



# COVID-19 and the clinical course of rheumatic manifestations

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## Abstract

The manifestations of COVID-19 have been evolving over time. Various post-COVID-19 syndromes are being recognised. Various viruses have been implicated in the pathogenesis of autoimmune diseases, and we expect a similar outcome with the severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2). The SARS-CoV-2 virus penetrates various tissues and organs and has a predisposition to lead to endotheliitis that may cause vascular manifestations including thrombosis. SARS-CoV-2 has been shown to activate Toll-like receptors and the complement system. It perpetuates NETosis and leads to autoantibody formation. These predispose to systemic autoimmunity. Both reactive arthritis and connective tissue disorders such as lupus and inflammatory myositis have been reported after COVID-19. Other reported autoimmune disorders include haemolytic anaemia, immune thrombocytopenia, cutaneous vasculitis, and Guillain Barré-like acute demyelinating disorders. The multi-system inflammatory syndrome in children and its adult counterpart are another post-COVID-19 entity that presents as an admixture of Kawasaki disease and staphylococcal toxic shock syndrome. Patients with preexisting rheumatic diseases may flare during the SARS-CoV-2 infection. They may develop novel autoimmune features also. The immune-suppressants used during the acute COVID-19 illness may confound the outcomes whereas comorbidities present in patients with rheumatic diseases may mask them. There is an urgent need to follow-up patients recovering from COVID and monitor autoantibody production in the context of rheumatic manifestations.

## Key Points

- COVID-19 is associated with both innate and acquired immune reactions and production of various autoantibodies.
- Various immune-mediated manifestations such as arthritis, myositis, haemolytic anaemia, thrombocytopenia, and acute demyelination may develop after COVID-19.
- Longitudinal cohort data are warranted to describe, predict, and test prevent various rheumatic manifestations in post-COVID-19 subjects.

**Keywords** Induced autoimmunity · Post-COVID-19 · Rheumatic diseases

## Introduction

Since its first detection at Wuhan in China, SARS-CoV-2 (novel coronavirus 2019) has engulfed the world with rapidly accumulating mutations and variants emerging at frequent intervals [1]. More than 100 million infections and 2.4 million deaths have been reported to the World Health Organization [2]. Various countries have experienced more than 1 wave of the epidemic, and it seems to be becoming endemic. Hence, future waves and seasonal outbreaks may be expected.

There is some evidence for the seasonality of coronavirus disease 2019 (COVID-19) [3]. The patterns of regional outbreaks along latitudes and regions of similar temperature and humidity seem to mirror those of a seasonal respiratory virus. In the initial year, the effect of seasonality was weak due to the rate of global spread but is likely to become more prominent from 2021 onwards [4].

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The implications of the novel virus variants and seasonality are that the infection can re-emerge from time to time in the near future. Also, the evolution of the virus would be towards less virulence and more prolonged infectivity as it becomes endemic. The latter may result in the prolonged exposure to the host immune system, increasing the likelihood of autoimmunity.

A powerful factor associated with both COVID-19 and autoimmunity is vitamin D. The vitamin D receptor has a role in innate cell activation, and low levels of vitamin D are associated with various autoimmune diseases [5]. A meta-analysis has confirmed the association between low vitamin D and severity of COVID-19 [6]. The latitude effect on COVID-19 mortality can be due to serum vitamin D levels [7].

COVID-19 is a heterogeneous disease ranging from asymptomatic course to multi-organ failure. The duality of inflammation and autoimmunity in COVID-19 has been compared with the two-faced Roman god Janus [8]. Although COVID-19 mortality seems to be decreasing, Europe is still battling the third wave. Vaccination has begun in most countries to safely achieve herd immunity.

The aftermath of the initial infections is being gradually recognised. Post-COVID-19 complications may manifest as pulmonary, cardiac, arthritic, cutaneous, and other affections [9]. It is unknown what proportion of these complications is reversible.

