










REVIEW

SARS-CoV-2 and dengue virus co-infection: Epidemiology, pathogenesis, diagnosis, treatment, and management

Chowdhury Nusaiba Binte Sayed Prapty^{1,2}  | Raad Rahmat^{1,2}  | Yusha Araf^{1,3}  |
 Samiha Kamal Shounak²  | Noor-A-Afrin²  | Tanjim Ishraq Rahaman⁴  |
 Mohammad Jakir Hosen³  | Chunfu Zheng^{1,5}  | Md. Golzar Hossain⁶ 

¹Department of Immunology, School of Basic Medical Sciences, Fujian Medical University, Fuzhou, China

²Biotechnology Program, Department of Mathematics and Natural Sciences, BRAC University, Dhaka, Bangladesh

³Department of Genetic Engineering and Biotechnology, School of Life Sciences, Shahjalal University of Science and Technology, Sylhet, Bangladesh

⁴Department of Biotechnology and Genetic Engineering, Faculty of Life Sciences, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj, Bangladesh

⁵Department of Microbiology, Immunology and Infectious Diseases, University of Calgary, Calgary, Alberta, Canada

⁶Department of Microbiology and Hygiene, Bangladesh Agricultural University, Mymensingh, Bangladesh

Correspondence

Chunfu Zheng, Department of Immunology, School of Basic Medical Sciences, Fujian Medical University, Fuzhou, China; Department of Microbiology, Immunology and Infectious Diseases, University of Calgary, Calgary, Alberta, Canada.
 Email: zheng.alan@hotmail.com

Md. Golzar Hossain, Department of Microbiology and Hygiene, Bangladesh

Abstract

SARS-CoV-2 and dengue virus co-infection cases have been on the rise in dengue-endemic regions as coronavirus disease 2019 (COVID-19) spreads over the world, posing a threat of a co-epidemic. The risk of comorbidity in co-infection cases is greater than that of a single viral infection, which is a cause of concern. Although the pathophysiologies of the two infections are different, the viruses have comparable effects within the body, resulting in identical clinical symptoms in the case of co-infection, which adds to the complexity. Overlapping symptoms and laboratory features make proper differentiation of the infections important. However, specific biomarkers provide precise results that can be utilised to diagnose and treat a co-infection, whether it is simply COVID-19, dengue, or a co-infection. Though their treatment is distinguished, it becomes more complicated in circumstances of co-infection. As a result, regardless of whatever infection the first symptom points to, confirmation diagnosis of both COVID-19 and dengue should be mandatory, particularly in dengue-endemic regions, to prevent health deterioration in individuals treated for a single infection. There is still a scarcity of concise literature on the epidemiology, pathophysiology, diagnosis, therapy, and management of SARS-CoV-2 and dengue virus co-infection. The epidemiology of SARS-CoV-2 and dengue virus co-infection, the mechanism of pathogenesis, and the potential impact on patients are summarised in this review. The possible diagnosis with biomarkers, treatment, and management of the SARS-CoV-2 and dengue viruses are also discussed. This review will shed light on the appropriate diagnosis, treatment, and

Abbreviations: ACE2, Angiotensin converting enzyme 2; ADE, Antibody dependent enhancement; Ag, Antigen; AIIMS, All India Institute of Medical Sciences; ALT, Alanine transaminase; ARDS, Acute respiratory distress syndrome; AST, Aspartate transaminase; AUII, Acute undifferentiated febrile illness; BAL, Bronchoalveolar lavage; BBB, Blood brain barrier; CBC, Complete blood count; CDC, Centres for Disease Control and Prevention; CNS, Central nervous system; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CSF, Cerebrospinal fluid; CT, Computerised tomography; CTSB, Cysteine proteases cathepsin B; CTSL, Cysteine proteases cathepsin L; DAD, Diffuse alveolar damage; DENV, Dengue virus; DF, Dengue fever; DHF, Dengue haemorrhagic fever; DIC, Disseminated intravascular coagulation; DSS, Dengue shock syndrome; ELISA, Enzyme-linked immunosorbent assay; FcγR, Fcγ receptors; GGT, Gamma glutamyl transferase; HMGB1, High mobility group box 1; ICTV, International Committee on Taxonomy of Viruses; ICU, Intensive care unit; IFN, Interferon; Ig, Immunoglobulin; IL, Interleukin; IP-10, Interferon gamma-induced protein 10; MCP-1, Monocyte chemoattractant protein-1; MERS-CoV, Middle East respiratory syndrome coronavirus; MIF, Migration inhibitory factor; NLR, Neutrophil-to-lymphocyte ratio; NSP1, Nonstructural protein-1; PCR, Polymerase chain reaction; PE, Pulmonary embolism; RBD, Receptor binding domain; RT-PCR, Reverse transcription-polymerase chain reaction; rRT-PCR, Real-time reverse transcription-PCR; SARS-CoV, Severe acute respiratory syndrome coronavirus; SGPT, Serum glutamic pyruvic transaminase; S protein, Spike protein; TNF, Tumour necrosis factor; TMRPSS2, Transmembrane serine protease 2; VEGF, Vascular endothelial growth factor; WHO, World Health Organization; ZO-1, Zona occludens protein 1.

Chowdhury Nusaiba Binte Sayed Prapty, Raad Rahmat, and Yusha Araf have contributed equally to this work.

Agricultural University, Mymensingh,
Bangladesh.
Email: mghossain@bau.edu.bd

management of the patients suffering from SARS-CoV-2 and dengue virus co-infection.

KEYWORDS

biomarkers, co-infection, dengue virus, epidemiology, management, mechanism, SARS-CoV-2

1 | INTRODUCTION

There was an influx of patients with pneumonia of unknown origin in Wuhan, Hubei Province, China, in December 2019.^{1,2} Sequencing the viral genome isolated from the pneumonia patients revealed that the etiological agent was the novel beta coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belonging to the Coronaviridae family, becoming the 7th member of the family to cause disease in humans.¹ The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 showed symptoms that resembled previous outbreaks of two other beta coronaviruses, Middle East respiratory syndrome coronavirus and SARS-CoV. The COVID-19 patients typically exhibit symptoms such as mild pneumonia, including fever, cough, and chest pains; however, the symptoms could become moderate to severe with the patients manifesting dyspnoea, elevated respiratory frequency, reduced blood oxygen saturation, and lung infiltration. Respiratory failure, septic shock, and multiple organ failure could be critical or fatal in some circumstances.³ However, having human-to-human transmission capabilities, the virus soon spread globally, compelling World Health Organization (WHO) to declare it a 'Public Health Emergency' on 30 January 2020, and eventually labelled the outbreak a 'pandemic' on 11 March 2020.^{2,4} As of 14 November 2021, 252,920,587 confirmed COVID-19 cases were reported in 224 countries with 5,095,436 confirmed fatalities.⁴

Dengue caused by the dengue viruses (DENV) is one of the major threats among vector-borne diseases in tropical and subtropical regions, infested with its vectors, *Aedes aegypti* and *Aedes albopictus*.^{5,6} It is caused by four serotypes of the virus, DENV-1, DENV-2, DENV-3, and DENV-4, belonging to the Flaviviridae family.⁵ Dengue might induce nonspecific febrile illness dengue fever when an infected mosquito bites a person.⁵ In some circumstances, however, the disease could become more serious, even fatal in some instances, if it leads to dengue haemorrhagic fever and dengue shock syndrome involving plasma leakage coagulopathy, circulatory shock, and multiorgan failure.⁵ According to WHO, there has been an alarming 8-fold increase in dengue infection during the last 2 decades. The incidence is estimated to be 100–400 million infections annually, while in 2015, it caused 4032 deaths.⁷

