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Characteristics of patients coinfecting with Severe Acute Respiratory Syndrome Coronavirus 2 and dengue virus, Lambayeque, Peru, May–August 2020: A retrospective analysis

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ARTICLE INFO

Keywords:

SARS-CoV-2

COVID-19

Dengue

Coinfection

COVIDengue

Peru

Latin America

ABSTRACT

Introduction: Before the Coronavirus Disease 2019 (COVID-19) arrival and its pandemic, dengue was already a significant cause of epidemics in South East Asia and Latin America. In 2020 with their cocirculation, coinfections began to be observed and reported in different countries. As expected, this syndemic is evident in different areas and deserves proper characterisation and studies in Peru.

Methods: We retrospectively assessed the clinical, epidemiological, diagnostic characteristics and outcomes in a Social Security Hospital of Chiclayo, Lambayeque, Peru, of patients that were diagnosed simultaneously with COVID-19 and dengue during May–August 2020.

Results: A total of 50 patients with COVID-19/dengue coinfection were identified. Of them, 60% presented thrombocytopenia, and 52% fever, among other findings. The case fatality rate in this group was 28%, being higher in those patients initially classified as severe dengue (100%), as well as in females (55%) than males (21%) (OR = 4.65; 95%CI 1.18–18.45).

Discussion: Co-occurrence of COVID-19/Dengue is growing as a consequence of the syndemic of these viral diseases in endemic areas, such as Latin America, and as both conditions may evolve to severe disease, their epidemiological but clinical interaction in terms of outcomes need further assessment in future studies in the region.

1. Introduction

Before the pandemic of Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), epidemics of different arbovirus have been affecting significantly Asia-Pacific and Latin American regions in a significant way over the last decade [1,2]. Dengue persists as the central viral disease transmitted by vectors such as *Aedes aegypti* in such regions [3,4].

Latin America has been one of the most significantly affected regions by COVID-19 [5], including Peru [6]. Therefore, as soon as COVID-19

arrived in Latin America, multiple implications were expected, considering the regional epidemiology of endemic diseases such as dengue [7–9], especially in Brazil [8], Colombia [10], Ecuador [9] and Peru [11], among others.

Dengue and COVID-19 share clinical findings, such as fever, myalgia, fatigue, headache, rash [12], and laboratory findings, making, in endemic areas or in travellers coming from, difficult to distinguish between both conditions. Additionally, as expected, coinfections COVID-19/Dengue have been reported in different countries, such as Mayotte (Indian ocean) [13], La Reunión (Indian ocean) [14], Argentina

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<https://doi.org/10.1016/j.tmaid.2021.102132>

Received 9 March 2021; Received in revised form 17 June 2021; Accepted 23 June 2021

Available online 26 June 2021

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[15–17], Colombia [18], among others.

Then, although COVID-19/Dengue coinfection is becoming a significant concern [17], only individual case reports [13–16] and one 13-patient cohort [17] have been described in the literature. Therefore, we report the clinical characteristics and outcomes in a cohort of patients co-infected with SARS-CoV-2 and Dengue virus in Chiclayo, Lambayeque department, Peru.

2. Methods

We retrospectively assessed patients coinfecting with SARS-CoV-2 and dengue virus during May–August 2020 in a Third Level Social Security Hospital in Chiclayo city, Lambayeque department, Peru. All patients had complete information regarding signs and symptoms at hospitalization and their hospital course and outcomes. In addition, clinical data were obtained in a predesigned clinical report form by reviewing medical records.

SARS-CoV-2 was diagnosed using real-time PCR of nasopharyngeal swab specimens or serological tests detecting IgM/IgG antibodies against SARS-CoV-2, as approved by the Ministry of Health in reference laboratories. Dengue was diagnosed by either detection of non-structural protein 1 (NS1) (for patients with less than five days of symptoms) or serological tests detecting IgM/IgG (for patients with symptoms more significant than five days). Real-time PCR for Dengue is not regularly used for diagnosis.

We included all the patients diagnosed simultaneously with COVID-19 and Dengue, or that said coinfection was after two weeks or more of the diagnosis of COVID-19. Hospitalised patients in the COVID-19 area of a Social Security Level III Hospital and patients followed up by telephone during May–August 2020 were included. Patients were included after detecting the *Aedes aegypti* vector after undergoing entomological surveillance of evolutionary forms such as eggs, larvae and adults, within the hospital environment. This finding motivated us to review the medical records of hospitalised patients in the COVID-19 area. The following were considered criteria for suspicion of dengue infection [19, 20]: Patients with a temperature greater than 38 °C for 2 to 3 consecutive days, after having received anti-inflammatory and antipyretic treatment for COVID-19 infection, control blood count with thrombocytopenia (<150,000 platelets/mL) and increased haematocrit, patients with arthralgia in hands and feet, retro-ocular pain, headache, low back pain, persistent abdominal pain, hypothermia, drowsiness and petechiae in the extremities and abdomen [19,20]. For this study, the case fatality (CFR%) rate was defined as the proportion of cases that died (CFR% = deaths/cases x100).

