Autoantibodies and autoimmune disorders in SARS-CoV-2 infection: pathogenicity and immune regulation

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Abstract
Coronavirus disease 2019 (COVID-19) is an infectious disease associated with the respiratory system caused by the SARS-CoV-2 virus. The aim of this review article is to establish an understanding about the relationship between autoimmune conditions and COVID-19 infections. Although majority of the population have been protected with vaccines against this virus, there is yet a successful curative medication for this disease. The use of autoimmune medications has been widely considered to control the infection, thus postulating possible relationships between COVID-19 and autoimmune diseases. Several studies have suggested the correlation between autoantibodies detected in patients and the severity of the COVID-19 disease. Studies have indicated that the SARS-CoV-2 virus can disrupt the self-tolerance mechanism of the immune system, thus triggering autoimmune conditions. This review discusses the current scenario and future prospects of promising therapeutic strategies that may be employed to regulate such autoimmune conditions.

Keywords COVID-19 · Autoantibodies · SARS-CoV-2 · Active immunity · Passive immunity · Autoimmunity

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide pandemic from the early months of 2020 (Hossain et al. 2020). Many countries had failed to contain this virus, resulting in more than 2 million deaths worldwide, with the USA reporting the most number of deaths from the coronavirus disease 2019 (COVID-19) (Coronavirus deaths worldwide by country | Statista n.d.). To date, there is no clinically proven pharmaceutical medication that could provide a potential treatment for COVID-19-positive patients. Therefore, in an effort to contain the pandemic, measures are being taken to prevent the transmission of the virus (SanJuan-Reyes et al. 2021). The SARS-CoV-2 has a range of transmission dynamics. The virus can largely be transmitted through contact transmission, where the contact may be a direct form of contact, an indirect form of contact of even close contact. In addition, viral particles may also be transmitted through droplet transmission by direct inhalation of the infected droplets. Another form of transmission is airborne transmission, where the viral particles may be suspended in air and eventually be inhaled. Moreover, fomite transmission, faecal-oral transmission, bloodborne transmission, mother-to-infant transmission, and animal-to-human transmission are other forms of transmission (Hossain et al. 2020). There are several risk factors that have been studied and reported. Age has been one of the important risk factors, where individuals who are elderly with weak immune systems have been the most vulnerable to contract the virus (Zhong et al., 2020). Apart from this, immune status of the individual has also been a risk factor, where less immune people were largely affected by the virus. An underlying disease condition is another risk factor, where it has been reported that, there were relatively a greater number of people who were infected who had some form of underlying pathological condition. Other minor risk factors are sex, blood group, and travel history to a geographical location where the virus is endemic. There have been reports of several antiviral medications and other medications that have been employed for the control and prevention of the virus. However, there is yet a clinically efficacious drug to be developed.

Autoimmune diseases are still being largely studied with relation to COVID-19 infections. A number of studies have reported that viral infections, particularly from pathogenic viruses such as parvovirus B19, hepatitis A & B, Epstein-Barr virus, and even the coronavirus, have been known to induce autoimmune disease conditions within infected individuals. These viruses are reported to have initiated conditions such as systemic lupus erythematosus (SLE), Kawasaki disease, Guillain-Barré syndrome (GBS), anti-phospholipid syndrome (APS), and several other conditions.

It is well-known that infectious diseases have always been correlated with the triggering of autoimmune conditions, mainly through molecular mimicry. SARS-CoV-2 has now been added to this list of infections (Galeotti et al., 2016). Moreover, a group of researchers in Italy have reported a 30-fold rise in the number of cases of Kawasaki disease, in which most of them are IgG or IgM specific to the SARS-CoV-2 virus. Autoimmune conditions are often linked to a dysregulated immune system, and most patients receive medications to modulate their immune system. However, due to the pandemic, patients suffering from autoimmune conditions, at least a proportion of them, have suspended their medications for several reasons, including the fear of being immunosuppressed as an effect of the medication and due to fewer follow-ups with their doctors. A report published by Ghosh et al. has indicated that the cytokines produced from the COVID-19 infections have also contributed to the elevation in the number of T-cells in asthmatic patients (Ghosh et al. 2021). A study conducted in Hubei, China, has indicated that patients suffering from autoimmune diseases are more susceptible to COVID-19 infection (Zhong et al., 2020).

Autoantibody production is triggered by immunological mechanisms resulting from COVID-19 infections. These series of events may result in the pathogenesis of autoimmune conditions or further initiate a pre-existing autoimmune disease.

Although there have been several studies published in the past addressing the pathophysiological nature of autoantibodies in SARS-CoV-2 infections, this current review is written to comprehensively provide an updated understanding on the role of autoantibodies in COVID-19 disease, its correlation with associated autoimmune disorders, along with possible therapeutic strategies and immune regulation in the management of such conditions.

We have primarily searched and collected the recent highlights and findings (January 2020 to April 2022) on autoantibodies in SARS-CoV-2 infection along with their pathogenicity and immune regulation. A total of 4 common search engines (PubMed, Scopus, Google Scholar, and SciFinder) were used to obtain information and data regarding the scope of our research question. This paper is aimed to correlate autoimmune conditions to COVID-19 infections. This includes severity and prevalence established in the past years due to the overwhelming number of studies conducted during the pandemic.

