Received: 5 June 2020 | Revised: 17 June 2020 | Accepted: 18 June 2020

DOI: 10.1111/1756-185X.13909

INVITED REVIEW

International Journal of Rheumatic Diseases

WILEY

Understanding immunopathological fallout of human coronavirus infections including COVID-19: Will they cross the path of rheumatologists?

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causing coronavirus disease 2019 (COVID-19) is the biggest pandemic of our lifetime to date. No effective treatment is yet in sight for this catastrophic illness. Several antiviral agents and vaccines are in clinical trials, and drug repurposings as immediate and alternative choices are also under consideration. Immunomodulatory agents like hydroxychloroquine (HCQ) as well as biological disease-modifying anti-rheumatic drugs (bDMARDs) such as tocilizumab and anakinra received worldwide attention for treatment of critical patients with COVID-19. This is of interest to rheumatologists, who are well versed with rational use of these agents. This brief review addresses the understandings of some of the common immunopathogenetic mechanisms in the context of autoimmune rheumatic diseases like systemic lupus erythematosus (SLE) and COVID-19. Apart from demographic comparisons, the role of type I interferons (IFN), presence of antiphospholipid antibodies and finally mechanism of action of HCQ in both the scenarios are discussed here. High risks for fatal disease in COVID-19 include older age, metabolic syndrome, male gender, and individuals who develop delayed type I IFN response. HCQ acts by different mechanisms including prevention of cellular entry of SARS-CoV-2 and inhibition of type I IFN signaling. Recent controversies regarding efficacy of HCQ in management of COVID-19 warrant more studies in that direction. Autoantibodies were also reported in severe acute respiratory syndrome (SARS) as well as in COVID-19. Rheumatologists need to wait and see whether SARS-CoV-2 infection triggers development of autoimmunity in patients with COVID-19 infection in the long run.

KEYWORDS

autoantibodies, COVID-19, cytokine storm, hydroxychloroquine (HCQ), interferon, systemic lupus erythematosus (SLE)

1 | INTRODUCTION

Since the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causing coronavirus disease 2019 (COVID-19) was declared as a pandemic by the World Health Organization (WHO), 6.43 million people have been infected and approximately 386 000 deaths have been reported as on 4 June 2020.[1] Currently, there is no specific therapeutic agent for treatment of COVD-19. Several drugs were repurposed for their use as antiviral treatment in COVID-19. Global attention and controversies related to use of hydroxychloroquine (HCQ) and successful use of several biological disease-modifying anti-rheumatic drugs (bDMARDs) have drawn attention of rheumatologists toward immunological understandings of COVID-19 pathology as well as scientific and rational use of these agents in this scenario.

SARS-CoV-2 affects the lower respiratory tract and infected patients develop common symptoms including fever, cough and fatigue.[2] SARS-CoV-2 differs from common human coronavirus (HCoV), SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) in terms of the time required for development of symptoms and fatality rate. Patients with COVID-19 can be classified, based on severity of diseases, as asymptomatic, mild to moderate, severe and critical cases. In severe and critical patients, SARS-CoV-2 causes atypical pneumonia associated with acute respiratory distress syndrome (ARDS). In some cases, other complications including multi-organ failure and disseminated intravascular coagulation increases fatality. Common laboratory markers like C-reactive protein (CRP), ferritin, lymphocyte count and lactate dehydrogenase are helpful in predicting severe illness in a patient.

Here, we have discussed common pathophysiological mechanisms involved in autoimmune diseases like systemic lupus erythematosus (SLE) and COVID-19, including the role of type I interferon (IFN), antiphospholipid antibodies, hypercytokinemia and finally mechanisms of actions of HCQ in these conditions (Figure 1). This review also outlines briefly immunopathogenesis of all human coronavirus diseases (HCoV). Most of the scientific information was retrieved from studies on animal models of SARS-CoV and MERS-CoV infections, apart from recent studies on patients with COVID-19.

2 | DOES SEQUELA OF HCOV INFECTIONS MIMIC AUTOIMMUNE FOOTPRINTS?

There are demographic, immunological and therapeutic similarities and dissimilarities between HCoV infections and autoimmunity.

2.1 | Gender based comparisons

In general, adult women have stronger immune response and they are protected more often from infectious disease compared to men of similar age.[3] Women appears to have robust antimicrobial immune responses, especially against viral infections. X chromosomes and sex hormones are thought to be responsible for this phenomenon. In addition, negative regulators of immune response are less marked in woman as compared to men, for example lower number of circulating T-regulatory cells and lower expression of immune checkpoint inhibitors like PD-L1 in T-cells of women.[3]

Coronavirus strains SARS-CoV and SARS-CoV-2 utilize angiotensin I converting enzyme (ACE) 2 as a receptor for entry into host cells.[4] ACE2 is differentially expressed in different organs; high levels are reported in the small intestine, colon, heart, muscle, kidney, testis and moderate levels in lungs. Expression of ACE2 is also higher in males compared to females, especially in liver and lung tissues even though its gene is present in the X chromosome.[5] ACE2 activity and expression is regulated by 17β-estradiol.[6] Messenger RNA (mRNA) expression of ACE2 correlates with immune signatures in lungs and it is dependent upon age and gender.

There is positive correlation between ACE2 expression and immune signatures in the lungs of men and older individuals, whereas negative correlation is observed in women and younger individuals.[7] This might be the reason for excessive immune response in the form of the cytokine storm observed in older-aged males that results in severe respiratory complications. However, SARS-CoV-2 infects both genders equally, although higher mortality is observed in males.[8,9]

In an animal model studies, males were found to be highly susceptible to SARS-CoV infection and more severe lung pathology. Mortality of male mice was higher than that of female mice and it was dependent on viral load. Blocking estrogen receptor signaling, however, led to an increase in mortality even among SARS-CoV infected female mice.[10] Enhanced Toll-like receptor (TLR)7 expression in female mice, on the other hand, can result in rapid viral clearance and improve disease outcome upon exposure to other RNA viruses like mouse hepatitis corona virus (MHV) infection as compared to male counterparts.

Similar to animal studies, male population is predominantly susceptible to SARS-CoV-2 infection and accounts for nearly 60% of all cases of COVID-19 with higher mortality.[11] Similar gender bias was also observed in MERS-CoV infection, although it was attributed to social activities and religious customs that involved more men than women in the Middle East.

