World Journal of Methodology

Submit a Manuscript: https://www.f6publishing.com

World J Methodol 2022 July 20; 12(4): 200-223

DOI: 10.5662/wjm.v12.i4.200

ISSN 2222-0682 (online)

REVIEW

COVID-19 disease and autoimmune disorders: A mutual pathway

Mohammed Al-Beltagi, Nermin Kamal Saeed, Adel Salah Bediwy

Specialty type: Rheumatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Naswhan AJ, Qatar; Wang MZ, China

Received: March 21, 2022
Peer-review started: March 21, 2022
First decision: June 16, 2022
Revised: June 17, 2022
Accepted: July 6, 2022
Article in press: July 6, 2022
Published online: July 20, 2022

Mohammed Al-Beltagi, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31527, Algharbia, Egypt

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Dr. Sulaiman Al-Habib Medical Group, Manama 26671, Manama, Bahrain

Nermin Kamal Saeed, Medical Microbiology Section, Department of Pathology, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain, Manama 12, Manama, Bahrain

Nermin Kamal Saeed, Microbiology Section, Department of Pathology, Irish Royal College of Surgeon, Bahrain, Busaiteen 15503, Muharraq, Bahrain

Adel Salah Bediwy, Department of Chest Disease, Faculty of Medicine, Tanta University, Tanta 31527, Algharbia, Egypt

Adel Salah Bediwy, Department of Chest Disease, University Medical Center, King Abdulla Medical City, Arabian Gulf University, Dr. Sulaiman Al-Habib Medical Group, Manama 26671, Manama, Bahrain

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, MSc, PhD, Chairman, Professor, Department of Pediatrics, Faculty of Medicine, Tanta University, Al Bahr street, Medical Complex, Tanta 31527, Algharbia, Egypt. mbelrem@hotmail.com

Abstract

Coronavirus disease 2019 (COVID-19) is a real challenge for humanity with high morbidity and mortality. Despite being primarily a respiratory illness, COVID-19 can affect nearly every human body tissue, causing many diseases. After viral infection, the immune system can recognize the viral antigens presented by the immune cells. This immune response is usually controlled and terminated once the infection is aborted. Nevertheless, in some patients, the immune reaction becomes out of control with the development of autoimmune diseases. Several human tissue antigens showed a strong response with antibodies directed against many severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins, such as SARS-CoV-2 S, N, and autoimmune target proteins. The immunogenic effects of SARS-CoV-2 are due to the sizeable viral RNA molecules with interrupted transcription increasing the pool of epitopes with increased chances of molecular mimicry and interaction with the host immune system, the overlap between some viral and human peptides, the viral induced-tissue damage, and the robust and complex binding between sACE-2 and SARS-CoV-2 S protein. Consequently, COVID-19 and its vaccine may trigger the development of many

autoimmune diseases in a predisposed patient. This review discusses the mutual relation between COVID-19 and autoimmune diseases, their interactive effects on each other, the role of the COVID-19 vaccine in triggering autoimmune diseases, the factors affecting the severity of COVID-19 in patients suffering from autoimmune diseases, and the different ways to minimize the risk of COVID-19 in patients with autoimmune diseases.

Key Words: COVID-19; SARS-CoV-2; Autoimmune Diseases; Vaccines

Core Tip: There is a mutual relation between coronavirus disease 2019 (COVID-19) and autoimmune diseases. Patients with immune deficiencies or autoimmune disorders are at a higher risk for infection with COVID-19, as they are frequently treated with anti-cytokine, glucocorticoids, and immunosuppressive drugs. Meanwhile, COVID-19 and its vaccine could trigger the development of autoimmune diseases. Therefore, a multi-purpose comprehensive social and family program with exercise and psychological support is highly needed for patients with autoimmune disorders to lessen the harmful effects of social isolation impeded during the COVID-19.

Citation: Al-Beltagi M, Saeed NK, Bediwy AS. COVID-19 disease and autoimmune disorders: A mutual pathway. *World J Methodol* 2022; 12(4): 200-223
URL: https://www.wjgnet.com/2222-0682/full/v12/i4/200.htm
DOI: https://dx.doi.org/10.5662/wjm.v12.i4.200

INTRODUCTION

The coronavirus disease 2019 (COVID-19), with its global pandemic, which started with the first reported case in December 2019, is a real challenge for humanity. These challenges are due to the uncertainty about the origin of the virus, its rapid transmission, the difference in racial susceptibility, the wide variety of clinical presentations, the conflict in diagnosis, the rapid mutations that continuously elaborate, the disparity of the treatment regimens in the different parts of the world, and the high morbidity and mortality rates[1,2]. The virus that causes COVID-19, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a member of the beta coronaviruses group. This group is a part of a Coronaviridae family with spherical, positive-sense, non-segmented, single-stranded, and large (100–160 nm) RNA viruses[1].

SARS-CoV-2 is a single-stranded RNA virus with a positive sense and a unique pleomorphic or spherical, non-segmented envelope with distinctive crown-shaped peplomers or spikes[3]. It has four main structural proteins: spike protein (S), small envelope glycoprotein (E), membrane glycoprotein (M), and nucleocapsid protein (N). Other several accessory proteins are present and have particular functions. S protein is a sizeable trimeric glycoprotein that facilitates viral binding to host cells through binding to angiotensin-converting enzyme II receptors with its two non-covalently associated subunits. The first subunit (S1) binds to angiotensin-converting enzyme II (ACE2) with its subunit receptor-binding domain (RBD). The second subunit (S2 subunit) controls the fusogenic ability of the virus-cell membrane and fixes the S protein to the cell membrane[4]. The E protein is a small envelope glycoprotein of three variants, participates in viral assembly and virion release, and plays a critical role in the virus pathogenesis. M glycoprotein shapes the viral envelope and is accountable for transmembrane nutrient transporting and bud release. N protein is formed from the matrix protein and is present near the viral nucleic acid material within a capsid to help pack the viral RNA genome inside the viral envelope. This process is a fundamental component of the self-assembly and replication of the virus[5,6]. The virus's genome encodes for the four essential structural proteins (S, M, E, and N), hemagglutinin esterase, and another six accessory genes occupying the main part of the viral genome (about two-thirds). There are three well-defined variants of SARS-CoV-2: A, B, and C, according to their genomic differences[7].

PATHOGENESIS AND IMMUNOGENICITY OF SARS-COV-2

Despite being primarily a respiratory illness, COVID-19 can affect nearly every human body tissue, causing a broad range of illnesses. Similar to SARS-CoV, SARS-CoV-2 uses ACE2 receptors to enter the host cells. It uses the surface S glycoprotein with its two domains (S1 and S2) to bind at the RBD with

the ACE2 receptor and fuse the viral envelope membrane with the cell membrane. However, SARS-CoV-2 S proteins bind stronger with human ACE2 receptors than SARS[8]. These spike proteins have high antigenicity, as indicated by the elevated plasma anti-S neutralizing antibodies levels in convalescent patients[9].

The body localization and expression of ACE2 receptors could determine the potential target organs of SARS-CoV-2 infection and outline the disease progression and clinical consequences. ACE2 receptors were first reported in the heart, kidneys, and type-I and II alveolar cells. Then, recently high expression of ACE2 receptors was reported in the brain, eyes, nasal and oral mucosa, thyroid, esophageal epithelium, gastric mucosa, liver, cholangiocytes, pancreas, the smooth muscle cells, and enterocyte from the small intestine to the colon, skin, testis, ovary, uterus, vagina, and urinary bladder[10,11]. All these organs should be considered as a potential target for SARS-CoV-2 infection. ACE2 receptor expression may be absent in the bone marrow, lymph nodes, thymus, spleen, and numerous immune system cells[12]. The patients' differences in ACE2 receptor distribution and ACE2-SARS-CoV-2 mutual interactions could affect the disease pathophysiology, progression, and consequences. Many factors could affect ACE2 receptors distribution, including heritability, patient demographics, lifestyle, comorbidities, and drugs[13]. Meanwhile, soluble ACE-2 (sACE-2) is found in the serum or plasma due to shedding from the cell surface. These sACE-2 strongly interact with SARS-CoV-2 S protein and vasopressin to initiate receptor-mediated endocytosis, enabling SARS-CoV-2 to enter the host cells[14].

After viral entry into the body, it attaches to the mucosal cell, entering the cell either at the plasma membrane or the endosome through receptor-triggered endocytosis[15,16]. The receptor-dependent endocytosis starts by latching the RBD part of the S1 protein of the viral envelope to a pocket in the ACE2 receptor, fixing the virus to the cell membrane. Then, the transmembrane protease serine 2 present near ACE2 receptors cleaves a protein between the S1 and S2 units in a specific location, with the help of the Furin enzyme, which enables the viral entry into the cell after binding. The enzymatically induced cutting of S protein exposes previously hidden parts of the S protein, which undergo a series of remarkable conformational changes and more fixation into the cell membrane. Once inserted, S proteins pull back on themselves, pulling the membranes of the cell and the virus together to fuse. When the viral envelope starts to merge with the host cell membrane, it creates a fusion pore that allows the virus to release its genetic material into the cell cytoplasm of the infected cell[17,18].

After receptor engagement and viral replication inside the affected epithelial cells of the nasal cavity, there will be an initial asymptomatic phase for one to two days. During this phase, the virus continues to replicate and multiply without significant resistance by the innate cellular immunity. After this initial stage, the symptoms appear from 2-14 d. Once the SARS CoV-2 virus spreads to the lower respiratory tract, it stimulates a vigorous innate immune response with a more significant pro-inflammatory response that may progress to viral sepsis and other consequences of acute respiratory distress syndrome that may end with multisystem organ failures and even death[19].

Viral antigen presentation

After viral infection, T lymphocytes can recognize the viral antigens presented by major histocompatibility complex (MHC) class I on the surface of all the nucleated human cells and the platelets. This step is crucial for cytokine release and promotes CD8+ T cells cytotoxic activity. However, MHC class II can occasionally present the viral epitopes to CD4+ T cells[20,21]. The human leukocyte antigens (HLA) association is not very well-identified for SARS-CoV-2 infection, which could be crucial for preventing and treating COVID-19. However, a study by Tomita *et al*[22] showed that patients with HLA genotypes (HLA-A*11:01 or HLA-A*24:02) might efficiently produce T-cell-mediated immune responses to SARS-CoV-2 than patients with HLA-A*02:01. At the same time, reports documented the ability of SARS-CoV-2 to inhibit the expression of HLA-antigens. Giamarellos-Bourboulis *et al*[23] showed that the plasma-derived from patients with severe SARS-CoV-2 infection could inhibit the expression of HLA-DR on CD14+ monocytes, which could partially be reversed by Tocilizumab (IL-6 blocker), indicating the role of hyper-inflammation and the sustained cytokine production in inducing this immune dysregulation.

The innate immunity

The immune responses to SARS-CoV-2 start with the innate immune response by the interferon (IFN)-mediated pathways and the adaptive cellular and humeral immunity through the T lymphocyte and the antibody-mediated pathways. However, SARS CoV-2 can antagonize the IFN-mediated antiviral responses, allowing viral replication with a high early viral load and transmissibility[24]. The innate immune response to SARS-CoV-2 infection in the respiratory tract is mediated through alveolar macrophages and dendritic cells, inducing a cascade of inflammation to restrict virus replication effectively. This cascade of inflammation arises from the release of pro-inflammatory cytokines, particularly IL-18 and IL-1β, which explains the distinguished characteristic of neutrophilia and leukopenia commonly observed in patients with severe COVID-19[25]. The released inflammatory mediators recruit T lymphocytes and monocytes primarily, but not neutrophils, to the site of infection, which explains the lymphopenia and the raised neutrophil-lymphocyte ratio observed in most patients with COVID-19 [26]. However, this induced inflammatory cascade plays a significant role in the pathogenesis of severe organ injury and adverse disease outcomes[27]. The differences in patients' susceptibility to coronavirus

infection may be related to the differences in the Mannose-binding lectin (MBL) protein, which has a significant role in pattern-recognition molecules, one of the first-line host defense mechanisms against SARS-CoV-2 infections[28]. MBL pathway activates the complement pathway that promotes thrombosis and coagulopathy in severe COVID-19[29]. The viral RNA also activates Toll-Like Receptor 3, 7, 8, and 9, which accordingly activates the pathway including Nuclear Factor kappa B (NF-κB)[30].

This immune response is usually controlled and terminated once the infection is aborted. Nevertheless, in some patients, the immune reaction becomes out of control with excessive unwanted response ending with a cytokine storm with a low level of IFN in early-stage and high levels in late-stage, an excessive increase of interleukin (IL)-6, IL-2, IL-7, and IL-10, massive increase of granulocyte-macrophage colony-stimulating factor (GM-CSF), Macrophage Inflammatory Protein 1α (MIP-1α), Tumor Necrosis Factor-alpha (TNF-α), plasma-induced protein 10 (IP-10), monocyte chemotactic protein-1 (MCP-1), and Inflammatory Protein 1α (MIP-1α)[31-33]. This deviated immune response's exact mechanism is unknown but may be related to the antagonistic effects of viral N protein on the interferon signaling pathway. Interferons-mediated innate immunity is the first defense mechanism against viral infections, including COVID-19, through activating macrophages and natural killer (NK) cells, which destroy the virus-infected cells[26]. Interferon deficiency causes an elevation in pro-inflammatory cytokines, an inadequate antiviral response, ACE2 receptor upregulation, high viral load, and subsequent excessive inflammatory response[34,35]. Complement activity is essential in immunity modulation and can predict the clinical outcome of SARS-CoV-2 infection. Complement protein C3 activation occurs early in the course of COVID-19. It plays a significant role in enhancing prothrombotic and pro-inflammatory conditions with immune complex deposition in different organs that may proceed to extensive endothelial damage, acute respiratory distress syndrome, and even end-organ damage observed in severe cases of COVID-19[36,37]. Consumption of the complement proteins in the immune complexes explains the low levels of C3 and C4 observed in instances of severe COVID-19. Detection of low levels of C3 and C4 can be a warning sign of the need for additional management in patients admitted with COVID-19[38]. Immune complexes depositions induced-vascular injury and antibody-dependent enhancement increase viral replication in Fc-receptor expressing cells[39].

The adaptive immunity

The three main types of lymphocytes, B cells, T cells, and natural killer cells, play a vital role in clearing infections once they begin. Their plasma numbers correlate well with better survival. Lower leukocyte and lymphocyte numbers help the virus avoid the host immune response with a high viral load and transmission rate[40]. Once activated by SARS-CoV-2, natural killer T cells can prevent viral spread from the upper airways to the rest of the body and, consequently, determine the severity of the symptoms, the viral load, transmission to the community, and the disease outcome[41].

Although T and B lymphocytes do not express ACE2 receptors, some of them can still be infected by the SARS-CoV-2 virus, which indicates the presence of other receptors participating in the viral entry in some lymphocytes. After a few days from SARS-CoV-2 infection, naïve lymphocytes differentiate into Th2 and produce Th2 cell serum cytokines. The higher the levels of Th2 cell serum cytokines are, the worse the outcome is[42]. Some memory T cells can be primed by a previous animal or human coronavirus infections, so they can recognize some of the viral proteins, help clear SARS-CoV-2 and produce asymptomatic infections in many patients even in the absence of antibodies in their serum[43]. SARS-CoV-2 induces a direct cytotoxic effect on the lymphocytes to evade the immune system, resulting in lymphopenia, preventing cytokine storm, and diminishing the innate immune responses[44]. SARS-CoV-2 also upregulates many apoptosis-involved genes, including P53, which helps develop lymphopenia. This SARS-CoV-2-induced lymphopenia is prevalent in patients with old age or other comorbidities such as obesity, hypertension, or diabetes mellitus[45]. Lymphopenia could also result from increased leukocyte adhesion and extravasation due to SARS-CoV-2-induced endothelial dysfunction, particularly in old age and with comorbidities, augmenting the problem of lymphopenia [46]. Effector T cells are the leading players driving immune responses to achieve immune functions. These cells have both promoting and inhibitory regulatory functions of innate immunity. The maturation and differentiation of naïve-T cells to mature fully functioning effector cells are controlled by cytokines produced by activated cells of the innate and adaptive immune systems. SARS-CoV-2 induces enhanced inhibitory receptor expression on the surface of T cells due to cytokine activity or reduction of the regulatory T-cells. These inhibitory effects negatively exhaust the effector T cells and reduce the defense against SARS-CoV-2[47]. CD4+ T cells, CD8+ T cells, and B cells have a crucial protective role against SARS-CoV-2 infections. A decrease in CD4+ T cell number and function causes cytokine, neutralizing antibody production reduction, and reduced lymphocyte recruitment to lung tissue. These effects cause an increased risk of interstitial pneumonitis and delay the clearance of infection from the lungs. However, depletion of CD8+ T cells at the beginning of SARS-CoV-2 infection does not affect the viral clearance or replication[48].

