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## THE INCIDENCE AND CHARACTERISTICS OF MISDIAGNOSED COVID-19 PATIENTS WITH DENGUE FEVER INFECTIONS AT UDAYANA UNIVERSITY HOSPITAL IN 2020-2021

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### ABSTRACT

The rise in dengue fever in recent decades combined with the emergence of COVID-19 at the end of 2019, has created new challenges in the healthcare sector. This research is a descriptive study with a cross-sectional research design and using medical record data at Udayana University Hospital in 2020–2021. According to the study, 1.22% cases of misdiagnosis out of a total of 2365 suspected cases of COVID-19 were found at Udayana University. The majority of cases of misdiagnosis involved people older than 60 years, namely 7 people (24.1%) and were dominated by men, namely 17 people (58.6%). The most common symptoms found are fever, cough, shortness of breath, headache, and malaise. According to laboratory results, dominant patients have thrombocytopenia, followed by high alanine transaminase (ALT), high aspartate transaminase (AST), and leukopenia. The appearance of thrombocytopenia in cases of COVID-19 with dengue fever is the result of suppressed platelet synthesis due to virus induction which causes bone marrow suppression and platelet clearance. Leukopenia and leukocytosis may coexist with lymphopenia as an indicator of disease severity. The similarity of symptoms and laboratory results between COVID-19 and dengue fever allows for misdiagnosis that will affect the patient's management. Therefore, the aim of this study is to determine the misdiagnosis rate of COVID-19 with dengue fever at Udayana University Hospital in 2020–2021, so that it can reduce misdiagnosis of the disease.

**Keywords:** misdiagnosis, clinical characteristics, COVID-19, dengue fever, thrombocytopenia

**Highlights:** The novelty of this research is that it discusses the emergence of cases of misdiagnosis and the clinical characteristics of misdiagnosed COVID-19 patients with dengue fever at Udayana University Hospital. The benefits of this study are expected to be a reference for future studies regarding the similarity of the clinical manifestations of COVID-19 and dengue fever.

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## INTRODUCTION

Coronavirus disease-19 (COVID-19) is an acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). COVID-19 can cause a series of signs of atypical respiratory disease.<sup>1,2</sup> The outbreak of COVID-19 originated in Wuhan, Hubei Province, China, and spread quickly to various countries.<sup>3</sup> Transmission of SARS-CoV-2 can be through a droplet or an aerosol, causing rapid transmission of the virus.<sup>4</sup> On COVID-19, the reproduction number ( $R_0$ ) ranges from 1.4 to 6.49.<sup>5</sup> The rapid transmission caused the World Health Organization (WHO) to declare COVID-19 a world pandemic on March 11, 2020.<sup>6</sup>

Dengue Fever is a disease that is transmitted by Arthropod. The vector that causes this disease is *Aedes spp.* especially *Aedes aegypti* and *Aedes albopictus*. Dengue virus has 4 types of serotypes namely DENV-1, DENV-2, DENV-3, and DENV-4.<sup>7–10</sup> This virus serotype is known to have different genotypes, these different serotypes and genotypes will affect the severity of dengue fever.<sup>11</sup> *Aedes spp.* mosquitoes have habitats in the tropical and subtropical regions of the world and have become endemic in several regions. The American, Asian, African, and Australian continents became several regions affected by the dengue fever epidemic.<sup>9</sup>

Dengue infections reported to the WHO have increased significantly over the past several decades, from 505.430 cases in 2000 to 5.2 million cases in 2019. Dengue fever is estimated to have occurred in around 390 million cases worldwide in every years. Around 96 million cases of dengue hemorrhagic fever cause clinical manifestations.<sup>12,13</sup> Meanwhile, COVID-19 has infected more than 650 million people in the world and resulted in more than 6.6 million people dying.<sup>14</sup> The increasing condition of dengue hemorrhagic fever and the emergence of the pandemic COVID-19 raise new challenges to establishing the

diagnosis of the two diseases. This is due to the similarity of the symptoms and the disease's laboratories' characteristics. This problem causes challenges in enforcing the diagnosis of the disease.<sup>15,16</sup> Therefore, we researched to find out the incidence and characteristics of misdiagnosed COVID-19 patients with dengue fever infections at Udayana University Hospital in 2020–2021.

