Review

Ming Guo, Shunlai Shang, Mengfei Li, Guangyan Cai, Ping Li, Xiangmei Chen* and Qinggang Li*

Understanding autoimmune response after SARS-CoV-2 infection and the pathogenesis/mechanisms of long COVID

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Abstract: COVID-19 posed a major challenge to the healthcare system and resources worldwide. The popularization of vaccines and the adoption of numerous prevention and control measures enabled the gradual end of the COVID-19 pandemic. However, successive occurrence of autoimmune diseases in patients with COVID-19 cannot be overlooked. Long COVID has been the major focus of research due to the long duration of different symptoms and the variety of systems involved. Autoimmunity may play a crucial role in the pathogenesis of long COVID. Here, we reviewed several autoimmune disorders occurring after COVID-19 infection and the pathogenesis of long COVID.

Keywords: COVID-19; SARS-CoV-2; long COVID; autoimmunity

Introduction

COVID-19 is an infectious disease caused by the SARS-CoV-2 coronavirus. The World Health Organization (WHO) reported 760 million confirmed COVID-19 cases and 7 million deaths worldwide on July 12, 2023 [1]. Although COVID-19 no longer constitutes a global health emergency, it is still a threat to human health [2]. Several challenges such as rebound positivity, virus variation, and long COVID, still exist.

While the majority of patients with COVID-19 completely recover in the weeks following acute infection with no sequelae, many patients may continue experiencing a range of symptoms after recovery, and some may even acquire new symptoms. The phrase “long COVID” was created by patients, and numerous authors have elaborated on the circumstances of its onset [3–5]. Approximately 57 % of participants in a retrospective cohort analysis involving 81 million individuals, including 273,618 COVID-19 survivors, had at least one long COVID symptom recorded within 180 days of the SARS-CoV-2 infection. The authors suggested a higher likelihood of developing long COVID in patients with severe COVID-19, including women and young people [6]. The results of another retrospective cohort study suggested that 14.8 % of outpatients had at least one long COVID symptom 12–20 weeks following their COVID-19 diagnosis [7]. In a nationwide, population cohort study, 71.5 % and 70.7 % of individuals who had previously been infected with COVID-19 reported one or more symptoms at 6 and 12 months, respectively [8]. Therefore, long COVID is a huge challenge that deserves our attention.

The long-term complications of COVID-19, especially the occurrence of autoimmune diseases, are becoming a major focus of research as the global disease burden increases. Several new-onset autoimmune illnesses, including systemic lupus erythematosus, myasthenia gravis and Graves’ disease, have been documented with COVID-19 [9–11]. Several cohort studies have highlighted that COVID-19 is linked to a markedly high risk of acquiring multiple autoimmune diseases. Zhou et al. analyzed the data of 21 patients with

Ming Guo, Shunlai Shang and Mengfei Li contributed equally to the study.

***Corresponding authors: Xiangmei Chen**, Department of Nephrology, First Medical Center of Chinese PLA General Hospital, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing Key Laboratory of Kidney Diseases Research, Beijing 100853, China; and Haihe Laboratory of Cell Ecosystem, China,
E-mail: xmchen301@126.com; and **Qinggang Li**, Department of Nephrology, First Medical Center of Chinese PLA General Hospital, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing Key Laboratory of Kidney Diseases Research, Beijing 100853, China, E-mail: lqgbj301@126.com. https://orcid.org/0000-0002-8788-6670
Ming Guo, Mengfei Li, Guangyan Cai and Ping Li, Department of Nephrology, First Medical Center of Chinese PLA General Hospital, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing Key Laboratory of Kidney Diseases Research, Beijing 100853, China. https://orcid.org/0009-0008-8340-2836 (M. Guo)
Shunlai Shang, Department of Nephrology, First Medical Center of Chinese PLA General Hospital, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing Key Laboratory of Kidney Diseases Research, Beijing 100853, China; and Department of Nephrology, China-Japan Friendship Hospital, Beijing, China

COVID-19 and identified the prevalence of autoimmune markers, such as antinuclear, anti-60 kDa SSA/Ro, and anti-52 kDa SSA/Ro antibodies in 50 %, 25 %, and 20 % of patients, respectively [12]. Qin et al. reported that the most severe cases of COVID-19 had higher levels of inflammatory cytokines and lower T-cell counts compared with less severe cases [13]. Furthermore, long COVID has been linked with the emergence of autoimmunity [14–17]. Son et al. found increased ANA/ENA cycling concentrations at 3 and 6 months after recovery in 106 patients with COVID-19 compared with healthy controls [14]. Wajnberg et al. reported that more than 90 % of seroconverters produced detectable neutralizing antibody responses, and these titers remained relatively stable for at least 5 months after infection in a dataset of 30,082 patients [15]. These findings suggest that autoimmunity is at least partly involved in the development of long COVID.

Although numerous researchers are evaluating the autoimmune aspect of long COVID after the diagnosis of COVID-19, the corresponding pathophysiology remains unclear. In this review, we outlined several typical new-onset autoimmune diseases occurring after COVID-19. In addition, we elaborated on the mechanism and biomarkers of long COVID. We believe that further research on the link between COVID-19 and its different complications will increase our understanding of the disease and eventually improve diagnosis, treatment, and patient outcomes.

Post-COVID-19 autoimmune complications

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus is a multifactorial autoimmune disease that can affect multiple organ systems, and lupus nephritis is a typical manifestation of kidney involvement [18]. Lupus nephritis can appear in the majority of patients with SLE within 5 years of diagnosis. It is a type of glomerulonephritis and one of the most severe organ presentations of SLE [19]. Several authors have suggested the correlation between SLE and various pathogens, including Epstein–Barr virus (EBV) human papilloma virus, and parvovirus [20–22]. Therefore, COVID-19 may potentially induce SLE. Nine cases (male: 4 and female: 5) of new-onset SLE caused by COVID-19 have been documented to date (Table 1) [9, 23–30]. Notably, four of these cases were complicated by lupus nephritis and two of them were complicated by antiphospholipid syndrome.

Although a link between SLE and COVID-19 infection has not been conclusively determined, some authors have outlined the mechanism of COVID-19-induced SLE. Extrafollicular B-cell activation is associated with an increase in the counts of antibody-secreting cells and the early synthesis of high concentrations of SARS-CoV-2 specific neutralizing antibodies, and this phenomenon has been observed in patients with severe COVID-19 [31]. Notably, extrafollicular B-cell activation is also involved in SLE [32]. In addition, patients with COVID-19 have a severe inflammatory cytokine storm with high expression of pro-inflammatory cytokines, such as IL-1, IL-2, IL-6, IL-10, tumor necrosis factor (TNF)-α, IFN-γ, granulocyte macrophage-colony stimulating factor (GM-CSF), and inducible protein 10 [33, 34]. Similarly, cytokines, such as IL-6, IL-17, IL-18, B-lymphocyte stimulating factor, and TNF-α, are highly expressed in SLE. These cytokines mediate the differentiation, maturation, and activation of several immune cells and promote immunologic dysregulation, resulting in local inflammation and tissue damage.

Interferons (Type I, II, and III IFNs) may also be associated with the development of autoimmune conditions after COVID-19. Type I IFNs include IFN-α and IFN-β, which play a dual role against viral infection. On the one hand, IFN-α or IFN-β can protect the host from viral infections by enhancing the activity of antigen-presenting cells, promoting the antiviral function of adaptive immune cells, and blocking the viral replication cycle. On the other hand, IFN-α or IFN-β can induce the synthesis of immunosuppressive cytokines such as IL-10, thereby decreasing T-cell activity [35]. Several patients with SLE and other systemic autoimmune disorders show increased type I IFN expression [36]. Low type I IFN concentrations have been linked to SARS-CoV-2 infection [37]. Bastard et al. reported that approximately 10 % of patients with serious COVID-19 had high concentrations of neutralizing autoantibodies against IFN-α or IFN-ω or both [38]. However, type I IFN responses significantly increase in some patients with severe COVID-19. Lee et al. suggested that the conflicting results regarding type I interferon responses in patients with COVID-19 may be attributed to different definitions of disease severity, sampling time points, and/or readout types in different studies [39]. Therefore, the association between COVID-19, IFNs, and SLE needs to be further investigated.

Myasthenia gravis (MG)

Myasthenia gravis is an autoimmune illness that affects neuromuscular connections, leading to muscle weakness, ptosis, and diplopia. Pathogenic antibodies against the

Table 1: Reported cases of *de novo* SLE after COVID-19 infection.

Authors	Age (years)	Sex	PMH	Symptoms	Serology profile	Diagnose	Treatment	Outcome
Bonometti et al.	85	F	N	Hypotension; proteinuria thrombocytopenia;edemas peripheral cyanosis pleural effusion	ANA; ANCA; low complement	SLE with vasculitis	Hydroxychloroquine; steroids	R
Kazzi et al.	37	M	Photosensitive rash; interphalangeal joints discomfort; alopecia	Fever; nausea and vomiting; proteinuria; anorexia; generalized weakness; diffuse skin rash; abdominal pain	ANA; ANCA; low complement	SLE with LN	Hydroxychloroquine; steroids;, mycophenolate mofetil	R
Ramachandran et al.	53	M	HTN; CKD; cholecystectomy	Fatigue; malaise; wrist pain; nausea and vomiting; bilateral lower extremity swelling; exertional dyspnea; decreased urine output; proteinuria	ANA; anti-dsDNA; low complement	SLE with LN	Hydroxychloroquine; steroids;, mycophenolate mofetil; plasmapheresis	R
Gracia-Ramosl et al.	45	M	N	Fever; dry cough;malaise; myalgia; arthralgia; swelling of the leg	ANA;anti-dsDNA; anti-SSA; low complement	SLE	Hydroxychloroquine; steroids; rituximab immunoglobulin; splenectomy	R
Mantovani Cardoso et al.	18	F	Autism spectrum disorder; panic disorder	Fever;productive cough; shortness of breath;malaise; upper respiratory symptoms; tachypneic;tachycardic;anuria hypotensive;cardiac arrest. Pericardial effusion; ARDS	ANA;anti-dsDNA; lupus anticoagulant; anti-cardiolipin B; low complement	SLE with APS	Hydroxychloroquine; steroids; plasmapheresis; anticoagulation	NR
Zamani et al.	39	M	N	Fever; ankle swelling scaling on the palms of the hands and feet; dry cough lower extremity edema; shortness of breath; wheezing; proteinuria	Anti-dsDNA; anti-CCP; anti- SSB; anti-SSA	SLE with LN	Hydroxychloroquine; steroids; cyclophosphamide	R
Kudose et al.	27	F	UK	Fever; cough; hypoxemia; shortness of breath; edema	UK	SLE with LN	Steroids	NR
Slimani et al.	23	F	N	Fever; fatigue; dry cough; skin rash; dyspnea; proteinuria	ANA;anti-dsDNA; lupus anticoagulant; low complement	SLE with APS	Steroids	NR
Hali et al.	25	F	N	Fever; rash; diffuse myalgias; asthenia; proteinuria; multiple labial and palatal erosions	ANA;anti-dsDNA; low complement	SLE with MAS	Steroids	UK

SLE, systemic lupus erythematosus; F, female; M, male; HTN, hypertension; CKD, chronic kidney disease; ARDS, acute respiratory distress syndrome; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; anti-dsDNA, anti-double-stranded deoxyribonucleic acid; anti-CCP, cyclic citrullinated peptide; anti-SSA, anti-Sjgren syndrome A antibody; anti-SSB, anti-Sjgren syndrome B antibody; N, none; UK, unknown; NR, no response; R, response.

acetylcholine receptor (AChR) and muscle-specific kinase (MuSK) are present in approximately 80 % and 1 %–10 % of patients with MG, respectively [40]. MG has been reported after infections with viruses, such as hepatitis B, hepatitis C, HIV, herpes simplex virus, Zika virus, and EBV [41]. Recently, some authors have suggested the possibility of new-onset MG after COVID-19 infection, and 19 such cases have been reported (Table 2). Anti-AChR antibodies were found in 16 cases and anti-MuSK antibodies were found in 2 cases. Surprisingly, both anti-AChR and anti-MuSK antibodies were not detected in one case. Approximately 47 % of the patients were males, and 58 % were aged above 50 years. Patient outcomes improved to varying degrees, except in two cases where treatment outcomes were not described [10, 42–54].

