Review Article

# Inflammatory Outcomes of COVID-19, Post-Complication Disorders, and Related Factors that Could Affect the Intensity of COVID-19

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## Abstract

**Background:** Coronavirus disease 2019 (COVID-19) is an infectious disease that has surrounded the world caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease is usually onset with symptoms like fever, cough, fatigue, respiratory problems, and loss of smell and taste. The majority of COVID-19 patients have mild or no symptoms, but a few demonstrate acute respiratory problems (ARDS) that can be life-threatening.

**Materials and Methods:** Authors searched English published articles in local and international journals over the period 2000 to 2022 using several databases including Scopus, PubMed, Scholar, and Science Direct. Then, the relevant articles were revised. During this period, different articles have been published, but we tried to choose and review articles that introduced effective data.

**Results:** Some people show symptoms long after their negative PCR test called post-COVID-19 syndrome, which studies showed can last more than 12 weeks after infection. Other than the complications patients confront amid the period of COVID-19 infection, there is an accumulation of evidence regarding the delayed complications of COVID-19, including auto-immune outbreaks such as multisystem inflammatory syndrome (MIS), idiopathic thrombocytopenic purpura (ITP), Guillain-Barre syndrome, Miller-Fisher syndrome, Autoimmune hemolytic anemia (AIHA), Autoimmune thyroid disease and also COVID-19 associated coagulopathies, have received remarkable attention since the early months of the pandemic. Microbiome changes in the gut and nasopharynx of patients with COVID-19 affect the severity of the disease, furthermore, some genes inherited from Neanderthals increase the severity of COVID-19.

**Conclusion:** COVID-19 infection, along with the immune suppression mechanism, has the potential to evoke destructive inflammation in the host. Clarifying the pathophysiology of the COVID- 19 injuries to the host could help to develop appropriate treatment.

**Keywords:** SARS- CoV- 2, Auto-inflammation, Coagulopathies, Multiple inflammatory syndromes after COVID-19, Autoimmune diseases, COVID-19

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# Introduction

Coronavirus disease 2019 (COVID-19) is a communicable disease that caused by the SARS-CoV-2 virus[1]. After a 1-14 day incubation period, the disease usually manifests itself through symptoms of fever, cough, fatigue, respiratory problems, and loss of taste and smell[2]. However, most COVID-19 patients are asymptomatic or mildly symptomatic[3,4]; While a few of them may develop acute respiratory distress syndrome (ARDS) which can be life-threatening[5,6].

We know that COVID-19 is the first pandemic and the third epidemic to occur in the SARS-CoV family[7]. There are risk factors for this disease, for example, its severe type in children below one year, adults over 65 years, pregnant women, immunocompromised patients, those with diabetes mellitus, respiratory disease, cardiovascular disease, hypertension, kidney disorders, and oncological complications[8–12]. The prevalence is higher in men[13] and obese people with a BMI above 30 have a higher mortality rate[14]. People with blood types A, B, and AB have a higher risk of ventilating and staying in the ICU than people with type O blood[15].

It is said that in mild COVID-19 we have some symptoms like fever, cough, sore throat, headache, fatigue, chills, pneumonia, nausea, and vomiting[16]. Nevertheless, in some patients, we have seen myocardial injury and kidney damage[17].

In many infections, loss of tolerance causes autoimmune responses. Following infection, patients may experience autoimmune conditions such as autoimmune hemolytic anemia, autoimmune thrombocytopenia, Guillain-Barré syndrome, vasculitis, and Multiple Sclerosis(MS) [18–21]. Auto-inflammation itself in children[22] such as Kawasaki is also one of the most common cases[23]. Some thrombotic phenomena have been associated with the production of antiphospholipid antibodies, complement depletion[24], deposition of the immune complex[25], production of ANA, and antibodies against DNA[26,27].

COVID-19 could be seen as an inclining factor towards auto-reactivity and is implicated in mechanisms contributing to the initiation of autoimmunization.

This review attempts to discuss short- and long-term inflammatory issues of post-COVID-19 complications.

**Inflammation and COVID-19**

The intensity expansion of COVID- 19 is associated with host resistance[28]. In mild infections, the host has moderate resistance and has a better chance of rehabilitation due to this disturbed homeostasis, but in the severe form of resistance, the host becomes overactive and causes a lot of inflammation, leading to a cytokine storm[29]. SARS-CoV-2 infects epithelial cells, dendritic cells, and macrophages to produce cytokines[30], and although these cells, with a few exceptions, produce interferon and in the first encountering the virus, large amounts of IP10, CCL3, CCL5, CCL2, TNF, GM CSF, ROS, IL1B, IL8, IL6 are produced in patients' serum[31,32]. In patients, IL2R and IL6 serum levels are associated with disease severity[33].