## MATERIALS AND METHODS

This research is a descriptive study with a cross-sectional research design. The study was conducted in 2020–2021 using medical record data at Udayana University Hospital. The technique used to determine the sample in this study is total sampling. The variables studied in this study were age, gender, complete blood count (CBC), alanine aminotransferase (ALT), aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine (SC), symptoms, and patient conditions. The inclusion criteria of this study are patients with suspected COVID-19. Meanwhile, the patients positively confirmed COVID-19 via real time polymerase chain reaction (RT-PCR) swabs and patients with a fever for 7 days are its exclusive criteria.

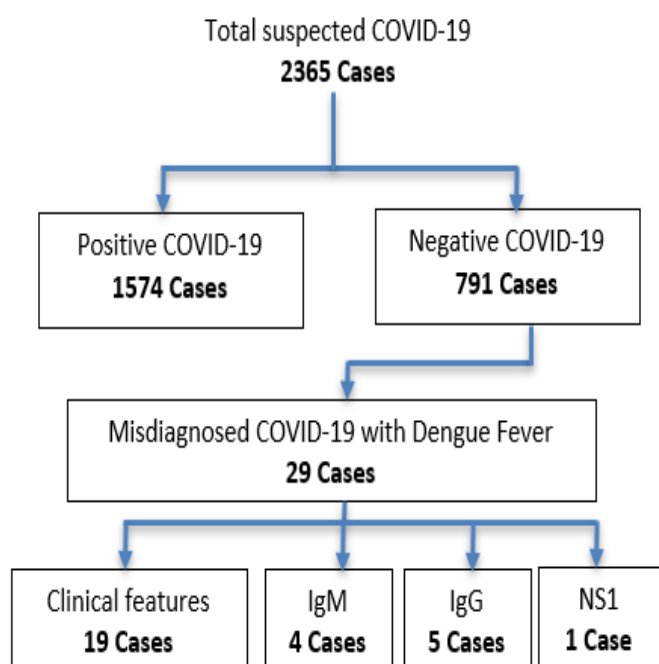
Misdiagnosis cases are defined by changes in the diagnosis of COVID-19-suspected patients to a negative diagnosis of COVID-19 and the diagnosis of dengue fever infections. The negative diagnosis of COVID-19 is determined by two negative RT-PCRs. The diagnosis of dengue fever was determined through WHO guidelines, namely fever < 7 days with two of the following: headache, arthralgia, retro-orbital pain, rash, myalgia, hemorrhagic manifestations, leukopenia, and laboratory results such as thrombocytopenia, serum creatine levels, and increased aminotransferases.<sup>17</sup>

Data is processed using the Statistical Package for the Social Sciences (SPSS) for Windows version 25. The study has obtained ethical clearance from the Research Ethics Commission of the Faculty of Medicine,

Udayana University with number: 531ruN 14.2.2.VII.14ILT12022.

## RESULTS AND DISCUSSION

The total number of cases of COVID-19 in Udayana University Hospital from March 1, 2020, to December 31, 2021, is 2365 and the demographic characteristics has serve on Table 1. Of these, 29 cases (1.22%) were misdiagnosed with COVID-19 with dengue fever.



**Figure 1.** Total Population of Suspected COVID-19

Based on Figure 1. There were a total of 2365 cases of suspected covid-19. Of the total, 1574 cases were diagnosed with COVID-19 via RT-PCR and 791 cases obtained negative results on RT- PCR. Of the COVID-19 negative numbers, 29 cases were diagnosed with dengue fever. Diagnosis of dengue fever was obtained through clinical features of 19 cases, IgM of 4 cases, IGG of 5 cases, and NS1 of 1 case.