SARS-CoV-2 infection may be involved in the pathogenesis of MG. Galassi et al. suggested that the epitopes of the virus are similar to the components of the neuromuscular junction (molecular mimicry). Therefore, antibodies generated against the SARS-CoV-2 protein may react with the AChR receptors [55]. Given their chemical distinctions, cross-reactivation is a less likely cause of the emergence of MuSK-associated MG than the failure of self-tolerance mechanisms [56]. In addition, SARS-CoV-2 infection induces cytokine storms, i.e., an increase in the expression of IL-6, IL-23, IL-7, IL-21, and TGF-β. IL-7 regulates the survival and growth of immature thymocytes, and IL-21 stimulates the growth of T follicular helper cells. The overexpression of AChR can increase the generation of anti-AChR antibodies [57–59]. Finally, medications, such as azithromycin and hydroxychloroquine sulfate, frequently prescribed to patients with COVID-19 may cause MG [60, 61].

Graves' disease (GD)

Graves' disease is an autoimmune disease caused by autoantibodies produced against the thyroid-stimulating hormone receptor, leading to an overactive thyroid. GD can affect people of all ages; however, it is more prevalent in women than in men [62]. Thirteen cases of *de novo* GD have been reported after COVID-19 infection, and the frequency is greater in women (9/13; 69 %) than in men (Table 3). Treatment of GD mainly comprises methimazole and beta-blockers. The sera of most patients with GD contained detectable antithyroid antibodies, including anti-thyrotrophin receptor, antithyroglobulin, and thyroid peroxidase antibodies. All patients favorably responded to the treatment and attained varied degrees of clinical remission except for two patients who did not disclose treatment outcomes [11, 63–74].

Numerous theories have been suggested to explain the association between COVID-19 infection and GD. Molecular mimicry is considered one of the potential mechanisms. SARS-CoV-2 virus binds to the angiotensin-converting enzyme-2 (ACE2) receptor to enter the host cells, which is highly expressed on thyroid cells [75]. Therefore, SARS-CoV-2 may enter thyroid cells through the ACE2 receptor to induce thyroid injury. Thyroid dysfunction may also be triggered by a cytokine storm linked to COVID-19. Lania et al. conducted a single-center retrospective study to evaluate thyroid function tests and IL-6 concentrations of 287 patients with COVID-19 and found a strong correlation between high concentrations of circulating IL-6 and thyrotoxicosis [76, 77]. IL-6 antagonists (e.g., tocilizumab, sarilumab, and siltuximab) were related to decreased mortality in patients with severe COVID-19 in a prospective meta-analysis based on 27 randomized clinical trials conducted by the WHO [78]. However, further definitive studies are required to understand whether COVID-19 is truly implicated in the emergence of GD.

Autoimmune hemolytic anemia (AIHA)

Autoimmune hemolytic anemia is a complex autoimmune disorder characterized by an increase in the autoimmune destruction of red blood cells (RBCs), typically caused by autoantibodies against erythrocyte surface antigens. The autoantibodies may be warm, cold, or mixed type [79]. We collected 37 cases of newly diagnosed AIHA after COVID-19 infection in adults (Supplementary Table 1). Warm AIHA was diagnosed in 19 out of 37 cases, and cold agglutinin syndrome was diagnosed in 17 cases. Interestingly, Evans syndrome was diagnosed in one case. Of the 37 patients, 12 were positive for IgG and complement, nine were only positive for complement, eight were only positive for IgG, and one was only positive for IgA. The relevant data was not available for seven patients. The mainstay treatment for most patients includes steroids and blood transfusion, and some patients may be treated with rituximab [80–105].

Infections with cytomegalovirus, EBV, and hepatitis A virus can lead to AIHA [106, 107]. Although the precise link between AIHA and COVID-19 is not yet understood, molecular simulations may play a significant role. The erythrocyte membrane protein ANK-1 is an essential component of erythrocyte development and function. ANK-1 and the SARS-CoV-2 surface glycoprotein (Spike protein) share a 100 % similar potentially immunogenic epitope (amino acids LLLQY). Therefore, cross-reaction between RBCs and an active immune system can lower hemoglobin levels [108]. Liu et al. discovered the presence of heme ligand binding sites in the SARS coronavirus ORF3a protein and confirmed that ORF3a can coordinate to attack heme on the hemoglobin

Table 2: Reported cases of *de novo* MG after COVID-19 infection.

Authors	Age (years)	Sex	PMH	Symptoms	Serology profile	Diagnose	Treatment	Outcome
Restivo et al.	68	M	N	Fever; diplopia; muscular fatigability	Anti-AChR Abs +	Generalized MG	Pyridostigmine; steroids	UK
	64	M	N	Fever; diplopia; dysphagia; muscular fatigability	Anti-AChR Abs +	Generalized MG	IVIG	R
	71	M	N	Fever; cough; diplopia bilateral ocular ptosis; hypophonia; dysphagia; respiratory failure	Anti-AChR Abs +	Generalized MG	Plasmapheresis; hydroxychloroquine	R
Huber et al.	21	F	Hashimoto's thyroiditis; pernicious anemia; Addison's disease	Double vision; right-sided ptosis	Anti-AChR Abs +	Ocular MG	IVIG; pyridostigmine	R
Perez et al.	48	M	Schizophrenia; inverse Psoriasis	Diplopia	Anti-AChR Abs +	Ocular MG	Hydroxychloroquine; azithromycin	R
Assini et al.	77	M	N	Chewing difficulty; dysphonia; diplopia; eyelid ptosis	Anti-MuSK Abs +	Oculobulbar MG	Azathioprine	R
Muhammed et al.	24	F	N	Diplopia; slurred speech; dysphagia; global limb weakness	Anti-MuSK Abs +	Generalized MG	IVIG; steroids pyridostigmine;	R
Muralidhar et al.	65	M	Diabetes;HTN	Dysphagia	Anti-AChR Abs +	Generalized MG	Steroids; pyridostigmine; azathioprine; ventilator support	R
Sriwastava et al.	65	F	Meningioma; pituitary adenoma; pulmonary carcinoma; left renal cell carcinoma status post partial nephrectomy	Diarrhea; myalgia; extreme fatigue; left eyelid ptosis	Anti-AChR Abs +	Ocular MG	Pyridostigmine; steroids	R
Karimi et al.	61	F	N	Dysphagia; nasal speech; ocular ptosis; diplopia; dyspnea proximal muscle weakness;	Anti-AChR Abs +	Generalized MG	Plasma exchange; pyridostigmine; steroids	R
	57	M	CHF and ICD	Fever; cough; muscle fatigue; diplopia; ptosis; dysphagia	Anti-AChR Abs +	Generalized MG	Pyridostigmine; steroids	R
	38	F	N	Fever; cough; myalgia; fatigue,	Anti-AChR Abs +	Generalized MG	Pyridostigmine; steroids	R
Bhandarwar et al.	61	M	Diabetes mellitus;bronchial asthma	Breathlessness; dysphagia; generalized weakness	Anti-AChR Abs +	Generalized MG	Steroids; thymoma with thymectomy	R
Jõgi et al.	65	M	HTN; hypercholesterolemia; cataract	Fever; cough; shortness of breath; dysarthria; dysphagia; difficulty pronouncing words; bilateral ptosis; right-sided oculomotor paralysis; weakness of neck muscles	Anti-AChR Abs +	Generalized MG	IVIG; steroids; pyridostigmine; azathioprine	R
Taheri et al.	35	F	N	Dyspnea; myalgia; sore throat; weakness; nausea; cough; severe weakness in her upper and lower limbs; blurred vision; droopy eyelids	Anti-AChR Abs +	Generalized MG	Steroids; remdesivir; pyridostigmine	R
Tereshko et al.	19	F	Hashimoto's thyroiditis; thalassemia; anemia; autoimmune gastritis	Diplopia; dysarthria; dysphagia right ptosis; generalized weakness	Anti-AChR Abs +	Oculobulbar and then generalized MG	IVIG; pyridostigmine; steroids; thymectomy	R

Table 2: (continued)

Authors	Age (years)	Sex	PMH	Symptoms	Serology profile	Diagnose	Treatment	Outcome
Rodrigues et al.	37	F	N	Dysphagia; dysphonia; post-prandial cough; diplopia bilateral ptosis; mild dyspnea	N	MGFA class IIIB	Rituximab; steroids; pyridostigmine.	R
	90	UK	Atrial fibrillation; HTN	UK	Anti-AChR Abs +	MGFA class IIIB	IVIG	UK
Essajee et al.	7	F	Multisystem inflammatory syndrome in children (MIS- C)	Fatigable bilateral orbital ptosis; diplopia	Anti-AChR Abs +	Ocular MG	Pyridostigmine; steroids; methotrexate	R

MG, myasthenia gravis; F, female; M, male; HTN, hypertension; CHF, congestive heart failure; ICD, implantable cardioverter defibrillator; IVIG, intravenous immunoglobulin; AChR, acetylcholine receptor; MGFA, myasthenia gravis foundation of America; N, none; UK, unknown; R, response.

Table 3: Reported cases of *de novo* GD after COVID-19 infection.