The likelihood of autoimmune and rheumatic diseases in COVID-19 survivors is a big issue. It is critically important to timely identify subjects with autoimmune and rheumatic manifestations. The acute SARS-CoV-2 infection may unmask previously undiagnosed rheumatic conditions and precipitate *de novo* disease, both of which may persist after resolution of the infection.

Various viral infections have been postulated to induce autoimmunity, including parvovirus B19, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes virus-6, HTLV-1, hepatitis A and C virus, and rubella virus [10]. SARS-CoV-2 has been shown to induce activation of different aspects of the immune system. It can activate interleukin-6 (IL-6)-dependent pathways, leading to cytokine storm and macrophage activation syndromes [11, 12]. It can also alter interferon signalling [13] and affect antigen presentation.

The NETosis (formation of neutrophilic extracellular traps) in COVID-19 [14] can provide a fertile ground for autoantibody formation, especially against intra-nuclear components (anti-nuclear antibody) [15].

Also, various autoantibodies have been reported in the serum of patients with COVID-19, including anti-nuclear antibodies such as anti-52 kDa SSA/Ro and anti-60 kDa SSA/Ro [16], and various anti-phospholipid antibodies [17]. Immune-mediated thrombocytopenia [18] and haemolytic anaemia [19] have also been reported in COVID-19.

The aim of this article is to overview some of the pathophysiological mechanisms in COVID-19 that may lead to rheumatic manifestations and propose strategies to prevent rheumatic diseases in the long-term.

## Search strategy

MEDLINE/PubMed and Scopus were searched with the keywords—COVID-19 and rheumatology/rheumatic disease/autoimmunity as per standard recommendations for a biomedical review [20]. Relevant articles were chosen and bibliographies of these articles were also explored.

## Multi-systemic penetrance and endotheliitis in COVID-19

SARS-CoV-2 entry into the human cells is enabled by the angiotensin-converting enzyme receptor 2 (ACE2) [21]. This is a rather ubiquitous receptor present in the respiratory epithelium, renal glomerular cells, gastrointestinal tract, endothelial cells, immune cells, and even nervous tissue [22].

Clinical manifestations associated with the infection may include acute respiratory distress syndrome, acute kidney injury, heart failure, diarrhoea, and thrombosis [23, 24]. While canonical ACE2 is not affected by interferon (IFN), an inducible (termed MIRb-ACE2) isoform can be upregulated by IFN [25]. STimulator of INterferon Genes (STING) has been postulated to overly activate late in the pathogenesis of severe COVID-19 [26].

The ACE2 receptor is present on endothelial cells, and endotheliitis with virion particle has been reported [27]. SARS-CoV-2 can invade artificially engineered *in vitro* blood vessel organoid [28]. The endothelial invasion can amplify with apoptosis and pyroptosis leading to vasculitis-like features [29]. This has led to the hypothesis that endotheliitis can induce immune reactions with thrombosis [30]. Although one study could not demonstrate SARS-CoV-2 invasion in human endothelial cells [31], it may be premature to reject this hypothesis.

## Persistence of SARS-CoV-2

Although viral illnesses are self-limiting, some viruses can persist in the host for years and decades. The persistent virus may be reactivated during periods of immune suppression as in the case of shingles or play a role in maintaining autoimmunity [32]. In the case of chikungunya infection, autoimmune chronic arthritis can develop and mimic rheumatoid arthritis [33].

The seasonality of autoimmunity is, at least partly, associated with viral infections [34]. Whether this is true for SARS-CoV-2 infection is unknown. Some patients have been found to shed the SARS-CoV-2 virion in their stool for weeks [35].

Younger children seem to shed the virus for longer periods [36]. Some patients test positive for SARS-CoV-2 for a long time, making it difficult to distinguish re-infection from virus persistence [37]. If there is a long-term persistence of the dormant virus, it may be completely harmless, or it may make a person prone to autoimmunity by prolonged innate immunity activation.

### Innate immunity and autoinflammation in COVID-19

Autoinflammatory diseases predominantly affect innate immunity pathways [38]. COVID-19 has been associated with activation of innate immunity via Toll-like receptors (TLRs), mostly TLR-3, 4, 7, and 8 [39]. Complement activation in COVID-19 has been shown to activate platelets and neutrophil extracellular traps (NETs) [40]. Such reactions may transform into autoimmunity.