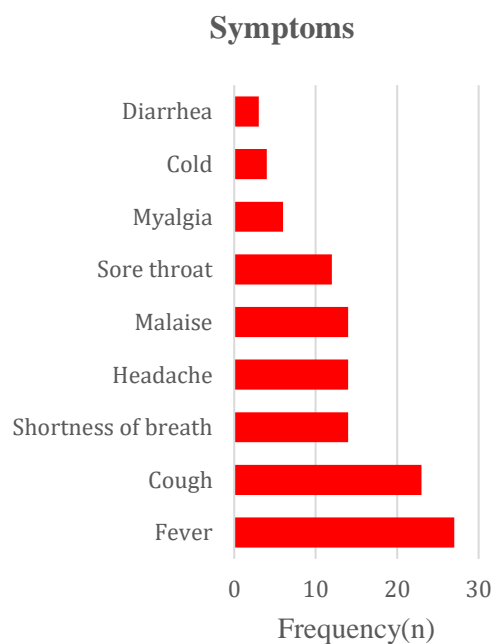
**Table 1.** Demographic Characteristics of Misdiagnosis in COVID-19 Patients with Dengue Fever

Characteristics	n(%)
<b>Age;</b>	
1-10	0(0)
11-20	2(6.9)
21-30	5(17.2)
31-40	5(17.2)
41-50	5(17.2)
51-60	5(17.2)
>60	7(24.1)
Age (years); Average ( $\pm$ SD)	45.69 ( $\pm$ 19.1)
<b>Gender;</b>	
Male	17(58.6)
Female	12(41.4)
<b>Profession;</b>	
Housewife	2(6.9)
Teacher	1(3.4)
Lecturer	1(3.4)
Pastor	1(3.4)
Private sector employee	6(20.7)
Self-employed	9(31)
Trader	1(3.4)
Farmer	2(6.9)
Retired	1(3.4)
Student	5(17)
<b>Residence;</b>	
Badung	9(31)
Tabanan	1(3.4)
Gianyar	8(27.6)
Denpasar	9(31)
Buleleng	1(3.4)
Bangli	1(3.4)

The condition of dengue fever which has increased in recent decades along with the emergence of COVID-19, and has caused new problems in the healthcare sector. The incidence of misdiagnosis in the disease will have an impact on the management and prognosis of the patient. This study found 29 cases (1.22%) of misdiagnosis of COVID-19 with dengue fever were found from a total of 2365 COVID-19 cases at Udayana University Hospital from 1 March 2020 to 31 December 2021. The emergence of cases of COVID-19 misdiagnosis with dengue fever is caused by the characteristics of the symptoms and similar laboratory results at the beginning of infection. In addition, it was also reported that the occurrence of false positives through a serological test affected the diagnosis of COVID-19 and dengue fever.<sup>18</sup> There are two possible causes of false positives in the diagnosis using a serological rapid diagnostic

