-19 Cohort (Avouac et al., 2021)	France	1,090 total; 63 treated with rituximab	Mean age: 55.2 years (Rituximab group: 59.1 years)	Not explicitly stated; 424/1090 hospitalized; higher rate in rituximab group	Rituximab group: 13/63 (21%); non-rituximab group: 76/1027 (7%)	Hypertension (25%), Cardiovascular disease (12%), Diabetes (10%), Interstitial lung disease (3%), Obesity	Rituximab (main focus), often combined with corticosteroids (54%), Methotrexate (33%), Leflunomide (8%), Hydroxychloroquine (5%)
BIOBADASER Registry (Sánchez-Piedra et al., 2020)	Spain	41	Mean: 59.4 years	68.3% (28/41)	7.3% (3/41)	Hypertension (36.6%), Smoking (34.2%), Obesity (BMI mean 27.7 kg/m^2), Diabetes (9.8%)	TNF inhibitors (43.9%), JAK inhibitors (17.1%), IL-6 inhibitors (12.2%), Rituximab (7.3%), Anakinra, Abatacept; csDMARDs: Methotrexate (41.5%), Hydroxychloroquine (9.8%); Glucocorticoids (83.3%)

AARD – Autoimmune and Autoinflammatory Rheumatic Diseases; **AZA** – Azathioprine; **bDMARDs** – Biologic Disease-Modifying Antirheumatic Drugs; **BIOBADASER** – Biologic Therapy Registry of the Spanish Society of Rheumatology; **C19-GRA** – COVID-19 Global Rheumatology Alliance; **CKD** – Chronic Kidney Disease; **csDMARDs** – Conventional Synthetic Disease-Modifying Antirheumatic Drugs; **CVD** – Cardiovascular Disease; **CYC** – Cyclophosphamide; **DMARDs** – Disease-Modifying Antirheumatic Drugs; **FAI2R** – French RMD COVID-19 Cohort (includes multiple French rheumatology societies); **IL-6** – Interleukin-6; **JAKi** – Janus Kinase Inhibitors; **MMF** – Mycophenolate Mofetil; **NSAIDs** – Nonsteroidal Anti-inflammatory Drugs; **RMD** – Rheumatic and Musculoskeletal Diseases; **SFR** – Société Française de Rhumatologie (French Society for Rheumatology); **SNFMI** – Société Nationale Française de Médecine Interne (French National Society of Internal Medicine); **SOFREMIP** – Société Française de Rhumatologie Pédiatrique (French Society of Pediatric Rheumatology); **TNF** – Tumor Necrosis Factor; **tsDMARDs** – Targeted Synthetic Disease-Modifying Antirheumatic Drugs

with rheumatic diseases, stratified by therapy type. Data are derived from the COVID-19 Global Rheumatology Alliance registry. Methotrexate monotherapy was used as the reference group (OR = 1.0). Therapies such as anti-TNF agents and NSAIDs were associated with reduced hospitalization risk (OR < 1), while glucocorticoids >10 mg/day and absence of DMARD therapy were linked to increased odds of hospitalization. These findings underscore the differential impact of immunomodulatory treatments on COVID-19 outcomes in rheumatic disease populations.

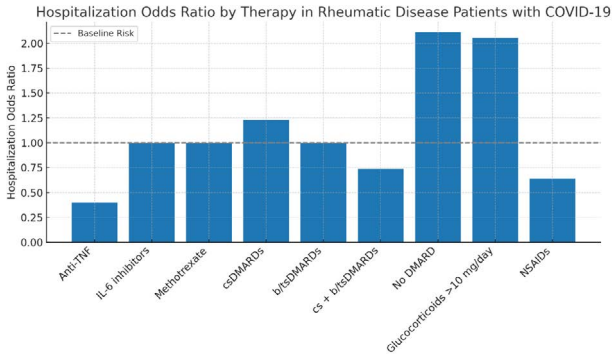


Figure 1. Hospitalization Odds Ratios by Therapy in Patients with Rheumatic Disease and COVID-19