Dengue is usually endemic or hyperendemic (circulation of multiple serotypes of DENVs) in countries that are relatively compromised in terms of health care systems. As a result, with the already existing pressure due to the COVID-19 pandemic, the increasing incidence of dengue during the monsoon season posed a serious threat due to the existence of simultaneous outbreaks of these diseases, which might be torrential for the health care system in these

countries, especially in cases involving co-infection by SARS-CoV-2 and DENV.⁷ Thirty-one such co-infection cases have been observed across multiple case studies in South American, South African, and South Asian regions.^{8–19} Despite differences in the pathophysiology, infections with the viruses simultaneously share several clinical symptoms and laboratory characteristics.⁴ These overlapping symptoms render it harder to diagnose the infection, leading to misdiagnosis and missing out on co-infection cases. For example, some common symptoms of both infections include fever, headache, nausea.⁴

The impact of co-infection, specifically in the dengue-endemic regions, can lead to the rise of a co-epidemic, possibly overburdening a nation's healthcare system. Therefore, along with the appropriate preventive measures, special care of patients coinfecting with SARS-CoV-2 and DENV in the context of diagnosis, treatment, and management should be taken based on the previous histories and COVID-19 and dengue-endemic prone regions. Therefore, this review focussed on the epidemiology, pathogenesis, diagnosis, treatment, and management of patients coinfecting with SARS-CoV-2 and DENV.

2 | EPIDEMIOLOGY

The COVID-19 pandemic surmounted substantial pressure on the countries' healthcare systems with the existing pressure from dengue in endemic and hyperendemic (co-occurrence of multiple serotypes of DENVs) regions, especially with cases of COVID-19 and dengue co-infection.⁷ The Centres for Disease Control and Prevention (Centres for Disease Control and Prevention) reported a total of 13 patients who had COVID-19 and dengue co-infection in Buenos Aires, Argentina, during a study from March to June 2020. Among them, 6 were female, 7 were males, and the median age was 37 (29–50 years). None of the patients were shown to have severe dengue, while only one patient had severe COVID-19, and all the patients were survived.⁸ A study involving patients from tertiary care hospitals in Singapore was carried out where nine patients were initially suspected of having been coinfecting with DENV and SARS-CoV-2. However, eight cases were later diagnosed as COVID-19 patients with false-positive dengue IgM. The ninth patient, a 31-year-old Bangladeshi male, tested positive for dengue nonstructural protein-1 (NSP1) and positive SARS-CoV-2 polymerase chain reaction (PCR) but negative for IgM. Dengue, therefore, was diagnosed as COVID-19 and probable dengue coinfecting patient. The patient fully recovered without complication.¹⁰ Another study in Pakistan

reported five patients who tested positive for COVID-19 and dengue (DENV2) following real-time reverse transcription PCR (rRT-PCR). The median age of the patients was 43 years (43.4 ± 17.98), among whom three were males and two were females. In this study, three of the patients passed away, while the remaining two were hospitalised during the study.¹¹

Additionally, eight different case studies involving nine patients were reported in Thailand, the Philippines, Africa, Reunion Island, India, the Maldives, and Brazil. In this study, a 50-year-old female flight attendant, 62-year-old female, 18- and 44-year-old males, a 9-month-old infant, 22-year-old pregnant female, 38- and 39-year-old Asian males, and a 56-year-old woman. All the patients, except the 9-month-old female child, had mild to moderate severity, while the latter exhibited moderate to severe symptoms. All the patients in these case report made a full recovery.¹²⁻¹⁸ Times of India further reported a case of a 68-year-old man who died suffering from COVID-19 and dengue at All India Institute of Medical Sciences, Bhopal.²⁰ Two patients of Bangladesh have also been reported to have co-infection with SARS-CoV-2 and DENV, causing one of the patients to succumb to it eventually.¹⁹

The COVID-19 pandemic, coupled with potential dengue outbreaks during the monsoon season in endemic countries, like Brazil, Paraguay, Bolivia, Argentina, Colombia, Mexico, Philippines, Malaysia, Singapore, Vietnam, Thailand, and Indonesia are at high risk of SARS-CoV-2 and DENV co-infection as already highlighted by 31 confirmed cases in Brazil, Argentina, Singapore, Thailand, Maldives, India, Pakistan, Bangladesh, and even a French island in the Indian Ocean, among whom five passed away (Figures 1 and 2).⁸⁻¹⁹ Considering the glaring death rate of SARS-CoV-2 and DENV co-infection of 16.13% (5 deaths among 31 coinfecting patients), significantly higher than the global death rates of single infection of both diseases. The COVID-19 has a death rate of around 2.04%, which varies between 0.8% and 2.5%. The SARS-CoV-2 and DENV co-infection in these regions will perhaps continue to burden the healthcare system substantially.⁸⁻¹⁹

3 | PATHOPHYSIOLOGY

The SARS-CoV-2 and DENV consist of a single-stranded, positive-sense RNA genome.²¹ However, SARS-CoV-2 contains spike glycoprotein, which interacts with the host cellular receptor angiotensin-converting enzyme-2 (ACE2) to enter the cells.^{21,22} In contrast, DENV enters into the cells through various groups of attachment factors, including C-type lectins DC-SIGN (CD209), mannose receptor (CD206), glycosaminoglycans (heparan sulphate), and immunomodulatory proteins (TIM/TAM receptors).^{20,23,24} SARS-CoV-2 infection and interaction with ACE2 stimulate an inflammatory immune response, a cytokine storm, during the COVID-19 infection.^{25,26} Such cytokine storms are also observed in dengue infections and elicited by increasing antibody concentrations.²⁷

Plasma leakage, including other vascular disorders and permeability, and disseminated intravascular coagulation that have been

observed in COVID-19 and dengue co-infection is linked to several immune-mediators, including proinflammatory cytokines, tumour necrosis factor, IL-6, and interferon (IFN)- γ , as well as chemokines, such as migration inhibitory factor.²⁸⁻³⁰ The COVID-19 and dengue exhibit similar pathophysiology for capillary leakage, thrombocytopenia, and coagulopathy during co-infection.³¹ In dengue, plasma leakage is linked to the interaction of NSP1-specific antibodies with endothelial cell surface proteins, leading to increased viral multiplication and inflammatory cytokine release.⁹ Endothelial cells are activated, and platelets are targeted by NSP1 antibodies, which are highly immunogenic and stimulate the production of autoantibodies.²⁹ In DENV-2, anti-NSP1 antibodies inhibit platelet aggregation and cause platelet lysis associated with transient thrombocytopenia.³²⁻³⁴ While COVID-19 is distinguished by elevated inflammatory cytokine production, particularly IL-6, and over-activation of effector T-cell activity, leading to capillary leakage and thrombocytopenia.³¹

Furin protease plays a crucial role in the SARS-CoV-2 infection and viral entry into the alveolar cells.^{35,36} The SARS-CoV-2 replicates in the alveolar epithelial cells, leading to alveolar damage, oedema, hyaline membrane formation, immune cell infiltration into the lungs, and the desquamation of pneumocytes that causes Acute respiratory distress syndrome.³⁷ Lung damage is further increased during DENV co-infection. DENV-infected monocytes primarily secrete monocyte chemoattractant protein-1 (MCP-1) that alters endothelial permeability through reorganization of the endothelial cell tight junction protein, zona occludens protein 1.²⁹ High mobility group box 1 protein is also observed to be secreted by DENV infected monocytes and dendritic cells stimulating endothelial cells to produce adhesion molecules and cytokines, which interfere with the barrier function of lung endothelial cells.³⁸