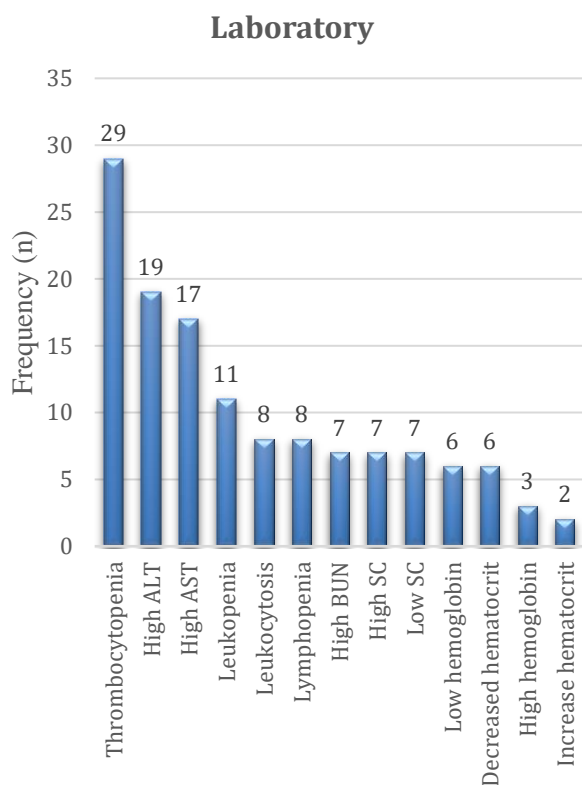
test (RDT). First, patients who experience a false positive have been or are being infected before entering the hospital due to COVID-19. Because of these conditions, it is possible to detect dengue by serological RDT in COVID-19 patients. Second, there was an antibody cross-reaction between COVID-19 and the dengue virus.<sup>15,19,20</sup> Cross-reactions from dengue IgG and IgM are also reported in malaria and leptospirosis. Furthermore, other flaviviruses, such as Zika and Japanese encephalitis, can cause a cross-reaction. The cross-reaction is probably caused by the dengue virus and other flaviviruses that have a large homological structure and sequence. This phenomenon is similar to what occurs in malaria and is thought to be the result of the elicitation of antibody cross-reactions or other immune responses in symptomatic and severe dengue fever to induce infer cross-protection or partial cross-protection.<sup>21</sup> Because of the emergence of a cross-reaction in the use of serological RDT that causes false positive results, the examination of COVID-19 patients and dengue fever patients should use the RT-PCR method to avoid the occurrence of false positive cases.<sup>15,21</sup>

Misdiagnosis cases of dengue fever in COVID-19 are dominated by people over the age of 60. This is most likely due to decreased immunity, which has already begun to decline at that age, making the body susceptible to disease infection. In this study, the majority of cases were found in men with a total of 17 people or 58.6%. Men tend to have higher mobility than women so they have the possibility of being exposed to COVID-19 or higher dengue. This was attributed to greater community contact, including increased outdoor activities, visiting shopping centres, dining in restaurants and bars, and gathering in colleges and universities.<sup>22</sup>



**Figure 2.** Characteristics of COVID-19 Misdiagnosis Symptoms with Dengue Fever

Based on Figure 2., it was found that the most dominant symptoms experienced by misdiagnosis patients were fever which was experienced by 27 people or 93.1%, followed by coughing which was experienced by 23 people or 79.3%. Shortness of breath, headaches, and sore throats affect 13 people, malaise affects as many as 12 people, myalgia, colds and diarrhea are only found in a few cases, as many as 6 people, 4 people and 3 people in sequence. A systematic review conducted by Tsheten et al. (2021) found similar results, namely that symptoms that arise from cases of misdiagnosis or coinfection with COVID-19 are: fever, shortness of breath, malaise, headache, coughing, rashes, diarrhea, myalgia, nausea or vomiting, and sore throat.<sup>22</sup> Hannan et al. (2022) also mentioned that in their research symptoms that often arise in misdiagnosed patients are fever, myalgia, headache, and diarrhea.<sup>23</sup>



**Figure 3.** Misdiagnosis COVID-19 Laboratory with Dengue Fever Characteristics

Laboratory characteristics found in misdiagnosed COVID-19 patients roughly serve on Figure 3. include: 29 thrombocytopenia (100%), high ALT in as many as 19 people (65.5%), high AST in 17 people (58.6%), leukopenia in as many as 11 people (37.9%), leukocytosis and lymphopenia in 8 people each (27.6%), high BUN, SC high, and SC low in 7 people each (24.1%), low hemoglobin and hematocrit decreased 6 people each (20.7%), hemoglobin high was 3 people (10.3%), and an increase in hematocrit by 2 people (6.9%). A systematic review conducted by Tsheten et al. (2021) found that in COVID-19, patients with dengue fever had the characteristics of laboratory yields: thrombocytopenia, followed by lymphopenia, high ALT, high AST, high levels of SC, decreased hematocrit, low Hb, leukocytosis, and an increased erythrocyte sedimentation rate (ESR).<sup>22</sup> Meanwhile, Hannan et al. (2022) found laboratory characteristics in COVID-

