

## Clinical manifestations of covid-19 and dengue coinfection in adults: integrative review

*Manifestações clínicas da coinfeção entre covid-19 e dengue em adultos: revisão integrativa*

*Manifestaciones clínicas de la coinfección entre covid-19 y dengue en adultos: revisión integrativa*

### ABSTRACT

**Objective:** to identify the evidence available in the scientific literature on the clinical manifestations of COVID-19 and Dengue coinfection in adults. **Method:** integrative review carried out in the MEDLINE/PUBMED, LILACS, IBECs, WoS and EMBASE databases, in June 2021. The descriptors “adult”, “Coronavirus Infections” and “dengue” together with their synonyms were crossed using the Boolean operators “AND” and “OR”. **Results:** twenty-three studies were included and case studies predominated 19 (82.6%). The main clinical manifestations identified from the studies were: fever, headache, dyspnea, cough, myalgia, retro-orbital pain and skin rash. Laboratory findings such as thrombocytopenia, lymphopenia and leukopenia were also reported. **Conclusion:** COVID-19 and Dengue coinfection was identified and the need for an immediate search for a differential diagnosis is stressed in order to prevent clinical problems and reduce unexpected outcomes.

**Keywords:** Dengue; COVID-19; Coinfection; Signs and symptoms; Adult.

### RESUMO

**Objetivo:** identificar as evidências disponíveis na literatura científica sobre as manifestações clínicas da coinfeção entre COVID-19 e Dengue em adultos. **Método:** revisão integrativa, realizadas nas bases MEDLINE/PUBMED, LILACS, IBECs, WoS e EMBASE, em junho de 2021. Os descritores “adulto”, “Infecções por Coronavírus” e “dengue” junto aos seus sinônimos, foram cruzados por meio de operadores booleanos “AND” e “OR”. **Resultados:** Foram incluídos 23 estudos, predominando estudos de caso 19 (82,6%). As principais manifestações clínicas identificadas a partir dos estudos foram: febre, cefaleia, dispneia, tosse, mialgia, dor retro orbital e rash cutâneo. Além de achados laboratoriais como: trombocitopenia, linfopenia e leucopenia. **Conclusão:** a coinfeção COVID-19 e Dengue foi identificada e aponta-se a necessidade da busca imediata do diagnóstico diferencial, para prevenir os agravos clínicos e diminuir os desfechos inesperados.


**Descritores:** Dengue; COVID-19; Coinfeção; Sinais e Sintomas; Adulto.

### RESUMEN


**Objetivo:** identificar la evidencia disponible en la literatura científica sobre las manifestaciones clínicas de la coinfección entre Covid-19 y Dengue en adultos. **Método:** revisión integrativa, realizada en las bases de datos MEDLINE / PUBMED, LILACS, IBECs, WoS y EMBASE, en junio de 2021. Los descriptores "adulto", "Infecciones por coronavirus" y "dengue" con sus sinónimos fueron cruzados mediante operadores booleanos “AND” y “OR”. **Resultados:** se incluyeron 23 estudios, con predominio de 19 estudios de casos (82,6%). Las principales manifestaciones clínicas identificadas en los estudios fueron: fiebre, cefalea, disnea, tos, mialgia, dolor retro orbital y erupción cutánea. Además de los hallazgos de laboratorio como: trombocitopenia, linfopenia y leucopenia. **Conclusión:** se identificó la coinfección por Covid-19 y Dengue y se señala la necesidad de una búsqueda inmediata de un diagnóstico diferencial, con el fin de prevenir problemas clínicos y reducir resultados inesperados.

**Descriptores:** Dengue; COVID-19; Coinfección; Signos y Síntomas; Adulto.


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## INTRODUCTION

In March 2020, the World Health Organization (WHO) declared the COVID-19 pandemic, an emerging disease caused by the new coronavirus (Sars-Cov-2). The effects of the disease have affected the most diverse sectors of society due to the high level of infectivity, contagion, and mortality caused by the virus, with serious repercussions for health systems<sup>(1)</sup>.

In the Brazilian context, in addition to the COVID-19 pandemic, there is also Dengue, endemic in Brazil since 1986. Failures in the control of the *Aedes Aegypti* mosquito have caused the increase in cases, especially in the months from March to June<sup>(2)</sup>.

The association of COVID-19 and Dengue generates concern because there is little scientific knowledge and many uncertainties about the behavior of Sars-Cov-2 in the human body and the relationship of synergism with other diseases, which can make it more lethal<sup>(3)</sup>.