Delay in the production and secretion of interferons in the early stages, prevents the antiviral response. In later stages, chemotactic mediators like CXCL8, attract neutrophils and monocytes and cause inflammation[34]. However, the severity of symptoms in patients depends on the type of immune response and inflammation of them. Depending on the type of response, the extent and variety of cytokines, and chemokines, the severity of the disease varies from person to person[35].

Whether the patient's immune function suppresses the virus at an early stage of infection, a patient will reach the recovery phase and will have a high amount of Spike(S) Pr-neutralizing Antibodies[36]. IgA is produced in the first week followed by IgM[6]. IgG titer is increased in the first 3 weeks[37]. Cellular immunity, $TCD4^+$, and $TCD8^+$, also is increased in the first one to two weeks[38]. COVID-19 patients also develop memory responses in the absence of specific antibody[39].

Following viral infection, in the early or late phase of the disease, patients may experience autoimmune conditions[40]. The chain of events can lead to the spread of inflammation, such as the infiltration of lymphoplasmacytic commonly into the lungs and the expression of cytokines such as IL1, IL6, TNFα, IL17, and markers such as CRP and ferritin[41]. Development of autoimmunity and disease has four phases: 1- The viral phase in which the virus enters the body 2-

Excessive defensive response by the immune system 3- The stage of increasing the coagulation of circulating blood components 4- Occurrence of damage and defects in the organs of the body[42].

In COVID-19, when lymphocyte depletion occurs in different categories such as TCD4$^{+}$, TCD8$^{+,}$ and Treg, it causes temporary lymphopenia. It has many reasons including induction of apoptosis[43], cytokine effects such as type I interferon[44], bone marrow shutdown (bone marrow suppression due to viral stress)[45], or redistribution with a severe recall of inflammatory cells occurring in the lung due to chemotaxis in the tissue. Redistribution of the immune system includes intrinsic immune components such as monocytes, macrophages, and dendritic cells[46].

After a temporary improvement in symptoms and immune system rehabilitation, the lymphocyte count increases again and can pave the way for preparation for an unregulated response[47]. The immunosuppression that occurs in SARS-CoV-2, like the redistribution of the immune system, is the result of primary tolerance or due to temporary weakness and reduced immune system regulation mechanisms [48]. It has been reported that regulatory T lymphocytes are also temporarily inhibited and can activate other lymphocyte lineages[49]. On the other hand, this autoreactivity may be associated with transient immunodeficiency of acquired and innate immune components that are unable to detect their antigens[40]. Furthermore, the development of autoimmunity depends on genetics[50], Human leukocyte antigen (HLA)[51], age, and sex[52], which are greater in women due to the effects of estrogen[53].

**Autoimmunity and Multiple Inflammatory Syndrome after COVID-19 in Children**

It is obvious that the intensity and frequency of COVID-19 infection are lower in children, However, children have reported symptoms similar to Kawasaki disease and toxic shock, referred to as multisystem inflammatory syndrome (MIS) [54,55]. The cause is a severe host immune response[56]. The primary cause of death is the inflammatory response caused by SARS-CoV-2. Cytokines play an important role in immunogenicity, and a sharp increase in them leads to a cytokine storm[57]. The release of inflammatory