Authors	Age (years)	Sex	PMH	Symptoms	Serology profile	Diagnose	Treatment	Outcome
Harris et al.	21	F	Asthma; GERD; prediabetes; class-I obesity	Tachycardia; palpitations; anxiety; shortness of breath.	TRAb	GD	Methimazole; beta blocker	R
Lanzolla et al.	33	F	N	Tachycardia; weight loss; heat intolerance; nervousness.	TRAb; TgAb	GD	Methimazole	R
Mateu et al.	53	F	N	Dyspnea; fever; asthenia; tremor;palpitations	TRAb; TgAb; TPOAb	GD	Methimazole; beta blocker	R
Feghali et al.	33	F	N	Palpitations; fatigue shortness of breath	UK	GD	Methimazole; beta blocker	R
Edwards et al.	27	M	N	Fever; confusion; tremulous; aggressive behavior; tachycardic	TRAb; TgAb;	GD	Methimazole; beta blocker; SSKI	R
Rockett et al.	16	M	N	Shortness of breath; anxiety; chest pain; ongoing tremor; thyroid was enlarged and tender	TRAb; TgAb; TPOAb	GD	Methimazole; beta blocker	R
Nham et al.	27	F	N	Fever; tachycardia; pricking chest pain	TPOAb	GD with subacute thyroiditis	Methimazole; beta blocker	UK
Franca et al.	30	F	Asthma; renal lithiasis; migraine with aura	Tachycardia; fatigue; palpitations; dizziness; tremors, excessive sweating; intolerance to physical exercise	TRAb	GD	Methimazole; beta blocker	R
Boyle et al.	65	F	N	Exertional dyspnea; palpitations	TRAb; TPOAb	GD	Methimazole; beta blocker	R
Bayar et al.	38	F	Leukopenia	Persisting asthenia; tremor; palpitations	TRAb	GD	Corticosteroid; propranolol	UK
Ghareebian et al.	48	M	N	Fatigue; shortness of breath; generalized muscle aches; cough	TSI	GD	Methimazole; beta blocker	R
Urbanovych et al.	22	F	N	Palpitation; tremor; muscle; weakness;anxiety; sleep disturbance	TRAb	GD	Methimazole; beta blocker; glucocorticosteroids	R
Sousa et al.	28	M	N	Fatigue; shortness of breath; palpitations; weight loss	TRAb; TgAb; TPOAb	GD	Methimazole; beta blocker	R

GD, Grave's disease; F, female; M, male; GERD, gastroesophageal reflux disease; TRAb, thyrotrophin receptor antibody; TgAb, thyroglobulin antibody; TPOAb, thyroidperoxidase antibodies; TSI, thyroid stimulating immunoglobulins; SSKI, saturated solution potassium iodide; N, none; UK, unknown; R, response.

beta chain. The virus can attack both oxygenated and deoxygenated hemoglobin; however, the deoxygenated one is more susceptible. In addition, viral structural proteins S and E have porphyrin-producing and binding domains that

can bind porphyrins to cause infection [109]. Lam et al. noted that SARS-CoV-2 infection activates complement *in vivo*, and RBCs from patients with COVID-19 contain complement activation products and viral antigens [110].

Other autoimmune complications

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system, characterized by the brain and spinal cord demyelinating lesions [111]. Numerous neurological symptoms, such as the MG, have been documented in patients with COVID-19. Nevertheless, COVID-19-induced demyelinating illnesses have not been characterized. Some authors have elaborated on MS caused by COVID-19, however the underlying mechanism is not well understood [112–116]. Demyelination-related immunopathologies include autoimmune, direct immune cytotoxicity, and indirect damage [117]. The coronavirus family is neurotropic, entering the central nervous system mostly through the blood-brain barrier (BBB) and the neuronal pathways [118]. Neurotropic virus-induced demyelination appears to be mediated by adaptive immunity rather than direct viral infection [119].

COVID-19 has also been linked to rheumatoid arthritis, vasculitis, type 1 diabetes, and Guillain–Barre syndrome [120–123]. Although the causative association between COVID-19 and autoimmune conditions is unclear, numerous theories attempt to explain the influence of SARS-CoV-2 infection on the onset of autoimmune responses.

The S1 domain of SARS-CoV-2 can bind to the transmembrane ACE2 receptor, mediating the direct entry of viruses into cells. SARS-CoV-2 and human proteins have similar peptide sequences, and antibodies against SARS-CoV-2 can cross-react with human proteins through molecular simulation [124, 125]. Bystander activation, epitope diffusion, and polyclonal activation of B-cells may also be involved in the occurrence of autoimmunity after SARS-CoV-2 infection [126–128]. Notably, the occurrence of new autoimmune illnesses after COVID-19 vaccination has also been linked to these pathways [129].

SARS-CoV-2 can downregulate the ACE2 expression, resulting in the imbalance of the renin–angiotensin–aldosterone system. In addition, SARS-CoV-2 infection increases cytokine release and activates inflammasome and complement, leading to endothelial dysfunction, hypercoagulable state, and thrombosis [130, 131]. SARS-CoV-2 can lead to immune cell imbalance by inducing the apoptosis and depletion of T-cells, which, in turn, may decrease the immunity of patients and increase the susceptibility to microbial infections. Neutrophils are then activated and recruited to form a neutrophil network, thereby promoting the development of inflammation [132]. Overall, various factors lead to the occurrence of post-COVID-19 autoimmune complications.

Long COVID

Definition and manifestations of long COVID

"Long COVID" is the term used to describe the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, which may last for at least 2 more months [133]. General symptoms (such as fatigue or fever), respiratory and heart symptoms (such as breathlessness, a persistent cough, or chest pain), neurologic symptoms (such as trouble speaking, cognitive dysfunction, and a loss of smell or taste), digestive symptoms (such as diarrhea and stomach pain), and other symptoms (such as muscle aches, rashes, or changes in menstrual cycles) are typically linked to long COVID. Approximately 10 %–20 % of individuals infected with SARS-CoV-2 may experience long-term effects that can be diagnosed as long COVID. Patients who have suffered from more severe COVID-19 or multisystem inflammatory syndrome are more likely to have long COVID. Moreover, it is more common in people who did not receive the COVID-19 vaccine [134].

Cellular and molecular biomarkers of long COVID

Long COVID is often difficult to diagnose because it affects multiple systems and has a wide array of symptoms. Therefore, it is critical to find biomarkers for long COVID to improve the diagnosis. Several cohort studies have reported long COVID-related biomarkers, including immune cells, immunoglobulins, cytokines, and other plasma proteins (such as chemokines). The most common biomarkers are C-reactive protein, IL-6, TNF-α, IFN-λ, D-dimer, lactate dehydrogenase, leukocytes, von Willebrand factor, α2-antiplasmin, and Tregs [135–137]. Erythropoietin concentrations are increased in patients with long COVID, which may be related to tissue hypoxia in these individuals. Moreover, high erythropoietin concentrations may be necessary for the generation of red blood cells [135]. Su et al. found a significant correlation between symptoms of preexisting type 2 diabetes and COVID-19 in 309 patients with COVID-19 compared with healthy controls. In addition, individuals who had higher RBC counts at diagnosis and those who were female or had chronic obstructive pulmonary disease or both were more likely to experience various symptoms. The latent period EBV and the

reactivation of SARS-CoV-2 RNAemia can predict the occurrence of long COVID. Autoantibodies are also biomarkers for predicting long COVID, and high concentrations of anti-SARS-CoV-2 nucleocapsid protein IgG are associated with neurologic symptoms. IFN-a2 autoantibodies are associated with respiratory symptoms, and increased levels of multiple autoantibodies are associated with gastrointestinal symptoms and sputum production [138]. The occurrence of fibrotic pulmonary sequelae may be predicted by evaluating early periosteal protein concentrations [139].

Pathophysiology and mechanism of long COVID (Figure 1)

Viral persistence and reactivation of latent viruses

Symptoms in certain individuals with long COVID may be linked to the persistence of the SARS-CoV-2 reservoir after acute infection. Cheung et al. revealed that SARS-CoV-2 viral antigens were present in the gastrointestinal tract and liver of five patients with COVID-19 up to 6 months after recovery [140]. Notably, the gastrointestinal system is the most extensively studied potential reservoir of residual virus [141–143]. Natarajan et al. documented that the shedding of fecal SARS-CoV-2 RNA in any patient with COVID-19 is the longest [144]. SARS-CoV-2 antigen persists in the intestinal mucosa for months following acute COVID-19 in the majority of individuals with inflammatory bowel disease regardless of immunosuppressive medication or intestinal inflammation [145]. SARS-CoV-2 can persist in the brain and penis for extended durations after the original human infection [146, 147]. These extrapulmonary organs can be considered SARS-CoV-2 reservoirs and a possible source of viral shedding [148]. Circulation spikes were observed in patients with long COVID up to 12 months after diagnosis in a retrospective pilot investigation using plasma samples of 63 adults with acute or chronic COVID-19 [149]. Desimmie et al. suggested that the likelihood of virus persistence, reactivation, or reinfection is high in immunocompromised patients [150].

The symptoms of long COVID are related to the reactivation of other viruses, such as EBV, HIV, HHV6, and cytomegalovirus [151–158]. Peluso et al. found that recent EBV reactivation was most closely related to fatigue (OR=2.12); however, it was less related to other symptoms of long COVID. Participants with underlying HIV were most strongly associated with neurocognitive symptoms (OR=2.5) followed by gastrointestinal symptoms (OR=2.33) [154]. Zubchenko et al. evaluated 88 patients and found that 68 (72.3 %) of them had EBV and HHV6 reactivation. EBV reactivation alone was present in 42.6 % of cases, HHV-6 reactivation alone was present in 25 % of cases, and both EBV and HHV-6 reactivation occurred in 32.4 % of cases [155]. Gold et al. found that approximately 30 % of patients reported long COVID-like symptoms after acute disease in a retrospective study of 185 individuals. EBV reactivation was detected in 66.7 % of long COVID individuals and 10 % of control subjects [156]. The discovery of virus reactivation highlights the importance of

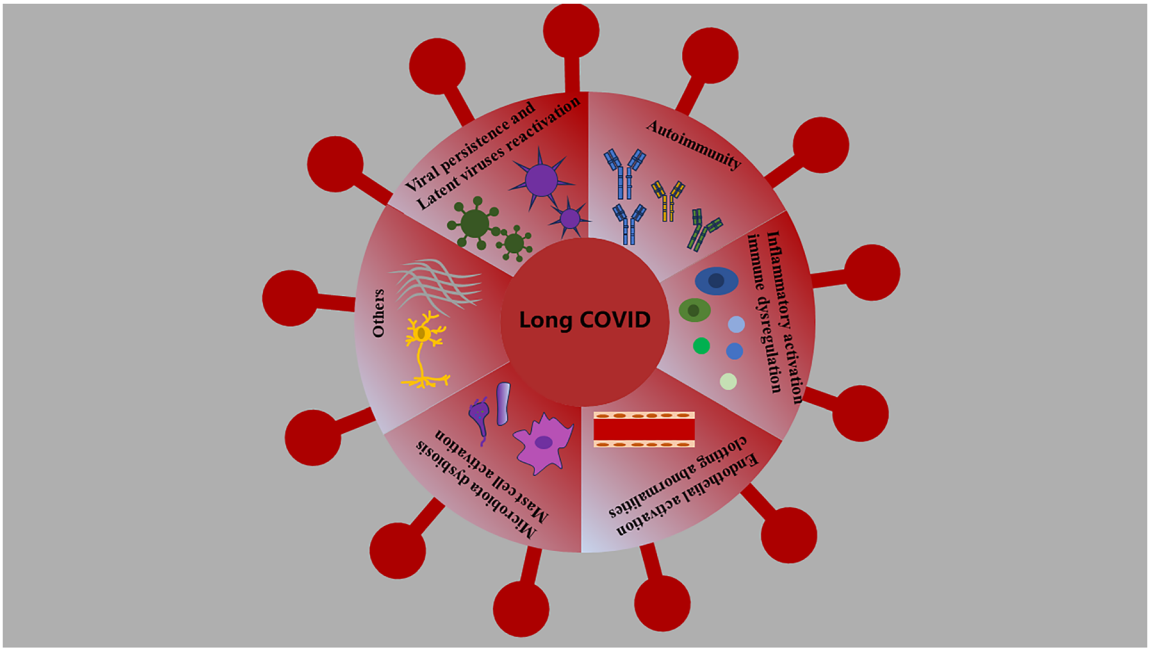

Figure 1: Multiple pathophysiologic mechanisms of long COVID.

determining whether the symptoms of long COVID are due to the SARS-CoV-2 virus directly or the result of the reactivation of other viruses in future studies.

