

REVIEW

Does dengue and COVID-19 co-infection have worse outcomes? A systematic review of current evidence

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Abstract

In dengue-endemic regions, the co-infection with SARS-CoV-2 and dengue is a significant health concern. Therefore, we performed a literature search for relevant papers in seven databases on 26 September 2021. Out of 24 articles, the mortality rate and intensive care unit (ICU) admission were 19.1% and 7.8%, respectively. The mean hospital stay was 11.4 days. In addition, we identified two pregnancies with dengue and COVID-19 co-infection; one ended with premature rupture of membrane and intrauterine growth restriction fetus, while the other one ended with maternal mortality and intrauterine fetal death. COVID-19 and dengue co-infection had worse outcomes regarding mortality rates, ICU admission, and prolonged hospital stay. Thus, wise-decision management approaches should be adequately offered to these patients to enhance their outcomes. Establishing an early diagnosis might be the answer to reducing the estimated significant burden of these conditions.

KEYWORDS

co-infection, COVID-19, dengue, SARS-CoV-2, systematic review

1 | INTRODUCTION

In late 2019, the world faced one of the most dangerous epidemics since the outbreak of the Spanish flu.¹ This epidemic was caused by coronavirus disease (COVID-19) that infected more than 300 million individuals, and more than 5 million patients died due to the infection itself or complications.² In addition, approximately more than 400 million cases are infected with dengue fever each year, transmitted by the *Aedes aegypti* mosquito.³ The high burden of dengue and COVID-19 infections increases the possibility of co-infection, which is a significant health concern due to the overlapped symptomatology and similar laboratory findings of the two conditions in dengue-endemic regions.^{4,5} This overlap would make reaching the correct diagnosis and, subsequently, the proper management challenging for both diseases.⁵ Furthermore, there are previous studies

about the co-infection of dengue and COVID-19 during the current pandemic, with reported worse clinical manifestations and higher complications.^{6,7} Nevertheless, there is scarce evidence on the outcomes and associated prognosis, which is essential to implement convenient public health policies. Therefore, we conducted this systematic review to give a summary of the available literature regarding the outcomes of dengue and COVID-19 co-infection.

2 | METHOD

2.1 | Search strategy and study selection

We aimed to identify relevant original papers reporting dengue patients suffering Covid-19 infection. On 26 September 2021, we

conducted a systematic search following the recommendations of PRISMA's checklist to detect our included studies. We used the search term '(Dengue Fever OR Dengue) AND (COVID-19 OR COVID 19 OR novel coronavirus OR SARS CoV 2)' through seven databases including PubMed, Google Scholar, Scopus, Web of Science (ISI), Virtual Health Library, The New York Academy of Medicine, and System for information on Grey Literature in Europe. Our search results were collected using EndNote software, where duplications were removed. Subsequently, we moved the results to Microsoft Excel sheets, and two phases of title and abstract screening followed by full-text screening were done. Two authors screened the results independently, and we included the study upon their agreement. A senior reviewer was added to solve any discrepancy in case of disagreement. We included all articles that reported dengue and COVID-19 co-infection and excluded reviews, conference papers, and no available full texts. In addition, a manual search was performed through references of

included articles and relevant articles in Google Scholar and PubMed (Figure 1).

2.2 | Data extraction and quality assessment

We made an excel sheet containing our outcomes of interest. The characteristics of each study included (study design, sample size, country, and sex) while the patients' outcomes were (mortality, intensive care unit (ICU) admission, hospital stay length, obstetric and foetal outcomes). We calculated the prevalence of mortality and ICU admission by dividing the number of deaths and ICU admissions, respectively, by the total number of cases. The extraction was done by three reviewers separately, and the final results were considered upon consensus. A senior author was added for the discussion if needed. Moreover, we did a quality assessment for our included papers using the Joanna Briggs Institute Critical Appraisal tool for