Coronavirus disease 2019 (COVID-19)

Origin of the virus

On the 21st of December 2019, four patients in Wuhan, China, had presented with pneumonia of an unknown origin. Bronchoalveolar-lavage fluid samples were obtained from these patients with extensive diagnostic analysis to identify
the novel pathogen. However, samples were negative after analysing with 18 viruses and four bacterial pathogens, which correlate with pneumonia. In January 2020, the causative agent of the pneumonia outbreak in Wuhan was identified as the 2019-novel coronavirus (2019-nCoV). After further genetic analysis, the World Health Organization (WHO) had officially named the virus as SARS-CoV-2 (Zhu et al. 2020). The genome of this novel coronavirus shared a similarity index with the β-CoV found in bats with 96.2% similarity. With this data, it is believed that the novel strain of the coronavirus or better-known SARS-CoV-2 originated from the bats found in the Huanan Seafood Market (Zhu et al. 2020). As of the 2nd of February 2020, the WHO reported 102.1 million global infections, with 2.2 million deaths (Asia 2021).

The transmission of the SARS-CoV-2 includes droplets expelled from face to face, with close contact through talking, sneezing, or even coughing. However, it is also confirmed that transmission is possible via contact surfaces, exposing yourself to contaminated surfaces. Vertical transmission of COVID-19 has been reported, with a very rare or low rate, and is still being studied (Bourouiba 2020; Lewis 2020).

**Structure of the virus**

The genome of the SARS-CoV-2 is 30 kb in size, and it encodes for a non-structural polyprotein (ORF1a/b) of large size. This polyprotein is then proteolytically cleaved, generating 15 or 16 proteins, four structural proteins, and five accessory proteins named ORF6, ORF 8, ORF7, ORF9, and ORF3a (Ramaiah and Arumugaswami 2020). The four proteins (Fig. 1) include the membrane (M) protein, the envelope (E) protein, spike (S) surface glycoprotein, and the nucleocapsid (N) protein. The prominent role of the S protein includes forming an attachment to the host cell, which is then cleaved by the host’s protease enzymes. Understanding the mechanism of the spike protein invasion can help us understand the various autoantibodies that induce severity in COVID-19 patients.

**Pathogenesis of COVID-19**

The primary human receptors available for the S proteins on the SARS-CoV-2 include dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme (ACE2). These receptors are most commonly found in the lower respiratory tract, making the pulmonary system a primary site of COVID-19 infection (Li et al. 2020a, b). ACE2 receptors are also found in the bronchus, heart, liver, oesophagus, kidney, and even ileum. This has been proven to as why some patients exhibit non-respiratory symptoms such as acute organ failures (Jin et al., 2020). Furthermore, the slight variance of S protein on SARS-CoV-2 from SARS-CoV is a 10- to 20-fold higher affinity, causing a rapid transmission from human to human and more severe clinical manifestation (Wrapp et al., 2020). Upon invasion of the alveolar tissues of the lungs, the virus replicates within the host cells, which triggers cytokine storm syndrome and tissue damage (Fig. 2).

**Sign and symptoms**

In a recent study conducted by Han et al., 94% of infected patients have manifested a mild to low fever followed by a 60% frequency of dried cough and fatigue that were observed in 39% of the infections (Han et al. 2020). Besides that, another study conducted by Huang et al. has also shown that the significant symptoms of this viral infection include the production of sputum, myalgia, and haemoptysis. Also, in their study, all 41 patients who were admitted showed abnormalities in chest x-rays. A typical image showed bilateral multiple lobular and subsegmental areas of consolidation (Huang et al. 2020).

**Screening tests**

At the initial stages of the outbreak, many companies were actively releasing different kits with rapid, sensitive, and specific to the SARS-COV-2 virus. However, reverse transcription-polymerase chain reaction (RT-PCR) has been the gold-standard testing
method due to its high sensitivity and specificity. Most of the RT-PCR techniques involve detecting two or more target regions, which aims to increase the testing kit’s sensitivity. Only when two or more of the target RNA regions are detected and amplified the result is known to be positive. The targeted RNA regions will be transcribed into complementary deoxyribonucleic acid (cDNA) by the enzyme reverse transcriptase during this process. These cDNAs will be then used as a template for extension. During extension, Taq Polymerase will add nucleotides from 5′ to 3′, releasing a reporter dye at 3′, releasing a fluorescence signal. The amount of amplified product is directly proportional to the signal produced (Ji et al. 2020). Although RT-PCR can analyse samples within a day, with over 95% sensitivity, the cross-reactivity of primers with the nucleic acid from other infections results in false-positive readings. False-negative readings are also possible from mutations (Corman et al. 2020; D'Cruz et al. 2020).

On the other hand, enzyme immunosorbent assay (EIA) is used to detect antibodies produced explicitly against SARS-COV-2. IgM usually spikes during the early onset of the disease. At the same time, IgG may peak from day 7 to day 25 and acts as a protective role for acquired immunity, and last IgA, the immunoglobulin, plays a significant role in the immune function of the mucous membrane. In this assay, the antigen is derived from the S protein and recombinant N protein of the SARS-COV-2 virus. These antigens are the target for detecting immunoglobulins (Kopecky-Bromberg et al. 2007; Walls et al. 2016). However, as we all understand, the production of antibodies can be less specific, and the test results may vary depending on the immune reaction.

