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Clinical characteristics and laboratory parameters in differentiating dengue from other acute febrile illnesses

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Abstract

Background: Dengue infection is one of the most common viral infections globally, with a broad spectrum of clinical manifestations, including hemorrhage and shock. Early diagnostic confirmation of dengue infection is essential, but some areas may not have the appropriate diagnostic tools while its clinical symptoms are similar to other diseases. We aim to determine some significant clinical characteristics and laboratory parameters in differentiating dengue from other causes of febrile.

Results: This study included 527 dengue patients and 268 control patients. Multivariate analysis showed older age (OR = 12.11; 95% 5.42–26.63, $p < 0.001$), the absence of diarrhea (OR = 0.12; 95% CI 0.06–0.25, $p < 0.001$), leukopenia (OR = 13.35; 95% CI 4.99–38.71, $p < 0.001$), thrombocytopenia (OR = 7.12; 95% CI 2.37–21.38, $p < 0.001$), and normal ESR (OR = 3.03; 95% CI 1.54–5.96, $p = 0.001$) are significant parameters in differentiating dengue with excellence (AUC value of 0.96) and good fit of the model (p value = 0.8). The cut-off is two significant variables with a sensitivity of 91.4% and specificity of 87.5%.

Conclusions: Two or more clinical signs can help clinicians differentiate dengue from other acute febrile illnesses.

Keywords: Dengue fever, Acute febrile illness, Clinical characteristics, Pediatrics

Background

Dengue is one of the most rapidly spreading viral diseases globally, especially in countries with tropical and subtropical climates [1–3]. From 2000 to 2019, the reported number of dengue infections had increased from 505,430 cases to 5.2 million, indicating an eightfold increase [3]. From 2004 through 2010, it is described that the Asia Pacific accounts for 75% of all dengue cases globally, with Indonesia being the second-largest contributor to the number of cases. There are 30 endemic areas in Indonesia [4]. There is an increasing trend in dengue fever infection in Indonesia, from 65,502 cases in 2018 to 138,127 cases in 2019. Deaths associated with dengue also rose by almost two-fold from 467 in 2018 to 919 in 2019 [2].

Dengue infection can manifest in a broad spectrum of clinical manifestations, ranging from subclinical disease to severe symptoms. Some even develop an acute febrile illness with hemorrhage, organ impairment, and shock, resulting in a high fatality rate. A severe manifestation of dengue mainly affects Asian and Latin American countries [3, 5]. Thus, early diagnostic confirmation is essential to allow early clinical intervention, etiological investigation, and disease control [6].

However, early diagnosis of dengue can be challenging. World Health Organization (WHO) has established some diagnostic methods [1], yet these diagnostic tests may not be available in some areas with limited health facilities [7]. In addition, dengue fever is not the only infectious

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disease [8], and it has various clinical symptoms, depending on age and the stage of illness. These manifestations can be overlapping with other causes of febrile illness [7]. For example, hepatitis, diarrhea, dysentery, urinary tract infection, and pneumonia can manifest in fever, malaise, nausea, and abdominal pain [9]. These masquerading symptoms can delay early dengue diagnosis. This study was conducted to determine some significant clinical characteristics and laboratory parameters in differentiating dengue from other causes of febrile illnesses, which may assist in differentiating these two entities in clinical settings.

Methods

This was a cross-sectional study with a purposive sampling method. Data were collected from medical records at Siloam Hospital Lippo Village from January 2015 through December 2020. We included inpatients children from 0 to 18 years old diagnosed with dengue fever and dengue hemorrhagic fever based on WHO 2009 guidelines [1]. The control group consisted of patients who presented with fever and were later diagnosed with hepatitis, diarrhea, dysentery, urinary tract infection, and pneumonia with International Classification of Diseases 10 (ICD 10) codes B15, B16, R19.7, A03.0, A06.0, N39.0, and J15. Patients from both groups will be excluded if they had coinfection with other pathogens, had a history of long-term steroid use, and had immunodeficiency conditions such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). The minimum sample was calculated based on unpaired categorical comparative analytic with a 5% error rate and power of 80% and yielded minimum of 75 samples for each group, with 150 samples. Universitas Pelita Harapan Ethics Committee has approved this study with an ethical clearance number 164/K-LKJ/ETIK/XII/2020.