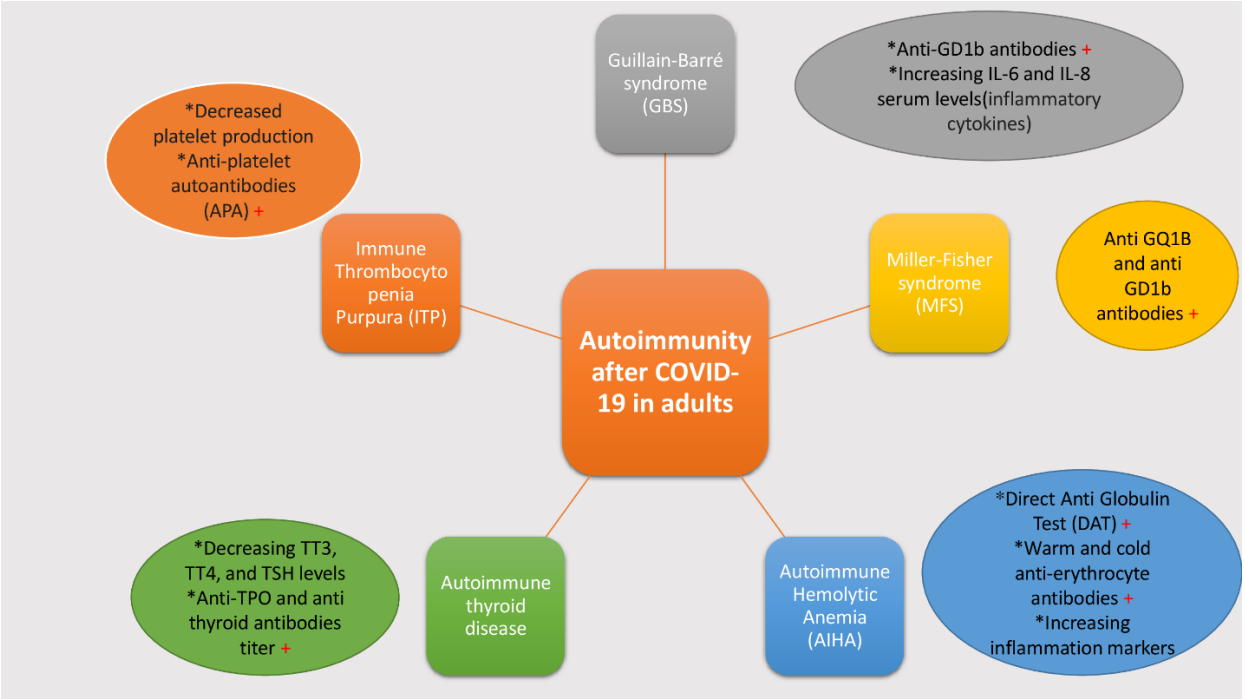


**Figure 1. Autoimmunity after COVID-19 in adults and some laboratory findings related to each autoimmunity. TSH, thyroid stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxine; TPO, thyroid peroxidase; APA, anti-platelet autoantibodies; GBS, Guillain-Barre syndrome; ITP, idiopathic thrombocytopenic purpura; AIHA, autoimmune haemolytic anaemia; MFS, Miller-Fisher syndrome; DAT, direct anti-globulin test; COVID-19, coronavirus disease of 2019; IL6, interleukin 6; IL8, Interleukin 8; GQ1B GD1B, ganglioside Q1B D1B.**

mediators is associated with overactive immune systems in conditions such as cytokine storms[56].

Neutrophils are the main actors in cytokine storms and can secrete ferritin, which is found in various inflammatory syndromes[58]. Ferritin is immunosuppressive and inhibits the differentiation of myeloid cells, B and T lymphocytes[58], although high ferritin levels and hemophagocytosis can be associated with inflammatory exacerbation and are seen in several diseases such as severe cases of COVID-19[11], macrophage activation syndrome, Multisystem Inflammatory Syndrome in children (MIS-C)[59], that shares some aspects with other inflammatory disorders and large amounts of cytokines cause dysfunction of several organs, including Kawasaki, sepsis, macrophage activation syndrome (MAS), and Hemophagocytosis LymphoHistiosis (HLH)[60].

In some people with symptoms similar to Kawasaki disease, changes in hemodynamic parameters have been observed with gastrointestinal manifestations. In a study in France and Switzerland, 35 children with symptoms of MIS-C were observed. In 31 of them, the PCR test was positive[61]. It is important to be aware that the spread of MIS-C following COVID-19 infection can be in the first and second weeks after infection[62], although in patients with negative PCR, the spread of MIS-C has been seen 6 weeks after exposure to COVID-19[63].

Kawasaki disease (KD) is a systemic vasculitis that usually occurs in children younger than 5 years of age[64]. It is generally self-limiting and can cause Coronary Artery Aneurysm (CAA)[65], the number one cause of acquired cardiac disease in children [66]. Kawasaki Shock Syndrome (KSS) is associated with capillary leakage syndrome or poor perfusion as a result of inflammatory myocarditis[67].

Kawasaki-like disease in COVID-19 is called Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), or Multiple Inflammatory Syndrome in Children[64]. Superantigens stimulate T cell clonal proliferation and produce many inflammatory cytokines[68], and there is evidence that KD can be triggered by a super antigenic response [69]. KSS is also associated with severe cytokine release. Inflammatory proliferation syndrome can be due to the autoantibodies formation through molecular mimicry, vascular damage because of deposition of the immune complex or ADE (antibody-dependent enhancement) may also be associated with the IgG immune complex, which increases the penetration of viral infection into FC receptor bearing cells[70,71].

The disease has not been seen in Asia, which could indicate that host genetics and differences in the virus genome play a role[64].PIMS has been shown to overlap with Kawasaki, but they must be distinguished. Kawasaki patients associated with COVID-19 are older[72] and have gastrointestinal and meningeal symptoms. They may have leukopenia with lymphopenia, thrombocytopenia, increased ferritin, and myocardial markers, a high prevalence of myocarditis, and cardiac interactions[62,63]. KD-COVID-19 is usually worse due to myocarditis and most can be hospitalized[73].