**Active and passive immunity against SARS-CoV-2**

As we understand, our body plays a crucial role in combating viral infections. Furthermore, effective and quick administration of vaccines have been reported to aid in curbing the wave of the infection, along with reducing the severity of the disease (Coccia, 2022b). Immunity against pathogens is generally divided into innate immunity, adaptive immunity, and passive immunity. Upon recognising the SARS-CoV-2 spike protein (S), nucleocapsid protein (N), and also the receptor-binding domain (RBD), the B cells will further differentiate into plasma cells, which then produce specific antibodies to combat the virus (Kumar et al. 2020). In terms of adaptive immunity, both CD8+ T cells and CD4+ T cells are involved in generating specific antibodies against the SARS-CoV-2 virus. In most viral infections, the adaptive system’s synergy and redundancy effect generally helps produce a successful control of the infection (Sette and Crotty, 2021). However, in the case of the SARS-CoV-2 infection, a few studies have shown a superior level of CD4+ T cells compared to the CD8+ T cells (Chen et al. 2010; Grifoni et al. 2020; Rydzynski Moderbacher et al. 2020; Sekine et al. 2020; Sette and Crotty 2021; Zhao et al. 2016). On the other hand, Krammer et al. have suggested that there has been a particular interest in the CD4+ T cells against S and N protein on the coronaviruses, producing antibodies specifically against them and the severity of the reaction depends on the volume of the antigen expression (Krammer, 2020). However, although (M) proteins are relatively small, some studies have shown their high availability towards CD4+ T cells, triggering an immune response against this protein (Mateus et al., 2020).

CD4+ T cells are known for their ability to recruit B cells and aid CD8+ T cells and possess the ability to differentiate into helper cells and effector cells specifically to combat viral infections. A widespread differentiation of CD4+ T cells is into T helper cells (Th1), which have anti-viral properties by stimulating the release of type 1 interferon (IFN) and T follicular cells (Tfh), which assists in B cell development into antibody production to combat the SARS-CoV-2 virus (Sette and Crotty, 2021). Besides that, CD8+ T cells have been commonly known for their
apoptotic ability towards virally infected cells. Just like the CD4+ T cells, CD8+ T cells are found during acute infections, allowing its detection as early as from day 1 (Schulien et al., 2020). Lymphopenia has been observed in COVID-19 patients, correlating the levels of lymphocytes to the severity of the disease (Azkur et al., 2020). Although lymphopenia is mainly found in human immunodeficiency virus (HIV)-positive patients, it is often detected during infection of several viral and bacterial pathogens. Wang F, Nie J, Wang H, et al. conducted a study that has concluded a reduction in total lymphocyte counts, including CD4+ T-cell, CD8+ T-cell, B-cell, and natural killer (NK)-cell. This study has also suggested that a reduction in CD8+ T-cell alone can be an independent detection of the severity of the COVID-19 infection (F. Wang et al. 2020a, b, c). However, the actual pathophysiology of lymphopenia is yet to be studied thoroughly. In addition, a study involving patients in the intensive care unit (ICU) showed that 85% of critically ill COVID-19 patients showed lymphopenia during a full white blood cell (WBC) count (Huang et al. 2020). The incubation period of the SARS-CoV-2 virus is believed to be 5–10 days. In this period, viral replication increases the viral load and acts as a survival mechanism for the virus. On the other hand, just like other viral infections, there will be a spike in virus-specific IgM during acute infection, followed by an increase in virus-specific IgG and IgA which are expected to be present for life-long immunity. As the infection involves mucosal irritation, mucosal specific IgA is also found to increase extensively and could be detected in saliva and serum samples (Renegar et al., 2004).

On the other hand, studies have shown that SARS-CoV and MERS viruses have the ability to escape anti-viral immune responses by suppressing the cytokine produced by the infected cells known as the type 1 IFN. This phenomenon contributes to the severity of the disease (De Wit et al. 2016). Based on genomic sequencing, it is proven that the RNA of SARS-CoV and SARS-CoV-2 are partially identical, speculating the ability of COVID-19 patients to undergo the same scenario of viral evasion. The coronavirus spike protein contains both S1 and S2 subunits, which are cleaved by the antibodies at two sides: the S1/S2 boundaries and the S2’ cleavage site. The distinction between the SARS-CoV-2 from SARS-CoV is the presence of additional four amino acids in the polybasic furin cleavage sequence (PRRARS) found on the spike protein of the coronavirus.

A recent study conducted by Bastard et al. has shown that 10% of COVID-19 patients trigger auto-antibodies against type I IFNs, which have been contributing in favour of the virus, allowing a more severe clinical manifestation of the COVID-19 infection (Bastard et al. 2020). It is imperative to study this at an earlier stage, providing the patients with the essential treatment to continue allowing the type I IFNs to combat the virus. Besides detecting anti-IFN-1, Wang et al. have discovered autoantibodies against interleukin-18 (IL-18), specifically on the 1L-18 receptor subunit named 1L-18Rβ, one of the heterodimer receptors of 1L-18R. This receptor plays a crucial role in the anti-viral activity, which involves triggering of the CD8+ T cells and natural killer cells (NK) cells (E. Y. Wang et al. 2020a, b, c).

