

REVIEW

Viral coinfections in COVID-19

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Abstract

The most consequential challenge raised by coinfection is perhaps the inappropriate generation of recombinant viruses through the exchange of genetic material among different strains. These genetically similar viruses can interfere with the replication process of each other and even compete for the metabolites required for the maintenance of the replication cycle. Due to the similarity in clinical symptoms of most viral respiratory tract infections, and their coincidence with COVID-19, caused by SARS-CoV-2, it is recommended to develop a comprehensive diagnostic panel for detection of respiratory and nonrespiratory viruses through the evaluation of patient samples. Given the resulting changes in blood markers, such as coagulation factors and white blood cell count following virus infection, these markers can be of diagnostic value in the detection of mixed infection in individuals already diagnosed with a certain viral illness. In this review, we seek to investigate the coinfection of SARS-CoV-2 with other respiratory and nonrespiratory viruses to provide novel insights into the development of highly sensitive diagnostics and effective treatment modalities.

KEYWORDS

COVID-19, diagnosis, mixed infection, SARS-CoV-2, viral coinfection, viral respiratory tract infection, virus infection

1 | INTRODUCTION

In December 2019, the first cases of Coronavirus Disease 2019 (COVID-19) were reported in Wuhan, China. Soon after, the rapid spread of COVID-19 in the world prompted nations to recognize it as a global threat. The causative virus, Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2), had infected 109,594,835 people as of May 7, 2020, resulting in 2,424,060 deaths.¹⁻³ The substantial disease burden associated with COVID-19 necessitated the development of novel techniques for detection of SARS-CoV-2 and repurposing of drugs with potential therapeutic value, including lopinavir, ritonavir, chloroquine/hydroxychloroquine, oseltamivir, darunavir, zanamivir, peramivir, and remdesivir.^{1,4-6}

Transmitted primarily through respiratory droplets released into the air upon coughing or sneezing, SARS-CoV-2 can frequently lead to pneumonia in individuals exposed to a sufficient amount of viral

particles.^{7,8} The virus is believed to target the upper respiratory tract, in particular, with a natural history characterized by high-grade fever, cough, and shortness of breath. Following the acute phase of COVID-19, some patients may experience clinical symptoms, such as nausea, exhaustion, headache, and low-grade fever.^{9,10} Beside SARS-CoV-2, infection with other viruses, including the influenza viruses, rhinoviruses, adenoviruses, human metapneumoviruses, and other coronaviruses (CoVs), namely, 229E, OC43, NL63, and HKU1, can also manifest as regular symptoms of the common cold.¹¹ Other notable CoVs, including the SARS-CoV and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which tend to target the lower respiratory tract, can also result in pneumonia and death.^{12,13} With a 79% genetic sequence identity, SARS-CoV and SARS-CoV-2 are remarkably similar strains.^{12,14} Furthermore, SARS-CoV-2 infection may occur in parallel to SARS-CoV, leading to the activation of inflammatory responses that result in lung damage. The

severity of the disease is distinguished by the host immune response to the virus infection.¹⁵⁻¹⁷

To date, several instances of SARS-CoV and MERS-CoV mixed infection have been reported; however, in the case of COVID-19, coinfection is less frequent.¹⁸ The prevalence of coinfection in different individuals with COVID-19 is thought to vary to a significant extent as only 50% of deaths associated with COVID-19 are suspected to stem from mixed infection.¹⁸ Coinfection can result in the inhibition of host immune response, resistance to antibacterial drugs, and an overall poor prognosis of the disease.¹⁹ One study discovered that 94.2% of people with COVID-19 were also coinfecting with several other microorganisms, such as viruses, bacteria, and fungi.²⁰ Important viral copathogens include the influenza A and B viruses, rhinovirus/enterovirus, parainfluenza virus, metapneumovirus, respiratory syncytial virus, human immunodeficiency virus (HIV), dengue virus (DENV), hepatitis B virus (HBV), cytomegalovirus (CMV), Epstein Barr virus (EBV), and other CoVs, among which the influenza A virus and rhinovirus/enterovirus are the most common copathogens.^{18,21} Nonetheless, due to the remarkable advances made in the diagnosis and treatment, influenza is significantly less associated with mortality.²²

Interestingly, the SARS-CoV-2 epidemic in December 2019 coincided with the seasonal outbreak of the influenza virus.²² An investigation by Xia et al.²³ found high levels of serum procalcitonin in pediatric patients with COVID-19 and other common respiratory

infections, suggesting that coinfection with other pathogens might have been responsible for the enhanced inflammatory response. A significant increase in the serum levels of D-dimer (>1 mcg/ml), LDH (lactate dehydrogenase; >350 U/L), and ferritin and troponin (>1000 ng/ml), along with a decline in the lymphocyte count to less than 800, stand among notable laboratory findings in patients with COVID-19, which could be helpful in determining the prognosis of the disease^{24,25} (Table 1). Nonetheless, there is no definite knowledge regarding the exact coincidence of other diseases with COVID-19.²⁶ With an emphasis on potential coinfections with SARS-CoV-2, the present review seeks to provide a more clear perspective to facilitate the development of strategies for diagnosis and containment of the disease.^{18,27}

1.1 | Coinfection with respiratory viruses and SARS-CoV-2

Identifying coinfections of more than one respiratory virus can help with understanding the various clinical symptoms, long-lasting effects on health, and appropriate methods of prevention. In the case of viral respiratory tract infections resulting in pneumonia, a mixed infection can lead to serious disease in individuals with a suppressed immune system.⁴⁴ There have been reports of disease exacerbation and hospitalization in children