Thus, coinfection with diseases such as Dengue and COVID-19 generates a significant impact on health systems, mainly due to the precariousness of the assistance provided, lack of supplies, problems with the physical structure and staff size<sup>(4)</sup>. In addition, the clinical symptoms of both diseases can be masked as they have similar manifestations, causing a delay in the clinical diagnosis, consequent aggravation, greater chances of death and loss in the health systems<sup>(5)</sup>.

Among the clinical aspects of classic dengue, there is high fever, headache, myalgia, arthralgia, asthenia, retro-orbital pain, nausea, vomiting, rash and skin itching, which vary according to the patient's age and may evolve even for hemorrhage and shock<sup>(6)</sup>. Similarly, COVID-19 is characterized by the presence of general symptoms such as fever, cough, sore throat, headache, arthralgia, fatigue and dyspnea, with clinical aspects ranging from asymptomatic to severe condition requiring ventilatory support<sup>(7)</sup>.

In this sense, the alert for a peak of contamination between Dengue and COVID-19 occurred as of March 2021 with an encumbrance on health services, rapid transmission and an incubation period that can be aggravated due to this pandemic<sup>(8)</sup>.

The lack of supplies and equipment necessary for the detection of SARS-CoV-2 led laboratories that had specificities in seasonal viral diseases, such as arboviruses, to redirect their efforts to diagnose COVID-19<sup>(9)</sup>. However, this attitude may end up in the neglect of other

diseases that potentiate the clinical aggravation of COVID-19, such as dengue. Thus, there is a need to invest in the clinical investigation through signs, symptoms and tests that make it possible to predict contamination or not with COVID-19 and dengue and contain consequences for health systems<sup>(10)</sup>.

Studies that correlate the clinical manifestations of dengue and COVID-19 are still scarce in the literature, indicating an important gap in scientific knowledge in this field of study that could support health care<sup>(5-9)</sup>. Therefore, gathering knowledge about the clinical characteristics of dengue and COVID-19 coinfection based on scientific production allows nurses to consider the clinical characteristics of both diseases in the initial care of the patients, favoring the directed referral within the network of services and the resolution of their health problem, offering better care conditions. Therefore, this study aimed to identify the scientific evidence on the clinical manifestations of COVID-19 and Dengue coinfection in adults.

## METHOD

This is an integrative literature review, used in Evidence-Based Practice, in six stages: 1) identification of the theme and selection of the hypothesis; 2) establishment of criteria for inclusion and exclusion of studies/sampling or literature search; 3) definition of the information to be extracted from the selected studies/categorization of the studies; 4) evaluation of studies included in the integrative review; 5) interpretation of results; 6) presentation of the review/synthesis of knowledge<sup>(11)</sup>.

The study was guided by the question: What evidence is available in the scientific literature on the clinical manifestations of COVID-19 and Dengue coinfection in adults? The Population, Variables and Outcomes (PVO)<sup>(12)</sup> strategy was used to build the guiding question, namely, Population (Adults), Variables (clinical manifestations) and Outcomes (Covid-19 and Dengue Coinfection).

The search was carried out through the journals portal of the Coordination for the Improvement of Higher Education Personnel, having as sources of research the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, Latin American and Caribbean Literature in Sciences of Health (LILACS), Excerpta Medica database (EMBASE) via Elsevier, Web of Science

(WoS) and Bibliographic Index Español en Ciencias de la Salud (IBECS).

The search was carried out in a paired manner, with the controlled descriptors Medical SubjectHeadings (MeSH) and the Descriptors in Health Science (DeCS), whose crossings were

performed using the Boolean operators AND and OR, shown in Figure 1. The strategy was developed by the authors and the collection time corresponds to the months of beginning and end of the research, respectively.

Figure 1 – Search strategies used in the selection of studies, Crato, CE, Brazil, 2021.