To gain a better understanding of the hyperinflammation in MIS-C and Kawasaki disease, peripheral blood mononuclear cells (PBMCs), were evaluated for expression and intensity of surface markers by flow cytometry. Differences were found in the distribution of T $CD4^+$ subtypes by CD45RO and CD27 expression, as well as the frequency of T Follicular Helper (TFH) expressed by CXCR5. The total number of T cells in both types was lower than in healthy individuals. Both groups of patients with SARS-CoV-2 infection had more central memory and executive T CD4 + but less naive $TCD4^+$ than Kawasaki patients. TFH levels have decreased in children with SARS-CoV-2, with or without MIS-C, compared with patients in Kawasaki. CD57 is a differential marker of T $CD4^+$ effector that was decreased in severe and acute COVID-19 patients[74]. Children with mild COVID-19, or MIS-C, had more of these differentiated cells than Kawasaki patients. T $CD8^+$ cells were lower in MIS-C children than in children with mild COVID-19[73].

Although MIS-C is temporarily related to SARS-CoV-2 infection in children, its immunogenicity isn't well caught on. Children suffering from MIS-C without the IL-17-based cytokine storm are typical of Kawasaki disease[73]. Proinflammatory cytokines associated with disease severity in children with COVID-19 have been shown to include IL-2, IL-6, IL-10, IL-13, and IL-17. However, children with MIS-C have higher TNF

levels, which may show a reduction of the viral infection or cytokine release syndrome (CRS), which is a systemic inflammatory response against viral infections [75,76].

Children with mild COVID-19 and mild MIS-C showed higher antibody binding and antibody affinity to non-structural protein2 (NSP2) and NSP13 compared to children with severe COVID-19 or severe MIS-C[77].

SARS-CoV-2 shares its epitope with the Kawasaki antigen, inositol triphosphate tri kinase c, because of its molecular similarity, and this could cause Kawasaki[78]. We will discuss molecular similarity more below.

**Autoimmunity after COVID-19 in adults**

The range of complications following COVID-19 in adults is wider in comparison to children and includes autoimmune diseases, but their prevalence is rare, such as idiopathic thrombocytopenic purpura, Guillain-Barre syndrome, Miller-Fisher syndrome, Autoimmune hemolytic anemia and Autoimmune thyroid disease [18–20,79,80]. Compared with PIMS, autoimmune symptoms occur in adults in the early phase of COVID-19[22] (Figure 1).

1. ITP, or Immune Thrombocytopenia Purpura Idiopathic, is a systemic autoimmune disease in which Platelet counts are low due to autoantibodies to glycoproteins expressed on platelets[64,86]. It is usually life-threatening if it occurs in children. Some viruses, such as CMV, EBV, rubella, measles, or HIV, can cause ITP because of their molecular similarity[87,88]. Many mechanisms have been proposed, such as inhibition of platelet production due to direct infection of bone marrow cells or platelets by the virus[89]. Platelets do not have ACE2 receptors, although studies have shown that platelets can bind to SARS-CoV-2 mRNA independent of ACE2[90]. COVID-19 patients have fewer regulatory cells due to immune dysregulation[48], and therefore cytotoxic T cells can directly kill platelets[89]. Molecular similarity can also play a role in this disease.
2. Guillain-Barré syndrome or GBS is a rare autoimmune disorder characterized by inflammatory demyelination and axonal neuropathy that causes progressive paralysis with reduced or no reflexes and can be associated with cranial neuropathy and pain[91,92]. One of the main mechanisms of GBS is molecular similarity[93,94]. The antibody binds to peripheral motor membrane surface gangliosides and sensory neurons, damaging myelin and axons[95]. We know that SARS-CoV-2 elicits an immune response, which in turn activates T and B lymphocytes and produces antibodies[96], but possibly causes a loss of tolerance due to the structural similarity of the ganglioside and virus sequences[97,98].
3. Miller-Fisher syndrome or MFS is a rare and acquired disease. It is a mild form of Guillain-Barré syndrome that affects approximately 5% of all GBS cases and can occur with areflexia, ophthalmoplegia, mild weakness of limbs, ptosis, facial paralysis, bulbar palsy, and overall respiratory muscle weakness[99]. The majority of people with MFS had specific antibodies that were Anti ganglioside Q1B (GQ1B) and anti-GD1b[100,101]. Large amounts of GQ1b gangliosides have been observed in the oculomotor and trochlear and abduces nerves, which is associated with ophthalmoplegia[10085].
4. Autoimmune Hemolytic Anemia (AIHA) is an autoimmune disorder that is developed in some cases of COVID-19 during infection[18,80,102]. Based on this report, all of them happens after the starting of the infection indications and within a time allotment consistent with that of the cytokine storm. The median time from the major side effects of COVID-19 to the onset of AIHA was nine days (4-13 days). All patients exhibited marked hemolysis and all patients had raised markers of inflammation[18]. The reason could be linked to an antigenic cross-reaction with red blood cells secondary to molecular mimicry[103]. Some drugs that can cause Coronary artery disease (CAD) can also be identified[102,104].
5. Autoimmune thyroid disease is one of the autoimmune disorders and some studies

reported that COVID-19 patients might experience that[79,105,106]. SARS-CoV-2 patients' thyroid glands were influenced by damage to the follicular and parafollicular epithelial cells[107]. Levels of the patient's total triiodothyronine (TT3), total thyroxine (TT4), and thyroid stimulating hormone (TSH) with SARS were impressively lower than those of controls in both the progression and recuperation stages[108]. In addition, the amount and intensity of TSH-positive cell staining have declined in the pituitary gland of SARS-CoV-2 patients, which appeared that the decrease in TSH concentration can be linked to the changes in TSH-secreting cells in the pituitary[109]. Patients with COVID-19 had low levels of TSH and TT3, and the higher the severity of COVID-19, the lower the levels of TSH and TT3[106].