We collected demographic data (age, sex, nutritional status) and clinical symptoms (fever, vomit, diarrhea, abdominal pain, and respiratory symptoms such as dyspnea, cough, rhinitis, and sore throat). The nutritional status was categorized into normal and abnormal (underweight, overweight, and obesity). We also collected data on laboratory parameters such as hemoglobin, hematocrit, leukocyte, differential count, platelet, erythrocyte sedimentation rate (ESR), and neutrophil to lymphocyte ratio (NLR). The total numbers of neutrophils were divided by the numbers of lymphocytes to get NLR. The laboratory parameters were evaluated based on the reference range of the laboratory parameters of the median age of the study.

Data analysis was done using IBM SPSS 23.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Normality test was carried out using the Kolmogorov–Smirnov test. Data with a normal distribution ($p > 0.05$) was tabulated using mean and standard deviation, while data with non-normal distribution were tabulated using median and range. Bivariate data were analyzed using the chi-square technique. The difference in the median from both groups was analyzed using the Mann–Whitney U test with a significant level $p < 0.05$. Variables with a p value less than 0.25 on bivariate analysis were included in multivariate logistic analysis. The results were further analyzed for their validity by assessing their discrimination and calibration. The area under the curve (AUC) from receiver operating curve (ROC) test was used to evaluate its discrimination with an AUC value of 90–100% interpreted as excellent classification, 80–90% interpreted as good classification, 70–80% interpreted as fair classification, 60–70% interpreted as poor classification [10]. Calibration (goodness of fit) was evaluated using the Hosmer–Lemeshow test with $p > 0.05$ indicating a good fit of the model [11]. Significant variables from the multivariate were further analyzed using AUC to determine the optimal cut-off number of variables required to differentiate dengue and other febrile illness using Youden's index [12].

Results

This study included 795 patients consisting of 527 patients in the dengue group and 268 patients in the control group (Table 1). Children in the dengue group had a significantly higher median age of 10.92 years old (0.04–18 years old) compared to the control group with a median age of 1.5 years old (0.0–17.92 years old) ($p < 0.001$). Both dengue and control groups were dominated by males with 58.82% and 63.8%, respectively. Most of the patients had normal nutritional status (62.4% and 62.7% for dengue and control groups, respectively). Both sex ($p = 0.2$) and nutritional status ($p = 1$) were found to have no significant association with dengue.

From clinical characteristics (Table 2), it appears that patients in the control group had more frequent vomiting (66.4%), diarrhea (77.2%), and respiratory symptoms (35.8%) compared to dengue patients (40.8%, 12.3%, and 34.3%, respectively). However, patients with dengue suffered more from abdominal pain (18.6%) than the control group (10.4%). Bivariate analysis showed a significantly higher risk of having abdominal pain among dengue patients than the control group (OR = 1.96; 95% CI 1.3–3.07, $p = 0.04$), while the risk of having vomit (OR = 0.348; 95% CI 0.26–0.47, $p < 0.001$) and diarrhea (OR = 0.04; 95% CI 0.03–0.06, $p < 0.001$) are significantly lower in the dengue group compared to the control group.

Laboratory values (Table 3) showed dengue patients had a higher level of hemoglobin compared to the control group with a median of 13.19 g/dL (8.2–18 g/dL) vs.

Table 1 Demographic characteristic of dengue and control

	Dengue (*n* = 527)	Control (*n* = 268)	*p* value	OR (CI)
Sex, *n* (%)				
Male	310 (58.82)	171 (63.8)	0.2*	1.23 (0.91–1.67)
Female	217 (41.18)	97 (36.2)		
Age (year), median (range)	10.92 (0.04–18)	1.5 (0.0–17.92)	< 0.001*	N/A
Nutritional status, *n* (%)	(*n* = 498)	(*n* = 110)	1	0.99 (0.65–1.51)
Normal	311 (62.4)	69 (62.7)		
Abnormal	187 (37.6)	41 (37.3)		

OR odds ratio, *CI* confidence interval, *N/A* not available

* *p* value < 0.05 is considered statistically significant

Table 2 Comparison of the clinical characteristic of dengue and control group

Variables	Dengue (*n* = 527)	Control (*n* = 268)	*p* value	OR (CI)
Vomit, *n* (%)	215 (40.8)	178 (66.4)	< 0.001*	0.35 (0.26–0.47)
Diarrhea, *n* (%)	65 (12.3)	207 (77.2)	< 0.001*	0.04 (0.03–0.06)
Abdominal pain, *n* (%)	98 (18.6)	28 (10.4)	0.004*	1.96 (1.25–3.07)
Respiratory symptoms, *n* (%)	181 (34.3)	96 (35.8)	0.738	0.94 (0.69–1.28)

