Trans R Soc Trop Med Hyg 2023; **117**: 241–254
https://doi.org/10.1093/trstmh/trac114 Advance Access publication 8 December 2022

Dengue and COVID-19 co-infections: an important consideration in the tropics

Chamara Dalugama[a] and Suranjith L. Seneviratne[b,c,*]

[a]*Department of Medicine, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka;* [b]*Institute of Immunity and Transplantation, Royal Free Hospital and University College London, London, UK;* [c]*Nawaloka Hospital Research and Education Foundation, Nawaloka Hospitals, Colombo, Sri Lanka*

*Corresponding author: Tel: 0094770274865; E-mail: suran200@yahoo.co.uk

Received 29 January 2022; revised 19 August 2022; editorial decision 11 November 2022; accepted 18 November 2022

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected >370 million individuals worldwide. Dengue is endemic in many countries and leads to epidemics at frequent intervals. In the tropics and subtropics, it is possible that individuals may be concurrently infected with both dengue and SARS-CoV-2. Differentiation between the two infections may be difficult from both a clinical and laboratory perspective. We have outlined the currently published findings (as of the end of December 2021) on patients with dengue and SARS-CoV-2 co-infections and have discussed the observed outcomes and management of such patients. Co-infections were more common in males >25 y of age, fever was not universal, 30–50% had medical comorbidities such as diabetes mellitus or hypertension and the case fatality rate was 16–28%.

Keywords: co-infection, Covid-19, dengue, SARS-CoV-2, tropics

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused >5.6 million deaths worldwide.[1] For many years, dengue viral infections have affected large numbers of individuals living in the tropics and subtropics.[2] During the past 2 y, dengue and COVID-19 have occurred at the same time in some regions of the world. At times this has led to diagnostic dilemmas, partly because of the similarities in clinical features and basic laboratory findings between the two conditions and because of the cross-interaction of some test results due to antibody cross-reactivity.[3,4] COVID-19 has a spectrum of clinical manifestations from asymptomatic infection to mild, moderate or severe disease, including respiratory distress, severe pneumonia, profound hypoxia, respiratory failure, multi-organ failure and death.[5–7] Older persons with comorbidities tend to be more severely affected.[8] Dengue, the most common arboviral infection in tropical countries, is primarily transmitted by *Aedes aegypti* mosquitoes.[9] It has a wide spectrum of clinical manifestations, from an asymptomatic infection to an acute undifferentiated febrile illness, to fluid leakage and dengue haemorrhagic fever in a small proportion and multisystemic involvement such as hepatitis, myocarditis, myositis or neurological involvement in a few.[10–13] Co-infection with dengue and SARS-CoV-2 viruses may be a clinical, diagnostic and therapeutic challenge for the treating physician. In this review we outline the currently known (as of the end of December 2021) demographic, clinical and investigative findings in patients with dengue and SARS-CoV-2 co-infections and discuss the clinical importance for a practising clinician.[3,4] The observed serological cross-reactivity, possible immunopathogenetic mechanisms, management and short-/long-term outcomes of such patients are also discussed.

Methods

A systematic search was done using the PubMed, Cochrane and Latin American and Caribbean Health Sciences Literature (LILACS) databases for reports published from 1 January 2020 to 31 December 2021 on dengue and SARS-CoV-2 co-infections. The search terms used were dengue, SARS-CoV-2, COVID-19, coronavirus and co-infection. All studies involving humans with laboratory-confirmed COVID-19 (SARS-CoV-2 polymerase chain reaction [PCR] positive) and dengue (positive dengue immunoglobulin M [IgM] or positive dengue NS1 antigen) were included. A total of 119 reports were identified and 52 full articles were screened after excluding duplicates; 26 eligible articles were selected for analysis (Figure 1). Animal and completely laboratory-based studies were excluded from this analysis.