There may be reasons for this disorder, such as a direct viral impact on the pituitary cells, indirect disease, or its therapeutic effects leading to hormonal changes in the input rings of the pituitary-endocrine axis [110,111]. Persistent stress from hypoxemia and glucocorticoids that most patients have been treated with may also reduce TSH levels in COVID-19 patients[106]. The presence of variables such as anti-thyroid peroxidase (TPO) antibodies or high levels of anti-thyroid antibodies, which may be evidence of the development of Graves' or Hashimoto's post-COVID-19 [79,112], could support the development of inflammatory disorders following COVID-19 that trigger autoimmunity[105] (Figure 2).

One of the analyzes that can be done for the etiopathology of this disease is the molecular similarity between the virus and human proteins. After infection, the immune response evoked against SARS-CoV-2 may react to human peptides that some virus sequences are identical to humans[64,113]. Like the SARS-CoV-2 spike glycoprotein heptapeptide "KLNDLCF" and "NASVVNI" that can overlap with human protein "interleukin-7" and "Thyroid adenoma-

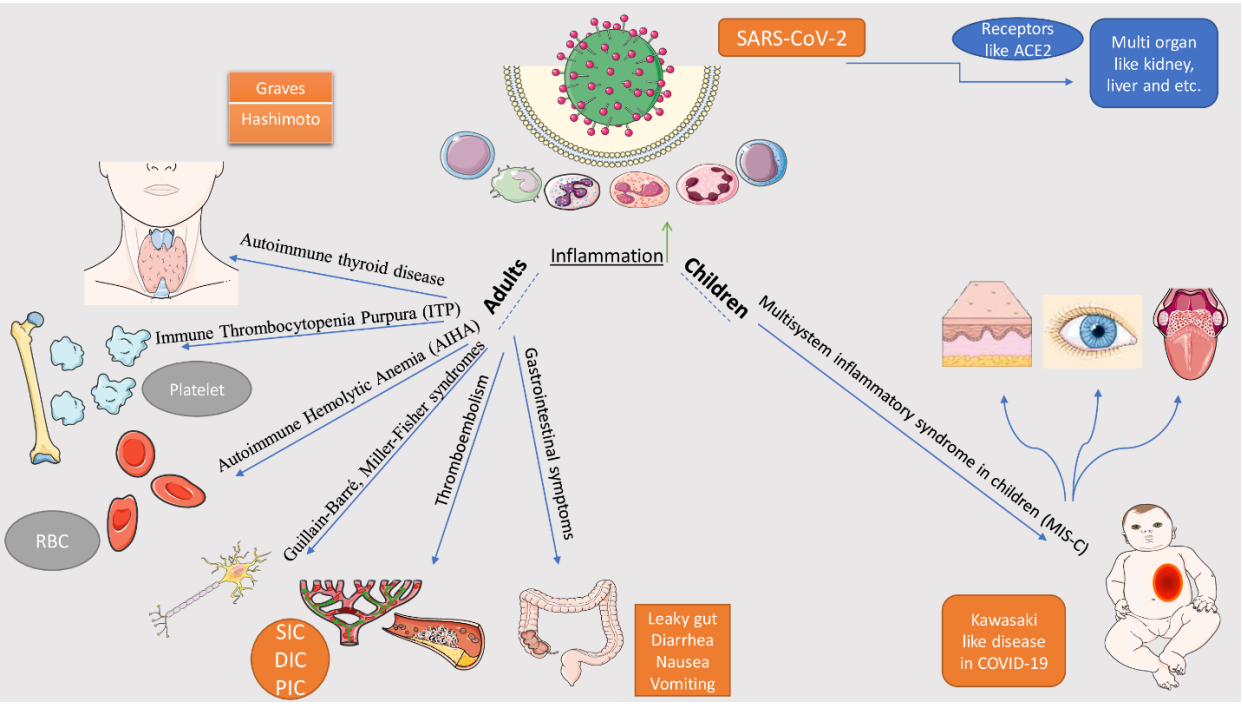


**Figure 2. Brief summary of Autoinflammation and autoimmunity in COVID-19 patients. GBS, Guillain-Barre syndrome; ITP, idiopathic thrombocytopenic purpura; AIHA, autoimmune haemolytic anaemia; MFS, Miller-Fisher syndrome; RBC, red blood cell; SIC, sepsis-induced coagulopathy; DIC, disseminated intravascular coagulation; PIC, pulmonary intravascular coagulopathy; MIS-C, multisystem inflammatory syndrome in children; COVID-19, coronavirus disease of 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2.**

impacts like the actuation of different proinflammatory cytokines caused by the infectious associated protein" respectively. Also, the association between human peptides and SARS-CoV-2

neuropathic complications can be observed. For example, histone-lysine N-methyltransferase 2C may be associated with neurodevelopmental disorders as well as behavioral abnormalities and seizures[114].