OR odds ratio, *CI* confidence interval

* *p* value < 0.05 is considered statistically significant

11.4 g/dL (6.1–15.4 g/dL). Hematocrit level is higher in dengue patients than in the control group with 39.4% (13.57–53.42%) vs. 34% (10.4–44.33%). Leukopenia is more prominent in the dengue group with a median leukocyte value of 4010/mm^3 (1080–24,520/mm^3) than a leukocyte value of 12,540/mm^3 (2860–34,850/mm^3) in the control group. Furthermore, thrombocytopenia is more severe in the dengue patients in comparison to the control group with thrombocyte level of 158,000/mm^3 (15,750–440,200/mm^3) vs 354,000/mm^3 (109,900–989,000/mm^3). Normal ESR is notable in the dengue group with a median value of 10 mm/h (1–78 mm/h) compared to the control group with a median value of 21 mm/h (1–215 mm/h). Higher hemoglobin, hematocrit, leukopenia, thrombocytopenia, and normal ESR are significant factors with a p value < 0.001. This study also found a higher range of basophil and monocyte in the dengue group (0–9% and 0–12%, respectively) compared to the control group (0–1% and 2–11%). Higher basophil and monocyte are significantly associated with dengue ($p < 0.001$ and $p = 0.002$, respectively).

Further analysis using logistic multivariate showed older age (OR = 12.11; 95% CI 5.42–26.63, $p < 0.001$), the absence of diarrhea (OR = 0.12; 95% CI 0.06–0.25,

Table 3 Numerical comparison of laboratory parameters of dengue and control group

Laboratory parameter	Reference range	Available data		Median (range)		*p* value
		Dengue	Control	Dengue	Control	
Hemoglobin	10–15.5 g/dL	525	254	13.19 (8.2–18)	11.4 (6.1–15.4)	< 0.001*
Hematocrit	32–44%	525	131	39.4 (13.57–53.42)	34 (10.4–44.33)	< 0.001*
Leukocyte	5–10 × 10^3/mm^3	525	253	4.01 (1.08–24.52)	12.54 (2.86–34.85)	< 0.001*
Basophil	0.5–1%	401	247	0 (0–9)	0 (0–1)	< 0.001*
Eosinophil	1–4%	401	247	0 (0–10)	0 (0–6)	0.974
Neutrophil	55–70%	401	247	58 (7–91)	59 (20–95)	0.705
Lymphocyte	20–40%	401	247	34 (4–84)	34 (3–75)	0.98
Monocyte	2–8%	401	247	8 (0–12)	7 (2–11)	0.002*
Platelet	150–400 × 100^3/mm^3	525	251	158 (15.75–440.2)	354 (109.9–989)	< 0.001*
Erythrocyte sedimentation rate	0–10 mm /h	374	241	10 (1–78)	21 (1–215)	< 0.001*
Neutrophil lymphocyte ratio	1–3	401	247	1.74 (0.08–22.75)	1.71 (0.27–31.67)	0.884

The reference range used in this table is based on normal values of children who are 7 years old (the median age of this study). These values are obtained from the Nelson Textbook of pediatrics [32] and Mosby's Manual of Diagnostic and Laboratory Tests [33]

* *p* value < 0.05 is considered statistically significant

$p < 0.001$), leukopenia (OR = 13.35; 95% CI 4.99–38.71, $p < 0.001$), thrombocytopenia (OR = 7.12; 95% CI 2.37–21.38, $p < 0.001$), and normal ESR (OR = 3.03; 95% CI 1.54–5.96, $p = 0.001$) are significant parameters in differentiating the dengue and control group (Table 4). The Hosmer–Lemeshow test showed a p value more than 0.05 ($p = 0.8$) which indicates a good fit of the model. The AUC for this model is 0.96 (95% CI 0.95–0.97, $p < 0.001$), demonstrating excellence discrimination. Figure 1 depicts the AUC curve of number of significant variables in differentiating dengue and other febrile illnesses. Using Youden index, two significant variables yield a sensitivity of 91.4% and specificity of 87.5% with an AUC value of 0.948 (95% CI 0.93–0.96, $p < 0.001$) which shows excellent results.

Table 4 Multivariate analysis

Variables	Odds ratio (95% CI)	*p* value (multivariate)
Age	12.11 (5.42–26.63)	< 0.001*
Diarrhea	0.12 (0.06–0.25)	< 0.001*
Leukopenia	13.35 (4.99–38.71)	< 0.001*
Thrombocytopenia	7.12 (2.37–21.38)	< 0.001*
Normal ESR	3.03 (1.54–5.96)	0.001*

CI Confidence interval

* *p* value < 0.05 is considered statistically significant

Discussion

Our study reported that older age, the absence of diarrhea, leukopenia, thrombocytopenia, and normal ESR are significant variables with excellence in discriminating dengue and other fever illnesses. Dengue patients are older, which is similar to other findings [7, 13–15]. This can be explained as older children often work in open fields during the day when *Aedes* mosquitoes are active, making them prone to *Aedes* bites [16].