The criteria for the classification of Dengue cases (Dengue without warning signs, dengue with warning signs, and Dengue Severe) were applied according to the clinical practice guidelines for dengue cases in Peru and the recommendations of the WHO [20]. Therefore, this study was waived of Ethics Committee approval, as is a retrospective analysis.

3. Results

A total of 50 patients who had coinfections with SARS-CoV-2 and Dengue virus were identified. Most patients were relatively young (median age 55.5 years, interquartile range 40.5–65, minimum 15, maximum 89), 78% were male (Table 1). Most patients had thrombocytopenia (60%, n = 30), and 52% (n = 26) had febrile disease at diagnosis (median temperature of 38.1 °C), among other clinical findings (Table 2). Rash appeared in 3 patients early in the disease and before the resolution of fever (Table 2). Of the total, 32% (n = 16) presented hypertension and type 2 diabetes mellitus (26%, n = 18), among other comorbidities (Table 2). No patients presented hypotension during their clinical presentations. No patients presented current or past malignancies.

From the total, 76% (n = 38) required hospitalization (Table 1). Diagnosis of COVID-19/Dengue was performed mainly with SARS-CoV-

Table 1

Characteristics of the patients with COVID-19 and Dengue (N = 50), Chiclayo, Peru.

Characteristics	N	%
<i>Sex</i>		
Male	39	78
Female	11	22
<i>Type of patient</i>		
Outpatient	12	24
Hospitalised	38	76
<i>Tests employed for COVID-19 diagnosis</i>		
SARS-CoV-2 IgM-IgG	39	78
SARS-CoV-2 IgM	4	8
RT-PCR for SARS-CoV-2 (nps)	4	8
SARS-CoV-2 IgG	3	6
<i>Tests employed for Dengue diagnosis</i>		
NS1 DENV	30	60
DENV IgM	19	38
DENV IgM-IgG	1	2
DENV IgG	0	0
<i>Comorbidities</i>		
High blood pressure	16	32
Type 2 Diabetes Mellitus	13	26
Chronic renal failure	7	14
Obesity	6	12
Cancer	4	8
Asthma	4	8
Pulmonary fibrosis	2	2
<i>Condition</i>		
Discharged	36	72
Death	14	28

NPS: Nasopharyngeal swab.

2 IgM/IgG Rapid Test and NS1 Antigen-DENV (54%, n = 27), followed by SARS-CoV-2 IgM/IgG Rapid Test and DENV IgM/IgG Antibodies (38%, n = 19), RT-PCR for SARS-CoV-2 and NS1 Antigen-DENV (6%, n = 3), and RT-PCR for SARS-CoV-2 and DENV IgM/IgG Antibodies (2%, n = 1), none (0%) by IgG (Table 3).

Of the 50 cases, 6% (n = 3) developed severe dengue (which were admitted to the intensive care unit [ICU]), 58% (n = 29) Dengue with warning signs, and 36% (n = 18) Dengue without warning signs (Table 2). Of the total, 76% (n = 38) of the patients presented COVID-19 pneumonia. The case fatality rate (CFR%) in the group was 28% (n = 14) (Table 4). All the patients with severe dengue died (100%, n = 3), whilst that occurred in 28% (n = 8) of those that developed warning signs and 17% (n = 3) of those without warning signs (Table 4). The case fatality rate was higher in females (55%, n = 6) than males (21%, n = 8) (OR = 4.65; 95%CI 1.18–18.45) (Table 5).

4. Discussion

December 31, 2019, marked the beginning of an epidemic that evolved up to a pandemic that has lasted more than a year since the first cases reported in Wuhan, Hubei province, China [21–24]. Latin America has been one of the most significantly affected regions by COVID-19 [5]. Multiple threats have been progressively growing with the interaction between COVID-19 and other infectious and non-infectious conditions in this region as in others. However, with the epidemiological overlapping in the tropics, the menace of COVID-19 and Dengue and potentially for other arboviral and tropical diseases is more a real additional burden during the ongoing pandemic [10]. An effective antiviral drug has been developed for none of these conditions, and although for dengue, a limited approved vaccine is available, but not available in Peru. For COVID-19, on February 10, 2021, the national plan of vaccinated started, applying COVID-19 vaccines, although slowly, only <7% of the population has been fully vaccinated (June 17, 2021). Currently, Sinopharm and Pfizer/Biontech vaccines are being applied. In Peru, the COVID-19 infection spread rapidly to all regions, being the northern departments such as Piura, Trujillo and Lambayeque,

Table 2
Clinical and laboratory characteristics in patients with COVID-19 and Dengue, classified according to the WHO 2009 Dengue Criteria.