Autoimmunity

Many studies on autoimmunity following COVID-19 infection have focused on the development of different autoantibodies (Figure 2). Autoantibodies against type I IFNs are significant contributors to the development of COVID-19, particularly in severe cases. Bastard et al. found that the prevalence of circulating type I IFN autoantibodies increases with aging and at least 10 % of patients with serious COVID-19 have neutralizing autoantibodies against type I IFNs, and the percentage of male patients was higher [159]. Son et al. discovered that COVID-19 survivors showed higher concentrations of circulating ANAs/ENAs 3 months after recovery compared with healthy or non-infected individuals. The occurrence of anti-U1-SnRNP and anti-SS-B/La, the two most prevalent ANAs/ENAs, predicted persistent dyspnea and fatigue in COVID-19 survivors at 12 months. Approximately one-third of the COVID-19 survivors in convalescence had at least one autoreactive IgG, whereas most of the healthy controls had no IgG autoantibodies [14]. The functionally active autoantibodies ($_f$AABs) targeting G-protein coupled receptors (GPCR-$_f$AABs) were also found in patients with severe COVID-19 infection. Wallukat et al. studied 31 patients who recovered from the acute phase of COVID-19 and found that all patients had 2–7 different GPCR-$_f$AABs. Two additional $_f$AABs were also present in 29 (90 %) patients that target the RAS receptors, angiotensin II AT1 receptor and angiotensin 1-7 MAS receptor [160]. GPCR-$_f$AABs may be related to autonomic dysfunction, central nervous system-related symptoms, heart failure, and impaired retinal microcirculation [161–164]. In addition, anti-CCP, anti-TG, and anti-DSG2 antibodies have also been found in patients with long COVID [165, 166]. These findings demonstrate that various AABs are produced after COVID-19, and some of them may be associated with long COVID.

Inflammatory activation and immune dysregulation

Cytokine storm refers to increased circulating concentrations of cytokines in response to various infections and immune-mediated conditions [167]. Acosta-Ampudia et al. noted that patients with long COVID had higher concentrations of pro-inflammatory cytokines (e.g., IL-6, IL1-β, IL-13, IL17A, IFN-α, TNF-α, and G-CSF). The majority of cellular immune components in these patients did not return to their pre-infection baseline even after 7–9 months of infection. Some patients with long COVID have higher concentrations of inflammatory indicators, such as C-reactive protein,

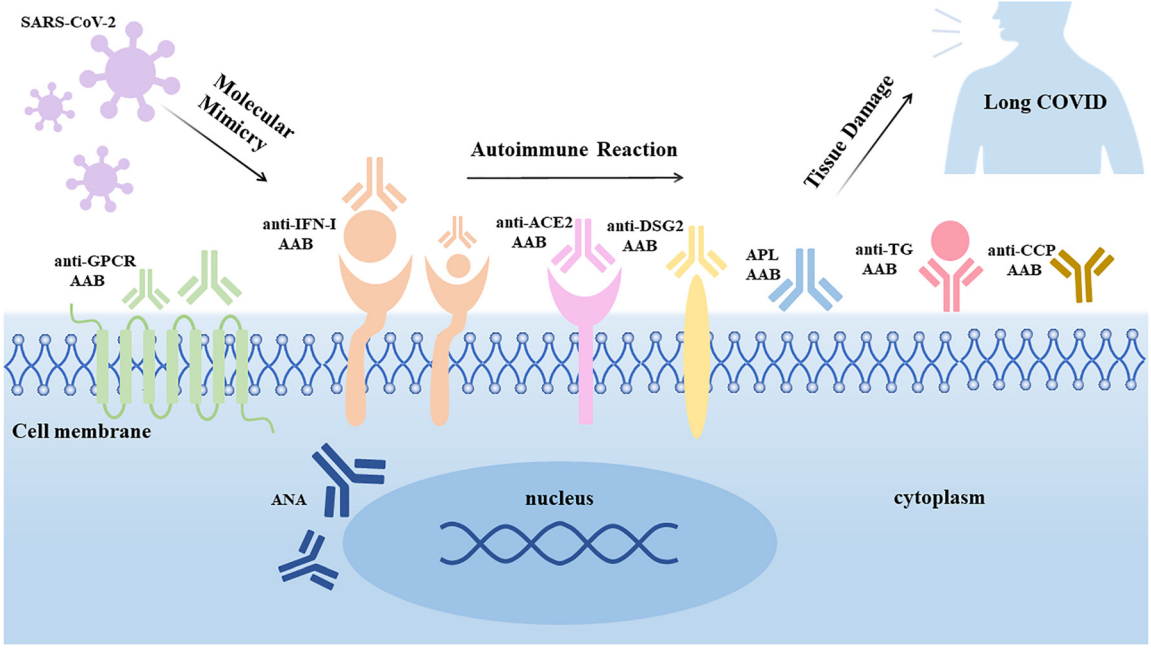

Figure 2: Autoimmune theory of long COVID and the production of autoantibodies (AABs). SARS-CoV-2 may induce the production of AABs, such as anti-GPCR, anti-IFN-1, anti-ACE2, and ANA AABs, due to the similarities between SARS-CoV-2 and human antigens (molecular mimicry). The excessive production of AABs causes and worsens autoimmune disorders. The development of long COVID may be influenced by the persistence of AABs.

D-dimer, IL-6, and IFNs [168]. Additionally, IFN-β, PTX3, IFN-γ, IFN-λ2/3, and IL-6 were strongly correlated with long COVID [169]. Rodriguez et al. noted higher levels of IL-8 and circulating nucleosomes in patients with severe long COVID compared with convalescent controls, indicating chronic neutrophil activation [170]. SARS-CoV-2 may cause aberrant pathogenic Th1 cells to release pro-inflammatory cytokines, such as GM-CSF and IL-6. Additional activation of $CD14^+$ $CD16^+$ inflammatory monocytes by GM-CSF results in an increase in the production of IL-6, TNF-α, and other cytokines. Furthermore, membrane-bound immune receptors, poor IFN-γ induction, and neutrophil extracellular traps may be involved in the release of cytokines [171].

Sin DD proposed that SARS-CoV-2 infection destroys the immune system of the host, and the immune system of patients with long COVID remains persistently overactivated even after the virus has been completely cleared from the host, resulting in immune system dysregulation [172]. Espin et al. reviewed 239 candidate biomarkers from 23 cohort studies and found a higher frequency of plasmacytoid dendritic cells expressing activation markers CD86 and CD38, inflammatory monocytes ($CD14^+$ $CD16^+$), NK cells expressing memory (CD57) and activation (NKG2C) markers, and Tregs ($CD4^+$ $CD25^+$ $CD127^{low}$) [173]. The presence of these markers indicates a sustained and uncontrolled immune response.

Endothelial activation and clotting abnormalities

Persistent endotheliopathy is a common observation in patients with long COVID. Fogarty et al. observed that plasma FVIII:C levels and thrombin production were significantly higher, the delay time was significantly shortened, endogenous thrombin potential and peak thrombin were significantly increased, and the time to peak was shorter in 50 COVID-19 convalescent patients compared with healthy controls. Furthermore, these patients had significantly higher amounts of soluble thrombomodulin, von Willebrand factor antigen, and VWF propeptide compared with healthy controls [174].

High D-dimer concentrations in convalescent patients may indicate active thrombosis and fibrinolytic activity in the blood vessels [175]. Fan et al. conducted a prospective observational trial and found that patients with COVID-19 had significantly greater levels of inflammation, endotheliopathy, and hypercoagulable state compared with controls [176]. Therefore, endothelial activation and hypercoagulability in patients with long COVID may be associated with thromboembolism complications; therefore, antithrombotic therapy should be performed at the earliest after diagnosis [177].

Mast cell activation (MCA)

The symptoms of long COVID have also been linked to MCA. Wechsler et al. reported that serum concentrations of CXCL1, IL-6, and active trypsin were significantly higher in patients with long COVID than in controls, suggesting systemic MCA. Further, active trypsin levels were associated with CXCL1 and IL-6 concentrations [178]. Several authors have reported the expression of trypsin in mast cells, which also contain the serine protease ACE2, the primary receptor for SARS-CoV-2 [179]. Pro-inflammatory factors, such as histamine, IL-1β, CCL2, GM-CSF, and TNF-α, can also be released after the activation of mast cells, and these molecules have been linked to COVID-19 symptoms [180].

Mast cell activation syndrome (MCAS) is a heterogeneous disorder characterized by severe symptoms resulting from the release of mast cell mediators. MCAS is of three types, namely primary, secondary, and idiopathic MCAS [181]. The symptoms and severity of MCAS are substantially identical to those of long COVID, and the prevalence of MCAS is comparable to that of severe COVID-19 in populations infected with SARS-CoV-2 [182, 183]. Since COVID-19 can induce mast cell dysfunction, the abnormal mast cells are prone to produce inappropriate and excessive responses, which may drive the occurrence of long COVID or aggravate the existing MCAS in patients [181, 183].

Other potential mechanisms

Recently, some authors have reported the potential role of microbiota dysbiosis, especially gut dysbiosis, in long COVID [184–187]. Liu et al. evaluated 106 patients with COVID-19 and 68 non-COVID-19 individuals for 6 months and observed that 76 % of patients had long COVID symptoms, and the most common symptoms were fatigue, hair loss, and poor memory. Patients with long COVID symptoms had different gut microbiomes than those without these symptoms. Moreover, gut microbiomes of patients without long COVID symptoms were similar to those of non-COVID-19 controls. The changes in the composition of the gut microbiota were closely related to the persistence of symptoms in patients with long COVID. For example, persistent respiratory symptoms were linked to opportunistic gut pathogens, whereas neuropsychiatric symptoms and exhaustion were linked to nosocomial gut pathogens [186]. Gut microbiota produces signals required to activate the adaptive immune system against microbial infections. On the contrary, the adaptive immune system can selectively modulate the innate system to maintain gut microbiota homeostasis [185, 188, 189]. Notably, the diversity of gut microbiota is a predictive indicator for severe COVID-19 [185, 190].