B lymphocytes represent 15% of peripheral white blood cells and are responsible for the humoral immunity and protection against various pathogens through various immunologic functions, including antibody production. Specific immunoglobulin M (IgM) anti-SARS antibodies appear within two weeks after infection, reaching the peak in the third week, to gradually disappear until the end of the third month[49]. Immunoglobulin G (IgG) started to appear by the end of the second week, reaching the peak

by the end of the fourth week, and persisted for longer but not for a long time [in SARS-CoV-1, Ig G lasts for about two years][50]. Consequently, antibody levels can be used to determine the stage of SARS-CoV-2 infection. The levels of anti-SARS-CoV-2 antibodies decrease by about 50% within 1-3 mo following the beginning of the infection[51]. However, some cases with agammaglobulinemia infected COVID-19 showed full recovery without functioning B-cells[52,53]. The antibody response may help inhibit viral replication through neutralization and blocking the viral entry, egress, or fusion with the host. However, enhancing antibodies may counteract the neutralizing antibodies. Antibodies can enhance viral infections and participate in COVID-19 pathogenesis *via* antibody-dependent enhancement. The level of enhancing antibodies is positively correlated with pro-inflammatory mediators levels and negatively correlated with anti-inflammatory mediators. Which has the upper hand, the neutralizing or enhancing antibodies depend on the dominant antibody type concentrations and affinity[54,55]. Abnormal B lymphocytes maturation and conversion to macrophage-like cells caused by the viral S protein impairs the immune system's humoral and cellular elements in responding to severe infection with SARS-CoV-2[56]. Table 1 shows the various factors that affect the severity of infection with COVID-19.

AUTOIMMUNITY AND CROSS REACTIVITY OF SARS-COV-2

In antigenic or molecular mimicry, common antigenic sites are shared between microorganisms and the host tissue. The microorganism-triggered immune response is directed against the microorganism and the host cells with the common antigenic determinant. This deviated autoimmune response is responsible for developing many autoimmune disorders in humans. Recently, it has been observed that several human tissue antigens showed a strong reaction with antibodies directed against SARS-Cov-2. This antigenic mimicry was observed for many SARS-CoV-2 proteins, including but not limited to SARS-CoV-2 S, N, and autoimmune target proteins[57]. These induced antibodies can react with a wide variety of human tissues and proteins such as skin, respiratory, digestive, cardiac, and nervous tissues, producing a wide array of autoimmune disorders with extensive cellular, tissue, and organ damage observed in severe COVID-19 cases[58]. The cross-reactivity of SARS-CoV-2 is not limited to the human body. SARS-CoV-2 also has cross-reactivity with SARS-CoV, as patients with COVID-19 can produce IgG and IgM antibodies able to react with SARS-CoV. This observation is fundamental as it helps understand that some patients may have mild or aggressive COVID-19. Previous infection with SARS-CoV with pre-exciting antibodies that can cross-react with SARS-CoV-2 may explain this variation in the clinical presentation in patients with COVID-19. However, recovery from SARS-CoV infection might not protect against SARS-CoV-2 and vice versa[59]. Cross-reactivity between SARS-CoV-2 and other human coronaviruses, especially beta coronaviruses (particularly SARS-CoV and MERS-CoV), may explain numerous phenomena. The increased pathogenicity and severity of SARS-CoV-2 infection in areas with common pre-existing SARS-CoV infection is due to the possible presence of enhancing cross-reactive antibodies against those common coronaviruses[60]. Enhancing cross-reactive antibodies to SARS-CoV-2 in patients previously exposed to SARS-CoV can explain the early response with higher titers in older age and the milder symptoms in the pediatric age[61,62]. However, the lower prevalence of COVID-19 in the pediatric age is multifactorial and could be related to the age-dependent immaturity of ACE2 receptors in children[63]. The tissue damage induced by the cross-reactive autoantibody induces the release of more self-antigens, activating more autoreactive T-cells, producing more self epitopes, and sparking autoimmunity[64]. Cross-reactive antibodies also raise a question about using convalescent plasma to treat patients with SARS-CoV-2 infection to neutralize SARS-CoV-2. However, convalescent plasma may lack effectiveness and, on the other hand, may induce endothelial damage due to the transmission of cross-reactive enhancing antibodies[65]. Cross-reactivity is also of paramount importance in the vaccination industry, considering SARS-CoV-2 cross-enhancing or neutralizing epitopes to minimize the vaccine side effects and vaccine-induced autoimmunity[66].

SARS-COV-2 INDUCED AUTOIMMUNE AND AUTO-INFLAMMATORY CONDITIONS

A variety of factors may trigger autoimmunity by generating a hyperstimulated immune system. The terms exposome, infectomes, and autoinfectomes are recently introduced in autoimmunity. Exposome describes all the environmental triggers (exogenous or endogenous) that the host could expose to it. Infectomes are all infectious microbes that the host can be exposed to during his/her life. In the same way, autoinfectomes are all infectious agents that can trigger autoimmunity upon exposure[67]. The ability of SARS-CoV-2 to initiate autoimmune and autoinflammatory responses is related to many factors. The SARS-CoV-2 can induce a state of the hyperstimulated immune system with changes in the circulating leukocyte and an extensive increase in the levels of the pro-inflammatory cytokines, known as "cytokine release syndrome" in patients with variable degrees of COVID-19[32]. The large RNA with 30,000 nucleotides and the complex transcriptome with the interrupted transcription and recombination activities increase the chance of interaction with the host immune system[68]. The interrupted RNA

Table 1 Factors affecting the severity of coronavirus disease 2019 infections

Factor		Example
Viral-related factors		The viral load[24]; Mutation/virulence; Previous infections with other Coronaviruses *e.g.*, SARS-CoV[43,59]
Host-related factors:	**Demographic factors**	Patients' age[61,62]
		Gender[80,182]
		Race/ethnic group
	Physiological	Pregnancy[215]; Personel differences in ACE2 receptors distribution[13]
	Pathological factors	Presence of comorbidities such as obesity, hypertension, tuberculosis, HIV, anemia, nutritional deficiencies, or diabetes mellitus[13,45,159,169,171,181]
	Immunological factors	The type of HLA-antigen[20-23]
		The plasma numbers of B cells, T cells, and natural killer lymphocytes[40,41]
		The hemoglobin and ferritin levels[216]
		The levels of C3 and C4[38]
		The differences in the MBL protein[28]
	Environmental factors	Socioeconomic status[217]
		Overcrowding[218]
		Smocking[205]
		Alcohol consumption[204]
		Particular occupations: Occupations that involve a higher degree of physical proximity to others over long periods [219]
	Pharmacological factors	Certain drugs increase the severity (*e.g.*, rituximab, high-dose corticosteroid)[140,187,191]. Certain drugs decrease the severity (*e.g.*, ubiquinone, ezetimibe, flecainide, rosuvastatin, artificial tears, licorice)[214]
		Vaccination status of the patients

ACE2: Angiotensin-converting enzyme II; HLA: Human leukocyte antigens; HIV: Human immunodeficiency virus; MBL: Mannose-binding lectin; SARS-CoV: Severe acute respiratory syndrome coronavirus 2.

transcription and recombination produce a wide variability of protein sequences with a powerful resource of epitopes with molecular mimicry, another reason for stimulating the immune system and inducing autoimmunity associated with COVID-19[69]. There is an overlap between some viral and human peptides, so that if altered or mutated could initiate autoimmunity. From these human peptides; cerebellum-2 (which protects against multiple sclerosis), follistatin-related protein 1 (which has anti-hypoxia-induced pulmonary hypertension), Solute carrier family 12 member 6 (responsible for electroneutral potassium-chloride cotransport), and olfactory receptor 7D4 (responsible for the sense of smell)[70]. Tissue damage may result from the viral infection causing cell death and the release of self-proteins to be identified by the host immune system as foreign material and spark the process of autoimmunity[71]. At the same time, there is a hypothesis that sACE-2, which usually binds strongly with SARS-CoV-2 S protein, forms a complex, stimulating the production of anti-ACE2 antibodies and triggering type II and III hypersensitivity reactions and Type IV cellular immune reactions against the viral particles attached to sACE-2, and autoimmunity cascade. The virus-activated T cells could injure the self-tissues by initiating an inflammatory milieu or directly damaging the cells[72]. Table 2 summarizes the causes of the increased immunogenic effect of SARS-CoV-2.

Infection with SARS-CoV-2 can serve as infectome induce a range of autoimmune and auto-inflammatory conditions such as Multisystem Inflammatory Syndrome in Adults (MIS-A), Multisystem Inflammatory Syndrome in Children (MIS-C), and various autoimmune/rheumatic manifestations with a proposed link between the autoimmune and autoinflammatory sequelae of SARS-CoV-2 infection[73]. MIS-C may include Kawasaki-like disease, toxic shock syndrome, Kawasaki disease (KD) shock syndrome, macrophage activation syndrome, and myocarditis. MIS-A, contrary to MIS-C, is not well defined with a hyperinflammatory state and inconsistent features of KD[74]. Although children usually encounter a milder COVID-19 than adults, the severe MIS-C that followed the disease in some children brought several unanswered questions to the scientific community[75].

Patients with COVID-19 may develop a wide variety of autoimmune disorders such as arthritis, antiphospholipid antibody syndrome (APS), MIS-A/C, Kawasaki and Kawasaki-like disease, antiphospholipid syndrome, systemic vasculitis, systemic lupus erythematosus (SLE), hemophagocytic lymphohistiocytosis, autoimmune blood disorders (such as idiopathic thrombocytopenic purpura, autoimmune

Table 2 Factors that increase the rate of autoimmunity in coronavirus disease 2019

The ability of the virus to infect nearly all the human body tissues
Large RNA with interrupted transcription increases the pool of epitopes with increased chances of molecular mimicry and interaction with the host immune system
The overlap between some viral and human peptides
The viral-induced tissue damage increases the chance of deviated immune system
The immunogenic effect of the robust and complex binding between sACE-2 and SARS-CoV-2 S protein

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

thrombotic thrombocytopenic purpura, and autoimmune hemolytic anemia), neurological autoimmune disorders (such as encephalitis, cranial neuropathies, Guliian Barre syndrome, myelitis, and optic neuritis, acute disseminated encephalomyelitis {ADEM}, and multiple sclerosis), interstitial lung disease, autoimmune ocular disorders (Retinal vein vasculitic occlusion), renal disorders (Crescentic glomerulonephritis, Goodpasture syndrome), inflammatory bowel disease, and autoimmune endocrine disorders (such as diabetes mellitus and subacute thyroiditis)[76].

Risk factors increasing the likelihood of autoimmune diseases in patients with COVID-19

Infections with SARS-CoV-2 increase the likelihood of autoimmune disease development as about 50% of the patients have autoantibodies in their blood, even with mild disease, and the risk increases with increasing severity. Severe disease is usually associated with a higher viral load with robust immune stimulation and higher antibody levels. There is a strong association between immune hyperactivation and excessive cytokine release in patients with severe COVID-19. However, mild COVID-19 or even asymptomatic infection may also trigger autoimmune disorders[77]. Demographic features such as female gender, old age, overweight, or obesity generally increase the risk of developing autoimmune diseases, particularly with COVID-19. Aging causes functional impairment of the immune with potentially higher autoreactive antibody levels[78]. Although females usually have milder diseases than males with higher recovery rates, they have more chance of autoimmune disorders. The risk difference of autoimmune disorders between males and females is related to sex hormone differences as androgens like testosterone are immunosuppressive, while estrogen may enhance or reduce immune response[79]. Particular ethnic populations are more genetically predisposed to have autoimmune disorders following SARS-CoV-2 infection, such as Caribbean descent, sub-Saharan, Asian, Black, and mixed ethnicity[80]. Nucleic acid vaccine administration may increase the risk of autoinflammatory and autoimmune disorders, especially in young females. In addition, a pre-existing autoimmune disorder is a risk factor for another autoimmune disorder or more severe symptoms following COVID-19[81]. Gut dysbiosis is a risk factor for both COVID-19 and autoimmune diseases. Ivermectin, a commonly used drug in managing COVID-19 in certain countries, induces significant alteration of gut microbiota, which may increase the risk of autoimmune disorders. However, more studies are needed to confirm this hypothesis[63,82].

Common autoantibodies with SARS-CoV-2 infection

Patients with COVID-19 may develop multiple categories of autoantibodies and autoimmune diseases. However, the clinical significance of these antibodies needs more elaboration. From these antibodies are anti-nuclear antibodies (ANA), antiphospholipid antibodies (as lupus anticoagulant, Anti-β2 glycoprotein 1, and anticardiolipin), anti-Interferon-gamma (Anti-IFN-ɣ) antibodies, anti-melanoma differentiation-associated gene 5 (Anti-MDA5) antibodies, and anti-ACE2 autoantibodies[83]. ANA antibodies are found in 4-50% of patients with COVID-19, especially with old age, even without autoimmune disease. Presence of ANA antibodies in patients with COVID-19 increases the incidence of neurologic and thrombotic complications and unfavorable outcomes[76]. Anti-type-I interferon (IFN) antibodies are present in 10.2% of patients presented with severe COVID-19 pneumonia[84]. Antiphospholipid antibodies (anticardiolipin and/or anti-β2 glycoprotein 1) are present in a significant portion of critically ill patients with COVID-19. These antibodies and elevated factor VIII may contribute to hypercoagulopathy in severe cases of COVID-19[85]. Anti-MDA5 antibodies are associated with the rare disease amyopathic dermatomyositis. They are also present in more than 40% of patients with severe COCID-19. Higher titers of Anti-MDA5 antibodies are associated with more severe disease and a higher risk of death[86]. Anti-ACE2 antibodies are present in many patients with COVID-19 and are associated with low plasma levels of sACE-2 and increasing angiotensin II levels, which triggers a pro-inflammatory state that causes symptoms of post-SARS-CoV-2 Acute Sequelae[87]. The SARS-CoV-2 virus causes damage to the human brain *via* complex indirect processes and stimulates autoantibody formation, predominantly against brain-based antigens (autoantibodies against contactin-associated protein 2, ganglioside GD1b, and myelin oligodendrocyte glycoprotein), inducing a wide variety of

COVID-19-triggered neurological complications[64].

COVID-19-INDUCED AUTOIMMUNE DISEASES

Multisystem inflammatory syndromes (MIS-A, MIS-C, and MIS-A/C)

Multisystem inflammatory syndrome (MIS) is a rare acute and non-chronic but seriously complicates COVID-19 in adults and children. It is currently a distinct phenomenon of severe COVID-19 due to the frequent absence of respiratory involvement. The MIS pathogenesis is unclear but primarily due to the autoimmune process. MIS-A associated with COVID-19 infection usually occurs in adults aged 35-54. Clinical recognition of MIS-A is confused with other hyperinflammatory manifestations of COVID-19, which makes MIS-A challenging to distinguish from acute biphasic COVID-19 and post-acute sequelae of SARS-CoV-2 infection[88]. To its name, MIS-A involves multiple organs and systems with at least one or more extrapulmonary organs (an average of 4-5 organs). The most affected organs are hematologic, cardiovascular (myocarditis, pericardial effusion, hypotension, cardiac dysfunction, heart failure, arterial or venous thrombosis, and cardiogenic shock), gastrointestinal tract (diarrhea), acute liver injury, respiratory system (dyspnea), skin manifestations (polymorphic rashes and other mucocutaneous manifestations), renal, and nervous system (severe mononeuritis multiplex[89-91].

It can be diagnosed according to the CDC criteria for defining MIS-A. It should occur in adults aged 21 years or older, with manifestations that need hospitalization for more than 24 h, as determined by clinical and laboratory criteria. Clinical criteria include fever (≥ 38.0 °C) for ≥ 24 h before hospitalization or within the first three hospitalization days plus three or more of the following clinical criteria; one of them at least should be from the primary criteria. Primary clinical criteria include severe cardiac involvement, skin rash, and non-purulent conjunctivitis. Secondary clinical criteria include; new-onset neurologic manifestations, non-medication-related hypotension or shock, abdominal manifestations (abdominal pain, vomiting, or diarrhea), and thrombocytopenia. Laboratory criteria include evidence of recent SARS-CoV-2 infection (positive PCR, antigen, or antibody) and elevated at least two inflammatory markers from the following: erythrocyte sedimentation rate, C-reactive protein, IL-6, ferritin, and procalcitonin[92]. MIS-A should be differentiated from meningitis, intra-abdominal sepsis, KD, drug reaction, and haemophagocytic lymphohistiocytosis. It is treated with corticosteroids, anticoagulants (*e.g.*, heparin, enoxaparin, aspirin), immune modulators such as Infliximab (TNF inhibitors), Tocilizumab (IL-6 receptor inhibitor), Anakinra (IL-1 receptor antagonist), and intravenous immunoglobulin (IVIG). Patients who develop shock/hypotension require intensive care unit admission, vasoactive medications, and respiratory support with mechanical ventilation[93].

MIS-C occurs in people younger than 21, a few weeks after infection with SARS-CoV-2. The affected children have a fever with clinical evidence of severe disease requires hospitalization and multisystem (more than two) organ involvement (heart, kidneys, respiratory, gastrointestinal, hematologic, skin, and/or nervous system) without other possible reasons explaining the manifestations, evidence of recent infection with SARS-CoV-2 (positive PCR, antigen or antibody), and presence of markers of systemic inflammation (high ferritin, fibrinogen, procalcitonin, lactic acid dehydrogenase, C-reactive protein, erythrocyte sedimentation rate, D-dimer, lactic acid dehydrogenase, or interleukin 6, reduced lymphocytes, elevated neutrophils, and low albumin)[94,95]. As MIS-C frequently affects the heart, we may need to perform B-type natriuretic peptide, cardiac enzymes and Troponin I or T, electrocardiogram, and echocardiography. According to the organs affected, other laboratory tests may be needed [96]. MIS-C is primarily treated with supportive care, fluid resuscitation, and inotropic support as a cardiogenic shock is one of the most severe presentations. Respiratory support is indicated with impending respiratory failure. Extracorporeal membranous oxygenation is rarely required. IVIG, steroids, other anti-inflammatories, and anticoagulants are frequently used. Antibiotics may be used with suspected sepsis. Aspirin is commonly prescribed due to the frequent involvement of coronary arteries[97,98].