Period	Bases	Search Strategy	Number of Articles
April to June/2021	MEDLINE	"adult" [MeSH Terms] AND "Coronavirus Infections" [MeSH Terms] OR "Covid-19" [synonym] AND "Dengue" [MeSH Terms] AND "Coinfection"[MeSH Terms]	MEDLINE (n= 55) EMBASE (n= 65)
	WoS		
	EMBASE	"Coronavirus Infections" [MeSH Terms] AND "Dengue" [MeSH Terms] AND "Coinfection"[MeSH Terms]	WoS (n= 15)
	LILACS		
	IBECS	"Covid-19" [MeSH Terms] AND "Dengue" [MeSH Terms] AND "Coinfection"[MeSH Terms]	LILACS (n= 7) IBECS (n= 0)

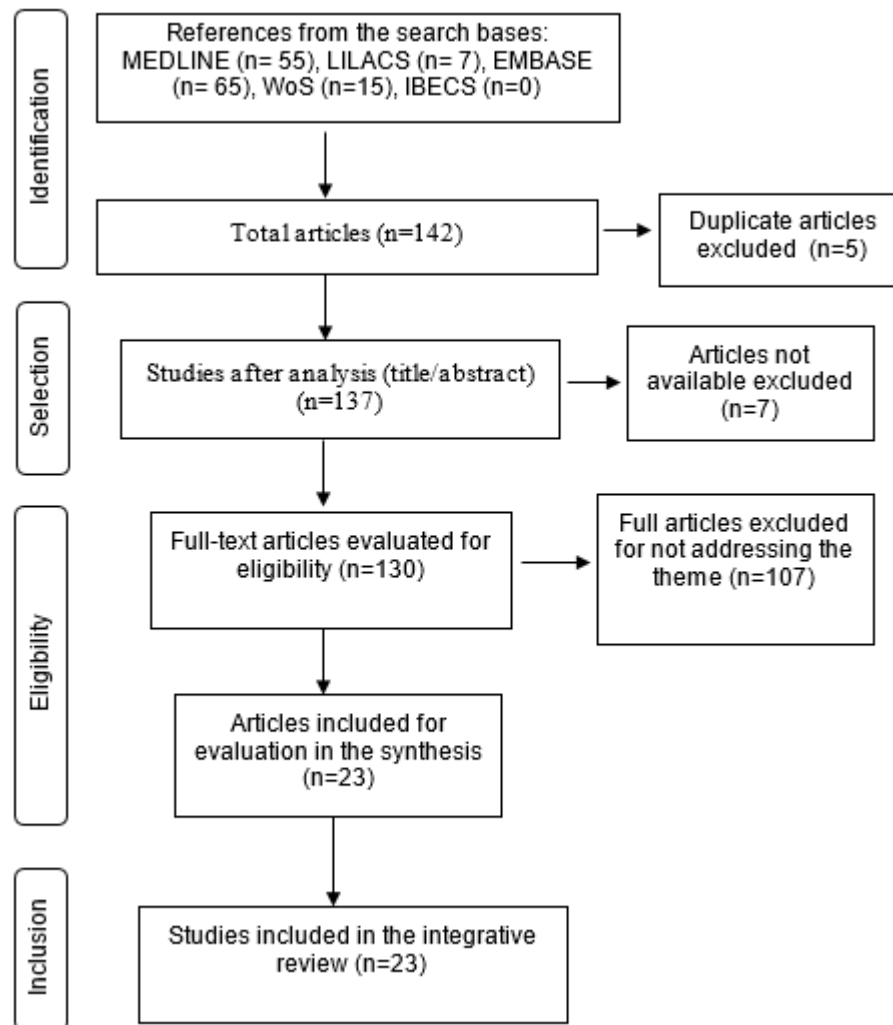
Source: Prepared by the authors, 2021.

The selection of studies was performed by two different researchers, in case of disagreement, a third evaluator was contacted. Mendeley - a reference management tool that makes it possible to identify duplicate studies and facilitates the process of identification - was used as support to aid in the selection. The following inclusion criteria were established: original article, specifically addressing the topic COVID-19 and Dengue coinfection in adult patients, published between December 2019 and June 2021 - the time frame was due to the first case of COVID-19 reported in

December of 2019<sup>(9)</sup>. The exclusion criteria were: studies that involved children or that did not address the research topic. Duplicate studies were considered only once.

For the selection of studies, the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) were observed, which makes use of a 27-item checklist, as well as a flowchart for the selection of articles arranged in four phases<sup>(12)</sup>; which is described in Figure 2.

Figure 2: Flowchart of selection of integrative review studies, Crato, CE, Brazil, 2021.



Source: Prepared by the authors, 2021.

A form prepared by the authors was used for data extraction. The form included the following variables: author, year of publication, country, study design, sample, objective, main results, conclusions and level of evidence.