The SARS-CoV-2 infection affects the coagulation system in the same way as dengue virus infection does. The progression of COVID-19 illness is aided by pulmonary intravascular coagulation. After alveolar injuries, resident alveolar macrophages are activated, resulting in the release of potent proinflammatory mediators and chemokines that promote the accumulation of neutrophils and monocytes, such as vascular endothelial growth factor, angiotensin II, glycosaminoglycans (GAGs), von Willebrand factor, and soluble intercellular adhesion molecule.³⁹ By releasing toxic mediators, activated neutrophils lead to additional injury. On the other hand, intravascular coagulation causes platelet aggregation and the production of microthrombi, which can worsen pulmonary damage.⁴⁰ Increased dead space is the most common result of intravascular coagulation (increased wasted ventilation and less efficient carbon dioxide removal). Inflammatory mediators from endothelial damage, on the other hand, may increase hypoxaemia by exacerbating ventilation-perfusion mismatching. Clinically, coagulation and thrombosis have been recognized as major COVID-19 signs. Initial anticoagulant treatment with low-molecular-weight heparin or aspirin reduced mortality and improved PaO₂ significantly and FiO₂ levels in some COVID-19 patients.⁴¹

Epidemiological summary of SARS-CoV-2 and DENV co-infection cases

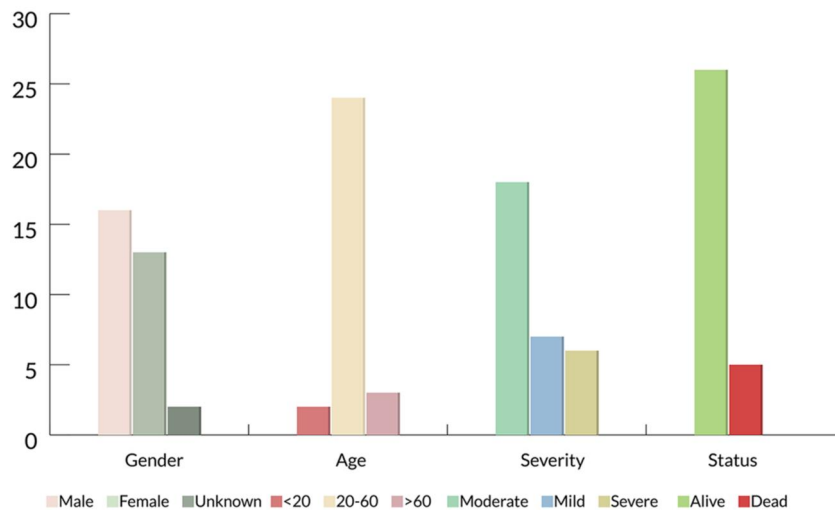


FIGURE 1 Epidemiological summary of SARS-CoV-2 and dengue viruses (DENV) co-infection cases. A total of 31 cases of SARS-CoV-2 and DENV co-infections have been reported throughout the world so far. Sixteen were male, thirteen were female, while two patients' genders were not reported. The majority (24) of the patients were within the 20–60 age group, while two were below 20 and the remaining 3 were older than 60 years. Eighteen patients were suffered from mild symptoms, whereas seven had moderate symptoms, and five endured severe symptoms. Twenty-six of the patients in the case studies survived; however, five died

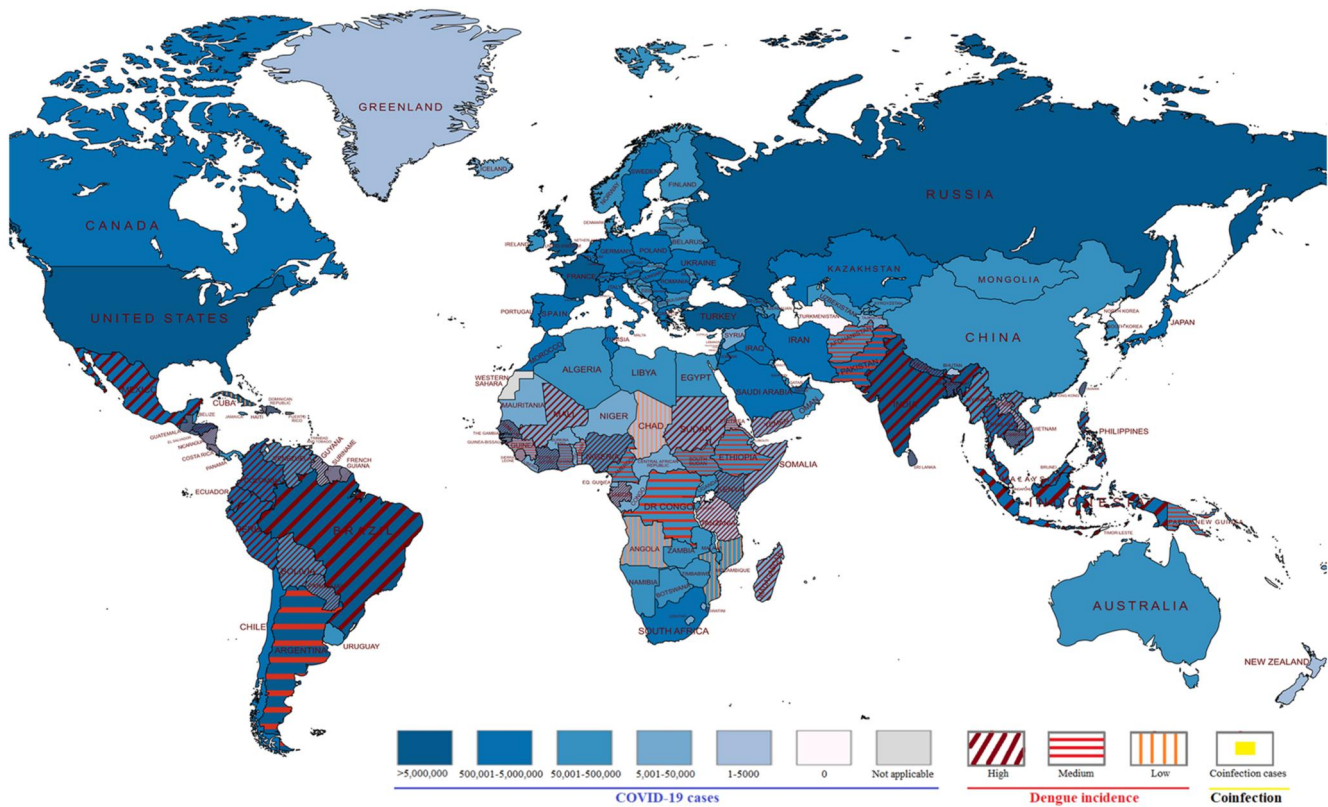


FIGURE 2 Global distribution of SARS-CoV-2 and dengue viruses (DENV) co-infection. The map illustrates the global cases of coronavirus disease 2019 (COVID-19) along with dengue-endemic regions with varying incidence. The countries with the 31 SARS-CoV-2 and DENV co-infection cases are also indicated on the map. The cases were primarily observed in the South American, South African, and South Asian regions