TABLE 1 Similar blood markers in viral disease

Serum biomarker for COVID-19	Prognostic value	Viral coinfection	Correlation with coinfections
C-reactive protein	Increased levels, especially in the early stages of the disease indicate an acute risk of pulmonary lesions and infection. ^{23,28}		
IL-6 and TNF- α	Increased levels predict the progression of the disease to severe forms. ²⁹	DENV ³⁰ CMV ³¹	Increased in coinfections
Lymphocyte count	Evaluation of the severity of the disease and the indication of hospitalization in the intensive care unit. It is less than 5% of the normal value in patients with a critical illness. ³²	HIV, ³³ BV, ³⁴ DENV	Decreased counts determine lymphopenia ³⁵
LDH	Increased levels are reported in mild and severe cases of COVID-19, especially in coinfection with adenovirus. ³⁶⁻³⁸	Adenovirus	Increased levels along with D-dimer and ferritin in coinfections
D-dimer	Increased levels are reported in vasculopathies and coinfection with adenovirus. ^{36,39}	Adenovirus ³⁶	
Procalcitonin	Prompts immune response against other viruses. ²³	Respiratory infection ²³	Increased in coinfection
Creatine kinase-MB	Increased levels are reported in COVID-19 patients with kidney failure ^{40,41}	CMV ⁴¹	Elevated along with ALT and IL-6, IL-10 and TNF- α in coinfections.
Platelet count	Predicts development of thrombocytopenia in rare cases and subsequent myocardial injury. ⁴²	DENV ⁴³	A decreased platelet count is associated with thrombocytopenia in dengue virus coinfection.

Abbreviations: CMV, cytomegalovirus; DENV, dengue virus; EBV, Epstein Barr virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IL, interleukin; LDH, lactate dehydrogenase; TNF- α , tumor necrosis factor- α .

under 3 years of age, following simultaneous infection with RSV and Human metapneumovirus (hMPV).⁴⁵ Furthermore, patients with viral respiratory tract coinfections are more likely to be admitted to the hospital than individuals with a single respiratory virus infection.⁴⁶ Moreover, due to the similarity of common clinical symptoms of COVID-19 with that of the diseases caused by other respiratory viruses, it has become quite challenging to precisely distinguish SARS-CoV-2 infection from other viral infections.⁴⁷ It is thought that coinfection with common respiratory viruses can still occur in individuals infected with other respiratory-specific strains.⁴⁸ Mixed infection of SARS-CoV-2 with other respiratory viruses has been reported to be uncommon, with a rate of 1.4%.^{27,49,50} It is speculated that the spread of another infection through aerosol production as a result of the respiratory symptoms of different pathogens might increase the likelihood of coinfection.⁴⁸ Thus, there are discussions about the utilization of routine tests, that may greatly help to detect SARS-CoV-2 and other respiratory viruses in cases suspected to have been coinfecting with SARS-CoV-2 and another pathogen of the respiratory tract.^{51,52} This has led to concerns about coinfection of SARS-CoV-2 with other respiratory microorganisms, especially unusual pathogens.^{49,53} Moreover, the

severity of COVID-19, in cases of mixed infection with other respiratory viruses, is correlated with lymphocyte count and serum levels of D-dimer.⁵⁴ High rates of interleukin (IL)-6, IL-10, and tumor necrosis factor- α (TNF- α) were also observed in high-risk groups; thus, the severity of COVID-19 disease can be assessed according to the levels of IL-10 and TNF- α .^{7,17,55}

It has been suggested that the incidence of coinfection with influenza virus in COVID-19 patients is lower than human adenovirus (HAdV) and human rhinovirus (HRV), which is also associated with lower mortality. In spite of low mortality, coinfection with influenza virus may result in a substantial economic burden due to the adverse effects accompanied by either infection.²⁰ The effect of the mixed infection of EBV and herpes simplex virus in COVID-19 still remains unclear.²⁰ CMV, human bocavirus, and hMPVs, the major causes of viral respiratory tract infection in children, are too different in terms of pathogenesis to be missed in COVID-19 patients²⁰ (Figure 1). More importantly, coinfection of SARS-CoV-2 with other upper and lower respiratory tract viruses can result in overlapping of clinical symptoms, and make it difficult for clinicians to rule out other infections.²⁰ As a result, infection with other viruses should also be appraised during the diagnosis and treatment of COVID-19. In general, coinfection could be

