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*ORIGINAL ARTICLE*

# DIFFERENCES INDICATORS IN CLINICAL EPIDEMIOLOGY AND LABORATORY FOR SUSPECT DENGUE HEMORRHAGIC FEVER IN KEBUMEN DISTRICT 2023

***Perbedaan Indikator Epidemiologi Klinis dan Laboratoris Pada Dugaan Penyakit Dengue Hemorrhagic Fever di Kabupaten Kebumen 2023***

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**ABSTRACT**

**Background:** The study in Asian and American-based surveillance data between Oct 18, 2011, and Aug 4, 2016 required 7428 patients with an estimated 2,694 (36%) diagnosed laboratory-confirmed dengue, 2,495 (34%) non-dengue and 2,237 (30%) not inclusion criteria. The clinical signs and suspected dengue symptom address a few other diseases, thus laboratory confirmatory is best solution for diagnosis of dengue. **Purpose:** To determine the difference between clinical epidemiological and laboratory diagnosis of dengue hemorrhagic fever in Kebumen District. **Methods:** The study design was cross-sectional with 395 samples of suspected dengue disease during the 2023 period, such as DHF and DD in Kebumen District area health services. The DHF diagnostic was confirmed with positive laboratory test and studied to see differences of the clinical epidemiology and laboratory data. The data collection was carried out by reviewing medical documents from health centers and hospitals. Data were analyzed with chi square test and independent t-test. **Results:** Clinical indicators proportion was higher for fever, 95.40% and much lower for bleeding 13.20%. The dominant contribution significant for clinical epidemiology indicator of DHF is muscle pain compared to bleeding and rash. The laboratory indicator for platelet is low, hemoglobin normal and hematocrit normal. The variable contributing significantly for DHF is platelet (β = 0.19) and comparison of hemoglobin (β = -0.09) and hematocrit (β = -0.06). **Conclusion:** Clinical indicators of DHF are higher for fever (95.40%), with muscle pain being the dominant factor. Laboratory indicators include low platelet count and normal hemoglobin and hematocrit.

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***ABSTRAK***

***Latar Belakang:*** *Penelitian pada data surveilans berbasis Asia dan Amerika antara 18 Oktober 2011 dan 4 Agustus 2016 memerlukan 7.428 pasien dengan estimasi 2.694 (36%) terdiagnosis dengue yang dikonfirmasi laboratorium, 2.495 (34%) bukan dengue dan 2237 (30%) bukan kriteria inklusi. Tanda-tanda klinis dan gejala dengue yang diduga menunjukkan beberapa penyakit lain, sehingga konfirmasi laboratorium merupakan solusi terbaik untuk diagnosis dengue.* ***Tujuan:*** *Untuk mengetahui perbedaan antara diagnosis klinis epidemiologis dan laboratorium demam berdarah dengue di Kabupaten Kebumen..* ***Metode:*** *Desain penelitian adalah cross-sectional dengan 395 sampel penyakit dengue yang diduga selama periode 2023, seperti DBD dan DD di layanan kesehatan daerah Kabupaten Kebumen. Diagnostik DBD dikonfirmasi dengan tes laboratorium positif dan dipelajari untuk melihat perbedaan epidemiologi klinis dan data laboratorium. Pengumpulan data dilakukan dengan meninjau dokumen medis dari puskesmas dan rumah sakit. Data dianalisis dengan uji chi square dan uji t independen.* ***Hasil:*** *Proporsi indikator klinis lebih tinggi untuk demam, 95,40% dan lebih rendah untuk perdarahan 13,20%. Kontribusi dominan yang signifikan untuk indikator epidemiologi klinis DBD adalah nyeri otot dibandingkan dengan perdarahan dan ruam. Indikator laboratorium untuk trombosit rendah, hemoglobin normal dan hematokrit normal. Variabel yang berkontribusi signifikan untuk DBD adalah trombosit (β = 0,19) dan perbandingan hemoglobin (β = -0,09) dan hematokrit (β = -0,06).* ***Simpulan:*** *Indikator klinis DBD lebih tinggi untuk demam (95,40%), dengan nyeri otot menjadi faktor dominan. Indikator laboratorium meliputi jumlah trombosit rendah dan hemoglobin dan hematokrit normal.*



