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Clinical characteristics and laboratory parameters in differentiating pediatric Dengue fever and Dengue hemorrhagic fever

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ABSTRACT:

— ***Objective:*** The mortality of dengue hemorrhagic fever (DHF) infection in children is still high. Discriminating dengue fever (DF) and DHF during the early phase is difficult, especially with limited diagnostic tools in peripheral areas. Hence, early identification of significant factors in diagnosing DHF is important, with rapid disease progression may lead to mortality. This study aims to determine early clinical and laboratory parameters significant in differentiating DF and DHF.

— ***Materials and methods:*** This is a cross-sectional study using secondary data from medical records collected by purposive sampling from January 2015 to December 2020. This study included children aged 0-18 years old diagnosed with DF and DHF based on World Health Organization (WHO) 2011 criteria.

— ***Results:*** From multivariate analysis of 528 dengue patients, presence of prior dengue infection (OR = 7.1; 95% CI: 2.1-23.7, p=0.001), transfusion administration (OR = 34; 95% CI: 8.7-132, p<0.001), present hepatomegaly (OR = 7.2; 95% CI 1.3-38.2, p=0.02) and other bleeding manifestations (OR = 3.5; 95% CI 1.3-9.3, p=0.012) are significant parameters to differentiate DF and DHF with good quality of discrimination (AUC value = 0.83) and the model is a good fit (Hosmer-Lemeshow value = 0.65). ROC analysis showed two significant variables yielded 55.6% of sensitivity and 86.3% of specificity.

— ***Conclusions:*** Two or more characteristics of present hepatomegaly, other bleeding manifestations, transfusion received, and prior dengue infection are specific to dengue infections yet less sensitive to differentiate DF and DHF.

— ***Keywords:*** Dengue fever, Dengue hemorrhagic fever, Clinical characteristics, Children.

INTRODUCTION

During the last three decades, there has been a major increase in frequency and disease incidence of dengue fever (DF) and dengue hemorrhagic fever (DHF). This infection has been an epidemic in tropical and subtropical regions over the world[1]. Indonesia is one of the tropical countries located in Southeast Asia. Almost all of its regions are endemic for *Aedes aegypti* and *Aedes albopictus* mosquitoes, the main vector of dengue virus (DENV)[2]. A total of 95,893 DHF patients were reported in 2020, with a substantial increase of deaths by 73.35%. The age group of 5-14 years old dominated the death proportion with staggering mortality of 34.13%[3].

Clinical presentation of dengue varies from being asymptomatic, mild cases to a severe and life-threatening form of hemorrhage, shock, and mortality[4]. The World Health Organization (WHO) had classified DF and DHF based on clinical and laboratory values, with evidence of plasma leakage being the main difference between

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DF and DHF[1]. Furthermore, early baseline hematocrit value was rarely known. Thus, it is not easy to discern the increasing value of hematocrit[5].

During the acute stage of the disease, it is difficult to distinguish DHF from DF. There are no pathognomonic signs or symptoms for DHF[6]. Several diagnostic methods were available to diagnose DF[1]. Yet, with rapid progression into severe form in its course of the disease, early identification of DHF becomes challenging, notably in peripheral or rural areas with limited availability of diagnostic methods previously mentioned[7].

Since patients with classical DF may experience evolving clinical spectrum and develop into its life-threatening form of DHF, it is essential to discover distinct signs, symptoms, and laboratory parameters to facilitate rapid identification of DHF[8]. Case fatality rate in DHF could reach 44%[9,10]. This mortality rate can be reduced to less than 1% with early treatment[11]. Hence, prompt intervention may be given with early diagnosis and identification of characteristics related to DHF.

Thus, with difficulty in differing DF and DHF, especially in rural endemic regions, this study was conducted to describe early clinical profile and laboratory parameters significantly associated with DHF to distinguish it from DF and reduce mortality.

MATERIALS AND METHODS

This was a cross-sectional study conducted at Siloam Hospitals Lippo Village (Banten, Indonesia) by collecting secondary data from medical records from January 2015 to December 2020. This study was approved by the Faculty of Medicine Universitas Pelita Harapan Ethical Committee with an ethical clearance number of 174/K-LKJ/ETIK/XII/2020 on December 4th, 2020.

