



Incidence of Autoimmune Rheumatic Diseases Following COVID-19 Infection

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Abstract

Background: The relationship between COVID-19 and autoimmune rheumatic diseases remains complex, with growing evidence suggesting that severe COVID-19 may trigger or exacerbate autoimmune rheumatic diseases. This study aimed to assess the prevalence of AIRDs following COVID-19 infection and identify factors associated with their onset.

Methods: A total of 183 patients diagnosed with Autoimmune Rheumatic Diseases (AIRDs) within 30 days post-COVID-19 were evaluated. Data were collected on demographics, comorbidities, disease severity, and inflammatory markers. Cox and logistic regression analyses were conducted to assess risk factors associated with AIRD development.

Results: The findings indicate a notable link between severe COVID-19 and the onset of AIRDs, with higher inflammatory markers significantly associated with increased risk. Interestingly, hypothyroidism appeared to have a protective effect, potentially due to the immunomodulatory effects of treatments like levothyroxine. These findings align with some literature suggesting an immune dysregulation following COVID-19. Despite the insights, the cross-sectional design of the study limits the ability to establish causality.

Conclusion: This study underscores the significant role of severe COVID-19 and elevated inflammatory markers in the development of AIRDs. The protective effect of hypothyroidism could open avenues for future therapeutic considerations. Further, longitudinal studies are essential to better understand the mechanisms driving these associations and explore interventions aimed at reducing AIRD risk in post-COVID-19 patients.

Keywords: Autoimmune diseases, COVID-19, Humans, Hypothyroidism, Rheumatic diseases, Thyroxine

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Introduction

The COVID-19 pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has dramatically reshaped global healthcare priorities and underscored the intricate interplay between infectious agents and chronic diseases (1). While much attention has been focused on the acute respiratory and systemic effects of COVID-19, there is growing evidence that the virus may also play a pivotal role in the imitation and exacerbation of Autoimmune Rheumatic Diseases (ARDs) (2,3). The link between viral infections and autoimmune disorders is not novel, but the scope and scale of COVID-19's impact on this interaction are only beginning to be understood (4).

Autoimmune diseases are often triggered by complex interactions between genetic predisposition and environmental factors, with microbial infections being a significant component (5,6). Numerous studies have demonstrated that pathogens, including viruses and bacteria, can initiate or exacerbate autoimmune processes through mechanisms such as molecular mimicry, where viral antigens resemble self-antigens, leading to an inappropriate immune response. Other mechanisms include bystander activation, where an immune response to a pathogen inadvertently targets self-tissues, and epitope spreading, where an initial immune response to a pathogen expands to include self-antigens (7).

Specific examples of this phenomenon include the association between Parvovirus B19 and Rheumatoid Arthritis (RA), as well as the link between *Helicobacter pylori* and Systemic Sclerosis (SSc) (8). In the case of COVID-19, early reports suggest that SARS-CoV-2 may similarly act as a trigger for ARDs, potentially through these well-established mechanisms. For instance, the virus's ability to induce a cytokine storm, a hyperinflammatory state characterized by excessive cytokine release, has been implicated in the disruption of immune homeostasis, leading to autoimmune manifestations. This dysregulated immune response can persist long after the acute infection has resolved, contributing to the development of chronic autoimmune conditions (9,10).

Recent studies have provided further insight into the specific autoimmune diseases that may be triggered

by SARS-CoV-2. For example, patients with pre-existing autoimmune conditions, such as RA and Systemic Lupus Erythematosus (SLE), have reported flare-ups or worsening of symptoms post-COVID-19 (11). Moreover, there have been documented cases of new-onset lupus, reactive arthritis, and vasculitis following COVID-19 infection (12). This suggests that SARS-CoV-2 may not only trigger new autoimmune responses but also exacerbate existing ones, particularly in individuals with underlying immune dysregulation.

Dysbiosis, or the imbalance of the gut microbiota, has also been linked to the development of autoimmune diseases (13). SARS-CoV-2 has been shown to alter the composition of the gut microbiome, potentially contributing to the onset or exacerbation of autoimmune conditions. For instance, patients with SSc have been found to have distinct gut microbiota profiles, with an over-representation of certain bacteria that may drive inflammation (14). Similar alterations have been observed in COVID-19 patients, suggesting a possible link between viral infection, gut microbiota changes, and autoimmune disease development (15).