## INTRODUCTION

The World Health Organization (WHO) reported that, in 2024, there were over 7.6 million cases of dengue with 3000 deaths (1). Ninety countries were estimated with active transmission, including Indonesia. The case of dengue infections worldwide is estimated at 100 million symptomatic infections. Dengue is a significant concern for public health (2). According to, the Centers for Disease Control and Prevention 2024 (3), based on surveillance data, 43,608 participants were diagnosed with the disease, of which an estimated 1,432 were confirmed dengue. Previous study (4) which addressed 395 febrile patients showed 158 (40%) were malaria positive and 67 (17%) were dengue positive and both 6.60% (26/395). In 2014, the Indonesian Ministry of Health stated that over 53,131 cases of dengue were reported in Indonesia reported with an estimated 404 deaths. The Indonesian Ministry of Health in 2023 stated that the incidence rate (IR) of DHF is ≤ 10/100,000 population. The Central Java province had an estimated 12,467 dengue cases (5). The Kebumen public health office (2022) estimated 306 cases of dengue (6).

Dengue disease is a serious cause of death. A study in Brazil found that of 1,857 cases of severe dengue 89.60% t were hospitalized and 51.20% died (7). A study in Indonesia which addressed 699 cases of suspected dengue found 614 (87.80%) had confirmed dengue infection and severe dengue occurred in 34.40% cases (8). In a study in Malaysia addressing 254 pediatric patients, 15.40% (n = 39) were diagnosed with severe dengue. Death from dengue is caused by such as gastrointestinal bleeding, dehydration, and respiratory failure (9). Severe pediatrics cases that died were from respiratory failure and gastrointestinal bleeding (7). It is important to identify this condition early through its severity. A study in Argentina found a 72-year-old man who was hospitalized in ICU for dengue through dehydration (10).

The clinical signs and symptoms of dengue are identified as such as fever, nausea, vomiting, pain, abdominal pain, headache, and back pain. Based on dengue cases, signs shown were abdominal pain 72% cases and vomiting 70% cases (8). The laboratory study of dengue identified such as

thrombocyte, hemoglobin, hematocrit as a condition of dengue disease (11). The laboratory results showed increase hematocrit as a clinical sign of dengue (8). A study in Karachi found thrombocytopenia as an indicator case for dengue disease through addressing severe dengue (12). A study in Colombia (13) concluded that laboratory tests of hematocrit and hemoglobin were indicators for severe dengue and a study in Vietnam (14) concluded laboratory tests as predicting condition of severe dengue through three days of illness.

The laboratory is important to confirm cases of disease by comparing clinical diagnosis for dengue disease. Study in Asia and America addressed 7,428 patients, and estimate 2,694 (36%) were diagnosed with laboratory-confirmed dengue and 2,495 (34%) non-dengue. Clinical signs and symptoms are addressed in other diseases and laboratory confirmation is the best solution for diagnosis of dengue, such as hematocrit, hemoglobin and platelet (15). A study in South Korea (16) concluded that early detection of severe dengue used acute phases through hematocrit, hemoglobin, and trombocite.

Decreasing severe dengue cases can be done through early detection and management of environment for vector development. The laboratory tests for dengue are crucial for early diagnosis and management of cases (17). The awareness of the severity of dengue is a public problem for early diagnosis of dengue. Study in Argentina concluded that clinical and laboratory tests during the dengue disease period are effective to reduce severe clinical dengue. The study findings included such as leukopenia, thrombocytopenia, and high transaminase (18). Study in Sudan concluded that training clinical epidemiologists and strengthening surveillance systems resulted in improvement of management of dengue disease (19). Study in Indonesia concluded that surveillance implemented focused on passive surveillance through some disease events had a late response (20).

Prevention effort should be addressed to surveillance response and laboratory confirmation for disease. A study by Soto-Garita et al (21) concluded that the way to decrease dengue disease was through epidemiological surveillance response. Another study by Rodriguez et al (17) recommended that accessible local diagnostics should be facilitated in public community, such as community health service. The surveillance officer is very important to an early warning system (20). On other hand, management of vectors is more important for decreased dengue transmission. Study by Dapari et al (22) concluded that mosquito control reduces transmission and decreases dengue disease. Study by Id et al (23) found that environment characteristics are important for early detection of vector development, such as rainfall and temperature for reduction transmission of vector. The study aims to determine the difference between epidemiological and laboratory diagnosis of dengue hemorrhagic fever in Kebumen District.