Samples were collected by purposive sampling. Data of pediatric patients with a range of age from 0-18 years old who met DF and DHF criteria by World Health Organization (WHO) 2011 were included in this study[1]. Patients were excluded if the age is above 18 years old, had a history of long-term corticosteroid consumption, had immunodeficiency condition such as human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), had co-infection with other pathogens prior to laboratory examinations, or congenital immunodeficiency. Diagnostic methods for detection of dengue infection were done by viral antigen detection of non-structural protein (NS1) and serologic testing of anti-dengue immunoglobulin M (IgM) or immunoglobulin G (IgG), and immunoglobulin A (IgA) antibody.

Data collected from the medical records were demographic data such as age, gender, past dengue infection status, fever duration before admission and overall fever duration, nutritional status, the temperature on admission, and Glasgow coma scale (GCS). Clinical manifestations and laboratory values (hemoglobin, hematocrit, leukocyte, thrombocyte, differential count, neutrophil-lymphocyte ratio, inflammatory markers, blood glucose, electrolyte panel, and liver enzyme). Laboratory values included in this study were the results of the first examination performed. Epistaxis, gum bleeding, hypermenorrhea were grouped as other bleeding manifestations, and respiratory symptoms manifested as cough, dyspnea, rhinitis, and sore throat. Additionally, antigen and serology test results were also recorded. Data of patients given with fluid bolus therapy, transfusion, intensive care unit (ICU) admission, and patient outcome were collected.

Normality test was done with Kolmogorov-Smirnov test, and data were normally distributed if the results of p-value >0.05. Numerical data was written with mean if the was normally distributed or median if the data was not normal. The Chi-square method used the bivariate analysis of the patient's characteristics, clinical symptoms, and laboratory parameters. The Fisher's-exact test was used for variables with any cell containing an expected count of less than five. The Student's t-test evaluated data of the patient's characteristics with numerical value if the data were normally distributed. Data with non-normal distribution were tabulated using Mann-Whitney-U test. Variables with a p-value less than 0.25 on bivariate analysis were included in logistic regression multivariate analysis. Further analysis was done to find its discrimination between variables to differentiate DF and DHF groups using the area under the curve (AUC) value from the receiver operating curve (ROC) test. AUC measures how well a parameter can distinguish between DF and DHF[12], in which AUC value of 90-100% was classified as excellent, 80-90% was interpreted as good, 70-80% was interpreted as fair, and 60-70% as poor[13]. The model was checked for its calibration or goodness-of-fit using Hosmer-Lemeshow test with *p-value* >0.05 accepted as a good fit for the model[14]. Youden's index was used to analyze significant multivariate variables through AUC further to determine the optimal cut-off number of requisite variables to distinguish between DF and DHF[15]. Sensitivity and specificity of the model were obtained as well using ROC curve[12]. Data were analyzed using Statistical Package for the Social Sciences SPSS 25.0 (IBM, Armonk, NY, USA).

RESULTS

Demographic data were summarized in Table 1. 528 pediatric patients were diagnosed with DF or DHF, with 452 DF patients and 76 DHF patients. Based on WHO 2011 dengue criteria, 39 patients were categorized as DHF Grade 1, 16 patients with DHF Grade 2, 17 patients with DHF Grade 3, followed by four patients with DHF Grade 4.

The median age for patients with DF was 10.6 (0.04-18) years old and 11.5 (0.5-17.8) years old for DHF patients. Most of the patients have normal nutritional status and never had previous dengue infections. In DF and DHF, the cases were predominantly male, but no significant association was observed between these groups (p=0.48). Both DF and DHF patients had more patients with the highest fever temperature above the total median temperature.

Table 1. Characteristics of subjects.