It is evident from these studies that in co-infection cases, both SARS-CoV-2 and DENV, either synergistically or individually, lead to damage to different organs, especially the lungs, liver, cardiovascular system, and the Central nervous system (CNS). As a result, COVID-19 and dengue co-infection correlate with more severe symptoms with poorer prognoses than single infections. Viruses can actively infiltrate the CNS during the SARS-CoV-2 and DENV co-infection.^{42,43} Though the entrance of DENV into the CNS is unclear, it is suggested that the disturbance mediated by cytokine during DENV infection alters neurovascular unit integrity. After that, DENV can access the CNS through the blood-brain barrier.⁴⁴ Anti-DENV IgM, viral RNA, and DENV NSP1 can be detected in the cerebrospinal fluid during infection that may account for the common neurological manifestations of dengue, such as encephalitis and encephalopathy, which are associated with the severe disease with slower recovery.⁴⁵⁻⁴⁸ Virus entrance into the cell may depend on the endosomal/lysosomal cysteine proteases cathepsin B and cysteine proteases cathepsin L even though the activity of these two enzymes is not essential to infect the cerebral nervous system, SARS-CoV-2 may also utilise the presumed complementary receptor CD147 (expressed in high levels in the brain).^{26,36} The neurological signs and symptoms during COVID-19 infection also reported headache, dizziness, acute cerebrovascular disease, epilepsy, ataxia, anosmia, and muscle pain demyelinating encephalomyelitis.⁴⁹ Thus, severe neurological complications may occur in COVID-19 and dengue co-infection cases. The possible mechanism and pathophysiology for SARS-CoV-2 and DENV co-infection have been illustratively summarized in Figure 3.

4 | BIOMARKERS

The COVID-19 and dengue both have certain biomarkers that act as measurable parameters to indicate the process and progress of pathogenesis and the results of therapeutic interventions. Among the plethora of biomarkers, some shared by both viral infections, individually, including increased levels of certain cytokines such as TNF- α , IL-8, IL-6, IL-10, increased infection biomarkers such as C-reactive protein (CRP) and interferon gamma-induced protein 10 (induced protein 10), particularly in severe COVID-19 cases.⁵⁰ In the case of COVID-19, the increase in IL-6 levels are more dramatic, whereas, for dengue, it is the rise in the concentration of IL-10 that is more prominent.⁵¹ Alternatively, the contrasting biomarkers for the two diseases include, more notably increased leucocytes and neutrophil count in COVID-19 infection compared to a decreased one in dengue, the high platelet count in COVID-19 versus low platelet count in dengue, lower Alanine transaminase (ALT) and Aspartate transaminase (AST) levels in the former and a higher than normal level in the latter, as well as a high neutrophil-to-lymphocyte ratio (NLR) in COVID-19 compared to a lower than normal levels in case of dengue.^{52,53} In co-infection of SARS-CoV-2 and the DENV, the biomarkers turned out to be a mixture from both; the level of ALT in the liver was elevated greatly along with slight increases of creatinine in

the kidneys, there was thrombocytopenia (low platelet counts), the numbers of lymphocytes and leucocytes reduced considerably too, alongside with high CRP, and reduced haemoglobin and haematocrit less commonly (Table 1 and Figures 4).⁶⁵

5 | DIAGNOSIS

It is often very difficult to diagnose and distinguish between COVID-19 and dengue in the same patients due to sharing some common symptoms. There are several common clinical features such as fever, headache, myalgia, asthenia, nausea, arthralgia, and sometimes cough in the case of COVID-19 and dengue (Figure 5). Frequent complaints of vomiting, retro-orbital pain, and skin rashes in certain cases are all more particular to dengue infection than COVID-19 (Figure 5). Moreover, in severe dengue cases, pulmonary oedema showed clinical and radiological features with severe pneumonia in COVID-19.⁶⁴ As a result, precise and accurate diagnosis based on the clinical symptoms poses a challenge.

COVID-19 is a multisystem disease with a heterogeneous spectrum, and rRT-PCR is most commonly used to confirm the infection. The tentative clinical diagnosis involves monitoring typical respiratory syndromes along with recent exposure (Figure 5). An early tentative diagnosis can be made by a Chest Computerised Tomography (CT) scan, which has a sensitivity of 97.2%. The rRT-PCR has a sensitivity of 83.3% though it sometimes showed false negatives. Therefore, simultaneous CT scans followed by the repeating rRT-PCR are necessary in case of further confirmatory diagnosis of COVID-19.⁶⁸

On the other hand, diagnosis of dengue infection is mainly performed by IgM capture enzyme-linked immunosorbent assay (ELISA), detection of nonstructural protein-1 antigen (NSP1Ag), dengue Reverse transcription-polymerase chain reaction (RT-PCR), and sometimes virus isolation.⁶⁹ The rapid NSP1 antigen and NSP1 ELISA are commonly used as initial diagnostic tools due to their availability, sensitivity, and specificity rates of 55.5% and 92%.⁷⁰ RT-PCR is then performed to confirm unclear/mixed symptoms.¹⁴

However, in the case of a co-infection, common laboratory tests, such as Complete blood count and ALT, can be useful and efficient. The NLR values indicate whether leukopenia or lymphopenia is occurring to distinguish between the infections. In the case of dengue, a common diagnostic test shows progressive leukopenia followed by a rapid fall in platelet count and a rising haematocrit. In contrast, in COVID-19, leukopenia or leucocytosis can occur with lymphopenia as the more common indicator of severity.⁷¹ For a case classified as dengue through initial clinical symptoms, a test reveals a significant increase of ALT than AST, which can indicate another infection, in some instances, which could be a SARS-CoV-2 and DENV co-infection. In almost all co-infection cases, thrombocytopenia is a prominent and consistent condition due to lower platelet synthesis resulting from bone marrow suppression by the viruses and immune-mediated clearing of the platelets. Another hypothesis is that the platelets are destroyed by the autoantibodies and immune complexes formed due to SARS-CoV-2 and DENV infection.⁷²