In addition to these microbial factors, the interaction between SARS-CoV-2 and the host's immune system is influenced by genetic factors. Specific Human Leukocyte Antigen (HLA) genotypes have been associated with an increased risk of autoimmune diseases, and there is emerging evidence that certain HLA types, especially *HLA-B*15:01*, may also predispose individuals to severe COVID-19 outcomes (16). This genetic predisposition, combined with the virus's ability to manipulate the immune response, may explain why some individuals develop autoimmune diseases following COVID-19, while others do not. The objective of this study is to investigate the incidence of AIRDs following COVID-19 infection in the Mashhad population. By analyzing the clinical data of patients diagnosed with AIRDs within 30 days of a confirmed COVID-19 infection, the study aims to identify patterns and potential risk factors associated with the development of these autoimmune conditions.

Materials and Methods

Study design and participants

This study was designed as a retrospective cross-sectional analysis conducted from March 2021 to March 2022 in Mashhad. The study population consisted of individuals diagnosed with AIRDs within one month following a confirmed COVID-19 infection. Data were collected from the rheumatology clinics at Imam Reza and Ghaem Hospitals and the private offices of collaborating rheumatologists.

Participants were included if they had a confirmed COVID-19 diagnosis *via* PCR and developed symptoms of AIRDs within 30 days, subsequently receiving a confirmed AIRD diagnosis from a rheumatologist. Exclusion criteria comprised a pre-existing autoimmune or inflammatory rheumatic disease, incomplete medical records, AIRD symptoms appearing more than 30 days post-COVID-19, and conditions related to mechanical pain such as osteoarthritis or fibromyalgia.

Data analysis

Descriptive statistics, including means and standard deviations for continuous variables and frequencies and percentages for categorical variables, were used to summarize baseline characteristics. To assess associations between clinical, demographic, and disease-specific variables and the timing of autoimmune rheumatic disease onset, both Cox proportional hazards regression and multivariate logistic regression analyses were conducted. The Cox model was used to estimate hazard ratios for earlier onset, while the logistic regression model categorized onset as early (<15 days) or late (>15 days) and provided adjusted Odds Ratios (ORs) with 95% Confidence Intervals (CIs). Statistical significance was set at a two-sided p -value < 0.05.

The Hosmer-Lemeshow goodness-of-fit test was applied to both regression models to ensure appropriate model specification. Statistical significance was determined at a 5% level.

The severity of COVID-19 infection was categorized as mild (mild symptoms), moderate (moderate symptoms, no lung involvement), and severe (required hospitalization or lung involvement).

Statistical software

Data were analyzed using SPSS version 27.0.1 (IBM Corp., Armonk, NY, USA).

Results

Prevalence, demographic and clinical characteristics

Prevalence: Overall, 77,634 Mashhad residents tested positive for COVID-19 between April and March 2021. Among those who tested positive for COVID-19, 183 patients developed symptoms of AIRDs within 30 days after infection and were eventually diagnosed with one of the autoimmune rheumatic diseases. Therefore, the incidence of autoimmune rheumatic diseases in this population was estimated at 0.23%.

Demographic and clinical characteristics:

The study population comprised 183 participants with a mean age of 38.15 years. The average levels of Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) were 49.56 mm/hr and 23.71 mg/L, respectively, and the mean time from COVID-19 infection to the diagnosis of autoimmune rheumatic diseases was 15.13 days. The majority of the participants were female, with 51.7% being unemployed, 40.4% self-employed, and 6.0% employed. Regarding educational attainment, 44.3% had a high school diploma, and 10.9% had a university degree. The most prevalent comorbidities were hypertension and diabetes, while 18.0% were smokers or substance users. In terms of COVID-19 infection history, 77.6% had been infected once, 16.4% twice, and 6.0% three times. Detailed information is provided in table 1.

Table 1. Demographic and clinical characteristics of patients with post-COVID-19 AIRDs

Variable	Measurement	No.	Percent
Age (Years)	Mean±SD	38.15±11.15	-
ESR (mm/hr)	Mean±SD	49.56±17.02	-
CRP (mg/L)	Mean±SD	23.71±25.27	-
Duration from infection until diagnosis (days)	Mean±SD	15.13±8.84	-
Gender			
Male		25	13.7%
Female		158	86.3%
Occupational status			
Unemployed		91	51.7%
Self-employed		74	40.4%
Employed		11	6.0%

Contd. table 1.