Symptoms	Dengue, classification (N = 50)						Total	%
	Without warning signs (n = 18)		With warning signs (n = 29)		Severe (n = 3)			
<i>Haematological manifestations</i>								
Thrombocytopenia	0	0.0	27	54.0	3	6.0	30	60.0
Haematocrit concentration	0	0.0	22	44.0	2	4.0	24	48.0
Bleeding or Hemorrhage	0	0.0	9	18.0	2	4.0	11	22.0
<i>Temperature-related manifestations</i>								
Fever	8	16.0	17	34.0	1	2.0	26	52.0
Chills	1	2.0	1	2.0	0	0.0	2	4.0
Hypothermia	0	0.0	0	0.0	1	2.0	1	2.0
<i>Osteoarticular manifestations</i>								
Arthralgia	2	4.0	6	12.0	0	0.0	8	16.0
General malaise	4	8.0	3	6.0	0	0.0	7	14.0
Myalgia	2	4.0	3	6.0	0	0.0	5	10.0
General Weakness	0	0.0	2	4.0	0	0.0	2	4.0
Low Back Pain	2	4.0	0	0.0	0	0.0	2	4.0
<i>Gastrointestinal manifestations</i>								
Abdominal pain	0	0.0	6	12.0	0	0.0	6	12.0
Nausea/Vomiting	0	0.0	4	8.0	0	0.0	4	8.0
Hepatomegaly	0	0.0	1	2.0	0	0.0	1	2.0
Splenomegaly	0	0.0	1	2.0	0	0.0	1	2.0
<i>Cutaneous and subcutaneous manifestations</i>								
Ecchymosis	0	0.0	5	10.0	0	0.0	5	10.0
Edema	2	4.0	3	6.0	0	0.0	5	10.0
Erythematous lesions	0	0.0	4	8.0	0	0.0	4	8.0
Petechiae	0	0.0	3	6.0	0	0.0	3	6.0
Rash	0	0.0	3	6.0	0	0.0	3	6.0
Bruises	0	0.0	2	4.0	0	0.0	2	4.0
Adenopathies	0	0.0	1	2.0	0	0.0	1	2.0
Pale	1	2.0	0	0.0	0	0.0	1	2.0
Pruritus	1	2.0	0	0.0	0	0.0	1	2.0
<i>Neuro-ophthalmological alterations</i>								
Headache	1	2.0	1	2.0	0	0.0	2	4.0
Retroocular pain	0	0.0	2	4.0	0	0.0	2	4.0
Disorientation	0	0.0	1	2.0	0	0.0	1	2.0
Organic Failure	0	0.0	1	2.0	2	4.0	3	6.0

Table 3
Laboratory diagnosis of COVID-19/Dengue coinfection.

Tests	Dengue		Total	
	NS1 Antigen-DENV	DENV IgM/IgG Antibodies		
COVID-19	RT-PCR for SARS-CoV-2	3 (6%)	1 (2%)	4 (8%)
	SARS-CoV-2 IgM/IgG Rapid Test	27 (54%)	19 (38%)	46 (92%)
	Total	30 (60%)	20 (40%)	50 (100%)

Table 4
Relationship of the Dengue Classification and the outcome of the patients coinfecting with COVID-19.

Outcome	Dengue, Classification			Total	p
	Without warning signs	With warning signs	Severe		
Dead	3 17.0%	8 28.0%	3 100.0%	14 28.0%	<0.05
Discharged	15 83.0%	21 72.0%	0 0.0%	36 72.0%	
Total	18 36.0%	29 58.0%	3 6.0%	50 100.0%	

and the North-eastern Peruvian regions such as Loreto that reported the most cases until August 2020. Besides, Lambayeque has reported more than 36,000 confirmed cases of COVID-19 in this department [25]. At the same time, these areas are historically endemic for dengue. Then, among the multiple implications, multiple factors suggest the risk that

Table 5
Relationship between sex and outcome among COVID-19/Dengue patients.