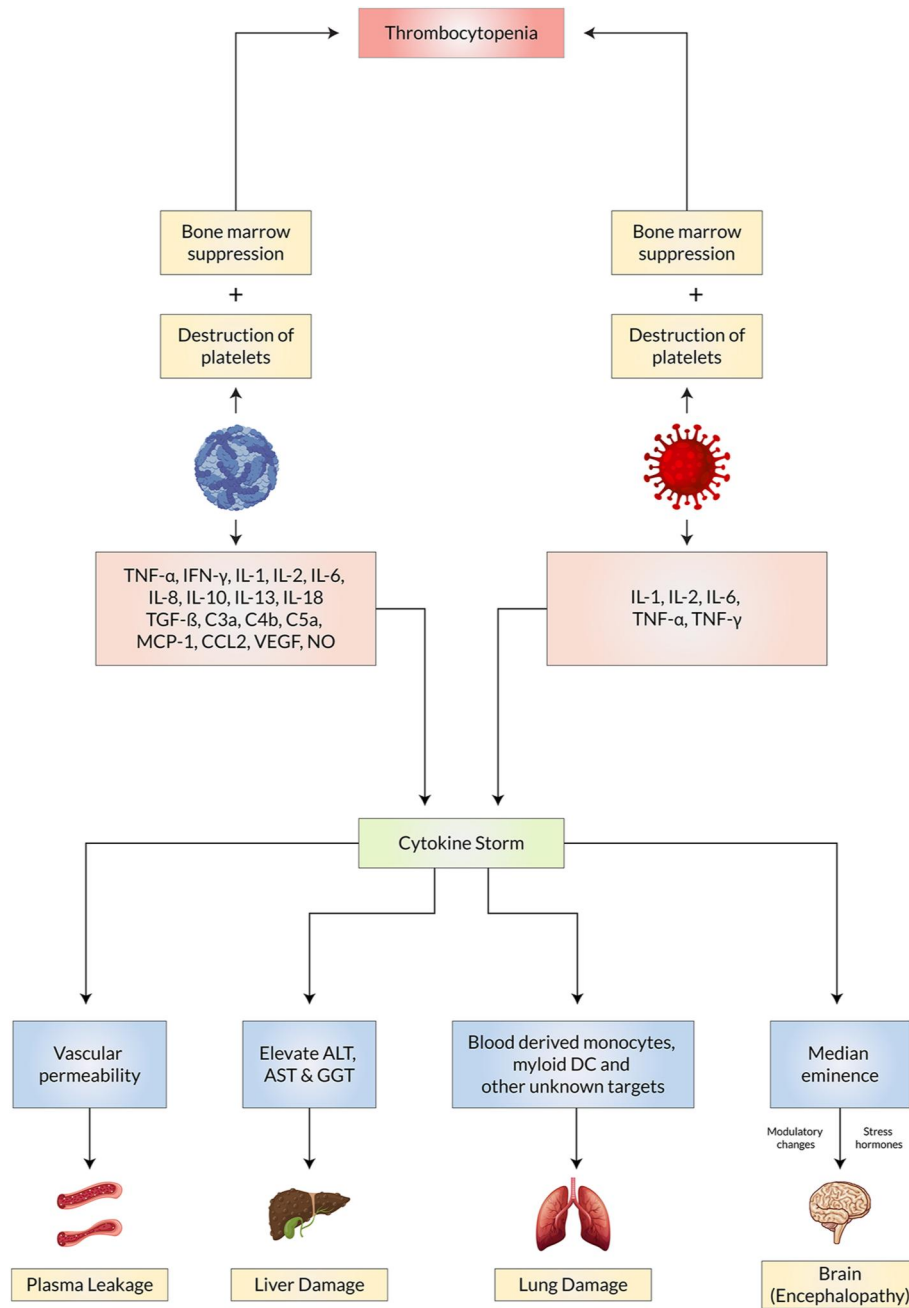


FIGURE 3 Pathophysiology of SARS-CoV-2 and dengue viruses (DENV) co-infection. The schematic figure shows possible mechanisms and pathophysiology of co-infection with SARS-CoV-2 and DENV. DENV infects cells through Fc γ R, particularly astrocytes and microglia, induces the discharge of inflammatory mediators (IL-6, vascular endothelial growth factor (VEGF), TNF- α , IFN- γ , IL-1 β and IL-10, MCP-1) and metalloproteinases. Similarly, SARS-CoV-2 infects cells through ACE2 receptor and release inflammatory mediators (IL-1, IL-2, IL-6, IFN- γ , IFN- α), which arbitrate the downregulation of adherents and tight junction proteins, resulting in increased blood-brain barrier (BBB) permeability, pulmonary embolism (PE), thrombocytopenia, diffuse alveolar damage (DAD), and can cause immune-mediated encephalopathy and encephalitis

6 | TREATMENT AND MANAGEMENT

The SARS-CoV-2 and DENV co-infection epidemic are more likely to be most significant (June to October), particularly in the tropical and subtropical regions, due to the onset of monsoon and simultaneous increase in dengue transmission.⁷³ Simultaneous COVID-19 and dengue in the same patient have overlapping clinical and laboratory

traits that are often difficult to differentiate, posing a considerable challenge to inaccurate diagnosis and treatment. Quarantining suspected individuals while awaiting test results is an ideal and well-established procedure in several institutes.⁶⁴ COVID-19 should be included in the differential diagnosis of individuals with fever in tropical locations, even in the absence of respiratory symptoms, a history of exposure, or travel. Vigilant awareness and inquiry are key

TABLE 1 Biomarkers for coronavirus disease 2019 (COVID-19), dengue, and co-infection by SARS-CoV-2 and dengue virus (DENV), along with their normal levels given for comparison

Characteristic	Normal range	Range in COVID-19	Range in dengue	Range in SARS-CoV-2 and DENV	References
Platelet count (/μL)	150,000–450,000	23,000–31,000	<100,000	41,000–106,000	14,54
White blood cell count (/μL)	3500–11,000	8000–12,000	<5000	1700–2380	14,54–63
Haemoglobin (g/dl)	11.5–16.5	13.5–14.2	9.5–18.8	16–16.9	57
AST (U/L)	8–33	28.75–33.20	>83.5	45–621	14,58–60,64
ALT (U/L)	7–55	26–30	>49 (>200 in severe cases)	75–545	14,58–60,64
CRP (mg/L)	<10	>26.9	>30	7.9–109	61–63