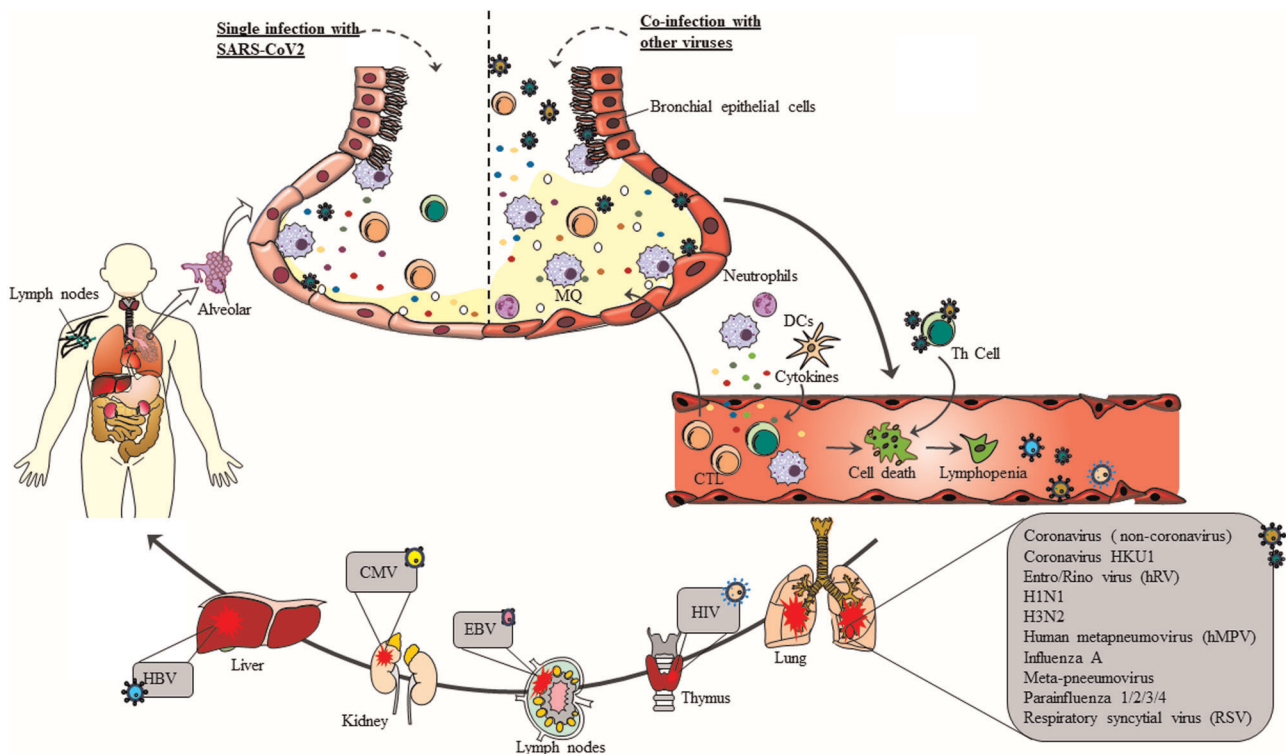


FIGURE 1 Coinfection of COVID-19 with other viruses. Coinfection of SARS-CoV-2 with other respiratory viruses, such as Flu, HRV, hMPV, RSV, and parainfluenza viruses, as well as systemic viruses, such as HIV, HBV, and CMV, can aggravate the clinical symptoms of the disease, increase the migration of inflammatory cells, such as macrophages and neutrophils, to the site of infection, and ultimately elevate the secretion of proinflammatory cytokines in organs infected with specific pathogens. Therefore, these events might lead to a severe form of the disease. In contrast, SARS-CoV-2 infection alone may only result in mild or absent clinical symptoms, as is the case with asymptomatic patients. In this respect, identification of coinfection of SARS-CoV-2 with other viruses can contribute to the development of novel approaches for the treatment of COVID-19. CMV, cytomegalovirus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HRV, human rhinovirus; hMPV, human metapneumovirus; SARS-CoV-2, severe acute respiratory Coronavirus 2

associated with a diminished immune response due to an already present SARS-CoV-2 virus infection.²⁰

1.2 | Coinfection with influenza virus and SARS-CoV-2

Epidemiological data from 2014 to 2020 were investigated by Sakamoto et al.^{22,56} in a study, which suggested a lower incidence of influenza in 2020, compared to the years before, indicating different levels of seasonal influenza virus infection with SARS-CoV-2. SARS-CoV-2 and influenza virus-mixed infection were found to be common during the COVID-19 outbreak. Individuals coinfecting with SARS-CoV-2 and influenza B were indicated to be affected by less severe complications compared with the coinfection of SARS-CoV-2 and influenza A virus, which was also found to be common.⁵⁷ Accordingly, coinfection with influenza A virus, an important respiratory tract pathogen, during the COVID-19 outbreak, might lead to false-negative results in individuals with SARS-CoV-2 infection.¹⁸ Nevertheless, a positive result for influenza A infection in patients with underlying COVID-19 can also bring about particular challenges in terms of diagnosis⁴⁷ as a clinical suspicion for COVID-19 is more likely to be neglected once an individual has been tested positive for influenza A virus.⁵⁷ Therefore, studying the clinical features and effects of coinfection in COVID-19 patients is important. A recent investigation on coinfection of SARS-CoV-2 with influenza viruses revealed a significantly high prevalence for these strains (Influenza A: 49.8% and Influenza B: 7.5%) during the initial phase of the outbreak of COVID-19 in Wuhan, with slightly different frequencies of mixed infection with Influenza A (0.9%) and Influenza B (0%) in a 3-week period (March 3–25).^{44,57} Studies have also shown that clinical symptoms and transmission dynamics are highly similar in patients with SARS-CoV-2 infection alone, and those with influenza virus coinfection.^{58,59} As a result, in patients with coinfection, rapid identification of the influenza virus might be of great diagnostic value in the case of simultaneous SARS-CoV-2 infection.⁵⁷ Also, in a study conducted by Hashemi et al.,⁶⁰ it was reported that in patients with mixed infection of SARS-CoV-2 and influenza virus, the presence of underlying diseases, such as heart disease, asthma, diabetes, and chronic neurological pathologies might lead to increased mortality. Arguably, patients with SARS-CoV-2 and influenza B virus coinfection are more likely to develop a chronic disease compared to individuals with influenza A virus coinfection.⁵⁷ In this regard, Yue et al.⁵⁷ showed that coinfection of SARS-CoV-2 and influenza B virus, unlike SARS-CoV-2 and influenza A virus, might accentuate the symptoms and result in chronic illness. Along the similarities of respiratory symptoms caused by both SARS-CoV-2 and influenza viruses, such as high-grade fever, cough, headache, and pneumonia, the pathogenicity of SARS-CoV-2 overlaps with that of the influenza virus in winter, leading to a rise in the number of individuals with undetected coinfection.^{27,47,61–63} Nevertheless, SARS-CoV-2 and influenza virus infection still differ in terms of epidemiology and clinical manifestations, due chiefly to immunity, as infection with the

latter usually results in asymptomatic to moderate illness. COVID-19 patients, on the contrary, experience complications for 5 to 7 days, and develop a serious disease.^{64–66} Furthermore, acute respiratory distress syndrome (ARDS) is uncommon in influenza outbreaks, with a mortality rate of less than 1%. In COVID-19, on the contrary, ARDS is more prevalent, with a mortality rate of 3%–4%. Besides, the span of virus shedding in influenza-related illnesses is 5–10 days, whereas it is 2–5 weeks in SARS-CoV-2 infection.^{67,68}

