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Original Article

Initial clinical and laboratory profiles to predict pediatric dengue infection severity

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Abstract

Background Prior to the critical phase of dengue infection, it is difficult to differentiate between mild and severe dengue. Identifying risk factors for severe dengue from patients' initial presentation would help decrease the need for hospitalization, increase physician awareness, and improve outcomes.

Objective To predict the severity of pediatric dengue infection based on initial patient characteristics as well as routine clinical and laboratory profiles.

Methods This cross-sectional study was based on medical records of children with dengue infection in Atma Jaya Hospital, Jakarta. Inclusion criteria were children aged 1-18 years with proven dengue infection and hospitalized in Atma Jaya Hospital during the study period (January to December 2016). Clinical profiles and laboratory parameters at the time of patient presentation were extracted and analyzed for possible relationships with dengue severity.

Results Data was collected from 110 patients with a mean age of 9.5 (SD 5) years. Initial clinical profiles that were significantly associated with severe dengue were: age ≤5 years (OR 0.113; 95%CI 0,025 to 0.510), hepatomegaly (OR 2.643; 95%CI 1.051 to 6.650), pleural effusion (OR 9.545; 95%CI 3.722 to 24.777), platelet ≤125,000/uL (OR 0.201; 95%CI 0.044 to 0.924), hyponatremia (OR 10.139; 95%CI 2.576 to 39.906), and AST >135 units/L (OR 5.112; 95%CI 1.564 to 15.710). Biological sex, duration of fever, additional symptoms, spontaneous bleeding, blood pressure, pulse pressure, hematocrit, leukocyte count, random blood glucose, calcium, and ALT level had no significant association with dengue severity.

Conclusion Physicians should be conservative in the management of pediatric dengue patients older than 5 years of age, presenting with hepatomegaly, pleural effusion, platelets >125,000/μL, hyponatremia, or AST more than three times the upper limits of normal. These patients have a higher risk of severe dengue than patients without those findings. **[Paediatr Indones. 2017;57:303-9 ; doi: http://dx.doi.org/10.14238/pi57.6.2017.303-9]**.

Keywords: *dengue; severity; children; clinical profiles; prognosisschool-aged children*

Dengue infection may present a broad range of clinical severity, from asymptomatic, dengue fever (DF), dengue hemorrhagic fever (DHF), and finally, dengue shock syndrome (DSS).[1] Prior to the critical phase, it is difficult to differentiate between mild and severe dengue. To date, there are no diagnostic or prognostic tools available to distinguish severe from non-severe dengue, or other febrile illnesses. Despite the recommendation to hospitalize only patients with severe dengue, many patients with suspected dengue are hospitalized for close monitoring.[2] Several clinical profiles and laboratory measures have been studied with regards to predicting dengue

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severity. Among them are sex, age, abdominal pain, hepatomegaly, abnormal bleeding, ascites, pleural effusion, leukopenia, thrombocytopenia, hemoconcentration, and elevated liver enzymes.[3] Most previous studies did not mention the timing of clinical profiles and laboratory parameters in the disease history. Therefore, we intended to explore clinical and laboratory parameters at the time of patient presentation as potential predictors for severe dengue. By identifying these risk factors at the initial patient presentation, we hope to decrease the need for hospitalization, increase physician awareness of the possibility of severe dengue, and improve outcomes of severe dengue by administering earlier treatment.

Methods

This cross-sectional study was based on medical records of pediatric patients in Atma Jaya Hospital, Jakarta. Inclusion criteria were inpatient pediatric patients aged 1-18 years with a final diagnosis of dengue infection, from January to December 2016. The data were retrieved from hospital medical records with the following ICD-10 codes: A90-dengue fever, A91-dengue hemorrhagic fever, and A910-dengue hemorrhagic fever with shock. Diagnosis of dengue infection was based on criteria mentioned in **Table 1** and confirmed by serologic parameters, i.e., NS1 or anti-dengue IgM. Exclusion criteria were signs of shock at the time of presentation, unproven dengue infection, and comorbidities with other illnesses.