2.2 | Ethnicity-related comparisons

African American women are at 4 times higher risk and Latino American as well as Asian women are at 2 times higher risk for developing SLE than European American women. SLE disease severity, number of clinical manifestations, prevalence of autoantibodies and nephritis as well as mortality are higher in African American, Asian and Hispanic populations as compared to the White populations. However, socio-economic and environmental background may also be confounding factors that influence ethnicity-based prevalence and phenotypic differences in SLE.[12]

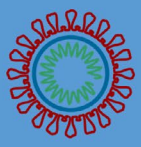
Parameters	COVID-19 	Systemic Lupus Erythematosus 
Gender difference	Infection equally common in both genders  Mortality higher in male 	Female predominant  Male lupus can be severe
Age	SARS-CoV-2 infects all age groups equally Mortality higher in older aged individuals 	Second & Third decade of age 
Affected ethnicity & mortality	Caucasians > Asians / African ancestry Disproportionately higher mortality among non Whites	Asians / Africans > Caucasian ancestry
Source of Type I interferon	plasmacytoid dendritic cells (pDCs),  Macrophages 	pDCs
Pathogen Recognition Receptors	TLR7, TLR3, cyclic GMP-AMP synthase (cGAS)	TLR7, cGAS
Cytokine storm	Severe disease	Occur with macrophage activation syndrome (MAS)
Anti-Phospholipid Antibodies	Prevalence unknown, reported in pediatric and elderly patients associated with infarcts	Seen in 20-40% patients
Management	Chloroquine (CQ) and hydroxychloroquine (HCQ), tocilizumab	CQ. HCQ, conventional DMARDs, bDMARD including rituximab, belimumab, tocilizumab

FIGURE 1 Comparison of demographic and clinical characteristics between COVID-19 and systemic lupus erythematosus (SLE). Demographic characteristics are dissimilar except ethnicity, and there are similarities in immuno-pathogenic features among the 2 diseases including type I interferon (IFN) expression, increased cytokine levels and therapeutic targets. Older males and non-White population may be at risk for fatal outcomes in COVID-19, whereas young females are less likely to develop severe COVID-19 disease. Will the surviving females develop lupus or antiphospholipid syndrome (APS) in the future?

As on 16 June 2020, mortality rate (deaths/ total cases) of COVID-19 infection in Europe, North America, Asia and Africa are 8.2%, 5.8%, 2.5% and 2.7% respectively.[13]

However, mortality rate of COVID19 in the USA is disproportionately higher among Blacks (92.3 deaths per 100 000 population) and Hispanics/Latino Americans (74.3 deaths per 100 000 population) than the White American population (45.2 deaths per 100 000).[14,15] Blacks, Asians and minority ethnic (BAME) groups are also found to have higher COVID19 mortality rates when compared to White ethnic groups in the UK. People of Chinese, Indian, Pakistani, other Asian and Caribbean origin as well as other Black ethnicities with COVID-19 infection had 10%-50% higher risk of death when compared to the White British population.[16]

These ethnic discrepancies in COVID-19 mortality, therefore, are not because of any genetic factors unlike that in SLE. It is essentially due to socioeconomic disadvantages, different cultural and health-seeking behavior as well as various disadvantages related to their occupations.

Or, do the lifestyle changes among the migrants in the USA and Europe unfold underlying metabolic syndrome (obesity/central obesity, hypertension/diabetes and related cardiovascular complications), a known risk factor for higher mortality in SARS-CoV illnesses?

3 | BASIC IMMUNE INJURIES IN COVID-19 - A DEJA VU OF LUPUS-LIKE AUTOIMMUNITY

Major immunological mechanisms in COVID-19 include:

1. Late Type I IFN-driven immune activities
2. Adaptive immune responses
3. Cytokine storm
4. Age-related differential immune response: innate versus adaptive immunity
5. Production of antiphospholipid antibodies as well as thromboembolic processes.

3.1 | Type I IFNs act as key players in HCoV-induced immuno-inflammation

Type I IFNs are produced by host cells against viruses including HCoV and recent strain like SARS-CoV-2.[17] Type I IFN is required at early stages of infection for proper T-cell activation. Type I IFN secretion and its response by receptor cells is highly dependent upon age. CD4 T-cells from younger individuals require less amount of IFN for activation and survival as compared to older individuals.[18] This might be the reason for older persons being highly susceptible to SARS-CoV2 infection.

Ethnicity also influences type I IFN secretion, as Asians and African Americans have higher type I IFN expression in peripheral blood cells as compared to Caucasians.[19,20] This observation goes hand in hand with prevalence of lupus in these ethnicities, a predominantly type 1 IFN-driven disease.

Type I IFN expression is also lower in male individuals compared to females, again keeping in line with high female predominance in lupus.

Body mass index (BMI) and smoking also increases type I IFN expression and inflammatory cytokines.[20] These 2 risk factors tend to adversely affect outcome of COVID-19 disease as well as lupus and other systemic autoimmune diseases.[21-23]

These reports suggest that gender, ethnicity, BMI and smoking affect type I IFN secretion. Hence, male gender, African ancestry, high BMI and smoking are risk factors for severe or critical COVID-19 disease[21]; interestingly, these are also risk factors for severe lupus.[23]

Several coronavirus proteins antagonize the IFN response in the host cell, thereby enhancing viral survival. Papain-like proteases (PLP) from SARS-CoV antagonize IFN-β induction by blocking STING (stimulator of interferon genes)-mediated signaling.[24]

On the other hand, impaired clearance of apoptosis products in SLE patients leads to generation of membrane vesicles containing double-stranded DNA (dsDNA) which induces Type I IFN production via the cyclic guanosine monophosphate – adenosine monophosphate (GMP-AMP) synthase (cGAS)–STING pathway.[25]

Delayed type I IFN secretion and response is associated with SARS and acute lung injury. Improper T-cell activation leads to infiltration of inflammatory monocytes-macrophages in the lung resulting in cytokine storm-mediated tissue injury and fatal outcome.[26]

Inhibition of type I IFN would be an effective choice to reduce mortality in a subset of SARS patients who have delayed and inappropriate type I IFN secretion.

Similar phenomenon is observed in animals infected with MERS-CoV and early IFN treatment is effective in preventing viral replication and delayed IFN response that causes fatal pneumonia with infiltrating monocytes, macrophages and neutrophils.[27]

Chloroquine (CQ) and HCQ are inhibitors of type I IFN secretion by preventing recognition of viral RNA by TLR7 and 8. However, type I IFN secretion during the early stage of coronavirus infection would protect and limit viral load in the host. Therefore, characterization of patients who would develop delayed type I IFN response is very crucial and antimalarial compounds could be effective in this subset of patients.

Major cellular source of type I IFN is plasmacytoid dendritic cells (pDCs), which recognize murine coronavirus MHV and human SARS-CoV viral RNA through TLR7.[28]

This mechanism of type I IFN induction is strikingly similar to that of SLE. Early secretion of type I IFN by pDCs is important for controlling viral replication and preventing dissemination of virus to major organs. Depletion of pDCs results in loss of antiviral type I IFN response and impaired survival of virus-specific natural killer (NK) or CD8+ T-cells.[29] Numbers of pDCs gradually decrease as age increases, whereas there is no change in conventional DC (cDC) cells.[30] This may be the reason for reduced antiviral IFN responses in older age and increased mortality among the elderly due to COVID-19.