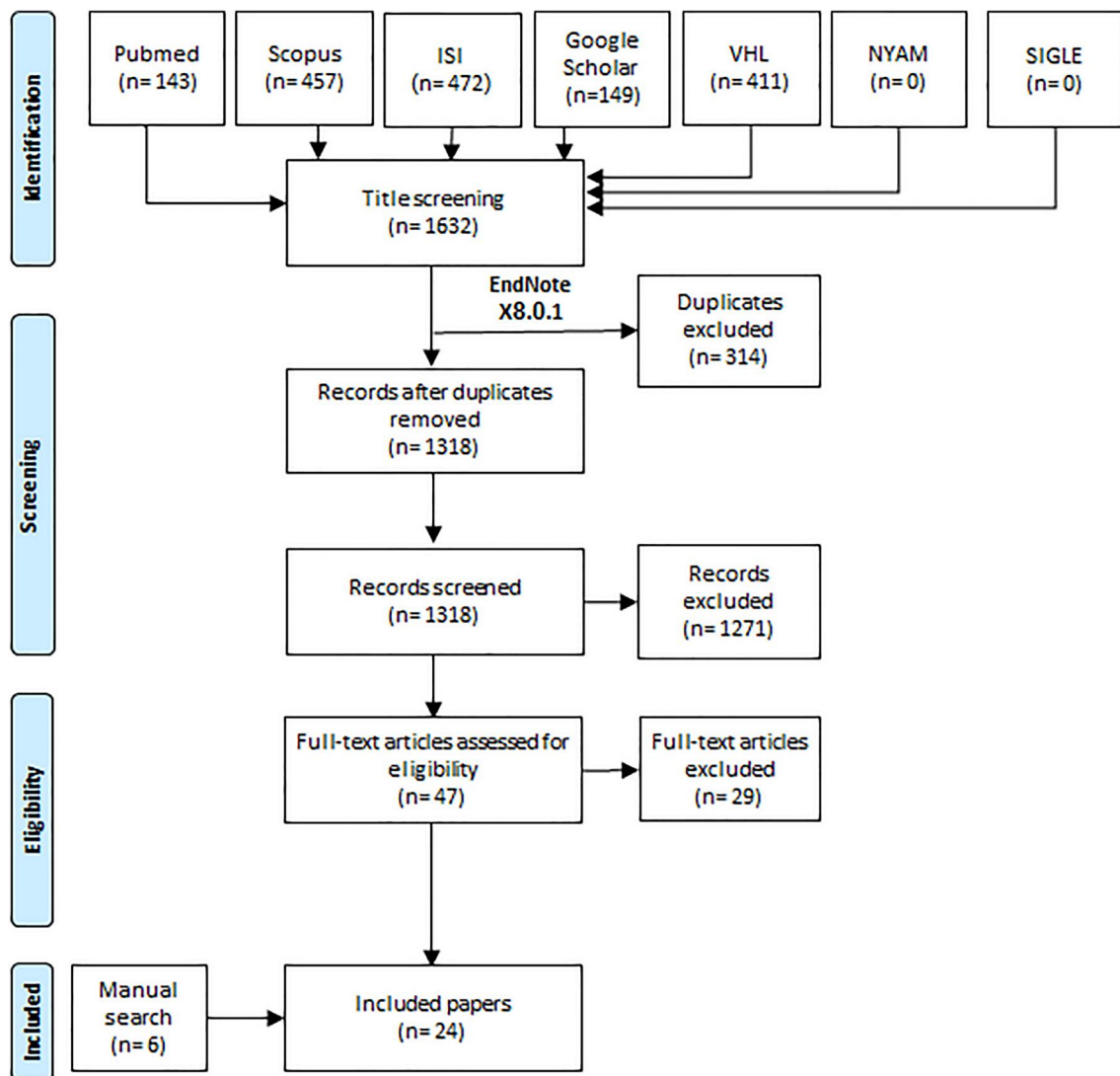


FIGURE 1 Flow diagram of the study process

case report papers and The National Institute of Health tool for cohort studies (Table S1 and S2).

3 | RESULTS

After screening 1318 papers, 47 papers were eligible for another phase of full text screening. Out of these, we included 18 papers together with additional 6 papers from manual search trials. Finally, we had 24 articles with a sample size of 89 patients with dengue and COVID-19 co-infection with a male prevalence of 63% (Table 1, Figure 1). Regarding study design, there were 22 case reports and two retrospective cohort studies. In terms of countries of patients, Peru, followed by Argentina, Saudi Arabia, and India, had the highest numbers of dengue-COVID-19 co-infected patients (Figure 2).

3.1 | Mortality

Out of 89 cases identified with dengue and COVID-19 co-infection, 17 patients passed away, with a prevalence of 19.1%. In addition, the mortality rates were higher among males than females, with a prevalence of 10.1% and 9%, respectively.

3.2 | Intensive care unit admission

Seven cases needed ICU admission, assuming a prevalence of 7.8%.