The absence of diarrhea is also found to be significant in differentiating dengue from other febrile illnesses. Previous studies have reported that dengue patients are less likely to experience diarrhea [7, 13]. A study reported that little is known about the relationship between diarrhea and dengue [15], meanwhile diarrhea is known to be the symptoms of acute uncomplicated diarrhea and dysentery [9].

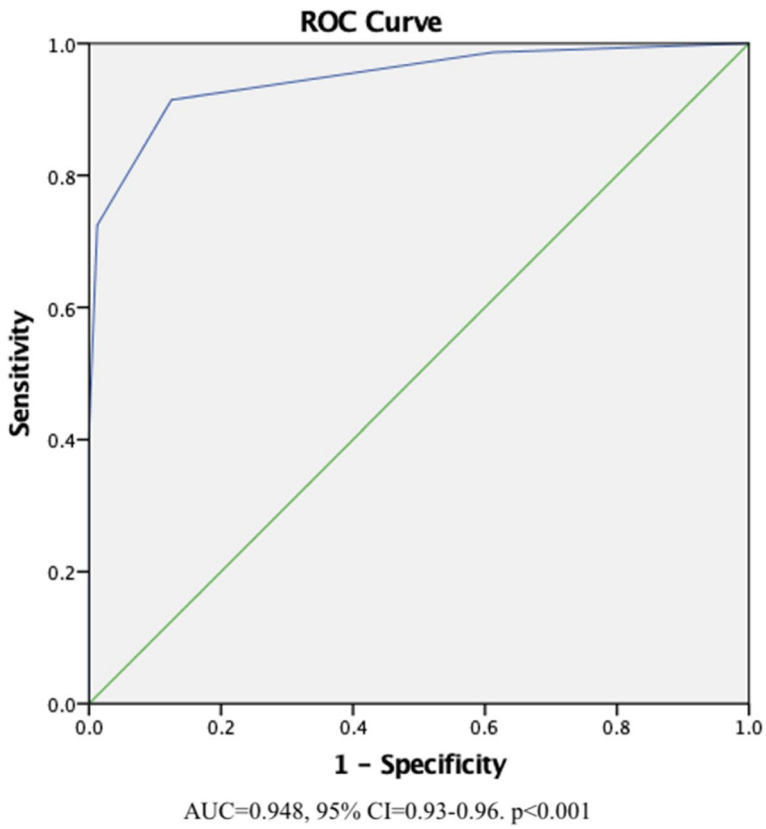

Fig. 1 ROC curve of number of significant variables in differentiating dengue and other febrile illnesses. ROC analysis revealed an AUC of 0.948 with CI = 0.93–0.96 and $p = < 0.001$

This study found leukopenia is more severe in the dengue group compared to other febrile illnesses, supported by previous studies [7, 13, 17–20]. Further analysis on this study also demonstrated leukopenia confers a 13 times risk towards dengue compared to other febrile illnesses. Leukopenia in dengue infection can be explained by the destruction or inhibition of myeloid progenitor cells, which is indicated by mild hypocellularity in the first 7 days of fever during bone marrow examination [21, 22]. We also recognized that instead of leukopenia, the control group appears to have elevated white blood cell (WBC). Our study included children with hepatitis as part of our control group. It has been reported that children with hepatitis A have a significantly lower WBC count than children without hepatitis A. However, when compared to our study, we observed that dengue patients have a lower median leukocyte ($5.44 \times 10^3/mm^3$ vs. $3.91 \times 10^3/mm^3$) [23]. In addition, it is reported that leucocytosis is present in most pneumonia cases [24], and normal-elevated leukocyte is found in both non-bacterial and bacterial diarrhea [25].