**COVID-19 associated thromboembolism**

Thrombotic events occur in 1/3 of COVID-19 patients, often pulmonary embolism associated with disease severity and mortality[120,121]. Venous thromboembolism or VTE has a high prevalence in viral diseases such as SARS-CoV-1 and H1N1, as well as a high rate in severe COVID-19[122,123]. In coagulopathy-related COVID-19, patients may have mild thrombocytopenia, increased prothrombin time, and increased fibrinogen and D-dimers[86,124]. This Pattern of coagulopathies associated with COVID-19 (CAC pattern) may have features in common with sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC)[117]. DIC and SIC may occur during COVID-19, but it is less common[117]. One of the most coagulation disorders in respiratory manifestation in COVID-19 is pulmonary intravascular coagulopathy (PIC) which is a part of systemic coagulopathies. The development of SIC and DIC leads to PIC, the symptomatic sign of coagulopathies or maybe as a local or systemic coagulation[118].

In some viral infections, a disorder similar to MAS occurs and although this disorder is part of secondary hemophagocytic lymphohistiocytosis (sHLH), in COVID-19 it has different features[125,126] [127]. Immunopathology of pulmonary macrophage activation syndrome in COVID-19 is different from classic sHLH [128]. These disorders are associated with organomegaly, thrombocytopenia, hemophagocytosis, and DIC[129]. Rapid onset of DIC can be associated with hyperferritinemia and indicates hemophagocytosis and clot failure. Pulmonary involvement without hyperplasia of the lymphatic organs is typically associated with COVID-19 pneumonia. Intrapulmonary hemophagocytosis can cause extracellular red blood cell hemolysis and cell damage by macrophages. DIC can also happen late during COVID-19 pneumonia[130].

Homeostasis and the immune system are interrelated. Physiological immunothrombosis can be disrupted and cause excessive clots to form effect on small vessels[131]. Immunothrombosis is one of the most important pathological mechanisms of COVID-19