## METHODS

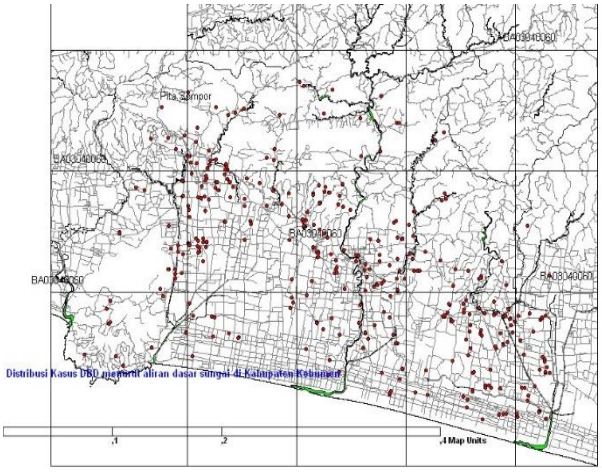
The study design used cross-sectional to measure epidemiology and laboratory indicator variables related to diagnosis of dengue hemorrhagic fever. The study population included 395 samples who were required through those diagnosed with suspected dengue disease during 2023. The sample required 395 sample for analysis. The study variables include clinical epidemiology indicators and laboratory indicators. Data collection was carried out by reviewing medical documents from health centers and hospitals from which data had been sent to the health service department through surveillance activity. The clinical indicator variables were such as fever, bleeding, headache, weakness, nausea and muscle aches. Laboratory indicator variables included platelets, hemoglobin and hematocrit. The variables of fever, bleeding, headache, weakness, nausea and muscle aches were collected through reviewing medical documents at hospitals and health centers service in the Kebumen District work area. The variables hematocrit, hemoglobin and platelet were collected by reviewing the patient's laboratory documents which included the results of laboratory hematocrit, laboratory hemoglobin and laboratory platelet-tests. The data diagnostic has been verified through doctor diagnosis in community health services and hospitals when the patient’s early treatment is differential diagnosis (DD) and the patients’ follow-up treatment and laboratory test result during treatment indicates dengue hemorrhagic fever (DHF).

The data collection on the diagnosis of dengue hemorrhagic fever was carried out by secondary data through reviewing the medical records of patients who had treatment at community health centers and hospitals around the work area health department of Kebumen District. The data were collected with study documents. Data were analyzed with chi square test and independent t-test. The chi square test analyzed related differences such as fever, bleeding, headache, weakness, nausea and muscle aches with dengue diagnosis.

The independent t-test analysis used laboratory indicators such as platelet, hemoglobin and hematocrit with dengue diagnosis. The multivariate test used logistic regression and ANOVA to determinate the dominant factor contributing to dengue diagnosis for clinical epidemiology and laboratory. The study has been submitted and passed ethical testing at the Faculty of Health Sciences with ethical no. 060.3/FIKES/PL/VI/2024.

## RESULTS

The study addressed 395 subjects with suspected dengue during 2023 in the health department of Kebumen District areas based on distribution of cases shown in Figure 1.




Source: Data Surveillance dengue in Kebumen District Analysis, 2023

**Figure 1.** Spatial Distribution of Dengue Cases Based in the Regional Zone Divided into North South and East West Zone in Kebumen District

The distribution of dengue disease in Kebumen District has a transverse stick shape. The East Zone is in south position but the west zone is in north position (See Figure 1). The geography condition south of Kebumen District is sea and the north of Kebumen District is mountains and forests. This is based on variable indicator epidemiology such as fever, bleeding, headache, weakness, nausea and muscle pain and laboratory indicators such as platelet, hemoglobin and hematocrit (See Table 1).

The study shows that, based on clinical indicator epidemiology, the majority of subjects had fever (95.40%), headache (66.30%), weakness (91.90%), nausea (78.00%) and rash (90.90%). In contrast, the majority of subjects followed without bleeding (86.80%), and muscle pain (54.90%) (See Table 1). The result interpretation is that subjects followed with fever, headache, weakness, nauseous and rash and on the other hand without bleeding and muscle pain. The laboratory indicator for platelets had a much lower average 73,816 (normal 150,000 – 450,000 microliter), the average hemoglobin was 13.00 g/dl in normal category (normal 12-16 g/dl) and the average of hematocrit 40.13 was in normal low (normal 36-54%).