Moreover, hyperinflammation, as well as disorders, such as shock, ARDS, myocarditis, acute kidney injury, and dysfunction of other organs are found in COVID-19 patients with influenza virus coinfection, owing to the stronger and more frequent activation of the cytokine cascade caused by the flu virus infection.^{25,69–71}

As early clinical symptoms of COVID-19 disease and the flu are so similar, false negatives in the diagnosis of COVID-19 might increase, resulting in increased, albeit overlooked, viral shedding. Furthermore, proinflammatory cytokine levels in the blood have been shown to rise considerably in these patients,^{35,71} leading to serious pulmonary sequelae, as well as increased neutrophil and macrophage penetration into the infected region.⁷¹ Furthermore, individuals with ARDS have a higher number of neutrophils in their blood and lungs.^{72,73} Increased neutrophil penetration into the pulmonary tissue, on the contrary, has been linked to lung injury and exacerbation of clinical symptoms in influenza patients.⁷⁴ In a study by Ma et al.,⁶⁹ neutrophil levels and proinflammatory cytokines were shown to be slightly higher in the deceased than in the recovered cases. They also discovered that the amount of D-dimer, which is a risk factor for mortality, was considerably higher in deceased patients than in recovered individuals.⁶⁹ Furthermore, D-dimer levels were slightly higher in flu patients than non-flu patients, indicating that these patients had died as the result of local vascular damage, ischemia, and thrombosis caused by a cytokine cascade triggered by virus infection.⁷⁵ Besides, according to a report by Wang et al.,⁷⁶ the frequency of coinfection with other CoVs and influenza A virus was 2.88% and 1%, respectively, suggesting that SARS-CoV-2 coinfection with influenza A, influenza B, and other CoVs might rather be uncommon. Nevertheless, coinfection with influenza A and B viruses might enhance the incidence of COVID-19.^{76,77} ARDS is one of the primary respiratory sequelae of SARS-CoV-2, influenza A (H1N1 and H3N2) and influenza B infection, which have resulted in major pandemics through the last century.^{77–79} Due to the similarities between the clinical manifestations of SARS-CoV-2 and the influenza virus, coinfection of these two viruses may potentially disrupt the patient response to therapeutic agents for either infection, thus a simultaneous diagnosis of these viruses is necessary to provide effective care.⁷⁸

1.3 | Coinfection with adenovirus and novel coronavirus (SARS-CoV-2)

Although rare, mixed infection of SARS-CoV-2 and adenoviruses, another family of respiratory viruses, in individuals with diabetes

mellitus may be associated with findings, such as elevated D-dimer, LDH, and ferritin, along with life-threatening conditions like hypoxia and ARDS, which could necessitate hospitalization in the intensive care unit (ICU).³⁶ SARS-CoV-2 and adenovirus coinfection can instigate a cascade of detrimental sequelae, for example, lymphopenia, thrombocytopenia, and septic shock, rendering the patient dependent on mechanical ventilation. To date, coinfection of adenovirus and SARS-CoV-2 has been reported in a limited number of patients over 15 years of age and adults.^{20,50,51} A case report of adenovirus coinfection with SARS-CoV-2 in a 4-month-old infant negated the misconception regarding the unlikelihood of adenovirus coinfection in infants, indicating that complete screening for COVID-19 in addition to other virus infections, in this particular case, significantly reduced the risk of being an asymptomatic carrier.⁸⁰

1.4 | Coinfection with human CoVs and SARS-CoV-2

CoVs are highly recombinant due to the large size of their RNA genome. Several investigations have reported a recombination rate of 25% throughout the entire viral genome, which is relatively high compared to other single-stranded RNA viruses, resulting in enhanced susceptibility to mutations.⁸¹ Of the seven human CoVs, four are endemic (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) and cause symptoms similar to the common cold and lower respiratory tract infections.⁸¹ Coinfection or super-infection with endemic or epidemic HCoVs (SARS-CoV-1, MERS-CoV, and SARS-CoV-2) can accentuate the patients' symptoms.⁸²⁻⁸⁴ In a study conducted by Grieven et al.,⁸⁵ on a population of Kenyan children residing in coastal endemic areas, with a seasonal rotation of about 4%, three cases of HCoV (HCoV-NL63, OC43, and 229E) were identified to be vulnerable to coinfection with other respiratory viruses, without any seasonal pattern. Considering the spread of SARS-CoV-2, the relatively high prevalence of seasonal MERS-CoV in the Middle East, for example, the Kingdom of Saudi Arabia, particularly in the spring, warrants careful screening for both viruses in these regions as MERS-CoV infection is significantly more fatal (34% mortality rate) than COVID-19.^{86,87} As a result, the possibility of coinfection with SARS-CoV-2 and other HCoVs, particularly in children who are susceptible to seasonal coronavirus infections, should not be overlooked.