**Cytokine storm syndrome (CSS)**

In normal circumstances, the innate immunity’s NK cells and the adaptive immunity’s CD8+ T are crucial in inducing apoptosis towards the viral-infected cells. But in some cases, either due to a genetic or acquired defect in the immune system, both NK cells and CD8+ T are unable to kill the infected cells, triggering and prolonging the immune reaction. Therefore, pro-inflammatory cytokines are continuously stimulated without a negative loop, causing a sudden rise of IL-1, IL-6, IL-18, IL-33, and TNF, leading to a cytokine storm (Soy et al. 2020).

Cytokine storm syndrome (CSS) is a group of disorders involving an over-reacting immune system, organ dysfunction, hemodynamic instability, and even death. It has been reported that COVID-19 patients have a significantly high level of cytokines in their plasma, especially in ICU patients. A study conducted by Huang et al. has identified the overwhelming presence of IL-6 in ICU patients as compared to non-ICU COVID-19-positive patients (Huang et al. 2020). Furthermore, another study conducted by Ruan et al. has also reported the extreme levels of IL-6 in a group of COVID-19 patients, which have been a predictive factor of mortality (Ruan et al., 2020). Furthermore, it was suggested by Zhang et al. that if an antagonist is made against IL-6, the fatality rates of COVID-19 will be tremendously lesser (Zhang et al. 2020). Besides that, COVID-19 patients have also been producing high levels of IFNγ and IL-18, which are particularly relevant to CSS (Fig. 3).

**Autoantibodies in COVID-19 patients**

There have been known autoantibodies detected in COVID-19 patients. In a study conducted by Pascolini et al., in all 33 patients that were studied, 45% of the patients were found to have at least one of the following autoantibodies: antiphospholipid (aPL), anticytoplasmic neutrophil antibodies (ANCA), and antinuclear antibodies (ANA) (Pascolini et al., 2021) (Beeneet, 2022). It was also found that patients with these autoantibodies had a worse prognosis, leading to severe consequences as compared to patients without these antibodies (Frasca et al., 2022). A case study reported in early 2022 indicated a 60-year-old lady with an autoimmune condition resulting in hepatitis due to COVID-19 (Montón Rodríguez et al., 2022). Besides that,
Amezcua-Guerra et al. have suggested that the presence of aPL in COVID-19 patients occurs at a higher frequency as compared to other autoantibodies and have been associated with conditions of hyperinflammation with high levels of C-reactive protein, IL-6, and ferritin (Amezcua-Guerra et al., 2021). Besides that, onconeural antibodies and anti-ganglioside antibodies were also detected in patients who suffered from the SARS-CoV-2 infection (Payus et al., 2022). A study conducted by Juanes-Velasco has also reported the detection of autoantibodies in COVID-19 patients (Juanes-Velasco et al., 2022). Therefore, the data compiled has proven the correlation between the SARS-CoV-2 infection and the production of autoantibodies, thus resulting in further complications (Table 1).

### Autoimmune diseases

Lucchese et al. have described the similarities in the proteome of SARS-COV-2 and three amino acids, GSQASS, LNEVAK, and SAAEAS, with three different amino acids, DAB1, AIFM, and SURF1. The proteins are found in the pre-Bötzinger complex, the brainstem respiratory pacemaker (Lucchese & Flöel, 2020). These similarities in proteome expression have been suggested to trigger autoimmunity when infected with the SARS-COV-2 virus. Besides that, a study has also shown that the S protein on the SARS-COV-2 virus triggers specific antibodies that have immune solid cross-reactions (Kanduc & Shoenfeld, 2020). This theory may suggest that the molecular similarities potentially cause autoimmune reactions in COVID-19 patients. A study conducted by Dalakas et al. has indicated that autoantibodies have been detected among IVIg donor patients pre-pandemic, resulting from a cross-reactivity during infection of the common cold (Dalakas et al., 2021).

### Antiphospholipid syndrome (APS)

There were reports of deep vein thrombosis, pulmonary embolism, and even stroke in severe cases of COVID-19 infections (Y. Li et al., 2020a, b). In patients with autoimmune diseases such as systemic lupus erythematosus (SLE),

| Autoantibodies               | Elaboration                                                        | Refs                  |
|------------------------------|--------------------------------------------------------------------|-----------------------|
| APL                          | Poor prognosis with increase chances of thrombosis and hyperinflammation | (Pinto et al. 2020)  |
| ANA                          | Poor prognosis                                                     | (Pascolini et al., 2021) |
| Anti-GD 1b antibody          | Unclear                                                            | (Liu et al., 2021)    |
| Red cell bound antibodies    | Severe anaemia                                                     | (Guilmot et al., 2021) |
| Anti-Casp antibodies         | Unclear                                                            | (Berzuini et al., 2020) |
| Lupus anticoagulant          | Increase rate of thrombosis                                        | (Gil et al. 2020)     |
| Anti-MOG antibody            | Unclear                                                            | (Pinto et al. 2020)   |
| Anto-RO                      | Possibility of severe pneumonia, cause respiratory failure         | (Fujii et al. 2020)   |
antiphospholipid antibodies (aPL) are most commonly associated with thrombosis in the arteries, veins, or even microangiopathy. However, in cases of COVID-19, aPL production may be triggered by the pulmonary surfactant, as it has a large number of phospholipid-binding proteins. The surfactants are mainly produced by type 2 pneumocytes, which contains a large amount of ACE2 receptors, and is a primary site of binding of the SARS-COV-2 spike proteins (Yu Zuo et al. 2020a, b). Furthermore, a therapeutic approach using the renin–angiotensin–aldosterone system (RAAS) as an approach towards the ACE2 receptor was studied to be an effective method to tackle the infection (Behl et al., 2020).