3.3 | Hospital stay

Twenty-one papers reported the hospital stay duration. The mean hospital stay for the included 37 patients was 11.4 days.

3.4 | Obstetric and foetal outcomes

We identified two pregnancies with dengue and COVID-19 co-infection. One ended with premature rupture of membrane (PROM) and intrauterine growth restriction (IUGR) foetus, while the other one ended with maternal mortality and intrauterine foetal death (IUFD).

4 | DISCUSSION

In the present systematic review, we mainly aimed to determine the clinical outcomes of patients suffering from dengue and COVID-19 co-infection. Our results indicated the high mortality rate among these patients (19.1%), based on cumulative evidence from relevant studies. It should be noted that this rate is remarkably higher than the estimated global rates for dengue and COVID-19 patients (1.3%

and 2.04%, respectively).^{8,9} Moreover, we noted that the prevalence of co-infection and mortality was higher among males. This is consistent with previous dengue investigations, which indicated that the prevalence of dengue infection is higher among males.¹⁰⁻¹⁴ Many reasons have been proposed for these differences, including using fully covered dresses by females, potential differences in healthcare services, and prioritising provisions of male individuals in societies where dengue is endemic.^{15,16}

To the best of our knowledge, advanced age is considered one of the major risk factors in patients with dengue fever or COVID-19 infections.^{17,18} In our study, two patients from two case reports who experienced death event had an age of 59 and 60 years.^{19,20} Moreover, in the case series of Parra and colleagues, mortality rate was 28% in patients with dengue and COVID-19 co-infection whose median age was 55.5 years.²¹ Due to the limited sample size in our study, we can not confirm the role of age in predicting mortality from dengue and COVID-19 co-infection. Therefore, more studies with bigger sample size and controlling of other confounders are needed for studying this association.

Our results also show a high rate of ICU admissions secondary to COVID-19 and dengue infection, being 7.8%. However, it should be noted that this rate is lower than the estimated one for COVID-19 patients, being 9.8%.²² This might be attributed to the different population characteristics and quality of care offered to both populations. The rate of patients requiring ICU admission secondary to severe dengue is also high. Previous dengue-related studies indicated that the mortality rate among patients admitted to the ICU secondary to severe dengue manifestations might be up to 23.1%.²³⁻²⁶ Such differences are usually attributed to the method of defining severe disease in these patients and the degree of severity of included participants, as reported among these studies. We furtherly found that our population had a mean hospital stay of 11.4 days. In the literature, the estimated median hospital stay for individual COVID-19 and dengue populations are 5 and 6 days, respectively.^{27,28} Previous dengue studies reported that hospital stay was remarkably longer among infants than children and adults. This has been attributed to the frequency of complications, which might affect this age group at a potentially higher rate secondary to the infection.^{15,29,30}

Many factors can contribute to severe COVID-19, including co-infection.³¹⁻³⁶ The current literature reveals a solid association between COVID-19 and co-infection with different viruses and bacteria. As a result, these patients usually have severe outcomes due to remarkable deterioration in their health status.³¹ A previous meta-analysis reported that the prevalence of bacterial co-infection with COVID-19 was 5.1%, while secondary infection accounted for 13.1%. Moreover, it has been shown that the rate of ICU admissions was significantly associated with bacterial infections among COVID-19 patients.³⁷ In addition, it is widely known that COVID-19 is associated with a high rate of complications that are usually life-threatening.³⁸⁻⁴⁰ Many previous studies also showed that among patients with severe dengue infection, up to 55.9% suffered from a concurrent bacterial infection.^{23,26} Dengue infection might also lead