Sex	Outcome		Total	p
	Discharged	Dead		
Female	5 45%	6 55%	11 100%	<0.05
Male	31 79%	8 21%	39 100%	
Total	36 72%	14 28%	50 100%	

(OR = 4.65; 95%CI 1.18–18.45).

both may lead to severe disease simultaneously. Both viral diseases may trigger secondary hemophagocytic lymphohistiocytosis [26–28], leading patients to present hypovolemic shock, vasoplegia, and cardiopulmonary collapse due to hyperinflammation and hyperactivation of the immune system. However, this was not explicitly observed in this cohort from Peru [29].

So far, no severe COVID-19/Dengue was reported in previous studies, nor required admission to an intensive care unit, or died during follow up [13–17]. However, in Peru, at this cohort of COVID-19/Dengue coinfecting patients, the largest until now, 28% of them died, which is usually higher than the CFR for mono-infection due to SARS-CoV-2 [30], as well as for Dengue [3]. At the same time, some studies indicated that the CFR for dengue in north Peru is relevant, and high as 1.3 per 1000 cases in Piura and 9.3 per 1000 in Lambayeque, where is Chiclayo located [31].

Simultaneously, various questions were created about how the various diseases with the epidemiological impact, such as dengue, could manifest themselves in the framework of COVID-19 [32–34]. Some

authors suggest that these diseases present significant similarities concerning pathophysiological events, signs and symptoms [12]. However, in our study, only some clinical manifestations were similar, such as fever, general malaise, headache, nausea and vomiting, and some rash. They were differentiating in the appearance of other added symptoms such as bleeding or haemorrhages, ecchymosis, edema, arthralgia of the feet and hands, retroocular pain, among others, more suggesting Dengue than COVID-19. In any case, some studies suggest that non-pharmaceutical interventions aimed against the spread of SARS-CoV-2 may facilitate the transmission of dengue fever. A study in Asia found that social distancing is expected to lead to 4.32 additional dengue cases per 100,000 individuals in Thailand per month, which equates to 170 more cases per month in the Bangkok province (95% CI: 100–242) and 2008 cases in the country as a whole (95% CI: 1170–2846) [35].

Due to this, in Ecuador, most dengue fever cases will overlap in health centres together with cases of COVID-19, sharing clinical characteristics. Furthermore, suppose we add the possibility of some false positives using rapid dengue tests. In that case, the lack of consideration of COVID-19 due to this result will have profound implications for the patient and local public health [9]. Laboratory diagnosis is one of the limitations of this study, as ideally, all cases should be diagnosed by RT-PCR for SARS-CoV-2 and Dengue virus, for multiple reasons, including possible cross-reactivity [36,37]; nevertheless, some studies in Brazil have suggested that the risk serological cross-reactivity between Dengue and COVID-19 is low [38].

In Brazil, it is often observed that the number of dengue cases increases at the beginning of the year due to the rainy season and high temperatures and peaks between March and April. Meanwhile, the peak of the COVID-19 outbreak in Brazil is forecast to occur in the winter season, when respiratory illnesses are found most frequently. This temporal coincidence implies that the two outbreaks can occur at the same time [8]. Thus, we have that in some cities in Brazil, it was observed that states in which a significant fraction of the population had contracted dengue fever in 2019–2020 reported fewer cases and deaths from COVID-19, and took longer to achieve exponential community transmission because the growth rates of SARS-CoV-2 infection are slower. This inverse correlation between COVID-19 and Dengue was observed in a sample of countries in Asia and Latin America and islands in the Pacific and Indian oceans [39].

On the other hand, a recent report described two cases of patients diagnosed with dengue by rapid test, false positives, due to a cross-reaction of the IgM and IgG antibodies SARS-CoV-2 [36]. Similarly, another report warns of a possible antibody-dependent enhancement (ADE), as they speculate that neutralising antibodies (Nab) against the RBD region of protein S (Spike) could favour the entry of SARS-CoV-2 to host cells and therefore increase viremia, thus, a worsening of the condition of patients with COVID-19 disease [40].

In Ecuador, some data found that most of the febrile Dengue cases would overlap the cases of COVID-19 because they share similar clinical characteristics [9]. In Brazil, some authors have warned that the coinfection of Dengue and COVID-19 could co-occur, especially from June to September [8]. Our hospital in Lambayeque, Peru, demonstrated that this coinfection is occurring with its clinical implications.

