

COVID-19, Epstein-Barr virus reactivation and autoimmunity: Casual or causal liaisons?

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ARTICLE INFO

Keywords:

Epstein-Barr virus
COVID-19
Inflammation
Long COVID
Autoimmunity

ABSTRACT

The coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 virus infection, has been associated with a substantial risk of autoimmune disease development or exacerbation. The postulated pathophysiological mechanisms linking COVID-19 with autoimmunity include reactivation of latent Epstein-Barr virus (EBV), whose dysregulated infection in the host can trigger or promote an autoimmune response.

This review summarizes recent studies highlighting a potential immunopathogenetic link between SARS-CoV-2 infection and EBV reactivation, which could underlie autoimmunity onset or worsening, as well as immune-related long COVID manifestations in COVID-19 patients. We offer our perspective on the direction that research should take to disentangle the nature (whether causal or casual) of the “COVID-19-EBV-autoimmunity” liaisons. Further advances in this research area may be crucial for designing strategies to prevent or treat EBV reactivation-related autoimmune conditions in COVID-19 patients, or patients with inflammatory co-infectious diseases, at the same time promising to improve our knowledge on the viral contribution to autoimmune phenomena.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by infection with the SARS-CoV-2 virus, has generated an escalating burden on society and health systems worldwide, due to both severity of symptoms in the acute infection phase, which primarily involves the respiratory system, but also to serious long-term complications known as long COVID, whose symptoms can affect multiple organs, including the nervous system.¹

Considerable data support the role of SARS-CoV-2 as both risk factor for the development of autoimmune disorders and disease exacerbating factor in patients affected by these conditions.^{2–4} This is likely due to the massive inflammatory immune response and immune system dysregulation induced by the virus in the host, as well as to the activation of immune responses triggered by latent viruses reactivated by SARS-CoV-2 during the acute phase of infection, such as Epstein-Barr virus (EBV).^{5,6} Growing evidence indicates that EBV can be reactivated after SARS-CoV-2 infection,⁵ thus explaining the link between COVID-19 and autoimmunity, in light of the association of EBV with autoimmune diseases.⁷

EBV is a human B-lymphotropic herpesvirus widely implicated in B

cell-mediated autoimmune conditions, as shown by serological, epidemiological, immunological, and histopathological studies, such as multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and myasthenia gravis (MG).^{7–10} In MS, EBV has been demonstrated to be the causative agent, necessary, although not sufficient, for the development of the disease.⁹ The exact EBV-induced mechanisms leading to autoimmunity development have not definitively and unequivocally understood. The strongest and most plausible hypothesis is that EBV can contribute to autoimmune initiation and perpetuation by its ability to disrupt B cell regulatory checkpoints and induce transformation of B cells that can lead to clonal expansion of pathogenic autoimmune plasma cells.^{7,8,11,12} A key step linking EBV with the pathophysiology of autoimmune conditions is EBV reactivation that may occur spontaneously or following acute or chronic stress, or triggered by other viruses.¹³ Disruption of the EBV-host balance, and reactivation of EBV, can favor inflammatory autoimmune responses or B-cell malignancies in susceptible individuals.^{8,11}

This review summarizes recent data highlighting the contribution of COVID-19 to autoimmune diseases and EBV reactivation, and the role of SARS-CoV-2-reactivated EBV in autoimmunity development or exacerbation, and immune-related long COVID manifestations. Better

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understanding of the biological relationship between SARS-CoV-2 and EBV could increase our knowledge of the viral contribution to autoimmune phenomena and promote the development of preventive and therapeutic strategies for SARS-CoV-2 infection to avoid or reduce the risk of autoimmunity and long COVID symptoms, by targeting EBV or key factors involved in EBV reactivation.

1.1. COVID-19 and autoimmune diseases

During the pandemic, it has become clear that different post-infectious complications can arise from COVID-19, including neurological and non-neurological autoimmune diseases.^{2–4,14} Numerous case reports, small series and systematic reviews have reported a high incidence of de novo autoimmunity in COVID-19 patients (Table 1).^{2–4,15,16} Moreover, among individuals with preexisting autoimmune conditions, SARS-CoV-2 infection has been reported to increase the risk of developing another autoimmune disease or to cause exacerbation of symptoms (Table 1).^{3,4} Conversely, autoimmune conditions seem to be a predisposing factor to severe SARS-CoV-2 infection, although this subject remains controversial.^{17,18}

1.1.1. COVID-19 and neurological autoimmune diseases

Evidence of a relationship between COVID-19 and the prototypical autoimmune disease myasthenia gravis (MG), which affects neuromuscular junction, has been sought (Table 1), demonstrating that some cases of new-onset MG (i.e., 18 cases in 14 publications between December 01, 2019 and June 30, 2023) occurred following SARS-CoV-2 infection, likely because of over-activation of the immune system.¹⁹ The median time interval between infection and the clinical onset of MG was 17 days, and all patients improved following symptomatic and conventional immunosuppressive treatment.¹⁹ Moreover, a systematic review revealed that SARS-CoV-2 infection can increase the risk of myasthenic crisis, respiratory failure and mortality of MG patients due to the cytokine storm.²⁰ In line with this observation, a recent study analyzed a cohort of 289 MG patients and showed that patients (80.9 %) who experienced SARS-CoV-2 infection had a higher likelihood of disease exacerbation compared to those without the infection (hazard ratio, HR: 3.38; 95 % CI 1.20–9.53, $p = 0.021$), indicating COVID-19 as a risk factor for MG crisis.²¹ Post-COVID-19 myasthenic exacerbation was reported in another retrospective study including 287 MG patients, with an infection rate of 84.7 %, also showing that patients exhibiting severe COVID-19 experienced disease exacerbation earlier than patients with non-severe infection.²² In another retrospective cohort study, generalized MG at onset, comorbidities, older age at onset and incomplete control of MG symptoms predicted the occurrence of poor outcomes in MG patients after SARS-CoV-2 infection.²³