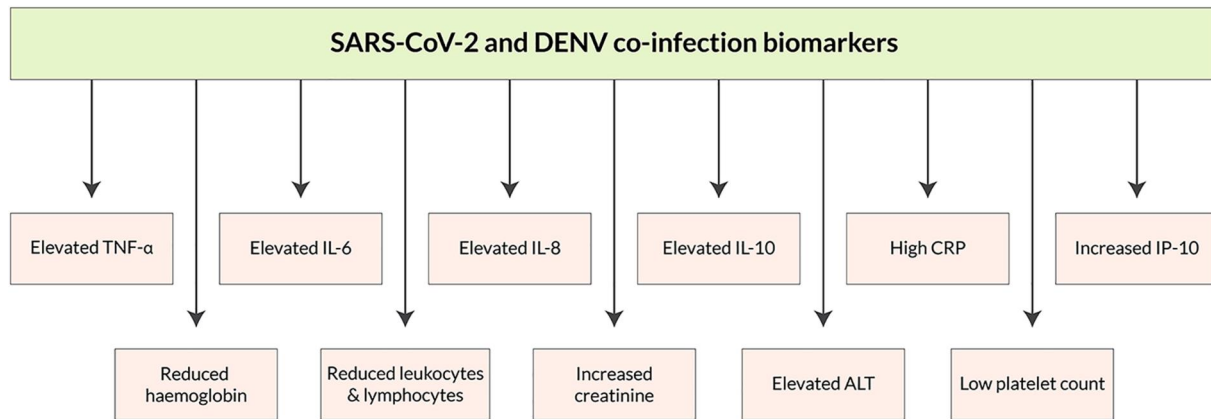


FIGURE 4 Biomarkers of SARS-CoV-2 and dengue virus (DENV) co-infection

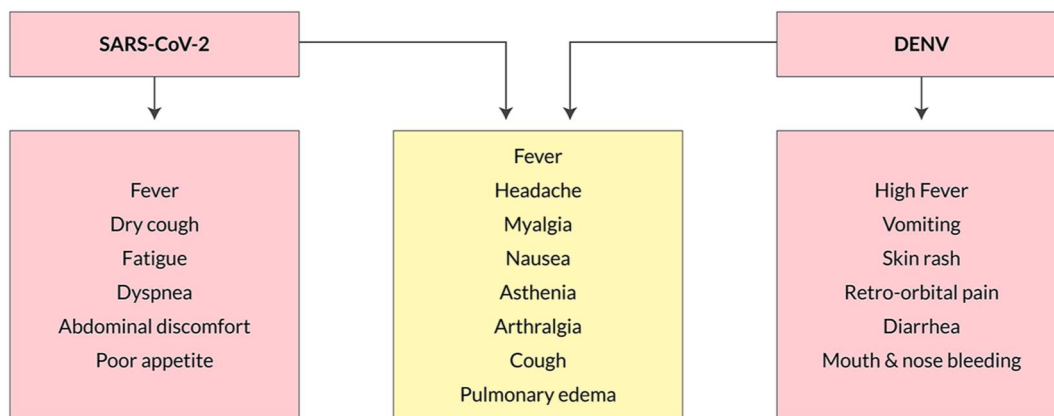


FIGURE 5 Common symptoms of SARS-CoV-2 and dengue virus (DENV) co-infection

for proper illness therapy and infection control.⁷⁴ Besides, it is still under observation if nAbs are more effective than vaccination. It is surely identified that nAbs from recovered COVID-19 patients' convalescent plasma are distinct from those formed due to vaccination injection. NABs are formed in proinflammatory circumstances, which may not always exist during vaccination.⁵⁵

On the other hand, a potential concern remains unchanged: the coexistence of fever after receiving the COVID-19 vaccination with an endemic tropical illness. An endemic haemorrhagic fever that may induce thrombocytopenia in a COVID-19 vaccination recipient must

be identified. This clinical issue might be misdiagnosed as a vaccine-related adverse event.⁵⁶ Mild to moderate Dengue and COVID-19 coinfecting patients should be constantly monitored, ideally in a hospital, since they can quickly develop to a severe stage, and they should be referred to a higher facility if warning symptoms are recognized.

Meanwhile, all secondary and tertiary level hospitals must be ready to handle severe dengue and COVID-19 cases. Co-infection has higher morbidity and must be treated with caution and care. Treatment should be decided based on the most severe symptoms;

for instance, patients with major respiratory problems should be admitted to the intensive care unit with high-flow O₂ supplementation containing proper oxygen saturation through non-rebreathing masks. Intubation and ventilation may be necessary in the most severe cases. For milder cases, monitored doses of vitamin C and prophylactic antimicrobials could be administered.⁷¹ The treatment options of SARS-CoV-2 and DENV co-infected patients have been summarized in Table 2. Overall, the treatment and management of co-infection cases necessitate timely and accurate diagnosis of the infection(s), along with a continuous supportive care regimen.

7 | CONCLUSION AND RECOMMENDATIONS

SARS-CoV-2 and DENV co-infection pose a serious threat to patient prognosis as both infections damage different parts of the body separately and collectively, leading to impairment of the respiratory, cardiovascular, CNS, kidneys, and liver. Despite the differences in pathophysiologies, overlapping symptoms and biomarkers make SARS-CoV-2 and DENV co-infection difficult to diagnose accurately, leading to inaccurate diagnosis and treatment of co-infection with only one of the infections being treated. As a result, testing for both DENV and SARS-CoV-2 is strongly advised in both COVID-19 patients exhibiting dengue symptoms or vice versa. Some contrasting

biomarkers might be used to suspect, test, and treat both infections, which is particularly important during the monsoon in the tropical and subtropical regions since the co-infection epidemic is more likely to be most significant during this period (June to October). Active participation of the city authorities and health department in developing dengue monitoring cells, designing vector control programs, and raising community awareness for eliminating mosquito breeding sites are just some of the preliminary recommendations to be followed.

Moreover, mandatory precautions for COVID-19 must be adhered to, including following excellent personal hygiene practices and maintaining social distancing. Awareness of the complexity of co-infection cases and the need for personal precautionary measures must be spread to the healthcare workers. The co-infection (suspected or confirmed) patients should also be constantly monitored to provide the different treatments required due to varying pathophysiology of the infections on time. The understanding of differential diagnosis and treatment must be disseminated from primary to tertiary healthcare levels. From the initial diagnosis to the treatment and management of patients, co-infection cases present a significant challenge, putting an enormous burden on the already lacking healthcare systems of regions where co-infection cases have been recorded or are likely to occur, which has a profound effect on individual patient prognosis, with lethality a very probable likelihood in

TABLE 2 Therapeutic approaches for coronavirus disease 2019 (COVID-19) and dengue co-infection cases

Therapy/drugs	Depending on	Doses	Days	Drawbacks	Reference
Fluid therapy	Haemodynamic status			May worsen the oxygen level	66
LMWH (low-molecular-weight heparin) /anticoagulation	Increased thrombosis			It needs to stop if co-infection with active bleeding is present	67
Favipiravir		1800 mg	9 tablets twice a day		12
		1800 mg	4 tablets twice a day for 13 days		12
Hydroxychloroquine		600 mg	1 per day for 5 days		13
Azithromycin		500 mg/250 mg	1 per day for 5 days		13
Chloroquine					18
Antibiotics and hydration therapy				If the intravenous fluid is not observed, patients may develop pulmonary oedema	16

absence or delay of treatments. Therefore, the public, the healthcare facilities, and the government must put up a united front to maintain high vigilance and take preventive measures against both DENV and SARS-CoV-2 as much as possible.

ACKNOWLEDGMENTS

We apologize to all colleagues whose contributions were not discussed and cited owing to space constraints.

CONFLICT OF INTEREST

The author declare no conflict of interest.


AUTHOR CONTRIBUTIONS

Yusha Araf conceived the study. Yusha Araf and Md. Golzar Hossain designed the study. Md. Golzar Hossain and Chunfu Zheng supervised the study. Chowdhury Nusaiba Binte Sayed Prapty, Raad Rahmat, Yusha Araf, Samiha Kamal Shounak, and Noor-A-Afrin wrote the initial draft manuscript. Yusha Araf and Tanjim Ishraq Rahaman illustrated the figures. Md. Golzar Hossain, Chunfu Zheng, Yusha Araf, and Mohammad Jakir Hosen edited the initial draft. Md. Golzar Hossain and Chunfu Zheng edited and revised the manuscript. All the authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Chowdhury Nusaiba Binte Sayed Prapty  <https://orcid.org/0000-0002-6899-0085>