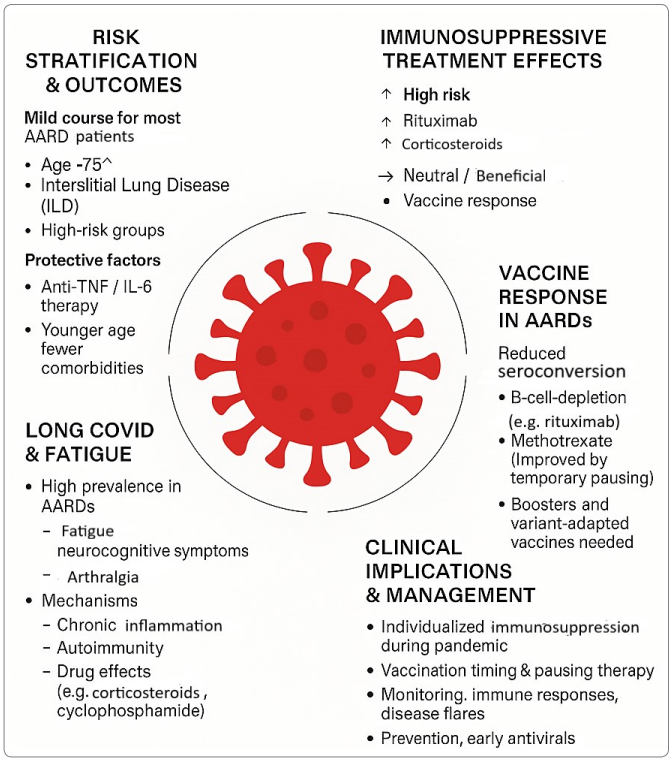
Risk Stratification: Role of Age, Comorbidities, and Lung Disease

Risk stratification has become essential in the management of COVID-19 among patients with AARDs, given the marked heterogeneity in clinical outcomes across different subgroups. Among the most consistently identified predictors of severe disease are advancing age and the presence of pre-existing pulmonary involvement, particularly interstitial lung disease (ILD).

In the Greek study by Bakasis et al.[1], older age emerged as an independent predictor of hospitalization and disease severity. This finding reflects broader trends observed across all major COVID-19 cohorts, where aging has been associated with immune senescence, increased comorbidity burden, and diminished capacity to mount effective antiviral responses. In the C19-GRA registry, age was the strongest and most consistent predictor of mortality in patients with rheumatic diseases, reinforcing its central role in outcome prediction[3]. The disproportionate impact of COVID-19 on older AARD patients may be attributed not only to comorbid burden but also to immunosenescence—a decline in adaptive immune capacity with age—which impairs viral clearance and may perpetuate inflammatory responses[16].

Pre-existing lung disease, and particularly ILD, has also been recognized as a major determinant of poor prognosis in COVID-19. Bakasis et al. reported that underlying lung disease conferred a significantly increased risk of hospitalization, with an odds ratio of 6.43[1]. This aligns with findings from a Spanish cohort of 123 AARD patients with COVID-19, in which pulmonary comorbidity was significantly associated with hospital admission ($p < 0.01$)[8]. ILD is particularly prevalent in conditions such as systemic sclerosis, which has been identified as a high-risk subgroup for severe COVID-19 outcomes[9].

The increased vulnerability of patients with ILD is likely multifactorial. It may stem from a combination of impaired pulmonary reserve, ongoing fibrotic remodeling,



and a predisposition to exaggerated inflammatory responses in the setting of viral pneumonia. Additionally, many of these patients are treated with agents such as mycophenolate mofetil or rituximab—both of which have been independently associated with adverse outcomes in COVID-19—thus compounding their risk profile[1,7].

Beyond rheumatic disease populations, patients with idiopathic pulmonary fibrosis (IPF)—a condition pathophysiologically analogous to fibrotic ILD in systemic sclerosis—have shown poor outcomes in COVID-19, with significantly increased mortality and oxygen requirements[17].

Furthermore, systemic lupus erythematosus (SLE) patients, according to international data, represent a particularly high-risk AARD subgroup. Multinational registry data highlight that individuals with SLE tend to experience more severe COVID-19, with disease activity, comorbidities, and immunosuppression contributing to outcomes[18].Together, these findings underscore the importance of stratifying AARD patients based on age, pulmonary status, and immunosuppressive regimens when assessing their risk for severe COVID-19. Identifying high-risk individuals allows for targeted preventive strategies, including prioritization for vaccination, pre-exposure prophylaxis, and early initiation of antiviral therapy.