Similarly, worsening of symptoms and neurological outcomes due to COVID-19 was widely described in MS patients (Table 1), and the severity of COVID-19 correlated with MS clinical disability.^{24,25} A recent umbrella review, systematically collecting and analyzing multiple meta-analyses, evaluated the association between MS and 12 viruses, including SARS-CoV-2, EBV, hepatitis B virus (HBV), varicella zoster virus (VZV), Human Herpesvirus (HHV)-6, HHV-7, HHV-8, Herpes Simplex virus (HSV)-1, HSV-2, cytomegalovirus (CMV), Human Papillomavirus (HPV) and influenza, reporting that SARS-CoV-2 has a significantly more potent negative effect, with an odds ratio of 3.74 ($p < 0.001$), on MS among the tested viral infections, followed by EBV (3.33 odds ratio, $p < 0.05$).²⁶ Nevertheless, a retrospective study comparing the risk of relapse in relapsing-remitting MS (RRMS) patients in the six months following COVID-19 contraction, showed a similar incidence of RRMS exacerbation in patients with and without COVID-19, and in the same COVID-19-experienced patients six months prior to the pandemic, suggesting that the infection may not increase the relapse risk shortly after virus contraction, possibly due to COVID-19-associated lymphopenia, which precludes autoreactive memory cells from expansion.²⁷

Neuromyelitis optica spectrum disorders, acute disseminated

encephalomyelitis, myelitis, and myelin oligodendrocyte glycoprotein antibody-associated disease are additional autoimmune disorders of the central nervous system described as post and para-infectious complications of COVID-19 (Table 1).²⁸ Some studies have also highlighted an association between COVID-19 and the Guillain-Barré syndrome (GBS), a neurological immune-mediated syndrome affecting peripheral nerves and known to develop post-infections. Cases of GBS have been documented after SARS-CoV-2 infection, with symptoms beginning on average 19 days after the onset of infection, highlighting SARS-CoV-2 as an additional virus potentially able to trigger or favor GBS in susceptible individuals (Table 1).²⁹

1.1.2. COVID-19 and non-neurological autoimmune diseases

The impact of COVID-19 on autoimmunity is strongly supported by a large retrospective cohort study carried out on 641,704 COVID-19 patients and 1,560,357 non-COVID individuals.³ Compared with non-COVID controls, patients with COVID-19, from 3 to 15 months after acute infection, had a 43 % (95 % CI: 37–48 %) higher likelihood of developing a first-onset autoimmune condition, including MS and non-neurological diseases, such as psoriasis, pernicious anaemia, spondyloarthritis, pemphigoid, Graves' disease, antiphospholipid antibody syndrome, immune-mediated thrombocytopenia, vasculitis, RA and autoimmune arthritis.³ Patients with a more severe course of COVID-19 were at a greater risk for incident autoimmune disease.³ An association between COVID-19 and the development of SLE was reported in several cases (Table 1), particularly in patients with hematologic and renal involvement.³⁰ Higher risk of autoimmune and autoinflammatory connective tissue disorders, including SLE, alopecia areata, alopecia totalis, vitiligo, Behçet's disease, Crohn's disease, ulcerative colitis, RA, Sjögren syndrome, ankylosing spondylitis and bullous pemphigoid, was observed in COVID-19 compared to non-COVID-19 patients in a wide retrospective study including 6,912,427 participants (i.e., 3,145,388 with COVID-19 and 3,767,039 controls) with an observational period of more than 180 days (Table 1), suggesting the importance of identifying susceptibility factors and performing long-term monitoring of patients after COVID-19 to check for the risk of developing these conditions.³¹ The impact of the pandemic on the prevalence of autoimmune rheumatic diseases, including RA, SLE and systemic sclerosis, was recently demonstrated in a retrospective study of the Greek population (approximately 10,000,000 people), indicating a significant increase over time in the prevalence of these diseases during the pandemic period, i.e., 2020–2023, compared to 2016–2019, although a direct association between SARS-CoV-2 infection and the disease onset was not demonstrated.³² According to SARS-CoV-2 ability to disrupt the thyroid function in a subset of patients, an association between COVID-19 and autoimmune thyroid diseases has been reported, thus adding these diseases to the list of autoimmune conditions favored by COVID-19, or by COVID-19-mediated damage (Table 1).³³

In a large retrospective cohort study including 1,028,721 COVID-19 patients and 3,168,467 non-COVID individuals, patients with COVID-19 presented an increased risk of developing various autoimmune diseases, but completion of two doses of COVID-19 vaccine was shown to provide a protective effect decreasing the risk of several conditions, including pemphigoid, Graves' disease, antiphospholipid antibody syndrome, immune-mediated thrombocytopenia, SLE, and autoimmune arthritis.³⁴

The impact of vaccination against SARS-CoV-2 on the development of de novo autoimmune conditions is not completely clear. However, the fact that autoimmune diseases were rarely observed among millions of vaccinated individuals does not support a causal connection between COVID-19 vaccines and these diseases.³⁵

A variety of autoantibodies (e.g., against type I interferons- IFNs, phospholipids, neutrophil extracellular traps) were detected in more than 50% of patients hospitalized with moderate to severe COVID-19.¹⁵ However, it remains to be determined whether de novo autoantibody formation is an epiphenomenon of the marked inflammation, or if these autoantibodies play a role in the development of autoimmune diseases.

