

# Rethinking the Kinetics of Extended WBC Differential Count and Inflammatory Index Marker in Secondary Dengue Infection: Case Report at University Hospital

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**Abstract:** Dengue infection is an emerging disease that continues to present a serious global public health challenge, contributing substantially to morbidity and mortality. Clinical and diagnostic management remain challenging due to the rapid progression of dengue among patients. This case report presents a comprehensive approach integrating clinical assessment with laboratory findings for the evaluation and management of secondary dengue infection. Key points highlighted include: (1) the negative kinetics of dengue antigen and antibody detection; and (2) the dynamic changes observed in extended white blood cell differential counts and inflammatory marker functions in relation to clinical outcomes. In summary, monitoring the extended white blood cell differential count and inflammatory index markers offers substantial value in detecting rapid escalation of disease severity. Furthermore, these parameters are notable for their repeatability, feasibility, and cost-effectiveness, thereby enhancing patient management efficiency.

**Keywords:** dengue infection, extended WBC differential count, inflammatory index marker, kinetics marker

## Introduction

Dengue infection is a prevalent viral disease that occurs in tropical countries and has become a major public health concern in recent decades. According to the WHO's global situation report on dengue in 2024, over 7.6 million cases of dengue were reported, including 3.4 million confirmed cases, more than 16,000 severe cases, and over 3000 deaths. In Indonesia, dengue has subsequently emerged as a significant public health issue over the past 50 years, characterized by consistently high incidence rates.<sup>1,2</sup>

Key environmental factors such as rainfall, temperature, and humidity are critical to the development of *Aedes aegypti* mosquitoes, which serve as the primary vectors for dengue transmission and underpin the endemic nature of dengue virus infection in Indonesia.<sup>2</sup> Clinically, dengue may present as a spectrum ranging from mild-to-severe illness ie. dengue without warning signs, dengue with warning signs and severe dengue. The detection of dengue virus non-structural 1 (NS1) antigen, along with dengue antibodies, is widely utilized for diagnosing acute dengue infections. However, access to these serological tests can be limited, particularly in remote healthcare facilities, and issues such as low sensitivity—dependent on the duration of fever and regional population differences—may impact diagnostic accuracy.<sup>3,4</sup> Moreover, inflammatory markers like C-Reactive Protein (CRP) and Procalcitonin may be useful in assessing the severity of the disease;<sup>5</sup> but, these parameters may



have limited availability in certain healthcare facilities, ie. primary health care settings. Recently, the use of hematology analyzers to perform complete blood count (CBC) tests has been implemented in primary health care over the past decade as an initial screening tool for diseases such as dengue. However, effective utilization of these instruments continues to be a challenge.<sup>6</sup> In addition, simple and cost-effective inflammatory index markers, ie. Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Monocyte-to-Lymphocyte Ratio (MLR) have demonstrated their utility in defining both diagnosis and prognosis of the disease.<sup>5</sup> Furthermore, advancements in flow cytometry-based hematology analyzers have enhanced the white blood cell (WBC) differential count by providing additional parameters that may be utilised for monitoring immune responses.<sup>7-9</sup> However, there is limited information regarding the application of these parameters in viral infections, particularly dengue.

Due to its diverse clinical manifestations, rapid progression, and potential life-threatening, updated clinical-laboratory findings of dengue infection are crucial. This report presents an evaluation of dengue infection occurring in university hospital which serves as secondary healthcare settings, with comprehensive clinical-laboratory findings related to the disease's pathophysiology, including inflammatory marker and extended WBC parameters from initial presentation until follow-up progression.