While advancing age is a well-established predictor of severe COVID-19 outcomes in the general population, its role may be further amplified in patients with AARDs due to the combined burden of immunosenescence and

Table 2. Risk Stratification of AARD Patients with COVID-19 Based on Age, Comorbidities, Disease Activity, and Immunosuppressive Therapy.

Risk Category	Patient Characteristics
Low Risk	- Age < 60 - No comorbidities - Mild/moderate AARD activity - On no immunosuppression or only conventional DMARDs (e.g., methotrexate, hydroxychloroquine)
Moderate Risk	- Age 60–75 OR - Presence of controlled comorbidities (e.g., hypertension) OR - Treated with low-dose prednisone (<10 mg/day) or anti-TNF/IL-6 biologics
High Risk	- Age > 75 OR - Active ILD or multiple comorbidities (e.g., diabetes, CKD) OR - Use of rituximab, mycophenolate, cyclophosphamide, or high-dose steroids ≥10 mg/day

AARD: Autoimmune and Autoinflammatory Rheumatic Disease; DMARDs: Disease-Modifying Anti-Rheumatic Drugs; TNF: Tumor Necrosis Factor; IL-6: Interleukin-6; ILD: Interstitial Lung Disease; CKD: Chronic Kidney Disease

disease-specific immune dysregulation. However, direct comparative analyses between age-matched AARD and non-AARD populations remain limited. Preliminary evidence from large registries such as the C19-GRA suggests that age retains its strong predictive value within AARD populations[2], but whether its relative risk is heightened compared to age-matched controls without autoimmune disease is not definitively established. Some studies have proposed that the compounded effect of aging and chronic immunosuppression may synergistically impair antiviral responses, potentially intensifying age-related vulnerability in AARDs[16,17]. Future comparative studies are needed to determine whether age acts merely as a parallel risk factor or as a disease-modifying amplifier in this specific population.

Table 2 summarizes the risk Stratification of AARD patients with COVID-19 based on age, comorbidities, disease activity, and immunosuppressive therapy.

Disease-Specific Risk Profiles in AARDs: Rheumatoid Arthritis, Psoriatic Arthritis, and Beyond

Patients with rheumatoid arthritis (RA) appear to face a modestly elevated risk for SARS-CoV-2 infection, hospitalization, ICU admission, and mortality compared to the general population, though not consistently for severe disease per se. A recent meta-analysis across 62 studies reported pooled prevalence rates of COVID-19 infection (11%), hospitalization (29%), ICU admission (10%), severe disease (18%), and mortality (8%) among RA patients, with odds ratios indicating significantly higher infection risk (OR ≈ 1.045), hospitalization (OR ≈ 1.32), ICU admission (OR ≈ 1.50), and death (OR ≈ 1.38) compared to non-RA individuals[19]. Importantly, while infection and adverse outcomes are elevated, RA was not universally associated with worse severe disease across all analyses[19]. Risk factors contributing to poorer outcomes in RA include high-dose glucocorticoids, rituximab, JAK inhibitors, interstitial lung disease, and comorbidities such as cardiovascular disease[20,21].

In contrast, individuals with psoriatic arthritis (PsA) and psoriasis appear to experience COVID-19 outcomes similar to the general population. In one prospective cohort[22], approximately 81% of PsA or psoriasis patients who contracted COVID-19 had mild disease, with hospitalization and mortality rates comparable to New York City's broader outbreak experience; severe outcomes were associated mainly with comorbidities such as hypertension and high BMI, not PsA itself. Another study investigating PsA progression and vaccination during COVID-19 found no clear signal of increased disease severity or worsening due to the infection, reinforcing the view of PsA as lower-risk in this context[23].

Together, these data underscore the heterogeneous nature of AARDs in the context of COVID-19: RA patients often display higher vulnerability to infection and worse outcomes, linked to both disease-specific immune dysregulation and treatments, while PsA patients generally fare better, with risk tied more to comorbidities than disease pathology. Broad categorization of AARDs risks obscuring these differences. A disease-specific lens—considering immunologic pathophysiology, therapeutic regimens, and comorbidity profiles—provides greater clinical relevance and precision in interpreting COVID-19 risks across AARD subgroups.