Table 1

Representative studies reporting a link between COVID-19 and autoimmune diseases, both neurological and non-neurological.

Disease	Type of study	Disease onset/ exacerbation	N. of patients/studies	Key finding	Reference
<i>Neurological autoimmune diseases</i>					
Myasthenia Gravis (MG)	Case report-based review	Disease onset	18 patients	Disease onset after COVID-19 (i.e., 5–56 day post-infection)	19
	Systematic review	Disease onset and exacerbation	10 case reports and 6 case series	Increased risk of MG crisis and mortality rate due to cytokine storm after SARS-CoV-2 infection	20
	Retrospective study	Disease exacerbation	289 patients	Higher likelihood of MG exacerbation in patients experienced COVID-19 (HR: 3.38; 95 % CI 1.20–9.53, $p = 0.021$)	21
	Retrospective study	Disease exacerbation	287 patients	Post-COVID-19 MG exacerbation earlier in patients with severe compared to non-severe infection	22
	Retrospective study	Disease exacerbation	845 patients	Association of poor outcomes in MG patients following COVID-19 with generalized disease at onset, late onset, comorbidities and incomplete symptoms' control	23
Multiple sclerosis (MS)	Retrospective study	Disease exacerbation	234 patients	Disease worsening following SARS-CoV-2 infection; protection against severe infection and worsening by vaccination	24
	Retrospective study	Disease exacerbation	111 patients	Neurologic worsening post-COVID-19, associated with hospitalization, treatment for COVID-19 and incomplete COVID-19 recovery	25
	Umbrella review/ systematic analysis of multiple meta- analyses	Disease exacerbation	20 studies included	Potent SARS-CoV-2 negative effect on MS compared to other viruses	26
	Retrospective study	Disease exacerbation	RRMS patients with (n = 56) and without COVID-19 (n = 69)	Similar incidence of RRMS exacerbation in patients with and without COVID-19; no significant difference in relapse rates before the pandemic and after contracting COVID-19, and between patients hospitalized due to COVID-19 severity and those not hospitalized	27
	Retrospective study	Disease onset	1,028,721 COVID-19 and 3,168,467 non-COVID individuals	Increased risk [(aHR: 2.66 (95 % CI: 1.17–6.05)] to develop the disease in COVID-19 compared to non-COVID-19 patients	34
MS, myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), optic neuritis (ON) and neuromyelitis optica spectrum disorders (NMOSD)	Descriptive literature analysis	Disease onset	18 patients	NMOSD was found to be the most common post-COVID manifestation (39 %), followed by MOGAD (28 %), MS (22 %), and isolated ON (11 %)	28
Guillain-Barré syndrome (GBS)	Systematic review	Disease onset	156 studies, 436 patients	GBS symptoms after an average of 19 days after COVID-19 onset	29
<i>Non-neurological autoimmune diseases</i>					
Systemic lupus erythematosus (SLE)	Case report and literature review	Disease onset	11 patients	New onset of SLE in COVID-19 patients, presenting with dermatological complications, joint pain, and positive autoantibodies	30
Autoimmune and autoinflammatory connective tissue disorders	Retrospective study	Disease onset	6,912,427 participants, 3,145,388 with COVID-19 and 3,767,039 controls	Higher risk of alopecia areata, alopecia totalis, vitiligo, Behçet disease, Crohn disease, ulcerative colitis, rheumatoid arthritis (RA), SLE, Sjögren syndrome, ankylosing spondylitis and bullous pemphigoid in the COVID-19 group	31
Autoimmune rheumatic diseases	Retrospective study	Disease onset	About 10,000,000 subjects	Significant increase of the prevalence of RA, SLE and systemic sclerosis, during 2020–2023 compared to 2016–2019	32
	Retrospective study	Disease onset	1,028,721 COVID-19 and 3,168,467 non-COVID individuals	Increased risk to develop RA [(aHR: 1.29 (95 % CI: 1.09–1.54)] or other autoimmune arthritis [aHR: 1.43 (95 % CI: 1.33–1.54)] in COVID-19 compared to non-COVID-19 patients	34
Autoimmune thyroid disease (AITD)	Retrospective study	Disease onset	2082 COVID-19 patients with AITD and 257 without AITD; 464 non-COVID-19 patients	Robust association between SARS-CoV-2 infection and thyroid dysfunction, and subsequent AITD that may aggravate COVID-19 prognosis.	33
	Retrospective study	Disease onset	1,028,721 COVID-19 and 3,168,467 non-COVID-19 individuals	Increased risk to develop Graves's disease [aHR: 1.30 (95 % CI: 1.10–1.54)] in COVID-19 compared to non-COVID-19 patients	34

aHR: adjusted hazard ratio; HR: hazard ratio; RRMS: relapsing-remitting MS.