KD-COVID-19

COVID-19 is usually milder, less frequent, and has less mortality in children than adults due to less maturity and function of ACE2 receptors. Since the early beginning of 2020, there has been an increased reporting of children presented with fever, signs, and features of systemic inflammation common with KD[99]. KD is an acute, usually self-limited systemic inflammatory disease of medium- and small-sized vessels. It mainly involves children under five years of age with higher frequency in children from Asian countries like Japan, where it was first described in 1967[100]. It is usually preceded by upper respiratory tract infections, particularly with RNA viral infection of the upper respiratory tract, as viruses were usually isolated from the mucous obtained from the bronchial epithelium[101]. Despite being a self-limited disease, hemodynamic instability and shock may occur in some cases, known as KD shock syndrome. About 20%–25% of untreated patients of KD develop changes in the coronary arteries, ranging from asymptomatic dilatation or aneurysms to massive aneurysmal dilatation of the coronary artery with thrombosis and myocardial infarction that could progress to sudden death[102].

Symptoms of COVID-19-associated MIS-C may have the standard features of KD. Therefore, it is essential to differentiate between classical KD and COVID-19 (KD-COVID-19). The table shows the differences between the classic KD and KD-COVID-19 [also known as pediatric inflammatory, multisystem syndrome temporally associated with SARS-CoV-2 infection' (PIMS-TS) in Europe and 'multisystem inflammatory syndrome in children (MIS-C)] in the United States. KD-COVID-19 usually occurs in older children, higher incidence of myocarditis and cardiac involvement, more gastrointestinal and meningeal manifestations, shock, hemodynamic failure, manifestations of macrophage activation syndrome, frequent leukopenia, significant lymphopenia, thrombocytopenia, high ferritin, procalcitonin, cardiac enzymes, and troponins than classic KD[103]. Recent or current evidence of SARS-CoV-2 infection is needed to diagnose KD-COVID-19. Patients with KD-COVID-19 have more severe diseases than those with classic KD and frequently need hospitalization and intensive care support[104]. Early diagnosis of COVID-19, recognition of KD-COVID-19, and rapid therapy initiation are vital for effective management, recovery, and prevention of end-organ damage and mortality[105]. IVIG therapy is usually effective in KD-COVID-19, but the resistance rate is more common than in children with classic KD, and steroid therapy is generally needed. In refractory cases to IVIG, pulse intravenous methylprednisolone therapy and aspirin are used, especially when a suspected cardiac injury is present[106]. Hydrogen gas inhalation treats KD-COVID-19 as a stable and efficient antioxidant that positively affects oxidative damage, improves inflammation and cell apoptosis, and antagonizes abnormal blood vessel inflammation[107]. Table 3 summarises the differences between the classic Kawasaki Disease and Kawasaki Disease -COVID-19.

APS

There is a high prevalence of venous thrombosis and embolism in patients with COVID-19, especially in severe cases (about 25% to 31% of those without thromboprophylaxis). Consequently, researchers investigated the possible underlying predisposing factors such as hypoxia, immobilization, or disseminated coagulopathy[108]. Serum antiphospholipid antibodies (aPLs), the whole mark of APS, are found in 1%-5% of the healthy population, and their titer increases with age. These rates are comparable to patients with COVID-19 (from 2.7% to 13.4%), which decreases the possibility of recognizable association with thrombosis[109,110]. Another study showed that serum antiphospholipid antibodies might be found transiently in up to 12% of young, healthy subjects, increased to 18% in older adults with chronic diseases[111]. The presence of aPL is not enough to develop APS; a second hit such as aging, critical illnesses, or infections is needed to trigger the development of APS. APS is characterized by documented thrombotic and/or pregnancy-related morbidity in the presence of persistent medium to a high titer of aPLs. To diagnose APS according to Sydney criteria, we need to have persistent high titers of lupus anticoagulant, anticardiolipin antibodies IgG or IgM, or anti-β2glycoprotein-1 IgG and/or IgM for at least 12 wk[112]. However, these criteria need to be modified to limit testing to lupus anticoagulant and anti-β2glycoprotein-1 IgG and to omit anticardiolipin antibodies and anti-β2glycoprotein-1 IgM from laboratory testing. Lupus anticoagulants and anti-β2glycoprotein-1 IgG are associated with a higher risk of thrombosis, particularly lupus anticoagulants[113].

Some studies elucidated high levels of lupus anticoagulants in patients with COVID-19. However, it is unknown whether lupus anticoagulant was newly produced with COVID-19 or increased in a previously present titer[114]. Another study by Xiao *et al*[115] showed that aPLs were present in 47% of critically ill patients due to COVID-19. They also analyzed the risk of developing cerebral infarction by the type of aPLs, with IgA anti-β2glycoprotein-1 being the aPL antibody associated with the highest infarction risk, followed by IgA anticardiolipin antibodies and IgG anti-β2glycoprotein-1. The study also showed that these antibodies need to appear five to six weeks after the disease onset, indicating that a long disease course increases the risk of developing APS and, consequently, thrombotic complications. A severe fatal form of APS (Catastrophic APS) was recorded in some patients with COVID-19. However, there is no current strong evidence of CAPS association with COVID-19. CAPS presented with acute multiorgan involvement (three or more organs, systems, and/or tissues), proof of widespread vascular occlusions, intense hypercoagulable state, and elevated titers of aPLs. Lupus anticoagulant, anticardiolipin IgG, and anticardiolipin IgM were seen in 83%, 81%, and 49% of patients with CAPS [116]. Some factors usually trigger CAPS, such as viral infections, including COVID-19, especially pulmonary infections. SARS-CoV-2 may aggravate the pathogenic effects of APS, initiating inflammatory and prothrombotic cascades. The positive tropism of SARS-CoV-2 towards the vascular endothelium may also alter the COVID-19 clinical presentation in susceptible patients and initiate flaring up of underlying vascular diseases. As CAPS has a high mortality rate, approaching 50%, timely identification and management are vital[117]. It responds to plasmapheresis or plasma exchange. However, it poorly responds to anticoagulant therapy with high mortality risk[118].

SLE

SLE is a chronic multisystem autoimmune disease with varied relapsing or remitting clinical manifestations. It is more common in females and certain ethnic groups, such as African Americans and Hispanics. Due to the aberrant immune system activity in SLE, immune complexes and autoimmune antibodies are significantly produced against cytoplasmic and nuclear antigens[119]. Few patients reports documented newly diagnosed SLE in patients with COVID-19. There is a wide variation in the

Table 3 Differences between the classic Kawasaki disease and Kawasaki disease - coronavirus disease 2019

	Classic KD	KD-COVID-19
Age	Children < 5 yr of age	Older age
General condition	Less ill than in KD-COVID-19	More severely ill
Gastrointestinal & meningeal signs	Less common	More common
CBC	Leucocytosis, anemia, & thrombocytosis. Thrombocytopenia may occur	Leukopenia with marked lymphopenia, thrombocytopenia
Ferritin	Increased	Markedly increased
Incidence of myocarditis	Subclinical myocarditis is nearly present in all patients. However, clinically evident myocarditis is uncommon.	Very high, up to 60.4% in patients with KD-like multisystemic disease.
Response to IV gamma globulins	Well-responding	Resistance to IVIG therapy is common.
Adjunct steroids	May be needed	Usually needed

COVID-19: Coronavirus disease 2019; CBC: blood cell count; KD: Kawasaki disease; IVIG: Intravenous immunoglobulin.

clinical presentation in the reported cases. It presented with manifestations of serositis (pericardial and pleural effusion), renal manifestations (nephritis, proteinuria), skin manifestations (varicella-like rash), cardiac dysfunctions (pericardial tamponade, ventricular dysfunction), secondary APS, neurological complications (neuropsychiatric symptoms, cerebral hemorrhage), hematological disorders (anemia, positive direct Coombs, hemolytic anemia, lymphopenia, thrombocytopenia,), finger vasculitis, low complement, and presence of autoantibodies (aPL, ANA, and anti- dsDNA). Patients with COVID-19-associated SLE had a high mortality rate reaching 50%. Hence appropriate and prompt diagnosis and management are highly indicated to decrease morbidity and mortality. Renal involvement carries the worst prognostic predictor with the highest mortality rate. The treatment should be individualized and may involve glucocorticoids, plasma exchange, hydroxychloroquine, anticoagulation, tocilizumab, and intravenous immunoglobulins[120-123].

Autoimmune-like neurologic disease

SARS-CoV-2-triggered inflammatory and autoimmune cascades may affect the nervous system, producing various neurological complications. About 60% of patients with COVID-19 suffer from anosmia (loss of smelling) and ageusia (loss of taste sensation), which verifies the hypothesis of its neurovirulence[48]. This high percentage of anosmia and ageusia observed with SARS-CoV-2 infection indicates the high viral neurotropism with the olfactory nerve serves as a portal of brain entry. However, anosmia and ageusia can be the first or only symptoms present in some patients with COVID-19[124]. Another portal of brain entry is through retrograde axonal transport *via* peripheral and cranial nerves. An example of this portal of entry is SARS-CoV-2-associated Guillain-Barre syndrome, an acute inflammatory, demyelinating, sensorimotor polyradiculoneuropathies frequently reported in patients with COVID-19. It results from the autoantibodies production that cross-react with myelin components gangliosides and glycolipids present in the peripheral nerves due to molecular mimicry. These autoantibodies cause peripheral nerve demyelination and axonal damage in a progressive ascending pattern[125]. It occurs primarily secondary to SARS-CoV-2-induced immune reaction, as the virus was not detected in the cerebrospinal fluid of any patient suffering from GBS[126].

Miller Fisher syndrome (MFS) and polyneuritis cranialis were rarely reported as autoimmune neurological complications of SARS-CoV-2 infection. They are other examples of the virus's neurotropism and its ability to rapidly spread to the different brain areas, including the thalamus and the brain stem. MFS is classically present with acute onset of a triad composed of external ophthalmoplegia, loss of tendon reflexes, and ataxia[127]. Polyneuritis cranialis is a rare, gradual, and slowly progressive disorder involving multiple cranial nerves (usually IV, V, VI, and VII). Viral infection often preceded these disorders, which triggered an immune-mediated mechanism. Few reported cases followed SARS-CoV-2 infection. CSF showed albuminocytological dissociation, and the patients had a significant elevation of inflammatory mediators, such as the interleukin-8. It can be successfully treated with IVIG[128]. Other reported neurological disorders related to COVID-19 aberrant immune response include acute motor-sensory axonal neuropathy, acute transverse myelitis, acute necrotizing encephalopathy, acute necrotizing myelitis, and acute disseminated encephalomyelitis[129].

Post-COVID-19 pneumonia lung fibrosis

Progressive pulmonary fibrosis following COVID-19 pneumonia is one of the severe complications of SARS-CoV-2 infections that could be associated with irreversible lung dysfunction. Post-COVID-19

pulmonary fibrosis is multifactorial, with many theories explaining the potential causes of post-COVID pulmonary fibrosis. One theory is the cytokine storm caused by an aberrant immune mechanism that triggers pulmonary fibrosis[130]. IL-6 is a pro-inflammatory cytokine with a pro-fibrotic activity that activates the neutrophils and their accumulation at the injury site. Neutrophil accumulation causes proteases and oxygen-free radical release causing pulmonary interstitial edema and acute inflammation [131]. Annexin A2 is crucial to protect against pulmonary fibrosis as it is essential to activate endogenous tissue plasminogen activator to lyse clots and promote fibrin clearance and pulmonary fibrinolysis[132]. Anti-Annexin A2 antibodies are associated with systemic thrombosis, cell death, and non-cardiogenic pulmonary edema. Annexin A2 inhibition can induce diffuse alveolar damage and pulmonary fibrosis in patients with severe COVID-19[133].

Arthritis

Arthritis was reported early in COVID-19 or lately after the resolution of the disease. Different types of arthritis were reported in patients with COVID-19; viral arthritis, reactive arthritis, chronic arthritis, and rheumatoid arthritis[134]. López-González *et al*[135] reported joint pain in some patients with COVID-19; some did not have other signs of arthritis. They also reported crystal-induced arthritis (gouty with monosodium urate and pseudogouty with calcium pyrophosphate) in some patients. Ono *et al*[136] reported the occurrence of reactive arthritis three weeks later in a patient who developed severe COVID-19 pneumonia. The patient improved with anti-Inflammatory non-steroidal drugs and intra-articular corticosteroid injection. Reactive arthritis generally develops one to three weeks after the infection. The precise mechanisms of COVID-19-induced arthritis are not entirely identified. It could be related to viral-induced macrophage activation with subsequent release of cytokines and chemokines in high amounts, sparking the inflammatory process[82]. Although viremia is expected in reactive arthritis, SARS-CoV-2 was detected only in the blood in 15% of cases with COVID-19. Consequently, molecular mimicry may explain arthritis pathogenesis[137]. Inflammatory mediators such as Interleukin 17 A are present in patients with reactive arthritis, spondyloarthritis, and COVID-19 -induced hyperinflammatory state[138].

COVID-19-induced vasculitis

SARS-COV-2 can directly infect the vascular endothelium causing endotheliopathy. Indirect damage to the vascular endothelium can also be induced by the inflammatory mediators triggered by COVID-19 [139]. Few case reports are documenting the development of COVID-19-associated vasculitis with positive anti-neutrophil cytoplasmic antibodies (ANCA). Uppal *et al*[140] described two cases of pauci-immune glomerulonephritis with high perinuclear-ANCA titer during SARS-CoV-2 infection. They clinically improved with the treatment of COVID-19 and the use of rituximab. Hussein *et al*[141] described a female patient who developed granulomatosis with polyangiitis and alveolar hemorrhage during COVID-19 infection. She was treated successfully with pulse steroid therapy, plasmapheresis, and IVIG. These reported cases clarify the importance of vascular endothelium in the pathophysiology and clinical course of COVID-19 and the need for a better understanding of the endothelial biology in patients with COVID-19[142].

Skin autoimmune disorders

Cutaneous manifestations of COVID-19 are common and may involve erythematous, maculopapular, urticarial petechial skin rashes, or diffuse disseminated erythema. The rashes may appear with the onset of the disease and may not correlate with the disease severity[143]. Pityriasis rosea-like rashes were reported in one patient with mild COVID-19[144]. Various reports described acral chilblain lesions due to vacuolar interface dermatitis with superficial and deep perivascular and periadnexal lymphohistiocytic infiltration[145,146]. Violaceous papules and digital swelling occur due to diffuse perivascular dense lymphoid infiltration of the dermis and hypodermis[147]. Desquamation of the peripheral digits may occur in younger children with severe disease or as a sign of KD-COVID-19[148]. Daneshgaran *et al* [149] showed that underlying mechanisms of skin involvement in patients with COVID-19 are related to cytokine release syndrome, coagulation and complement systems activation, or direct virus-induced skin damage with endothelial damage of the dermal vasculatures.

POST-VACCINATION AUTOIMMUNE DISORDERS

The vaccines work by provoking an immune response against specific antigens in the target organism that causes the disease with a long-lasting memory T-cell response. Vaccine adjuvants are used to enhance the immune response against the vaccine. However, these adjuvants can trigger autoimmune responses[150]. Vaccines have been involved in triggering autoimmune diseases for a long time. GBS was reported with Flu and Human Papilloma vaccines, and idiopathic thrombocytopenia occurred in some patients receiving the Measles-Mumps-Rubella vaccine[151]. COVID-19 vaccines can trigger a wide range of skin reactions; from non-specific local injection-site reactions to Type-I hypersensitivity reactions (*e.g.*, urticarial rashes, angioneurotic edema, and even anaphylaxis) to Type-IV delayed

hypersensitivity reactions (including delayed large skin lesions ("COVID arm") at the injection site, inflammatory reactions in a previous skin lesion, and more frequently erythema multiforme-like and morbilliform rashes[152]. COVID-19 vaccination-induced autoimmune skin disorders include immune thrombocytopenia, leukocytoclastic vasculitis, and lupus erythematosus[153].

Severe anaphylaxis was reported with Pfizer-BioNTech and Moderna vaccines. Consequently, the CDC recommends that prefilled epinephrine syringes be available in vaccination centers and observe the vaccinees for 15 or 30 min[154]. Delayed-type or T-cell mediated hypersensitivity adverse reactions were reported in 0.8% of the vaccinees near the injection site[155]. SARS-CoV-2 vaccination may also be complicated by autoimmune diseases that involve the skin, such as lupus erythematosus (LE), bullous pemphigoid, vitiligo, alopecia areata, and leukocytoclastic vasculitis[156,157]. Akinosoglou *et al*[159] reported bilateral elbow itchy annular granulomatous rash due to cutaneous small cell vasculitis after the first dose of the Pfizer-BioNTech vaccine. The rashes spontaneously resolved without medications within three to four days[158]. These vaccine-related adverse effects could be related to a pre-existing dysregulated immune status that could enhance polyclonal B-cell expansion with increased immune complex formation resulting in clinically significant vasculitis in genetically susceptible individuals [159].