Post-COVID Fatigue and Long-Term Immune Dysregulation in AARDs

As part of a comprehensive risk stratification framework for AARD patients affected by COVID-19, it is essential to consider not only acute outcomes but also the long-term sequelae that influence functional status and ongoing care needs. Post-COVID fatigue, a prominent component of long COVID, represents an additional layer of vulnerability in this population and requires targeted management strategies.

While much attention has focused on the acute phase of COVID-19 in patients with AARDs, increasing evidence highlights the significance of persistent symptoms and immune dysfunction following recovery. Among these, fatigue has emerged as one of the most frequently reported and debilitating sequelae. In the study by Bakasis et al.[1], fatigue was reported by 58.4% of patients, with a higher prevalence among those with systemic autoimmune rather than autoinflammatory conditions.

Post-COVID fatigue has been recognized as a core feature of Long COVID and is believed to arise from a complex interplay of sustained immune activation, altered cytokine signaling, and possibly autoimmune mechanisms. Elevated levels of pro-inflammatory cytokines, such as IL-6 and tumor necrosis factor-alpha (TNF-α), along

with evidence of T-cell exhaustion, have been reported in individuals suffering from persistent fatigue months after mild or moderate SARS-CoV-2 infection[11,24]. Such immunologic alterations are especially relevant in patients with AARDs, who already possess a baseline state of immune dysregulation and may be more susceptible to exacerbated or prolonged inflammatory responses.

These theoretical mechanisms are supported by clinical findings in prospective studies. For instance, Marques et al. followed patients with AARDs for six months after SARS-CoV-2 infection and observed persistent fatigue and psychological distress, often accompanied by fluctuations in underlying disease activity[10]. This suggests a bidirectional relationship between post-viral immune phenomena and rheumatic disease flares, possibly mediated by overlapping immunological pathways. The overlap between post-COVID fatigue and autoimmune symptomatology, including myalgias, neurocognitive dysfunction, and mood disturbances, raises the possibility that Long COVID may amplify or unmask subclinical autoimmunity in predisposed individuals.

AARD patients require long-term follow-up after SARS-CoV-2 infection. Monitoring should focus on detecting disease flares, as well as managing fatigue and other signs of ongoing immune dysregulation.Tailored rehabilitation strategies, psychological support, and close immunologic follow-up may be required to mitigate the functional burden of post-COVID sequelae in this vulnerable group.

In a recent systematic review and meta-analysis, the authors found a higher prevalence of Long COVID among patients with AARDs compared with the general population. Furthermore, the frequency of arthralgia and pain appeared to be greater in AARD patients experiencing long COVID. The prevalence of long COVID was comparable between patients with systemic autoimmune rheumatic diseases (SARDs) and those with non-autoimmune rheumatic diseases (NARDs). The severity of the acute COVID-19 infection was associated with an increased risk of developing long COVID among ARD patients. Although the number of available studies was limited, the use of immunomodulatory medications may influence the risk of Long COVID in this patient population [25].

The use of immunomodulatory medications may influence the risk of developing Long COVID among patients with AARDs. In the included studies, certain drugs commonly used in AARD management—such as corticosteroids, hydroxychloroquine, and cyclophosphamide—were associated with a higher likelihood of persistent post-COVID symptoms[25]. For example, corticosteroid use during COVID-19 infection was linked to an increased risk of Long COVID, ORs ranging from 3.17 to 4.95 in different analyses. Similarly, hydroxychloroquine use was associated with a modestly increased risk (OR 2.52), and prior treatment with cyclophosphamide showed an even stronger association (OR 11.35). These findings suggest that immunosuppressive therapy might impair viral clearance or exacerbate immune dysregulation, thereby contributing to the persistence of symptoms. However, confounding factors cannot be excluded, and further large-scale studies are needed to clarify the causal role of immunomodulatory treatment in the pathogenesis of Long COVID in AARD populations [25].