Amyloid fibrin microclots have been linked to the progression of long COVID. High levels of amyloid fibrin microclots have been found in platelet-poor plasma of patients with long COVID. These microclots can block capillaries to prevent RBCs from passing through, thereby limiting oxygen exchange and causing tissue hypoxia. In addition, these clots may potentially present new antigens, trigger the generation of autoantibodies, and exacerbate symptoms [191–193]. High concentrations of various inflammatory molecules, fibrinogen chains, serum amyloid A, and α(2)-antiplasmin and obvious platelet hyperactivation suggest that patients of long COVID may have a failed fibrinolysis phenomenon [192, 193].

Neuropsychiatric disorders are the most commonly reported symptoms in a large majority of patients with COVID-19 [194]. Xu et al. found that the hazard ratio of any neurologic sequelae in the COVID-19 group was 1.42 and the disease burden per 1,000 people was 70.69 at 1 year, indicating a high risk and burden of neurologic diseases in patients with COVID-19 [195]. Oaklander et al. analyzed 17 patients with long COVID with no history or risk of neuropathy (as defined by the WHO) and showed that small fibrous neuropathy was the most common [196]. CCL11 concentrations increased in patients who experienced ongoing cognitive impairments after COVID-19 [197]. The neurologic manifestations of long COVID may be driven by inflammation, endothelial cell damage, generalized vascular dysfunction, complement activation, and neurodegenerative changes [198–201].

Overall, numerous pathophysiologic factors contribute to the occurrence of long COVID. In addition to the abovementioned pathways, melatonin deficiency, bacteriophage-like actions, multiple organ damage, and tissue hypoxia may also be involved in the occurrence of long COVID [202, 203].

Can COVID-19 vaccines cause long COVID?

Long COVID may be a cluster of autoimmune diseases induced by the SARS-CoV-2 spike protein [204]. Antibodies produced against the SARS-CoV-2 spike protein after vaccination may cross-react with the host antigens (molecular mimicry), leading to autoimmune diseases [129]. Therefore, some scholars suggest that vaccines containing spike proteins may play the same role in inducing long COVID. However, the National Institute for Clinical Excellence (NICE) of the UK or WHO standards defines long COVID based on a previously confirmed diagnosis of COVID-19. We believe that even if similar symptoms occur after vaccination, it cannot be called long COVID; however, the phenomenon can be called long-COVID-like symptoms [205]. Moreover, vaccination may help ameliorate the symptoms of long COVID [206, 207]. The association between vaccination and long COVID is unclear, and elimination of the residual viral reservoir by increasing antibody titers may be one of the possible reasons. In conclusion, vaccines may play a dual role in patients with long COVID. On one hand, vaccines can readjust the immune capacity of these patients and ameliorate their symptoms. On the other hand, vaccines may cause excessive immune response and aggravate symptoms. In addition, the COVID-19 vaccine can also elicit long COVID-like symptoms in people who have not been diagnosed with COVID-19. The interval between the beginning of symptoms and infection or vaccination appears to be an important differentiating factor [205]. Overall, the protective effect of vaccines on the human body is much higher than their side effects, and the vaccination of COVID-19 is crucial in the future.

Conclusions

The COVID-19 pandemic was a huge global challenge. Although the fear of COVID-19 has gradually decreased among the population owing to the sustained efforts of all countries and the universality of the SARS-CoV-2 infection, various complications after the COVID-19 infection, including the appearance of the long COVID, have once again raised serious concerns. It is still controversial whether long COVID can be regarded as an autoimmune disease. Given that the autoimmune mechanism is crucial to the occurrence and progression of long COVID, we describe long COVID as an autoimmune complication that occurs after initial recovery from COVID-19.

The autoimmune diseases after COVID-19, including long COVID, will continue to develop for many years. Therefore, it is critical to comprehend the likelihood of acquiring post-COVID-19 complications, such as autoimmune diseases, and their possible mechanisms. Although we do not have a comprehensive record due to the wide variety of autoimmune diseases caused by COVID-19, our review provides comprehensive information on the link between COVID-19 and autoimmune diseases that develop after initial recovery from the disease. We aim to increase awareness among patients and healthcare professionals for the early diagnosis and treatment of post-COVID-19 autoimmune complications to lower morbidity and mortality.

Research ethics: The local Institutional Review Board deemed the study exempt from review.
Informed consent: Not applicable.

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References

1. WHO. WHO coronavirus (COVID-19) dashboard. n.d. Available from: https://covid19.who.int (Accessed August 22, 2023).
2. WHO. WHO director-general's opening remarks at the media briefing – 5 May 2023. n.d. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing—5-may-2023 (Accessed August 22, 2023).
3. Callard F, Perego E. How and why patients made long Covid. Soc Sci Med 2021;268:113426.
4. Higgins V, Sohaei D, Diamandis EP, Prassas I. COVID-19: from an acute to chronic disease? Potential long-term health consequences. Crit Rev Clin Lab Sci 2021;58:297–310.
5. Long COVID: let patients help define long-lasting COVID symptoms. Nature 2020;586:170.
6. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: a 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med 2021;18:e1003773.
7. Sedgley R, Winer-Jones J, Bonafede M. Long COVID incidence in a large US ambulatory electronic health record system. Am J Epidemiol 2023;192:1350–7.
8. Hastie CE, Lowe DJ, McAuley A, Mills NL, Winter AJ, Black C, et al. Natural history of long-COVID in a nationwide, population cohort study. Nat Commun 2023;14:3504.
9. Bonometti R, Sacchi MC, Stobbione P, Lauritano EC, Tamiazzo S, Marchegiani A, et al. The first case of systemic lupus erythematosus (SLE) triggered by COVID-19 infection. Eur Rev Med Pharmacol Sci 2020;24:9695–7.
10. Restivo DA, Centonze D, Alesina A, Marchese-Ragona R. Myasthenia gravis associated with SARS-CoV-2 infection. Ann Intern Med 2020;173:1027–8.
11. Harris A, Mushref MA. Graves' thyrotoxicosis following SARS-CoV-2 infection. AACE Clin Case Rep 2021;7:14–6.
12. Zhou Y, Han T, Chen J, Hou C, Hua L, He S, et al. Clinical and autoimmune characteristics of severe and critical cases of COVID-19. Clin Transl Sci 2020;13:1077–86.
13. Qin C, Zhou LQ, Hu ZW, Zhang SQ, Yang S, Tao Y, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020;71:762–78.
14. Son K, Jamil R, Chowdhury A, Mukherjee M, Venegas C, Miyasaki K, et al. Circulating anti-nuclear autoantibodies in COVID-19 survivors predict long-COVID symptoms. Eur Respir J 2023;61:2200970.
15. Wajnberg A, Amanat F, Firpo A, Altman DR, Bailey MJ, Mansour M, et al. Robust neutralizing antibodies to SARS-CoV-2 infection persist for months. Science 2020;370:1227–30.
16. Iyer AS, Jones FK, Nodoushani A, Kelly M, Becker M, Slater D, et al. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci Immunol 2020;5:eabe0367.
17. Bertin D, Kaphan E, Weber S, Babacci B, Arcani R, Faucher B, et al. Persistent IgG anticardiolipin autoantibodies are associated with post-COVID syndrome. Int J Infect Dis 2021;113:23–5.
18. Lazar S, Kahlenberg JM. Systemic lupus erythematosus: new diagnostic and therapeutic approaches. Annu Rev Med 2023;74:339–52.
19. Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C. Lupus nephritis. Nat Rev Dis Primer 2020;6:7.
20. Vista ES, Weisman MH, Ishimori ML, Chen H, Bourn RL, Bruneret BF, et al. Strong viral associations with SLE among filipinos. Lupus Sci Med 2017;4:e000214.
21. Segal Y, Dahan S, Calabrò M, Kanduc D, Shoenfeld Y. HPV and systemic lupus erythematosus: a mosaic of potential cross reactions. Immunol Res 2017;65:564–71.
22. Hemauer A, Beckenlehner K, Wolf H, Lang B, Modrow S. Acute parvovirus B19 infection in connection with a flare of systemic lupus erythematodes in a female patient. J Clin Virol 1999;14:73–7.
23. Kazzi B, Fine D, Geetha D, Chung M, Trujillo MM, Timlin H. New-onset lupus nephritis associated with COVID-19 infection. Lupus 2022;31:1007–11.
24. Ramachandran L, Dontaraju VS, Troyer J, Sahota J. New onset systemic lupus erythematosus after COVID-19 infection: a case report. AME Case Rep 2022;6:14.
25. Gracia-Ramos AE, Saavedra-Salinas MÁ. Can the SARS-CoV-2 infection trigger systemic lupus erythematosus? A case-based review. Rheumatol Int 2021;41:799–809.
26. Cardoso EM, Hundal J, Feterman D, Magaldi J. Concomitant new diagnosis of systemic lupus erythematosus and COVID-19 with possible antiphospholipid syndrome. Just a coincidence? A case report and review of intertwining pathophysiology. Clin Rheumatol 2020;39:2811–5.
27. Zamani B, Moeini Taba SM, Shayestehpour M. Systemic lupus erythematosus manifestation following COVID-19: a case report. J Med Case Rep 2021;15:29.
28. Satorul K, Ibrahiml B, Dominickl S, Katherine X, Jonathan B, Yonatan P, et al. Kidney biopsy findings in patients with COVID-19. J Am Soc Nephrol 2020;31:1959–68.
29. 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;93:1184–7.