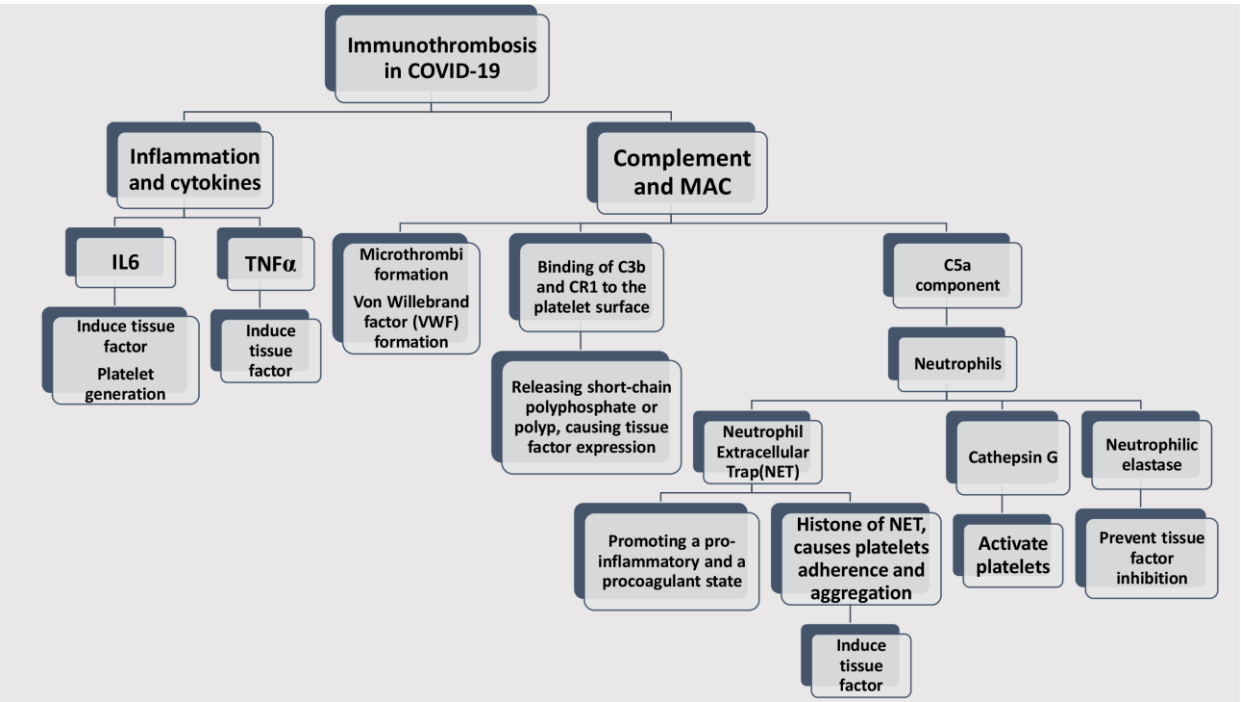


**Figure 3. Immunothrombosis in COVID-19. COVID-19, coronavirus disease of 2019; MAC, membrane attack complex; IL6, interleukin 6; TNF, tumor necrosis factor; VWF, von Willebrand factor; C3b, complement component 3; CR1, complement receptor 1; C5a, complement factor 5a; NET, neutrophil extracellular traps.**

activation of innate immunity, excessive coagulation, and endothelial dysfunction can lead to the development of prothrombotic stages[132]. Primary binding of SARS-CoV-2 to type 2 pneumocytes, infiltrates innate immune cells such as macrophages, monocytes, and neutrophils[131,133]. The cytokines released from these cells, cause a hypercoagulable state by various mechanisms. IL6 itself causes platelet generation [134].

Neutrophil-producing serine protease, cathepsin G, can also actuate platelets. TNF- α and IL-6 can induce tissue factor that is expressed by a variety of cells such as monocytes, macrophages, and endothelium[133–135]. One of the most important coagulation-inducing factors is the membrane attack complex (MAC), which causes the killing of target[136]. This causes coagulopathy with the onset of microthrombi formation and von Willebrand factor (VWF) formation[137]. Like the increase in prothrombin activity, another mechanism is the binding of complement component 3 (C3b) and complement receptor 1 (CR1) to the platelet surface, which releases short-chain polyphosphate or polyp, causing tissue factor expression[133].

Complement factor 5a (C5a) invokes neutrophils and Neutrophil Extracellular Trap(NET) induces coagulation[137]. Although NETosis is considered in health as a mechanism for clearing foreign and dangerous factors, viral infections such as COVID-19 are one of the causes of autoimmune reactions so the patient's plasma with SRAS-CoV-2 is a NETosis activator. [138,139]. NETs with promoting a pro-inflammatory and procoagulant state are involved in the pathogenesis of COVID-19 [138]. In severe COVID-19 patients, neutrophil's NET is related to cytokine storm [138]. Histone, a major component of NET, causes platelets to adhere and aggregate, thereby inducing tissue factor[140]. Neutrophilic elastase breaks down tissue factor inhibitors and prevents tissue factor inhibition[141,142] (Figure 3).

**Complications of Inflammation and Autoimmunity Following COVID-19 Infection According to Hygiene Theory**

The hygiene hypothesis was linked to autoimmune diseases in the early 2000s[143]. Genetic factors such as HLA, epialleles, and underlying diseases such as diabetes mellitus or Insulin-dependent diabetes mellitus (IDDM) play a role in the severity and persistence of symptoms and signs of inflammation. Environmental factors such as viruses and other microorganisms are also involved in autoimmunity[144]. It is concluded that Hygiene is related to the microbiota gut, especially in the gastrointestinal tract and other mucosal surfaces of the body, and plays a role in immunity[145]. The main purpose of the epidemiological function of health theory is to show the relationship between the multiplicity of infections and the multiplicity of allergic and autoimmune diseases[144].

Regarding the evolution of modern humans, it can be mentioned that Homo sapiens, a species to which all modern humans belong, evolved from a cross between African humans and Neanderthals. Some haplotypes that exist in modern humans and are derived from Neanderthals contain important genes in the immune response[144,146]. It has been discovered recently that certain genes leading to a greater vulnerability in people with COVID-19 are found in Neanderthals[147]. From a genetic point of view, the severity of COVID-19 can be linked to chromosome 3, and in particular to a genomic region that encodes chemokine receptors mediating different cellular responses[148]. Chromosome 3 is the main source of genetic risk factors of COVID-19 severity that contains a gene cluster encoding chemokine receptors. The chemokine genes *CCR1*, *CCR2*, *CCR3*, *CCR5*, *CCR9*, *XCR1*, and *CXCR6* are all at risk of severe COVID-19[149]. This major genetic risk factor of severe COVID-19 is inherited from Neanderthals[150].