**Table 1**
The Distribution of Fever, Bleeding, Headache, Weakness, Nausea and Muscle Aches, Platelet, Hemoglobin and Hematocrit in Kebumen District

| Variable | n | % |
|---|---|---|
| Fever | | |
| Yes | 377 | 95.40 |
| No | 18 | 4.60 |
| Bleeding | | |
| Yes | 52 | 13.20 |
| No | 343 | 86.80 |
| Headache | | |
| Yes | 262 | 66.30 |
| No | 133 | 33.70 |
| Weakness | | |
| Yes | 363 | 91.90 |
| No | 32 | 8.10 |
| Nauseous | | |
| Yes | 308 | 78 |
| No | 87 | 22 |
| Muscle pain | | |
| Yes | 178 | 45.10 |
| No | 217 | 54.90 |
| Rash | | |
| Yes | 359 | 90.90 |
| No | 36 | 9.10 |
| Average platelet | 395 | 73,816.19 ±51,128.85 |
| Average hemoglobin | 395 | 13.00 ± 2.23 |
| Average hematocrit | 395 | 40.13±7.43 |

The bivariate analysis addressed clinical epidemiology such as fever, bleeding, headache, weakness, nausea and muscle aches and laboratory indicators such as platelet, hemoglobin and hematocrit. The analysis showed that clinical indicators with significant difference are bleeding and muscle pain. The variable bleeding had a significant difference OR = 1.89; 95% CI (1.04 < OR < 3.43), muscle pain OR = 1.53; 95% CI (1.03

< OR < 2.29) for diagnosis of dengue hemorrhagic fever. The variables with no significant difference were such as fever OR = 1.34; 95% CI (0.51 < OR < 3.55), headache OR = 1.31; 95% CI (0.86 < OR < 2.00), weakness OR = 1.45; 95% CI (0.68 < OR < 3.05), nausea OR = 1.11; 95% CI (0.69 < OR <1.80), and rash OR = 0.50; 95% CI (0.25 < OR < 1.01) between DHF and DD. Laboratory indicators were such as platelet p = 0.000 with α = 0.05, hemoglobin p = 0,028 with α = 0.05 and hematocrit p = 0,023 with α = 0.05 significant differences between DHF and DD (See Table 2).

**Table 2**
The Relation of Clinical Indicators and Laboratory Indicators for Dengue Hemorrhagic Fever Diagnosis in Kebumen District

| Clinical | DHF | DD | | | |
|---|---|---|---|---|---|
| Epidemiology | n (%) | n (%) | X | p | OR |
| Fever | | | | | |
| Yes | 174 (44.10) | 203 (51.40) | 0.36 | 0.54 | 1.34 (0.51-3.55) |
| No | 7 (1.80) | 11 (2.80) | | | |
| Bleeding | | | | | |
| Yes | 31 (7.80) | 21 (5.30) | 4.58 | 0.03 | 1.89 (1.04-3.43) |
| No | 150 (38) | 193 (48.90) | | | |
| Headache | | | | | |
| Yes | 126 (31.90) | 136 (34.40) | 1.61 | 0.20 | 1.31 (0.86-2.00) |
| No | 55 (13.90) | 78 (19.70) | | | |
| Weakness | | | | | |
| Yes | 169 (42.80) | 194 (49.10) | 0.97 | 0.32 | 1.45 (0.68-3.05) |
| No | 12 (3) | 20 (5.10) | | | |
| Nauseous | | | | | |
| Yes | 143 (36.20) | 165 (41.80) | 0.20 | 0.64 | 1.11 (0.69-1.80) |
| No | 38 (9.60) | 49 (12.40) | | | |
| Muscle pain | | | | | |
| Yes | 92 (23.30) | 86 (21.80) | 4.48 | 0.03 | 1.53 (1.03-2.29) |
| No | 89 (22.50) | 128 (32.40) | | | |
| Rash | | | | | |
| Yes | 159 (40.30) | 200 (50.60) | 3.72 | 0.05 | 0.50 (0.25-1.01) |
| No | 22 (5.60) | 14 (3.50) | | | |
| Laboratory | n (Mean±SD) | n (Mean±SD) | | p | t |
| Average platelet | 181 (62595.32±41057) | 214 (83306±56688.31) | | 0.00 | -4.19 |
| Average hemoglobin | 181 (13.27±2.09) | 214 (12.78±2.32) | | 0.02 | 2.21 |
| Average hematocrit | 181 (41.05±8.53) | 214 (39.34±6.27) | | 0.02 | 2.28 |
| Total | 181 | 214 | | | |

Multivariate analysis of variable clinical epidemiology significance such as bleeding, muscle pain and rash is shown In Table 3. The multivariate analysis shows that the dominant variable having significant contribution for clinical indicator of DHF is muscle pain compared to bleeding and rash in the case study of Kebumen District (See Table 3). The multivariate analysis for laboratory indicators such as variable domain contributing significantly to diagnosis of DHF is platelet (β = 0.19) compared to hemoglobin (β = -0.09) and hematocrit (β = -0.06) (See Table 4).