2 | COINFECTION WITH SYSTEMIC DISEASE-CAUSING VIRUSES AND SARS-COV-2

In addition to the respiratory viruses mentioned earlier, many systemic disease-causing viruses, including HIV, HBV, CMV, EBV, and dengue fever virus, can be superimposed on SARS-CoV-2 infection amid the widespread outbreak of this virus.^{88,89} However, the severity of infection remains unknown. Coinfection with SARS-CoV-2

and HIV has also been demonstrated to be more severe because of immune deficiencies, severe infection, and slower development of antibodies.⁷⁶ It has also been documented that the risk of reinfection with SARS-CoV-2 is increased in HIV-infected patients due to immunosuppression, as well as deficiency or failure of the humoral immune response. Thus, it is imperative to avoid any exposure to SARS-CoV-2 in these patients.⁹⁰ Studies suggest that the HBV virus is either reactivated or suppressed following coinfection with another viral strain.⁹¹ For example, the rate of coinfection with HIV and HBV is high due to the similarity of their transmission. In this respect, studies have indicated that, after the suppression of the immune system during HIV infection, the amount of antibodies associated with hepatitis B as a result of its reactivation declines, ultimately leading to chronic hepatitis B.⁹² The innate immune response associated with hepatitis C virus (HCV) infection can also suppress the replication of HBV if a coinfection with HCV is present.⁹³ In addition, Liu et al.⁹⁴⁻⁹⁶ discovered that secreted cytokines, including IL-6 and TNF- α , counteract HBV replication and pathogenicity during COVID-19 disease.

2.1 | Coinfection with HIV and SARS-CoV-2

Despite the expansion of information regarding the SARS-CoV-2 infection, little is known about the potential impact of HIV infection on COVID-19.³³ As common diseases including lymphoma and opportunistic infections, such as pneumocystis pneumonia, have been observed in people with HIV/acquired immunodeficiency syndrome (AIDS); the compromise in the immune system caused by HIV often contributes to the enhanced occurrence of SARS-CoV-2 infection.⁹⁷⁻¹⁰¹ An investigation on HIV-infected patients reported a significantly lower number of CD4⁺ T cells before coinfection with SARS-CoV-2. Considering that tissue damage in the case of SARS-CoV-2 infection is triggered by cytokine-induced cascades,¹⁰² deaths from mixed infection of HIV and SARS-CoV-2 are rare due to the inadequacy of CD4⁺ T cells, preventing upregulation of immune cytokines. Lymphopenia has been documented in extreme cases with HIV-negative COVID-19; however, the distribution of immune cells in patients coinfecting with HIV and SARS-CoV-2, as well as in patients with COVID-19 alone, is slightly different.^{103,104} Nonetheless, the precise impact of lymphocyte deficiency in peripheral blood on the clinical outcome of HIV and SARS-CoV-2 coinfection is yet to be elucidated.¹⁰⁰ Patients with AIDS, especially those with comorbidities, and a high load of HIV RNA in their general circulation are more vulnerable to SARS-CoV-2 infection. However, the clinical symptoms of simultaneous infection with HIV and SARS-CoV-2 are not clearly defined.^{33,105,106} Interestingly, a lower prevalence of comorbidities, such as high blood pressure, high body mass index, diabetes, chronic kidney disease, and chronic liver disease has been documented in patients with SARS-CoV-2 or HIV infection alone compared to those with coinfection.^{33,107,108}

In the case of HIV infection, factors determining disease severity, including lymphocyte or platelet loss, as well as increased IL-6

levels are associated with reduced CD4⁺ T-lymphocyte counts. Accordingly, the count of CD4⁺ T lymphocytes in individuals with severe coinfection with HIV and SARS-CoV-2 appears to be much lower than in patients with moderate symptoms.^{33,35,109} Despite the lack of any particular association between the CD4⁺ lymphocytes and COVID-19, inhibition of the immune system might still contribute to the severity of disease, resulting in adverse consequences and persistence of viral infection.³³

Delayed antibody response could be another complication associated with such coinfection, as indicated by a case report regarding a patient with mixed infection of SARS-CoV-2, HIV-1, and HCV.¹¹⁰ This, in turn, denotes the impact of HIV-1 on the function of the immune system, in relation to SARS-CoV-2.¹¹⁰ However, the grade of infection with SARS-CoV-2 due to the compromised immune state of the host is controversial. A major decrease in the count of B and T lymphocytes, as well as natural killer (NK) cells, was shown in patients with severe COVID-19, in contrast to those with mild symptoms. According to a report by Qin et al., the function of the immune system after SARS-CoV-2 infection is also impaired in the chronic phase of HIV infection, leading to a decline in the count of T lymphocytes.¹¹¹ In addition, an analysis by Suwanwongse & Shabarek,¹¹² on clinical symptoms in individuals with SARS-CoV-2/HIV coinfection, found that CD4⁺ T-cell dysfunction was inversely correlated with the clinical outcome in COVID-19 patients with HIV infection.¹¹²

It was documented that individuals with AIDS were neither immune to SARS-CoV-2 nor developed a less serious COVID-19. Though, patients with reduced T lymphocyte counts had poorer outcomes.¹¹³ Owing to the regular administration of immunosuppressive drugs, or antiviral agents, such as protease inhibitors, nucleoside reverse transduction inhibitors, or non-nucleoside reverse transduction inhibitors (NNRTIs), the risk of SARS-CoV-2 infection and the severity of its clinical symptoms are markedly mitigated.^{102,114,115}

2.2 | Coinfection with hepatitis B virus (HBV) and SARS-CoV-2

In individuals with SARS-CoV-2 infection, impaired liver function is identified in addition to common symptoms.¹¹⁶⁻¹¹⁸ This inordinate hepatic activity, in turn, contributes to the development of severe disease, and ultimately, death from SARS-CoV-2 infection. However, the exact cause of liver injury in COVID-19 patients has not been explained.¹¹⁷⁻¹¹⁹ Due to the globally high prevalence of hepatitis B, and the high serum levels of HBsAg in these patients, hepatitis B is considered to be a major public health concern.¹²⁰ Furthermore, according to an investigation by Huang et al.,²¹ people with SARS-CoV-2 infection are more likely to develop severe hepatitis and hepatic failure if they become infected with HBV. However, there is no reliable information on the clinical outcome of SARS-CoV-2/HBV coinfection.¹²¹