Characteristics	Dengue Fever (n=452)	DHF (n=76)	*p*-value	Odds Ratio (95% CI)
Age – median (range)	10.78 (0.11-18)	0.671	1.1 (0.7-1.8)	
Sex – n (%)				
Male	263 (58.2)	47 (61.8)	0.48	0.8 (0.5-1.4)
Female	189 (41.8)	29 (38.2)		
Nutritional status – n (%)				
Obesity	55 (12.9)	8 (11.1)	0.427	N/A
Overweight	52 (12.2)	11 (15.3)		
Normal	272 (63.7)	40 (55.6)		
Underweight	45 (10.5)	13 (18)		
Severe underweight	3 (0.7)	0 (0)		
Diagnostic test – n (%)				
Positive NS1	283 (71.8)	43 (70.5)	0.317	0.8 (0.5-1.3)
Positive IgM	56 (14.2)	9 (14.75)	0.85	1 (0.5-2.3)
Positive IgG	45 (11.5)	9 (14.75)	0.38	0.7 (0.3-1.5)
Positive IgA	10 (2.5)	0 (0)	0.37	N/A
Prior Infection Status – n (%)				
Positive	21 (4.6)	9 (11.8)	0.14	2.8 (1.2-6.3)
Negative	431 (95.4)	67 (88.2)		
Temperature - median (range) n=525	38.4 (36-42)	38.4 (36.7-41)	0.711	1.1 (0.7-1.8)
Pulse pressure (mmHg) n=422	40 (10-80	40 (10-60)	0.171	1.4 (0.8-2.4)
GCS - median (range)	15 (15-15)	15 (13-15)	0.146	N/A
Weight - median (range) kg n=443	38.5 (3.5-133)	39 (6.3-104)	0.915	1.1 (0.6-1.7)
Height - median (range) cm n=437	143 (60-182)	129.8 (65-174.5)	0.718	1 (0.7-1.8)
Fever duration before admission n=451	3 (1-10)	3 (1-6)	0.867	0.96 (0.6-1.6)
Overall duration of fever – median (range) n=451	5 (1-15)	5 (2-10)	0.22	1.4 (0.8-2.3)
Transfusion				
FFP	2 (0.4)	2 (2.6)	<0.001	21.2 (0.9-52.6)
TC	2 (0.4)	4 (5.3)		
FFP + TC	0 (0)	2 (2.6)		
Unspecified	4 (0.9)	11 (14.5)		
Fluid Bolus Therapy – n (%)	1 (0.2)	5 (6.6)	<0.001	0.03 (0.004-0.3)
ICU Admission				
Positive	0 (0)	1 (1.3)	0.15	N/A
Negative	452 (100)	75 (98.7)		
Outcome – n(%)				
Alive	452 (100)	75 (98.7)	0.146	7 (5.7-8.7)
Dead	0	1 (1.3)		
Length of stay – median (range)	5 (2-11)	5 (2-10)	0.529	1.2 (0.7-2)

GCS, Glasgow Coma Scale; FFP, fresh frozen plasma; TC, thrombocyte concentrate; ICU, Intensive care unit.

From the results of the consciousness examination using the GCS, one DHF patient had a GCS score of 13 while the rest had scores of 15. Blood transfusion with fresh frozen plasma or thrombocyte concentrate or both and fluid bolus therapy were given more in DHF patients and significantly associated with DHF ($p<0.001$).

Clinical features presented on admission are shown in Table 2. Every admitted patient had a fever and both in fever duration before admission and overall fever duration. There was no significant difference between DF and DHF.

Both DF and DHF had low appetite, followed by vomiting as their common symptoms. Another common symptom in DHF is abdominal pain (36.8%, OR = 3.3, 95% CI: 1.9-5.5, $p<0.001$). Pleural effusion (10.5%, $p<0.001$) and ascites (3.9%, $p<0.001$) were only found in DHF patients. DHF patients had higher numbers of back pain (7.8%, OR = 3.4, 95% CI: 1.2-9.6, $p=0.018$), hepatomegaly (18.4%, OR = 14.4, 95% CI: 5.6-37, $p<0.001$), and other bleeding manifestations (21.1%, OR = 3.8, 95% CI: 2-7.2, $p<0.001$). Hematemesis was only found in 0.4% of DF patients, and melena was found in 0.4% of DF and 1.3% of DHF patients.

Laboratory results are presented in Table 3. Hemoconcentration and thrombocytopenia were more common in DHF patients than in DF. Bivariate analysis was done to assess laboratory values in differentiating DF and DHF. We noted a significant association of thrombocytopenia (OR = 0.5; 95% CI 0.3-0.8, $p= 0.002$), rising hematocrit ($p<0.001$), and basophilia (OR = 0.2; 95% CI 0.1-0.2, $p=0.02$) with DHF. Inflammatory biomarkers, blood glucose, electrolyte, and liver enzyme value shows no significant difference between DF and DHF.