The diagnosis and management of long COVID in AARD patients present unique clinical challenges. Fatigue, myalgias, cognitive impairment, and mood disturbances—hallmarks of long COVID—often overlap with symptoms of underlying rheumatic disease or treatment-related side effects, complicating attribution and delaying intervention. There are currently no validated criteria for long COVID specifically tailored to immunocompromised populations, and standardized diagnostic algorithms are lacking[26]. Multidisciplinary care models involving rheumatologists, pulmonologists, rehabilitation specialists, and mental health professionals are essential to distinguish long COVID manifestations from disease flares or comorbidity progression and to guide individualized management[27].

The COVID-19 pandemic exerted a substantial toll on the psychosocial well-being of individuals with AARDs, a population already predisposed to psychiatric comorbidities. Longitudinal evidence shows that patients with rheumatic diseases, particularly those with SLE, experienced significant declines in the ability to participate in social activities, satisfaction with social roles, and worsening depressive symptoms following the pandemic[28]. Depression and low satisfaction with social roles emerged as key predictors of diminished social participation. These findings are consistent with broader evidence indicating that the pro-inflammatory state inherent in AARDs, coupled with the stressors of the pandemic—such as social isolation, reduced access to care, and disruption of physical activity routines—acted synergistically to amplify mental health challenges[29]. Notably, female sex, younger age, and socioeconomic insecurity were additional risk factors for psychological distress[24]. The high prevalence of underdiagnosed depression and anxiety symptoms underscores the need for integrating routine psychological screening and tailored mental health support within rheumatology care, especially in post-pandemic recovery periods. Establishing multidisciplinary care models that include mental health professionals may help mitigate long-term psychological sequelae and improve overall disease management and quality of life in this vulnerable population.

Antibody Response and Implications for Vaccination

Evaluating the variability of vaccine-induced immune responses among AARD patients is vital for optimizing protective strategies and adjusting immunization protocols based on individual risk profiles.

The serologic response to SARS-CoV-2 in patients with AARDs has raised significant clinical concerns, particularly regarding their ability to mount effective immunity after infection or vaccination. In the Greek cohort described by Bakasis et al.[1], antibody responses were observed in 72.4% of tested patients. Notably, the rate of seroconversion was markedly higher among patients with AARDs(80.0%) compared to those with autoinflammatory conditions (25.0%). Although these figures reflect a generally preserved capacity for humoral response in many patients, they remain somewhat lower than the approximate 90% seroconversion rate reported in the general population at two months post-infection.

Several factors may account for this diminished response, including the underlying immune dysregulation associated with AARDs and, more importantly, the use of immunosuppressive therapies. Rituximab, a B-cell depleting agent, has been consistently shown to severely impair the generation of anti-SARS-CoV-2 antibodies. In multiple cohorts, patients receiving rituximab demonstrated significantly reduced or absent serologic responses following natural infection[7] or vaccination[13,15]. Similarly, agents such as mycophenolate mofetil and high-dose corticosteroids have also been implicated in blunted vaccine immunogenicity[13].

These findings have important implications for vaccination strategies. While mRNA-based vaccines elicit robust immune responses in the general population, AARD patients on immunosuppressive therapy—especially those receiving B-cell depletion—may require alternative approaches to achieve adequate protection. T-cell immunity, although not routinely measured, may play a compensatory role in such individuals, offering partial protection against severe disease. Nevertheless, breakthrough infections in this population tend to be more severe, reinforcing the need for layered preventive strategies, including vaccine boosters, monoclonal antibody prophylaxis, and early antiviral treatment where indicated[13].

The variability in serologic responses also suggests the need for individualized vaccine timing in relation to immunosuppressive dosing, particularly for agents with long-lasting effects on lymphocyte function. Ongoing surveillance and immunologic monitoring should be prioritized in patients at risk of poor vaccine response to guide personalized interventions and optimize protection against COVID-19.

Recent cohort studies during the Omicron wave reaffirm the importance of intensified booster strategies in AARD patients. Kim et al. demonstrated that a third mRNA dose significantly reduced breakthrough infections in a Korean cohort of 1,814 AARD patients[30]

Similarly, Hanberg et al.[31] reported a 65% reduction in severe COVID-19 following a fourth mRNA dose in DMARD users. These findings underscore the continued vulnerability of immunosuppressed patients and support multi-dose regimens as a cornerstone of protection.