## Case Synopsis and Laboratory Investigation

A 21-year-old male patient arrived at the university hospital emergency room (ER) with fever, rash, headache, and nausea. He had been experiencing continuous fever for three days, slightly improved with antipyretic drugs. He had recently stayed in a remote area identified as endemic for dengue infection. Vital sign revealed a high temperature of 39.1°C, heart rate of 102 beats per minute, respiratory rate of 102 per minute, and blood pressure of 137/81 mmHg. The physical examination was notable for epigastric tenderness and a rash on both upper extremities. Laboratory tests, including complete blood count and dengue antigen testing (shown in Table 1, days 3), indicated mild thrombocytopenia and leukopenia, with a negative result for dengue antigen. Despite this, the patient was diagnosed with dengue fever and discharged as an outpatient, as no significant warning signs were observed. The next day, he returned to the ER with a higher fever of 40.1°C and worsening symptoms, leading to hospitalization.

**Table 1** Laboratory Finding of Complete Blood Count and Extended Differential Count

Test Parameter	Result							Unit	Reference Range
	D-3 11/2	D-5 13/2	D-6 14/2	D-7 15/2	D-8 16/2	D-9 17/2	D-11 19/2		
HGB	15.4	14.7	15.2	13.7	13.2	14.1	15.6	g/dL	13.2–17.3
HCT	45.8	42.8	43.7	<b>38.9</b>	<b>37.0</b>	40.3	45.4	%	40-52
WBC	<b>4.1</b>	<b>3.0</b>	<b>4.4</b>	4.6	5.1	6.2	8.6	10 <sup>3</sup> /uL	4.5–11.3
RBC	5.0	4.8	4.9	<b>4.4</b>	<b>4.2</b>	4.6	5.1	10 <sup>6</sup> /uL	4.4–5.9
PLT	<b>137</b>	<b>115</b>	<b>94</b>	<b>101</b>	<b>122</b>	186	409	10 <sup>3</sup> /uL	150-450
MCV	91.2	90.1	89.5	89.1	89.2	88.6	89	fL	80-96
MCH	30.8	31.1	31.1	31.5	31.8	31.1	30.5	pg	28-33
MCHC	33.7	34.5	34.8	35.3	35.7	35	34.3	g/dL	33-36
<b>DIFF.Count</b>									
NEU	<b>72.5</b>	<b>81.9</b>	<b>83.2</b>	<b>74.0</b>	69.2	<b>80.4</b>	<b>72.7</b>	%	50-70
LYM	<b>17.2</b>	<b>12.2</b>	<b>9.7</b>	<b>13.6</b>	<b>14.7</b>	<b>10.6</b>	<b>16</b>	%	25-40

(Continued)