There is nearly 8-fold higher secretion of type I IFN by pDCs upon recognition of MERS-CoV compared to that of SARS-CoV.[31] This may be one of the factors contributing to the higher mortality rate observed in MERS than SARS and COVID-19.

Type III IFN (IFN-λ) secretion is also higher by coronavirus-infected pDC and its levels were similar to that of type I IFN. Signal transducer and activator of transcription 1 (STAT1) knockout mice were more susceptible to SARS-CoV infection compared to IFN receptor knockout mice.[32] SARS ORF6 protein blocks nuclear translocation of phosphorylated STAT1 (p-STAT1), thereby preventing downstream signaling of type I IFN. In contrast, MERS-CoV doesn't prevent p-STAT translocation in IFN-α treated cells.[33] This implicates that STAT1-mediated IFN response plays an important role in SARS pathogenesis.

In addition to TLR7 and STING, TLR3 also contributes protective immune response against SARS-CoV infection in early disease through TRIF-mediated signaling and induction of IFN-β.[34] Early recognition of TLR3 is required for mounting viral-specific T-cell responses in mice infected with a mouse-adapted version of the coronavirus (MA15).[35] TLR3/7-mediated recognition of viral RNA results in induction of type I IFN, and it also activates nuclear factor-κβ thereby promoting expression of various pro-inflammatory cytokines in host cells.[34]

In summary, both HCoV-mediated diseases and SLE have robust production of type I IFN. In both conditions, pDC is a major cellular source for type I IFN via TLR7 and cGAS–STING signaling, as well as via the TLR3 pathway, a relatively lesser known mechanism.

3.2 | Adaptive immune responses

Early response to SARS-CoV-2 infection is mediated by CD8 cells. Dramatic reduction in the number of CD4 and CD8 T-cells during the acute phase of infection in patients of SARS and COVID-19 are uniformly reported. Decrease in activated CD8 T cells and increase in antibody-secreting B-cells as well as circulating T follicular helper cells (cTFH cells) during convalescence phase of COVID-19 are other encountered observations.[36] Low levels of T-cells (CD3+), both CD4 + T-cells and CD8 + T-cells, are also associated with severity and hospital death in COVID-19.[8,9,37]

Neutrophil to lymphocyte ratio as a predictor for severity in COVID-19 has also been studied.[11] IFN-γ-producing CD4 T-cells were much lower in number in severe cases compared to moderate COVID-19 patients.[9] However, Wang et al reported that IFN-γ-producing CD4 T-cells and CD8 T-cells were higher in critically severe and severe cases compared to mild patients.[38]

SARS-CoV-2-specific antibodies can be detected from day 7 of illness and they last for 50 days in patients with COVID-19.[39] This shows that antibody-producing plasma B-cells are increased in blood and they are protective against SARS-CoV-2 infection.[40] In summary, low T-cells and B-cells in patients with COVID-19 during early periods of SARS-CoV-2 infection may be warning of ensuing severe disease; and antibody-secreting B-cells rise in number during the recovery stage. Further studies on profiling of immune cells in longitudinal samples at various stages of illness will be required to understand the role of adaptive immune response in COVID-19.

Most of the evidence for the role of memory T-cell response in HCoV was obtained from animal studies of SARS-CoV. CD4 T-cells are required for activation of B-cells during SARS-CoV and SARS-CoV-2 infection. During the early period of SARS-CoV infection, rapid response cytotoxic lymphocyte (CTL) actions contribute to clearance of viruses in mice.[41] SARS-CoV Ag-specific immune responses were measured in a study after 6 years of SARS outbreak and showed that memory T-cell responses can be seen in 60% of patients, but memory B cell responses were undetectable.[42] Memory T-cells reside in the lung for long-term protection against SARS-CoV.

Similar observations were noted from other studies showing persistence of memory T-cells against coronavirus up to a decade following the infection.[43,44]

Type I IFN is required for activation of CD4 Th1 cells that sustain antiviral response of CD8 CTLs. In parallel, type I IFN is also required for differentiation of TFH cells that mediate B cell differentiation and antibody production.[45] Therefore, type 1 IFN are crucial for immediate and long-term protection against COVID-19.

3.3 | Cytokine storm

Wide variability in cytokine secretion patterns that is noticed among patients with SARS and COVID-19 determines the course of disease.

Pre-existing comorbidities of these patients also synergistically alter cytokine levels and decide outcome. ARDS, disseminated intravascular coagulation and multiple-organ failure rapidly progress in severe COVID-19 patients, leading to death within 7 to 14 days of intensive care unit admission. Increased infiltration of neutrophils and macrophages as well as secretion of high levels of pro-inflammatory cytokines result in a condition called cytokine storm.[46] Cytokine storm could be the leading cause for respiratory complications and multi-organ failure in patients with COVID-19.

Reduced lymphocytes, increased cytokine levels and abnormal coagulation parameters are frequent in these cases. Reduced IFN levels and increased viral load are higher in critical and severe cases as compared to mild to moderate patients with COVID-19.[47] In view of diminished lymphocyte and dendritic cell function, neutrophils and macrophages take over antiviral defense response.[47] Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) are major pro-inflammatory cytokines secreted by these cells that induce tissue damage, eventually leading to alveolar flooding and fibrosis.[48]

Cytokine storm is also a relatively common complication in patients with SLE, systemic juvenile idiopathic arthritis (SoJIA) and adult-onset Still's disease in the form of the severe complication called macrophage activation syndrome (MAS). Pattern and serum levels of cytokines in COVID-19, mainly that of IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-6, IL-10, IFN-γ inducible protein (IP-10), and TNF-α in severe and critical cases of COVID-19 is similar to that of MAS and hemophagocytic lymphohistiocytosis (HLH).[49,50] Clinical and laboratory markers of HLH/MAS such as fever, elevated levels of acute phase reactants (CRP, serum amyloid A, ferritin) are common in patients with severe COVID-19.[50-52]

Thus COVID-19 in severe and critical patients display features like MAS leading to severe respiratory failure.[50] Treatment regimes designed to reduce cytokine levels that are shown to be beneficial for critical patients with COVID-19 include infusion of tocilizumab (IL-6 blocker), anakinra (IL-1 blocker) and plasma exchange.[50,52,53] Immunosuppression by conventional DMARDs including low-dose glucocorticoids may be useful in these patients as reported by some, even though there is no evidence or supportive data yet from any clinical trials.