Raad Rahmat  <https://orcid.org/0000-0001-7312-0845>

Yusha Araf  <https://orcid.org/0000-0002-0144-5875>

Samiha Kamal Shounak  <https://orcid.org/0000-0003-2270-1978>

Noor-A-Afrin  <https://orcid.org/0000-0002-0041-8533>

Tanjim Ishraq Rahaman  <https://orcid.org/0000-0001-5225-5767>

Mohammad Jakir Hosen  <https://orcid.org/0000-0001-6444-0214>

Chunfu Zheng  <https://orcid.org/0000-0002-8797-1322>

Md. Golzar Hossain  <https://orcid.org/0000-0002-1487-5444>

REFERENCES

- Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl J Med.* 2020.
- Sapkal G, Shete-Aich A, Jain R, et al. Development of indigenous IgG ELISA for the detection of anti-SARS-CoV-2 IgG. *Indian J Med Res.* 2020;151:444.
- da Silva Teles SG, de Castro MCSR, Dutra SN, Santos LMS. Uso da saliva como um espécime alternativo para diagnóstico de COVID-19: uma revisão sistemática. *Archives HEALTH Investigation.* 2020;9.
- Burgess L. Leukopenia: causes, treatment, and outlook. *Medical News Today.* 2020.
- Guzman MG, Gubler DJ, Izquierdo A, Martinez E, Halstead SB. Dengue infection. *Nat Rev Dis Prim.* 2016;2:1-25.
- Ross TM. Dengue virus. *Clin Lab Med.* 2010;30:149-160. <https://doi.org/10.1016/j.cll.2009.10.007>
- Cogan JE. Dengue and severe dengue. *World Health Organization.* 2021.
- Carosella LM, Pryluka D, Maranzana A, et al. Characteristics of patients Co-infected with severe acute respiratory syndrome coronavirus 2 and dengue virus, Buenos Aires, Argentina, March–June 2020. *Emerg Infect Dis.* 2021;27:348-351.
- Halstead SB. Dengue. *lancet.* 2007;370:1644-1652.
- Wee LE, Cherng BPZ, Conceicao EP, et al. Experience of a tertiary hospital in Singapore with management of a dual outbreak of COVID-19 and dengue. *Am J Trop Med Hyg.* 2020;103:2005-2011.
- Saddique A, Rana MS, Alam MM, et al. Emergence of co-infection of COVID-19 and dengue: a serious public health threat. *J Infect.* 2020;81:e16-e18.
- Saipen A, Demot B, De Leon L. Dengue–COVID-19 coinfection: the first reported case in the Philippines. *Western Pacific Surveill Res J WPSAR.* 2021;12:35-39.
- Epelboin L, Blondé R, Nacher M, Combe P, Collet L. COVID-19 and dengue co-infection in a returning traveller. *J Travel Med.* 2020;27:taaa114.
- Verduyn M, Allou N, Gazaille V, et al. *Co-infection of Dengue and COVID-19: A Case Report.* Public Library of Science. 2020.
- Kazi MA, Ghosh S, Roychowdhury S, Giri PP, Sarkar M. A case study of dual infection of dengue and COVID-19: presenting as multiorgan dysfunction in an infant. *J Trop Pediatr.* 2021;67:fmaa080.
- Mahajan NN, Kesarwani SN, Shinde SS, et al. Co-infection of malaria and dengue in pregnant women with SARS-CoV-2. *Int J Gynecol Obstet.* 2020;151:459-462.
- Hilmy AI, Dey RK, Imad HA, Yoosuf AA, Nazeem A, Latheef AA. Coronavirus disease 2019 and dengue: two case reports. *J Med Case Rep.* 2021;15:1-5.
- Bicudo N, Bicudo E, Costa JD, Castro JALP, Barra GB. Co-infection of SARS-CoV-2 and dengue virus: a clinical challenge. *Braz J Infect Dis.* 2020;24:452-454.
- Miah MA, Husna A. Coinfection, coepidemics of COVID-19, and dengue in dengue-endemic countries: a serious health concern. *J Med Virol.* 2020.
- Limon-Flores AY, Perez-Tapia M, Estrada-Garcia I, et al. Dengue virus inoculation to human skin explants: an effective approach to assess in situ the early infection and the effects on cutaneous dendritic cells. *Int J Exp Pathol.* 2005;86:323-334.
- Trougakos IP, Stamatelopoulos K, Terpos E, et al. Insights to SARS-CoV-2 life cycle, pathophysiology, and rationalized treatments that target COVID-19 clinical complications. *J Biomed Sci.* 2021;28:1-18.
- Weiss Susan R, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus/Susan R. Weiss, Sonia Navas-martin. *Microbiol Mol Biol Rev.* 2005;69:635-664.
- Wu S-JL, Grouard-Vogel G, Sun W, et al. Human skin Langerhans cells are targets of dengue virus infection. *Nat Med.* 2000;6:816-820.
- Diamond MS, Pierson TC. Molecular insight into dengue virus pathogenesis and its implications for disease control. *Cell.* 2015;162:488-492.
- Pollard CA, Morran MP, Nestor-Kalinowski AL. The COVID-19 pandemic: a global health crisis. *Physiol Genom.* 2020;52:549-557. <https://doi.org/10.1152/physiolgenomics.00089.2020>
- Cuervo NZ, Grandvaux N. ACE2: evidence of role as entry receptor for SARS-CoV-2 and implications in comorbidities. *Elife.* 2020;9:e61390.
- Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *lancet.* 2020;395:565-574.
- Ferreira RAX, de Oliveira SA, Gandini M, et al. Circulating cytokines and chemokines associated with plasma leakage and hepatic dysfunction in Brazilian children with dengue fever. *Acta Trop.* 2015;149:138-147.