The data extracted by the two researchers were organized in Microsoft Excel version 2016 by similarity and divergence and were presented in a descriptive way through a table, allowing the synthesis. The analysis was performed through the synthesis of evidence given by convergence of information presented in the studies. Each primary source was thoroughly reviewed for further presentation.

Seven levels of evidence were applied according to a modification of the Agency for Health care Research and Quality (AHRQ)<sup>(13)</sup>: level 1, systematic review or meta-analysis of randomized controlled clinical trials/clinical guidelines containing the aforementioned review studies; level 2, well-designed, randomized

controlled trial; level 3, controlled clinical trial, but without randomization; level 4, well-designed case-control or cohort studies; level 5, systematic review of descriptive and qualitative studies; level 6, descriptive or qualitative studies; and level 7 expert opinion. The information obtained was interpreted in tables and descriptive synthesis, and later discussed according to the relevant literature.

Regarding ethical aspects, the data contained in the articles with reliable citation of the ideas, concepts and definitions of the authors were respected under the precepts of resolution 510 of 2016 of the National Health Council.

## RESULT

The 23 studies are identified in Figure 3. Seven (30.4%) of the studies are from Brazil, and there was a sample variation between one and 370 participants. There are 19 case studies (82.6%) with evidence level 6, of which 14 (60.8%) described

coinfection with outcomes related to clinical prognosis. Most studies were published in 2020 (60.8%). The studies addressed the importance of early diagnosis, preparation

of health systems for overload, cross-reactivity, serological tests and clinical manifestations of both diseases.

Figure 3- Characterization of the studies included in the review, Crato, CE, Brazil, 2021.

Author (Year)/ Country	Study design and Sample	Objective of the study	Main results and Conclusions	Level of Evidence
Teotônio et al (2021) <sup>(14)</sup> Brazil	Prospective cohort 178	To detect COVID-19 and Dengue coinfection.	Coinfection with Dengue brings an overload to health systems.	4
Joubert et al (2021) <sup>(15)</sup> France	Prospective cohort 370	To identify the clinical and epidemiological profiles of SARS-CoV-2 and DENV infections.	Individuals who show symptoms of Dengue and are ruled out for coinfection with COVID-19 can potentially evolve to death.	4
Oliveira et al (2020) <sup>(16)</sup> Brazil	Prospective cohort 198	To assess the cross-reactivity of COVID-19 with Dengue.	The tests performed showed high sensitivity, specificity and good agreement with the control assays.	4
Carosella et al (2021) <sup>(17)</sup> Argentina	Control case 13	To describe the clinical features of patients hospitalized for coinfection.	Co-infected individuals may not suffer significant harm when identified early.	4
Bandeira et al (2020) <sup>(18)</sup> Brazil	Case study 1	To describe a clinical case of COVID-19 and Dengue.	Maculopapular pruritus was a previous manifestation of COVID-19.	6
Bicudo et al (2020) <sup>(19)</sup> Brazil	Case study 1	To report the first case of a patient with COVID-19 and Dengue coinfection.	The diagnostic accuracy is highlighted. Also, contagions need to be prevented and the transmission delayed.	6
Giovannini; Ferro (2020) <sup>(20)</sup> Brazil	Case study 1	To report the case of an elderly woman with differential diagnoses of COVID-19 and Dengue.	COVID-19 can have the same manifestations as Dengue.	6
Hilmy et al (2021) <sup>(21)</sup> Maldives	Case study 2	To describe the clinical manifestation and laboratory profile of Dengue and SARS-CoV-2. coinfecting patients	In cases of COVID-19 with increased hematocrit, platelets and transaminases, tests for Dengue should be performed.	6
Masyeni et al (2021) <sup>(22)</sup> Indonesia	Case study 3	To delimit three cases of suspected mixed infection with COVID-19 and Dengue.	There is cross-reactivity between DENV and SARS-CoV-2, leading to false-positive serology among Dengue patients.	6
Yan et al (2020) <sup>(23)</sup> Singapore	Case study 2	To describe two patients with a false-positive results for Dengue who had a severe SARS-CoV-2 infection.	COVID-19 can simulate false-positive results for Dengue	6
Ratnarathon et al (2020) <sup>(24)</sup> Thailand	Case study 1	To describe a patient with Dengue and SARS-CoV-2 coinfection.	Dengue positivity before COVID-19 diagnosis can make the clinical prognosis of patients with Sars-CoV-2 difficult.	6
Quental et al (2021) <sup>(25)</sup> Brazil	Case study 5	To describe cases of DENV and COVID-19 infection in the state of Ceará	Patients with dengue symptoms should seek to be tested for COVID-19.	6
Verduyn et al (2020) <sup>(26)</sup> France	Case study 1	To describe the case of coinfection with COVID-19 and Dengue	In tropical areas, COVID-19 and Dengue can co-exist and clinical diagnosis can be more difficult.	6