3.4 | Age-related differential immune responses in COVID-19: innate versus adaptive immunity

Age-dependent altered innate immune response to HCoV was studied in a mice model. Young mice infected with SARS-CoV efficiently cleared the virus. In contrast, aged mice showed exacerbated immune response to virus with increased lymphocyte infiltration in lungs. During initial infection in young mice, activation of innate immune cells, namely pDC, macrophages and NK cells were involved in viral clearance. However, this response was not effective in aged mice to contain the virus; instead, a robust cytokine storm and altered lung pathology followed the immunological war against the virus in older mice.[54] In a macaque model of SARS-CoV infection too, aged macaques had more severe lung pathology, lower expression of type I IFN and higher expression of pro-inflammatory cytokines as compared to younger macaques.[55] As mentioned earlier, SARS-CoV2 infects hosts equally across all age groups, but complications

and fatality are noted much more commonly in older populations. Early type I IFN response is important for preventing HCoV-mediated inflammation and severe disease.[27] Both IFN secretion from innate cells like pDC and response threshold by its receptor in T-cells are impaired in older age as compared to young individuals.[18,29,30] Delayed IFN response causes apoptosis of T-cells and recruitment of monocytes and neutrophils, leading to cytokine storm and lung injury.[26,48] Inflammation in the form of chronic subclinical systemic inflammation and immune senescence, that is reflected by blunted and impaired immune response, are other factors contributing to age-related differential COVID-19 pathogenesis.[56]

On the other hand, SARS-CoV-2-associated multisystem inflammatory syndrome in children (MIS-C), mimicking Kawasaki disease (KD) are reported across several nations of the world.[59-61] Such inflammatory responses are often associated with elevated serum ferritin levels. Kawasaki-like diseases have also been reported in some immunodeficiency states.[60] It is likely that children with MIS-C may have some underlying immunodeficiency state that is triggered into an auto-inflammatory syndrome by COVID-19 infection; only future studies can reveal exact immunological mechanisms behind this unique mimic of KD.

3.5 | Antiphospholipid antibodies

Presence of antiphospholipid antibodies (aPL) were reported in several case series and case reports including pediatric patients with COVID-19 infection.[53,61,62] aPL was associated with coagulopathy and multiple infarcts in these patients. aPL is seen in patients with several post-viral infection states and usually those are transient. Plasma exchange decreases aPL titer levels in patients with COVID-19.[53] Positive lupus anticoagulant (LAC) is also seen in patients with COVID-19 and is often associated with thrombosis.[63-65] However, associations of aPL negative state in COVID-19 patients with thrombotic complications (venous thromboembolism) were also observed.[66] Recommendation of American Society of Hematology (ASH) is against testing of aPL in COVID-19 unless there is prior history of antiphospholipid syndrome (APS) and other clinical indications exist.[67] aPL Ab can be transiently positive at times in several acute infections as mentioned above, various states of inflammation, or thrombosis. The International Society on Thrombosis and Haemostasis (ISTH) guideline recommends repeat confirmatory laboratory testing 12 weeks apart to diagnose APS. Therefore, ASH recommendation in isolation may be a hindrance to the understanding of an important immunological event in COVID-19, even if the presence of aPL Ab is transient.

4 | THE HCQ STORY - BIOLOGICAL BASIS FOR ITS USE IN COVID-19 INFECTION AND LUPUS SPECTRUM DISEASES

During recent times, HCQ has been subjected to huge discussions in relation to its benefit and harm in COVID-19; its role in autoimmune diseases like rheumatoid arthritis (RA) and lupus are already established.

4.1 | Mechanisms of action by antimalarials in SARS, COVID-19 and SLE

Antimalarial agents, chloroquine (CQ) and HCQ are drugs of choice for various connective tissue diseases. Both are immunomodulatory agents; unlike immunosuppressants, these drugs are safer for patients with chronic diseases. Role and mechanism of HCQ in management of autoimmune rheumatic diseases is discussed in a recent review.[68] Here we discuss its perspectives in COVID-19 (Figure 2).

CQ and HCQ not only interfere with TLR7/8-mediated signaling, there is evidence that it has an effect on TLR3 also. CQ inhibit IFN-β secretion and phosphorylation of STAT1 in human mesangial cells treated with TLR3 agonist polyinosinic-polycytidylic acid (poly I:C).[69] This may be one more effective mechanism of CQ and HCQ in treatment of lupus nephritis patients. As mentioned above, TLR3 also recognize SARS-CoV dsRNA and activates transcription factors IFN regulatory factor 3 (IRF3) and NF-κB, which in turn induces gene expression of type I IFN and several pro-inflammatory cytokines. CQ reduces poly I:C, ligand for TLR3-induced human lung endothelial barrier permeability by inhibition of pro-inflammatory cytokines and by increasing expression of tight junction protein.[70] Thus CQ and HCQ are effective in treatment of SARS and COVID-19 by preventing immunological injury to lungs. CQ and HCQ also inhibit the cGAS–STING pathway, thereby suppressing IFN-β secretion.[68,71,72]

ACE2 and transmembrane serine protease 2 (TMPRSS2) are IFN inducible proteins in humans, but not in mice. Coronavirus strains SARS-CoV-2 and SARS-CoV exploits these protein machineries to gain entry into host cells.[73] Inhibition of expression of IFN inducible genes by CQ and HCQ could have a role in prevention of cellular entry of these human coronavirus strains.

CQ and HCQ may also inhibit entry of SARS-CoV-2 by preventing maturation of endosomes due to its alkalization action and thereby impair viral replication.[74] CQ can also inhibit SARS-CoV multiplication by interfering in glycosylation of cellular receptor ACE2 and S-protein of virion.[75]

Moreover, CQ and HCQ are antithrombotic in action and they are approved drugs for APS. Hence it may be all the more relevant in COVID-19, especially in the light of several autopsy studies showing extensive thromboembolic processes in lungs, heart and elsewhere as a major finding. However, CQ or HCQ should be avoided if a patient has myocarditis or QT prolongation by electrocardiogram (ECG) due to COVID itself or induced by any other agent including other concurrently used drugs.

In summary, antimalarials CQ and HCQ mechanistically prevent interaction of ligand-receptors of TLR7, TLR3 and cGAS–STING and thereby inhibit type I IFN response. They also may prevent thromboembolic events in COVID-19 with or without the presence of antiphospholipid antibodies.