1.1.3. Proposed mechanisms linking COVID-19 and autoimmunity

As with other viruses, the proposed mechanisms by which SARS-CoV-2 may trigger autoimmunity onset in susceptible individuals include: i) hyper-stimulation of inflammatory responses with over-production of inflammatory cytokines and chemokines (i.e., cytokine storm); ii) molecular mimicry; iii) dysregulation of innate and adaptive immune system cells; iv) bystander activation, tissue damage and loss of tolerance to self-antigens, and v) establishment of a persistent infection (as observed in long COVID conditions), that can generate a chronic autoimmune response.¹⁵

By exploring the impact of COVID-19 on the immune system, considerable evidence showed COVID-19 ability to promote over-activation of viral RNA-recognizing innate immune receptors (i.e., Toll-like receptor 7), which can favor autoreactivity in genetically susceptible individuals.³⁶ Moreover, the virus can trigger both hyper-activation of innate immune system cells and B-cell activation, as well as antibody-producing cell expansion and defective germinal center formation,^{36–38} thus acting as a cross-linker between innate immunity and adaptive autoimmunity. In particular, Phetsouphanh and colleagues showed highly activated innate immune cells and persistent over-expression of type I and II IFNs and inflammatory mediators (i.e., IL-6) as key features in COVID-19 patients for more than 8 months following convalescence, along with the absence of inactivated naïve T and B cells, T cell exhaustion and increased plasmablasts, thus linking COVID-19-related inflammatory/anti-viral response to adaptive autoimmunity.³⁹ In MS, blood-brain barrier disruption, CD8⁺ T cell infiltration, microgliosis, and increased axonal damage – resulting from central nervous system (CNS) attacks by peripheral immune effectors – are suspected to contribute to CNS autoimmunity and the development or exacerbation of the disease by COVID-19, alongside viral reactivation.⁴⁰

The overall data associate SARS-CoV-2 natural infection with autoimmunity phenomena. The challenge now will be to prove a direct causality, and identify the individual susceptibility factors that lead to pathogenic virus-host interactions, which may favor the initiation or relapse of autoimmune diseases. This understanding is crucial for developing preventive or therapeutic strategies to counteract autoimmune processes in COVID-19 patients.

1.2. EBV reactivation in COVID-19 patients

The overall impact of SARS-CoV-2 infection on the immune system remains a source of many unanswered questions. Considerable data indicate that SARS-CoV-2 induces immune suppression and exhaustion of immune system cells in mild/moderate infections, and over-activation of these cells in severe cases, which results in a dangerous cytokine storm responsible for systemic hyper-inflammation and imbalanced innate and adaptive immune responses.⁴¹ Both these situations (i.e., immune suppression and hyper-inflammation) can be associated with reactivation of latent viruses in the host, such as EBV,⁴² suggesting additional indirect effects of SARS-CoV-2 on the immune system through the reactivated viruses. Acute infection by different pathogens may provide suitable conditions for EBV to reactivate, increasing the risk for EBV-associated pathologies.¹³ During infection by other pathogens, an active immune response can stimulate the molecular machinery involved in EBV reactivation, particularly the immediate early genes like BZLF1 (protein ZEBRA or Zta) and BRLF1 (protein Rta) that mediate the first stage of the latent-to-lytic switch.¹³ However, this does not necessarily occur in every co-infection case involving EBV-infected individuals.¹³

1.2.1. Viral reactivations and COVID-19

Viral reactivations and co-infections have been reported among COVID-19 patients (Table 2). In a systematic review of Kim and colleagues,⁴³ EBV was one of the most frequently observed viruses by studies (n = 53) reporting viral reactivation in patients affected by

Table 2
Representative studies reporting EBV reactivation in patients with COVID-19.

Type of study	N. of patients/ studies	Viruses tested	Key finding	Reference
Systematic review	53 studies, 895 COVID-19 patients with signs of viral reactivation	EBV, HSV-1, CMV, HHV- 6, HBV, HHV-8, VZV	519 (58 %) COVID-19 patients presented signs of EBV reactivation	⁴³
Systematic review	19 studies, 539 COVID-19 patients with HHV infection	EBV, HSV-1, VZV, CMV, HHV-6	CMV, HSV and EBV reactivation was frequent in COVID-19 patients and associated with mortality and mechanical ventilation	⁴⁴
Retrospective study	106 patients, including 54 positive and 52 negative for COVID-19	EBV	Higher frequency of EBV reactivation (i.e., higher levels of IgM to EBV lytic genes and plasma EBV DNA) in COVID-19 compared to non-COVID-19 patients	⁵
Retrospective study	67 COVID-19 patients with onset time within 2 weeks	EBV	High incidence of EBV co-infection in COVID-19 patients: 55.2 % of patients seropositive for EBV viral capsid antigen (VCA) IgM antibodies	⁴⁵
Retrospective study	185 COVID-19 patients	EBV	Prevalence of long COVID symptoms in 30.3 % of COVID-19 patients; high rate of EBV reactivation (66.7 % of cases) in long COVID patients	⁴⁶
Retrospective study	117 patients with severe COVID-19	EBV, CMV	Evidence of EBV reactivation in patients with severe COVID-19 patients treated on ICU	⁴⁸
Retrospective study	104 COVID-19 patients, including 42 hospitalized in ICU and 62 in a SICU	EBV, CMV, Parvovirus B19, HHV-6	Consistent detection of EBV DNA, as sign of viral reactivation, in whole blood from ICU and SICU patients, with higher levels in the ICU group, associated with B cell increase	⁴⁹
Retrospective study	128 COVID-19 patients admitted in ICU	EBV	Identification of EBV reactivation in 13.3 % of patients. Higher incidence of respiratory failure and of	⁵⁰