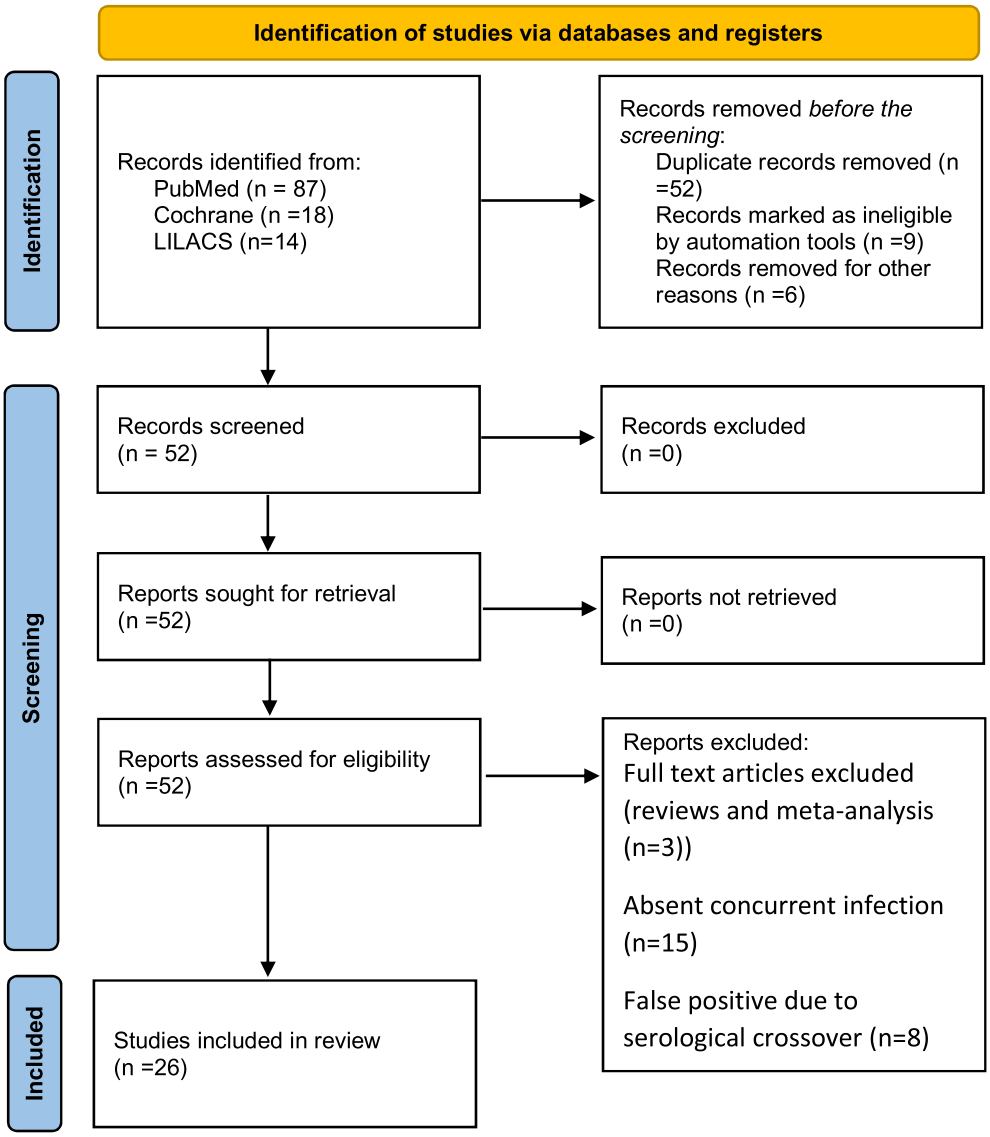

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart
Source: Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

A single case and case series with two to five patients were considered as small reports.

Results

Demographic, clinical, investigative, management and outcome findings in the included studies are shown in Table 1. The collated clinical characteristics of the analysed groups are shown in Table 2. The analysis included 37 patients from small reports and two larger studies consisting of 50 and 13 dengue and COVID-19 co-infected individuals. The small reports were combined to make the overall comparisons clearer. However, one needs to remember that the reported studies were from different geographical locations, including a few case reports from Brazil.

Demographic and clinical findings

All the cases were from Asia (South, 19; Southeast, 4), Africa (4 cases) and South America (71 cases), with a possible imported case in France. The trend was for males >25 y of age to be affected and a sizeable proportion had no classic COVID-19 symptoms. Fever was reported in all the small reports but was not observed in sizeable proportions of individuals in the cohort studies. In the Peruvian study, only 52% had fever, but this may be because of its retrospective nature (with information collected from medical records and telephone interviews and as asymptomatic patients were tested for dengue). The use of antipyretic and anti-inflammatory medications may have also affected the findings. Classic dengue symptoms (headache, arthralgia, myalgia, retro-orbital pain) were observed in a majority. Rash was found in a fair proportion and a few developed

Table 1: Findings in dengue–COVID-19 co-infection studies

Author (year) (Ref)	Country	Cases, n	Age (years)	Sex	Presentation	Comor-bidities	Laboratory findings	Imaging	Serology	Management	Outcome	Limitations/ comments
Adarsh et al. (2021)[14]	India	2	30, 54	M, M	C1: fever, headache, no respiratory symptoms C2: fever, myalgia	None	C1: WBC 2.9, LYM 27%, PLT 53 C2: WBC 4.8, LYM 40%, PLT 20	N/A	C1 and C2: DENV NS1 Ag +, Covid PCR +	C1: supportive treatment C2: dexamethasone	Full recovery	Possible synergistic effect of dual infection in causing severe thrombocytopenia
Agudelo Rojas et al. (2021)[15]	Colombia	2	24, 59	F, M	C1: fever, odynophagia, myalgia, arthralgia, vomiting, diarrhoea. No respiratory symptoms. C2: fever for 20 d, cough, respiratory distress	C1: None C2: DM, obe-sity, HPT	C1: PLT 76, WBC 1.5, NEU 57.8%, LYM 33.4%, AST 666, ALT 516, DD 0.648. C2: PLT 138, leucocytosis, lymphopenia, ALT 1507, AST 3049, elevated DD	C1: CXR, NAD C2: CXR, interstitial infiltrates in both lung fields	C1 and C2: DENV NS1 Ag +, DENV IgM Ab +, COVID PCR +	C1: supportive treatment C2: ITU, fluids, inotropes, steroids and anticoagulation	C1: uneventful recovery C2: pulmonary emboli, AKI and death	None
Bicudo et al. (2020)[16]	Brazil	1	56	F	Headache, fever, dry cough, anosmia, dyspnoea, MP rash on day 3	None	WBC 2.2, LYM 0.49, PLT 143, elevated DD, CRP 16, ALT 60, AST 40, ferritin 559	CT chest, bilateral ground glass opacities	DENV NS1 Ag +, DENV IgM and IgG Abs +, DEN 1 serotype, COVID PCR +	Chloroquine, azithromycin	Full recovery	None
Epelboin et al. (2020)[17]	France	1	44	M	Headache, fever, fatigue, diarrhoea and maculopapular rash	None	Leucopenia, thrombocytopenia, transaminitis	N/A	DENV NS1 Ag +, COVID PCR +	Supportive treatment, HCQ, azithromycin	Full recovery	None
Estofolete et al. (2021)[18]	Brazil	1	60	F	Fever, myalgia, headache, retro-orbital pain, dry cough. Day 8 paresis of right-upper member, respiratory failure needing invasive mechanical ventilation	None	WBC 5.3, PLT 89, elevated ALT and AST	CT chest, basal and posterior consolidation, CTH, hypodense injury involving the left cerebral and cerebellar hemispheres, subacute ischaemic vascular injury, oedema in the left cerebral hemisphere, with a compressive effect	DENV NS1 Ag +, DENV IgM +, COVID PCR +	Vasoactive drugs, haemodialysis, high fraction of inspired oxygen, and high positive end-expiratory pressure, ceftriaxone, azithromycin, oseltamivir	Death due to refractory hypoxia	Extensive stroke could be due to many possibilities, could be indirect causes like watershed infarction due to hypotension and hypoxia, pre-existing vascular disease augmented by haemodynamic compromise or thromboembolic phenomenon due to hypercoagulabi-lity of COVID infection