Table 1. Dengue infection diagnosis criteria[4]

1. Dengue infection (DF): acute or abrupt onset of fever, accompanied by a positive tourniquet test, and white blood count ≤ 5,000/µL;
2. Dengue hemorrhagic fever (DHF)
   All of the following items:
   (i) Acute or abrupt fever for 2–7 days,
   (ii) At least one of the following bleeding episodes:
      a. positive tourniquet test,
      b. petechiae, ecchymoses, or purpura,
      c. bleeding from mucosa, gastrointestinal tract, injection sites, or other locations,
      d. hematemesis or melena,
   (iii) Platelet count ≤ 100,000/µL,
   (iv) At least one of the following evidences of plasma leakage:
      a. hemoconcentration assessed by an increase in hematocrit ≥ 20% from previous hematocrit,
      b. signs of plasma leakage, such as pleural effusion or ascites, or evidence of hypoalbuminemia;
3. Dengue shock syndrome (DSS): all items for dengue hemorrhagic fever above, accompanied by evidence of circulatory failure:
   (i) pulse pressure ≤ 20mmHg,
   (ii) or manifested by hypotension, cold body temperature or irritability.

Table 2. Dengue severity

Dengue severity was classified into 4 grades, based on bleeding episodes and shock, as follows:
Grade 1: no evidence of bleeding, positive tourniquet test
Grade 2: evidence of bleeding episodes
Grade 3: presence of weak and rapid pulse rate, low blood pressure, or narrow pulse pressure
Grade 4: non-measurable blood pressure or non-palpable pulse
Grades 1-2 were classified as DHF and grades 3-4 were classified as DSS.

Clinical profiles at the time of patient presentation in the emergency room or outpatient clinic were extracted from medical records and tested as variables. Clinical profiles at the time of presentation were: (1) age and sex, (2) duration of fever at presentation, (3) signs and symptoms, (4) hemodynamic parameters (systolic and diastolic blood pressure, pulse pressure), (5) routine laboratory measures (hematocrit, leukocyte, and platelet counts), (6) random blood glucose, (7) electrolytes (sodium and calcium), (8) and liver function tests [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. Laboratory parameters used were the first laboratory data at the time of presentation, before starting intravenous fluid.

Age was categorized as ≤ 5 years (toddler) and > 5 years (school age), as it has been reported that extremes of age are related to dengue severity.[5] Cut-off values for systolic, diastolic, and mean arterial blood pressures were based on minimum values in children aged > 1 year. We used a hematocrit cut-off of 50%, as set by the WHO as the warning value. For platelet analysis, we set the cut-off value at 125,000/µL, a little lower than the minimum normal value to achieve high predictive sensitivity. An AST cut-off point of 135 units/L was used, as it was three-times the normal upper limit and other studies noted mean liver enzyme values in dengue patients to be 2-3 times the normal value. For analysis, dengue cases were categorized as mild dengue (dengue fever, grades I and II DHF) and severe dengue (grades III and IV DHF) (**Table 2**).

All data were analyzed using the *Statistical Packages for Social Sciences (SPSS) software version 22.0*. Potential predictors mentioned above were tested against the categories of dengue cases using Chi-square or Fisher's exact test, as appropriate. The predictive ability was presented with odds ratio. P values <0.05 were considered to be statistically significant. This study was approved by the Ethics Committee of Atma Jaya Hospital, Jakarta.

Results

One hundred ten subjects' medical records were analyzed. Most of the cases were dengue fever (51%), followed by DHF grade III (16%), DHF grade IV (15%), DHF grade I (10%), and DHF grade II (8%). There were 56% male and 44% female subjects, with mean age 9.5 (SD 5) years. The most common symptoms at presentation were vomiting (83%), abdominal pain (66%), and headache (55%). Myalgia, pleural effusion, hepatomegaly, diarrhea, and cough were found to lesser extents. The mean values of hemodynamic parameter and laboratory tests are presented in **Table 3**. Data on sodium, calcium, blood glucose, AST, and ALT were incomplete; the missing data were replaced by the mean value of each corresponding group.