**Table 1** (Continued).

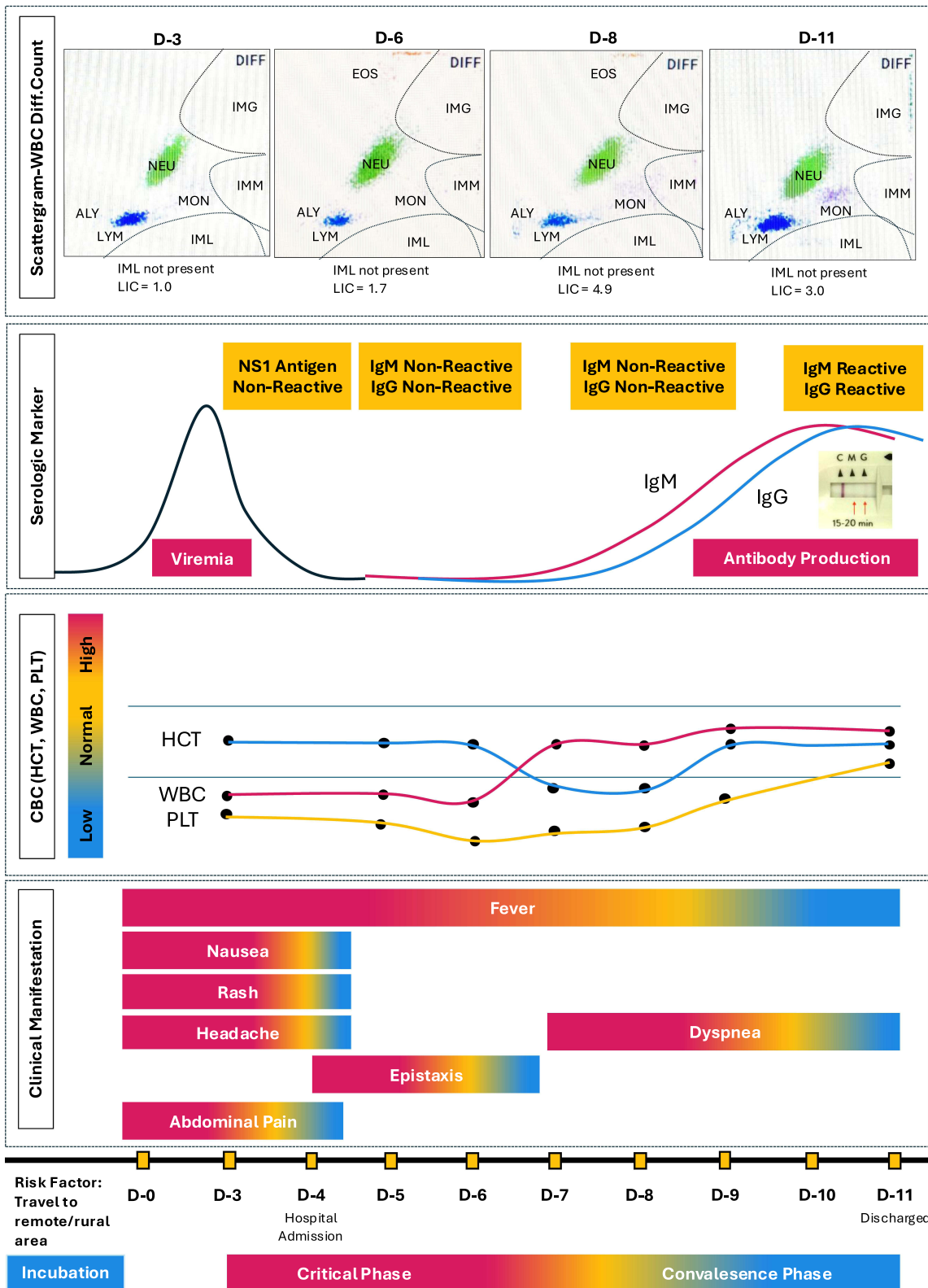
Test Parameter	Result							Unit	Reference Range
	D-3 11/2	D-5 13/2	D-6 14/2	D-7 15/2	D-8 16/2	D-9 17/2	D-11 19/2		
MON	<b>9.7</b>	2.9	2.7	7.9	<b>13.3</b>	<b>8.8</b>	<b>11</b>	%	2-8
EOS	0.6	<b>2.4</b>	<b>3.9</b>	<b>4.3</b>	<b>2.2</b>	0.2	0.2	%	2-4
BAS	0.0	0.6	0.5	0.2	0.6	0.0	0.1	%	<1
<b>Extended-5 DIFF</b>									
LIC	1.0	1.4	1.7	4.1	4.9	3.3	3	%	n/a
IMG	0.4	0.9	0.9	1.8	1.6	1.2	2.1	%	n/a
IMM	0.2	0.2	0.3	0.5	0.9	1	0.3	%	n/a
IML	0	0	0	0	0	0	0	%	n/a
ALY	1.2	0.9	0.6	1.7	3.3	2	2.2	%	n/a
<b>Inflammatory Index Marker</b>									
NLR	4.2	6.7	8.6	5.4	4.7	7.6	4.5	n/a	n/a
PLR	194.3	314.2	220.2	161.4	162.7	283	297.2	n/a	n/a
MLR	0.6	0.2	0.3	0.6	0.9	0.8	0.7	n/a	n/a