aPL is an autoantibody that has been responsible for some autoimmune diseases, resulting in primary antiphospholipid syndrome (PAPS) (Khamashta et al., 2016). APS is a thrombophilia that is found in at least 1 in 2000 people. It has also been commonly found in several viral infections such as adenovirus, parvovirus, Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), varicella-zoster, and even cytomegalovirus infections (Khamashta et al., 2016). Moreover, detection of aPL is also common in some bacteria and parasitic infections. Therefore, it is not surprising that aPL has been reportedly detected with COVID-19 infections. Functional coagulation test for lupus anticoagulant (LA), the test used for the detection of aPL has been found positive in 25 out of 56 COVID-19-positive patients (Harzallah et al., 2020a). Besides that, COVID-19 patients who were admitted have also been reported to have high levels of neutrophil extracellular traps (NETS) in their blood, and these traps may have also been involved in the prothrombotic milieu (Shi et al. 2021; Y Zuo et al. 2020a, b). APS in COVID-19 patients often worsens due to the synergic effects of the aPL and the immune cells, which results in a worsened clinical manifestation known as catastrophic APS (CAPS) (Cervera et al. 2018). CAPS results in multiglue organs, which 73% of the time starts from the kidneys, but in COVID-19 patients, involving the lungs (Cervera et al. 2018; Rodríguez-Pintó et al. 2016). It is without question that the prognosis of the patient could worsen with multiple organ failures, and thus, APS resulting from COVID-19 infections have to be further studied and understood to reduce fatalities.

Several studies have reported the relation between coagulopathy and severe viral infection (Tang et al. 2020; D. Wang et al. 2020a, b, c; Zhou et al. 2020). The inflammatory state of the COVID-19 infection as with most infections includes the SARS-CoV and MERS-CoV infections. The laboratory results of the COVID-19-infected patients have shown increased levels of D-dimers, which have been commonly known as a cytokine storm. As mentioned above, the cytokine storm has been responsible for the severity of the disease. In addition to that, D-dimer has been suggested to be an independent biomarker for the poor prognosis of viral infection (Zhou et al. 2020). A recent report has reported elevated D-dimer levels in intensive care unit patients, with poor prognosis and frequent result in death (Fogarty et al. 2020).

Kawasaki disease

Kawasaki disease (KD) is an acute inflammatory disease involving vasculitis with the preposition of coronary heart diseases and in some cases involves the gastrointestinal, pulmonary, and neurological systems in children below the age of 5. This disease has been more prevalent amongst children in Japan (Kawasaki 2014; Kawasaki and Singh 2018). On the other hand, severe uncontrolled immune response in children with regard to the disease is known to mimic KD due to the similarities in clinical entities (Damoiseaux et al., 2022). Moreover, the main symptoms of KD include fever, polymorphic rash, cervical lymphadenopathy, conjunctivitis, and erythema in the oral mucosa as well. Despite the abundant amount of research on this disease, the pathogenesis is still unknown. However, genetic factors have been known to contribute to the manifestation of the disease. In Japan, for instance, siblings of diagnosed children are more susceptible to the disease. This genetic linkage has been associated with single nucleotide polymorphisms (SNPs) in multiple genes, increasing the chances of being diagnosed with KD (McCrindle et al. 2017; Noval Rivas & Ardit 2020). The involvement of the innate immunity is proven by the increased levels of neutrophils, interleukin (IL)-1, IL-6, and tumour necrosis factor TNFα (Matsubara et al. 2005). However, adaptive immunity is also involved with studies showing the elevation of Th17 and regulatory T cells in KD patients (Franco et al. 2014). Jones et al. reported the first case associating a paediatric patient diagnosed with KD, during her COVID-19 infection (Jones et al. 2020).

The potential transmission of the virus to the brain is also reported through a direct transmission via blood stream and nerve endings (Haidar et al., 2022).

Viral epidemics have been closely related to KD. For instance, during the H1N1 outbreak, KD infections have increased tremendously. It is noticed that KD cases have been rising along with the COVID-19 outbreak. It was later understood that viral infections contribute to the manifestation of this disease, suggesting a correlation between SARS-COV-2 and KD. A study conducted in Italy has reported on a 30-fold increase in KD diagnosis since the beginning of the pandemic (Verdoni et al., 2020). A study conducted by Jones et al. has described a previously very healthy 6-month-old...
baby that developed symptoms of KD upon admission. It was then reported that the baby had a positive RT-PCR test for the SARS-COV-2 virus.

Furthermore, Belhadjer et al. have reported 35 children with both SARS-COV-2 positive and acute heart failure. Most of these patients have shown significant symptoms of KD, which have led to more studies being conducted to determine the correlation between KD and COVID-19 (Belhadjer et al., 2020). Besides that, Labe et al. have also reported 2 life-threatening cases which have shown KD symptoms and have later tested positive for SARS-COV-2 (Labé et al. 2020). Based on these cases, it is important to acknowledge the relation between KD and COVID-19. With the mechanism of KD still remaining unknown, the correlation of KD and SARS-COV-2 should be further studied.