**Molecular mechanisms in microbiome changes in the gut and Nasopharyngeal of COVID-19 patients**

Dysbiosis means an imbalance of commensal bacteria that puts the intestinal microbiota in pathogenic conditions [151]. Many studies have shown commensal bacteria responsible for regulating autoimmunity, and their absence or reduction can lead to autoimmunity[152], such as probiotics and lactobacilli. In the case of COVID-19, there is also evidence that the intestinal microbiota is disordered[153,154]. Metagenomic sequencing (MGS) analysis shows that clear changes in intestinal bacterium have occurred in COVID-19 hospitalized patients and the diversity of intestinal microbiota and beneficial bacteria decreased[155].

Conversely, opportunistic pathogens such as

*Streptococcus* / *Rotia* / *Actinomycetes* associated with gastrointestinal problems such as abdominal pain, nausea, vomiting, and diarrhea were increased[151,154]. COVID-19 infection is associated with the immune system and microbiota like fingerprints, and the source of dysbiosis is a severe immune response and inflammation. The function of the gut microbiota and its composition in each individual can determine a person's sensitivity or resistance to COVID-19, as well as response to medication and treatment[155].

Angiotensin-converting enzyme 2 (ACE2) metabolizes angiotensin (Ang) II into the Ang 1-7 peptides and regulates the renin-angiotensin system (RAS)[156]. ACE2 is abundantly found in the gut to control $B^0AT_1$expression[157]. $B^0AT_1$ is a transporter involved in the uptake of sodium coupled to neutral amino acids such as tryptophan[158]. $B^0AT_1$ substrates, especially glutamine and tryptophan, downregulate proinflammatory cytokines, form a tight junction, activate the release of antimicrobial peptides, and regulate mucosal cell autophagy as a defense mechanism[159,160]. All of this can be disrupted by COIVD-19 and causes leaky gut. COIVD-19 patients may experience diarrhea, nausea, and vomiting[119], which can cause the virus to spread in the stool and leads to fecal-oral transmission[161–163]. In the large intestine, the dysbiotic gut microbiome increases the release of inflammatory cytokines, loss of tight junction, and changes in mucosal cell autophagy[164].

Also, about the nasopharyngeal microbiome, Patients with severe type showed reduced microbial diversity and also less abundance of beneficial bacteria like *Corynebacterium* and *Dolosigranulum* than healthy individuals and patients with moderate severity. Decreased diversity of microbiota and beneficial compounds is associated with the spread of not only *Staphylococcus* but also Prevotella and *Peptostreptococcus*[165].

**Humoral immunity and COVID-19**

Humoral immunity plays a dual role in COVID-19 While neutralizing antibodies can play a protective role against COVID-19[166,167], unregulated humoral immunity can cause COVID-19 immunopathology and autoimmunity [168,169]. These autoantibodies can affect many functions, such as disrupting cellular signaling or killing specific cells by FCR or compliment. These indicate that these patients' autoantibodies can directly inhibit cytokine and chemokine activity and reduce immune cells[170]. Patients with anti-IFN_1 autoantibody have increased viral load and show impaired virus clearance[169].

Patients with $CD_{38}$ autoantibodies have normal B and NK cells but have low levels of TCD4$^+$, TCD8$^{+,}$ and NKT lymphocytes, and patients with autoantibodies to CD38 have low activated NK, TCD4$^+$, and TCD8$^+$ cells. It has been observed that patients' IgG or plasma can cause Ab-dependent cellular phagocytosis or ADCP versus Jurkat or Raji cells. They even observed anti-tissue autoantibodies, such as vascular cells, coagulation factor, and platelets, connective tissue, extracellular matrix components, and organs such as lungs, central nervous system, skin, gastrointestinal tract[170].

Various autoantigens such as Neurexophilin-1 (NXPH1), proprotein convertase subtilisin/kexin-type 1 (Pcsk1), anti-hypocretin receptor 2 (HCRTR2), solute carrier family 2 members 10 (SLC2A10) are associated with markers associated with COVID-19 severity, such as D-dimer, ferritin, CRP, lactate[171,172]. They also observed an HCRTR2 autoantibody, the Orexin receptor (which is highly expressed in the brain and is involved in the central response mechanisms that control behavior) in the hypothalamus that interferes with its activity[170,173].

## Conclusion

It is not yet a good time to accept autoimmunity as the primary comet complication of COVID-19, and many of the immune-related disorders in SARS-CoV-2 can indicate a temporary secondary disorder following a viral infection. Anti-inflammatory therapies and immunosuppressants can help prevent autoimmune disease. But information is still evolving and we need more time to give a definitive answer to this question.

Today's world is waiting for the future and other pandemics. COVID-19 infection, along with the immune suppression mechanism, has the potential to evoke destructive inflammation in the host.

As we have witnessed a wave of inflammatory autoimmune disorders and subsequent complications of viral infections, not only to combat this

phenomenon but also to try to prevent it, the front line of the fight against these complications must be included.

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None.

## Conflict of Interest

The authors further declare that, they have no conflict of interest.

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