Educational level			
Illiterate	20	10.9%	
Elementary school	62	33.9%	
High school diploma	81	44.3%	
University degree	20	10.9%	
Past medical history			
No	-	67	36.6%
	- Hypertension	36	20.6%
	- Diabetes	36	20.6%
Yes	- Dyslipidemia	32	17.7%
	- Hypothyroidism	15	8.3%
Substance use			
Smokers/Substance users	33	18.0%	
Non-users	150	82.0%	
COVID-19 infection times			
1 Time	142	77.6%	
2 Times	30	16.4%	
3 Times	11	6.0%	

Prevalence of AIRDs

The study found that the most prevalent AIRDs among the participants were vasculitides, with skin vasculitis being the most common, followed by Behçet's disease and other ANCA-associated vasculitides. Seronegative spondyloarthropathies, particularly reactive arthritis, accounted for 22.4% of cases. Additionally, RA affected 12.0% of patients, and undifferentiated inflammatory arthritis was observed in 10.4% of the cohort. SLE and Sjögren's syndrome were present in 7.1 and 4.4% of participants, respectively. Less frequent conditions included inflammatory myopathies, autoimmune uveitis, and scleroderma, while the rarest disorders were antiphospholipid syndrome, sarcoidosis, and granulomatous mastitis, each affecting less than 1.1% of the study population (Table 2).

Time-to-event analysis

Cox regression analysis: In the Cox proportional hazards model, significant variables include elevated

Table 2. Rheumatologic diagnoses in post-COVID-19 patients

Rheumatologic diagnosis		Frequency (n)	Percent (%)
Vasculitides	Skin vasculitis	28	15.3%
	Behçet's disease	8	4.4%
	Other ANCA-associated vasculitides	6	3.3%
	Takayasu arteritis	6	3.3%
	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome)	5	2.7%
	Temporal arteritis	5	2.7%
	Granulomatosis with polyangiitis (Wegner's Disease)	1	0.5%
	Isolated eye vasculitis	1	0.5%
	Total	60	32.7%
Seronegative Spondyloarthropathies	Reactive Arthritis (RA)	22	12.0%
	Psoriatic Arthritis (PsA)	15	8.2%
	Ankylosing Spondylitis (AS)	4	2.2%
	Total	41	22.4%
Inflammatory Myopathies	Dermatomyositis	6	3.3%
	IBM polymyositis	1	0.5%
	Total	7	3.82%
Rheumatoid Arthritis (RA)		22	12.0%

Contd. table 2.

Undifferentiated inflammatory arthritis	19	10.4%
Systemic Lupus Erythematosus (SLE)	13	7.1%
Sjögren's Syndrome (SS)	8	4.4%
Autoimmune uveitis	4	2.2%
Scleroderma	4	2.2%
Sarcoidosis	2	1.1%
Antiphospholipid Syndrome (APS)	2	1.1%
Granulomatous mastitis	1	0.5%

CRP, with an HR of 1.01 ($p=0.033$), indicating that higher CRP levels increased the risk of earlier diagnosis of AIRDs. Antiphospholipid Syndrome (APS) was associated with a strikingly high hazard ratio of 14.08 ($p=0.018$), showing that patients diagnosed with APS had a significantly higher likelihood of early AIRD onset. Similarly, Behçet's disease showed an increased risk with an HR of 3.90 ($p=0.034$). On the other hand, hypothyroidism appeared to have a protective effect, with an HR of 0.29 ($p=0.014$) (Table 3).

Multivariate logistic regression: The logistic regression analysis identified several key factors associated with the timing of AIRDs diagnosis following COVID-19 infection. Age, substance use, and gender were not significant predictors. While diabetes showed a trend toward earlier diagnosis, hypertension, and dyslipidemia did not significantly affect the timing. Notably, hypothyroidism was a strong predictor of delayed diagnosis. Biomarker levels were also significant, with higher ESR linked to a later diagnosis and higher CRP associated with

Table 3. Cox model for time to development of AIRDs

Variable	B	Exp(B)	95%CI (Lower-Upper)	p-value
Age	0.006	1.006	0.983-1.030	0.611
Gender	0.340	1.405	0.735-2.685	0.303
Substance use	-0.273	0.761	0.356-1.627	0.481
Past medical history	-0.096	0.908	0.355-2.320	0.840
Diabetes	0.528	1.696	0.761-3.780	0.197
Hypertension	-0.191	0.826	0.278-2.459	0.732
Dyslipidemia	0.098	1.103	0.445-2.736	0.832
Hypothyroidism	-1.223	0.294	0.111-0.783	0.014
Covid-19 infection times	0.206	1.229	0.649-2.327	0.526
ESR	-0.011	0.989	0.975-1.004	0.161
CRP	0.010	1.010	1.001-1.019	0.033
Systemic Lupus Erythematosus (SLE)	-0.598	0.550	0.212-1.427	0.219
Antiphospholipid Syndrome	-2.644	0.071	0.008-0.634	0.018
Rheumatoid Arthritis (RA)	-0.764	0.466	0.176-1.236	0.125

Contd. table 3.