30. Hali F, Jabri H, Chiheb S, Hafiani Y, Nsiri A. A concomitant diagnosis of COVID-19 infection and systemic lupus erythematosus complicated by a macrophage activation syndrome: a new case report. Int J Dermatol 2021;60:1030–1.
31. Woodruff MC, Ramonell RP, Nguyen DC, Cashman KS, Saini AS, Haddad NS, et al. Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19. Nat Immunol 2020;21:1506–16.
32. Jenks SA, Cashman KS, Zumaquero E, Marigorta UM, Patel AV, Wang XQ, et al. Distinct effector B cells induced by unregulated toll-like receptor 7 contribute to pathogenic responses in systemic lupus erythematosus. Immunity 2018;49:725–39.e6.
33. Gao ZW, Wang X, Lin F, Dong K. The correlation between SARS-CoV-2 infection and rheumatic disease. Autoimmun Rev 2020;19:102557.
34. Hejazian SS, Hejazian SM, Farnood F, Azar SA. Dysregulation of immunity in COVID-19 and SLE. Inflammopharmacology 2022;30: 1517–31.
35. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. Type I interferons in infectious disease. Nat Rev Immunol 2015;15:87–103.
36. Rönnblom L. The type I interferon system in the etiopathogenesis of autoimmune diseases. Ups J Med Sci 2011;116:227–37.
37. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 2020;181:1036–45.e9.
38. Bastard P, Orlova E, Sozaeva L, Lévy R, James A, Schmittet MM, et al. Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. J Exp Med 2021;218:e20210554.
39. Lee JS, Shin EC. The type I interferon response in COVID-19: implications for treatment. Nat Rev Immunol 2020;20:585–6.
40. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren JJGM, et al. Myasthenia gravis. Nat Rev Dis Primer 2019;5:30.
41. Gilhus NE, Romi F, Hong Y, Skeie GO. Myasthenia gravis and infectious disease. J Neurol 2018;265:1251–8.
42. Huber M, Rogozinski S, Puppe W, Framme C, Höglinger G, Hufendiek K, et al. Postinfectious onset of myasthenia gravis in a COVID-19 patient. Front Neurol 2020;11:576153.
43. Álvarez ÁIP, Cuervo CS, Menéndez SF. Infección por SARS-CoV-2 asociada a diplopía y anticuerpos antirreceptor de acetilcolina. Neurologia 2020;35:264–5.
44. Assini A, Gandoglia I, Damato V, Rikani K, Evoli A, Sette MD. Myasthenia gravis associated with anti-MuSK antibodies developed after SARS-CoV-2 infection. Eur J Neurol 2021;28:3537–9.
45. Muhammed L, Baheerathan A, Cao M, Leite MI, Viegas S. MuSK antibody–associated myasthenia gravis with SARS-CoV-2 infection: a case report. Ann Intern Med 2021;174:872–3.
46. Reddy YM, Osman S, Murthy JMK. Temporal association between SARS-CoV-2 and new-onset myasthenia gravis: is it causal or coincidental? BMJ Case Rep 2021;14:e244146.
47. Sriwastava S, Tandon M, Kataria S, Daimee M, Sultan S. New onset of ocular myasthenia gravis in a patient with COVID-19: a novel case report and literature review. J Neurol 2021;268:2690–6.
48. Karimi N, Okhovat AA, Ziaadini B, Ashtiani BH, Nafissi S, Fatehi F. Myasthenia gravis associated with novel coronavirus 2019 infection: a report of three cases. Clin Neurol Neurosurg 2021;208:106834.
49. Bhandarwar A, Jadhav S, Tandur A, Dhimole N, Wagh A, Bhondve S. Management of thymomatous myasthenia gravis – case report of a rare Covid19 infection sequelae. Int J Surg Case Rep 2021;81:105771.
50. Jõgi K, Sabre L, Rosental M, Leheste AR, Vilisaar J. New onset generalized myasthenia gravis evolving following SARS-CoV-2 infection. COVID 2022;2:464–71.
51. Taheri A, Davoodi L, Soleymani E, Ahmadi N. New-onset myasthenia gravis after novel coronavirus 2019 infection. Respirol Case Rep 2022; 10:e0978.
52. Tereshko Y, Gigli GL, Pez S, Pellegrin AD, Valente M. New-onset Myasthenia Gravis after SARS-CoV-2 infection: case report and literature review. J Neurol 2023;270:601–9.
53. Rodrigues CL, de Freitas HC, Lima PRO, de Oliveira Junior PH, Fernandes JMA, D'Almeida JAC, et al. Myasthenia gravis exacerbation and myasthenic crisis associated with COVID-19: case series and literature review. Neurol Sci 2022;43:2271–6.
54. Essajee F, Lishman J, Solomons R, Abraham DR, Goussard P, Toorn RV. Transient acetylcholine receptor-related myasthenia gravis, post multisystem inflammatory syndrome in children (MIS-C) temporally associated with COVID-19 infection. BMJ Case Rep 2021;14:e244102.
55. Galassi G, Marchioni A. Myasthenia gravis at the crossroad of COVID-19: focus on immunological and respiratory interplay. Acta Neurol Belg 2021;121:633–42.
56. Shah SMI, Yasmin F, Memon RS, Jatoi NN, Savul IS, Kazmi S, et al. COVID-19 and myasthenia gravis: a review of neurological implications of the SARS-COV-2. Brain Behav 2022;12:e2789.
57. Berrih-Aknin S. Role of the thymus in autoimmune myasthenia gravis. Clin Exp Neuroimmunol 2016;7:226–37.
58. Cuvelier P, Roux H, Couëdel-Courteille A, Dutrieux J, Naudin C, de Muylder BC, et al. Protective reactive thymus hyperplasia in COVID-19 acute respiratory distress syndrome. Crit Care 2021;25:4.
59. Hong CW, Luckey MA, Park JH. Intrathymic IL-7: the where, when, and why of IL-7 signaling during T cell development. Semin Immunol 2012; 24:151–8.
60. Solé G, Salort-Campana E, Pereon Y, Stojkovic T, Wahbi K, Cintas P, et al. Guidance for the care of neuromuscular patients during the COVID-19 pandemic outbreak from the French rare health care for neuromuscular diseases network. Rev Neurol 2020;176:507–15.
61. Varan O, Kucuk H, Tufan A. Myasthenia gravis due to hydroxychloroquine. Reumatismo 2016;67:125.
62. Davies TF, Andersen S, Latif R, Nagayama Y, Barbesino G, Brito M, et al. Graves' disease. Nat Rev Dis Primer 2020;6:52.
63. Lanzolla G, Marcocci C, Marinò M. Graves' disease and Graves' orbitopathy following COVID-19. J Endocrinol Invest 2021;44:2011–2.
64. Mateu-Salat M, Urgell E, Chico A. SARS-COV-2 as a trigger for autoimmune disease: report of two cases of Graves' disease after COVID-19. J Endocrinol Invest 2020;43:1527–8.
65. Feghali K, Atallah J, Norman C. Manifestations of thyroid disease post COVID-19 illness: report of Hashimoto thyroiditis, Graves' disease, and subacute thyroiditis. J Clin Transl Endocrinol Case Rep 2021;22:100094.
66. Edwards K, Hussain I. Two cases of severe autoimmune thyrotoxicosis following SARS-CoV-2 infection. J Investig Med High Impact Case Rep 2021;9:23247096211056497. https://doi.org/10.1177/23247096211056497.
67. Rockett J, Nelson C, Pierce R, Morlan AV. A case report of Graves' disease following SARS-CoV-2 infection. Int J Contemp Pediatr 2021;8: 1260–3.
68. Nham E, Song E, Hyun H, Seong H, Yoon JG, Noh JY, et al. Concurrent subacute thyroiditis and Graves' disease after COVID-19: a case report. J Korean Med Sci 2023;38:e134.
69. França ÂS, Pinto SM, Vieira DC, Silva MT, Pinho PL. Graves disease: a new association with COVID-19? Semergen 2023;49:101834.
70. Boyle DC, Mullally JA. Thyrotoxicosis after COVID-19 infection with a delay in Graves' disease antibody positivity. Case Rep Endocrinol 2023;2023:8402725.

71. Bayar I, Tahri S, Hajji E, Amor BB, Sayadi H, Marmouch H, et al. A case of Grave's disease following SARS-Cov 2 infection. Endocr Abstr 2021; 73:AEP657.
72. Ghareebian H, Mariash C. COVID-19-Induced Graves' disease. Cureus 2022;14:e22260.
73. Urbanovych A, Laniush F, Borovets M, Kozlovska K. Coronavirus as a trigger of Graves' disease. Acta Endocrinol Buchar 2021;17:413–5.
74. Sousa B, Santos CP, Ferreira AG, Judas T. Graves' disease caused by SARS-CoV-2 infection. Eur J Case Rep Intern Med 2022;9:003470.
75. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 2020;9:45.
76. Duntas LH, Jonklaas J. COVID-19 and thyroid diseases: a bidirectional impact. J Endocr Soc 2021;5:bvab076.
77. Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G. Thyrotoxicosis in patients with COVID-19: the THYRCOV study. Eur J Endocrinol 2020;183:381–7.
78. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Mur I, Mateo GM, Gutierrez MM, Pomar V, de Benito N, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. JAMA 2021;326:499–518.
79. Berentsen S, Barcellini W. Autoimmune hemolytic anemias. N Engl J Med 2021;385:1407–19.
80. Lazarian G, Quinquenel A, Bellal M, Siavellis J, Jacquy C, Re D, et al. Autoimmune haemolytic anaemia associated with COVID-19 infection. Br J Haematol 2020;190:29–31.
81. Campos-Cabrera G, Mendez-Garcia E, Mora-Torres M, Campos-Cabrera S, Campos-Cabrera V, Garcia-Rubio G, et al. Autoimmune hemolytic anemia as initial presentation of COVID-19 infection. Blood 2020;136:8.
82. Capes A, Bailly S, Hantson P, Gerard L, Laterre PF. COVID-19 infection associated with autoimmune hemolytic anemia. Ann Hematol 2020; 99:1679–80.
83. Hindilerden F, Yonal-Hindilerden I, Akar E, Yesilbag Z, Kart-Yasar K. Severe autoimmune hemolytic anemia in COVID-19 infection, safely treated with steroids. Mediterr J Hematol Infect Dis 2020;12: e2020053.
84. Hsieh TC, Sostin O. Severe warm autoimmune hemolytic anemia in COVID-19 managed with least incompatible RBC product and glucocorticoids. Ann Hematol 2022;101:431–2.
85. Huda Z, Jahangir A, Sahra S, Niazi MRK, Anwar S, Glaser A, et al. A case of COVID-19-associated autoimmune hemolytic anemia with hyperferritinemia in an immunocompetent host. Cureus 2021;13: e16078.
86. Jacobs J, Eichbaum Q. COVID-19 associated with severe autoimmune hemolytic anemia. Transfusion 2021;61:635–40.
87. Jawed M, Hart E, Saeed M. Haemolytic anaemia: a consequence of COVID-19. BMJ Case Rep 2020;13:e238118.
88. Li M, Nguyen CB, Yeung Z, Sanchez K, Rosen D, Bushan S. Evans syndrome in a patient with COVID-19. Br J Haematol 2020;190:e59–61.
89. Liput JR, Jordan K, Patadia R, Kander E. Warm autoimmune hemolytic anemia associated with asymptomatic SARS-CoV-2 infection. Cureus 2021;13:e14101.
90. Lopez C, Kim J, Pandey A, Huang T, DeLoughery TG. Simultaneous onset of COVID-19 and autoimmune haemolytic anaemia. Br J Haematol 2020;190:31–2.
91. Patil NR, Herc ES, Girgis M. Cold agglutinin disease and autoimmune hemolytic anemia with pulmonary embolism as a presentation of COVID-19 infection. Hematol Oncol Stem Cell Ther 2022;15:8.
92. Ramos-Ruperto L, García-Pérez E, Hernández-Maraver D, Kerguelén-Fuentes A, Viejo-Llorente A, Robles-Marhuenda Á, et al. A 3-case series of autoimmune haemolytic anaemia and COVID-19: is plasma exchange an alternative? SN Compr Clin Med 2021;3:1420–3.
93. Zagorski E, Pawar T, Rahimian S, Forman D. Cold agglutinin autoimmune haemolytic anaemia associated with novel coronavirus (COVID-19). Br J Haematol 2020;190:e183–4.
94. Lakshmi JN, Aravind R. COVID-19-Associated severe autoimmune hemolytic anemia: a rare case report. Saudi J Med Med Sci 2021;9: 276–9.
95. Moonla C, Watanaboonyongcharoen P, Suwanpimolkul G, Paitoonpong L, Jantarabenjakul W, Chanswangphuwana C, et al. Cold agglutinin disease following SARS-CoV-2 and Mycoplasma pneumoniae co-infections. Clin Case Rep 2020;8:2402–5.
96. Maslov DV, Simenson V, Jain S, Badari A. COVID-19 and cold agglutinin hemolytic anemia. TH Open 2020;04:e175–7.
97. Kaur J, Mogulla S, Khan R, Krishnamoorthy G, Garg S. Transient cold agglutinins in a patient with COVID-19. Cureus 2021;13:e12751.
98. Jensen CE, Wilson S, Thombare A, Weiss S, Ma A. Cold agglutinin syndrome as a complication of Covid-19 in two cases. Clin Infect Pract 2020;7–8:100041.
99. Huscenot T, Galland J, Ouvrat M, Rossignol M, Mouly S, Sène D. SARS-CoV-2-associated cold agglutinin disease: a report of two cases. Ann Hematol 2020;99:1943–4.
100. Aldaghlawi F, Shammah A, Kio E. SARS-CoV-2 infection complicated with cold agglutinin disease and myositis. Clin Case Rep 2021;9: 2196–9.
101. Nesr G, Koshy R, Foldes D, Kagdi H. Autoimmune haemolytic anaemia and a marked rise in the lymphocyte count associated with COVID-19 in a patient with treatment-naïve chronic lymphocytic leukaemia: a case report. Br J Haematol 2020;190:e326–8.
102. Sujana IPS, Widiasari NPA, Arisanti NLPE, Rai IBN, Rena NMRA. Autoimmune hemolytic anemia as a novel complication of COVID-19 infection in Sanglah General Hospital Bali, Indonesia. Open Access Maced J Med Sci 2020;8:509–13.
103. Raghuwanshi B. Serological blood group discrepancy and cold agglutinin autoimmune hemolytic anemia associated with novel coronavirus. Cureus 2020;12:e11495.
104. Pelle MC, Tassone B, Ricchio M, Mazzitelli M, Davoli C, Procopio G, et al. Late-onset myocardial infarction and autoimmune haemolytic anaemia in a COVID-19 patient without respiratory symptoms, concomitant with a paradoxical increase in inflammatory markers: a case report. J Med Case Rep 2020;14:246.
105. Mausoleo A, Henriquez S, Goujard C, Roque-Afonso AM, Noel N, Lambotte O. Severe IgA-mediated autoimmune hemolytic anemia triggered by SARS-CoV-2 infection. Leuk Lymphom 2021;62: 2037–9.
106. Khalifeh HK, Mourad YM, Chamoun CT. Infantile cytomegalovirus-associated severe warm autoimmune hemolytic anemia: a case report. Children 2017;4:94.
107. Jandale OA, Jumah H, Jamil H. Hepatitis A virus infection is complicated by both pancytopenia and autoimmune hemolytic anemia (AIHA). Ann Med Surg 2022;78:103765.
108. Angileri F, Légaré S, Gammazza AM, de Macario EC, Macario AJL, Cappello F. Is molecular mimicry the culprit in the autoimmune haemolytic anaemia affecting patients with COVID-19? Br J Haematol 2020;190:e92–3.
109. Liu W, Li H. COVID-19: attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv 2021.