Table 1: Continued

Author (year) (Ref)	Country	Cases, n	Age (years)	Sex	Presentation	Comorbidities	Laboratory findings	Imaging	Serology	Management	Outcome	Limitations/ comments
Gupta et al. (2021)[19]	India	1	65	M	Fever, chills, cough and erythematous rash in the lower limbs and abdomen, bradycardia, respiratory distress	None	Leucocyte count 2.2, NEU 55%, LYM 40%, PLT 20, AST 187, ALT 46, CRP 49, elevated creatine kinase MB, normal troponin	CT chest, bilateral ground glass opacities	DENV NS1 Ag +, DENV IgM and IgG Abs +, DEN 1 serotype, COVID PCR +	Intravenous steroids, oxygen, supportive treatment	Ful recovery	Prophylactic anticoagulation is recommended as a management in COVID-19 given the increased risk of thrombosis, but concurrent dengue infection might hinder the use due to severe thrombocytopenia increasing the risk of bleeding
Hilmy et al. (2021)[20]	Maldives	2	39, 38	M, M	C1: high-grade fever, retro-orbital headache, fatigue, myalgia, right upper abdominal pain, vomiting, loose stools. Day 5 non-productive cough, sore throat C2: intermittent fever, headache, sore throat, anosmia	None	C1: haemoconcentration and transaminitis C2: leucopenia, thrombocytopenia, transaminitis	C1: CXR NAD C2: CXR NAD	C1 and C2: DENV NS1 Ag -, DENV IgM and IgG Ab +, COVIDPCR +	Both received supportive treatment	Full recovery	In both cases platelet count was normal, which could be due to dual infection changing the natural history of the presentation
Hossain et al. (2021)[21]	Bangladesh	1	30	M	Fever, headache, generalized body aches, episode of hematemesis, respiratory distress	Beta thalassaemia trait	No thrombocytopenia or leucopenia, Hb 12.8 with low MCV (60)	CT Chest- ill-defined ground-glass opacification in the lower left and right lung areas	DENV NS1 Ag +, DENV IgM and IgG Abs +, DEN 1 serotype, Covid-PCR +	Supportive treatment	Full recovery	Mild case of described. Could haemoglobinopathies confer a protective effect no arboviral/corona viral infections

Table 1: Continued.

Author (year) (Ref)	Country	Cases, n	Age (years)	Sex	Presentation	Comor-bidities	Laboratory findings	Imaging	Serology	Management	Outcome	Limitations/ comments
Jose et al. (2021)[22]	Mexico	1	7	M	Fever, rash, pharyngitis, hypotension, fits	None	leucocytosis, thrombocytopenia	N/A	Covid-PCR +, Dengue RT PCR +	Antibiotics, steroids	full recovery	None
Kariyappa et al. (2021)[23]	India	1	5*	N/A	5-month-old infant presenting with fever, refusal of feeds, developing altered sensorium and convulsions during the hospital course	None	anaemia, PLT-65, AST 869, ALT 486, CRP and pro-calcitonin elevated, elevated DD and LDH	CXR pulmonary oedema, MRI brain restricted diffusion and oedematous changes in subcortical white matter; suspected acute demyelinating encephalomyeli-tis	DENV NS1 Ag +, DENV IgM Ab +, COVID PCR +	Intravenous steroids and antibiotics, supportive treatment	ALERD with secondary West syndrome	Likely explanation would be dengue and COVID-19 co-infection surmounting a massive cytokine storm in our infant, leading to ALERD, an immune-mediated encephalopathy
Kazi et al. (2021)[24]	India	1	9[a]	N/A	Fever, diarrhoea, lethargy, reduced appetite, seizures, generalized non-pruritic erythematous skin rash and oedema of limbs, cracked lips, strawberry tongue, hepatos-plenomegaly and lymphadenopathy	None	Hb 7.4, PLT 53, WBC 7.5, NEU 57%, LYM 37%, SGPT 1000, SGOT 4756, INR 1.57, APTT >180, elevated ferritin, CRP 14	2D echo pleural effusion, EEG encephalitic changes, MRI brain-cortical shrinkage	DENV NS1 Ag +, DENV IgM Ab +, COVID PCR +	Intravenous fluids, inotropes, antibiotics, anti-epileptic medications	Uneventful recovery	Presentation could be due to hyperinflammatory state leading to multi-organ dysfunction (MIS-C). Could co infection of dengue and COVID-19 lead to cytokine surge leading to MODS?

Table 1: Continued.

Author (year) (Ref)	Country	Cases, n	Age (years)	Sex	Presentation	Comorbidities	Laboratory findings	Imaging	Serology	Management	Outcome	Limitations/ comments
Khalil et al. (2020)[25]	Saudi Arabia	4	63, 53, 48, 46	M, F, F, M	C1: fever, headache, sore throat and myalgia. Later developed dry cough, wheezing and vomiting with low saturations C2: Fever, nausea, vomiting, diarrhoea and developing respiratory symptoms on day 4 C3: fever, cough, shortness of breath, arthralgia, myalgia and headache C4: fever, sore throat, dry cough, retro-orbital headache and bone pain	C1: CKD, type2 DM C2: BA C3: hypothyroidism C4: none	All patients had leucopenia, lymphopenia and thrombocytopenia. Mild transaminitis noted in C1, C2 and C4. Elevated ferritin noted in C1 and C2	All four patients had bilateral peripheral airspace opacities, more prominent at the lung bases	C1 and C3: DENV NS1 Ag +, negative PCR and DENV IgM Ab + in C2 and C3 C4: both DENV NS1 Ag and DENV PCR were +, COVID PCR + in all four cases	C2 and C3 received dexamethasone. All cases received supportive treatment and fluids	All four patients made a full recovery	All four patients had CXR findings compatible with COVID pneumonitis, but dengue serology was inconsistent. Possibility of serological cross-reactivity needs to be considered
Kumarihamy et al. (2021)[26]	Sri Lanka	4	56, 34, 16, 33	All M	Fever, headache and myalgia in all four, no respiratory symptoms	C1: hypertension and dyslipidaemia C2, C3 and C4: none	Leukopenia and thrombocytopenia noted	C3: CXR left-sided small pleural effusion None had XR changes suggestive of COVID	All cases DENV NS1 Ag +, COVID PCR +	C2 and C3: complicated with DHF	Uneventful recovery	None

Table 1: Continued.