MIS-A was reported in three patients within three to fourteen days after COVID-19 vaccination; one of them presented with shock. The three patients had underlying comorbidities such as asthma, depression, and hyperlipidemia[160]. Mild myocarditis was reported in six male patients between 16 and 49 years from Israel following BNT162b2 mRNA COVID-19 vaccination. Five presented one to three days after the second dose, while only one presented after 16 days from the first dose. All of them completely recovered within 4-8 d[161]. Autoimmune thyroid diseases (subacute thyroiditis and Graves' disease) were reported in a few persons following SARS-CoV-2 vaccinations, which could be a form of adjuvants-induced autoimmune/inflammatory syndrome (ASIA). Subacute thyroiditis and Graves' disease had developed in the reported cases within a few days following SARS-CoV-2 vaccination. ASIA was the underlying mechanism for several autoimmune endocrinopathies that developed after vaccination[150,162,163]. An *et al*[164] reported reactive arthritis in the left knee in a 23-year female; three days following the first and second doses of Sinovac-CoronaVac COVID-19 (inactivated whole virus) vaccine. She has a history of a similar condition two years before following a common cold which may indicate the genetic susceptibility of this patient.

Autoimmune hematological disorders were also observed following COVID-19 vaccination. Lee *et al* [165] reported that twenty patients between 22 and 73 years old developed immune thrombocytopenia and bleeding without thrombosis following Pfizer and Moderna SARS-CoV-2 (mRNA) vaccination. These patients tested positive for anti-platelet antibodies; some have other autoimmune conditions such as Crohn's disease or autoimmune hypothyroidism. Meanwhile, Cines *et al*[166] analyzed three independent reports describing 39 persons who developed immune thrombotic thrombocytopenia following the AstraZeneca COVID-19 vaccine (vaccine with modified recombinant adenovirus to encode SARS-CoV-2 S protein). Most patients had high antibody titer against platelet factor 4–polyanion complexes. Fourty% of the patients died from a cerebral hemorrhage, infarction, or both. Fatima *et al*[167] reported a 66-year-old woman who developed IgG-mediated autoimmune hemolytic anemia after Moderna COVID-19 (mRNA) vaccine. The patient had a history of psoriasis for five years before the vaccination.

Gaignard *et al*[168] also reported 77-year- males without previous comorbidities who developed autoimmune hemolytic anemia due to warm antibodies following Moderna COVID-19 (mRNA) vaccine. Brito *et al*[169] reported severe autoimmune hemolytic anemia in an 88-year-old Caucasian woman two days after the second dose of the COVID-19 mRNA vaccine. She had very high levels of anti-erythrocyte IgG and anti-C3d autoantibodies but without cold agglutinins. Murdych also reported severe autoimmune hemolytic anemia in an 84-year-old man with multiple comorbidities after the first dose of the Pfizer-BioNTech COVID-19 mRNA vaccine. The patient tested positive for direct antiglobulin, anti-IgG, direct antiglobulin, polyspecific antihuman globulin, and negative anti-C3[170]. There are several other reports of autoimmune hepatitis following mRNA or viral vector COVID-19 vaccines. Drug-induced hepatitis was also reported following the inactivated whole virus vaccine[171].

Neurological side effects of the COVID-19 vaccine are usually mild. However, severe adverse autoimmune neurological sequelae were reported. Waheed *et al*[172] reported GBS in an 82-year-old highly functional woman without significant comorbidities 14 d after the first shot of the Pfizer COVID-19 vaccine. She was successfully treated with IVIG. Other neurological complications such as Bell's palsy, acute transverse myelitis, acute demyelinating polyneuropathy, and transverse myelitis were reported, especially with mRNA vaccine[173]. Cerebral venous sinus thrombosis was also described in women of childbearing age, especially with adenovector-based vaccination[174]. The importance of developing vaccine-related autoimmune reactions or diseases is related to their impact on the intake of second dose vaccination and the morbidity rate. However, being cautious is preferable until reliable data and a more extended experience are established[175]. It is also essential to be highly suspicious when reporting vaccine-related side effects and rule out actual SARS-CoV-2 infection.

EFFECTS OF AUTOIMMUNE DISEASES ON THE COURSE OF COVID-19

Patients with immune deficiencies or autoimmune disorders are at a higher risk for infection with COVID-19, as they are frequently treated with anti-cytokine, glucocorticoids, and/or immunosuppressive drugs. The infection rate with COVID-19 among people with immune diseases is twice that of the general population[176]. The data derived from international registries of patients with rheumatic diseases (C19-GRA3) who encountered COVID-19 showed poor outcomes depending on their medications[177]. For example, patients treated with antitumor necrosis factor (TNF) showed decreased hospitalization risk, indicating the protective effects of anti-TNF monotherapy against severe COVID-19. Antimalarial drugs (such as hydroxychloroquine), non-steroidal anti-inflammatory drugs, and biologic therapies were not related to increasing the risk of hospitalization due to COVID-19. In contrast, patients who received moderate to high dose glucocorticoids had poor prognoses and clinical outcomes[177,178]. However, other factors may also play a role in the clinical outcome that need more studies.

Meanwhile, the study by Gianfrancesco *et al*[179] showed that most patients with autoimmune disorders who encountered COVID-19 had entirely recovered from the infection, which could help assure these patients. A meta-analysis by Akiyama *et al*[176] showed that while patients with autoimmune disorders have an increased prevalence of COVID-19, their prognosis and clinical outcome were not significantly worse than individuals without autoimmune diseases. They related the higher rate of COVID-19 in patients with an autoimmune disorder to the increased rate of glucocorticoid use. A recent study by Malek Mahdavi *et al*[180] showed that the presence of other comorbidities (female gender, obesity, hypertension, cardiac disease, diabetes mellitus, pulmonary disease, and chronic renal disease) in patients with rheumatoid arthritis in addition to treatment with prednisolone > five mg/day and TNFα inhibitors were independent predictors of COVID-19 outcome. They also observed that symptoms such as anosmia, dyspnea, and taste loss were more common than in the general population. When comparing the effects of COVID-19 with influenza on patients with autoimmune diseases, Tan *et al*[181] found that the hospitalized patients due to COVID-19 had poor outcomes and higher mortality rates than with influenza. However, this study had many limitations, so we can not generalize their findings. Both autoimmune disease and COVID-19 are known to increase the risk of venous thromboembolism. Consequently, the co-occurrence of COVID-19 in patients with autoimmune diseases may heighten this risk. D'Silva *et al*[182] found that patients with autoimmune disorders had a higher risk of venous thromboembolism when infected with SARS-CoV-2 than the general population, independent of comorbidities.

Factors affecting the severity Of COVID-19 in patients with autoimmune diseases

Table 4 summarises the factors that affect the severity of COVID-19 in patients with autoimmune disorders. The male sex and old age worsen the prognosis in patients with autoimmune diseases, similar to what is observed in the general population[183]. Freites Nuñez *et al*[184] indicated that age over fifty is an independent risk factor for hospitalization due to COVID-19 in patients with autoimmune diseases. Peach *et al*[185] found that the COVID-19-related mortality risk is higher in patients with autoimmune diseases with age equal to or higher than 35 years. They also showed that women with autoimmune diseases have a higher COVID-19-related mortality rate than men, contrary to the previous studies. The type of autoimmune disease can affect the severity of infection with SARS-CoV-2. For example, patients with SLE are at higher risk of severe COVID-19 than patients with rheumatoid arthritis. Patients with SLE may have a high rate of hypomethylation and ACE2 overexpression that may ease the viral entry into the cell[186].

On the other hand, Ayala Gutiérrez *et al*[183] found that patients with rheumatoid arthritis, polymyalgia rheumatica, vasculitis, and spondyloarthropathies had a worse prognosis; In comparison, patients with primary Sjögren syndrome and systemic sclerosis had a better prognosis. The presence of medical comorbidities (such as diabetes, hypertension, and obesity) in patients with autoimmune disorders increases the probability of hospitalization, intensive care unit (ICU) admission, and acute renal failure when they encounter SARS-CoV-2 infection[182]. The type of medication used can alleviate or worsen the course of COVID-19. Some drugs used to treat autoimmune diseases (such as Tocilizumab, Anakinra, Baricitinib, or hydroxychloroquine) might have a preventive effect in patients with severe COVID-19 infections. This finding may illustrate the underlying pathogenetic relationship between COVID-19 and autoimmune diseases[187]. Patients with autoimmune diseases treated with rituximab may be at greater risk of severe SARS-CoV-2-induced pneumonia than the general population [188]. Disruption of the medical care continuity and lack of medication adherence due to the restrictions during the pandemic may make the patient prone to flare-up and worsen the associated autoimmune disease activity[189].

Table 4 Factors that affect the severity of coronavirus disease 2019 in patients with autoimmune diseases

The age and sex of the patients
The type of the autoimmune disease
The severity of the autoimmune disease.
Presence of comorbidities
The type of medication used
Disruption of the medical care continuity
Lack of medication adherence
Other factors that increase COVID-19 severity in the general population

COVID-19: Coronavirus disease 2019.

CONCERN ABOUT COVID-19 VACCINATION IN PATIENTS WITH AUTOIMMUNE DISORDERS

The immunogenicity and safety data of COVID-19 vaccines are still limited because patients with chronic diseases, including autoimmune diseases and immunosuppressed patients, were excluded from most experimental vaccine studies. Patients with autoimmune diseases are more liable for a more severe and complicated course of COVID-19 than the general population. Hence, the vaccination benefits far outweigh the risks[190]. According to the general vaccination guidelines in patients with immune deficiency or autoimmune diseases, giving these patients non-live vaccines (including mRNA vaccines) is recommended, providing adequate cellular and humoral immune response. It is preferable to give these patients the immunization during the disease's remission and without concurrent infections[191].

Patients on high doses of corticosteroids or Rituximab may avoid the vaccination. Preferably, COVID-19 vaccinations should be given before initiating any biological disease-modifying agents. Patients may receive the COVID-19 vaccine one month before or at least six months after the last Rituximab infusion, as Rituximab impairs the antibody responses for at least six months after administration[192]. Patients with autoimmune diseases or immune deficiency should receive annual influenza and Streptococcus pneumonia vaccination. COVID-19 vaccine should be given alone and at least two weeks before or after other vaccines. Coordinating timing with dosing regimens of COVID-19 vaccines may optimize the vaccine safety and efficacy, especially in patients with autoimmune diseases[193].

WAYS TO MINIMIZE THE RISK OF COVID-19 IN PATIENTS WITH AUTOIMMUNE DISEASES

Patients with autoimmune diseases are more liable to nutritional inadequacy due to the effects of the disease itself or related to the medications used. The nutritional inadequacy may increase the susceptibility to infection, especially to COVID-19, and permit infections to be more serious, even fatal[194]. Immune-regulator micronutrients such as vitamin A, D, and zinc are essential for immune cell metabolism and may provide antibacterial or anti-viral effects. Other micronutrients such as arginine may be needed as substrates for immune-active metabolites production, such as nitric oxide, one of the most crucial players in immunity[195]. Vitamin D decreases the risk of respiratory tract infections and other respiratory disorders. It is better to be taken daily to obtain maximum effects[196,197]. Vitamin E, Vitamin C, selenium, zinc, plant polyphenols, and long-chain omega-3 fatty acids have anti-oxidative effects and protect against inflammatory stress[198]. Adequate nutrition is essential for healthy gut microbiota, which plays a fundamental role in immunity modulation[199]. Several studies showed the efficacy of probiotics in gut microbial modification, improving gastrointestinal manifestation, and reducing multiorgan inflammation in different autoimmune diseases[200,201]. Licorice is a traditional herb used as a drink in Egypt for many centuries. It has many beneficial effects, such as anti-inflammatory, antitussive, antibacterial, immunomodulatory, and detoxifying agents for many disorders, especially respiratory diseases. It has a solid potential to be an effective adjuvant to prevent and treat COVID-19 with significant anti-inflammatory, anti-ACE2, and the ability to alleviate the clinical symptoms of the disease such as dry cough, shortness of breath, and fever[63].

Gut microbiota is an essential determinant of immunity. COVID-19 causes disruption of the intestinal flora and microbiota dysbiosis, which induces Th17 cell polarization in the small intestine with excessive interleukin (IL)-17A production, recruitment of neutrophils, and more intestinal mucosal immune damage[202]. Several studies highlighted the pathogenetic prole of the microbiome in the

development of autoimmune diseases, especially in systemic lupus erythematosus. Peng *et al*[203] showed that probiotics successfully adjunctive therapy in SARS-CoV-2 infection[204]. Consequently, improving the host nutrition and general condition increases the ability to fight infection and enhances the vaccination response. Alcohol consumption and smoking should be avoided during the COVID-19 pandemic, particularly in patients with autoimmune diseases. Alcohol exacerbates intestinal inflammation, alters intestinal microbiota's composition and function, increases intestinal permeability, and disturbs intestinal immune homeostasi[205]. Cigarette smoking impairs various body functions such as cardiovascular, respiratory, and immune systems and exacerbates autoimmune diseases and allergies. Smoking impairs the nuclear factor-kappaB (NFκB), mitogen-activated protein kinases, and histone modification. It also impairs innate and adaptive immunity and makes the smoker more prone to infection[206].

Sleep hygiene has a direct impact on immunity upkeep and immunological response. Disordered Circadian rhythm, due to physical, social, or psychological disorders encountered during the COVID-19 pandemic, compromises the sleep quality and hence the immune system. Good sleep quality improves the response to vaccination and increases the resistance to infectious diseases[207]. Poor sleep quality is associated with increased pro-inflammatory interleukin levels (IL-1β, TNF-α, and IL-6)[208]. Exercise during the COVID-19 pandemic promotes health, improves host immunity, and should be encouraged. Acute and chronic exercise of moderate intensity can control excessive respiratory inflammation through multiple pathways. It also enhances and regulates the immune defense mechanism, particularly innate immunity, and improves metabolic health[209].

The enforced social isolation and stress during the pandemic negatively affect individual health, especially in children and the elderly[210,211]. Social isolation and anxiety disturb the various biological systems and the circulating stress hormones, glutamate, and immune system components[212]. Social isolation also triggers neuroinflammation and microglia overactivation and disturbs gut microbiota, inducing various neurological and autoimmune disorders. Therefore, a multi-purpose comprehensive social and family program with exercise and psychological support is highly needed for patients with autoimmune diseases to lessen the harmful effects of social isolation impeded during the COVID-19 [213-219].

CONCLUSION

Mutual relations exist between COVID-19 and autoimmune diseases. Patients with autoimmune disorders are at an increased risk for COVID-19, and COVID-19 or its vaccine can trigger autoimmune diseases. Patients with autoimmune diseases should continue their medication but could be modified according to their clinical condition. Vaccination with non-living viruses, including mRNA, is safe and could prevent serious COVID-19. However, the COVID-19 vaccination could also trigger autoimmune disease. Consequently, precautions and strict follow-up are needed for these patients.

ACKNOWLEDGEMENTS

We thank the anonymous referees and editors for their valuable suggestions.

FOOTNOTES

Author contributions: Al-Biltagi M, Saeed NK, and Bediwy AS collected the data and wrote and revised the manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Country/Territory of origin: Bahrain

ORCID number: Mohammed Al-Beltagi 0000-0002-7761-9536; Nermin Kamal Saeed 0000-0001-7875-8207; Adel Salah Bediwy 0000-0002-0281-0010.