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Table 2 (continued)

Type of study	N. of patients/ studies	Viruses tested	Key finding	Reference
Longitudinal study	120 COVID-19 patients with severe pneumonia at admission in ICU subjected to longitudinal viral screening (i.e., every week until discharge or death)	HSV-1, HSV- 2, CMV, EBV	14- or 28-day mortality rates in patients with, than those without EBV reactivation Multiple reactivations in most (63 %) patients, with EBV being the most (65 % of patients) and earliest reactivated HHV; identification of EBV as an independent risk factor for in- hospital mortality (OR = 2.46, 95 % CI 1.02–5.89)	51

EBV: Epstein-Barr virus; HHV: Herpesvirus; CMV: Cytomegalovirus; HBV: Hepatitis B virus; ICU: intensive care unit; SICU: sub-intensive care unit; OR: Odd ratio; VZV: Varicella-zoster virus.

COVID-19 with severe illness (Table 2). Specifically, there were a total of 895 cases of reactivations, among which 519 (58 %) were reactivation of EBV, 157 (17.5 %) of HSV-1, 154 (17.2 %) of CMV, 47 (5.3 %) of HHV-6, 14 (1.6 %) of HBV, 2 (0.2 %) of HHV-8, and 1 (0.11 %) of VZV.⁴³ Additionally, some studies (n = 7) reported 336 patients who experienced co-reactivations of different viruses.⁴³ Very recently, data from 539 patients infected with both COVID-19 and Herpesviridae were reviewed: HSV-1, VZV, CMV, EBV, and HHV-6 were the detected viruses in the reviewed studies (n = 19), with CMV reactivation being the most detected concomitant infection, followed by HSV and EBV (Table 2).⁴⁴ Viruses known to cause systemic infection (CMV, EBV, HSV) have been found to be associated with mortality, with a significant correlation to the need for invasive mechanical ventilation.⁴⁴

1.2.2. EBV reactivation and COVID-19

Systematic reviews have limitations related to the lack of homogeneity in sampling and diagnostic methods for determining viral reactivation. However, in most studies, evidence of EBV reactivation was derived from serological analysis of anti-EBV antibodies, including anti-viral capsid antigen (VCA) IgM and IgG, anti-early antigen (EA) IgG, and anti-EBV nuclear antigen (EBNA) IgG, often accompanied (or not) by molecular analysis of EBV DNA in plasma samples (i.e., EBV viremia). In the study of Bernal and colleagues (Table 2),⁵ the frequency of EBV reactivation in COVID-19 patients, as estimated by the detection of antibodies against EBV lytic genes and EBV DNA, was significantly higher (27.1 % versus 12.5 % based on qPCR detection of EBV genomes) compared to that in COVID-19-negative subjects, supporting a relationship between SARS-CoV-2 infection and EBV reactivation. A high incidence (55.2 %) of EBV co-infection/reactivation in COVID-19 patients was also observed in the study of Chen and colleagues,⁴⁵ who showed that SARS-CoV-2-positive patients with EBV co-infection, according to EBV serological results, had an increased risk (i.e., 3.09-fold risk, p = 0.03) of fever and inflammatory symptoms than patients with SARS-CoV-2 infection alone (Table 2).

EBV reactivation can occur soon after or even simultaneously with SARS-CoV-2 infection, as well as following initially asymptomatic infections.⁴⁶ It may contribute to the more common COVID symptoms, as well as additional manifestations, typical of EBV lytic replication,

including cardiovascular, hematological, and neurological complications, which are observed in COVID-19 patients.^{46,47} A direct positive correlation has been reported between EBV reactivation and the severity of SARS-CoV-2 infection and its symptoms.^{6,48,49} Specifically, in a retrospective cohort study, patients with severe COVID-19 treated in intensive care unit (ICU) showed signs of both EBV and CMV reactivation (Table 2),⁴⁸ which could be either a cause or a consequence of hyper-inflammation, although the effect of concomitant immunosuppressive treatment cannot be excluded.⁴⁸ Evidence of EBV reactivation has been reported in a high percentage (92.5 %) of severe COVID-19 patients hospitalized in the ICU (Table 2).⁴⁹ Notably, higher levels of EBV DNA were found in whole blood from ICU patients compared to those hospitalized in a sub-intensive care unit, and a significant correlation was found between these levels and COVID-19 severity.⁴⁹ Moreover, ICU patients exhibited a reduction of CD8⁺ T and NK lymphocyte counts, along with a significant increase in B cell proportions, supporting the hypothesis of defective cell-mediated control and B cell expansion due to EBV reactivation.⁴⁹ Individuals suffering from long COVID also showed signs of EBV reactivation,⁴⁶ suggesting a potential contribution of EBV to both short- and longer-term symptoms of SARS-CoV-2 infection. Reactivation of EBV was found to occur earlier after admission to an ICU and was associated with longer hospitalization (Table 2).⁵⁰ The mortality rate in COVID-19 patients, and the need for more intense immunosuppressive therapies, were higher in patients with evidence of EBV reactivation compared to those without EBV co-infection, indicating a strong impact of EBV in the patho-immunological alterations and outcomes of COVID-19 illness.⁵⁰ Recently, the incidences of HSV-1, HSV-2, CMV, and EBV reactivations, estimated as viral load in plasma samples, were evaluated in critically ill COVID-19 patients (n = 120) with severe pneumonia at admission in ICU and weekly thereafter until discharge or death (Table 2).⁵¹ Multiple reactivations occurred in the majority (63 %) of patients, with EBV being the most (65 % of patients) and earliest reactivated herpesvirus. Notably, multivariate analysis demonstrated that viral reactivation is a strong independent risk factor for in-hospital mortality (odds ratio = 2.46, 95 % CI 1.02–5.89).⁵¹