110. Lam LKM, Reilly JP, Rux AH, Murphy SJ, Kuri-Cervantes L, Weisman AR, et al. Erythrocytes identify complement activation in patients with COVID-19. Am J Physiol Lung Cell Mol Physiol 2021;321:L485–9.
111. Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, et al. Multiple sclerosis. Nat Rev Dis Primers 2018;4:43.
112. Palao M, Fernandez-Díaz E, Gracia-Gil J, Romero-Sánchez CM, Díaz-Maroto I, Segura T. Multiple sclerosis following SARS-CoV-2 infection. Mult Scler Relat Disord 2020;45:102377.
113. Fragoso YD, Pacheco FAS, Silveira GL, Oliveira RA, Carvalho VM, Martimbianco ALC. COVID-19 in a temporal relation to the onset of multiple sclerosis. Mult Scler Relat Disord 2021;50:102863.
114. Karsidag S, Sahin S, Ates MF, Cinar N, Kendirli S. Demyelinating disease of the central nervous system concurrent with COVID-19. Cureus 2021;13:e17297.
115. Florea AA, Sirbu CA, Ghinescu MC, Plesa CF, Sirbu AM, Mitrica M, et al. SARS-CoV-2, multiple sclerosis, and focal deficit in a postpartum woman: a case report. Exp Ther Med 2021;21:92.
116. Aghajanian S, Shafiee A, Akhondi A, Abadi SRF, Mohammadi I, Ehsan M, et al. The effect of COVID-19 on multiple sclerosis relapse: a systematic review and meta-analysis. Mult Scler Relat Disord 2024;81:105128.
117. Houtman JJ, Fleming JO. Pathogenesis of mouse hepatitis virus-induced demyelination. J Neurovirol 1996;2:361–76.
118. Cheng Q, Yang Y, Gao J. Infectivity of human coronavirus in the brain. EBioMedicine 2020;56:102799.
119. Savarin C, Bergmann CC. Viral-induced suppression of self-reactive T cells: lessons from neurotropic coronavirus-induced demyelination. J Neuroimmunol 2017;308:12–6.
120. Baimukhamedov C, Barskova T, Matucci-Cerinic M. Arthritis after SARS-CoV-2 infection. Lancet Rheumatol 2021;3:e324–5.
121. Dominguez-Santas M, Diaz-Guimaraens B, Abellas PG, del Real CMG, Burgos-Blasco P, Suarez-Valle A. Cutaneous small-vessel vasculitis associated with novel 2019 coronavirus SARS-CoV-2 infection (COVID-19). J Eur Acad Dermatol Venereol 2020;34:e536–7.
122. Anindya R, Rutter GA, Meur G. New-onset type 1 diabetes and severe acute respiratory syndrome coronavirus 2 infection. Immunol Cell Biol 2023;101:191–203.
123. Fernandes M, Nwachukwu I. GUILLAIN-BARRÉ syndrome and hemolysis in COVID-19. Chest 2021;160:A443.
124. Gusev E, Sarapultsev A, Solomatina L, Chereshnev V. SARS-CoV-2-Specific immune response and the pathogenesis of COVID-19. Int J Mol Sci 2022;23:1716.
125. Kanduc D, Shoenfeld Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. Immunol Res 2020;68:310–3.
126. Tough DF, Borrow P, Sprent J. Induction of bystander T cell proliferation by viruses and type I interferon *in vivo*. Science 1996;272:1947–50.
127. Cornaby C, Gibbons L, Mayhew V, Sloan CS, Welling A, Poole BD. B cell epitope spreading: mechanisms and contribution to autoimmune diseases. Immunol Lett 2015;163:56–68.
128. Dörner T, Gieseck C, Lipsk PE. Mechanisms of B cell autoimmunity in SLE. Arthritis Res Ther 2011;13:243.
129. Guo M, Liu X, Chen X, li Q. Insights into new-onset autoimmune diseases after COVID-19 vaccination. Autoimmun Rev 2023;22:103340.
130. Jin Y, Ji W, Yang H, Chen S, Zhang W, Duan G. Endothelial activation and dysfunction in COVID-19: from basic mechanisms to potential therapeutic approaches. Signal Transduct Target Ther 2020;5:293.
131. Xu SW, Ilyas I, Weng J. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. Acta Pharmacol Sin 2023;44:695–709.
132. Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, et al. COVID-19: immunopathogenesis and immunotherapeutics. Signal Transduct Target Ther 2020;5:128.
133. WHO. Post COVID-19 condition (long COVID). Available from: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition (Accessed August 24, 2023).
134. CDC. Post-COVID conditions; 2023. Available from: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html (Accessed 24 August 2023).
135. Estefanía E, Yang CL, Shannon CP, Assadian S, He D, Tebbutt SJ. Cellular and molecular biomarkers of long COVID: a scoping review. EBioMedicine 2023;91:104552.
136. Yong SJ, Halim A, Halim M, Liu SL, Aljeldah M, Shammari BRA, et al. Inflammatory and vascular biomarkers in post-COVID-19 syndrome: a systematic review and meta-analysis of over 20 biomarkers. Rev Med Virol 2023;33:e2424.
137. Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, Hare SS, et al. Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax 2021;76:396–8.
138. Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. Cell 2022;185:881–95.
139. Mulet A, Tarrasó J, Rodríguez-Borja E, Carbonell-Asins JA, Lope-Martínez A, Martí-Martinez A, et al. Biomarkers of fibrosis in patients with COVID-19 one year after hospital discharge: a prospective cohort study. Am J Respir Cell Mol Biol 2023;69:321–7.
140. Cheung CCL, Goh D, Lim X, Tien TZ, Lim JCT, Lee JN, et al. Residual SARS-CoV-2 viral antigens detected in GI and hepatic tissues from five recovered patients with COVID-19. Gut 2022;71:226–9.
141. Marx V. Scientists set out to connect the dots on long COVID. Nat Methods 2021;18:449–53.
142. Leppkes M, Neurath MF. Rear window—What can the gut tell us about long-COVID? Gastroenterology 2022;163:376–8.
143. Xing YH, Ni W, Wu Q, Li WJ, Li GJ, Wang WD, et al. Prolonged viral shedding in feces of pediatric patients with coronavirus disease 2019. J Microbiol Immunol Infect 2020;53:473–80.
144. Natarajan A, Zlitni S, Brooks EF, Vance SE, Dahlen A, Hedlin H, et al. Gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA suggest prolonged gastrointestinal infection. Med 2022;3:371–87.e9.
145. Zollner A, Koch R, Jukic A, Pfister A, Meyer M, Rössler A, et al. Postacute COVID-19 is characterized by gut viral antigen persistence in inflammatory bowel diseases. Gastroenterology 2022;163:495–506.e8.
146. Stein SR, Ramelli SC, Grazioli A, Chung JY, Singh M, Yinda CK, et al. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. Nature 2022;612:758–63.
147. Kresch E, Achua J, Saltzman R, Khodamoradi K, Arora H, Ibrahim E, et al. COVID-19 endothelial dysfunction can cause erectile dysfunction: histopathological, immunohistochemical, and ultrastructural study of the human penis. World J Mens Health 2021;39:466–9.
148. Kalkeri R, Goebel S, Sharma GD. SARS-CoV-2 shedding from asymptomatic patients: contribution of potential extrapulmonary tissue reservoirs. Am J Trop Med Hyg 2020;103:18–21.