Platelets play a role in the coagulation system and the inflammatory system for the host defence. Platelets can release multiple pro-inflammatory cytokines; thus, the increase in platelet has been reported as a normal response to infection [26]. However, we found the decrease in platelet level is more severe in the dengue group compared to the control group, supported by other studies [14, 17, 18, 20]. Furthermore, we found that thrombocytopenia is a significant variable after multivariate analysis, similar to Gregory et al. [18] Thrombocytopenia in dengue fever can be explained by various mechanisms infected bone marrow megakaryocyte, apoptosis platelet, and increased platelet destruction in reticuloendothelial, spleen, and liver. The reason for increased platelet destruction is not known precisely, but it is believed that the dengue viral itself, complement system, and endothelial cell damage are the cause. Moreover, cross-reaction of antibodies against platelet also resulted in thrombocytopenia [21, 22, 27]. This is in contrast to platelet count in the control group, such as pneumonia. Ghoneim et al. [26] found that 13.2% of patients with community-acquired pneumonia experience thrombocytosis, 80.8% of patients had normal platelet, and only 6% experience thrombocytopenia.

Our study reports that dengue patients are more likely to have normal ESR, supported by other studies [28, 29]. A study by Kalayanarooj et al. [30] compare the mean ESR value between dengue hemorrhagic patients (DHF) (10.71 mm/h), other viral infection (20.46 mm/h), bacterial infection (34.81 mm/h), and various illnesses (20.46 mm/h). It showed DHF patients had the lowest ESR mean, with more than half of patients having normal ESR. This can be explained by plasma leakage in dengue. Since blood is composed of plasma and blood cells, plasma leakage will increase blood cell percentage and decrease plasma proportion. Thus, during the Westergren method, the reading of column plasma will be reduced, and the ESR value will be within normal limits [29].

Previous multivariate studies had reported several predictive models. A study by Sawant et al. [7] has built a predictive model of dengue with three variables (myalgia, WBC count less than $5000/mm^3$, and aspartate aminotransferase (AST) > 40 IU) with a sensitivity of 86.7% and specificity of 83.3%. Another study by Kumar et al. [31] reported three significant variables after logistic regression: age, rash, and elevated serum alanine aminotransferase (sALT) level > 40 units. All three variables yielded a specificity of 99.2%, while the presence of one or more variables yielded a sensitivity of 89.3%. Gregory et al. [18] also proposed a predictive model to differentiate dengue for children aged 1–9. The study reported three variables: retro-orbital pain, no cough, and platelet < 240,000 cells/mm^3. This model yielded an AUC of 0.7435. Our study reported five variables in differentiating dengue with an AUC value of 0.96. The presence of two or more significant variables yielded a sensitivity of 91.4% and specificity of 87.5%.

However, our study could not assess some of the symptoms that other studies reported as significant, such as retro-orbital pain [18], AST level [7, 31], and rash [31], because those variables were not recorded in the control group's medical record; thus, we could not compare those variables and only limited clinical information can be analyzed in this study. This is our limitation as we only collect data from medical records. The control group also focuses more on gastrointestinal, urinary, and pneumonia conditions. Although the clinical diagnosis of dengue group was confirmed based on WHO 2009 guidelines, the control group was selected based on ICD10 codes registered in medical record, thus there may be classification bias in the process. Another limitation is that we could not test our model in a perspective model; therefore, the validity and reliability need to be studied again upon a different population. However, this study serves as a starting point for researchers to validate our findings. This study also included a large number of samples from the last 5 years in an endemic region, which is expected to provide a good representation of the dengue population. This model can be used in some rural areas in Indonesia with limitations in diagnosing dengue to increase suspicion of dengue, which is abundant in the monsoon season in Indonesia.

Conclusions

Older age, the absence of diarrhea, leukopenia, thrombocytopenia, and normal ESR is helpful clinical characteristics and laboratory parameters in discriminating dengue from other causes of febrile illness. Two of these variables will yield a sensitivity of 91.4% and a specificity of 87.5%. These variables can help clinicians discriminate dengue from other febrile illnesses, thus helping clinicians detect dengue earlier.

Abbreviations

AST: Aspartate aminotransferase; AUC: Area under the curve; DHF: Dengue hemorrhagic patients; ESR: Erythrocyte sedimentation rate; HIV/AIDS: Human immunodeficiency virus/acquired immunodeficiency syndrome; ICD 10: International Classification of Diseases 10; NLR: Neutrophil to lymphocyte ratio; RCO: Receiver operating characteristic; sALT: Serum alanine aminotransferase; WBC: White blood cell; WHO: World Health Organization.

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Authors' contributions

AJ, GSO, and CLB participated in study conception and design. CLB, FM, MPM, RSH, SC, and GSO participated in data collection. CLB and GSO participated in the analysis interpretation of results. AJ, CLB, FM, MPM, RSH, SC, and GSO wrote the original draft. The authors read and approved the final manuscript.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

Universitas Pelita Harapan Ethics Committee has approved this study with an ethical clearance number 164/K-LKJ/ETIK/XII/2020.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.s

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