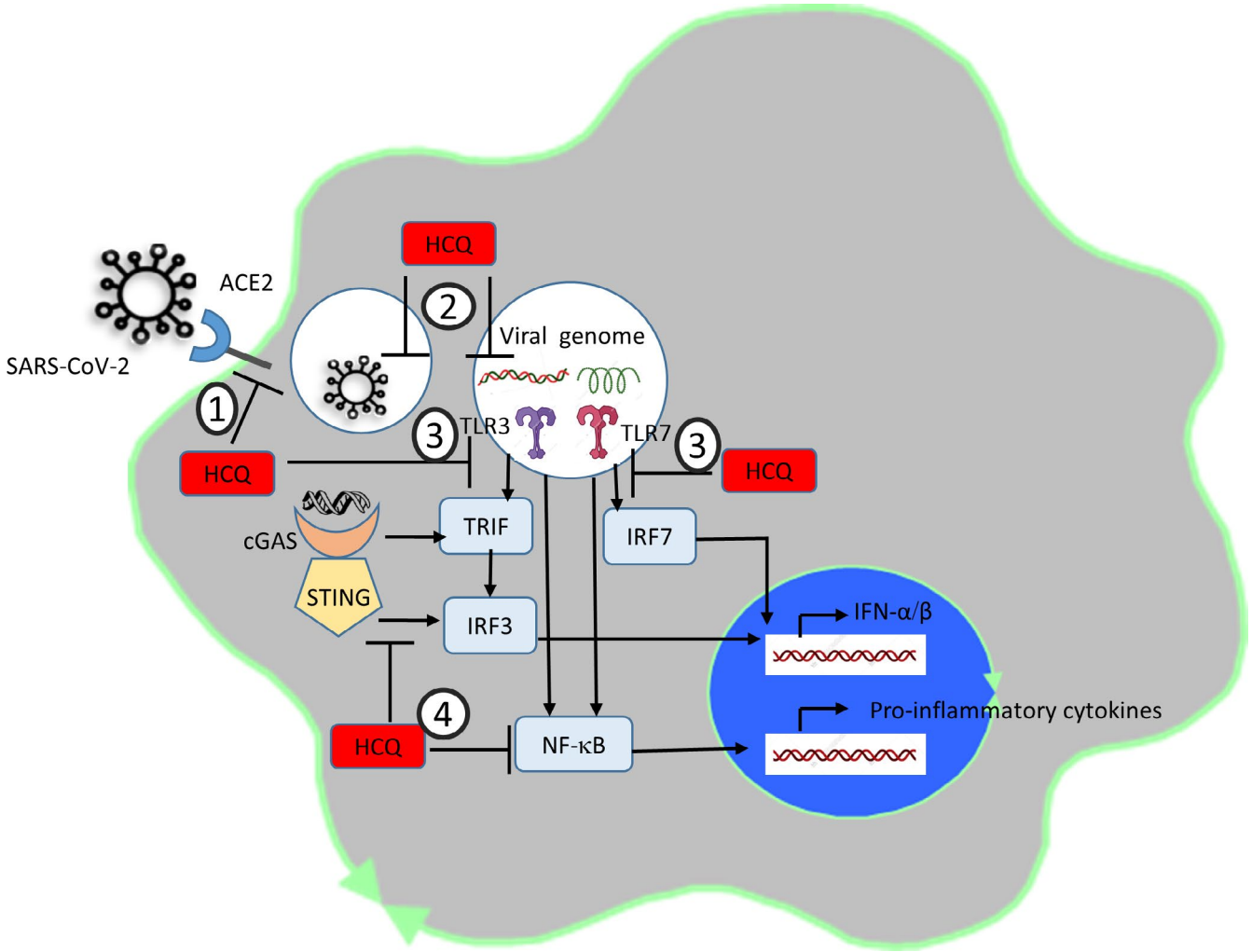


FIGURE 2 Hydroxychloroquine (HCQ) inhibits SARS-CoV-2 entry and inhibits virus-induced type I interferon (IFN) signaling and pro-inflammatory cytokines production. Here are the various pathways: 1. Angiotensin I converting enzyme 2 (ACE2) is an inducible gene. HCQ inhibit type I IFN, thereby inhibit ACE expression. Also HCQ may inhibit n-terminal glycosylation of ACE2. 2. HCQ can also inhibit viral entry by disrupting endosomal acidification. 3. HCQ alters endosomal pH, there by disrupts ligand binding to Toll-like receptor 3 (TLR3) and TLR7. 4. HCQ inhibit cGAS–STING (stimulator of interferon genes) signal and thereby reduce type I IFN and pro-inflammatory cytokines expression

4.2 | Clinical scenario – HCQ in COVID-19

In a small randomized controlled trial, treatment with HCQ was associated with reduced viral load and improvement in radiological progression on computed tomography images in patients with COVID-19.[76] However, another clinical study involving 11 patients showed failure of HCQ to clear viral load and no clinical benefit.[77]

In an observational study, administration of HCQ in severe COVID-19 patients has shown no benefit in preventing intubation or death.[78] In other randomized and clinical observational studies, HCQ was not shown to be beneficial for patients who are transferred to the intensive care unit.[79]

These studies were different in terms of dose of medication, day of starting treatment, primary endpoint and selection bias of severity (Table S1). Therefore, randomized clinical trials with larger sample size is warranted for testing its efficacy.

On the other hand, HCQ has been recommended as prophylactic regimen specifically for healthcare workers in India.[80] HCQ has not shown any benefit in severe forms of SARS-CoV-2 infection among patients with SLE.[81] However currently there is paucity of studies to establish its prophylactic role, till results of several ongoing studies are out. Results of larger studies from European Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy) and registry from Global Rheumatology Alliance will provide data regarding efficacy of HCQ in treatment of COVID-19. Based on biological basis, it appears feasible that HCQ may be useful in patients who have delayed type I IFN response even if the results of these trials are negative. Measurement of IFN signature score may be employed to identify these subsets of patients in order to prescribe HCQ in COVID-19 infection in a more personalized manner. Physicians need to understand while recommending HCQ to patients with COVID-19 that it is a mild immunomodulatory

agent and not an immunosuppressant. While its use in hospitalized COVID-19 patients are not yet proven to be beneficial, several developing nations are using it in early disease and as a pre-exposure prophylaxis for frontline healthcare workers exposed to SARS-CoV-2, as recommended by Indian Council of Medical Research (ICMR)[80] (Table S1).

5 | IMPLICATIONS FOR RHEUMATOLOGISTS IN THE POST-COVID-19 ERA

Presumable viral etiologies have been known for many connective tissue diseases. We might very well expect SARS-CoV-2 triggered development of autoantibodies. Some available evidence to support this notion are discussed in the following paragraphs.

Autoantibodies seen in patients with SARS are mostly targeted to antigens expressed in lung tissue. Human long interspersed nuclear element 1 (LINE1) gene endonuclease (EN) domain protein is one such autoantigen. Anti-EN antibody is seen in 40% of patients with SARS.[82] LINE1 is a well characterized autoantigen in patients with SLE. LINE1 encoded RNA induces type I IFN in patients with SLE and primary Sjögren's syndrome through the TLR7-dependent pathway in pDC and TBK1/IKKε pathways in monocytes.[83] A recent study found that antinuclear antibodies (ANA) (35%), antiphospholipid antibodies (4%) and lupus anticoagulant (40%) were present in COVID-19 patients with pneumonia.[84] Around 80% of patients in this study were male and this observation strongly suggests that elderly male COVID-19 patients may develop autoimmune rheumatic diseases in the future. Further confirmatory studies are warranted to reproduce this finding.

Injection of convalescent sera from SARS patients to rhesus macaques also causes lung injury with similar histopathological features as in human disease.[85] Thus convalescent sera containing autoantibodies or other antiviral antibodies might cross-react with antigens expressed in the lung. This has to be kept in mind while recommending over enthusiastic use of convalescent sera/plasma therapy in critically ill covid 19 cases.