**Abbreviations:** ALY, atypical lymphocytes; BAS, basophil; Bold letter, refers to abnormal value compared to a reference range; D, refer to the day of observation based on symptom onset; EOS, eosinophil; HGB, hemoglobin; HCT, hematocrit; IMG, immature granulocytes; IMM, immature monocytes; IML, immature lymphocytes; LIC, large immature cells; LYM, lymphocyte; MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Hemoglobin; MCHC, Mean Corpuscular Hemoglobin Concentration; MLR, monocyte-to-lymphocyte ratio; MON, monocyte; NEU, neutrophil; NLR, neutrophil-to-lymphocyte ratio; n/a, not applicable; PLT, platelet; PLR, platelet-to-lymphocyte ratio; RDW, Red Cell Distribution Width; RBC, Red Blood Cell; WBC, White Blood Cell.

In [Table 1](#), a complete blood count with differential was required to identify the etiology based on the onset of clinical symptoms. Mild thrombocytopenia (100,000–150,000/uL) to moderate thrombocytopenia (50,000–100,000/uL) occurred between day 3 and day 8, ranging from 137,000/uL on day 3 to the lowest value of 94,000/uL on day 6. During this time, the patient experienced epistaxis and was treated with adrenaline nasal tampons. Leukopenia was also observed during the critical phase (days 3, 5, and 6). The differential count is a significant parameter in this case, reflecting the cellular immune response to pathogens. Between days 3 and 6, the percentage of lymphocytes decreased from 17.2% to 9.7%. Conversely, from days 7 to 11, the percentage of lymphocytes increased in response to clinical changes.

Nowadays, hematology analyzers have improved in their capability to determine the development process of blood cell, from immature cells to mature cells, particularly leukocyte differentiation. Utilizing flow cytometry methods, the expression of molecules such as trans-membrane proteins or RNA/DNA content enables differentiation of leukocytes into various lineages (eg, immature monocytes (IMM), immature lymphocytes (IML), immature granulocytes (IMG), atypical lymphocytes (ALY)), flagged with certain global parameters in the instrument (LIC, large immature cells).<sup>10</sup> The presence of immature cells (IMG, IMM, and ALY) can be observed from day 5 to day 10/11 ([Table 1](#)). An increase in the percentage of IMG (from 0.9% to 2.1%) and IMM (from 0.2% to 1%) suggests an innate immune response to dengue viral infection. Additionally, an increase in atypical lymphocytes (ALY) may indicate the severity of the disease, particularly during the initial critical phase (day 3) ([Figure 1](#)).

On day 7, the patient's fever and epistaxis improved; however, he experienced dyspnea with peripheral oxygen saturation levels between 91–93% ([Figure 1](#)). A chest X-ray revealed non-cardiogenic pulmonary edema, as the electrocardiogram showed a normal sinus rhythm. The dyspnea was managed with oxygenation using a non-rebreathing mask (NRM) at 10–12 liters per minute. The pulmonary edema resulted from fluid leakage from the



**Figure 1** Color scale graph of clinical manifestation, complete blood count, serologic marker and scattergram-WBC Differential count.  
**Abbreviations:** ALY, atypical lymphocytes; D, refer to the day of observation based on symptom onset; EOS, eosinophil; HCT, hematocrit; IMG, immature granulocytes; IML, immature lymphocytes; IMM, immature monocytes; LIC, large immature cells; LYM, lymphocyte; MON, monocyte; NEU, neutrophil; PLT, platelet; WBC, White Blood Cell.