Author (year) (Ref)	Country	Cases, n	Age (years)	Sex	Presentation	Comorbidities	Laboratory findings	Imaging	Serology	Management	Outcome	Limitations/ comments
Mahajan et al. (2020)[27]	India	1	22	F	Mild fever for 4 d, no petechiae, no bleeding tendencies, no respiratory symptoms	None	WBC 16, PLT 196	CXR no pulmonary infiltrates, US abdomen intrauterine growth restriction	DENV NS1 Ag +, DENV IgM Ab +, COVID PCR +	Supportive treatment	Premature rupture of membranes at 2 d, labour augmentation, vaginal delivery, low birthweight (2.2 kg)	COVID PCR + on universal testing and patient clinically or radiologically not suggestive of COVID infection
Nair et al. (2021)[28]	Malaysia	1	62	M	Fever, chills, rigors, arthralgia, myalgia and a generalized pinpoint rash over the chest and abdomen	Diabetes mellitus, hypertension, ischaemic heart disease	Thrombocytopenia, mild transaminitis, normal WBC	CXR ground glass opacity in middle and lower lobes	DENV NS1 Ag −, DENV IgM and IgG Ab +, COVID PCR +	Supportive treatment	Uneventful recovery	None
Nasomsong et al. (2021)[29]	Thailand	1	50	F	Fever, myalgia, nausea, and vomiting, no upper or lower respiratory tract symptoms	None	WBC 3.7, LYM 0.2, PLT normal, transaminitis, mild hyponatremia and hypokalaemia	CXR no pulmonary infiltrates	DENV NS1 Ag +, DENV IgM and IgG Abs +, DEN 2 serotype COVID PCR +	Supportive treatment, fluids	Full recovery	CT would have been the best imaging modality to look for lung involvement, serological cross-reactivity of COVID and dengue need to be considered and no COVID Abs done

Table 1: Continued.

Author (year) (Ref)	Country	Cases, n	Age (years)	Sex	Presentation	Comorbidities	Laboratory findings	Imaging	Serology	Management	Outcome	Limitations/ comments
Pontes et al. (2020)[30]	Brazil	1	39	M	Fever, myalgia, diarrhoea and ageusia	None	N/A	N/A	DENV NS1 Ag +, DENV IgM Ab +, COVID PCR +, COVID IgM/IgG Ab +	Supportive treatment	Uneventful recovery	None
Radisic et al. (2020)[31]	Argentina	1	57	F	Diarrhoea, abdominal pain, headache, retro-orbital pain, aching joints, dyspnoea, pruritic rash, unspecific thoracic pain and non-blanching, generalized rash with scattered petechiae	Chronic obstructive pulmonary disease	A skin biopsy showed epidermal atrophy and marked superficial angiectasia, dermis with intense oedema and no associated inflammatory changes	Not applicable	DENV NS1 Ag +, DENV IgM and IgG Abs + DEN 1 serotype, COVID PCR +	Supportive treatment	Full recovery	Dermatological manifestations are described both in dengue and COVID infection
Reyes-Ruiz et al. (2021)[32]	Mexico	1	42	F	Fever, headache, diarrhoea, chest pain, chills, odynophagia, myalgia and arthralgia	None	Lymphopenia, leucopenia, thrombocytopenia, elevated ALT and AST, normal clotting profile	CT chest normal, CT abdomen hepatosplenomegaly	DENV NS1 Ag +, DENV IgM and IgG Abs +, DEN 2 serotype, COVID PCR +	Azithromycin, ivermectin	Full recovery	Other causes for hepatosplenomegaly, drug-induced liver injury
Saddique et al. (2020)[33]	Pakistan	5	43.4[b]	M 2, F 3	Fever in all, rash in 3, cough in 3, diarrhoea in 3	Cardiovascular in 2, diabetes in 2	Leucopenia in 3, normal WBC in 2, transaminitis in 4	N/A	In all, DENV NS1 Ag +, COVID PCR +	Supportive treatment	Death in 3	None

Table 1: Continued.

Author (year) (Ref)	Country	Cases, n	Age (years)	Sex	Presentation	Comorbidities	Laboratory findings	Imaging	Serology	Management	Outcome	Limitations/ comments
Saipen et al. (2021)[34]	Philippines	1	62	F	Fever, headache, retro-orbital pain, generalized body ache, myalgia, arthralgia, no respiratory symptoms, maculopapular rash on day 7	Hypertension	WBC 3.16 , Hb normal, PLT normal, elevated ferritin, ESR 35, CRP 18, LDH 317, AST 100, ALT 65	CXR right lower lobe consolidation, CT chest posterior basal pneumonia with features atypical of SARS-CoV-2	DENV NS1 Ag +, DENV IgM Ab +, COVID PCR +	Intravenous fluids, favipiravir	Uneventful recovery	None
Somasetia et al. (2020)[35]	Indonesia	1	6	M	Fever 5 d with abdominal pain	None	Hb 2.9, WBC 18, PLT 213, AST 510, ALT 173, CRP 0.09	CXR no pulmonary infiltrates	SARS-Cov-2 IgM +, SARS-CoV-2 IgG −, SARS CoV-2 PCR −, DENV IgM +, DENV IgG Ab −	Fluids, antibiotics and inotropes	Death due to multi-organ failure	Patient has both positive dengue and COVID IgM but negative NS1 Ag and COVID PCR. Possibility of serological cross-reactivity
Tiwari et al. (2020)[36]	India	1	14	F	Fever, headache, generalized abdominal pain, vomiting, respiratory distress with shock, GCS13 with right extensor plantar and brisk reflexes	None	Leucopenia, thrombocytopenia and mild transaminitis	CT scan brain ill-defined hypodensities in both frontal and temporal lobes, right parietal lobe, basal ganglia, corpus callosum, mid-brain and pons suggestive of viral encephalitis. CXR bi-basal reticular-nodular opacities	DENV NS1 Ag and DENV IgM Ab both + on day 14, COVID PCR +	Supportive treatment including fluids, inotropes	Full recovery	Cerebral involvement could be due to COVID-associated encephalitis, dengue-associated encephalitis or MIS-C

Table 1: Continued.