(continue)

Author (Year)/ Country	Study design and Sample	Objective of the study	Main results and Conclusions	Level of Evidence
Estofolete et al (2020) <sup>(27)</sup> Brazil	Case study 1	To describe the case of SARS-CoV-2 and Dengue coinfection in São José do Rio Preto, São Paulo, Brazil	Patient evolved with stroke after identification of Dengue and COVID-19 coinfection.	6
Radisic et al (2020) <sup>(28)</sup> Argentina	Case study 1	To describe the case of coinfection of a man in Argentina.	There was an evolution with headache, asthenia and muscle pain, pulmonary infiltrate and splenomegaly, and Dengue and COVID-19 coinfection.	6
Rosso et al (2021) <sup>(29)</sup> Argentina	Case study 1	To describe the case of SARS-CoV-2 and Dengue virus coinfection	Patient with generalized rash and scattered petechiae.	6
Malibari et al (2020) <sup>(30)</sup> Saudi Arabia	Case study 1	To present the case of positive serology for Dengue and detectable non-structural protein-1 (NS1) antigen of dengue and COVID-19.	Patient diagnosed with dengue and COVID-19 presented fever, malaise and generalized body aches.	6
Kembuan (2020) <sup>(31)</sup> Indonesia	Case study 5	To show patients with COVID-19 and Dengue with false-positive serology for Dengue.	Similar symptoms and laboratory findings between COVID-19 and Dengue pose a diagnostic challenge.	6
Giacomelli et al (2021) <sup>(32)</sup> Italy	Case study 1	To describe the case of a woman positive for Sars-Cov-2 and manifestations of Dengue.	Clinical signs and symptoms were anosmia, ageusia, skin rash, thrombocytopenia and increased liver enzymes.	6
Khalil et al (2020) <sup>(33)</sup> Saudi Arabia	Case study 4	To describe four patients with Dengue and COVID-19 coinfection.	The manifestations were fever, myalgia, nausea, headache, vomiting, cough, and diarrhea and retro-orbital pain.	6
Nasomsong, Luvira e Phiboonbanakit (2021) <sup>(34)</sup> Thailand	Case study 1	To report a case of a woman with Dengue and COVID-19.	There was lymphopenia, increased aspartate and aminotransferase levels, fever, nausea, myalgia and vomiting, and pulmonary infiltrate.	6
Lokida et al (2020) <sup>(35)</sup> Indonesia	Descriptive 32	To characterize the presentation of COVID-19 to assess DENV infection status.	There was the presence of fever, cough, dyspnea, headache, diarrhea, lymphopenia, leukopenia, thrombocytopenia, anosmia and dysgeusia.	6
Wee et al (2020) <sup>(36)</sup> Singapore	Epidemiological 868	To describe the experience with the challenge of a double outbreak of COVID-19 and Dengue.	Presence of thrombocytopenia, pulmonary infiltrate and skin rash.	6

Source: Prepared by the authors, 2021.