S-Editor: Liu JH
L-Editor: A

P-Editor: Liu JH

REFERENCES

1 **Saeed NK**, Al-Biltagi M, Bediwy AS. Molecular Testing for COVID-19: What the Clinician Should Know. *Dr. Sulaiman Al Habib Medical Journal* 2021; 53-59 [DOI: 10.2991/dsahmj.k.210427.002]

2 **Saeed NK**, Al-Khawaja S, Alsalman J, Almusawi S, Albalooshi NA, Al-Biltagi M. Bacterial co-infection in patients with SARS-CoV-2 in the Kingdom of Bahrain. *World J Virol* 2021; **10**: 168-181 [PMID: 34367932 DOI: 10.5501/wjv.v10.i4.168]

3 **Paules CI**, Marston HD, Fauci AS. Coronavirus Infections-More Than Just the Common Cold. *JAMA* 2020; **323**: 707-708 [PMID: 31971553 DOI: 10.1001/jama.2020.0757]

4 **Kumar R**, Nagpal S, Kaushik S, Mendiratta S. COVID-19 diagnostic approaches: different roads to the same destination. *Virusdisease* 2020; **31**: 97-105 [PMID: 32656306 DOI: 10.1007/s13337-020-00599-7]

5 **Astuti I**, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. *Diabetes Metab Syndr* 2020; **14**: 407-412 [PMID: 32335367 DOI: 10.1016/j.dsx.2020.04.020]

6 **Khailany RA**, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. *Gene Rep* 2020; **19**: 100682 [PMID: 32300673 DOI: 10.1016/j.genrep.2020.100682]

7 **Forster P**, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-CoV-2 genomes. *Proc Natl Acad Sci U S A* 2020; **117**: 9241-9243 [PMID: 32269081 DOI: 10.1073/pnas.2004999117]

8 **Walls AC**, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* 2020; **181**: 281-292.e6 [PMID: 32155444 DOI: 10.1016/j.cell.2020.02.058]

9 **Dwyer CJ**, Cloud CA, Wang C, Heidt P, Chakraborty P, Duke TF, McGue S, Jeffcoat B, Dunne J, Johnson L, Choi S, Nahhas GJ, Gandy AS, Babic N, Nolte FS, Howe P, Ogretmen B, Gangaraju VK, Tomlinson S, Madden B, Bridges T, Flume PA, Wrangle J, Rubinstein MP, Baliga PK, Nadig SN, Mehrotra S. Comparative analysis of antibodies to SARS-CoV-2 between asymptomatic and convalescent patients. *iScience* 2021; **24**: 102489 [PMID: 33969281 DOI: 10.1016/j.isci.2021.102489]

10 **Salamanna F**, Maglio M, Landini MP, Fini M. Body Localization of ACE-2: On the Trail of the Keyhole of SARS-CoV-2. *Front Med (Lausanne)* 2020; **7**: 594495 [PMID: 33344479 DOI: 10.3389/fmed.2020.594495]

11 **Xu H**, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci* 2020; **12**: 8 [PMID: 32094336 DOI: 10.1038/s41368-020-0074-x]

12 **Feng Y**, Yue X, Xia H, Bindom SM, Hickman PJ, Filipeanu CM, Wu G, Lazartigues E. Angiotensin-converting enzyme 2 overexpression in the subfornical organ prevents the angiotensin II-mediated pressor and drinking responses and is associated with angiotensin II type 1 receptor downregulation. *Circ Res* 2008; **102**: 729-736 [PMID: 18258853 DOI: 10.1161/CIRCRESAHA.107.169110]

13 **Rodrigues R**, Costa de Oliveira S. The Impact of *Angiotensin-Converting Enzyme 2* (*ACE2*) Expression Levels in Patients with Comorbidities on COVID-19 Severity: A Comprehensive Review. *Microorganisms* 2021; **9** [PMID: 34442770 DOI: 10.3390/microorganisms9081692]

14 **Allison S**. Soluble ACE2 in SARS-CoV-2 infection. *Nat Rev Nephrol* 2021; **17**: 297 [PMID: 33758362 DOI: 10.1038/s41581-021-00422-6]

15 **Zhang Q**, Chen CZ, Swaroop M, Xu M, Wang L, Lee J, Wang AQ, Pradhan M, Hagen N, Chen L, Shen M, Luo Z, Xu X, Xu Y, Huang W, Zheng W, Ye Y. Heparan sulfate assists SARS-CoV-2 in cell entry and can be targeted by approved drugs *in vitro*. *bioRxiv* 2020 [PMID: 32699847 DOI: 10.1101/2020.07.14.202549]

16 **Tortorici MA**, Veesler D. Structural insights into coronavirus entry. *Adv Virus Res* 2019; **105**: 93-116 [PMID: 31522710 DOI: 10.1016/bs.aivir.2019.08.002]

17 **Scialo F**, Daniele A, Amato F, Pastore L, Matera MG, Cazzola M, Castaldo G, Bianco A. ACE2: The Major Cell Entry Receptor for SARS-CoV-2. *Lung* 2020; **198**: 867-877 [PMID: 33170317 DOI: 10.1007/s00408-020-00408-4]

18 **Jackson CB**, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. *Nat Rev Mol Cell Biol* 2022; **23**: 3-20 [PMID: 34611326 DOI: 10.1038/s41580-021-00418-x]

19 **Shah VK**, Firmal P, Alam A, Ganguly D, Chattopadhyay S. Overview of Immune Response During SARS-CoV-2 Infection: Lessons From the Past. *Front Immunol* 2020; **11**: 1949 [PMID: 32849654 DOI: 10.3389/fimmu.2020.01949]

20 **Hewitt EW**. The MHC class I antigen presentation pathway: strategies for viral immune evasion. *Immunology* 2003; **110**: 163-169 [PMID: 14511229 DOI: 10.1046/j.1365-2567.2003.01738.x]

21 **Liu J**, Wu P, Gao F, Qi J, Kawana-Tachikawa A, Xie J, Vavricka CJ, Iwamoto A, Li T, Gao GF. Novel immunodominant peptide presentation strategy: a featured HLA-A*2402-restricted cytotoxic T-lymphocyte epitope stabilized by intrachain hydrogen bonds from severe acute respiratory syndrome coronavirus nucleocapsid protein. *J Virol* 2010; **84**: 11849-11857 [PMID: 20844028 DOI: 10.1128/JVI.01464-10]

22 **Tomita Y**, Ikeda T, Sato R, Sakagami T. Association between HLA gene polymorphisms and mortality of COVID-19: An in silico analysis. *Immun Inflamm Dis* 2020; **8**: 684-694 [PMID: 33047883 DOI: 10.1002/iid3.358]

23 **Giamarellos-Bourboulis EJ**, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntaganou M, Kyriakopoulou M, Dimopoulos G, Koutsodimitropoulos I, Velissaris D, Koufargyris P, Karageorgos A, Katrini K, Lekakis V, Lupse M, Kotsaki A, Renieris G, Theodoulou D, Panou V, Koukaki E, Koulouris N, Gogos C, Koutsoukou A. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. *Cell Host Microbe* 2020; **27**: 992-1000.e3 [PMID: 32320677 DOI: 10.1016/j.chom.2020.04.009]

24 **Alefishat E**, Jelinek HF, Mousa M, Tay GK, Alsafar HS. Immune response to SARS-CoV-2 variants: A focus on severity, susceptibility, and preexisting immunity. *J Infect Public Health* 2022; **15**: 277-288 [PMID: 35074728 DOI:

10.1016/j.jiph.2022.01.007]
25 **Ahmed-Hassan H**, Sisson B, Shukla RK, Wijewantha Y, Funderburg NT, Li Z, Hayes D Jr, Demberg T, Liyanage NPM. Innate Immune Responses to Highly Pathogenic Coronaviruses and Other Significant Respiratory Viral Infections. *Front Immunol* 2020; **11**: 1979 [PMID: 32973803 DOI: 10.3389/fimmu.2020.01979]
26 **Tay MZ**, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; **20**: 363-374 [PMID: 32346093 DOI: 10.1038/s41577-020-0311-8]
27 **Henry BM**. COVID-19, ECMO, and lymphopenia: a word of caution. *Lancet Respir Med* 2020; **8**: e24 [PMID: 32178774 DOI: 10.1016/S2213-2600(20)30119-3]
28 **Ip WK**, Chan KH, Law HK, Tso GH, Kong EK, Wong WH, To YF, Yung RW, Chow EY, Au KL, Chan EY, Lim W, Jensenius JC, Turner MW, Peiris JS, Lau YL. Mannose-binding lectin in severe acute respiratory syndrome coronavirus infection. *J Infect Dis* 2005; **191**: 1697-1704 [PMID: 15838797 DOI: 10.1086/429631]
29 **Eriksson O**, Hultström M, Persson B, Lipcsey M, Ekdahl KN, Nilsson B, Frithiof R. Mannose-Binding Lectin is Associated with Thrombosis and Coagulopathy in Critically Ill COVID-19 Patients. *Thromb Haemost* 2020; **120**: 1720-1724 [PMID: 32871607 DOI: 10.1055/s-0040-1715835]
30 **Khanmohammadi S**, Rezaei N. Role of Toll-like receptors in the pathogenesis of COVID-19. *J Med Virol* 2021; **93**: 2735-2739 [PMID: 33506952 DOI: 10.1002/jmv.26826]
31 **Ye Q**, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. *J Infect* 2020; **80**: 607-613 [PMID: 32283152 DOI: 10.1016/j.jinf.2020.03.037]
32 **Wang J**, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. *J Leukoc Biol* 2020; **108**: 17-41 [PMID: 32534467 DOI: 10.1002/JLB.3COVR0520-272R]
33 **Kaur S**, Bansal R, Kollimuttathuillam S, Gowda AM, Singh B, Mehta D, Maroules M. The looming storm: Blood and cytokines in COVID-19. *Blood Rev* 2021; **46**: 100743 [PMID: 32829962 DOI: 10.1016/j.blre.2020.100743]
34 **Banji D**, Alqahtani SS, Banji OJF, Machanchery S, Shoaib A. Calming the inflammatory storm in severe COVID-19 infections: Role of biologics- A narrative review. *Saudi Pharm J* 2021; **29**: 213-222 [PMID: 33850422 DOI: 10.1016/j.jsps.2021.01.005]
35 **de Lang A**, Osterhaus AD, Haagmans BL. Interferon-gamma and interleukin-4 downregulate expression of the SARS coronavirus receptor ACE2 in Vero E6 cells. *Virology* 2006; **353**: 474-481 [PMID: 16860835 DOI: 10.1016/j.virol.2006.06.011]
36 **Perico L**, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nat Rev Nephrol* 2021; **17**: 46-64 [PMID: 33077917 DOI: 10.1038/s41581-020-00357-4]
37 **Skendros P**, Mitsios A, Chrysanthopoulou A, Mastellos DC, Metallidis S, Rafailidis P, Ntinopoulou M, Sertaridou E, Tsironidou V, Tsigalou C, Tektonidou M, Konstantinidis T, Papagoras C, Mitroulis I, Germanidis G, Lambris JD, Ritis K. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. *J Clin Invest* 2020; **130**: 6151-6157 [PMID: 32759504 DOI: 10.1172/JCI141374]
38 **Fang S**, Wang H, Lu L, Jia Y, Xia Z. Decreased complement C3 levels are associated with poor prognosis in patients with COVID-19: A retrospective cohort study. *Int Immunopharmacol* 2020; **89**: 107070 [PMID: 33039965 DOI: 10.1016/j.intimp.2020.107070]
39 **Lee WS**, Wheatley AK, Kent SJ, DeKosky BJ. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. *Nat Microbiol* 2020; **5**: 1185-1191 [PMID: 32908214 DOI: 10.1038/s41564-020-00789-5]
40 **Li T**, Qiu Z, Zhang L, Han Y, He W, Liu Z, Ma X, Fan H, Lu W, Xie J, Wang H, Deng G, Wang A. Significant changes of peripheral T lymphocyte subsets in patients with severe acute respiratory syndrome. *J Infect Dis* 2004; **189**: 648-651 [PMID: 14767818 DOI: 10.1086/381535]
41 **Zaki AM**, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; **367**: 1814-1820 [PMID: 23075143 DOI: 10.1056/NEJMoa1211721]
42 **Berthelot JM**, Lioté F, Maugars Y, Sibilia J. Lymphocyte Changes in Severe COVID-19: Delayed Over-Activation of STING? *Front Immunol* 2020; **11**: 607069 [PMID: 33335532 DOI: 10.3389/fimmu.2020.607069]
43 **Li CK**, Wu H, Yan H, Ma S, Wang L, Zhang M, Tang X, Temperton NJ, Weiss RA, Brenchley JM, Douek DC, Mongkolsapaya J, Tran BH, Lin CL, Screaton GR, Hou JL, McMichael AJ, Xu XN. T cell responses to whole SARS coronavirus in humans. *J Immunol* 2008; **181**: 5490-5500 [PMID: 18832706 DOI: 10.4049/jimmunol.181.8.5490]
44 **Gallais F**, Velay A, Nazon C, Wendling MJ, Partisani M, Sibilia J, Candon S, Fafi-Kremer S. Intrafamilial Exposure to SARS-CoV-2 Associated with Cellular Immune Response without Seroconversion, France. *Emerg Infect Dis* 2021; **27** [PMID: 33261718 DOI: 10.3201/eid2701.203611]
45 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]
46 **Nägele MP**, Haubner B, Tanner FC, Ruschitzka F, Flammer AJ. Endothelial dysfunction in COVID-19: Current findings and therapeutic implications. *Atherosclerosis* 2020; **314**: 58-62 [PMID: 33161318 DOI: 10.1016/j.atherosclerosis.2020.10.014]
47 **Zheng HY**, Zhang M, Yang CX, Zhang N, Wang XC, Yang XP, Dong XQ, Zheng YT. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cell Mol Immunol* 2020; **17**: 541-543 [PMID: 32203186 DOI: 10.1038/s41423-020-0401-3]
48 **Qin C**, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 2020; **71**: 762-768 [PMID: 32161940 DOI: 10.1093/cid/ciaa248]
49 **Tobón GJ**, Izquierdo JH, Cañas CA. B lymphocytes: development, tolerance, and their role in autoimmunity-focus on systemic lupus erythematosus. *Autoimmune Dis* 2013; **2013**: 827254 [PMID: 24187614 DOI: 10.1155/2013/827254]
50 **Guo L**, Ren L, Yang S, Xiao M, Chang, Yang F, Dela Cruz CS, Wang Y, Wu C, Xiao Y, Zhang L, Han L, Dang S, Xu Y,

Yang QW, Xu SY, Zhu HD, Xu YC, Jin Q, Sharma L, Wang L, Wang J. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). *Clin Infect Dis* 2020; **71**: 778-785 [PMID: 32198501 DOI: 10.1093/cid/ciaa310]

51 **Anna F**, Goyard S, Lalanne AI, Nevo F, Gransagne M, Souque P, Louis D, Gillon V, Turbiez I, Bidard FC, Gobillion A, Savignoni A, Guillot-Delost M, Dejardin F, Dufour E, Petres S, Richard-Le Goff O, Choucha Z, Helynck O, Janin YL, Escriou N, Charneau P, Perez F, Rose T, Lantz O. High seroprevalence but short-lived immune response to SARS-CoV-2 infection in Paris. *Eur J Immunol* 2021; **51**: 180-190 [PMID: 33259646 DOI: 10.1002/eji.202049058]

52 **Quinti I**, Lougaris V, Milito C, Cinetto F, Pecoraro A, Mezzaroma I, Mastroianni CM, Turriziani O, Bondioni MP, Filippini M, Soresina A, Spadaro G, Agostini C, Carsetti R, Plebani A. A possible role for B cells in COVID-19? *J Allergy Clin Immunol* 2020; **146**: 211-213.e4 [PMID: 32333914 DOI: 10.1016/j.jaci.2020.04.013]

53 **Soresina A**, Moratto D, Chiarini M, Paolillo C, Baresi G, Focà E, Bezzi M, Baronio B, Giacomelli M, Badolato R. Two X-linked agammaglobulinemia patients develop pneumonia as COVID-19 manifestation but recover. *Pediatr Allergy Immunol* 2020; **31**: 565-569 [PMID: 32319118 DOI: 10.1111/pai.13263]

54 **Tirado SM**, Yoon KJ. Antibody-dependent enhancement of virus infection and disease. *Viral Immunol* 2003; **16**: 69-86 [PMID: 12725690 DOI: 10.1089/088282403763635465]

55 **Yasui F**, Kai C, Kitabatake M, Inoue S, Yoneda M, Yokochi S, Kase R, Sekiguchi S, Morita K, Hishima T, Suzuki H, Karamatsu K, Yasutomi Y, Shida H, Kidokoro M, Mizuno K, Matsushima K, Kohara M. Prior immunization with severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) nucleocapsid protein causes severe pneumonia in mice infected with SARS-CoV. *J Immunol* 2008; **181**: 6337-6348 [PMID: 18941225 DOI: 10.4049/jimmunol.181.9.6337]

56 **Chiang SF**, Lin TY, Chow KC, Chiou SH. SARS spike protein induces phenotypic conversion of human B cells to macrophage-like cells. *Mol Immunol* 2010; **47**: 2575-2586 [PMID: 20667598 DOI: 10.1016/j.molimm.2010.06.014]

57 **Rodríguez Y**, Novelli L, Rojas M, De Santis M, Acosta-Ampudia Y, Monsalve DM, Ramírez-Santana C, Costanzo A, Ridgway WM, Ansari AA, Gershwin ME, Selmi C, Anaya JM. Autoinflammatory and autoimmune conditions at the crossroad of COVID-19. *J Autoimmun* 2020; **114**: 102506 [PMID: 32563547 DOI: 10.1016/j.jaut.2020.102506]

58 **Kanduc D**, Shoenfeld Y. On the molecular determinants of the SARS-CoV-2 attack. *Clin Immunol* 2020; **215**: 108426 [PMID: 32311462 DOI: 10.1016/j.clim.2020.108426]

59 **Ou X**, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, Xiang Z, Mu Z, Chen X, Chen J, Hu K, Jin Q, Wang J, Qian Z. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat Commun* 2020; **11**: 1620 [PMID: 32221306 DOI: 10.1038/s41467-020-15562-9]

60 **Stukalov A**, Girault V, Grass V, Karayel O, Bergant V, Urban C, Haas DA, Huang Y, Oubraham L, Wang A, Hamad MS, Piras A, Hansen FM, Tanzer MC, Paron I, Zinzula L, Engleitner T, Reinecke M, Lavacca TM, Ehmann R, Wölfel R, Jores J, Kuster B, Protzer U, Rad R, Ziebuhr J, Thiel V, Scaturro P, Mann M, Pichlmair A. Multilevel proteomics reveals host perturbations by SARS-CoV-2 and SARS-CoV. *Nature* 2021; **594**: 246-252 [PMID: 33845483 DOI: 10.1038/s41586-021-03493-4]