Emerging evidence suggests that temporary discontinuation of immunosuppressive therapy—particularly methotrexate—around the time of SARS-CoV-2 vaccination can enhance antibody responses. Several studies have investigated whether temporary discontinuation of methotrexate enhances the humoral immune response to COVID-19 vaccination in patients with autoimmune rheumatic diseases. Habermann et al. found that pausing methotrexate after a COVID-19 booster significantly improved neutralizing antibody levels against the SARS-CoV-2 wild-type strain as well as Omicron BA.1 and BA.2 variants, achieving responses comparable to non-immunosuppressed individuals, without evidence of increased disease activity or flares[32]. Similarly, Arumahandi de Silva et al. demonstrated that patients who held methotrexate during at least one vaccination—particularly those aged ≥60 years—developed substantially higher antibody titers compared to those who continued therapy, with the most critical factor being a pause of at least 10 days after vaccination[33]. These findings are in line with expert guidance from the American College of Rheumatology, which recommends holding methotrexate for one week after each vaccine dose to optimize immunogenicity, noting that this strategy carries a low risk of disease flare[34].

Table 3 summarizes the recommended timing of COVID-19 vaccination relative to immunosuppressive therapy in AARD patients.

Implications for Clinical Practice and Preventive Strategies

The cumulative evidence regarding COVID-19 in patients with AARDs has significant implications for clinical decision-making, especially concerning prevention, immunosuppression management, and long-term monitoring. While the majority of AARD patients appear to experience a mild course of COVID-19—as demonstrated in the Greek cohort by Bakasis et al.[1]—certain subgroups consistently emerge as high-risk and require targeted strategies to mitigate morbidity and mortality.

Patients of older age, those with pre-existing ILD, and those receiving immunosuppressants such as rituximab, mycophenolate mofetil, or high-dose corticosteroids are particularly vulnerable to severe disease outcomes[1,2,7]. These individuals should be prioritized for pre-emptive

Table 3. Recommended Timing of COVID-19 Vaccination Relative to Immunosuppressive Therapy in AARD Patients

Immunosuppressive Agent	Vaccination Timing Recommendation	Reference(s)
Rituximab (anti-CD20)	Vaccinate ≥4 weeks before next dose; delay rituximab 2–4 weeks after vaccination if possible.	[7, 13, 34]
Methotrexate (MTX)	Hold for 1 week after each vaccine dose (especially in patients ≥60 years), if disease is stable.	[32, 33, 34]
Mycophenolate mofetil (MMF)	Consider holding for 1 week after each dose if disease is well-controlled.	[13, 15, 34]
JAK Inhibitors	Hold for 1 week after each dose if disease activity permits.	[34]
Abatacept (IV)	Hold 1 week before and 1 week after first vaccine dose (skip 1 IV dose); no hold after second dose.	[34]
Abatacept (SC)	Hold 1 week before and after the first dose of vaccine only.	[34]
TNF Inhibitors (e.g., etanercept, adalimumab)	No hold required; continue during vaccination.	[14, 34]
IL-6 Inhibitors (e.g., tocilizumab)	No hold required; continue during vaccination.	[14, 34]
Corticosteroids (<10 mg/day)	Continue during vaccination.	[2, 34]
Corticosteroids (≥10 mg/day)	Continue, but expect blunted response; consider additional vaccine doses.	[2, 15, 34]
Cyclophosphamide (IV)	Schedule vaccine at least 1 week before or after infusion.	[34]

interventions, including timely access to COVID-19 vaccination, booster doses, and pre-exposure prophylactic measures such as monoclonal antibodies or long-acting antivirals when available.

Importantly, the choice and timing of immunosuppressive therapy may require reconsideration in the context of ongoing viral transmission. Pausing high-risk treatments like rituximab before vaccination may improve immune response.