**Table 3**
The Multivariate Analysis Clinical Indicators for Contribution of DHF Diagnosis such as Bleeding, Muscle Pain and Rash

| Variable | β | Wald | OR 95%CI |
|---|---|---|---|
| Bleeding | -0.52 | 2.87 | 0.59 (0.32-1.08) |
| Muscle pain | -0.40 | 3.85 | 0.66 (0.44-0.99) |
| Rash | 0.59 | 2.59 | 1.80 (0.88-3.70) |

**Table 4**
The Multivariate Analysis Laboratory Indicators for Contribution of DHF Diagnosis such as Platelet, Hemoglobin and Hematocrit

| Variable | β | F | p |
|---|---|---|---|
| Platelet | 0.19 | 24.96 | 0.00 |
| Hemoglobin | -0.09 | 0.79 | 0.45 |
| Hematocrit | -0.06 | 0.29 | 0.74 |

## DISCUSSION

The geography of Kebumen District shows that the southern region borders the ocean and the northern region borders the mountains. Description of population in Kebumen District is that the population density in the eastern part is in the Southern zone and population density in the western part is in the Northern zone while the population density in the central part is in the central. The study shows the spread of dengue disease is more likely in the Central zone. This situation can be related to the population density, transportation system and geographical conditions of the Kebumen District area. Population density is one of the factors increasing the transmission of dengue disease. Transportation also has an impact on increasing population mobility so that the transmission of dengue disease is inevitable. Migration and socioeconomics are factors of transmission for ongoing dengue through outbreak prediction (24).

The map shows spread of dengue in the eastern region tends to the Southern zone, the central region in the Central zone and the eastern region tends to the Northern zone. The situation is interesting in viewed the risk of zone-based disease. The Central Statistics Agency of Kebumen District shows the population density tends to be central (6). This situation causes transmission in the central area. The main factors contributing for ongoing dengue transmission is related to population density. The epidemiology approach factors show interaction between host, agent and environment play a part in continuous transmission. The host factors caused disease by continued transmission interactions between persons supported by the environment (25). The vectors are an important factor for transmission of dengue disease related to ongoing breeding. Study by Id et al (23), found environment characteristics are important for early detection of vector development, such as rainfall and temperature for reduction of transmission of vector.

The population in the study area with the central region is dense compared to west or east and has high mobility. This condition risks to develop dengue and continuous transmission. Compared to Bali province, the dengue hemorrhagic fever incidence case shows fluctuations through the season (26). Efforts to prevent dengue developing are related to early detection of disease and case management. Study in Costa Rica concluded that the intervention for decrease dengue disease is through epidemiological surveillance response. The surveillance system is effective in early detection of dengue disease such as clinical indicators and laboratory indicators (21). Study in South Florida concluded that laboratory tests for dengue are crucial for early diagnosis and management of cases. The awareness of the severity of dengue is a public problem regarding early diagnosis of dengue (17). Study recommends accessible local diagnostic facilities in the public community such as community health service.

A study focused for signs and symptoms of dengue showed that a clinical sign is fever (95.50%). The signs and symptoms of fever are typical for initial diagnosis of dengue disease. a previous study (4) in Sudan addressed 395 febrile patients and showed 158 (40%) were malaria positive and 67 (17%) were dengue positive and both 6.60% (26/395). Study in Asia and America addressed 7,428 patients and estimated 2,694 (36%) were diagnosed laboratory-confirmed dengue and 2,495 (34%) non-dengue. The signs and symptoms found that most of the febrile conditions occurred in

the differential diagnosis (15). This situation can be caused by fever conditions caused by other diseases such as malaria and diarrhea. The signs and symptoms of dengue are such as pain and nausea related virus in the blood. Previous study showed that signs of dengue case were abdominal pain 72% cases and vomiting 70% cases (8).