61 **Lv H**, Wu NC, Tsang OT, Yuan M, Perera RAPM, Leung WS, So RTY, Chan JMC, Yip GK, Chik TSH, Wang Y, Choi CYC, Lin Y, Ng WW, Zhao J, Poon LLM, Peiris JSM, Wilson IA, Mok CKP. Cross-reactive antibody response between SARS-CoV-2 and SARS-CoV infections. *bioRxiv* 2020 [PMID: 32511317 DOI: 10.1101/2020.03.15.993097]

62 **Lu X**, Zhang L, Du H, Zhang J, Li YY, Qu J, Zhang W, Wang Y, Bao S, Li Y, Wu C, Liu H, Liu D, Shao J, Peng X, Yang Y, Liu Z, Xiang Y, Zhang F, Silva RM, Pinkerton KE, Shen K, Xiao H, Xu S, Wong GWK; Chinese Pediatric Novel Coronavirus Study Team. SARS-CoV-2 Infection in Children. *N Engl J Med* 2020; **382**: 1663-1665 [PMID: 32187458 DOI: 10.1056/NEJMc2005073]

63 **Al-Beltagi M**, Saeed NK, Bediwy AS, El-Sawaf Y. Paediatric gastrointestinal disorders in SARS-CoV-2 infection: Epidemiological and clinical implications. *World J Gastroenterol* 2021; **27**: 1716-1727 [PMID: 33967552 DOI: 10.3748/wjg.v27.i16.1716]

64 **Gupta M**, Weaver DF. COVID-19 as a Trigger of Brain Autoimmunity. *ACS Chem Neurosci* 2021; **12**: 2558-2561 [PMID: 34213312 DOI: 10.1021/acschemneuro.1c00403]

65 **Joyner MJ**, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, Wiggins CC, Senefeld JW, Klompas AM, Hodge DO, Shepherd JRA, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Herasevich V, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, van Buskirk CM, Winters JL, Stubbs JR, van Helmond N, Butterfield BP, Sexton MA, Diaz Soto JC, Paneth NS, Verdun NC, Marks P, Casadevall A, Fairweather D, Carter RE, Wright RS. Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. *Mayo Clin Proc* 2020; **95**: 1888-1897 [PMID: 32861333 DOI: 10.1016/j.mayocp.2020.06.028]

66 **Reche PA**. Potential Cross-Reactive Immunity to SARS-CoV-2 From Common Human Pathogens and Vaccines. *Front Immunol* 2020; **11**: 586984 [PMID: 33178220 DOI: 10.3389/fimmu.2020.586984]

67 **Dotan A**, Mahroum N, Bogdanos DP, Shoenfeld Y. COVID-19 as an infectome paradigm of autoimmunity. *J Allergy Clin Immunol* 2022; **149**: 63-64 [PMID: 34826507 DOI: 10.1016/j.jaci.2021.11.009]

68 **Kim D**, Lee JY, Yang JS, Kim JW, Kim VN, Chang H. The Architecture of SARS-CoV-2 Transcriptome. *Cell* 2020; **181**: 914-921.e10 [PMID: 32330414 DOI: 10.1016/j.cell.2020.04.011]

69 **Dotan A**, Muller S, Kanduc D, David P, Halpert G, Shoenfeld Y. The SARS-CoV-2 as an instrumental trigger of autoimmunity. *Autoimmun Rev* 2021; **20**: 102792 [PMID: 33610751 DOI: 10.1016/j.autrev.2021.102792]

70 **V'kovski P**, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. *Nat Rev Microbiol* 2021; **19**: 155-170 [PMID: 33116300 DOI: 10.1038/s41579-020-00468-6]

71 **Getts DR**, Chastain EM, Terry RL, Miller SD. Virus infection, antiviral immunity, and autoimmunity. *Immunol Rev* 2013; **255**: 197-209 [PMID: 23947356 DOI: 10.1111/imr.12091]

72 **McMillan P**, Dexhiemer T, Neubig RR, Uhal BD. COVID-19-A Theory of Autoimmunity Against ACE-2 Explained. *Front Immunol* 2021; **12**: 582166 [PMID: 33833750 DOI: 10.3389/fimmu.2021.582166]

73 **Galeotti C**, Bayry J. Autoimmune and inflammatory diseases following COVID-19. *Nat Rev Rheumatol* 2020; **16**: 413-414 [PMID: 32499548 DOI: 10.1038/s41584-020-0448-7]

74 **Tenforde MW**, Morris SB. Multisystem Inflammatory Syndrome in Adults: Coming Into Focus. *Chest* 2021; **159**: 471-

472 [PMID: 33285106 DOI: 10.1016/j.chest.2020.09.097]
75 **Riphagen S**, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; **395**: 1607-1608 [PMID: 32386565 DOI: 10.1016/S0140-6736(20)31094-1]
76 **Tang KT**, Hsu BC, Chen DY. Autoimmune and Rheumatic Manifestations Associated With COVID-19 in Adults: An Updated Systematic Review. *Front Immunol* 2021; **12**: 645013 [PMID: 33777042 DOI: 10.3389/fimmu.2021.645013]
77 **Rodriguez L**, Brodin P. Unraveling the Immune Response in Severe COVID-19. *J Clin Immunol* 2020; **40**: 958-959 [PMID: 32827284 DOI: 10.1007/s10875-020-00849-9]
78 **Bajaj V**, Gadi N, Spihlman AP, Wu SC, Choi CH, Moulton VR. Aging, Immunity, and COVID-19: How Age Influences the Host Immune Response to Coronavirus Infections? *Front Physiol* 2020; **11**: 571416 [PMID: 33510644 DOI: 10.3389/fphys.2020.571416]
79 **Khan D**, Ansar Ahmed S. The Immune System Is a Natural Target for Estrogen Action: Opposing Effects of Estrogen in Two Prototypical Autoimmune Diseases. *Front Immunol* 2015; **6**: 635 [PMID: 26779182 DOI: 10.3389/fimmu.2015.00635]
80 **Mathur R**, Rentsch CT, Morton CE, Hulme WJ, Schultze A, MacKenna B, Eggo RM, Bhaskaran K, Wong AYS, Williamson EJ, Forbes H, Wing K, McDonald HI, Bates C, Bacon S, Walker AJ, Evans D, Inglesby P, Mehrkar A, Curtis HJ, DeVito NJ, Croker R, Drysdale H, Cockburn J, Parry J, Hester F, Harper S, Douglas IJ, Tomlinson L, Evans SJW, Grieve R, Harrison D, Rowan K, Khunti K, Chaturvedi N, Smeeth L, Goldacre B; OpenSAFELY Collaborative. Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit admission, and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform. *Lancet* 2021; **397**: 1711-1724 [PMID: 33939953 DOI: 10.1016/S0140-6736(21)00634-6]
81 **Talotta R**. Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? *Clin Immunol* 2021; **224**: 108665 [PMID: 33429060 DOI: 10.1016/j.clim.2021.108665]
82 **Peron JPS**, Nakaya HI, Schlindwein MAM, Gonçalves MVM. COVID-19 Pandemic and Dysbiosis: Can the Ivermectin Hysteria Lead to an Increase of Autoimmune Neuroinflammatory Diseases? *Crit Rev Immunol* 2020; **40**: 537-542 [PMID: 33900697 DOI: 10.1615/CritRevImmunol.2020036242]
83 **Halpert G**, Shoenfeld Y. SARS-CoV-2, the autoimmune virus. *Autoimmun Rev* 2020; **19**: 102695 [PMID: 33130000 DOI: 10.1016/j.autrev.2020.102695]
84 **Bastard P**, Zhang Q, Cobat A, Jouanguy E, Zhang SY, Abel L, Casanova JL. Insufficient type I IFN immunity underlies life-threatening COVID-19 pneumonia. *C R Biol* 2021; **344**: 19-25 [PMID: 34213846 DOI: 10.5802/crbiol.36]
85 **Zhang Y**, Cao W, Jiang W, Xiao M, Li Y, Tang N, Liu Z, Yan X, Zhao Y, Li T, Zhu T. Profile of natural anticoagulant, coagulant factor and anti-phospholipid antibody in critically ill COVID-19 patients. *J Thromb Thrombolysis* 2020; **50**: 580-586 [PMID: 32648093 DOI: 10.1007/s11239-020-02182-9]
86 **Wang G**, Wang Q, Wang Y, Liu C, Wang L, Chen H, Jiao T, Hu C, Lei X, Guo L, Ren L, Li M, Zhao Y, Zeng X, Zhang D, Cao B, Wang J. Presence of Anti-MDA5 Antibody and Its Value for the Clinical Assessment in Patients With COVID-19: A Retrospective Cohort Study. *Front Immunol* 2021; **12**: 791348 [PMID: 34987516 DOI: 10.3389/fimmu.2021.791348]
87 **Arthur JM**, Forrest JC, Boehme KW, Kennedy JL, Owens S, Herzog C, Liu J, Harville TO. Development of ACE2 autoantibodies after SARS-CoV-2 infection. *PLoS One* 2021; **16**: e0257016 [PMID: 34478478 DOI: 10.1371/journal.pone.0257016]
88 **Patel P**, DeCuir J, Abrams J, Campbell AP, Godfred-Cato S, Belay ED. Clinical Characteristics of Multisystem Inflammatory Syndrome in Adults: A Systematic Review. *JAMA Netw Open* 2021; **4**: e2126456 [PMID: 34550381 DOI: 10.1001/jamanetworkopen.2021.26456]
89 **Gurin MI**, Lin YJ, Bernard S, Goldberg RI, Narula N, Faillace RT, Alviar CL, Bangalore S, Keller NM. Cardiogenic shock complicating multisystem inflammatory syndrome following COVID-19 infection: a case report. *BMC Cardiovasc Disord* 2021; **21**: 522 [PMID: 34715788 DOI: 10.1186/s12872-021-02304-y]
90 **Altunisik Toplu S**, Ersoy Y, Bayindir Y, Kilic T, Bayazit V. Multisystem Inflammatory Syndrome in Adults (MIS-A) Associated with SARS-CoV-2 Infection in a Young Adult Case from Turkey. *Medeni Med J* 2021; **36**: 180-184 [PMID: 34239770 DOI: 10.5222/MMJ.2021.95422]
91 **Yao Q**, Waley L, Liou N. Adult presentation of multisystem inflammatory syndrome (MIS) associated with recent COVID-19 infection: lessons learnt in timely diagnosis and management. *BMJ Case Rep* 2021; **14** [PMID: 34598958 DOI: 10.1136/bcr-2021-243114]
92 National Center for Immunization and Respiratory Diseases; Multisystem Inflammatory Syndrome in Adults (MIS-A) Case Definition Information for Healthcare Providers (October 2021). Last accessed on Mar 4, 2022. Available from: https://www.cdc.gov/mis/mis-a/hcp.html
93 **Simon Junior H**, Sakano TMS, Rodrigues RM, Eisencraft AP, Carvalho VEL, Schvartsman C, Reis AGADC. Multisystem inflammatory syndrome associated with COVID-19 from the pediatric emergency physician's point of view. *J Pediatr (Rio J)* 2021; **97**: 140-159 [PMID: 32946801 DOI: 10.1016/j.jped.2020.08.004]
94 National Center for Immunization and Respiratory Diseases; Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). (2021) Last accessed on Mar 4, 2022.Available from: https://www.cdc.gov/mis/mis-c/hcp/index.html
95 The Centers for Disease Control and Prevention (CDC) Health Alert Network. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). CDC. (2020). Available from: https://emergency.cdc.gov/han/2020/han00432.asp
96 **Tran VL**, Parsons S, Nuibe A. The Trilogy of SARS-CoV-2 in Pediatrics (Part 2): Multisystem Inflammatory Syndrome in Children. *J Pediatr Pharmacol Ther* 2021; **26**: 318-338 [PMID: 34035676 DOI: 10.5863/1551-6776-26.4.318]
97 **Abdel-Haq N**, Asmar BI, Deza Leon MP, McGrath EJ, Arora HS, Cashen K, Tilford B, Charaf Eddine A, Sethuraman U, Ang JY. SARS-CoV-2-associated multisystem inflammatory syndrome in children: clinical manifestations and the role of infliximab treatment. *Eur J Pediatr* 2021; **180**: 1581-1591 [PMID: 33452570 DOI: 10.1007/s00431-021-03935-1]
98 **Licciardi F**, Baldini L, Dellepiane M, Covizzi C, Mogni R, Pruccoli G, Orsi C, Rabbone I, Parodi E, Mignone F, Montin

D. MIS-C Treatment: Is IVIG Always Necessary? *Front Pediatr* 2021; **9**: 753123 [PMID: 34805048 DOI: 10.3389/fped.2021.753123]

99 **Pavlyshyn H**, Slyva V, Dyvonyak O, Horishna I. Multisystem inflammatory syndrome in children (MIS-C) temporally associated with SARS-CoV-2: the first clinical case in Ternopil, Ukraine. *Germs* 2021; **11**: 120-127 [PMID: 33898350 DOI: 10.18683/germs.2021.1249]

100 **Kawasaki T**. Kawasaki disease. *Proc Jpn Acad Ser B Phys Biol Sci* 2006; **82**: 59-71 [PMID: 25792773 DOI: 10.2183/pjab.82.59]

101 **Sadeghi P**, Izadi A, Mojtahedi SY, Khedmat L, Jafari M, Afshin A, Yarahmadi P, Hosseinali Beigi E. A 10-year cross-sectional retrospective study on Kawasaki disease in Iranian children: incidence, clinical manifestations, complications, and treatment patterns. *BMC Infect Dis* 2021; **21**: 368 [PMID: 33874899 DOI: 10.1186/s12879-021-06046-2]

102 **McCrindle BW**, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2017; **135**: e927-e999 [PMID: 28356445 DOI: 10.1161/CIR.0000000000000484]

103 **Verdoni L**, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020; **395**: 1771-1778 [PMID: 32410760 DOI: 10.1016/S0140-6736(20)31103-X]

104 **Toubiana J**, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, Debray A, Basmaci R, Salvador E, Biscardi S, Frange P, Chalumeau M, Casanova JL, Cohen JF, Allali S. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ* 2020; **369**: m2094 [PMID: 32493739 DOI: 10.1136/bmj.m2094]

105 **Rodriguez-Gonzalez M**, Castellano-Martinez A, Cascales-Poyatos HM, Perez-Reviriego AA. Cardiovascular impact of COVID-19 with a focus on children: A systematic review. *World J Clin Cases* 2020; **8**: 5250-5283 [PMID: 33269260 DOI: 10.12998/wjcc.v8.i21.5250]

106 **Vukomanovic V**, Krasic S, Minic P, Petrovic G, Nesic D, Paripovic A, Vasiljevic M, Gobeljic B. Kawasaki-like disease and acute myocarditis in the SARS-CoV-2 pandemic - reports of three adolescents. *Bosn J Basic Med Sci* 2021; **21**: 252 [PMID: 33119481 DOI: 10.17305/bjbms.2020.5037]

107 **Chen KD**, Lin WC, Kuo HC. Chemical and Biochemical Aspects of Molecular Hydrogen in Treating Kawasaki Disease and COVID-19. *Chem Res Toxicol* 2021; **34**: 952-958 [PMID: 33719401 DOI: 10.1021/acs.chemrestox.0c00456]

108 **Klok FA**, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020; **191**: 145-147 [PMID: 32291094 DOI: 10.1016/j.thromres.2020.04.013]

109 **Kungwankiattichai S**, Nakkinkun Y, Owattanapanich W, Ruchutrakool T. High Incidence of Antiphospholipid Antibodies in Newly Diagnosed Patients With Lymphoma and a Proposed aPL Predictive Score. *Clin Appl Thromb Hemost* 2020; **26**: 1076029620928392 [PMID: 32633133 DOI: 10.1177/1076029620928392]

110 **Gatto M**, Perricone C, Tonello M, Bistoni O, Cattelan AM, Bursi R, Cafaro G, De Robertis E, Mencacci A, Bozza S, Vianello A, Iaccarino L, Gerli R, Doria A, Bartoloni E. Frequency and clinical correlates of antiphospholipid antibodies arising in patients with SARS-CoV-2 infection: findings from a multicentre study on 122 cases. *Clin Exp Rheumatol* 2020; **38**: 754-759 [PMID: 32723434]

111 **Pineton de Chambrun M**, Frere C, Miyara M, Amoura Z, Martin-Toutain I, Mathian A, Hekimian G, Combes A. High frequency of antiphospholipid antibodies in critically ill COVID-19 patients: a link with hypercoagulability? *J Intern Med* 2021; **289**: 422-424 [PMID: 32529774 DOI: 10.1111/joim.13126]

112 **Gardiner C**, Hills J, Machin SJ, Cohen H. Diagnosis of antiphospholipid syndrome in routine clinical practice. *Lupus* 2013; **22**: 18-25 [PMID: 22988029 DOI: 10.1177/0961203312460722]

113 **Galli M**, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. *Blood* 2003; **101**: 1827-1832 [PMID: 12393574 DOI: 10.1182/blood-2002-02-0441]

114 **Harzallah I**, Debliquis A, Drénou B. Lupus anticoagulant is frequent in patients with Covid-19. *J Thromb Haemost* 2020; **18**: 2064-2065 [PMID: 32324958 DOI: 10.1111/jth.14867]