Beyond molecular mimicry, this (hyper)inflammation and dysregulated immune responses seem to be a viable mechanism by which COVID-19 can bring on autoimmunity [41]. It has been shown that innate activation by viral infections can cause flares of diseases with predominant autoinflammatory pathogenesis like psoriasis [42]. NETosis has been proposed in the causation of post-COVID-19 syndrome [43]. Also, there is some evidence that the SARS-CoV-2 infection is aided by autoantibodies such as anti-interferon antibodies that are found in about 10% of severe COVID-19 cases [44].

### Thrombosis in COVID-19

Thrombosis is an integral part of COVID-19. Conversely, the mortality benefit of heparin in COVID-19 seems to extend beyond the conventional anti-coagulation properties [45]. The various roles of endothelial cells, turbulent blood flow, and platelet dysfunction included in Virchow's triad are discussed in detail elsewhere [24].

Antiphospholipid antibodies (APLA) found in COVID-19 are a sign of autoimmunity. Initially, these were presumed to be pathological [46]. In cohorts of severe COVID-19, it was shown that almost half had at least one APLA [47]. At least 30% are above stringent cut-offs (> 40 IU) [48] required in the classification criteria for the anti-phospholipid syndrome (APS). More recent studies have shown that APLA in COVID-19 have different epitope specificities as opposed to the ones in classic APS [49]. One target of antibodies in APS could be annexin-A2. Antibodies to this phospholipid-binding protein have been shown to correlate with mortality in COVID-19 [50]. The persistence of these antibodies can herald an increased predisposition to thrombosis and may be indistinguishable from APS [48].

The timing of pro-thrombotic effects of COVID-19 is still uncertain. Although there is no evidence of highly prevalent thrombotic disease among COVID-19 survivors, it may take

some time before sufficient data emerge to rule out this possibility.

### Antinuclear antibodies in COVID-19

About 30% of COVID-19 patients have at least one antibody against a nuclear antigen. Most of these are detectable at low titre without high specificity [51]. However, considering the number of COVID-19 patients worldwide, it is likely that some patients may develop a persistent autoantibody response resulting in autoimmunity.

The entire “autoantigenome” of SARS-CoV-2-positive patients has been mapped [52]. This has provided valuable links of autoimmunity with thrombosis, fibrosis, and smooth muscle dysfunction in COVID-19. Also, there is a lot of overlap of these antibodies with various neural antigens pointing towards future neurological sequelae.

### Rheumatic manifestations in COVID-19

Some of the initially reported autoimmune manifestations of COVID-19 include haemolytic anaemia [19] and immune thrombocytopenia [53]. There are reports of Guillain-Barré syndrome associated with COVID-19 [54, 55]. Even cranial nerve palsies have been reported [56].

Also, autoimmune endocrine disorders have been reported [57]. A variety of arthritic and other musculoskeletal affections in COVID-19 are described in case studies summarized in Table 1.

Cutaneous vasculitis in association with COVID-19 is also reported in case reports [64, 65]. There are two published cases of urticarial vasculitis [66]. However, a couple of systematic reviews have pointed out that most cutaneous manifestations could be traced to various drugs the patients were on [67, 68]. The cause of purpura could be traced to thrombosis in several cases, and these would usually appear early in the disease onset. Thus, the association of cutaneous vasculitis with COVID-19 is not strong.

Three cases of lupus have been diagnosed with the onset of COVID-19 (Table 2). Other COVID-19-related rheumatic conditions include inflammatory myositis [72]. Myalgia has been commonly reported in various cohorts of COVID-19 [73].