Possible cross-reactions of IgM/IgG-DENV rapid test results concerning antibodies developed after infection with SARS-CoV-2, as mentioned by some reports, are not ruled out when describing cases of false positives in rapid tests DENV [36]. However, there would be no cross-reaction between the rapid test of the NS1-DENV antigen and the IgM and IgG antibodies of SARS-CoV-2 since the patients hospitalised with COVID-19 days later presented an unfavourable and unusual evolution after detecting the presence of the *Aedes aegypti* vector.

This study is the first coinfection assessment in Peru, as well as the largest in Latin America. Although many limitations may be highlighted, we can observe the main clinical features and outcomes associated. Many questions may be raised in this context, including if dengue is a

risk factor for severe COVID-19 and a worse outcome in patients without coinfection than those only presenting COVID-19 or Dengue.

4.1. Limitations

We should acknowledge that although 40% of the dengue cases infection were not diagnosed by RT-PCR or NS1 antigen, it is essential to emphasise that IgM diagnosed 38% of them, suggesting acute infection and not a past infection 2% by IgM/IgG and 0% by IgG. Nevertheless, the recommendation for COVID-19/Dengue coinfection is to use RT-PCR for SARS-CoV-2 and dengue viruses [18].

As this was a retrospective study, no other coinfections were initially assessed. Excluding coinfections will be very important or consider other arboviruses' possibilities (CHIKV, ZIKV, MAYV, YFV) or other chronic infections by HIV or Hepatitis viruses and bacterial infections causing secondary pneumonia. Nevertheless, CHIKV and MAYV and YFV, circulate with the low transmission in different areas of Peru, as is the case of the Peruvian Amazon jungle. Although the 2015–2016 ZIKV epidemics in the Americas also affected Peru, the number of cases was low compared with other countries, and currently, there are very few cases. Despite the possible clinical overlap in these patients and other arboviral diseases, HIV, hepatitis, or bacterial infections should be suspected and further investigated. Also, in further studies, other potential confounding factors, such as the use of antipyretics and anti-inflammatory agents, should be considered to explain why the fever was only detected in around half of the cases. When suspecting coinfections [37–40], with other arboviruses are important to perform the RT-PCR, as not only with serological antibody testing cross-reactivity has been reported, also with NS1 antigen testing [41], but still is not clear how substantial is this cross-reactivity and its magnitude.

5. Conclusions

Coinfection of COVID-19 and Dengue is possible, especially if the *Aedes aegypti* vector is present in endemic areas such as Lambayeque. Likewise, it is possible to diagnose dengue even when the patient was diagnosed with COVID-19. The patients manifest an unfavourable and unusual evolution despite having an anti-inflammatory and antipyretic treatment. On the other hand, it is recommended that entomological and epidemiological surveillance should be carried out and the breeding grounds of the dengue vector to prevent this coinfection from recurring and causing instability in the health system. Besides, mosquito nets in environments where patients are cared for and where the vector is present are decisive to avoid intrahospital infections, although acceptance is lower in summer. In this context, the planning of epidemiological strategies that reinforce the control of *A. aegypti* is mandatory, even in the ongoing context of the COVID-19 pandemic, especially in Latin America. Therefore, future studies should also assess the prevalence of coinfection COVID-19 and Dengue among the patients with dengue and the COVID-19 patients in the institutions as in the overall epidemiology of endemic countries.

Funding source

None.

Ethical approval

Approval was not required.

CRediT authorship contribution statement

Jorge Luis Mejía-Parra: Writing – review & editing, contributed to data collection. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript. **Sergio Aguilar-Martinez:** Writing – review

& editing, contributed to data collection. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript. **Jorge Luis Fernández-Mogollón:** Writing – review & editing, contributed to data collection. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript. **Camila Luna:** Writing – original draft, Writing – review & editing, contributed to the translation of the first draft, the literature review, and the manuscript's organisation. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript. **D. Katterine Bonilla-Aldana:** Writing – original draft, Writing – review & editing, contributed to the translation of the first draft, the literature review, and the manuscript's organisation. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript. **Alfonso J. Rodríguez-Morales:** Writing – original draft, Writing – review & editing, contributed to the translation of the first draft, the literature review, and the manuscript's organisation. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript. **Cristian Díaz-Vélez:** Writing – original draft, formulated the research questions, designed the study, collect data, and drafted the first manuscript. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

Declaration of competing interest

All authors report no potential conflicts.

Acknowledgements

Thanks to Lic. Biol. Indira Casos Dávila, Lic. Gladys Fernandez Reque, and Lic. Enf. Marcia Daniela Martínez Gutiérrez, for their support in the data collection; and to Dr. Gustavo Ganoza Tresierra, for his logistical support in the outbreak control, that allow to obtain information for the study.

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