Guillain-Barré syndrome (GBS)

Guillain-Barré syndrome (GBS) is categorised under an autoimmune condition, which mainly affects the peripheral nervous system. As a neuronal condition, GBS shows clinical manifestations such as progressive weakness of the limbs, hyporeflexia (reduced tendon reflex), or even areflexia (complete loss of tendon reflexes). The laboratory diagnosis of GBS includes an increase in protein concentration in the cerebrospinal fluid, but an average leucocyte level (Guillain et al. 1999; Van der Meché et al. 2001). GBS is usually triggered by either bacterial or viral infections, which then induce an immune response. These are mistaken by the peripheral nerves as foreign antigens due to the similar myelin and axon structure with the foreign antigen (Yuki and Hartung 2012). Some of the many pathogens that have been inducing GBS include cytomegalovirus, Mycoplasma pneumoniae, Haemophilus influenza, Campylobacter jejuni, and Epstein–Barr virus. Besides that, even MERS and SARS, along with Zika virus have been reported to be associated with GBS (Rahimi, 2020). As mentioned previously, the ACE2 receptors are the primary site of binding of the SARS-COV-2 S proteins. In the cases of GBS, the ACE2 receptors on the neuronal tissues are directly invaded, triggering inflammation in the neurons. It was recorded that IL-6 levels increases tremendously, as a result of the cytokine storm caused by the COVID-19 infection, which is responsible for the manifestation of neurological conditions in GBS patients (Carod-Artal 2020; Helms et al. 2020; Sedaghat and Karimi 2020).

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a painful autoimmune disease categorised as chronic and more prevalent in women. This disease has also been reported to be one of the leading causes of death amongst young women around the globe. The absence of self-tolerance within the immune cells in SLE patients can be due to many factors, including genetic predisposition and environmental factors as well. SLE is mainly caused by the autoantibodies produced by the B cells, an increase in cytokines and aberrant pro-inflammatory T cell responses, which eventually leads to tissue and organ damage and joint and skin inflammation (Spihlman et al. 2020; Yen and Singh 2018). To date, there is no cure for SLE; however, immunosuppressants and corticosteroids have been recommended medications to control the severity of the disease. Therefore, SLE patients have been considered a vulnerable group, increasing the risk of severity when infected with COVID-19 disease. Upon infection, the hyperactive immune system has resulted in the manifestation of CSS and tissue damage in COVID-19 patients (Spihlman et al., 2020).

On the other hand, the adaptive immune system of SLE patients is also dysfunctional and could contribute to the severeness of the SARS-COV-2 infection. Moreover, various studies have stated that SLE patients generally have an increase in Th1 cells and CD8 + T cells differentiate into B cells and autoantibodies (Susanna Esposito et al. 2015). Therefore, the continuous presence of these cells will stimulate TNF alpha, II-1, and II-2 cytokines, which will compromise the Th1 responses and result in a less effective viral response. Also, the shift from Th1 to Th2 cells is commonly found in HIV patients, occurring in patients with autoimmune situations (Mantovani Cardoso et al., 2020). Reports have also associated SLE with other viral infections such as parvovirus B19, retrovirus, and cytomegalovirus (Doaty et al. 2016; Perl 1999). This theory may explain why SLE cases are being reported along with SLE.

Several studies have been relating SLE with COVID-19 infections (Bowles et al. 2020; Gupta et al. 2020; Harzallah et al. 2020b; Kichloo et al. 2020; Spihlman et al. 2020). The first case associating SLE with COVID-19 was reported by Zanani et al., indicating a 39-year-old male patient who complained of fever and rashes 2 weeks post-infection of COVID 19. Upon further laboratory analysis, it was confirmed that the patient was positive for SLE (Zamani et al., 2021). Besides that, type 1 IFNs are elevated in both SLE and COVID-19 patients, which is now a link that has been converging both diseases. Studies have shown that 25% of COVID-19 patients have developed autoantibodies against type 1 IFNS (Harris et al. 2020; Howe and Leung 2020; Panem et al. 1982; Slavikova et al. 2003). The two common types 1 IFNs’ autoantibodies detected in COVID-19 patients are IFN-α2 and IFN-ω (Slavikova et al., 2003). However, whether or not these anti-IFN antibodies contribute to the severity of the infection is still being studied (Morimoto et al. 2011). Both the IFN-α2 and IFN-ω were recently found in 101 out of 987 COVID-19 patients, accounting for 10% of the patients. Moreover, authors have proven that 5 of these patients developed these autoantibodies dominantly because of the COVID-19 infection (Bastard et al. 2020).
Therapeutic approaches

**IL-6 inhibitors (Tocilizumab and Sarilumab)**

As mentioned above, the fatalities of COVID-19-infected patients have been closely related to the activation of cytokine storm, leading to shock, hypoxia, and even acute renal failure. Tocilizumab is known to be an antibody that targets the recombinant humanised IL-6, which on binding can disrupt signal transduction. The US FDA has also reviewed and approved for COVID-19 respiratory syndrome (CRS) treatment. Michot et al. have reported the first case of using Tocilizumab as a COVID-19 therapeutic approach. Although many limitations of the study have been noted, the treatment remained successful (Michot et al., 2020).