### Multi-system inflammatory syndrome associated with COVID-19

Kawasaki disease (KD)-like syndrome was first reported in association with COVID-19 in children [74]. The incidence of this syndrome was almost 10 times the incidence of the usual KD [74]. It was termed as multi-system inflammatory syndrome associated with COVID-19 in children (MIS-C) and found to have clinical features overlapping with vasculitis of KD and cutaneous manifestation and cardiovascular collapse

**Table 1** Post-COVID-19 reactive arthritis

Place	Age, sex	Joints affected	Lab parameters	Treatment	Outcome
Turkey [58]	73, male	Metatarso-phalangeal, proximal, and distal interphalangeal of toes	RF, ACPA were negative	NSAIDs	Resolved
Japan [59]	50s, male	Bilateral ankles arthritis, with mild enthesitis	ANA, RF, and ACPA were negative; No crystals on arthrocentesis HLA-B27 negative	NSAID and intra-articular steroids	Moderate improvement
Jeddah, SAU [60]	39, female	Distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints of the hands	ANA, RF, ACPA were negative	NSAIDs (celecoxib)	Resolved
Norwich, UK [61]	53, male	Inflammatory back pain	HLA-B27-positive	Intra-muscular methylprednisolone 120mg and oral diclofenac 75mg	Resolved at 3 months
Erlangen, Germany [62]	65, female	Ankles, wrists, and knee joints; Associated with cutaneous vasculitis	Auto-antibody tests were negative. HLA-B27 was positive	Oral prednisolone	Resolved
Singapore [63]	47, male	Right knee; with “swelling” of penis	No crystals on arthrocentesis	Etoricoxib and intra-articular triamcinolone	Not mentioned

*ACPA* anti-citrullinated peptide antibody, *ANA* antinuclear antibodies, *HLA* human leukocyte antigen, *IAS* intra-articular steroids, *NSAID* non-steroidal anti-inflammatory drugs, *RF* rheumatoid factor

of staphylococcal toxic shock syndrome [75]. Later on, the adult counterpart was recognised and named as “MIS-A.” Variants have been described including a case presenting as status epilepticus [76].

Although the pathogenesis of MIS is unclear, it is likely an (auto)immune manifestation that occurs mostly post-COVID-19 (concomitantly in a very limited number of cases). Unlike most other rheumatic diseases, both KD and MIS are not chronic.

### COVID-19 in patients with various autoinflammatory and autoimmune rheumatic diseases

Despite the use of immunosuppressants and intrinsic immune dysfunction in various autoimmune diseases, there has been no report of an increased susceptibility to COVID-19. Initial epidemiological data from the COVID-19 Global Rheumatology Alliance international physician registry has

demonstrated that patients on higher glucocorticoid doses have higher chances of hospitalization while those on anti-TNF-alpha inhibitors have lesser chances [77]. In an analysis of data from primary care, patients with a diagnosis of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or psoriasis were at higher risk for death during the pandemic [78]. But these data need to be carefully interpreted since there may be confounding by indication.

Overall, the risks of severe COVID-19 in patients with rheumatic diseases have gradually reduced over time [79]. Rheumatic diseases have multiple comorbidities that may predispose to severe disease and worse outcomes [80].

It has been shown that patients with preexisting rheumatic diseases can flare during COVID-19 and develop new manifestations. A male patient with lupus presenting with arthritis and thrombocytopenia developed Coombs’ positive haemolytic anaemia along with APLA positivity [81]. A review has found two novel cases of lupus, along with flares in

**Table 2** Case reports of de novo post-COVID-19 systemic lupus erythematosus

Place	Age, sex	Clinical features	Lab	Management	Outcome
Italy [69]	85, female	Severe hypotension, thrombocytopenia, pleural effusion	Positivity for ANA; Ku positivity and atypical ANCA	Steroids	Dried gangrene in three fingers; antibodies persistent at 2 months
Connecticut, US [70]	18, female	Fever, pericardial tamponade, acute heart failure, and pleural effusion	Positive anti-nuclear and anti-double-stranded DNA antibodies, lupus anti-coagulant, and anti-cardiolipin B. C3 and C4 levels were low.	Steroids, antibiotics, hydroxychloroquine	ARDS, renal failure and death
Mexico [71]	45, male	Fever, dry cough, myalgia, and arthralgia; oedema; thrombocytopenia	Positive anti-nuclear antibodies	Steroids, IV immunoglobulin, and rituximab	Recovered

another five during COVID-19 [71]. A large multi-centric cohort has shown that patients with autoimmune diseases may be at higher risks for developing COVID-19 than the general population [82].