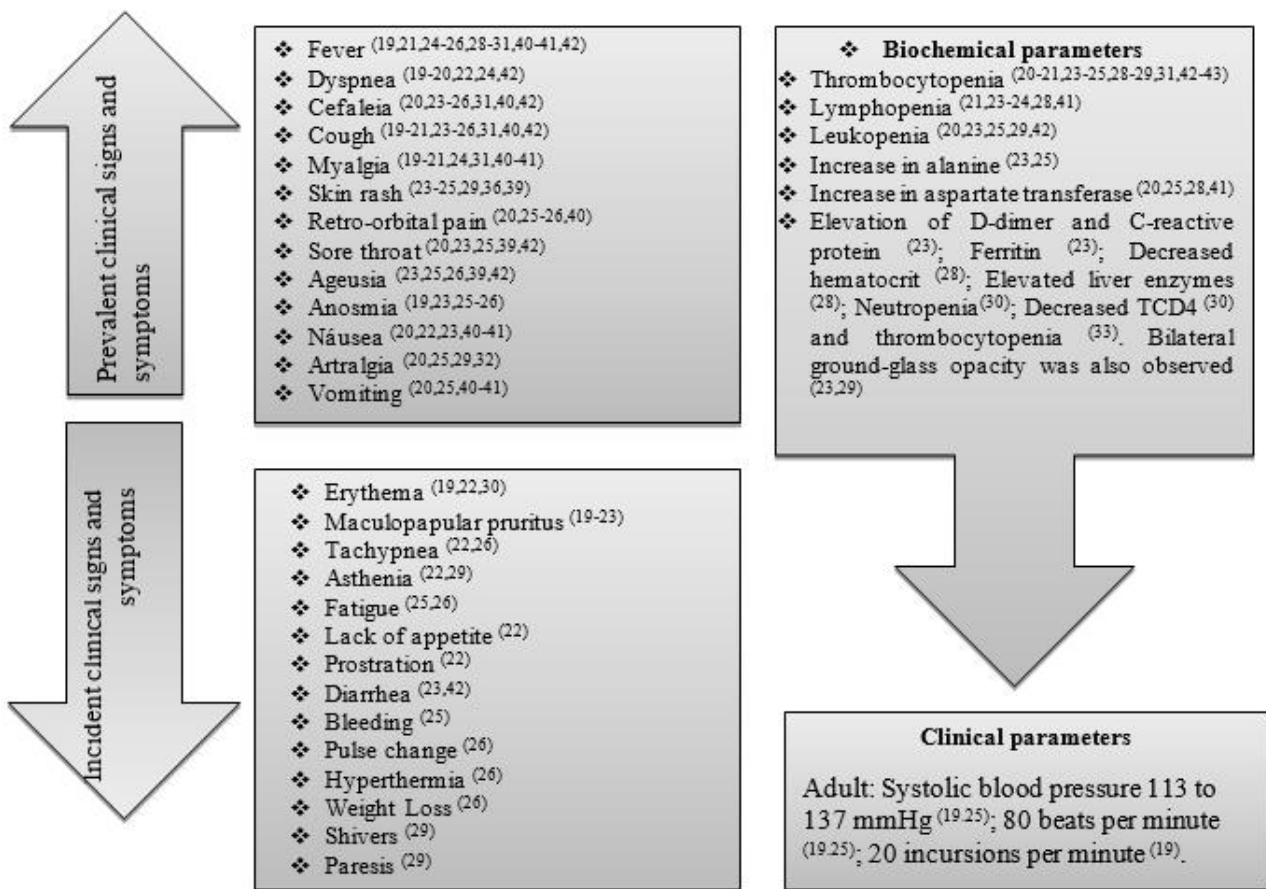
Evidence of Dengue and COVID-19 coinfection was presented in the studies, with the occurrence of 38.4% to 44.6% of cases of people who contracted COVID-19 and developed Dengue or vice versa<sup>(14)</sup>. Regarding the age of the participants, they were: young people between 18 and 26 years old<sup>(16,20,24,26)</sup>, young adults between 31 and 37 years old<sup>(15,17,21,24-25)</sup>, adults between 41 and 57 years old<sup>(14, 15,23-25)</sup>, and elderly people aged between 60 and 80 years<sup>(20,22,27,35)</sup>. Covid-19

simulated false-positive results for Dengue<sup>(23)</sup> due to the serological window and the serum conversion process, which made clinical diagnosis and effective treatment difficult.

The evidence pointed to the main clinical manifestations, as shown in Figure 4. The prevalence and incidence followed the criterion that defines the prevalence with four signs and/or symptoms and the incidence with one or more signs and/or symptoms<sup>(37)</sup>.



Figure 4- Signs and symptoms, biochemical and clinical parameters of COVID-19 and Dengue coinfection, Crato, CE, Brazil, 2021.



Source: Prepared by the authors, 2021

Regarding the evolution of the disease, it was possible to identify that the clinical manifestations associated with coinfection led to an increase in the rates of pulmonary involvement<sup>(14)</sup>; evolution of maculopapular pruritus, erythema in different regions of the limbs, chest and neck<sup>(18)</sup>; pneumonia<sup>(17)</sup>; cardiovascular arrest<sup>(20)</sup>; dehydration<sup>(26)</sup> and stroke<sup>(27)</sup>. This increased the length of stay<sup>(14)</sup> and made the care process more difficult<sup>(14,18)</sup>.