Author (year) (Ref)	Country	Cases, n	Age (years)	Sex	Presentation	Comor-bidities	Laboratory findings	Imaging	Serology	Management	Outcome	Limitations/ comments
Verduyn et al. (2020)[37]	Reunion Island	1	18	M	Fever (38.7°C), arthralgia, myalgia, dyspnoea with polypnoea (respiratory rate of 24 breaths/min) and itchy maculopapular rash	None	Thrombocytopenia, leucopenia, lymphopenia and neutropenia, AST 51, ALT 23, CRP normal	CT chest no ground glass opacification	DENV NS1 Ag +, DENV IgM and IgG Abs +, DEN 1 serotype, COVID PCR +	Supportive treatment, fluids	Full recovery	Dermatological manifestations in dengue and COVID could overlap
Mejia-Parra et al. (2021)[38]	Peru	50	Median 55.5 y (range 15–89)	M 39, F 11	Fever 52%, rash 6%	HT in 16, DM in 18	Severe dengue (admitted to ICU) 6%, dengue with warning signs 58%, dengue without warning signs 36%, COVID pneumonia 76%	N/A	COVID-PCR + in all, DENV NS1 Ag + in 30, DENV IgG/IgM Abs + in 20	The case fatality rate was 28%. 100% of those with severe dengue died, while it was 28% and 17% in those with and without warning signs of dengue. The case fatality rate was higher in females (55%) than males (21%)		Retrospective study, so many confounders were not eliminated in the study, such as the presence of other infections, use of medications etc.
Schulte et al. (2021)[39]	Brazil	13	N/A	F 7, M 6	Myalgia in 10, fever in 7 and dyspnoea in 6	DM in 4, HT in 2	PLT 150	N/A	DENV NS1 Ag + in 6, dengue IgM Ab + in 7, COVID PCR + in all	4 needed hospital admission, supportive treatment	Uneventful recovery	Possibility of a hospital-acquired SARS-CoV-2 infection is also a factor to be taken into consideration in patients hospitalized due to severe dengue

Ab: antibody; Ag: antigen; ALERD: acute leukoencephalopathy with restricted diffusion ALT: alanine aminotransferase (IU/L); APTT: activated partial thromboplastin time; AST: aspartate aminotransferase (IU/L); BA: bronchial asthma; C: case number; CKD: chronic kidney disease; CRP: C-reactive protein (U/L); CT: computed tomography; CXR: chest X-ray; DD: D-dimer; DM: diabetes mellitus; EEG: electroencephalogram; F: female; Hb: haemoglobin (g/dl); HT: hypertension; INR: international normalised ratio; LDH: lactate dehydrogenase; LYM: lymphocyte (%); M: male; MIS-C: multisystem inflammatory syndrome in children; MODS: multiple organ dysfunction syndrome; N/A: no information available; NEU: neutrophil (%); PLT: platelets ($\times 10^6$/L); SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transferase; WBC: white blood cell count ($\times 10^9$/L); 2D: two-dimensional.

[a]Months.

[b]Mean age.

Table 2. Collated findings in the dengue–COVID-19 co-infection studies

Characteristics		Small studies (n=37), %	Peruvian study [30] (n=50), %	Brazilian study [31] (n=13), %
Sex	Male	60	78	54
	Female	35	22	46
	Unknown	5	0	0
Age (years)	<1	5	55.5 (mean)	NA
	1–25	19		
	26–50	38		
	51–80	38		
Symptoms	Fever	100	52	53
	Classic dengue symptoms	65	48	77
	Classic COVID symptoms	40	NA	46
	Rash	27	6	0
	GI symptoms	30	12	0
Laboratory tests	Leucopenia	49	NA	92
	Leucocytosis	11	NA	0
	Normal WBC	16	NA	0
	Thrombocytopenia	57	60	46
	Anaemia	5	NA	NA
	Transaminitis	35	NA	NA
Comorbidity	None	54	28	46
	Diabetes	14	26	23
	Hypertension	16	32	8
	CKD	3	14	0
	No information	14	0	23
Imaging	Abnormal CXR/CT	32	NA	NA
	Normal imaging	22		
	No information	46		
Serology	NS1 Ag	90	60	46
	Dengue IgM	62	40	54
	Dengue IgG	24	0	
	Covid PCR	100	100	100
Outcome	Uneventful recovery	73	72	100
	Complications	11	0	0
	Death	16	28	0

Ag: antigen; CXR: chest X-ray; CT; computed tomography; WBC: white blood cell count.

respiratory distress and gastrointestinal (GI) symptoms. Around 30–50% had a comorbidity, which were predominantly diabetes or hypertension.

Laboratory findings

The predominant investigative findings were thrombocytopenia, leucopenia and transaminitis. In most, the transaminitis was mild to moderate. All had positive COVID-19 PCR test results and a high number had a positive NS1 antigen test. Dengue antibodies were positive in some, but one needs to remember the potential for antibody cross-reactivity. In the reports where chest imaging findings were given, they was normal in two-thirds. One patient had a right-sided hemiplegia with ischaemic changes and oedema/mass effect on a computed tomography head scan. Two children (5 months and 14 y) had an altered sensorium with magnetic resonance imaging findings suggestive of acute disseminated encephalomyelitis and viral encephalitis, respectively. In the Peruvian cohort, nearly 28% of the co-infected individuals died, and mortality was 16% in the smaller reports. The listed causes of death included pulmonary embolism, refractory hypoxaemia and multi-organ dysfunction syndrome.