### Immunosuppressant therapy in COVID-19

Although various immune-mediated therapies were initially proposed for COVID-19 [83], only a few have stood the rigour of randomized trials [84]. A much-purported drug, hydroxychloroquine, did not meet endpoints in various RCTs [85]. Colchicine has shown some promise in moderate COVID-19 in an RCT though the primary end-point was not met [86]. Evidence is sparse for various biologic agents such as tocilizumab and anakinra, and current practice guidelines do not support their routine use [87]. It is possible that individuals with autoimmune features might respond to these therapies while others do not. However, to explore such possibilities, a personalised medicine approach is required.

What is interesting is that some of these drugs have been used in the pandemic and such off-label use could have influenced the development of autoimmunity. They may offset the development of autoimmunity. The use and withdrawal may paradoxically induce autoimmunity. It has been hypothesized that transient immunosuppression followed by inappropriate immune reconstitution itself may result in autoimmunity [88].

Moreover, gout can also be precipitated by anti-virals such as favipiravir and lopinavir-ritonavir combination that were initially used for COVID-19 [89]. Similarly, the use of convalescent serum may lead to delayed serum sickness (systemic Arthus-like reaction) [90].

### Comorbidities and post-COVID-19 rheumatic manifestations

A survey of COVID-19 survivors has shown a high prevalence of fatigue and various complications such as myocardial ischemia syndromes, stroke, and pulmonary fibrosis [91]. Initially, the manifestation of various autoimmune diseases may be masked by symptoms attributed to these manifestations. For example, large-vessel stroke in the young might be attributed to accelerated thrombosis due to COVID-19 and underlying *de novo* vasculitis.

### Predicting and preventing post-COVID-19 rheumatic diseases

The prediction will depend on genetic susceptibility to vasculitis and prothrombotic diseases. A genome-wide association study in patients with COVID-19 has found the loci 3p21.31 and 9q34.2 associated with severe disease [92]. The 3p21.31 locus contains genes like C–C chemokine receptor type 9; C–X–C motif chemokine receptor 6 and XCR1, the receptor for

lymphotactins-1 and -2 [92]. These can be associated with vasculitis, and autoimmune colitis [93]. XCR-1 is associated with antigen cross-presentation and has been reported in RA synovium [94]. The 9q34.2 locus coincides with the ABO group, and there is a hypothesis that stabilization of the von-Willebrand factor can predispose to thrombosis and severe COVID-19 [92]. However, the work done is preliminary and needs to be backed up with more clinical correlations.

At least half of patients with severe COVID-19 develop autoantibodies [95]. There is a need of cohort studies to estimate how long these persist. If they persist, it should be seen whether they predispose to autoimmune disease.

The post-COVID-19 pulmonary syndrome is well recognised [96]. Similarly, there is a possibility of a post-COVID-19 cardiac syndrome [97]. A meta-analysis of cohorts of survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks has shown a low diffusing capacity for carbon monoxide and reduced exercise capacity in at least a quarter [98].

One question that arises is how much of this is due to immune dysregulation and vascular endotheliitis. If this hypothesis is true, there may be a role of DMARDs such as methotrexate and colchicine in the prevention of post-COVID-19 syndromes. These should be explored in the context of clinical trials.

### Conclusion

Various autoimmune and rheumatic diseases have been reported among COVID-19 survivors. COVID-19 can also result in flares of preexisting rheumatic diseases. Cohort studies to identify rheumatologic manifestations in the short- and long-terms after surviving COVID-19 are the need of the hour. This will clarify the burden of rheumatic and other manifestations after COVID-19 as well as help to recognise vulnerable groups for screening and preventive strategies.

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### Declarations

**Disclosures** None.

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