High titers of anticardiolipin antibodies are also seen in SARS patients presenting with osteonecrosis.[86]

In vitro experiments also reveal that sera of SARS patients contain autoantibodies targeting pulmonary epithelial cells and endothelial cells.[87]

Another in vitro experimental study demonstrated anti-S2 spike antibodies in sera of SARS patients that can bind to epithelial cells inducing cytotoxic injury.[88]

Sera from patients with autoimmune diseases like mixed connective tissue disease, and RA were found to have higher positivity for anti-SARS-CoV IgG and IgM as compared to healthy controls.[89] False positivity was also reported for anti-SARS-CoV antibodies in patients with SLE.[90] Cross-reactivity between anti-SARS-CoV antibodies and autoantibodies targeting the same antigenic target is possible. However, autoantibodies in SARS specifically bind to antigens expressed in lung tissue, and are not expected against cell nuclei (like ANA), against smooth muscles (like SMA) or against parietal cells (like PCA).[91] These studies show that both SARS-CoV and SARS-CoV-2 infections might induce expression of ANA and aPL antibodies.[84] Further studies are needed to delineate the spectrum and pattern of developing autoantibodies in patients with COVID-19.

Systemic vasculitis was noted in an autopsy study from 3 patients who died from SARS.[92] Simultaneous diagnosis of COVID-19 and KD was also made in a 6-month-old child.[93] Outbreak of Kawasaki-like diseases is reported in 10 children, 8 of them were positive for either SARS-CoV-2 by nasal swab or antibodies.[57] Pediatric patients who were positive for SARS-CoV-2 IgG also developed cutaneous vasculitis lesions.[94] Development of cutaneous small vessel vasculits was seen in elderly female COVID-19 patients also on the 7th day after onset of symptoms.[95] SARS-CoV-2 infects endothelial cells and induces apoptosis as well as pyroptosis resulting in multi-organ dysfunction.[96] These show HCoV not only targets lungs, but can infect blood vessels, thereby causing multi-organ damage.

In summary, ANA and aPL autoantibodies can be seen in patients with SARS and COVID-19. Theoretically, these patients may have higher chances to develop autoimmune diseases in future, like APS or a lupus spectrum disorder. Rheumatologists will have to wait for the post-COVID-19 era to witness any unfolding of events towards a rising prevalence of lupus, vasculitic process or APS.

6 | CONCLUSION

Complications and fallouts of COVID-19 disease have some similarities as well as dissimilarities with autoimmune diseases like SLE. While male gender, older age and people with metabolic syndrome seem to be at a higher risk of contracting more severe SARS-CoV-2 infection, younger females of African and Asian ancestry have higher risk for developing SLE; male gender among lupus patients, however, is an independent risk factor for severe disease.

Delayed type I IFN secretion contributes to pneumonia-like complications in COVID-19. Increased type I IFN secretion, presence of aPL antibodies and cytokine storm are common immunological pathologies in lupus as well as COVID-19. Management of COVID-19 using HCQ as a pre-exposure prophylactic agent and biological DMARDs (like tocilizumb) in advanced disease are reported to be useful in specific subsets of patients. It will be interesting to note if rheumatologists encounter newer presentations of systemic autoimmune rheumatic diseases in the near future, especially that of any unusual lupus spectrum disease following a recent trigger by SARS-CoV-2 infection.

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REFERENCES

1. COVID-19 Map [Internet]. Johns Hopkins Coronavirus Resource Center. [cited 2020 Jun 2]. Available from: https://coronavirus.jhu.edu/map.html
2. Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. *J Infect*. 2020;80(6):656-665.
3. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol*. 2016;16(10):626-638.
4. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271-280.e8.
5. Tukiainen T, Villani A-C, Yen A, et al. Landscape of X chromosome inactivation across human tissues. *Nature*. 2017;550(7675):244-248.
6. Stelzig KE, Canepa-Escaro F, Schiliro M, Berdnikovs S, Prakash YS, Chiarella SE. Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. *Am J Physiol Lung Cell Mol Physiol*. 2020;318:L1280-L1281.
7. Li M-Y, Li L, Zhang Y, Wang X-S. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty*. 2020;9(1):45.
8. Xu BO, Fan C-Y, Wang A-L, et al. Suppressed T cell-mediated immunity in patients with COVID- 19: A clinical retrospective study in Wuhan, China. *J Infect*. 2020;81(1):e51-e60.
9. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Investig*. 2020;130(5):2620-2629.
10. Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S. Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. *J Immunol Baltim Md*. 1950;198(10):4046-4053.
11. Li L-Q, Huang T, Wang Y-Q, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol*. 2020;92(6):577-583.
12. Carter EE, Barr SG, Clarke AE. The global burden of SLE: prevalence, health disparities and socioeconomic impact. *Nat Rev Rheumatol*. 2016;12(10):605-620.
13. Coronavirus Update (Live): 8,120,087 Cases and 439,228 Deaths from COVID-19 Virus Pandemic - Worldometer [Internet]. [cited 2020 Jun 16]. Available from: https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1?%22.
14. Kirby T. Evidence mounts on the disproportionate effect of COVID-19 on ethnic minorities. *Lancet Respir Med*. 2020;8(6):547-548.
15. Bhala N, Curry G, Martineau AR, Agyemang C, Bhopal R. Sharpening the global focus on ethnicity and race in the time of COVID-19. *Lancet*. 2020;395(10238):1673-1676. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31102-8/abstract
16. Beyond the Data: Understanding the Impact of COVID-19 on BAME Communities. *69*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/892376/COVID_stakeholder_engagement_synthesis_beyond_the_data.pdf
17. Mantlo E, Bukreyeva N, Maruyama J, Paessler S, Huang C. Antiviral activities of type I interferons to SARS-CoV-2 infection. *Antiviral Res*. 2020;179:104811.
18. Li G, Ju J, Weyand CM, Goronzy JJ. Age-associated failure to adjust type I IFN receptor signaling thresholds after T cell activation. *J Immunol*. 2015;195(3):865-874.
19. McDade TW, M. Ross K, L. Fried R, et al. Genome-wide profiling of RNA from dried blood spots: convergence with bioinformatic results derived from whole venous blood and peripheral blood mononuclear cells. *Biodemography Soc Biol*. 2016;62(2):182-197.
20. Cole SW, Shanahan MJ, Gaydosh L, Harris KM. Population-based RNA profiling in add health finds social disparities in inflammatory and antiviral gene regulation to emerge by young adulthood. *Proc Natl Acad Sci*. 2020;117(9):4601-4608.
21. Ho FK, Celis-Morales CA, Gray SR, et al. Modifiable and non-modifiable risk factors for COVID-19: results from UK Biobank [Internet]. *Epidemiology*. 2020. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.28.20083295. [Epub ahead of print].
22. Santos MJ, Vinagre F. Body composition phenotypes in systemic lupus erythematosus and rheumatoid arthritis: a comparative study of Caucasian female patients. *Clin Exp Rheumatol*. 2011;29:470-476.
23. Andrade RM, Alarcón GS, Fernández M, Apte M, Vilá LM, Reveille JD. Accelerated damage accrual among men with systemic lupus erythematosus: XLIV. Results from a multiethnic US cohort. *Arthritis Rheum*. 2007;56(2):622-630.
24. Sun L, Xing Y, Chen X, et al. Coronavirus papain-like proteases negatively regulate antiviral innate immune response through disruption of STING-mediated signaling. *PLoS One*. 2012;7(2):e30802.
25. Kato Y, Park JH, Takamatsu H, et al. Apoptosis-derived membrane vesicles drive the cGAS–STING pathway and enhance type I IFN production in systemic lupus erythematosus. *Ann Rheum Dis*. 2018;77(10):1507-1515.
26. Channappanavar R, Fehr A, Vijay R, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. *Cell Host Microb*. 2016;19(2):181-193.
27. Channappanavar R, Fehr AR, Zheng J, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. *J Clin Invest*. 2019;29(130):3625-3639.
28. Cervantes-Barragan L, Züst R, Weber F, et al. Control of coronavirus infection through plasmacytoid dendritic-cell–derived type I interferon. *Blood*. 2007;109(3):1131-1137.
29. Swiecki M, Gilfillan S, Vermi W, Wang Y, Colonna M. Plasmacytoid dendritic cell ablation impacts early interferon responses and antiviral NK and CD8+ T cell accrual. *Immunity*. 2010;33(6):955-966.
30. Pérez-Cabezas B, Naranjo-Gómez M, Fernández MA, Grífols JR, Pujol-Borrell R, Borràs FE. Reduced numbers of plasmacytoid dendritic cells in aged blood donors. *Exp Gerontol*. 2007;42(10):1033-1038.
31. Scheuplein VA, Seifried J, Malczyk AH, et al. High secretion of interferons by human plasmacytoid dendritic cells upon recognition of middle east respiratory syndrome coronavirus. *J Virol*. 2015;89(7):3859-3869.
32. Frieman MB, Chen J, Morrison TE, et al. SARS-CoV pathogenesis is regulated by a STAT1 dependent but a type I, II and III interferon receptor independent mechanism. *PLoS Pathog*. 2010;6:e1000849.
33. de Wilde AH, Raj VS, Oudshoorn D, et al. MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-α treatment. *J Gen Virol*. 2013;94(8):1749-1760.
34. Totura AL, Baric RS. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon. *Curr Opin Virol*. 2012;2(3):264-275.
35. Zhao J, Zhao J, Van Rooijen N, Perlman S. Evasion by stealth: inefficient immune activation underlies poor T cell response and severe disease in SARS-CoV-infected mice. *PLoS Pathog*. 2009;5(10):e1000636.
36. Thevarajan I, Nguyen THO, Koutsakos M, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. *Nat Med*. 2020;26(4):453-455.
37. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *J Infect Dis*. 2020;221(11):1762-1769.
38. Wang F, Hou H, Luo Y, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. *JCI Insight*. 2020;5(10):e137799.