Discussion

Dengue and COVID-19 co-infections are a new challenge for treating physicians in several regions of the world. Adult males form a large segment of the working population in dengue-hyperendemic regions and this group may have needed to go to

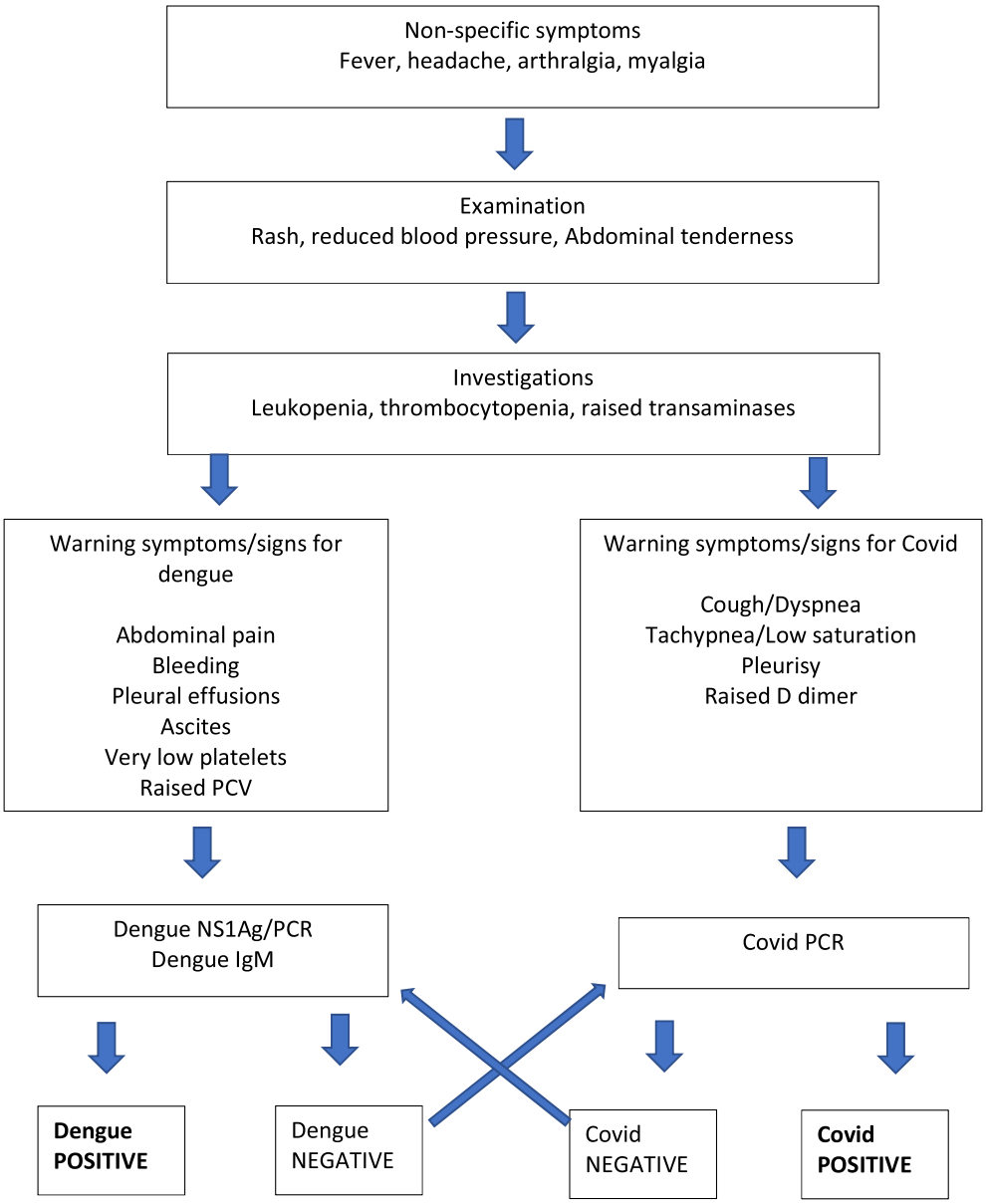

Figure 2: Diagnostic algorithm for dengue-endemic tropical/subtropical countries.

work even during the different peaks of the COVID-19 pandemic. In such areas, if an adult male presents with an acute febrile illness, the possibility of dengue, COVID-19 or a co-infection needs to be considered by the attending physician (Figure 2). Prevention strategies such as the use of mosquito repellents and proper clothing, wearing masks and maintaining social distancing would help reduce the risk of dengue and COVID-19 transmission. Such preventive measures should be regularly emphasized to such high-risk populations that form the backbone of their countries' economy.

Fever was the most common symptom seen in those with dengue and COVID-19 co-infections. However, in itself, this is a non-specific finding, as it is found in many other conditions. A majority presented with fever, myalgia and arthralgia. In the pre-COVID era, this triad of clinical presentations in an individual from the tropics would have directed clinicians towards a possible diagnosis of dengue. However, currently one also needs to remember the possibility of a co-infection. Looking for additional symptoms that may favour COVID (dyspnoea, cough, loss of smell) or dengue (arthralgia and myalgia) may be of some help. Respiratory symptoms were only noted in a small proportion. Thus a high degree of suspicion of possible dengue–COVID-19 co-infections is needed for making a timely diagnosis. GI symptoms and skin rashes that were noted in some have low diagnostic sensitivity.

Most patients with co-infections had leukopenia and thrombocytopenia. These are common findings in dengue and thus are not helpful in recognizing a co-infection. One-third of patients with co-infections in the small studies had transaminitis, which is also a common biochemical abnormality seen in dengue. Thus, in general, basic haematological and biochemical tests do not help in differentiating dengue from co-infections, but a relative lymphopenia may point towards a co-infection.[40] A few patients with co-infection had significantly elevated D-dimer levels, but this test was only mentioned in some of the reports. Elevated D-dimer levels are not generally seen in dengue. Thus high D-dimer levels may potentially help in differentiating COVID-19 or a co-infection from dengue (Figure 2).