Sjögren's Syndrome (SS)	0.154	1.166	0.398-3.415	0.779
Scleroderma	0.539	1.715	0.328-8.966	0.523
Psoriatic Arthritis (PsA)	-0.334	0.716	0.275-1.869	0.495
Isolated eye vasculitis	-0.958	0.383	0.033-4.513	0.446
Behçet's disease	-1.362	0.256	0.073-0.905	0.034
Eosinophilic granulomatosis with polyangiitis	0.507	1.660	0.335-8.242	0.535
Ankylosing spondylitis	-0.798	0.450	0.052-3.880	0.468
Dermatomyositis	-0.139	0.870	0.253-2.989	0.825
Granulomatous mastitis	-1.251	0.286	0.020-4.063	0.355
Reactive arthritis	-0.228	0.796	0.341-1.859	0.598
Skin vasculitis	-0.304	0.738	0.323-1.685	0.470
Other ANCA-associated vasculitides	1.115	3.051	0.792-11.755	0.105
Autoimmune uveitis	0.396	1.486	0.420-5.257	0.539
Takayasu arteritis	-0.064	0.938	0.274-3.210	0.919
Temporal arteritis	-0.957	0.384	0.104-1.420	0.152
IBM polymyositis	-1.366	0.255	0.029-2.234	0.217
Severity	0.182	1.199	0.678-2.121	0.532

an earlier diagnosis. Additionally, certain conditions, including SLE, RA, and Behçet's disease, were also associated with delayed diagnosis. Interestingly,

moderate disease severity was linked to an earlier diagnosis (Table 4).

Table 4. Predictors of time interval between COVID-19 infection and diagnosis of AIRDs

Variable	B	Exp(B)	95%CI for EXP(B)	p-value
Age	-0.016	0.984	0.937-1.034	0.532
Gender	-1.021	0.360	0.073-1.780	0.210
Substance use	0.704	2.022	0.308-13.280	0.464
Diabetes	-1.512	0.220	0.038-1.281	0.092
Hypertension	0.566	1.761	0.102-30.364	0.697
Dyslipidemia	-2.405	0.090	0.003-2.751	0.168
Hypothyroidism	5.390	219.173	5.758-8342.851	0.004
COVID times	-0.829	0.437	0.096-1.994	0.285
ESR	0.036	1.037	1.001-1.074	0.044
CRP	-0.035	0.965	0.938-0.993	0.014
Systemic Lupus Erythematosus (SLE)	2.757	15.752	1.139-217.804	0.040
Antiphospholipid Syndrome (APS)	21.644	2510538961.671	0.000-∞	1.000

Contd. table 4.

Rheumatoid Arthritis (RA)	5.890	361.412	9.873-13230.066	0.001
Behçet's disease	4.110	60.924	1.641-2261.676	0.026
Moderate severity	-1.522	0.218	0.051-0.944	0.042

Discussion

This study examined the incidence and characteristics of AIRDs following COVID-19 infection in Mashhad, Iran. The overall prevalence of AIRDs was estimated at 0.23%. The most common conditions were vasculitides, seronegative spondyloarthropathies, RA, and SLE. Time-to-event analysis revealed that elevated CRP levels, antiphospholipid syndrome, and Behçet's disease were associated with earlier AIRD onset, while hypothyroidism was linked to delayed diagnosis. Logistic regression showed that hypothyroidism, higher erythrocyte sedimentation rate, and certain diseases like systemic lupus erythematosus and RA were predictors of delayed AIRD diagnosis. In contrast, higher CRP and moderate disease severity were associated with earlier diagnosis.

The potential for viral infections to precipitate autoimmune diseases is a well-established concept, and COVID-19 appears to align with this broader framework (17). Similar studies have reported comparable findings regarding vasculitis flares in Behçet's disease triggered by COVID-19 infection (18,19). In our sample, Behçet's disease accounted for 4.4% of the observed AIRDs following COVID-19 infection, reinforcing the idea that the systemic inflammation induced by COVID-19 may accelerate the onset or exacerbate pre-existing autoimmune conditions. This finding is particularly relevant given the chronic nature of Behçet's disease and its association with heightened inflammatory responses. The study found an elevated prevalence of RA at 12.0%, which is notably higher than figures reported in meta-analyses of post-COVID-19 autoimmune responses (20). This suggests that the study population may be more susceptible to developing RA following viral infections, potentially due to genetic predispositions or other region-specific factors. Previous literature has documented viral infections as triggers for RA in

genetically vulnerable populations (21).