The role of COVID-19 vaccination in EBV reactivation remains unclear. A systematic review evaluating the effects of COVID-19 vaccines, mostly mRNA-based, on EBV and other viruses, reported EBV reactivation in 6 of 149 cases with herpesvirus reactivation out of a total of 1000 vaccinations.⁵² These data suggest that vaccination may have a very low or no impact on the EBV infection status, implying that the immunological and inflammatory context generated by natural SARS-CoV-2 infection may be crucial for the reactivation of latent EBV. Nevertheless, further observational studies are needed to draw definitive conclusions about the relationship between COVID-19 vaccination and EBV.

1.2.3. Proposed mechanisms linking EBV reactivation and COVID-19

The molecular mechanisms underlying EBV contribution to COVID-19 are not fully understood and require further investigation. In addition to the impact of EBV reactivation on the immune system, Verma and colleagues demonstrated that reactivated EBV promotes the expression of angiotensin converting enzyme 2 (ACE2), the primary surface receptor for SARS-CoV-2, which facilitates the entry of the virus into epithelial cells.⁵³ Furthermore, they found that the ACE2 promoter enhances Z transcriptional activator (Zta) response, which favors EBV reactivation, thus creating a vicious circle in which SARS-CoV-2 entry into epithelial cells and EBV reactivation mutually reinforce each other. Since EBV replication is known to involve both B cells and the oropharyngeal and nasopharyngeal epithelium,⁵⁴ the site of SARS-CoV-2 infection, subclinical EBV reactivation could potentially influence the degree or severity of SARS-CoV-2 infection by affecting the virus's entry into epithelial cells.⁵³

1.3. EBV reactivation, SARS-CoV-2-related autoimmune phenomena and long COVID

Despite the significant decrease in SARS-CoV-2-related mortality thanks to vaccination, COVID-19 continues to impose a high public health burden due to the high rate of post-COVID-19 pathological conditions.¹ Similarities between the immune response in COVID-19 and chronic autoimmune diseases² support the idea that morbidities and organ damages in long COVID may be largely immune-mediated and strictly associated with antiviral immune responses and inflammatory autoimmune phenomena. Gold and colleagues reported a high rate of EBV reactivation (66.7 %) in patients developing long COVID manifestations (Table 3).⁴⁶ These data, along with the observation that many of the conditions developed in these patients^{2–4,34} are EBV-associated autoimmune diseases (e.g., SLE, RA), and the known EBV ability to cause symptoms similar to those observed in long COVID (e.g. fatigue),⁴⁶ corroborate the view that long COVID may not be merely due to

Table 3
Representative studies linking EBV reactivation and long COVID.

Type of study	N. of patients/ studies	Viruses tested	Key finding	Reference
Retrospective study	185 COVID-19 patients	EBV	Prevalence of long COVID symptoms in 30.3 % of COVID-19 patients; high rate of EBV reactivation (66.7 % of cases) in long COVID patients	⁴⁶
Prospective study	30 long COVID patients; 20 patients, fully recovered after SARS-CoV-2 infection (i.e., controls)	EBV	Higher percentage (50 % vs 20 %, p = 0.0411) of EBV DNA detection in throat washings of long COVID patients compared to controls	⁵⁶
Cross- sectional study	280 patients at about 4 months following diagnosis of acute SARS-CoV-2 infection	EBV, CMV	Independent association between long COVID symptoms (e.g., fatigue and neurocognitive dysfunction) and serological evidence of recent EBV reactivation (i.e., EA-diffuse IgG positivity, OR = 2.12; high EBNA IgG levels, i.e., >600 U/mL)	⁵⁷
Longitudinal study	309 COVID-19 patients throughout infection (from initial diagnosis to convalescence, i.e., 2–3 months later)	EBV	Significant association of EBV viremia (>50 copies of EBV DNA/mL of plasma) at T1 (COVID-19 diagnosis) with post-acute sequelae of COVID-19: EBV viremia as biomarker for developing sustained long COVID disease	⁵⁸

EBV: Epstein-Barr virus; CMV: Cytomegalovirus; EA: early antigen; EBNA: EBV nuclear antigen.

a direct SARS-CoV-2 effect but also the consequence of the SARS-CoV-2/inflammation-induced EBV reactivation.⁴⁶