However, this strategy must be weighed against the risk of triggering a disease flare.Current recommendations support individualized approaches, factoring in disease activity, patient comorbidities, and local COVID-19 epidemiology[15],

These considerations must also be interpreted within the broader context of SARS-CoV-2 variant evolution, which has significantly shaped disease risk and vaccine responsiveness in AARD populations. Emerging variants have modified both the clinical and immunological landscape of COVID-19 in AARD patients. Alpha and Delta were associated with heightened transmissibility and severity—including in populations with rheumatic disease—especially among those on rituximab, high-dose corticosteroids, or with lung comorbidities. Conversely, during Omicron-dominant waves, registry data indicate declining rates of hospitalization and mortality among systemic autoimmune rheumatology patients, likely reflecting a combination of variant-specific attenuation and widespread prior immunity[35]. While data directly comparing variant-specific outcomes in AARD cohorts are scarce, booster vaccination has been linked to reduced long-term autoimmune sequelae after Omicron infection[36] and post-vaccination flare rates remain low and mostly mild, even among SLE patients[37].

Infection prevention efforts should also include enhanced surveillance for breakthrough infections in vaccinated but immunocompromised patients. Although some AARD patients—particularly those on B-cell depleting therapies—fail to generate adequate antibody responses, many may retain functional T-cell immunity, which could reduce the risk of severe outcomes. Nonetheless, real-world data indicate that these patients remain at higher risk of hospitalization and complications compared to immunocompetent individuals, highlighting the continued need for booster campaigns, masking in high-risk settings, and access to early antiviral treatment[7].

Although some AARD patients—particularly those on B-cell depleting therapies—fail to generate adequate antibody responses, a subset may still retain functional T-cell immunity, which could offer partial protection against severe disease. However, T-cell responses in AARD patients are far from uniform and are influenced by multiple variables, including the type of immunosuppressive therapy, underlying disease activity, and patient age. For instance, in a study by Bonelli et al.[38], patients receiving rituximab exhibited impaired humoral responses but preserved SARS-CoV-2-specific T-cell reactivity. Conversely, T-cell responses were also found to be blunted in some patients with high disease activity or prolonged immunosuppression, particularly in those receiving high-dose corticosteroids or combination therapies[38,39].

Moreover, Deepak et al.[15] demonstrated that while T-cell responses were detectable in the majority of immunosuppressed patients following mRNA vaccination, their magnitude and functionality were significantly reduced compared to immunocompetent controls, especially among those receiving mycophenolate mofetil or glucocorticoids. Importantly, age-related immune senescence also impairs T-cell proliferation and cytokine production, further complicating the picture in older AARD patients. Lastly, clinicians should remain vigilant

for post-COVID complications in AARD patients. Persistent fatigue, disease flares, and immune dysregulation require structured follow-up and coordinated multidisciplinary care. Integration of rheumatologists, infectious disease specialists, and rehabilitation services may improve outcomes and quality of life for those recovering from COVID-19 in the context of chronic autoimmune disease[10].

Limitations

Although the Greek cohort by Bakasis et al. provides valuable real-world insights into the clinical trajectory of AARD patients with COVID-19, its relatively small sample size poses inherent limitations. The lack of multivariable adjustment and the monocentric nature of the study reduce statistical power and may limit the representativeness of findings. Selection bias cannot be excluded, particularly given potential differences in healthcare access, diagnostic criteria, or hospitalization thresholds in the local context. Moreover, geographical, demographic, and healthcare system-specific factors may influence outcomes and limit extrapolation to broader international populations. These limitations underscore the need to interpret the findings alongside larger, multicenter registries such as C19-GRA and FAI2R, which offer more robust statistical frameworks and greater generalizability.

Conclusions

Patients with AARDs generally experience a mild course of COVID-19; however, certain subgroups are at significantly higher risk. Older age, pre-existing lung disease, and the use of immunosuppressive agents such as rituximab and corticosteroids are consistently associated with severe outcomes. In contrast, therapies targeting cytokines like TNF and IL-6 may be safer and potentially beneficial. Post-COVID fatigue and prolonged immune dysregulation are common in this population, underscoring the need for structured follow-up and supportive care. Blunted antibody responses in some patients further highlight the importance of individualized vaccination and preventive strategies. Going forward, clinical decisions should focus on risk stratification, optimizing immunosuppressive regimens, and ensuring access to vaccination, boosters, and early antiviral therapies for those at highest risk.

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None

Conflict of interest

The authors declare no conflict of interest.

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