Angiotensin-converting enzyme 2 (ACE2) has been recognized by numerous studies as an important receptor for SARS-CoV-2, which can be found on the surface of the liver cells in the bile

ducts.^{55,122} Accordingly, due to the binding of SARS-CoV-2 to ACE2-expressing hepatocytes, normal liver function is impaired and the illness is aggravated. Still, increased serum level of alkaline phosphatase (ALP), a bile duct injury marker, was not reported in COVID-19 patients.³⁹ It has also been shown that elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are related to impaired liver function in COVID-19 patients. There is a possibility for liver damage in COVID-19 patients with moderate symptoms.¹¹⁸ As a result, the liver is a target organ for SARS-CoV-2.²¹

SARS-CoV-2 and HBV coinfection can result in the depletion of pre-albumin deposits in the liver.²¹ Interestingly, the extent of impairment in liver function is not substantially different in patients with HBV coinfection, and those without HBV coinfection. However, pre-albumin levels in HBsAg-negative individuals were higher than HBsAg+ individuals.²¹ In general, SARS-CoV-2/HBV coinfection does not seriously affect the progression of COVID-19, including disease severity, mortality, and hospitalization. Yet, it has recently been suggested that SARS-CoV infection might lead to increased liver damage and induction of HBV activity in people with hepatitis B.¹²³ The clinical effects of COVID-19 have been confirmed not to be associated with HBV infection, although some patients might present with elevated liver enzymes.¹²⁴ Accordingly, a few theories can be considered in such situations:

1. Long-term use of HBV antiviral medications has been linked to the progression of COVID-19 disease, as have nucleoside analogs, such as entecavir, tenofovir, and others. As a result, tenofovir binds to the RNA-dependent RNA polymerase (RdRp) enzyme of SARS-CoV-2, halting the synthesis of its RNA.^{125,126} As a consequence, during the COVID-19 pandemic, nucleotide analogs might be considered as potential therapeutic agents.¹²⁴

2. Immune system dysfunction plays a key role in the development of COVID-19 in individuals with chronic HBV infection. It has been shown that the persistence of viral genes can lead to a decrease in CD4⁺ and CD8⁺ T cells in these patients.^{127,128} In this case, a disruption in the proinflammatory cytokine secretion, such as IL-2 and TNF- α , may result in repressed antiviral function.¹²⁹ Furthermore, the release of IL-2, IL-6, and TNF- α is suggested to be correlated with the development of COVID-19, as well as increased mortality. In individuals with chronic HBV infection, however, immune system dysfunction and a reduction in the number of T cells may cause moderate symptoms of COVID-19, preventing appropriate immune response to SARS-CoV-2.¹²⁴

3. In the case of coinfection with SARS-CoV-2 and HBV, viral interference, a mechanism in which one virus suppresses the replication of another strain, can be observed. Autoantibodies and genetic mutations are also affected by defective interferon type 1 activity in acute COVID-19.^{130,131} As a result, increased IFN-I secretion in viral coinfections can suppress the replication of the other strain.¹³²

HBV reactivation, on the contrary, has been confirmed in coinfection with SARS-CoV-2 and HBV. Immunosuppressive drugs like tosilizumab and siltosimab; IL-6 receptor antagonists,

namely tosilizumab and siltximab; IL-1 receptor antagonists, including anakinra and high-dose corticosteroids, are used to regulate the aggravated cytokine cascade upon HBV reactivation when viral DNA is present in the peripheral blood.¹³³⁻¹³⁵ As a consequence, an important risk factor for HBV reactivation following COVID-19 could be the disequilibrium of the immune system and virus replication.¹²⁴

Accordingly, there is a possibility of SARS-CoV-2/HBV coinfection in individuals with COVID-19.²¹

2.3 | Coinfection with DENV and SARS-CoV-2

One of the most significant public health concerns in Asian countries is DENV,¹¹⁶ which is more prevalent in rainy seasons, causing conditions varying from mild dengue fever (DF) to severe hemorrhagic DF and dengue shock syndrome.^{136,137} High-grade fever and flu-like symptoms are the most important clinical prognostic manifestations of both DENV disease and COVID-19, and the similarity of these symptoms can increase the risk of misdiagnosis. An investigation conducted by Yan et al.¹³⁸ suggested the possibility of DENV and SARS-CoV-2 coinfection, characterized by prolonged fever. Similarly, in Thailand, Yan et al.¹³⁸ and Joob et al.¹³⁹ reported mixed infection of DENV and SARS-CoV-2, characterized by petechial rash, and respiratory symptoms as a result of COVID-19. In this respect, it was speculated that patients with fever could be coinfecting with SARS-CoV-2 and DENV, a condition most prevalent in areas, including Singapore, Thailand, Malaysia in South East Asia and Brazil in South America. In terms of clinical manifestations, 87.9% of COVID-19 patients presented with fever, 67.7% reported cough and 13.7% complained of headache. On the contrary, all patients with DENV infection had fever, whereas only 25.7% reported headache.^{61,140}