**Table 2** Laboratory Finding of Clinical Chemistry and Serological Marker

Test Parameter	Result							Unit	Reference Range
	D-3 11/2	D-4 12/2	D-5 13/2	D-7 15/2	D-8 16/2	D-9 17/2	D-11 19/2		
<b>Clinical Chemistry</b>									
Sodium	-	-	136	-	136	-	-	mmol/L	135-145
Potassium	-	-	3.8	-	<b>3.4</b>	-	-	mmol/L	3.5–5.1
Chlorida	-	-	102	-	-	-	-	mmol/L	98-107
Urea	-	-	-	-	-	<b>18</b>	-	mg/dL	19-44
Creatinine	-	-	-	-	-	0.9	-	mg/dL	0.9–1.3
<b>Serological Marker</b>									
NSI Dengue	NR	-	-	-	-	-	-	n/a	NR
IgM Dengue	-	NR	-	NR	-	-	<b>R</b>	n/a	NR
IgG Dengue	-	NR	-	NR	-	-	<b>R</b>	n/a	NR
<b>Blood Gas Analysis</b>									
Blood pH					7.45				7.37–7.45
pCO <sub>2</sub>					37.7			mmHg	33-44
HCO <sub>3</sub>					25.4			mmol/L	22-26

**Notes:** Bold letter, refers to abnormal value compared to a reference range; D, refer to the day of observation based on symptom onset; HCO<sub>3</sub>, bicarbonate; n/a, not applicable; (-), not tested.

**Abbreviations:** NR, non-reactive; pCO<sub>2</sub>, partial pressure of carbon dioxide; R, reactive.

capillaries due to dengue-related inflammation and plasma leakage. This condition was substantiated by alterations in inflammatory index markers observed between day 8 and day 11, indicating both local tissue and systemic inflammatory responses. Inflammatory markers serve different purposes:<sup>5</sup> (a) NLR indicates physiological stress in critically ill patients, regardless of the disease etiology; (b) MLR helps predict viral disease outcomes; (c) PLR signals inflammation and its prognostic value. In this case, the trend of the inflammatory index marker increases in correlation with the progression of clinical manifestation. Additionally, the patient's metabolic status remained stable, as indicated by electrolyte parameters and blood gas analysis (Table 2).

By day 11, all symptoms improved, and only abnormal lab result was a positive IgM and IgG dengue antibody test, with higher inflammatory markers (Table 1). Therefore, dengue antibody seroconversion occurred on days 11, aligning with clinical and hematological improvements. The patient was discharged from the hospital on day 11, and the follow-up visit a week later showed an unremarkable physical examination without any additional laboratory tests performed.

## Discussion

Dengue infection remains a significant public health concern, primarily as a mosquito-borne acute febrile illness. Transmission occurs via dengue viruses (DENV), which comprise four major serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. Humans become infected with DENV through the bites of female *Aedes* mosquitoes, notably *Aedes albopictus* and *Aedes aegypti*. Distinct DENV serotypes are associated with varying risks of severe complications.<sup>2,11–13</sup> In this case, we highlighted several clinico-laboratory findings within the case, ie.<sup>1</sup> the negative kinetics of antigen and antibody dengue in the first week of illness;<sup>2</sup> the kinetics of extended-WBC differential count and inflammatory markers function related with dengue clinical outcome.

First, in this case, the NS1 and IgM/IgG dengue tests were negative during the first week of illness (days 3–7); however, by day 11, IgM/IgG reactivity was detected. NS1 is present in both primary and secondary dengue infections during the acute phase, beginning from the first day of illness. In primary infections, NS1 detection persists for at least nine days after symptom onset, whereas in secondary infections, levels tend to decrease by days 6–7. The highest detection rates for both types of infection occur on days 3–4. Lower NS1 concentrations may be observed in primary dengue compared to secondary infection due to a reduced viral load. Conversely, higher NS1 levels in secondary cases may result from antibody-dependent enhanced infection and could serve as a predictive marker for progression to more severe disease. The presence of NS1, as an endothelial toxin during dengue infection, is contributed to the development of vascular leakage.<sup>14–17</sup> Subsequently, elevated levels of anti-NS1 IgG may result in the rapid clearance or reduction of circulating NS1, leading to the formation of immune complexes. These complexes can deposit on the surface of endothelial cells, thereby playing a role in the pathogenesis of vascular leak.<sup>18</sup> This finding accounts for the negative NS1 result observed on day 3 of the acute phase. During this period, there is an overlap between the declining phase of NS1 and the increasing levels of IgG/IgM antibodies. The use of anti-NS1 IgG against NS1 leads to low IgG levels on days 4 and 7, resulting in non-reactive test outcomes.<sup>19</sup> Another possible explanation for a negative NS1 result is that amino acid variations in the NS1 protein may decrease assay sensitivity by affecting monoclonal antibody binding in commercial kits, as previously reported.<sup>3</sup> These amino acid differences in NS1 have also been linked to the DENV-2 serotype. Although specific serotype data were not available in this case study, recent epidemiological research from Yogyakarta shows that DENV-2 is currently the most prevalent serotype in *Aedes aegypti* (25%), followed by DENV-1 (22.3%) and DENV-3 (17%).<sup>11</sup> Based on these findings, this case is consistent with a secondary dengue infection attributable to the DENV-2 serotype.