TABLE 1 Characteristics of the included studies

Study ID	Country	Sample size	Age	Gender	Diagnosis of dengue	Diagnosis of COVID-19	Outcome	ICU admission	Hospital stay (days)
Irwindi-2021	Indonesia	1	23	F	NS1 antigen or IgM DENV	PCR	Died	Yes	5
Alam-2021	Indonesia	1	10 months	F	NS1 antigen	PCR	Survived	No	16
Hariadi-2021	Indonesia	1	68	F	DENV IgM and IgG	PCR	Survived	No	11
Verduyn-2020	France	1	18	M	NS1 antigen	PCR	Survived	No	7
Khalil-2020	Saudi Arabia	1	63	M	NS1 antigen and IgG DENV	PCR	Survived	No	6
		1	53	F	DENV IgM, IgG and PRC	PCR	Survived	No	5
		1	48	F	NS1 antigen, IgM and IgG DENV	PCR	Survived	No	4
		1	46	M	NS1 antigen and PCR	PCR	Survived	No	0
Malibari-2020	Saudi Arabia	1	58	M	NS1 antigen, IgM and IgG DENV	PCR	Survived	No	7
Reyes-Ruiz-2021	Mexico	1	42	F	PCR	PCR	Survived	No	18
Wahiduzzaman-2021	Bangladesh	1	34	M	NS1 antigen	PCR	Survived	No	-
Gupta-2021	India	1	65	M	DENV IgM	PCR	Survived	No	17
Kasi-2020	India	1	9 months	F	NS1 antigen, IgM DENV	PCR	Survived	No	14
Kariyappa-2021	India	1	5 months	F	DENV IgM and ELISA	PCR	Survived	No	21
Mahajan-2020	India	1	22	F	NS1 antigen	PCR	Survived	No	9
Krishna-2021	India	1	28	F	NS1 antigen, IgM DENV	PCR	Survived	No	7
Estofolete-2020	Brazil	1	60	F	NS1 antigen, IgM and IgG DENV	PCR	Died	Yes	5
Bicudo-2020	Brazil	1	56	F	NS1 antigen, IgM and IgG DENV	PCR	Survived	No	6
Pontes-2020	Brazil	1	39	M	PCR	PCR	Survived	No	-
Rojas-2021	Colombia	1	24	F	NS1 antigen and PCR	PCR	Survived	Yes	6
		1	59	M	DENV IgM and IgG	IgG SARS-CoV-2	Died	Yes	63
Villamil-Gómez-2021	Colombia	1	52	M	DENV IgM and IgG	PCR	Survived	No	7
Nasomsong-2021	Thailand	1	50	F	PCR	PCR	Survived	No	11
Roso-2021	Argentina	1	57	F	PCR	PCR	Survived	No	5
Carosella-2021	Argentina	13	37 (29–50) ^a	6 F, 7 M	NS1 antigen, PCR or serologic conversion	PCR	All survived	0 patients	12 (10–14) ^a
Radisic-2020	Argentina	1	25	M	NS1 antigen, IgM DENV	PCR	Survived	No	8
Saipen-2021	Philippines	1	62	F	NS1 antigen, IgG DENV	PCR	Survived	No	9
Mejía-Parra-2021	Peru	50	55.5 (40.5–65) ^a	11 F, 39 M	PCR, NS1 antigen, IgM and IgG DENV	PCR, IgM and IgG SARS-CoV-2	14 died	3 patients	-

Abbreviations: M, male; F, female.

^aMedian (IQR).