149. Swank Z, Senussi Y, Manickas-Hill Z, Yu XG, Li JZ, Alter G, et al. Persistent circulating severe acute respiratory syndrome coronavirus 2 spike is associated with post-acute coronavirus disease 2019 sequelae. Clin Infect Dis 2023;76:487–90.
150. Desimmie BA, Raru YY, Awadh HM, He P, Teka S, Willenburg KS. Insights into SARS-CoV-2 persistence and its relevance. Viruse 2021;13: 1025.
151. Drago F, Ciccarese G, Rebora A, Parodi A. Human herpesvirus-6, -7, and Epstein-Barr virus reactivation in pityriasis rosea during COVID-19. J Med Virol 2021;93:1850–1.
152. Simonnet A, Engelmann I, Moreau AS, Garcia B, Six S, Kalioubie AE, et al. High incidence of Epstein–Barr virus, cytomegalovirus, and human-herpes virus-6 reactivations in critically ill patients with COVID-19. Infect Dis Now 2021;51:296–9.
153. Lehner GF, Klein SJ, Zoller H, Peer A, Bellmann R, Joannidis M. Correlation of interleukin-6 with Epstein–Barr virus levels in COVID-19. Crit Care 2020;24:657.
154. Peluso MJ, Deveau TM, Munter SE, Ryder D, Buck A, Beck-Engeser G, et al. Chronic viral coinfections differentially affect the likelihood of developing long COVID. J Clin Invest 2023;133:e163669.
155. Zubchenko S, Kril I, Nadizhko O, Matsyura O, Chopyak V. Herpesvirus infections and post-COVID-19 manifestations: a pilot observational study. Rheumatol Int 2022;42:1523–30.
156. Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of long COVID prevalence and its relationship to Epstein-Barr virus reactivation. Pathogens 2021;10:763.
157. Chen B, Julg B, Mohandas S, Bradfute SB, RECOVER Mechanistic Pathways Task Force. Viral persistence, reactivation, and mechanisms of long COVID. Elife 2023;12:e86015.
158. Vojdani A, Vojdani E, Saidara E, Maes M. Persistent SARS-CoV-2 infection, EBV, HHV-6 and other factors may contribute to inflammation and autoimmunity in long COVID. Viruses 2023;15:400.
159. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science 2020;370:eabd4585.
160. Wallukat G, Hohberger B, Wenzel K, Fürst J, Schulze-Rothe S, Wallukat A, et al. Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. J Transl Autoimmun 2021;4:100100.
161. Shoenfeld Y, Ryabkova VA, Scheibenbogen C, Brinth L, Martinez-Lavin M, Ikeda S, et al. Complex syndromes of chronic pain, fatigue and cognitive impairment linked to autoimmune dysautonomia and small fiber neuropathy. Clin Immunol 2020;214:108384.
162. Hohberger B, Harrer T, Mardin C, Kruse F, Hoffmanns J, Rogge L, et al. Case report: neutralization of autoantibodies targeting G-protein-coupled receptors improves capillary impairment and fatigue symptoms after COVID-19 infection. Front Med 2021;8:754667.
163. Szewczykowski C, Mardin C, Lucio M, Wallukat G, Hoffmanns J, Schröder T, et al. Long COVID: association of functional autoantibodies against G-protein-coupled receptors with an impaired retinal microcirculation. Int J Mol Sci 2022;23:7209.
164. Düngen HD, Dordevic A, Felix SB, Pieske B, Voors AA, McMurray JJV, et al. β 1-adrenoreceptor autoantibodies in heart failure: physiology and therapeutic implications. Circ Heart Fail 2020;13:E006155.
165. Lingel H, Meltendorf S, Billing U, Thurm C, Vogel K, Majer C, et al. Unique autoantibody prevalence in long-term recovered SARS-CoV-2-infected individuals. J Autoimmun 2021;122:102682.
166. Lee ECY, Tyler RE, Johnson D, Koh N, Ong BC, Foo SY, et al. High frequency of anti-DSG 2 antibodies in post COVID-19 serum samples. J Mol Cell Cardiol 2022;170:121–3.
167. Mangalmurti N, Hunter CA. Cytokine storms: understanding COVID-19. Immunity 2020;53:19–25.
168. Acosta-Ampudia Y, Monsalve DM, Rojas M, Rodríguez Y, Zapata E, Ramírez-Santana C, et al. Persistent autoimmune activation and proinflammatory state in post-COVID syndrome. J Infect Dis 2022;225: 2155–62.
169. Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol 2022;23:210–6.
170. Rodriguez L, Tan ZY, Lakshmikanth T, Wang J, Barcenilla H, Gonzalez L, et al. Immune system perturbations in patients with severe long COVID. J Immunol 2023;210:233.07.
171. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol 2021;93:250–6.
172. Sin DD. Is long COVID an autoimmune disease? Eur Respir J 2023;61: 2202272.
173. Espín E, Yang CL, Shannon CP, Assadian S, He D, Tebbutt SJ. Cellular and molecular biomarkers of long COVID: a scoping review. EBioMedicine 2023;91:104552.
174. Fogarty H, Townsend L, Morrin H, Ahmad A, Comerford C, Karampini E, et al. Persistent endotheliopathy in the pathogenesis of long COVID syndrome. J Thromb Haemost 2021;19:2546–53.
175. Townsend L, Fogarty H, Dyer A, Martin-Loeches I, Bannan C, Nadarajan P, et al. Prolonged elevation of D-dimer levels in convalescent COVID-19 patients is independent of the acute phase response. J Thromb Haemost 2021;19:1064–70.
176. Fan BE, Wong SW, Sum CLL, Lim GH, Leung BP, Tan CW, et al. Hypercoagulability, endotheliopathy, and inflammation approximating 1 year after recovery: assessing the long-term outcomes in COVID-19 patients. Am J Hematol 2022;97:915–23.
177. Jing HJ, Wu XM, Xiang MQ, Liu LJ, Liu VA, Shi JL. Pathophysiological mechanisms of thrombosis in acute and long COVID-19. Front Immunol 2022;13:992384.
178. Wechsler JB, Butuci M, Wong A, Kamboj AP, Youngblood BA. Mast cell activation is associated with post-acute COVID-19 syndrome. Allergy 2022;77:1288–91.
179. Theoharides TC. COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. Biofactors 2020;46:306–8.
180. Kempuraj D, Selvakumar GP, Ahmed ME, Raikwar SP, Thangavel R, Khan A, et al. COVID-19, mast cells, cytokine storm, psychological stress, and neuroinflammation. Neuroscientist 2020;26:402–14.
181. Arun S, Storan A, Myers B. Mast cell activation syndrome and the link with long COVID. Br J Hosp Med 2022;83:1–10.
182. Weinstock LB, Brook JB, Walters AS, Goris A, Afrin LB, Molderings GJ. Mast cell activation symptoms are prevalent in long-COVID. Int J Infect Dis 2021;112:217–26.
183. Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis 2020;100:327–32.
184. Liu Q, Su Q, Zhang F, Tun HM, Mak JWY, Lui GCY, et al. Multi-kingdom gut microbiota analyses define COVID-19 severity and post-acute COVID-19 syndrome. Nat Commun 2022;13:6806.
185. Alharbi KS, Singh Y, Almalki WH, Rawat S, Afzal O, Altamimi ASA, et al. Gut microbiota disruption in COVID-19 or post-COVID illness association with severity biomarkers: a possible role of pre/pro-biotics in manipulating microflora. Chem Biol Interact 2022;358:109898.
186. Liu Q, Mak JWY, Su Q, Yeoh YK, Lui GCY, Ng SSS, et al. Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. Gut 2022;71:544–52.

187. Hashimoto K. Detrimental effects of COVID-19 in the brain and therapeutic options for long COVID: the role of Epstein–Barr virus and the gut–brain axis. Mol Psychiatry 2023;28:4968–76.
188. Hirota K, Turner JE, Villa M, Duarte JH, Demengeot J, Steinmetz OM, et al. Plasticity of TH17 cells in Peyer's patches is responsible for the induction of T cell–dependent IgA responses. Nat Immunol 2013;14: 372–9.
189. Peterson DA, McNulty NP, Guruge JL, Gordon JI. IgA response to symbiotic bacteria as a mediator of gut homeostasis. Cell Host Microbe 2007;2:328–39.
190. Moreira-Rosário A, Marques C, Pinheiro H, Araújo JR, Ribeiro P, Rocha R, et al. Gut microbiota diversity and C-reactive protein are predictors of disease severity in COVID-19 patients. Front Microbiol 2021;12:705020.
191. Kell DB, Laubscher GJ, Pretorius E. A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications. Biochem J 2022;479:537–59.
192. Pretorius E, Vlok M, Venter C, Bezuidenhout JA, Laubscher GJ, Steenkamp J, et al. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. Cardiovasc Diabetol 2021;20: 172.
193. Kruger A, Vlok M, Turner S, Venter C, Laubscher GJ, Kell DB, et al. Proteomics of fibrin amyloid microclots in long COVID/post-acute sequelae of COVID-19 (PASC) shows many entrapped pro-inflammatory molecules that may also contribute to a failed fibrinolytic system. Cardiovasc Diabetol 2022;21:190.
194. Majolo F, Silva GL, Vieira L, Anli C, Timmers LFSM, Laufer S, et al. Neuropsychiatric disorders and COVID-19: what we know so far. Pharmaceuticals 2021;14:933.
195. Xu E, Xie Y, Al-Aly Z. Long-term neurologic outcomes of COVID-19. Nat Med 2022;28:2406–15.
196. Oaklander AL, Mills AJ, Kelley M, Toran LS, Smith B, Dalakas MC, et al. Peripheral neuropathy evaluations of patients with prolonged long COVID. Neurol-Neuroimmunol Neuroinflammation 2022;9: e1146.
197. Fernández-Castañeda A, Lu P, Geraghty AC, Song E, Lee MH, Wood J, et al. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. Cell 2022;185:2452–68.
198. Spudich S, Nath A. Nervous system consequences of COVID-19. Science 2022;375:267–9.
199. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–8.
200. Song WC, FitzGerald GA. COVID-19, microangiopathy, hemostatic activation, and complement. J Clin Invest 2020;130:3950–3.
201. Baig AM. Chronic long-COVID syndrome: a protracted COVID-19 illness with neurological dysfunctions. CNS Neurosci Ther 2021;27:1433–6.
202. Turner S, Khan MA, Putrino D, Woodcock A, Kell DB, Pretorius E. Long COVID: pathophysiological factors and abnormalities of coagulation. Trends Endocrinol Metab 2023;34:321–44.
203. Altmann DM, Whettlock EM, Liu S, Arachchillage DJ, Boyton RJ. The immunology of long COVID. Nat Rev Immunol 2023;23:618–34.
204. Moss JI. Long haul COVID 19 is the result of B lymphocyte anergy reversal. Mod Appl Pharm Pharmacol 2023;3:MAPP.000554.
205. Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): similarities and differences. Pathol Res Pract 2023;246:154497.
206. Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, et al. Trajectory of long Covid symptoms after Covid-19 vaccination: community based cohort study. BMJ 2022;377:e069676.
207. Venkatesan P. Do vaccines protect from long COVID? Lancet Respir Med 2022;10:e30.

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