EBV DNA and anti-EBV antibody analyses failed to show an association between EBV and long COVID in individuals with asymptomatic or mild SARS-CoV-2 disease courses.⁵⁵ However, a prospective study assessing whether long COVID fatigue may be triggered by EBV reactivation showed a significantly higher percentage (50 % vs 20 %, p = 0.0411) of EBV DNA detection in throat washings of long COVID patients compared to control patients who had fully recovered after SARS-CoV-2 infection (Table 3), suggesting EBV as a co-factor in a subgroup of patients who develop long COVID fatigue.⁵⁶ In line with these findings, Peluso and colleagues⁵⁷ showed that long COVID symptoms, such as fatigue and neurocognitive dysfunction, at a median of 4 months following initial diagnosis, were independently associated with serological data indicative of recent EBV reactivation, in cohort of patients with prior SARS-CoV-2 infection (n = 280) (Table 3). These data included positivity for EA-diffuse IgGs or high EBNA IgG levels, but not ongoing viremia.⁵⁷ In another study correlating long COVID patient symptoms with in-depth multi-omic profiling data derived from blood cells and plasma components from COVID-19 patients (n = 309) throughout infection (from initial diagnosis to convalescence, i.e., 2–3 months later), EBV viremia was defined as one of the main risk factors for developing long COVID and a predictive biomarker of sustained disease (Table 3).⁵⁸

Evidence of overlapping symptoms and disease features in patients with long COVID, autoimmune diseases, and EBV-related conditions,^{2–4,34,46} highlights a link between long COVID and immune dysfunction leading to autoimmunity.

The overall findings support the idea that EBV reactivation may be a risk factor for developing a specific pattern of long COVID syndromic symptoms in patients with chronic EBV infection.

1.4. Putative model of the pathophysiological link between COVID-19 and EBV

Growing data are pinpointing EBV as co-infecting factor contributing to COVID-19 severity and its early or long-term complications, including the initiation or worsening of autoimmune diseases.

COVID-19-induced systemic hyper-inflammation, overproduction of inflammatory cytokines and chemokines, dysregulation of the innate immune system, and exhaustion or hyper-activation of adaptive immune system cells are all putative mechanisms favoring reactivation of latent EBV in SARS-CoV-2 hosts. Due to its ability to disrupt B-cell tolerance, reactivated EBV may increase the risk of developing autoimmunity in COVID-19 patients susceptible to autoimmune diseases or exacerbate symptoms in patients already affected by an autoimmune condition at the time of SARS-CoV-2 infection. A putative model of the pathophysiological link between COVID-19 and EBV is depicted in Fig. 1. Data supporting this link can be summarized as follows:

- i) SARS-CoV-2 infection has been associated with an increased risk of presentation or worsening of autoimmune diseases, including EBV-associated autoimmune diseases;^{2–4,34}
- ii) a high frequency of EBV reactivation has been reported in COVID-19 patients with severe illness and patients suffering from long COVID symptoms, including autoimmune diseases, with EBV reactivation being estimated by serological analysis of anti-EBV antibodies and molecular analysis of EBV DNA in plasma (i.e., EBV viremia);^{46,48–51}
- iii) temporal associations between SARS-CoV-2 infection and EBV reactivation have been demonstrated in COVID-19 patients;⁴⁶
- iv) patients with EBV/SARS-CoV-2 co-infection have an increased risk of severe symptoms compared to patients with SARS-CoV-2 infection alone;^{6,49–51}
- v) the severity of COVID-19 symptoms was found to correlate positively with parameters related to EBV reactivation;^{6,48,51}