In dengue-hyperendemic regions, elevated D-dimer levels or abnormal chest radiographs during an acute febrile illness should point a physician towards consideration of a co-infection. One limitation is that all patients with clinically and biochemically suggestive dengue in a hyperendemic area do not have chest radiography unless they develop respiratory symptoms. More than half of the patients in the reports who had chest radiography had an abnormality suggestive of COVID-19. Thus the threshold for doing chest radiography may need to be lowered in relevant settings. Most of the co-infected patients did not have medical comorbidities, and this may be because mainly middle-aged males are affected.

SARS-CoV-2 antibodies may produce false positive results with dengue IgG and IgM rapid tests.[41] Similarly, dengue antibodies may produce false positive SARS-CoV-2 antibody test responses.[42] Modelling studies have found some dengue virus envelope antibodies (these circulate in the blood of persons who have recovered from a dengue infection) recognise specific motifs on the receptor binding domain (RBD) of the SARS-CoV-2 spike protein. The primary interacting amino acids include K417, Y449, Y453, Q493, G495, Q498, T500 and Y505. These amino acids are in direct contact with the angiotensin-converting enzyme 2 receptor.[43, 44] As serological cross-reactivity may lead to false positive dengue serology, clinical correlation and the use of PCR/antigen–enzyme-linked immunosorbent assay testing is recommended to confirm a diagnosis of dengue.[45]

The limitations of our analysis include the small numbers of individuals in some of the subgroups, thus making it difficult to be precise with some estimates. There could have been an element of selection bias, as only two reviewers were involved in the search, but repeated cross-checking was done of the databases and the reference lists of the analysed papers were manually cross-checked to minimise this. We used three databases (PubMed, Cochrane and LILACS) for our search and it is possible that a study may not have been listed in these databases. Furthermore, it is possible that the cases published so far represent only those that develop sufficient symptoms for the individual to seek medical advice. It is well recognised that most dengue and SARS-CoV-2 infections are either asymptomatic or present as an uncomplicated acute febrile illness.[46, 47] In the tropics, serological antibody cross-reactivity may also occur with other arboviral infections. Thus not all positive dengue antibody test results are consistent with a co-infection. There was missing clinical, biochemical and outcome information in some of the reports.

Conclusions

The current COVID-19 pandemic has put dengue-hyperendemic areas under a considerable strain. It is important to suspect and identify co-infections early, as treatment needs to consider the pathogenetic mechanisms of both conditions. Serological cross-reactivity needs to be remembered, as false positive dengue serology tests could mislead a clinical team. Whether one infection predisposes or protects an individual from another infection is currently still unclear. During a co-infection, the adverse immune responses from each could be magnified and lead to higher rates of complications. The continued study of this aspect should provide more evidence-based answers to important questions such as when to suspect COVID-19 and dengue co-infection, do any clinico-biochemical parameters suggest co-infection, what group of people are at high risk of acquiring a co-infection and how should these patients be managed?

Authors' contributions: SLS and CD designed the study; conducted the search; assessed article titles, abstracts and full texts; and reviewed and approved the final version. CD wrote the first version of the manuscript. SLS performed the final editing. Both authors had full access to the data in the study and final responsibility for the decision to submit for publication.

Acknowledgements: None.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

Data availability: Data analyzed in this study were a re-analysis of existing data, which are openly available at locations cited in the reference section.

References

1 World Health Organization. Coronavirus disease (COVID-2019) situation reports. Geneva: World Health Organization; 2020.

2 Aliaga-Samanez A, Cobos-Mayo M, Real R, et al. Worldwide dynamic biogeography of zoonotic and anthroponotic dengue. PLoS Negl Trop Dis. 2021;15(6):e0009496.

3 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(2):e2161.

4 Tsheten T, Clements ACA, Gray DJ, et al. Clinical features and outcomes of COVID-19 and dengue co-infection: a systematic review. BMC Infect Dis. 2021;21(1):729.

5 Kariyawasam JC, Jayarajah U, Riza R, et al. Gastrointestinal manifestations in COVID-19. Trans R Soc Trop Med Hyg. 2021;115(12):1362–88.

6 Rahman A, Niloofa R, De Zoysa IM, et al. Neurological manifestations in COVID-19: a narrative review. Sage Open Med. 2020;8:2050312120957925.

7 Rahman A, Niloofa R, Jayarajah U, et al. Hematological abnormalities in COVID-19: a narrative review. Am J Trop Med Hyg. 2021;104(4):1188–201.

8 Brodin P. Immune determinants of COVID-19 disease presentation and severity. Nat Med. 2021;27(1):28–33

9 Kularatne SA, Dalugama C. Dengue infection: global importance, immunopathology and management. Clin Med (Lond). 2022;22(1):9–13.

10 Kularatne SAM, Ralapanawa U, Dalugama C, et al. Series of 10 dengue fever cases with unusual presentations and complications in Sri Lanka: a single centre experience in 2016. BMC Infect Dis. 2018;18(1):674.

11 Dalugama C, Gawarammana IB. Dengue hemorrhagic fever complicated with acute liver failure: a case report. J Med Case Rep. 2017;11(1):341.

12 Medagama A, Dalugama C, Meiyalakan G, et al. Risk factors associated with fatal dengue hemorrhagic fever in adults: a case control study. Can J Infect Dis Med Microbiol. 2020;2020:1042976.

13 Ng D, Ghosh A, Jit M, et al. Mini-review: can non-human leucocyte antigen genes determine susceptibility to severe dengue syndromes? Trans R Soc Trop Med Hyg. 2017;111(9):384–92.

14 Adarsh MB, Abraham A, Kavitha P, et al. Severe thrombocytopenia in COVID-19: a conundrum in dengue-endemic areas. Indian J Crit Care Med. 2021;25(4):465–6.

15 Agudelo Rojas OL, Tello-Cajiao ME, Rosso F. Challenges of dengue and coronavirus disease 2019 coinfection: two case reports. J Med Case Rep. 2021;15(1):439.

16 Bicudo N, Bicudo E, Costa JD, et al. Co-infection of SARS-CoV-2 and dengue virus: a clinical challenge. Braz J Infect Dis. 2020;24(5):452–4.

17 Epelboin L, Blondé R, Nacher M, et al. COVID-19 and dengue co-infection in a returning traveller. J Travel Med. 2020;27(6):taaa114.