The findings above suggested that DF and COVID-19 may present with similar clinical signs and symptoms. For example, thrombocytopenia is observed in both infections.¹⁴¹ However, serious respiratory symptoms were not found in individuals with either SARS-CoV-2 or DENV infection or coinfection.¹⁴² Due to the similarity among the symptoms of DF and COVID-19, including fever, cough, myalgia, and petechiae, it is not readily possible to discriminate the two diseases from each other.¹⁴² Skin rashes and reduced platelet counts can also be observed in COVID-19 patients, increasing the likelihood of misdiagnosis.^{139,142} Symptoms such as reduced lymphocyte and monocyte counts, elevated glucose levels, and serious respiratory disorders have been reported in cases with SARS-CoV and DENV coinfection.¹⁴³ In the absence of any major clinical symptoms in dormant DENV infection, serious clinical manifestations and a need for hospitalization have been confirmed during the active phase of DENV infection.¹⁴³ In cases with no history of DENV-related symptoms, coinfection with SARS-CoV-2 might result in the exacerbation of respiratory complications, mandating hospitalization. Although the number of lymphocytes and monocytes can decrease in coinfection with SARS-CoV-2 and DENV, leukopenia has only been documented in patients with classic DF.¹⁴⁴ The number of

lymphocytes in the peripheral blood may increase in the mixed infection of DENV and SARS-CoV-2, hence, the reports of impaired innate and acquired immune systems in these patients.¹⁴⁵ It should be noted that coinfection with SARS-CoV-2 and DENV are associated with elevated blood glucose levels, which favor replication of SARS-CoV-2.¹⁴⁶

Therefore, it is necessary to utilize the fastest and most sensitive serological tests, such as antibodies against the nonstructural glycoprotein 1 (NS1), secreted by all flaviviruses, at the appropriate time after the onset of symptoms (5 days after onset of fever), especially in endemic areas.¹⁴⁷ Increased IL-6 levels in DENV infection are associated with enhanced severity of symptoms.³⁰ However, serum studies of cases with acute symptoms of COVID-19 revealed increased amounts of proinflammatory cytokines (TNF- α , IL-1, and IL-6).¹⁴⁸ One of the markers facilitating the identification of individuals suspected to have COVID-19 is lymphocytopenia, which may incapacitate the immune system against DENV infection.^{61,149} Bleeding disorders have been identified in a few cases during COVID-19. The most frequent sign of DF is bleeding, which might aggravate the infection.¹⁵⁰ Lymphopenia has been documented to contribute to bleeding in the presence of SARS-CoV-2 and DF infection alone; therefore, the ratio of neutrophils to lymphocytes in DENV infection can become inverse.¹⁵¹

Coinfection with two viruses can either alleviate or increase the severity of the disease.¹⁵² A common consequence in such cases is viral interference. During viral interference, one virus competes with another, interfering with the replication mechanism.¹⁵³ Accordingly, this mechanism might have a major impact on the development of DF and its natural history.¹⁵⁴

2.4 | Coinfection with CMV and SARS-CoV-2

CMV can predispose individuals to severe cases of COVID-19 through disruption of peripheral blood T-cell differentiation, and upregulation of inflammatory cytokines, including IL-6, especially in the elderly.³¹ T-cell dysfunction is mostly due to decreased thymic function, determined by the age of the patient. T cells are highly important in the regulation of immune responses against viral infections.^{155,156} The prevalence of CMV infection in elderly patients compromises the immune response to subsequent viral infections, including SARS-CoV-2, by mitigating the diversity in the population of naïve T cells. The correlation between the ineffectiveness of influenza vaccine in the elderly patients and the decreased count of CD8⁺ T cells due to thymic dissolution,¹⁵⁷ as well as the increase in the count of T-reg and CD4⁺ T cells in individuals with CMV reactivation,⁴⁰ explains the pivotal role of cellular immunity mediated by T cells in viral infections.

The serum level of IL-6 is usually increased in individuals infected with CMV,¹⁵⁷ which is very similar to COVID-19 patients, who exhibit increased levels of cytokines (IL-6, IL-10, and TNF- α), decreased lymphocytes (CD4⁺ and CD8⁺ T cells), and diminished IFN- γ secretion from CD4⁺ T cells.⁴¹ On the contrary, the clinical use

of tocilizumab as a monoclonal antibody versus IL-6, has been demonstrated to be very effective in the treatment of COVID-19 patients admitted to the ICU.¹⁵⁸ Therefore, it can be concluded that coinfection with CMV or activated CMV in COVID-19 patients can exacerbate the underlying disease and induce cytokine storms. Thus, identification of this latent virus can be effective in adopting appropriate treatment methods for suppressing the inflammation.

ACE2 is the major receptor mediating the entry of SARS-CoV-2 into the host cells, which is expressed in large amounts in organs, such as the kidneys and lungs.¹⁵⁹ Patients with renal insufficiency due to immunosuppression stand among the most sensitive groups and are at risk of death from COVID-19.¹⁶⁰ Carll et al.¹⁶¹ investigated the clinical symptoms of systemic coinfection or CMV reactivation in SARS-CoV-2 infection with hemorrhagic enterocolitis. In this regard, the pathogenesis of CMV and serious enterocolitis in severe COVID-19 has been the subject of several speculations, such as:

1. Serious lymphocytopenia occurs in severe SARS-CoV-2 infection, which leads to cellular immune system deficiencies and, as a result, CMV reinfection or reactivation.⁷⁰ Subsequently, impairment of the reticuloendothelial and hematopoietic systems, such as the bone marrow, spleen, and lymph nodes may result in the death of T cells in severe COVID-19.^{162,163} In this respect, as the population of effector and CD8⁺ cytotoxic T cells decline, the effects of SARS-CoV-2 infection become more serious, leading to innate and adaptive immune system failure and eventually predisposing individuals to viral infections.^{162,164,165}