Multivariate logistic regression analysis is shown in Table 4. Prior dengue infection (OR = 7.1; 95% CI: 2.1-23.7, $p=0.001$), transfusion administration (OR = 34; 95%

Table 2. Symptoms.

Symptoms	Dengue Fever (n=452)	DHF (n=76)	*p*-value	Odds Ratio (95% CI)
Headache	146 (32.3)	23 (30.3)	0.54	0.8 (0.5-1.4)
Retroorbital pain	35 (7.7)	10 (13.2)	0.54	1.1 (0.7-2)
Arthralgia	74 (16.4)	16 (21)	0.32	1.3 (0.7-2.5)
Back pain	12 (2.4)	6 (7.8)	0.02	3.4 (1.2-9.6)
Low appetite	188 (41.8)	38 (50)	0.14	0.7 (0.4-1.1)
Vomiting	185 (40.9)	30 (39.5)	0.89	1 (0.6 -1.7)
Hematemesis	2 (0.4)	0 (0)	1	N/A
Diarrhea	53 (11.7)	13 (17.1)	0.17	1.6 (0.8-3)
Melena	2 (0.44%)	1 (1.3)	0.38	3 (0.3-33)
Other bleeding manifestations	33 (7.1)	16 (21.1)	<0.001	3.8 (2-7.2)
Rash	31 (6.9)	7 (9.2)	0.44	1.3 (0.6-3.3)
Pleural effusion	0 (0)	8 (10.5)	<0.001	N/A
Hepatomegaly	7 (1.5)	14 (18.4)	<0.001	14.4 (5.6-37)
Abdominal pain	69 (15.2)	28 (36.8)	<0.001	3.3 (1.9-5.5)
Ascites	0 (0)	3 (3.9)	0.003	N/A
Edema	0 (0)	1 (1.3)	0.14	N/A
Respiratory symptoms	156 (34.5)	24 (31.6)	0.88	0.8 (0.5-1.5)

N/A, Not available.

CI 8.7-132, $p<0.001$), presence of hepatomegaly (OR = 7.2; 95% CI 1.3-38.2, $p=0.02$) and presence of other bleeding manifestations (OR= 3.5; 95% CI 1.3-9.3, $p=0.012$) were significant parameters to differentiate DF and DHF. From the ROC curve (Figure 1), the area under the curve (AUC) was 0.83 (95% CI 0.78-0.89, $p<0.001$), interpreted as a good quality to discriminate DF and DHF. Hosmer-Lemeshow test showed a *p*-value above 0.05 ($p=0.65$), indicating this model was well calibrated or a good fit. Four significant variables from multivariate logistic regression analysis were analyzed further using ROC curve and yielded a minimum of two significant variables in this model results in a sensitivity of 55.6% and a specificity of 86.3% to distinguish between DF and DHF.

Table 3. Laboratory examinations.

Variable	#Patients with available data	Reference range	DF	DHF	*p*-value	OR (95% CI)
Hematology						
Hemoglobin (g/dl)	525	11.5 - 13.5	13.2 (8.2-17.8)	13.5 (9.5-18)	0.19	1.4 (0.8-2.3)
Hematocrit (%)	526	35-40	39.5 (27.7-53.4)	40.4 (13.5-52.4)	<0.001	N/A
Platelet (103/µl)	526	150-350	156.9 (15.75-440.2)	124 (12-333.6)	0.002	2.3 (1.4-3.9)
Leukocyte (103/µl)	526	4.5-13.5	3.9 (1.08-24.5)	4.1 (1.5-16.1)	0.38	1.2 (0.7-2)
Basophil (%)	399	0.5-1	0 (0-1)	0 (0-9)	0.02	0.2 (0.1-0.2)
Eosinophil (%)	402	1-4	0 (0-10)	0 (0-9)	0.06	5.4 (0.7 – 39)
Band neutrophil (%)	402	0-15	3 (0-8)	3 (0-4)	1	N/A
Segment neutrophil (%)	401	40-60	55 (4-89)	55 (20-86)	0.76	1.1 (0.6 -1.9)
Lymphocyte (%)	401	20-40	34 (4-84)	33.5 (4-69)	0.88	1 (0.6-1.8)
Monocyte (%)	401	2-8	8 (0-20)	8 (0-11)	0.3	1.5 (0.7-3)
Total Neutrophil (%)	401	55-70	58 (3-91)	52 (0-88)	0.19	1.5 (0.8-2.5)
NLR	399	1-3	1.71 (0.08-22.8)	1.74 (0.34-22)	0.3	1.35 (0.8-2.4)
ESR (mm/h)	375	0-10	10 (1-78)	10 (2-35)	0.64	0.87 (0.5-1.5)
CRP (mg/L)	195	0.1-1	9 (1-185)	11.5 (0-108)	0.27	0.2 (0.2-2.4)
Blood glucose (mg/dl)	84	70-110	97 (33.3-163)	103 (69-204)	0.4	1.55 (0.5-4.3)
Electrolyte						
Natrium (mmol/L)	87	136-143	135 (4-145)	132 (128-139)	0.44	0.5 (0.1-2.4)
Potassium (mmol/L)	90	3.5-5.1	3.8 (3-102)	3.7 (3-4)	0.25	0.4 (0.1-1.7)
Chloride (mmol/L)	90	101-107	102 (88-111)	103 (94-108)	0.75	1.3 (0.4-4.8)
Liver enzymes						
ALT (µ/L)	69	18-36	33 (9-302)	50 (10-290)	0.56	1.5 (0.4-5.1)
AST (µ/L)	77	9-25	56 (16-233)	80.5 (12-362)	1	0.9 (0.2-3.9)

ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; NLR, Neutrophil-lymphocyte ratio; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase
Reference range was obtained from Harriet Lane Handbook43 and Mosby's Manual of Diagnostic and Laboratory Tests44 according to normal values of children aged 10-11.

Table 4. Multivariate analysis.

Variable	Multivariate analysis		
	p-value	Odds ratio	95% CI
Prior dengue infection	<0.001	7.1	2.1-23.7
Transfusion	<0.001	34	8.7-132
Other bleeding manifestations	0.012	3.5	1.3-9.3
Hepatomegaly	0.02	7.2	1.3-38.2

DISCUSSION

Based on the descriptive results, DHF patients have a slightly higher number of patients above ten years old and gender distribution shows that the majority of DF and DHF patients are male.

From multivariate analysis, prior dengue infection, needing a transfusion, presence of hepatomegaly, and other bleeding manifestations are significant predictors of DHF. In DHF patients with different serotypes, the secondary infection produces more severe manifestations than primary infection through antibody-dependent enhancement (ADE)[16,17]. This phenomenon enhances T-cell activation in secondary infection with excessive inflammatory cytokines, which promote vascular leak[18]. A meta-analysis[19] also concludes that antibodies produced from primary infection are incapable of neutralizing the virus, forming immune complexes, and enhancing viral entry. This mechanism allows patients with prior dengue infection have more tendency to develop DHF. This is further evidenced in a study by Changal et al[20], which reports that secondary dengue cases have a significantly higher incidence of DHF. A previous multivariate analysis[8] has also reported prior dengue infection as one of the risk factors of DHF[8]. Two other studies[21,22] from Southeast Asia reported that secondary dengue infection were risk factors of dengue shock syndrome (DSS) encompassing grade 3 and grade 4 DHF, and even associated with deaths.

Hepatomegaly shows significant association with DHF and is included in this study to distinguish between DF and DHF. Direct viral toxicity to the liver or dysregulated immunologic injury results in hepatic manifestations. Hepatocytes and Kupffer cells are prime targets for DENV infection, which causes cellular apoptosis[23]. DENV infected cells then induce the production of proinflammatory cytokines and chemokines, which mediate the increase in vascular permeability leading to plasma leakage in DHF[24]. Following decreased liver perfusion as a result of plasma leakage[1,25], hepatomegaly may occur in DHF patients. Under WHO 2011 dengue criteria, hepatomegaly is one of the warning signs of severe dengue. This finding is supported by a previous study of Ferreira et al[26], concluding that hepatomegaly