Study showed that the variable clinical epidemiology significantly differently related to positive and negative diagnosis dengue are bleeding, muscle pain and rash. The variables fever, headache, nausea, weakness are not significantly different. This situation shows that bleeding, muscle pain and rash are clinical indicators of severe dengue conditions. The severity of dengue disease can cause death with study in Brazil finding that many treated in hospital with severe dengue were at high risk of death (7). The study showed that there was a high number of patients with severe dengue (8). Study in Malaysia also showed t high patient numbers diagnosed with severe dengue (9). This shows that dengue if very dangerous for life-related high mortality.

The laboratory indicators show a dominant factors contributing for dengue is platelet. A laboratory study found thrombocytopenia as a case indicator for dengue disease drawing on severe dengue situation (12). The laboratory signs and symptoms that can be seen apart from platelets are hematocrit and hemoglobin. The study concluded that increased hematocrit is addressed as a clinical sign of dengue (8). Previous study by Mar et al (13) found that clinical signs and symptoms for dengue are such as pain, hematocrit, hemoglobin while another study concluded that early detection of severe dengue used the acute phase with such as hematocrit, hemoglobin, and platelet (16).

Multivariate analysis found that the signs and symptoms that contributed most to dengue were muscle pain. Muscle pain can cause breathing problems related to oxygen circulation being disrupted. Dengue disease which developed severity and led to death in pediatrics cases were respiratory failure which is related to the importance to identify early through the level of severity (7). According to study data, dengue diagnosed through bleeding, muscle pain and rash. The compared indicators between bleeding, muscle pain and rash shows that muscle pain is the main focus for true dengue. The study provides instruction that severe dengue conditions are followed by bleeding. This study also shows that signs of pain are the main factor for clinical epidemiological diagnosis.

The laboratory indicator shows that the main factors contributing for accurate diagnosis are platelet, hemoglobin and hematocrit. The multivariate analysis shows that platelet is a main factor for accurate dengue diagnosis compared to hemoglobin and hematocrit. PCR is an indicator for laboratory diagnosis of dengue with low sensitivity. This condition for early diagnosis is suitable for dengue surveillance but for is still low for accurate diagnosis. Study in Vietnam showed that PCR positivity rate among hospitalized patient dengue was 68% It is concluded that PCR sensitivity is still low compared to laboratory indicators such as platelet (27). Study in tropical areas showed differences in indicator score for dengue and malaria. The indicators score for malaria are such as endemic area 1, thrombocytopenia 2, anemia 1, lymphocytopenia 1, neutropenia 1, and fever > 39.50C 1 with total score 0 – 7. Scores for dengue are such as endemic area 1, leucopenia 2, thrombocytopenia 1, muscle pain 1, and rash 1 with total 0 – 6 score. The total scores ≥3 cutoff point for malaria indicated >80% sensitivity and specificity, but for dengue sensitivity and specificity it was >90% for children and adults (28).

The effort of interventions are to prevent disease developing and causing death. These efforts are such as vector control, reducing transmission and rapid disease management. Previous study concluded that mosquito control reduces transmission and decreases dengue disease (22). A study in Vietnam concluded that laboratory tests served as predicting condition of severe dengue through three days of illness (14). A study in Argentina (18) concluded that clinical and laboratory indicators during the dengue period are effective for reducing severe clinical dengue. A study in Sudan (19) concluded that training clinical epidemiologists and strengthening surveillance system led to improvement of management of dengue disease. The Kebumen District is a disaster area of floods so strengthening surveillance is very important in disaster areas such as floods and volcanic eruption (29). The disease and outbreak post disaster is related to the environment through vector disease. Study in East Java shows that increasing disease is related to environment (30). A surveillance system is goods practice for implementing efforts related to decreased mortality and morbidity.

**Research Limitations**

The study used data surveillance report in 2023 collected in the health department of Kebumen District. It couldn't access community detail and

spatial data were used in internet mapping related to low accuracy in ordinate points.

## CONCLUSION

The clinical indicators showing significant difference for dengue diagnosis are bleeding, muscle pain, rash and the dominant contributing factors is muscle pain. The laboratory indicators showing significant difference are platelets, hemoglobin, hematocrit and the main factor for dengue diagnosis is platelets.

## CONFLICT OF INTEREST

There are no conflicts of interest disclosed by all authors in this work.

## AUTHOR CONTRIBUTIONS

NS: research concept, paper preparation, data analysis, review, editing. WRH: reference collecting and support for report in research. TS: data collecting in health center surveillance.

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