18 Estofolete CF, Machado LF, Zini N, et al. Presentation of fatal stroke due to SARS-CoV-2 and dengue virus coinfection. J Med Virol. 2021;93(3):1770–5.

19 Gupta S, Arora S, Gupta M, et al. Dengue myocarditis complicated by COVID-19: a case report on dual viral infection. Cureus. 2021;13(8):e17076.

20 Hilmy AI, Dey RK, Imad HA, et al. Coronavirus disease 2019 and dengue: two case reports. J Med Case Rep. 2021;15(1):171.

21 Hossain MR, Sarmin M, Rahman H, et al. SARS-CoV-2 and dengue virus coinfection in an adult with beta-thalassemia (trait): a case report from Bangladesh with literature review. Heliyon. 2021;7(10):e08229.

22 Jose PM, Paola ZS, Eduardo DG, et al. A case of coinfection of a pediatric patient with acute SARS-COV-2 with MIS-C and severe DENV-2 in Mexico: a case report. BMC Infect Dis. 2021;21(1):1072.

23 Kariyappa M, Govindarajan V, Kommalur A. Acute leukoencephalopathy with restricted diffusion in an infant with severe COVID-19 and dengue coinfection progressing to West syndrome. J Trop Pediatr. 2021;67(2):fmab026.

24 Kazi MA, Ghosh S, Roychowdhury S, et al. A case study of dual infection of dengue and COVID-19: presenting as multiorgan dysfunction in an infant. J Trop Pediatr. 2021;67(1):fmaa080.

25 Khalil A, Badr B, Wright H, et al. Dengue fever and COVID-19 co-infection at the emergency department of a tertiary care hospital in Jeddah, Saudi Arabia. Eur J Case Rep Intern Med. 2020;7(12):002167.

26 Kumarihamy P, Ratnayake A, Gunaratne S, et al. Dengue and SARS-CoV-2 co-infection: a case series from Sri Lanka and literature review. J Clin Images Med Case Rep. 2021;2(5):1343.

27 Mahajan NN, Kesarwani SN, Shinde SS, et al. Co-infection of malaria and dengue in pregnant women with SARS-CoV-2. Int J Gynaecol Obstet. 2020;151(3):459–62.

28 Nair S. COVID-19 pneumonia and dengue fever coinfection in an individual from Southeast Asia. Cureus. 2021;13(10):e18846.

29 Nasomsong W, Luvira V, Case Phiboonbanakit D. report: dengue and COVID-19 coinfection in Thailand. Am J Trop Med Hyg. 2020;104(2):487–9.

30 Pontes RL, de Brito BB, da Silva FAF, et al. Coinfection by SARS-CoV-2 and dengue virus in a dual viral circulation setting. Travel Med Infect Dis. 2020;37:101862.

31 Radisic MV, Piro MA, Mori I, et al. SARS-CoV-2 and dengue virus co-infection. A case report. Infez Med. 2020;28(3):416–9.

32 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(2):363–7.

33 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(6):e16–8.

34 Saipen A, Demot B, De Leon L. Dengue-COVID-19 coinfection: the first reported case in the Philippines. Western Pac Surveill Response J. 2021;12(1):35–9.

35 Somasetia DH, Malahayati TT, Andriyani FM, et al. A fatal course of multiple inflammatory syndrome in children coinfection with dengue. A case report from Indonesia. IDCases. 2020;22:e01002.

36 Tiwari L, Shekhar S, Bansal A, et al. COVID-19 with dengue shock syndrome in a child: coinfection or cross-reactivity? BMJ Case Rep. 2020;13:e239315.

37 Verduyn M, Allou N, Gazaille V, et al. Co-infection of dengue and COVID-19: a case report. PLoS Negl Trop Dis. 2020;14(8):e0008476.

38 Mejía-Parra JL, Aguilar-Martinez S, Fernández-Mogollón JL, et al. Characteristics of patients coinfected with severe acute respiratory syndrome coronavirus 2 and dengue virus, Lambayeque, Peru, May–August 2020: a retrospective analysis. Travel Med Infect Dis. 2021;43:102132.

39 Schulte HL, Brito-Sousa JD, Lacerda MVG, et al. SARS-CoV-2/DENV co-infection: a series of cases from the Federal District, Midwestern Brazil. BMC Infect Dis. 2021;21(1):727.

40 Abeysuriya V, Seneviratne SL, de Silva AP, et al. Combination of cycle threshold time, absolute lymphocyte count and neutrophil:lymphocyte ratio is predictive of hypoxia in patients with SARS-CoV-2 infection. Trans R Soc Trop Med Hyg. 2021;116(7):628–35.

41 Yan G, Lee CK, Lam LTM, et al. Covert COVID-19 and false-positive dengue serology in Singapore. Lancet Infect Dis. 2020;20(5):536.

42 Masyeni S, Santoso MS, Widyaningsih PD, et al. Serological cross-reaction and coinfection of dengue and COVID-19 in Asia: experience from Indonesia. Int J Infect Dis. 2021;102:152–4.

43 Wang Q, Zhang Y, Wu L, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell. 2020;181(4):894–904.e9.

44 Sanches PRS, Charlie-Silva I, Braz HLB, et al. Recent advances in SARS-CoV-2 Spike protein and RBD mutations comparison between new variants Alpha (B.1.1.7, United Kingdom), Beta (B.1.351, South Africa), Gamma (P.1, Brazil) and Delta (B.1.617.2, India). J Virus Erad. 2021;7(3):100054.

45 Ulrich H, Pillat MM, Tárnok A. Dengue fever, COVID-19 (SARS-CoV-2), and antibody-dependent enhancement (ADE): a perspective. Cytometry A. 2020;97(7):662–7.

46 Perera L, De Zoysa N, Jayarajah U, et al. Transfusion-transmissible dengue infections. Trans R Soc Trop Med Hyg. 2020;114(11):866–82.

47 Seneviratne SL, Jayarajah U, Abeysuriya V, et al. COVID-19 vaccine landscape. J Ceylon Coll Physicians. 2020;51(2):120–31.