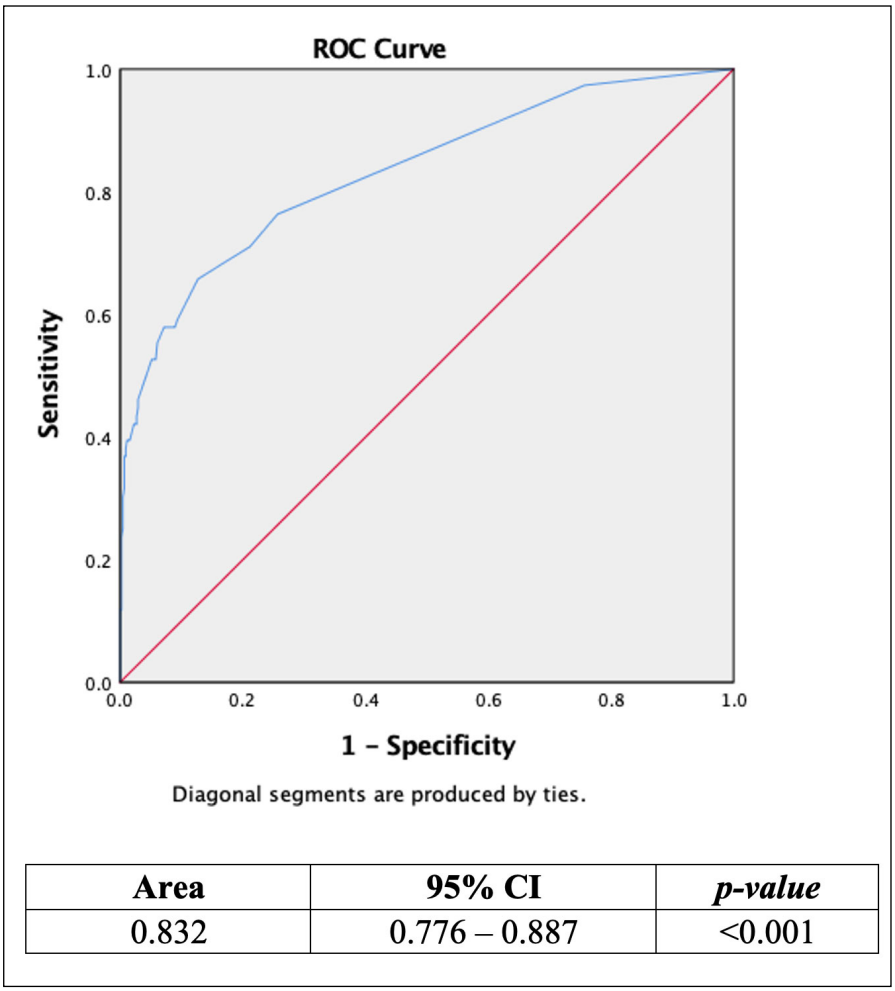

Figure 1. ROC curve analysis for the variables.

is a significant predictor of DHF. Pongpan et al[27] also reported that hepatomegaly is one of the characteristics that increase the risk of DSS (OR = 43.44) and other two studies[28,29] from Indonesia reported the same findings. The disease course of DF patients has not progressed to plasma leakage. Therefore, early signs such as hepatomegaly were not present in DF patients.

The presence of other bleeding manifestations is also found to be significant to distinguish between DF and DHF. Bleeding may be caused by thrombocytopenia, contributing to decreased bone marrow function, shortened platelet survival, and escalation of platelet consumption in DHF patients[30]. In addition, as the disease progresses to DHF, the coagulation system may also be impaired. Regarding this condition, DHF patients have a higher tendency and occurrence of other bleeding manifestations, hence significant in differentiating DF and DHF[31]. Several multivariate studies[21,32,33] have also reported hepatomegaly and bleeding manifestations as significant clinical signs of DSS. Two other studies by Tantracheewathorn et al[21] and Pongpan et al[27] also reported that bleeding episodes are risk factors of DSS with OR of 5.1 and 5.58, respectively. Bleeding manifestations may exacerbate plasma volume loss due to leakage, thus accelerating the occurrence of shock, resulting in mortality[33].

The need for transfusion is another significant parameter to distinguish DHF and DF. In this study, several dengue patients received fresh frozen plasma transfusion, thrombocyte concentrate transfusion, or both. In conjunction with the presence of other bleeding manifestations as a significant factor in DHF, this event leads to requirements of platelet transfusion therapy in DHF patients compared to DF as a consequence of the bleeding. DHF patients have an increased tendency to undergo severe hemorrhage, associated with abnormal immune response[34]. Haemostatic system is also impaired in DHF and increased endothelial dysfunction leading to capillary fragility and induce plasma leakage[24], therefore DHF patients may require plasma transfusion to manage shock. On the other hand, severe hemorrhage and plasma leakage are not found in DF patients, thus transfusion is unnecessary. Hence, transfusion is given with massive bleeding or very low platelet counts to prevent bleeding complications. Chuansumrit et al[35] report that transfusion requirements correlate with the occurrence of bleeding ($p<0.008$). However, findings from Kabra et al[36] show no significant effect on the duration of haemorrhage with platelet concentrate transfusion and the outcome was also not affected. Another study by Chairulfatah et al[37] also suggests that platelet transfusions do not influence the incidence of severe bleeding in most DHF cases.