IL-6 is released by immune cells such as B-cells, monocytes, dendritic cells, and T-cells. It is even released by most stromal cells. In normal conditions, the level of IL-6 remains low and is only activated to combat infections (Hedrick et al. 2020). The mechanism of action of the IL-6 cytokine is relatively straightforward. It binds to its receptor known as the IL-6R and forms a complex (Guzik et al. 2020; Hedrick et al. 2020; Stone et al. 2020). This complex then binds to a signal transducer glycoprotein 130 (gp-130), which triggers the signal transduction and continues the gene expression. In the classical pathway, the IL-6 will bind to the membrane-bound form receptor (mIL-6R), which binds to the gp-130 and causes a downstream reaction. However, the IL-6 binds to a soluble receptor (sIL-6R) in the trans-signalling pathway, which initiates intracellular signal transduction (Soy et al. 2020) (Fig. 4).

Sarilumab, just like Tocilizumab, is also an IL-6 inhibitor and binds to both the sIL-6R and mIL-6R, which eventually inhibits signal transduction. However, Sarilumab has only been approved by the FDA to treat RA patients who have not been responding got at least one of the disease-modifying anti-rheumatic drugs (DMARD) (Silvano Esposito et al. 2020; Kardeş et al. 2021). As of October 2020, 11 clinical studies are being conducted to study the safety and efficiency of Sarilumab in the treatment of COVID-19. The studies share a common primary endpoint: the improvement of lung function, the need for intubation, and many more (Khiali et al. 2021). However, when anti-viral T-cell projects harmful effects onto the body, the use of immunosuppressants will come in handy (McGonagle et al. 2022).

**JAK 2 inhibitors**

Janus kinases (JAKs) are a group of receptors that consists of JAK1, JAK2, and JAK3, along with tyrosine kinase 2 (TYK2), which transmits signals from various pro-inflammatory cytokines in the extracellular compartments to activate the signal transducers and activators of transcription (STATs) (Roskoski, 2016). A recent study by Richardson et al. has shown that Baricitinib, a JAK1&2 inhibitor, has the ability to disrupt the endocytosis of the SARS-Cov-2 by inhibiting the receptors involved (Richardson et al. 2020). In addition to that, Stebbing et al. further confirmed this statement by reporting the success of Baricitinib treatment against COVID-19 infections in four patients (Stebbing et al., 2020). In addition to that, as Baricitinib has minimal interaction with the drug metabolism enzymes, CYPs, it is also found that this drug can be combined with other drugs to produce synergistic effects as a potential treatment towards COVID-19 (Luo et al. 2020).

**Impact of the environment on COVID-19 and autoimmune diseases**

Considerable studies have demonstrated that various environmental factors such as outdoor air pollution, traffic-related air pollution, and poorly ventilated indoor environment have impact on COVID-19 transmission (Azuma...
et al. 2020; Xiang et al. 2020). Therefore, these environmental factors may be a contributing factor to the pandemic. For example, air/traffic pollution may be associated with increased severity and lethality in COVID-19 infection due to its impact on chronic diseases, such as cardiovascular disease and diabetes (Bourdrel et al., 2021).

Other environmental factors, such as temperature, humidity, and stability on fomites and filtering systems, could significantly influence the COVID-19 infection (Azuma et al. 2020; Coccia 2020a; Morris et al. 2021). A recent meta-analysis from Europe found that the mortality risk of COVID-19 patients in hospitals estimated the odds ratio per 1-day increase in the admission date to be 0.981 and an increase in ambient temperature of 1 °C to 0.854.

Interestingly, the severity of COVID-19 infection in European countries reduced remarkably between March and May 2021 which explain the seasonal variation of rate of COVID-19 infection (Kifer et al., 2021). The features of air quality and various environmental surfaces contaminated by the SARS-CoV-2 are crucial factors that predict the infectivity rate and pace of the spread. The extensive persistence of the aforementioned ecological factors facilitates the spread of COVID-19 infection (Aboubakr et al., 2021). van Doremalen et al. conducted a comparative study (SARS-CoV-2 vs SARS-CoV-1) to reveal the survival rate and the half-life of viruses within 3 h of aerosolisation at a temperature of 21–23 °C and a relative humidity (RH) of 65%. Both SARS-CoV-2 and SARS-CoV-1 were detectable after 3 h of aerosolisation, and the median half-lives were 1.09 and 1.18 h for SARS-CoV-2 and SARS-CoV-1, respectively (van Doremalen et al. 2020). In another cross-sectional analysis, Kim et al. (2021) studied the relationship between long-term exposure to particulate matter (PM$_{2.5}$) and ozone (O$_3$) and COVID-19 confirmed mortality in 177 neighbourhoods in New York city, USA, between the 29th of February 2020, and the 5th of January 2021, obtained from the health department website. Interestingly, the results revoked that people residing in the neighbourhoods with increased O$_3$ levels may have a poorer prognosis of COVID-19 (Kim and Bell 2021).

As we discuss the impact of the COVID-19 infection on autoantibodies, it is also crucial to understand the impact environmental conditions have on the progression of autoimmune conditions. Besides apparent genetic predispositions, environmental factors such as ultraviolet light (UV), smoking, silica solvents, and pollutants are generously being studied as a crucial causative agent towards the progression of autoimmune diseases (Colafrancesco et al., 2014; L. Wang et al. 2015)(Bernardo et al. 2022). Its wavelength generally categorises UV with UVB (320–280 nm) has irradiation potential of translocating La/SSB and Ro/SSA antigens from the cytoplasm and nucleus of the apoptotic human keratinocytes, allowing a higher susceptibility of these segments to bind to its circulating autoantibodies (Wolf et al. 2018). Patients with autoimmune conditions have been reported to overexpress type 1 IFN when exposed to UV radiation chronically.