39. Wang B, Wang L, Kong X, et al. Long-term coexistence of SARS-CoV-2 with antibody response in COVID-19 patients. *J Med Virol*. 2020. https://doi.org/10.1002/jmv.25946. [Epub ahead of print].
40. Wen W, Su W, Tang H, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discov*. 2020;6:31.
41. Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to respiratory coronaviruses. *Immunol Res*. 2014;59(1):118-128.
42. Tang F, Quan Y, Xin Z-T, et al. Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. *J Immunol*. 2011;186(12):7264-7268.
43. Ng O-W, Chia A, Tan AT, et al. Memory T cell responses targeting the SARS coronavirus persist up to 11 years post-infection. *Vaccine*. 2016;34(17):2008-2014.
44. Da Guan W, Mok CKP, Chen ZL, et al. Characteristics of traveler with Middle East Respiratory Syndrome, China, 2015. *Emerg Infect Dis*. 2015;21(12):2278-2280.
45. Snell LM, Osokine I, Yamada DH, De la Fuente JR, Elsaesser HJ, Brooks DG. Overcoming CD4 Th1 cell fate restrictions to sustain antiviral CD8 T cells and control persistent virus infection. *Cell Rep*. 2016;16(12):3286-3296.
46. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev*. 2020;19(6):102537.
47. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and exacerbated inflammatory responses in severe Covid-19 patients. *medRxiv*. 2020:20068015. https://doi.org/10.1101/2020.04.19.20068015
48. Vardhana SA, Wolchok JD. The many faces of the anti-COVID immune response. *J Exp Med*. 2020;217(6):e20200678.
49. Yang Y, Shen C, Li J, et al. Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. *medRxiv*. 2020.
50. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microb*. 2020;27:992-1000.
51. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*. 2020;395(10229):1054-1062.
52. Henderson LA, Canna SW, Schulert GS, et al. On the alert for cytokine storm: immunopathology in COVID-19. *Arthritis Rheumatol*. 2020;72:1059-1063.
53. Ma J, Xia P, Zhou Y, et al. Potential effect of blood purification therapy in reducing cytokine storm as a late complication of critically ill COVID-19. *Clin Immunol*. 2020;214:108408.
54. Baas T, Roberts A, Teal TH, et al. Genomic analysis reveals age-dependent innate immune responses to severe acute respiratory syndrome coronavirus. *J Virol*. 2008;82(19):9465-9476.
55. Smits SL, de Lang A, van den Brand JMA, et al. Exacerbated innate host response to SARS-CoV in aged non-human primates. *PLoS Pathog*. 2010;6(2):e1000756.
56. Bonafè M, Prattichizzo F, Giuliani A, Storci G, Sabbatinelli J, Olivieri F. Inflamm-aging: Why older men are the most susceptible to SARS-CoV-2 complicated outcomes. *Cytokine Growth Factor Rev*. 2020;53:33-37.
57. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771-1778.
58. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020. https://doi.org/10.1001/jama.2020.10369. [Epub ahead of print].
59. Pouletty M, Borocco C, Ouldali N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. *Ann Rheum Dis*. 2020. https://doi.org/10.1136/annrheumdis-2020-217960. [Epub ahead of print].
60. Johnson RM, Bergmann KR, Manaloor JJ, Yu X, Slaven JE, Kharbanda AB. Pediatric Kawasaki disease and adult human immunodeficiency virus Kawasaki-like syndrome are likely the same malady. *Open Forum Infect Dis*. 2016;3(3):ofw160.
61. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med*. 2020;382(17):e38.
62. Pain CE, Felsenstein S, Cleary G, et al. Novel paediatric presentation of COVID-19 with ARDS and cytokine storm syndrome without respiratory symptoms. *Lancet Rheumatol*. 2020;2(7):e376-e379.
63. Beyrouti R, Adams ME, Benjamin L, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry*. 2020. https://doi.org/10.1136/jnnp-2020-323586. [Epub ahead of print].
64. Harzallah I, Debliquis A, Drénou B. Lupus anticoagulant is frequent in patients with Covid-19. *J Thromb Haemost*. 2020;https://doi.org/10.1111/jth.14867. [Epub ahead of print].
65. Bowles L, Platton S, Yartey N, et al. Lupus anticoagulant and abnormal coagulation tests in patients with Covid-19. *N Engl J Med*. 2020;https://doi.org/10.1056/NEJMc2013656. [Epub ahead of print].
66. Zuo Y, Yalavarthi S, Shi H, et al. Neutrophil extracellular traps in COVID-19. *JCI Insight*. 2020;5(11):e138999. https://doi.org/10.1172/jci.insight.138999
67. COVID-19 and aPL Ab - Hematology.org [Internet]. [cited 2020 Jun 14]. Available from: https://www.hematology.org:443/covid-19/covid-19-and-apl-ab
68. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol*. 2020;16(3):155-166.
69. Imaizumi T, Hayakari R, Matsumiya T, et al. Chloroquine attenuates TLR3/IFN-β signaling in cultured normal human mesangial cells: A possible protective effect against renal damage in lupus nephritis. *Mod Rheumatol*. 2017;27(6):1004-1009.
70. Huang L-Y, Stuart C, Takeda K, D'Agnillo F, Golding B. Poly(I:C) induces human lung endothelial barrier dysfunction by disrupting tight junction expression of claudin-5. *PLoS One*. 2016;11(8):e0160875.
71. Ding C, Song Z, Shen A, Chen T, Zhang A. Small molecules targeting the innate immune cGAS-STING-TBK1 signaling pathway. *Acta Pharm Sin B*. 2020;https://doi.org/10.1016/j.apsb.2020.03.001. [Epub ahead of print].
72. An J, Woodward JJ, Sasaki T, Minie M, Elkon KB. Cutting edge: antimalarial drugs inhibit IFN-β production through blockade of cyclic GMP-AMP synthase–DNA interaction. *J Immunol*. 2015;194(9):4089-4093.
73. Ziegler CGK, Allon SJ, Nyquist SK, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell*. 2020;181(5):1016-1035.e19. https://doi.org/10.1016/j.cell.2020.04.035
74. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6(1):1-4.
75. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005;2(1):69.

76. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. *Zhejiang Xue Xue Bao Yi Xue Ban J Zhejiang Univ Med Sci*. 2020;49(2):215-219.
77. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Médecine Mal Infect*. 2020;50(4):384.
78. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med*. 2020;382(25):2411-2418.
79. Mahévas M, Tran V-T, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ*. 2020;14(369):m1844.
80. Revised advisory on the use of Hydroxychloroquine (HCQ) as prophylaxis for SARS-CoV-2 infection (in supersession of previous advisory dated 23rd March, 2020). 4. https://www.mohfw.gov.in/pdf/RevisedadvisoryontheuseofhydroxychloroquineasprophylaxisforSARSCOVID19infection.pdf
81. Mathian A, Mahevas M, Rohmer J, et al. Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine. *Ann Rheum Dis*. 2020;79(6):837-839.
82. He W, Shu C, Li B, Zhao J, Cheng Y. Human LINE1 endonuclease domain as a putative target of SARS-associated autoantibodies involved in the pathogenesis of severe acute respiratory syndrome. *Chin Med J (Engl)*. 2008;121(7):608-614.
83. Mavragani CP, Sagalovskiy I, Guo Q, et al. Long interspersed nuclear element-1 retroelements are expressed in patients with systemic autoimmune disease and induce type I interferon. *Arthritis Rheumatol*. 2016;68(11):2686-2696.
84. Gazzaruso C, Carlo Stella N, Mariani G, et al. High prevalence of antinuclear antibodies and lupus anticoagulant in patients hospitalized for SARS-CoV2 pneumonia. *Clin Rheumatol*. 2020;39(7):2095-2097
85. He W, Li B, Zhao J, Cheng Y. Safety of convalescent sera for the treatment of viral severe acuterespiratory syndrome: an experimental model in rhesus macaque. *Chin Med J (Engl)*. 2013;126(19):3790-3792.
86. Sun W, Wang B-L, Liu B-L, et al. Osteonecrosis in patients after severe acute respiratory syndrome (SARS): possible role of anticardiolipin antibodies. *JCR J Clin Rheumatol*. 2010;16(2):61-63.
87. Yang Y-H, Huang Y-H, Chuang Y-H, et al. Autoantibodies against human epithelial cells and endothelial cells after severe acute respiratory syndrome (SARS)-associated coronavirus infection. *J Med Virol*. 2005;77(1):1-7.
88. Lin YS, Lin CF, Fang YT, et al. Antibody to severe acute respiratory syndrome (SARS)-associated coronavirus spike protein domain 2 cross-reacts with lung epithelial cells and causes cytotoxicity. *Clin Exp Immunol*. 2005;141(3):500-508.
89. Wang Y, Sun S, Shen H, et al. Cross-reaction of SARS-CoV antigen with autoantibodies in autoimmune diseases. *Cell Mol Immunol*. 2004;1(4):304-307.
90. Wang YS, Shen H, Sun SH, et al. Analysis of false-positive associated with antibody tests for SARS-CoV in SLE patients. *Shi Yan Sheng Wu Xue Bao*. 2003;36(4):314-317.
91. Li B, He W, Liu Y, et al. Detection of autoimmune parameter of SARS patients. Zhonghua Shi Yan He Lin Chuang Bing Xue Za Zhi Zhonghua Shiyan He Linchuang Bingduxue Zazhi. *Chin J Exp Clin Virol*. 2005;19(2):121-123.
92. Ding Y, Wang H, Shen H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. *J Pathol*. 2003;200(3):282-289.
93. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. *Hosp Pediatr*. 2020;10(6):537-540. https://doi.org/10.1542/hpeds.2020-012
94. Papa A, Salzano AM, Di Dato MT, Varrassi G. Images in practice: painful cutaneous vasculitis in a SARS-Cov-2 IgG-positive child. *Pain Ther*. 2020. https://doi.org/10.1007/s40122-020-00174-4. [Epub ahead of print].
95. Dominguez-Santas M, Diaz-Guimaraens B, Abellas PG, del Real CM-G, Burgos-Blascoa P, Suarez-Valle A. Cutaneous small-vessel vasculitis associated with novel 2019 coronavirus SARS-CoV-2 infection (COVID-19). *J Eur Acad Dermatol Venereol*. 2020. https://doi.org/10.1111/jdv.16663. [Epub ahead of print].
96. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395(10234):1417-1418.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Kabeerdoss J, Danda D. Understanding immunopathological fallout of human coronavirus infections including COVID-19: Will they cross the path of rheumatologists?. *Int J Rheum Dis*. 2020;23:998–1008. https://doi.org/10.1111/1756-185X.13909