## DISCUSSION

Studies point to a correlation between COVID-19 and Dengue, assuming coinfection, albeit early. In this sense, it is worth noting that the COVID-19 pandemic can greatly increase the rates of coinfection in the population.

The main findings reveal the concentration of research on the subject in Brazil, although investigations were also found in Argentina, France, Indonesia, Singapore and Maldives. Case reports prevailed. In Brazil, there is concern about

cases of Dengue and COVID-19 coinfection, especially due to the vulnerability of risk groups, where the endemic scenario of Dengue has led to the need to intensify vector control measures in order to reduce morbidity and mortality<sup>(38)</sup>.

In this study, an infectivity of up to 46% of the population was found for COVID-19 and Dengue coinfection, mainly in individuals up to 57 years of age. Studies on this topic also observed similar ages and high infectivity for both diseases<sup>(14,15,19,23,24)</sup>. The burden on health systems, clinical simulation with other diseases and mimicry of signs, symptoms and biochemical markers are also pointed out in the literature<sup>(39)</sup> according to the findings of the present study.

The main clinical signs and symptoms that indicate coinfection with COVID-19 and Dengue were: fever, headache, dyspnea, cough, myalgia, skin rash, retro-orbital pain, sore throat, anosmia, nausea and arthralgia, in addition to thrombocytopenia, lymphopenia and leukopenia. These findings reinforce that symptoms are recurrent in the hospitalization scenario and are

present in a considerable part of patients with coinfection<sup>(3,40)</sup>.

It was also found that during the coinfection there may be an elevation of biomarkers and actions in the cutaneous, gastrointestinal, respiratory and circulatory systems<sup>(3)</sup>. Other similarities point to asthenia, retro-orbital pain, skin rash, purpura and myalgia closer to Dengue and cough, chest pain, cyanosis, pharyngitis, rhinorrhea, anosmia, ageusia closer to COVID-19 which can help in the differential diagnosis<sup>(40)</sup>. These data corroborate the findings of the present study.

In this study, the tests that identify Dengue and had positive results for COVID-19 (false-positive results) showed controversial reliability. In this sense, the relationship of false-positive results for COVID-19 hindered diagnostic accuracy<sup>(41)</sup>. Thus, there is a need for a differential diagnosis to check diagnostic sensitivity.

Symptoms of COVID-19 and Dengue can be confused because these diseases share similar characteristics. Thus, the presence of a positive IgM for Dengue may induce clinicians not to consider Sars-CoV-2<sup>(41)</sup>, which corroborates the data found in this research.

Also in the present study, we identified elements that are related to the clinical evolution of the coinfection. Therefore, the criteria for cases of Dengue and COVID-19 must be reinforced with a view to early recognition<sup>(4,34)</sup>, as well as an immediate care protocol depending on the severity of the cases.

In terms of government initiatives, this study shows that a focus on public policies should be the guiding framework for society. Therefore, strict decrees of social isolation are encouraged, as observed in Peru and Colombia, with a view to reducing COVID-19 cases and better monitoring of Dengue<sup>(36-37)</sup>.

In the global context, health systems have encountered difficulties with imminent collapses due to the combination of Dengue and COVID-19 in conjunction with the conditions of urban, demographic, social, economic and physical vulnerabilities, which have demonstrated the possibility of recurrent disasters<sup>(42)</sup>. To this end, it is necessary that public bodies designate surveillance fronts to combat both diseases.

## CONCLUSION

Coinfection with Dengue and COVID-19 may represent an emerging public health threat in countries such as Brazil. The clinical and

epidemiological characteristics of the two diseases can make the diagnosis difficult and delay the treatment of both pathologies. Rapid identification and differentiation for clinical care is necessary.

Nurses become primarily responsible for screening critical or non-critical patients in urgency and emergency sectors. In this sense, this study brings substantial contributions to differentiate signs and symptoms presented during coinfection, helping the clinical reasoning and critical judgment of the professionals, directly impacting the time of patient care.

Studies suggest the coinfection based on tests performed and the symptoms presented. Interventions related to clinical and care aspects are needed in order to attempt to prevent clinical problems and minimize unexpected outcomes. It is noteworthy, therefore, that further studies with greater methodological rigor are necessary to predict the indications presented here.

As limitations of this study, we highlight the difficulty in comparing the results due to the low scientific production found about clinical data of coinfection, diagnostic tests and accurate assessment of the health situation involving history, as well as associations with false-negative results which led to heterogeneity in the presentation of results.

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