On the other hand, air pollution is generally defined as a mixture of both gases and particulate matter released into the atmosphere, with a contribution to the surroundings (Sierra-Vargas & Teran 2012). A recent case study has proven that SLE patients’ exposure to silica, solvents, pesticides, and other inhaled substances has contributed to the development and progression of the condition (Cooper et al. 2010). Although the mechanism of air pollution and autoimmune diseases is still unclear, a couple of hypotheses have linked oxidative stress and nitrosative stress’s contributions to the production of autoantigens triggering immune responses (Gawda et al., 2017). In addition to inhaling unnatural substances, tobacco and tar present in smoking have also been highly linked with autoimmune conditions and have been further tied to severe symptoms in COVID-19 patients (Bao et al., 2020). The particulate phases in cigarette smoking contain free radicals, which interact and damage the DNA, producing DNA adducts (Speyer and Costenbader 2018). Linking this theory with COVID-19 infections, it is obvious that pollution largely contributes to the progression of the COVID-19 infections amongst autoimmune disease patients.

Impact of COVID-19 on the environment

From another point of view, during the pandemic, most governments have imposed strict lockdowns in most countries and have directly improved the situation and environment. This includes a halt to daily transportation systems (trains, buses, cars, etc.), water and air pollution due to the temporary shutdowns of various factories and large companies, greenhouse gas emissions, and black carbon which have drastically reduced (Shakil et al., 2020). Taking Malaysia, for example, the country’s particulate matter reduced by 58.4% specifically during the lockdown period (Abdullah et al. 2020). In regard to that, a report has suggested that an increase in particulate leads to more COVID-19 cases and mortality rates (Srivastava 2021). A study conducted by Tobias et al. has shown that in Barcelona, Spain, alone, the air pollution of black carbon (BC) and nitrogen oxide (NO2) had significantly reduced by 50% (Tóbias et al., 2020). Similar to many other infections, the transmission of COVID-19 is severely affected by the environment (Coccia, 2022c). The humidity, the speed of the wind, temperature, and frequency of rain have a large consequence of the spread of the virus (Bashir et al. 2020; Coccia 2020b).

However, it is also widely reported that the humidity and temperature of certain countries contribute to the spread of the SARS-CoV-2 virus. A couple of scientists have argued that the virus is unstable when exposed to heat, and it is
often relatable to countries with climates and temperatures that are high such as India (Shakil et al., 2020).

In a nutshell, the environment plays a huge role in the context of both COVID-19 and autoimmune diseases. The correlation between these factors is largely being explored and a meta-analysis can be carried out in the future to correlate the impact of the environment towards COVID-19 and vice versa.

Future perspectives

As the virus evolves and undergoes genetic mutations, several variants of concern (VOC) emerge and may further contribute to the severity of the infections. This aspect has to be considered to understand further the impacts of the VOCs on the autoimmune conditions of the infected patients. It is crucial to understand that the transition to the “endemic” phase may be soon achieved but may be delayed due to the VOCs. Furthermore, countries with larger populations may face challenges to handle the post-pandemic state with an increase in healthcare expenditure and other related issues (Coccia, 2022a). By achieving herd immunity, the disease may be controlled but may not be immediately possible to eliminate it completely. The pandemic has also been an eye-opener to the importance of technical aspects to prevent the spread of the virus and act as a drive to cope with the virus (Ardito et al., 2021). Alongside that, it is also crucial to develop proper crisis management skills and practice policies to constrain the negative impacts of the infection towards the community (Coccia, 2021b).

Furthermore, crisis management concerning the COVID-19 outbreak, including multi-government policies and urban and rural strategies to combat the situation, should be kept in place with proper regulations for the future (Coccia, 2021a, 2021c). Therefore, it is crucial to understand the implications of the SARS-CoV-2 virus on individuals with autoimmune conditions or on those who are prone to it. Despite the considerable attention being put on the COVID-19 infection, further studies are crucial to understand the autoimmune mechanism of this virus and its impact on the community soon. Future studies can also focus on the multi-climate areas and their autoimmune mechanisms concerning COVID-19.

Conclusion

This review was aimed to identify the relationship between autoimmune conditions and COVID-19. This infection has led to a pandemic, presenting with both systemic and heterogeneous clinical manifestations and, to an extent, has caused deaths. Amongst the many autoimmune diseases reported, this review discusses on APS, KD, GBS, and SLE. The SARS-CoV-2 infections have also been shown to disrupt the self-tolerance mechanism, which leads to autoimmune conditions. Similar to autoimmune diseases, COVID-19 infections have also resulted in organ failure, primarily affected by the immune response and lack of self-tolerance. This review has discussed on several therapies that have been considered useful as a therapeutic approach to the immune system. The infection has manifold impact on the immune system and the environment. There has been a severe economic slowdown due to the disease. In addition, there has been an increase in medical waste accumulation leading to an increased burden of medical waste management. The limitations of this review include non-interpretation of the clinical data available and absence of in-depth analysis of the roles of autoantibodies in disease states after COVID-19 infections. Furthermore, this review has only considered published data in English language. More studies and data are required to further understand the correlation between the SARS-CoV-2 and complications arising from autoantibodies.

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Declarations

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