115 **Xiao M**, Zhang Y, Zhang S, Qin X, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, Du B, Qin Y, Gao P, Lu M, Hou X, Wu X, Zhu H, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y. Antiphospholipid Antibodies in Critically Ill Patients With COVID-19. *Arthritis Rheumatol* 2020; **72**: 1998-2004 [PMID: 32602200 DOI: 10.1002/art.41425]

116 **El Hasbani G**, Taher AT, Jawad A, Uthman I. COVID-19, Antiphospholipid Antibodies, and Catastrophic Antiphospholipid Syndrome: A Possible Association? *Clin Med Insights Arthritis Musculoskelet Disord* 2020; **13**: 1179544120978667 [PMID: 33328777 DOI: 10.1177/1179544120978667]

117 **Chidharla A**, Syed SB, Chatterjee T, Tarantino MD. A Case Report of COVID-Associated Catastrophic Antiphospholipid Syndrome Successfully Treated with Eculizumab. *J Blood Med* 2021; **12**: 929-933 [PMID: 34744467 DOI: 10.2147/JBM.S324873]

118 **Al turk Y**, Bachler J, Hussain S, Patel V, Abu Sayf A. COVID-19-related catastrophic antiphospholipid syndrome: Case report. *Chest* 2021; **160**: A720 [DOI: 10.1016/j.chest.2021.07.683]

119 **Kiriakidou M**, Ching CL. Systemic Lupus Erythematosus. *Ann Intern Med* 2020; **172**: ITC81-ITC96 [PMID: 32479157 DOI: 10.7326/AITC202006020]

120 **Bonometti R**, Sacchi MC, Stobbione P, Lauritano EC, Tamiazzo S, Marchegiani A, Novara E, Molinaro E, Benedetti I, Massone L, Bellora A, Boverio R. The first case of systemic lupus erythematosus (SLE) triggered by COVID-19 infection. *Eur Rev Med Pharmacol Sci* 2020; **24**: 9695-9697 [PMID: 33015814 DOI: 10.26355/eurrev_202009_23060]

121 **Slimani Y**, Abbassi R, El Fatoiki FZ, Barrou L, Chiheb S. Systemic lupus erythematosus and varicella-like rash following COVID-19 in a previously healthy patient. *J Med Virol* 2021; **93**: 1184-1187 [PMID: 32926434 DOI: 10.1002/jmv.26513]

122 **El Aoud S**, Morin C, Lorriaux P, Obert J, Sorial D, Chaabouni T, Thomas L. COVID-19 Presenting as Lupus Erythematosus-Like Syndrome. *Disaster Med Public Health Prep* 2021; **15**: e12-e15 [PMID: 32907688 DOI: 10.1017/dmp.2020.358]

123 **Raghavan S**, Gonakoti S, Asemota IR, Mba B. A Case of Systemic Lupus Erythematosus Flare Triggered by Severe Coronavirus Disease 2019. *J Clin Rheumatol* 2020; **26**: 234-235 [PMID: 32826658 DOI: 10.1097/RHU.0000000000001531]

124 **Vaira LA**, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: Common Findings in COVID-19 Patients. *Laryngoscope* 2020; **130**: 1787 [PMID: 32237238 DOI: 10.1002/lary.28692]

125 **de Andrade da Silva R**, Cremaschi RC, Rebello Pinho JR, de Oliveira JB, Coelho FM. Guillain-Barré syndrome-the challenge of unrecognized triggers. *Neurol Sci* 2019; **40**: 2403-2404 [PMID: 31093786 DOI: 10.1007/s10072-019-03926-z]

126 **Finsterer J**, Scorza FA. Guillain-Barre syndrome in 220 patients with COVID-19. *Egypt J Neurol Psychiatr Neurosurg* 2021; **57**: 55 [PMID: 33967575 DOI: 10.1186/s41983-021-00310-7]

127 **Gutiérrez-Ortiz C**, Méndez-Guerrero A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Mañas R, de Aragón-Gómez F, Benito-León J. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology* 2020; **95**: e601-e605 [PMID: 32303650 DOI: 10.1212/WNL.0000000000009619]

128 **Manganotti P**, Bellavita G, D'Acunto L, Tommasini V, Fabris M, Sartori A, Bonzi L, Buoite Stella A, Pesavento V. Clinical neurophysiology and cerebrospinal liquor analysis to detect Guillain-Barré syndrome and polyneuritis cranialis in COVID-19 patients: A case series. *J Med Virol* 2021; **93**: 766-774 [PMID: 32662899 DOI: 10.1002/jmv.26289]

129 **Brouwer MC**, Ascione T, Pagliano P. Neurologic aspects of covid-19: a concise review. *Infez Med* 2020; **28**: 42-45 [PMID: 32532937]

130 **Ali RMM**, Ghonimy MBI. Post-COVID-19 pneumonia lung fibrosis: a worrisome sequelae in surviving patients. *Egypt J Radiol Nucl Med* 2021; **52**: 101 [DOI: 10.1186/s43055-021-00484-3]

131 **Mohammadi A**, Balan I, Yadav S, Matos WF, Kharawala A, Gaddam M, Sarabia N, Koneru SC, Suddapalli SK, Marzban S. Post-COVID-19 Pulmonary Fibrosis. *Cureus* 2022; **14**: e22770 [PMID: 35371880 DOI: 10.7759/cureus.22770]

132 **Hajjar KA**. The Biology of Annexin A2: From Vascular Fibrinolysis to Innate Immunity. *Trans Am Clin Climatol Assoc* 2015; **126**: 144-155 [PMID: 26330668]

133 **Zuniga M**, Gomes C, Carsons SE, Bender MT, Cotzia P, Miao QR, Lee DC, Rodriguez A. Autoimmunity to annexin A2 predicts mortality among hospitalised COVID-19 patients. *Eur Respir J* 2021; **58** [PMID: 34244321 DOI: 10.1183/13993003.00918-2021]

134 **Zacharias H**, Dubey S, Koduri G, D'Cruz D. Rheumatological complications of Covid 19. *Autoimmun Rev* 2021; **20**: 102883 [PMID: 34237419 DOI: 10.1016/j.autrev.2021.102883]

135 **López-González MD**, Peral-Garrido ML, Calabuig I, Tovar-Sugrañes E, Jovani V, Bernabeu P, García-Sevila R, León-Ramírez JM, Moreno-Perez O, Boix V, Gil J, Merino E, Vela P, Andrés M. Case series of acute arthritis during COVID-19 admission. *Ann Rheum Dis* 2021; **80**: e58 [PMID: 32471899 DOI: 10.1136/annrheumdis-2020-217914]

136 **Ono K**, Kishimoto M, Shimasaki T, Uchida H, Kurai D, Deshpande GA, Komagata Y, Kaname S. Reactive arthritis after COVID-19 infection. *RMD Open* 2020; **6** [PMID: 32763956 DOI: 10.1136/rmdopen-2020-001350]

137 **Wendling D**, Prati C, Chouk M, Verhoeven F. Reactive Arthritis: Treatment Challenges and Future Perspectives. *Curr Rheumatol Rep* 2020; **22**: 29 [PMID: 32458153 DOI: 10.1007/s11926-020-00904-9]

138 **Coskun Benlidayi I**, Kurtaran B, Tirasci E, Guzel R. Coronavirus disease 2019 (COVID-19) in a patient with ankylosing spondylitis treated with secukinumab: a case-based review. *Rheumatol Int* 2020; **40**: 1707-1716 [PMID: 32591970 DOI: 10.1007/s00296-020-04635-z]

139 **Iba T**, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. *Inflamm Res* 2020; **69**: 1181-1189 [PMID: 32918567 DOI: 10.1007/s00011-020-01401-6]

140 **Uppal NN**, Kello N, Shah HH, Khanin Y, De Oleo IR, Epstein E, Sharma P, Larsen CP, Bijol V, Jhaveri KD. *De Novo* ANCA-Associated Vasculitis With Glomerulonephritis in COVID-19. *Kidney Int Rep* 2020; **5**: 2079-2083 [PMID: 32839744 DOI: 10.1016/j.ekir.2020.08.012]

141 **Hussein A**, Al Khalil K, Bawazir YM. Anti-Neutrophilic Cytoplasmic Antibody (ANCA) Vasculitis Presented as Pulmonary Hemorrhage in a Positive COVID-19 Patient: A Case Report. *Cureus* 2020; **12**: e9643 [PMID: 32923243 DOI: 10.7759/cureus.9643]

142 **Evans PC**, Rainger GE, Mason JC, Guzik TJ, Osto E, Stamataki Z, Neil D, Hoefer IE, Fragiadaki M, Waltenberger J, Weber C, Bochaton-Piallat ML, Bäck M. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. *Cardiovasc Res* 2020; **116**: 2177-2184 [PMID: 32750108 DOI: 10.1093/cvr/cvaa230]

143 **Günther C**, Aschoff R, Beissert S. Cutaneous autoimmune diseases during COVID-19 pandemic. *J Eur Acad Dermatol Venereol* 2020; **34**: e667-e670 [PMID: 32534461 DOI: 10.1111/jdv.16753]

144 **Ehsani AH**, Nasimi M, Bigdelo Z. Pityriasis rosea as a cutaneous manifestation of COVID-19 infection. *J Eur Acad Dermatol Venereol* 2020; **34**: e436-e437 [PMID: 32359180 DOI: 10.1111/jdv.16579]

145 **Landa N**, Mendieta-Eckert M, Fonda-Pascual P, Aguirre T. Chilblain-like lesions on feet and hands during the COVID-19 Pandemic. *Int J Dermatol* 2020; **59**: 739-743 [PMID: 32329897 DOI: 10.1111/ijd.14937]

146 **Piccolo V**, Neri I, Filippeschi C, Oranges T, Argenziano G, Battarra VC, Berti S, Manunza F, Fortina AB, Di Lernia V, Boccaletti V, De Bernardis G, Brunetti B, Mazzatenta C, Bassi A. Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. *J Eur Acad Dermatol Venereol* 2020; **34**: e291-e293 [PMID: 32330334 DOI: 10.1111/jdv.16526]

147 **Recalcati S**, Barbagallo T, Frasin LA, Prestinari F, Cogliardi A, Provero MC, Dainese E, Vanzati A, Fantini F. Acral cutaneous lesions in the time of COVID-19. *J Eur Acad Dermatol Venereol* 2020; **34**: e346-e347 [PMID: 32330324 DOI: 10.1111/jdv.16533]

148 **Jones VG**, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, Nguyen EL, Barsh GR, Maskatia S, Mathew R. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. *Hosp Pediatr* 2020; **10**: 537-540 [PMID: 32265235 DOI: 10.1542/hpeds.2020-0123]

149 **Daneshgaran G**, Dubin DP, Gould DJ. Cutaneous Manifestations of COVID-19: An Evidence-Based Review. *Am J Clin Dermatol* 2020; **21**: 627-639 [PMID: 32865778 DOI: 10.1007/s40257-020-00558-4]

150 **Guimarães LE**, Baker B, Perricone C, Shoenfeld Y. Vaccines, adjuvants and autoimmunity. *Pharmacol Res* 2015; **100**: 190-209 [PMID: 26275795 DOI: 10.1016/j.phrs.2015.08.003]

151 **Toussirot É**, Bereau M. Vaccination and Induction of Autoimmune Diseases. *Inflamm Allergy Drug Targets* 2015; **14**: 94-98 [PMID: 26728772 DOI: 10.2174/1871528114666160105113046]

152 **Gambichler T**, Boms S, Susok L, Dickel H, Finis C, Abu Rached N, Barras M, Stücker M, Kasakovski D. Cutaneous findings following COVID-19 vaccination: review of world literature and own experience. *J Eur Acad Dermatol Venereol* 2022; **36**: 172-180 [PMID: 34661927 DOI: 10.1111/jdv.17744]

153 **Temiz SA**, Abdelmaksoud A, Wollina U, Kutlu O, Dursun R, Patil A, Lotti T, Goldust M, Vestita M. Cutaneous and Allergic reactions due to COVID-19 vaccinations: A review. *J Cosmet Dermatol* 2022; **21**: 4-12 [PMID: 34791757 DOI: 10.1111/jocd.14613]

154 **Brüssow H**. COVID-19: vaccination problems. *Environ Microbiol* 2021; **23**: 2878-2890 [PMID: 33928745 DOI: 10.1111/1462-2920.15549]

155 **Blumenthal KG**, Freeman EE, Saff RR, Robinson LB, Wolfson AR, Foreman RK, Hashimoto D, Banerji A, Li L, Anvari S, Shenoy ES. Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2. *N Engl J Med* 2021; **384**: 1273-1277 [PMID: 33657292 DOI: 10.1056/NEJMc2102131]

156 **Damiani G**, Pacifico A, Pelloni F, Iorizzo M. The first dose of COVID-19 vaccine may trigger pemphigus and bullous pemphigoid flares: is the second dose therefore contraindicated? *J Eur Acad Dermatol Venereol* 2021; **35**: e645-e647 [PMID: 34169578 DOI: 10.1111/jdv.17472]

157 **Pérez-López I**, Moyano-Bueno D, Ruiz-Villaverde R. [Bullous pemphigoid and COVID-19 vaccine]. *Med Clin (Barc)* 2021; **157**: e333-e334 [PMID: 34119340 DOI: 10.1016/j.medcli.2021.05.005]

158 **İremli BG**, Şendur SN, Ünlütürk U. Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Postvaccination ASIA Syndrome. *J Clin Endocrinol Metab* 2021; **106**: 2600-2605 [PMID: 34043800 DOI: 10.1210/clinem/dgab373]

159 **Akinosoglou K**, Tzivaki I, Marangos M. Covid-19 vaccine and autoimmunity: Awakening the sleeping dragon. *Clin Immunol* 2021; **226**: 108721 [PMID: 33823270 DOI: 10.1016/j.clim.2021.108721]

160 **Salzman MB**, Huang CW, O'Brien CM, Castillo RD. Multisystem Inflammatory Syndrome after SARS-CoV-2 Infection and COVID-19 Vaccination. *Emerg Infect Dis* 2021; **27**: 1944-1948 [PMID: 34034858 DOI: 10.3201/eid2707.210594]

161 **Abu Mouch S**, Roguin A, Hellou E, Ishai A, Shoshan U, Mahamid L, Zoabi M, Aisman M, Goldschmid N, Berar Yanay N. Myocarditis following COVID-19 mRNA vaccination. *Vaccine* 2021; **39**: 3790-3793 [PMID: 34092429 DOI: 10.1016/j.vaccine.2021.05.087]

162 **Caso F**, Costa L, Ruscitti P, Navarini L, Del Puente A, Giacomelli R, Scarpa R. Could Sars-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? *Autoimmun Rev* 2020; **19**: 102524 [PMID: 32220633 DOI: 10.1016/j.autrev.2020.102524]

163 **Vera-Lastra O**, Ordinola Navarro A, Cruz Domiguez MP, Medina G, Sánchez Valadez TI, Jara LJ. Two Cases of Graves' Disease Following SARS-CoV-2 Vaccination: An Autoimmune/Inflammatory Syndrome Induced by Adjuvants. *Thyroid* 2021; **31**: 1436-1439 [PMID: 33858208 DOI: 10.1089/thy.2021.0142]

164 **An QJ**, Qin DA, Pei JX. Reactive arthritis after COVID-19 vaccination. *Hum Vaccin Immunother* 2021; **17**: 2954-2956 [PMID: 34033732 DOI: 10.1080/21645515.2021.1920274]

165 **Lee EJ**, Cines DB, Gernsheimer T, Kessler C, Michel M, Tarantino MD, Semple JW, Arnold DM, Godeau B, Lambert MP, Bussel JB. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol* 2021; **96**: 534-537 [PMID: 33606296 DOI: 10.1002/ajh.26132]

166 **Cines DB**, Bussel JB. SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia. *N Engl J Med* 2021; **384**: 2254-2256 [PMID: 33861524 DOI: 10.1056/NEJMe2106315]

167 **Fatima Z**, Reece BRA, Moore JS, Means RT Jr. Autoimmune Hemolytic Anemia After mRNA COVID Vaccine. *J Investig Med High Impact Case Rep* 2022; **10**: 23247096211073258 [PMID: 35045762 DOI: 10.1177/23247096211073258]

168 **Gaignard ME**, Lieberherr S, Schoenenberger A, Benz R. Autoimmune Hematologic Disorders in Two Patients After mRNA COVID-19 Vaccine. *Hemasphere* 2021; **5**: e618 [PMID: 34263143 DOI: 10.1097/HS9.0000000000000618]

169 **Brito S**, Ferreira N, Mateus S, Bernardo M, Pinto B, Lourenço A, Grenho F. A Case of Autoimmune Hemolytic Anemia Following COVID-19 Messenger Ribonucleic Acid Vaccination. *Cureus* 2021; **13**: e15035 [PMID: 34150386 DOI: 10.7759/cureus.15035]

170 **Murdych TM**. A case of severe autoimmune hemolytic anemia after a receipt of a first dose of SARS-CoV-2 vaccine. *Int J Lab Hematol* 2022; **44**: e10-e12 [PMID: 34258873 DOI: 10.1111/ijlh.13653]

171 **Ghorbani H**, Rouhi T, Vosough Z, Shokri-Shirvani J. Drug-induced hepatitis after Sinopharm COVID-19 vaccination: A case study of a 62-year-old patient. *Int J Surg Case Rep* 2022; **93**: 106926 [PMID: 35284210 DOI: 10.1016/j.ijscr.2022.106926]