19 diseases and dengue fever: thrombocytopenia, lymphopenia, and hematocrit changes.<sup>23</sup>

The emergence of thrombocytopenia in cases of COVID-19 misdiagnosis with dengue fever is due to decreased platelet synthesis caused by virus induction, which causes bone marrow suppression and platelet clearance. After that, platelets will be destroyed by autoantibodies and immune complexes produced in response to SARS-CoV-2 and dengue virus infections which will cause thrombocytopenia.<sup>22</sup> Leukopenia is characterized by severe thrombocytopenia with an increase in hematocrit due to plasma leakage.<sup>24</sup> Leukopenia and leukocytosis can occur together with lymphopenia as an indicator of the severity of the disease. Leukopenia and lymphopenia can be used as markers to distinguish infections.<sup>25</sup> The occurrence of lymphopenia is caused by dengue virus infection of hematopoietic progenitor cells, dengue T cell activation, and marrow stromal cell infection. This results in the release of cytokines that cause lymphopenia.<sup>24</sup>

Aminotransferase (ALT and AST) is an enzyme used as a marker of hepatocellular damage. In dengue fever, increased aminotransferase becomes a sign of the severity of the disease due to the dengue virus will make the liver a target of infectious organs. Meanwhile, in COVID-19 aminotransferase levels are generally normal or experience a slight increase.<sup>26</sup>

**Table 2.** Conditions and length of stay of COVID-19 misdiagnosis patients with dengue fever.

Conditions	n (%)
Recovered	24(82.8)
Dead	5(17.2)
Length of stay	4.38 days

Based on Table 2. The length of stay the patient has been hospitalized has an average of 4.38 days. The patients included 24 people (82.8%) who healed and 5 people (17.2%)



who died. The occurrence of misdiagnosis of COVID-19 and dengue fever will result in mistakes in disease management. This affects mortality and morbidity, worsening the patient's prognosis.<sup>22</sup>

## STRENGTH AND LIMITATION

The strength of this study was that it is the first literature to discuss the co-infection of COVID-19 with dengue fever so that it can be used as a guide and literacy material for future research. With this research, it is expected to be a benchmark in diagnosing COVID-19 and dengue fever so that there are no errors in the diagnosis of the disease.

The limitation of this study was that it was conducted using a cross-sectional research design with a small sample and a limited period time. It is expected that in the future research can be carried out with a larger sample and a longer period time so that the results of the study can represent the general population. The study was carried out in a single hospital, so it described only a limited population. Data collection for the study is carried out using secondary medical records, so further validation is needed for data acquisition. In addition, the diagnosis of dengue fever doesn't use virus isolation and nucleic acid detection techniques such as RT-PCR. In this study, the diagnosis of dengue fever was established based on clinical symptoms, laboratory results, and serological tests such as IgG, IgM, and NS1, thus allowing for false positives in making the diagnosis.

## CONCLUSIONS

The incidence of misdiagnosis of COVID-19 with dengue fever at Udayana University Hospital in 2020-2021 was 29 people (1.22%) of a total of 2365 COVID-19 cases. The most common symptoms complained of by patients are fever, followed by coughing, shortness of breath, headache, and sore throat. The laboratory results obtained in this study were thrombocytopenia, followed by

lymphopenia, high ALT, high AST, high BUN, high SC, low SC, decreased hematocrit, low Hb, high Hb, and increase in hematocrit. Misdiagnosis COVID-19 with dengue fever must receive special attention. The similarity of the symptoms and laboratory results of the two diseases allows for a diagnosis error that will affect the patient's management.

## AUTHOR CONTRIBUTION

Writer, literature searcher, collecting data from literature: IKHA, Conceptor and supervision: IKS, review and supervision: IKS and NLPED. Both IMS and CAWP contributed to the review and editing of the final version of the manuscript and Project administration of the manuscript.

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## CONFLICT OF INTEREST

There was no conflict of interest in making this scientific work.

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