Based on DHF criteria of WHO 2011, the main hematological parameters to differentiate DHF and DF are hematocrit rise ≥20% and thrombocyte level of <100,000/µl[1]. These findings are constant features of DHF. An increase in hematocrit describes the condition of hemoconcentration. Plasma leakage through the damaged blood vessels to the extravascular leads to an increased percentage of hematocrit consequent to deficiency in blood plasma related to blood viscosity[38]. Thrombocytopenia results from an immunological reaction as DENV binds to platelets. These events enhance platelet aggregation and platelet destruction through apoptosis[30,39]. Proliferative capacity of hematopoietic cells is also suppressed as a result of DENV infection[30]. However, in this study, thrombocytopenia is not a significant variable to distinguish DHF and DF through multivariate analysis. This may be consequent to some DHF patients who had not yet reached thrombocytopenia below 100.000/µl but already had evidence of plasma leakage. Thus, they were still categorized as DHF patients. One explanation is that platelet counts gradually fall and then reach the minimum later in the disease[40]. Furthermore, the patients may be admitted at the late stage of the disease in which the platelet count has increased gradually. This causes thrombocytopenia is not found to be a significant variable to distinguish DHF and DF. Moreover, this study could not analyze the significance of hematocrit as a factor to differentiate DHF and DF as all patients with DHF had a rise of hematocrit ≥20%. Therefore we could not obtain the *p*-value of this variable by logistic regression.

Through ROC analysis of Youden's index, the predictor model in this study has good specificity of 86.3% yet is less sensitive with a sensitivity value of 55.6%. This model has less ability to differentiate DHF and DF patients. However, this model is specific enough to reduce false positives, in which by fulfilling at least two significant variables, it is specific to identify the patients to have dengue infection. This is because these significant variables can be encountered in other diseases. Patients with coagulation or hematologic disorders may have bleeding manifestations[41], requiring transfusion therapy of thrombocyte and/or FFP, or patients with hepatitis, hepatic abscess, or other infections may result in hepatomegaly[42]. Thus, this model is less sensitive as various diseases with similar manifestations may overlap with significant variables found in this study.

This study has some limitations. As the data were collected from medical records, some laboratory values and demographic data were incomplete. Patients in this study did not receive reverse transcriptase polymerase chain reaction (RT-PCR) examination therefore, we were unable to identify serotypes of current DENV infection in patients with a history of previous dengue infection. Hence, we could not verify the significant association between prior dengue infection and DHF. The model in this study was also less sensitive to different DHF with other febrile illnesses commonly found in tropical countries. Therefore, further studies with prospective methods in different populations are needed to find more sensitive and specific variables. However, this study included a large sample representing the clinical and laboratory characteristics of DF and DHF patient populations. In addition, this study yielded a good predictive model shown by the AUC value. Thus, this study may benefit countries and regions with few populations with limited advanced laboratory methods for rapid identification to prevent disease progression into a severe form of DHF.

CONCLUSIONS

Several significant factors to discriminate DF and DHF are the presence of prior dengue infection, the presence of hepatomegaly, the presence of other bleeding manifestations, and the transfusion received with a cut-off of a minimum of two variables are specific enough for dengue infection with the specificity of 86.3%, yet less sensitive to distinguish DHF and DF with a sensitivity of 55.6%. Thus, further studies to find more sensitive and specific variables are needed to help clinicians differentiate DHF and DF for early detection.

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The authors confirm contribution to the paper as follows: research conception and design: AJ, FM, GSO; data acquisition: FM, CLB, MPM, RSH, SC, GSO; analysis or interpretation of results: FM, GSO; draft manuscript preparation and revision: AJ, FM, CLB, MPM, RSH, SC, GSO. All authors reviewed the results and approved the final version of the manuscript.

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