172 **Waheed S**, Bayas A, Hindi F, Rizvi Z, Espinosa PS. Neurological Complications of COVID-19: Guillain-Barre Syndrome Following Pfizer COVID-19 Vaccine. *Cureus* 2021; **13**: e13426 [PMID: 33758714 DOI: 10.7759/cureus.13426]

173 **Garg RK**, Paliwal VK. Spectrum of neurological complications following COVID-19 vaccination. *Neurol Sci* 2022; **43**: 3-40 [PMID: 34719776 DOI: 10.1007/s10072-021-05662-9]

174 **Butler-Manuel W**, Rana UI, Zafar M, Gadi A, Kiani A. Post COVID-19 Vaccine Related Cerebral Venous Sinus Thrombosis and Thrombocytopenia. *Cureus* 2022; **14**: e20932 [PMID: 35004085 DOI: 10.7759/cureus.20932]

175 **Bonetto C**, Trotta F, Felicetti P, Alarcón GS, Santuccio C, Bachtiar NS, Brauchli Pernus Y, Chandler R, Girolomoni G, Hadden RD, Kucuku M, Ozen S, Pahud B, Top K, Varricchio F, Wise RP, Zanoni G, Živković S, Bonhoeffer J; Brighton

Collaboration Vasculitis Working Group. Vasculitis as an adverse event following immunization - Systematic literature review. *Vaccine* 2016; **34**: 6641-6651 [PMID: 26398442 DOI: 10.1016/j.vaccine.2015.09.026]

176 **Akiyama S**, Hamdeh S, Micic D, Sakuraba A. Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. *Ann Rheum Dis* 2021; **80**: 384-391 [PMID: 33051220 DOI: 10.1136/annrheumdis-2020-218946]

177 **Gianfrancesco M**, Yazdany J, Robinson PC. Epidemiology and outcomes of novel coronavirus 2019 in patients with immune-mediated inflammatory diseases. *Curr Opin Rheumatol* 2020; **32**: 434-440 [PMID: 32675715 DOI: 10.1097/BOR.0000000000000725]

178 **Brenner EJ**, Ungaro RC, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, Ng SC, Rahier JF, Reinisch W, Ruemmele FM, Steinwurz F, Underwood FE, Zhang X, Colombel JF, Kappelman MD. Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. *Gastroenterology* 2020; **159**: 481-491.e3 [PMID: 32425234 DOI: 10.1053/j.gastro.2020.05.032]

179 **Gianfrancesco M**, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, Izadi Z, Jacobsohn L, Katz P, Lawson-Tovey S, Mateus EF, Rush S, Schmajuk G, Simard J, Strangfeld A, Trupin L, Wysham KD, Bhana S, Costello W, Grainger R, Hausmann JS, Liew JW, Sirotich E, Sufka P, Wallace ZS, Yazdany J, Machado PM, Robinson PC; COVID-19 Global Rheumatology Alliance. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020; **79**: 859-866 [PMID: 32471903 DOI: 10.1136/annrheumdis-2020-217871]

180 **Malek Mahdavi A**, Varshochi M, Hajialilo M, Dastgiri S, Khabbazi R, Khabbazi A. Factors associated with COVID-19 and its outcome in patients with rheumatoid arthritis. *Clin Rheumatol* 2021; **40**: 4527-4531 [PMID: 34189674 DOI: 10.1007/s10067-021-05830-4]

181 **Tan EH**, Sena AG, Prats-Uribe A, You SC, Ahmed WU, Kostka K, Reich C, Duvall SL, Lynch KE, Matheny ME, Duarte-Salles T, Bertolin SF, Hripcsak G, Natarajan K, Falconer T, Spotnitz M, Ostropolets A, Blacketer C, Alshammari TM, Alghoul H, Alser O, Lane JCE, Dawoud DM, Shah K, Yang Y, Zhang L, Areia C, Golozar A, Recalde M, Casajust P, Jonnagaddala J, Subbian V, Vizcaya D, Lai LYH, Nyberg F, Morales DR, Posada JD, Shah NH, Gong M, Vivekanantham A, Abend A, Minty EP, Suchard M, Rijnbeek P, Ryan PB, Prieto-Alhambra D. COVID-19 in patients with autoimmune diseases: characteristics and outcomes in a multinational network of cohorts across three countries. *Rheumatology (Oxford)* 2021; **60**: SI37-SI50 [PMID: 33725121 DOI: 10.1093/rheumatology/keab250]

182 **D'Silva KM**, Jorge A, Cohen A, McCormick N, Zhang Y, Wallace ZS, Choi HK. COVID-19 Outcomes in Patients With Systemic Autoimmune Rheumatic Diseases Compared to the General Population: A US Multicenter, Comparative Cohort Study. *Arthritis Rheumatol* 2021; **73**: 914-920 [PMID: 33305544 DOI: 10.1002/art.41619]

183 **Ayala Gutiérrez MDM**, Rubio-Rivas M, Romero Gómez C, Montero Sáez A, Pérez de Pedro I, Homs N, Ayuso García B, Cuenca Carvajal C, Arnalich Fernández F, Beato Pérez JL, Vargas Núñez JA, Letona Giménez L, Suárez Fernández C, Méndez Bailón M, Tuñón de Almeida C, González Moraleja J, de Guzmán García-Monge M, Helguera Amezua C, Fidalgo Montero MDP, Giner Galvañ V, Gil Sánchez R, Collado Sáenz J, Boixeda R, Ramos Rincón JM, Gómez Huelgas R, On Behalf Of The Semi-Covid-Network. Autoimmune Diseases and COVID-19 as Risk Factors for Poor Outcomes: Data on 13,940 Hospitalized Patients from the Spanish Nationwide SEMI-COVID-19 Registry. *J Clin Med* 2021; **10** [PMID: 33922777 DOI: 10.3390/jcm10091844]

184 **Freites Nuñez DD**, Leon L, Mucientes A, Rodriguez-Rodriguez L, Font Urgelles J, Madrid García A, Colomer JI, Jover JA, Fernandez-Gutierrez B, Abasolo L. Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020; **79**: 1393-1399 [PMID: 32769150 DOI: 10.1136/annrheumdis-2020-217984]

185 **Peach E**, Rutter M, Lanyon P, Grainge MJ, Hubbard R, Aston J, Bythell M, Stevens S, Pearce F. Risk of death among people with rare autoimmune diseases compared with the general population in England during the 2020 COVID-19 pandemic. *Rheumatology (Oxford)* 2021; **60**: 1902-1909 [PMID: 33271595 DOI: 10.1093/rheumatology/keaa855]

186 **Sawalha AH**, Zhao M, Coit P, Lu Q. Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients. *Clin Immunol* 2020; **215**: 108410 [PMID: 32276140 DOI: 10.1016/j.clim.2020.108410]

187 **Liu Y**, Sawalha AH, Lu Q. COVID-19 and autoimmune diseases. *Curr Opin Rheumatol* 2021; **33**: 155-162 [PMID: 33332890 DOI: 10.1097/BOR.0000000000000776]

188 **Bachiller-Corral J**, Boteanu A, Garcia-Villanueva MJ, de la Puente C, Revenga M, Diaz-Miguel MC, Rodriguez-Garcia A, Morell-Hita JL, Valero M, Larena C, Blazquez-Cañamero M, Guillen-Astete CA, Garrote S, Sobrino C, Medina-Quiñones C, Vazquez-Diaz M. Risk of Severe COVID-19 Infection in Patients With Inflammatory Rheumatic Diseases. *J Rheumatol* 2021; **48**: 1098-1102 [PMID: 33722949 DOI: 10.3899/jrheum.200755]

189 **Hassen LM**, Almaghlouth IA, Hassen IM, Daghestani MH, Almohisen AA, Alqurtas EM, Alkhalaf A, Bedaiwi MK, Omair MA, Almogairen SM, Alarfaj HF, Alarfaj AS. Impact of COVID-19 outbreak on rheumatic patients' perceptions and behaviors: A cross-sectional study. *Int J Rheum Dis* 2020; **23**: 1541-1549 [PMID: 32940963 DOI: 10.1111/1756-185X.13959]

190 **Furer V**, Rondaan C, Agmon-Levin N, van Assen S, Bijl M, Kapetanovic MC, de Thurah A, Mueller-Ladner U, Paran D, Schreiber K, Warnatz K, Wulffraat NM, Elkayam O. Point of view on the vaccination against COVID-19 in patients with autoimmune inflammatory rheumatic diseases. *RMD Open* 2021; **7** [PMID: 33627440 DOI: 10.1136/rmdopen-2021-001594]

191 **Soy M**, Keser G, Atagunduz P, Mutlu MY, Gunduz A, Koybaşi G, Bes C. A practical approach for vaccinations including COVID-19 in autoimmune/autoinflammatory rheumatic diseases: a non-systematic review. *Clin Rheumatol* 2021; **40**: 3533-3545 [PMID: 33751280 DOI: 10.1007/s10067-021-05700-z]

192 **Arnold J**, Winthrop K, Emery P. COVID-19 vaccination and antirheumatic therapy. *Rheumatology (Oxford)* 2021; **60**: 3496-3502 [PMID: 33710296 DOI: 10.1093/rheumatology/keab223]

193 **Kelly H**, Sokola B, Abboud H. Safety and efficacy of COVID-19 vaccines in multiple sclerosis patients. *J Neuroimmunol* 2021; **356**: 577599 [PMID: 34000472 DOI: 10.1016/j.jneuroim.2021.577599]

194 **Calder PC**. Nutrition and immunity: lessons for COVID-19. *Nutr Diabetes* 2021; **11**: 19 [PMID: 34168111 DOI: 10.1038/s41387-021-00165-0]

195 **Bogdan C**. Nitric oxide and the immune response. *Nat Immunol* 2001; **2**: 907-916 [PMID: 11577346 DOI: 10.1038/ni1001-907]

196 **Hewison M**. An update on vitamin D and human immunity. *Clin Endocrinol (Oxf)* 2012; **76**: 315-325 [PMID: 21995874 DOI: 10.1111/j.1365-2265.2011.04261.x]

197 **Al-Beltagi M**, Rowiesha M, Elmashad A, Elrifaey SM, Elhorany H, Koura HG. Vitamin D status in preterm neonates and the effects of its supplementation on respiratory distress syndrome. *Pediatr Pulmonol* 2020; **55**: 108-115 [PMID: 31815370 DOI: 10.1002/ppul.24552]

198 **Méndez L**, Medina I. Polyphenols and Fish Oils for Improving Metabolic Health: A Revision of the Recent Evidence for Their Combined Nutraceutical Effects. *Molecules* 2021; **26** [PMID: 33922113 DOI: 10.3390/molecules26092438]

199 **Zhang QH**, Huang HZ, Qiu M, Wu ZF, Xin ZC, Cai XF, Shang Q, Lin JZ, Zhang DK, Han L. Traditional Uses, Pharmacological Effects, and Molecular Mechanisms of Licorice in Potential Therapy of COVID-19. *Front Pharmacol* 2021; **12**: 719758 [PMID: 34899289 DOI: 10.3389/fphar.2021.719758]

200 **Wu HJ**, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes* 2012; **3**: 4-14 [PMID: 22356853 DOI: 10.4161/gmic.19320]

201 **Saeed NK**, Al-Beltagi M, Bediwy AS, El-Sawaf Y, Toema O. Gut microbiota in various childhood disorders: Implication and indications. *World J Gastroenterol* 2022; **28**: 1875-1901 [PMID: 35664966 DOI: 10.3748/wjg.v28.i18.1875]

202 **De Luca F**, Shoenfeld Y. The microbiome in autoimmune diseases. *Clin Exp Immunol* 2019; **195**: 74-85 [PMID: 29920643 DOI: 10.1111/cei.13158]

203 **Peng J**, Zhang M, Yao G, Kwok LY, Zhang W. Probiotics as Adjunctive Treatment for Patients Contracted COVID-19: Current Understanding and Future Needs. *Front Nutr* 2021; **8**: 669808 [PMID: 34179059 DOI: 10.3389/fnut.2021.669808]

204 **Liu Y**, Alookaran JJ, Rhoads JM. Probiotics in Autoimmune and Inflammatory Disorders. *Nutrients* 2018; **10** [PMID: 30340338 DOI: 10.3390/nu10101537]

205 **Bishehsari F**, Magno E, Swanson G, Desai V, Voigt RM, Forsyth CB, Keshavarzian A. Alcohol and Gut-Derived Inflammation. *Alcohol Res* 2017; **38**: 163-171 [PMID: 28988571]

206 **Qiu F**, Liang CL, Liu H, Zeng YQ, Hou S, Huang S, Lai X, Dai Z. Impacts of cigarette smoking on immune responsiveness: Up and down or upside down? *Oncotarget* 2017; **8**: 268-284 [PMID: 27902485 DOI: 10.18632/oncotarget.13613]

207 **Silva ESME**, Ono BHVS, Souza JC. Sleep and immunity in times of COVID-19. *Rev Assoc Med Bras (1992)* 2020; **66Suppl** 2: 143-147 [PMID: 32965373 DOI: 10.1590/1806-9282.66.S2.143]

208 **Milrad SF**, Hall DL, Jutagir DR, Lattie EG, Ironson GH, Wohlgemuth W, Nunez MV, Garcia L, Czaja SJ, Perdomo DM, Fletcher MA, Klimas N, Antoni MH. Poor sleep quality is associated with greater circulating pro-inflammatory cytokines and severity and frequency of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) symptoms in women. *J Neuroimmunol* 2017; **303**: 43-50 [PMID: 28038892 DOI: 10.1016/j.jneuroim.2016.12.008]

209 **Ranasinghe C**, Ozemek C, Arena R. Exercise and well-being during COVID 19 - time to boost your immunity. *Expert Rev Anti Infect Ther* 2020; **18**: 1195-1200 [PMID: 32662717 DOI: 10.1080/14787210.2020.1794818]

210 **Loades ME**, Chatburn E, Higson-Sweeney N, Reynolds S, Shafran R, Brigden A, Linney C, McManus MN, Borwick C, Crawley E. Rapid Systematic Review: The Impact of Social Isolation and Loneliness on the Mental Health of Children and Adolescents in the Context of COVID-19. *J Am Acad Child Adolesc Psychiatry* 2020; **59**: 1218-1239.e3 [PMID: 32504808 DOI: 10.1016/j.jaac.2020.05.009]

211 **Sepúlveda-Loyola W**, Rodríguez-Sánchez I, Pérez-Rodríguez P, Ganz F, Torralba R, Oliveira DV, Rodríguez-Mañas L. Impact of Social Isolation Due to COVID-19 on Health in Older People: Mental and Physical Effects and Recommendations. *J Nutr Health Aging* 2020; **24**: 938-947 [PMID: 33155618 DOI: 10.1007/s12603-020-1469-2]

212 **Campagne DM**. Stress and perceived social isolation (loneliness). *Arch Gerontol Geriatr* 2019; **82**: 192-199 [PMID: 30825769 DOI: 10.1016/j.archger.2019.02.007]

213 **Al Omran AJ**, Shao AS, Watanabe S, Zhang Z, Zhang J, Xue C, Watanabe J, Davies DL, Shao XM, Liang J. Social isolation induces neuroinflammation and microglia overactivation, while dihydromyricetin prevents and improves them. *J Neuroinflammation* 2022; **19**: 2 [PMID: 34983568 DOI: 10.1186/s12974-021-02368-9]

214 **Donovan M**, Mackey CS, Platt GN, Rounds J, Brown AN, Trickey DJ, Liu Y, Jones KM, Wang Z. Social isolation alters behavior, the gut-immune-brain axis, and neurochemical circuits in male and female prairie voles. *Neurobiol Stress* 2020; **13**: 100278 [PMID: 33344730 DOI: 10.1016/j.ynstr.2020.100278]

215 **Israel A**, Schäffer AA, Cicurel A, Cheng K, Sinha S, Schiff E, Feldhamer I, Tal A, Lavie G, Ruppin E. Identification of drugs associated with reduced severity of COVID-19 - a case-control study in a large population. *Elife* 2021; **10** [PMID: 34313216 DOI: 10.7554/eLife.68165]

216 **Wang CL**, Liu YY, Wu CH, Wang CY, Wang CH, Long CY. Impact of COVID-19 on Pregnancy. *Int J Med Sci* 2021; **18**: 763-767 [PMID: 33437211 DOI: 10.7150/ijms.49923]

217 **Taneri PE**, Gómez-Ochoa SA, Llanaj E, Raguindin PF, Rojas LZ, Roa-Díaz ZM, Salvador D Jr, Groothof D, Minder B, Kopp-Heim D, Hautz WE, Eisenga MF, Franco OH, Glisic M, Muka T. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. *Eur J Epidemiol* 2020; **35**: 763-773 [PMID: 32816244 DOI: 10.1007/s10654-020-00678-5]

218 **Hawkins RB**, Charles EJ, Mehaffey JH. Socio-economic status and COVID-19-related cases and fatalities. *Public Health* 2020; **189**: 129-134 [PMID: 33227595 DOI: 10.1016/j.puhe.2020.09.016]

219 **Hawkins D**. Differential occupational risk for COVID-19 and other infection exposure according to race and ethnicity. *Am J Ind Med* 2020; **63**: 817-820 [PMID: 32539166 DOI: 10.1002/ajim.23145]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com