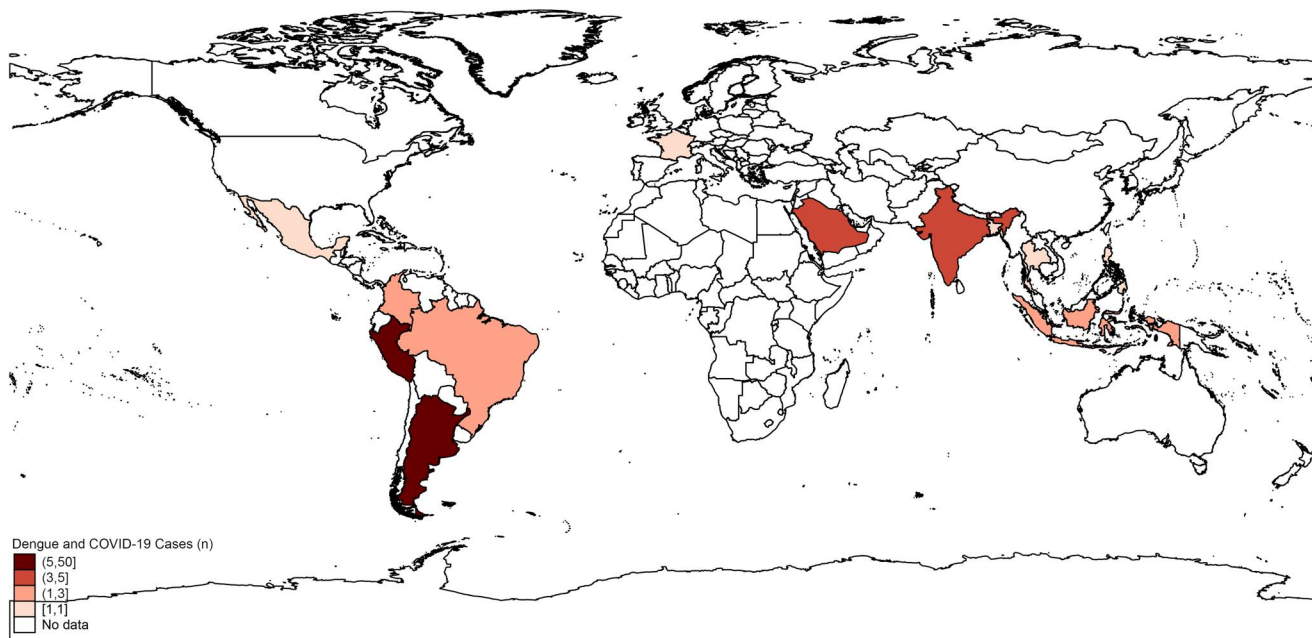


FIGURE 2 The worldwide distribution of the reported cases of dengue and COVID-19 co-infection

to serious morbidities such as dengue shock syndrome and dengue haemorrhagic fever,⁴¹⁻⁴⁶ contributing to the estimated high rates of mortality and ICU admissions in the current study.

Regarding obstetric and foetal outcomes, we only found two pregnancies with COVID-19 and dengue co-infection occurred, both of which were complicated; one with PROM and IUGR and the other with maternal mortality and IUFD. Evidence from various studies in the literature indicates that neonatal dengue infection is attributed to vertical transmission of the virus from an affected mother. Based on these investigations, the diagnosis of dengue in these neonates was related to maternal dengue infection (occurring amid delivery by 10 days).⁴⁷⁻⁴⁹ Many relevant studies also demonstrated that dengue infection in this population is usually associated with premature birth, stillbirth, or low birth weight.^{48,50-53} On the other hand, some studies suggested that vertical transmission of protective antibodies from infected mothers to their infants during placental transfer might reduce the severity of the disease and enhance the outcomes.²⁸ However, it has been demonstrated that these antibodies are age-dependent and usually decrease with advancing age.⁵⁴ Accordingly, the current evidence needs further elaboration by more relevant studies. Moreover, only minimal cases with maternal co-infection are reported. Therefore, further studies with larger sample sizes are needed to provide more solid evidence.

Establishing an early diagnosis of dengue infection in these patients is critical in the management process. In this context, some studies indicate that conducting the NS1 rapid test might provide an early diagnosis of dengue infection in the newborns of mothers that acquired the infection within the perinatal period. Besides, detecting IgM Dengue Antibody (MAC-ELISA) is very useful in these cases and might be a good alternative to the NS1 rapid test. However, it should be noted that the sensitivity of these tests is not

consistent among these studies and depends on the course and duration of illness.^{28,55} It should also be noted that once the diagnosis of dengue has been established, closely monitoring (for severe haemorrhagic events and warning signs) of patients is favourable to enhance the prognosis. However, such an approach is difficult to conduct because of COVID-19-related strict isolation measures, as these patients usually have limited visits to reduce the rates of transmitting the rapidly spreading SARS-CoV-2 viral infection.^{56,57} Furthermore, it has been previously demonstrated that the rate of misdiagnosis of neonatal dengue is considerable.^{58,59} Therefore, some authors suggested that a differential diagnosis in critical settings should be considered with sepsis because of the similar clinical manifestations.

Although the current systematic review provides cumulative evidence regarding COVID-19 and dengue co-infection outcomes, the reported results might have limitations. The main limitation is the limited studies in this context and the minimal sample size in the included studies. This has been a limitation to conducting a proper analysis to identify the potential predictors of this co-infection and potentially enhance the interventional and management approaches.

5 | CONCLUSION

COVID-19 and dengue co-infection had worse outcomes regarding mortality rates, ICU admission, and prolonged hospital stay. Thus, wise-decision management approaches should be adequately offered to these patients to enhance their outcomes. Establishing an early diagnosis might be the answer to reducing the estimated significant burden of these conditions. Shedding more light on the management and prevention of COVID-19 in areas where other diseases are

endemic is also encouraged, owing to the remarkable burden over these populations. Finally, further studies are needed due to the limitations of the currently available data.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Amr Ehab El-Qushayri was responsible for the idea and the study design. All authors shared in screening, extraction, and writing of the full text. Sherief Ghozy supervised all steps, and all authors approved the final version before submission.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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