2. Immune modulators like tocilizumab suppress the biological and pathological effects of hemophagocytosis caused by cytokine secretion and, as a result, intensify COVID-19 symptoms.^{35,161} B and T lymphocytes, macrophages, dendritic cells, fibroblasts, and endothelial cells also secrete IL-6.¹⁶¹ In H1N1 flu, a decrease in the IL-6 activity has also been associated with serious pulmonary complications.¹⁶⁶ As a consequence, immune modulators, according to reports, might play a key role in the development of CMV coinfection.¹⁶⁷⁻¹⁶⁹

CMV is the most common viral infection among patients with kidney failure, especially kidney transplant recipients.¹⁷⁰ Studies show that COVID-19-induced cytokines increase creatine kinase, which, in turn, elevates serum creatinine (Cr) and blood urea nitrogen (BUN), particularly in patients with kidney transplants.^{171,172} Accordingly, SARS-CoV-2 and CMV coinfection in kidney transplant recipients may potentially aggravate the clinical status of these patients. Thus, continuous monitoring of Cr, BUN, ALT, and CRP levels, as prognostic factors, as well as the lymphocyte count is recommended to be regularly measured in these patients to mitigate the risk of death.¹⁷³

2.5 | Coinfection with EBV and SARS-CoV-2

The causative agent of infectious mononucleosis, EBV is involved in the development of chronic active infections due to a variety of

lymphoproliferative disorders, for example, Hodgkin's lymphoma, Burkitt's lymphoma, B-cell lymphoma, plasma myeloma, NK/T-cell lymphoma, and NK cell carcinoma, especially in individuals with immunodeficiency or patients with transplantation.¹⁷⁴ As patients with COVID-19 may frequently develop lymphocytopenia, it is advised to rule out SARS-CoV-2 and EBV coinfection, especially in the elderly or patients with transplants, who are susceptible to both viruses.³⁴ This is because the decrease in the count of lymphocytes, and the inability of the cellular immune system to eliminate the infectious agent can lead to the development of dysplasia, and ultimately, malignancy. In this regard, the mortality rate can increase as a result of simultaneous infection with EBV and SARS-CoV-2.³⁴

3 | DIAGNOSIS OF VIRAL COINFECTIONS

On the basis of their prevalence, the clinical signs and symptoms associated with SARS-CoV-2 infection include fever (more than 90%), cough (69.8%), shortness of breath (34.5%), myalgia (27.7%), sore throat (17.4%), headache (7.2%), diarrhea (6.1%), and rhinorrhea (4.0%).^{90,175} COVID-19 also causes radiological changes in the lungs, such as ground-glass opacity, thickened bronchial wall, and pleural effusion.¹⁷⁶ As a result, due to changes in radiological imaging and similarity of clinical symptoms caused by SARS-CoV-2 with those of other viral respiratory tract infections, it is difficult to distinguish the exact type of virus and the count of viruses that might have infected the patients, which, in turn, leads to misdiagnosis of COVID-19 and other respiratory diseases.^{90,177,178} SARS-CoV-2 infection is also associated with lymphopenia, prolonged prothrombin time (PT), high levels of LDH, ALT, AST, D-dimer, C-reactive protein (CRP), and troponin, along with neutrophilia and eosinophilia.¹¹¹ Lymphocytopenia and increased levels of CRP are believed to be the most important lab findings, which are frequently observed in other viral infections, too.¹⁷⁹ Despite the multiple diagnostic indicators, reverse transcription-polymerase chain reaction (RT-PCR) is one of the most reliable methods to identify coinfection with SARS-CoV-2 and other viruses.^{90,180} The test is performed on the sputum or nasopharyngeal secretions of individuals suspected to be infected. The risk of bias, false-negative reports, and the necessity to repeat the test for proper diagnosis should be considered by clinicians.^{90,181}

4 | CONCLUSION

Coinfections, compared with single infections, may lead to changes in transmission of the pathogen, progression of clinical symptoms, and the adverse effects associated with any given infection, which ultimately determines the management of infectious diseases.¹⁸²⁻¹⁸⁵ The inability of conventional methods to detect coinfection, in the absence of sufficient evidence, in turn, can result in underdiagnosis of coinfections.¹⁸⁶ Coinfections or mixed infections have been reported to negatively affect the efficiency of diagnostic methods used for detection of SARS-CoV-2; for instance, RT-PCR may not be the

optimal diagnostic test for diagnosis of COVID-19 in patients with influenza A virus coinfection.¹⁸ In contrast, nucleic acid amplification test would be a suitable method for detection of influenza virus RNA in the case of coinfection with SARS-CoV-2.⁷⁸ Similarly, a proper diagnosis of DENV and SARS-CoV-2 coinfection in countries endemic to DF can only be made through the adoption of reliable laboratory tests, such as the PCR of the nasopharyngeal swab and anal swab, NS1 DENV, immunoglobulin (Ig) M and IgG assays.¹⁸⁷ It is also necessary to develop new strategies to better understand the clinical signs of coinfections and discover suitable therapeutic options for them.¹⁸⁸ Accordingly, early detection of coinfections is important due to the discrepancies in treatment and appropriate prognosis.¹⁸⁹ Considering the fact that there is more than one mechanism involved in the occurrence of coinfections, one might hypothesize that the mere existence of a virus and its impact on the immune system may provide the foundation for the replication of the other virus and suppression of the molecular mechanism of normal cells. For instance, in the case of COVID-19, the triad of lymphocytopenia, overexpression of inflammatory cytokines, and dysfunction of the acquired immune system pave the way for the development of coinfection, which may result in detrimental sequelae in an otherwise healthy individual.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Hossein B. Baghi was involved in the study design, review of the manuscript, and is the corresponding author. Parisa S. Aghbash was involved in literature search, figure design, manuscript preparation, and review of the manuscript. Nergar Eslami was involved in table design and review of the manuscript. Milad Shirvaliloo was involved in editing and reviewing of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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