Second, in this study, we evaluate the kinetics of differential WBC count and their extended parameters as immune response of dengue infection. As reported in previous studies,<sup>4</sup> clinical features and complete blood count (CBC) parameters may facilitate the dengue infection from other causes. As summary, the changes of CBC in first week of dengue case show lowest WBC count on day 5, lowest platelet count on day 6, meanwhile the differential WBC count shows highest monocytes and eosinophil on day 8 and 7, respectively. Higher atypical lymphocytes were shown on day 8. This finding was in agreement with observational study in Thailand which observed over 154 patient confirmed serologically dengue. The occurrence of leukopenia was caused by the destruction or inhibition of myeloid progenitor cells. Increase of monocytes in the first few days of the fever related with hypothesis that monocytes and macrophages are the part of the primary immune which carry out phagocytosis of microorganisms and present the resulting carried antigen to T helper cells. Monocytosis is also considered as the parameter to predict the severity of dengue infection. Meanwhile, eosinopenia in acute phase of dengue infection due to the response to the inflammatory process. The higher atypical lymphocytes are more likely found in dengue hemorrhagic fever and useful in the prediction of the severity of dengue infection. Lastly, the occurrence of cytopenia is the major finding of CBC can help to distinguish dengue infection from other diseases. Cytopenia is considered as protective mechanism to limit the injury to the marrow stem cells during subsequent process of the eradication of infected cells. Moreover, the dengue-infected endothelial cells are potentially bound to WBC, neutrophils, lymphocytes, platelets, and large lymphocytes in vitro but not with monocytes, basophils, and eosinophils. The increased binding of neutrophils and platelets to infected endothelial cells may explain the occurrence of neutropenia and thrombocytopenia in dengue case.<sup>4,20</sup>

Third, this study evaluates the utility of extended white blood cell (WBC) differential count and inflammatory index markers in dengue cases. Advancements in flow cytometry-based hematology analyzers have enabled more comprehensive assessment of leukocyte differentiation and counts related to hematopoiesis. While the use of extended WBC differential counts remains limited and variable, several studies have demonstrated their benefit in patient management. For instance, research involving sepsis populations has shown that extended WBC differential counts can aid in infection prediction, patient outcomes, and hospital sepsis management.<sup>9,21,22</sup> Comparable approaches and findings have been reported in systemic viral infections, such as in moderate and severe COVID-19 cases,<sup>23,24</sup> as well as in differentiating the etiologic agents responsible for acute febrile illness.<sup>20</sup>

Regarding inflammatory index markers, such as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), literature suggests each marker serves a specific function—for example, NLR reflects physiological stress in critically ill patients, whereas MLR and PLR are associated with prognostic or predictive value for clinical outcomes in infection.<sup>5</sup> In this case study, the dynamic changes of these markers corresponded with the observed clinical presentations. It is notable, however, that some fluctuations in marker values



## Acknowledgments

We would like to express our gratitude to PT HORIBA Indonesia and PT Dexa Arfindo Pratama for technical and scientific support during writing the case report.

## Funding

The study did not receive external funding.

## Disclosure

The authors report no conflicts of interest in this work.

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