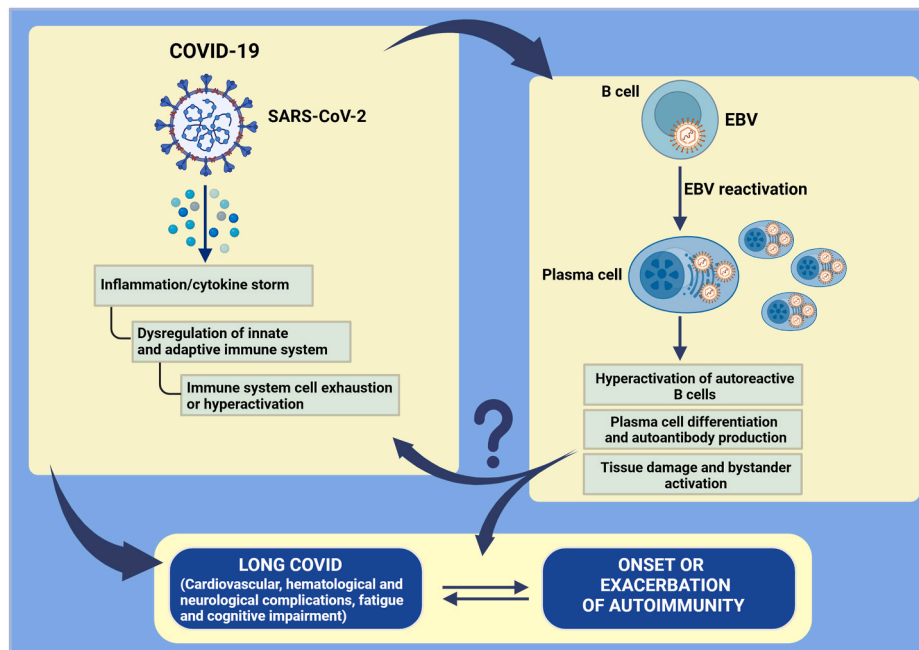


Fig. 1. EBV reactivation as possible mechanism contributing to COVID-19-associated autoimmunity and immune-related long COVID manifestations. Infection with SARS-CoV-2 triggers uncontrolled hyper-production of pro-inflammatory cytokines (i.e., cytokine storm), systemic hyper-inflammation, dysregulated innate immune responses, exhaustion or hyper-activation of immune system cells overall can promote presentation or worsening of autoimmune diseases, as well as long COVID manifestations. COVID-19-induced immune dysregulation favors reactivation of latent Epstein-Barr virus (EBV) in the host. EBV itself has the ability to cause autoimmunity onset in susceptible individuals, or exacerbation of autoimmunity in patients affected by autoimmune diseases through different mechanisms, including hyper-activation and proliferation of autoreactive B cells, plasma cell differentiation and autoantibody production, tissue damage and by-stander activation. EBV reactivation could contribute to the COVID-19-related immunological alterations, also enhancing the risk to develop long COVID pathological conditions. Figure created with [BioRender.com](https://www.biorender.com).

- vi) reactivated EBV promotes the expression of ACE2, the main SARS-CoV-2 surface receptor, which facilitates the entry of SARS-CoV-2 into epithelial cells;⁵³
- vii) the ACE2 promoter enhances Zta response, which favors EBV reactivation.⁵³

2. Conclusions

Evidence is accumulating on the contribution of COVID-19 to the onset or worsening of autoimmune diseases, as well as on EBV reactivation in COVID-19 patients, both early after infection and in those developing long COVID manifestations, the latter including autoimmune conditions. EBV reactivation has been associated with the severity of SARS-CoV-2 infection and its immune-related complications, as those occurring in long COVID. However, data on post-COVID EBV reactivation in the context of new or pre-existing autoimmune conditions are limited, making difficult to establish a direct role for EBV in the development or worsening of these conditions following SARS-CoV-2 infection. The exact relationship among COVID-19, EBV and autoimmunity is still not completely deciphered. It remains debated whether there is a casual or causative association between SARS-CoV-2 infection and EBV reactivation, and between EBV reactivation by SARS-CoV-2 and autoimmune disease relapse or first presentation or long COVID immune-related manifestations. The boundary between the immunological effects of SARS-CoV-2 alone and the effects of latent co-infecting viruses, such as EBV, which may undergo reactivation during SARS-CoV-2 infection, also remains unclear and deserve further investigation.

2.1. Perspectives

Large retrospective and prospective longitudinal studies exploring EBV infection status and immunological changes (i.e., autoimmunity biomarkers) in large cohorts of patients with and without autoimmune

disorders over a long time course following initial SARS-CoV-2 infection could help to clarify the relationship among COVID-19, EBV, long COVID symptoms and autoimmunity. This could further elucidate the role of co-infecting EBV in autoimmune diseases following SARS-CoV-2 infection.

The exact mechanisms underlying EBV reactivation in COVID-19 patients remain unclear, and it is unclear whether they involve immune system cell exhaustion or hyper-activation, or both.

Molecular in vitro functional studies, carefully designed to assess the SARS-CoV-2 impact on innate and adaptive immune system cells and on EBV reactivation, could advance current knowledge on the “COVID-19-EBV” cross talk. Such studies would help to clarify the role of virus-virus synergy and co-infections in autoimmune diseases.

Advances in this research area could open new avenues towards future development of strategies to precisely treat co-infections and/or novel therapeutics to target key factors of this cross-talk in the early SARS-CoV-2 infection phase. This could help prevent or treat autoimmunity and long COVID disease. Given the critical role of EBV in autoimmunity, anti-EBV therapies or vaccination should be considered for patients infected with COVID-19, or in cases of co-infection involving EBV and viruses other than SARS-CoV-2. However, drugs that inhibit EBV lytic reactivation are still under investigation, and vaccination against the virus remains a challenge despite over two decades of trials.⁵⁹ A better understanding of the mechanisms that lead to EBV reactivation in the context of inflammatory immune-related disorders, such as COVID-19, could hopefully facilitate the design of innovative and effective drugs to counteract the wide spectrum of autoimmune conditions associated with EBV.

CRedit authorship contribution statement

Maria Cristina Tarasco: Writing – original draft. **Nicola Iacomino:** Writing – review & editing. **Renato Mantegazza:** Writing – review &

editing, Funding acquisition. **Paola Cavalcante:** Writing – review & editing.

Funding

This work has been supported by the Fondazione Regionale per la Ricerca Biomedica (Regione Lombardia), Project ERAPERMED2022-258, GA 779282, under the frame of ERA PerMed, and by the Italian Ministry of Health (RRC).

Abbreviations

ACE2	Angiotensin converting enzyme 2
CMV	Cytomegalovirus
EBV	Epstein-Barr virus
EA	Early antigen
EBNA	EBV nuclear antigen
GBS	Guillain-Barré syndrome
HBV	Hepatitis B virus
HHV	Herpesvirus
HSV	Herpes Simplex virus
ICU	Intensive care unit
IFNs	Interferons
MG	Myasthenia Gravis
MOGAD	Myelin oligodendrocyte glycoprotein antibody-associated disease
MS	Multiple sclerosis
NMOSD	Neuromyelitis optica spectrum disorders
ON	Optic neuritis
RA	Rheumatoid arthritis
SICU	Sub-intensive care unit
SLE	Systemic lupus erythematosus
VCA	Viral capsid antigen
VZV	Varicella-zoster virus
Zta	Z transcriptional activator

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