29. Vervaek P, Vermeire K, Liekens S. Endothelial dysfunction in dengue virus pathology. *Rev Med Virol.* 2015;25:50-67.
30. Monteleone G, Sarzi-Puttini PC, Ardizzone S. Preventing COVID-19-induced pneumonia with anticytokine therapy. *Lancet Rheumatol.* 2020;2:e255-e256.
31. Harapan H, Ryan M, Yohan B, et al. Covid-19 and dengue: double punches for dengue-endemic countries in Asia. *Rev Med Virol.* 2021;31:e2161. <https://doi.org/10.1002/rmv.2161>
32. Lin CF, Lei HY, Liu CC, et al. Generation of IgM anti-platelet autoantibody in dengue patients. *J Med Virol.* 2001;63:143-149.
33. Sun DS, King CC, Huang HS, et al. Antiplatelet autoantibodies elicited by dengue virus non-structural protein 1 cause thrombocytopenia and mortality in mice. *J Thromb Haemostasis.* 2007;5:2291-2299. <https://doi.org/10.1111/j.1538-7836.2007.02754.x>
34. Cheng HJ, Lei HY, Lin CF, et al. Anti-dengue virus nonstructural protein 1 antibodies recognize protein disulfide isomerase on platelets and inhibit platelet aggregation. *Mol Immunol.* 2009;47:398-406. <https://doi.org/10.1016/j.molimm.2009.08.033>
35. Cantuni-Castelvetri L, Ojha R, Pedro L. *Neuropilin-1 Facilitates SARS-CoV-2 Cell Entry and Provides a Possible Pathway into the Central Nervous System*; bioRxiv, 2020.
36. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020;181:271-280.e278.
37. Cloutier M, Nandi M, Ihsan AU, Chamard HA, Ilangumaran S, Ramanathan S. ADE and hyperinflammation in SARS-CoV2 infection-comparison with dengue hemorrhagic fever and feline infectious peritonitis. *Cytokine.* 2020;136:155256. <https://doi.org/10.1016/j.cyto.2020.155256>
38. Wolfson RK, Chiang ET, Garcia JG. HMGB1 induces human lung endothelial cell cytoskeletal rearrangement and barrier disruption. *Microvasc Res.* 2011;81:189-197. <https://doi.org/10.1016/j.mvr.2010.11.010>
39. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in covid-19. *N Engl J Med.* 2020;383:120-128. <https://doi.org/10.1056/NEJMoa2015432>
40. Gómez-Mesa JE, Galindo-Coral S, Montes MC, Muñoz Martin AJ. Thrombosis and coagulopathy in COVID-19. *Curr Problems Cardiol.* 2021;46:100742. <https://doi.org/10.1016/j.cpcardiol.2020.100742>
41. Yuan S, Jiang S-C, Zhang Z-W, Fu Y-F, Hu J, Li Z-L. The role of alveolar edema in COVID-19. *Cells.* 2021;10:10. <https://doi.org/10.3390/cells10081897>
42. Domingues RB, Kuster GW, Onuki-Castro FL, Souza VA, Levi JE, Pannuti CS. Involvement of the central nervous system in patients with dengue virus infection. *J Neurol Sci.* 2008;267:36-40. <https://doi.org/10.1016/j.jns.2007.09.040>
43. Harapan H, Ryan M, Yohan B, et al. Covid-19 and dengue: double punches for dengue-endemic countries in Asia. *Rev Med Virol.* 2021;31:e2161. <https://doi.org/10.1002/rmv.2161>
44. Calderón-Peláez M-A, Velandia-Romero ML, Bastidas-Legarda LY, Beltrán EO, Camacho-Ortega SJ, Castellanos JE. Dengue virus infection of blood-brain barrier cells: consequences of severe disease. *Front Microbiol.* 2019;10:1435.
45. Gupta M, Nayak R, Khwaja GA, Chowdhury D. Acute disseminated encephalomyelitis associated with dengue infection: a case report with literature review. *J Neurol Sci.* 2013;335:216-218.
46. Sahu R, Verma R, Jain A, et al. Neurologic complications in dengue virus infection: a prospective cohort study. *Neurology.* 2014;83:1601-1609.
47. Solbrig MV, Perng G-C. Current neurological observations and complications of dengue virus infection. *Curr Neurology Neurosci Rep.* 2015;15:29.
48. Misra UK, Kalita J, Mani VE, Chauhan PS, Kumar P. Central nervous system and muscle involvement in dengue patients: a study from a tertiary care center. *J Clin Virol.* 2015;72:146-151.
49. Niazkhar HR, Zibae B, Nasimi A, Bahri N. The neurological manifestations of COVID-19: a review article. *Neurol Sci.* 2020;41:1667-1671.
50. Hou H, Zhang B, Huang H, et al. Using IL-2R/lymphocytes for predicting the clinical progression of patients with COVID-19. *Clin Exp Immunol.* 2020;201:76-84.
51. Flores-Mendoza LK, Estrada-Jiménez T, Sedeño-Monge V, et al. IL-10 and socs3 are predictive biomarkers of dengue hemorrhagic fever. *Mediat Inflamm.* 2017;2017.
52. John DV, Lin Y-S, Perng GC. Biomarkers of severe dengue disease—a review. *J Biomed Sci.* 2015;22:1-7.
53. Jaime A, Kovy A-L, Wilmer E, et al. Dengue and COVID-19, overlapping epidemics? An analysis from Colombia. *J Med Virol.* 2021.
54. Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. *Pathobiology.* 2021;88:14-26.
55. Ulrich H, Pillat MM, Tárnok A. Dengue fever, COVID-19 (SARS-CoV-2), and antibody-dependent enhancement (ADE): a perspective. *Cytom.* 2020;97:662-667. <https://doi.org/10.1002/cyto.a.24047>
56. Kebayoon A, Wiwanitkit V. Dengue after COVID-19 vaccination: possible and might be missed. *Clin Appl Thromb Hemost.* 2021;27:10760296211047229. <https://doi.org/10.1177/10760296211047229>
57. Reyes-Ruiz JM, Campuzano-Vences R, Osuna-Ramos JF, et al. Case report: extrapulmonary manifestations of COVID-19 and dengue coinfection. *Am J Trop Med Hyg.* 2021;105:363-367.
58. Lee LK, Gan VC, Lee VJ, Tan AS, Leo YS, Lye DC. Clinical relevance and discriminatory value of elevated liver aminotransferase levels for dengue severity. *Plos Neglected Trop Dis.* 2012;6:e1676.
59. Bzeizi K, Abdulla M, Mohammed N, Alqamish J, Jamshidi N, Broering D. Effect of COVID-19 on liver abnormalities: a systematic review and meta-analysis. *Sci Rep.* 2021;11:1-18.
60. Liu Z, Que S, Xu J, Peng T. Alanine aminotransferase-old biomarker and new concept: a review. *Int J Med Sci.* 2014;11:925-935.
61. Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. *J Med Virol.* 2020.
62. Vuong NL, Le Duyen HT, Lam PK, et al. C-reactive protein as a potential biomarker for disease progression in dengue: a multi-country observational study. *BMC Med.* 2020;18:1-13.
63. Khalil A, Badr B, Wright H, Talo M, Atteiya M. Dengue fever and COVID-19 Co-infection at the emergency department of a tertiary care hospital in Jeddah, Saudi Arabia. *European Journal of Case Reports in Internal Medicine.* 2020;7.
64. Nasomsong W, Luvira V, Phiboonbanakit D. Case report: dengue and COVID-19 coinfection in Thailand. *Am J Trop Med Hyg.* 2021;104:487-489.
65. Seputra DPGS, Saraswati KSD, Dewi AAISK. Co-infection of COVID-19 and dengue: a case report. *Int J Adv Med.* 2021;8:4. <https://doi.org/10.18203/2349-3933.ijam20212869>
66. Biswas S, Sukla S, Roy S, Nath H, Mallick A. Regarding: Masyeni S, Santoso MS, Widyarningsih PD, Wedha Asmara DG, Nainu F, Harapan H, et al. Serological cross-reaction and co-infection of dengue and COVID-19 in Experience from Indonesia. *Int J Infect Dis.* 2020;102:152-4. <https://doi.org/10.1016/j.ijid.2020.10.043>. *International J Infect Dis.* 2021;104:737-738.
67. Tiwari L, Shekhar S, Bansal A, Kumar P. COVID-19 with dengue shock syndrome in a child: coinfection or cross-reactivity? *BMJ Case Rep CP.* 2020;13:e239315.
68. Cheng Y-W, Chao T-L, Li C-L, et al. Furin inhibitors block SARS-CoV-2 spike protein cleavage to suppress virus production and cytopathic effects. *Cell Rep.* 2020;33:108254. <https://doi.org/10.1016/j.celrep.2020.108254>

69. Guzmán MG, Kouri G. Dengue diagnosis, advances and challenges. *Int J Infect Dis.* 2004;8:69-80.
70. Solanke V, Karmarkar M, Mehta P. Early dengue diagnosis: role of rapid NS1 antigen, NS1 early ELISA, and PCR assay. *Trop J Med Res.* 2015;18:95.
71. Kembuan GJ. Dengue serology in Indonesian COVID-19 patients: coinfection or serological overlap? *IDCases.* 2020;22:e00927.
72. Rosso F, Parra-Lara LG, Agudelo-Rojas OL, Martinez-Ruiz DM. *Differentiating Dengue from COVID-19: Comparison of Cases in Colombia.* The American Journal of Tropical Medicine and Hygiene; 2021.
73. Chowdhury PB, Hossain S, Biswas RK. A combination of COVID-19 and dengue fever in Bangladesh: preparedness of Bangladesh. *Journal of Global Health.* 2020;10.
74. Nunthavichitra S, Prapaso S, Luvira V, Muangnoicharoen S, Leaungwutiwong P, Piyaphanee W. Case report: COVID-19 presenting as acute undifferentiated febrile illness—a tropical world threat. *Am J Trop Med Hyg.* 2020;103:83-85.

How to cite this article: Prapty CNBS, Rahmat R, Araf Y, et al. SARS-CoV-2 and dengue virus co-infection: Epidemiology, pathogenesis, diagnosis, treatment, and management. *Rev Med Virol.* 2022;e2340. <https://doi.org/10.1002/rmv.2340>