A particularly novel aspect of this study was the relationship between disease severity and AIRD onset. While mild COVID-19 severity appeared to act as a protective factor, reducing the likelihood of developing autoimmune diseases, severe disease severity was associated with an increased risk. This observation is consistent with emerging research showing that severe COVID-19 disrupts immune system homeostasis, leading to hyperactivation of immune cells and, in some cases, autoimmune responses (22-24).

Hypothyroidism, an unexpected protective factor, warrants special attention. While hypothyroidism is typically linked to autoimmunity, especially in autoimmune thyroid diseases (25), the results of the present study suggest it may protect against the onset of other autoimmune diseases following COVID-19. This could be attributed to the immunomodulatory effects of levothyroxine, a standard treatment for hypothyroidism, which has been reported to reduce immune hyperactivity in specific contexts (26). Although this association remains speculative, it offers a promising avenue for future research, particularly regarding the interaction between thyroid hormones and immune regulation in the context of viral infections.

In comparing present study's Cox and logistic regression results, complementary insights were observed. Cox regression focused on identifying time-to-event relationships, highlighting APS and Behçet's disease as conditions that accelerate AIRD onset post-infection. On the other hand, logistic regression brought more attention to the role of inflammatory markers like ESR and CRP, which may not significantly affect the timing of disease onset, but rather the likelihood of disease development itself. Both methods identified moderate and severe disease severity as critical variables, though logistic

regression underscored the protective effect of moderate severity more clearly. These comparisons highlight the importance of using multiple statistical approaches to capture the nuanced relationships between viral infections and autoimmune responses (27). The findings on antiphospholipid syndrome, Behçet's disease, and RA align with the idea that COVID-19 may trigger immune system disruption. However, studies emphasizing on other autoimmune conditions, such as ankylosing spondylitis and vasculitis, have shown mixed results, with some reporting increased disease onset and others finding no significant associations (28). This suggests that COVID-19's impact on autoimmunity may depend on specific disease mechanisms, genetic factors, and the intensity of the immune response.

Finally, the role of CRP and ESR, two key inflammatory markers, in predicting disease onset emphasizes the importance of monitoring these markers in post-COVID-19 patients. Elevated ESR and reduced CRP values were both significant predictors of AIRD onset in the present study. These markers likely reflect ongoing systemic inflammation, which may serve as a precursor to more severe immune dysregulation and subsequent autoimmune disease (29-31).

Strengths and limitations

The strengths of this study include the use of robust statistical models, which allow us to examine time-to-onset and the likelihood of AIRD development from different analytical angles. Additionally, the inclusion of a diverse range of AIRDs in a single study provides a comprehensive overview of the autoimmune conditions that may follow COVID-19 infection.

However, some limitations should be acknowledged. The incidence rate reported in this study is derived from a specialist rheumatology clinic setting. This selection bias may have resulted in an over-representation of severe cases, while milder cases that do not require specialist referral may have been underestimated. Additionally, while a 30-day window was chosen to capture the early post-infectious onset of AIRDs, some autoimmune conditions, particularly those with insidious onset, may develop beyond this timeframe. Another inherent limitation is the cross-sectional design, which restricts causal inferences regarding the role of COVID-19 in triggering autoimmunity. A

prospective cohort study with a broader recruitment strategy, including patients from primary care and general internal medicine settings, would provide a more representative estimate of incidence and severity distribution. Despite these limitations, this study remains a valuable contribution to the growing body of literature on post-COVID autoimmunity, providing compelling evidence that COVID-19 may act as a trigger for AIRDs in susceptible individuals. These findings warrant further research through longitudinal studies to better delineate the risk factors, mechanisms, and long-term outcomes of COVID-19-associated autoimmunity.

Conclusion

This study highlights the potential role of COVID-19 in triggering the onset of AIRDs, particularly APS, Behçet's disease, and RA. The findings of this study suggest that severe COVID-19 increases the risk of developing these conditions, while moderate severity may offer a protective effect. Elevated inflammatory markers such as ESR and CRP were also associated with AIRD onset, underscoring the importance of monitoring these parameters in post-COVID-19 patients. The unique protective role of hypothyroidism, likely mediated by levothyroxine's immunomodulatory effects, offers a novel insight into immune regulation during infection. However, due to the cross-sectional nature of present study, further longitudinal research is needed to establish causality and explore the underlying mechanisms driving these associations.

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Conflict of Interest

The authors declare no conflict of interest.

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