Bivariate analysis revealed that the clinical profiles significantly related to severe dengue were age ≤5 years (OR 0.113; 95%CI 0.025 to 0.510; P=0.001), hepatomegaly (OR 2.643; 95%CI 1.051 to 6.650; P=0.035), pleural effusion (OR 9.545; 95%CI 3.722 to 24.777; P=0.000), platelets ≤125,000/uL (OR 0.201; 95%CI 0.044 to 0.92; P=0.025), hyponatremia ≤128 mmol/L (OR 10.139; 95%CI 2.576 to 39.906; P=0.000), and AST >135 units/L (OR 5.112; 95%CI 1.564 to 15.710; P=0.004). Initial data on biological sex, duration of fever, symptoms, bleeding manifestation, hemodynamic parameter, hematocrit, leukocyte, random blood glucose, calcium, and ALT were not significantly related to severe dengue (**Table 4**).

Table 3. Characteristics of subjects

Characteristics	Value
Sex, n(%)	
Male	62 (56)
Female	48 (44)
Mean age (SD), years	9.5 (5)
Mode of presentation, n(%)	
Headache	61 (55)
Myalgia	34 (30)
Vomiting	91(83)
Cough	7 (6)
Abdominal pain	73 (66)
Diarrhea	25 (23)
Hepatomegaly	25 (23)
Pleural effusion	32 (29)
Petechiae	30 (27)
Any bleeding manifestation	17 (15)
Hemodynamics	
Mean SBP (SD), mmHg	102 (10
Mean DBP (SD), mmHg	677 (13)
Mean pulse pressure (SD), mmHg	79 (11)
Laboratory findings	
Mean hematocrit (SD), %	40 (5)
Mean leucocytes (SD), /µL	4,600 (3,400)
Mean platelet (SD), /µL	87,000 (53,000)
Mean random blood glucose (SD), g/dL	107 (19)
Electrolytes	
Mean sodium (SD), mEq/L	127 (2.5)
Mean calcium (SD), mEq/L	1.0 (0.3)
Liver function	
Mean ALT (SD), unit/L	134 (125)
Mean AST (SD), unit/L	54 (51)
Diagnosis, n(%)	
DF	56 (51)
DHF I	11 (10)
DHF II	9 (8)
DHF III	18 (16)
DHF IV	16 (15)

Discussion

Predicting dengue severity based on clinical profiles at the initial time of patient presentation at the health facility is a potential way to reduce morbidity, mortality, and hospital costs. Although most dengue cases do not progress to severe disease, a small percentage of cases that do so are often not predicted initially. Dengue patients in the early course of infection often present to the emergency department or as outpatients in a generally healthy condition, obscuring the potential for severe dengue. Potts *et al.* showed that early clinical indicators could be used to differentiate between mild and severe dengue before plasma leakage occurred.[2]

Table 4. Bivariate analysis between initial clinical data and dengue severity

	Mild dengue (n=76)	Severe dengue (n=34)	Total (N=110)	OR	95%CI	P value (2 sided)
Sex, n(%)						
Male	33 (69)	15 (31)	48	0.972	0.430 to 2.196	0.946
Female	43 (69)	19 (31)	62			Ref
Age, n (%)					0.025 to 0.510	0.001
≤ 5 years old	49 (60)	32 (40)	81	0.113		Ref
> 5 years old	27 (93)	2 (7)	29			
Fever						
≤3 days	20 (65)	11 (35)	31	0.747	0.309 to 1.803	0.515
>3 days	56 (71)	23 (29)	79			Ref
Headache, n(%)	41 (67)	20 (33)	61	1.220	0.538 to 2.765	0.634
Myalgia, n(%)	21 (62)	13 (38)	34	1.621	0.689 to 3.813	0.266
Vomiting, n(%)	60 (66)	31 (34)	91	2.756	0.746 to 10.183	0.117
Cough, n(%)	6 (86)	1 (14)	7	0.354	0.041 to 3.057	0.325
Abdominal pain, n(%)	50 (68)	23 (32)	73	1.087	0.460 to 2.571	0.849
Diarrhea, n(%)	17 (68)	8 (32)	25	1.068	0.409 to 2.785	0.893
Hepatomegaly, n(%)	13 (52)	12 (48)	25	2.643	1.051 to 6.650	0.035
Pleural effusions, n(%)	11 (34)	21 (66)	32	9.545	3.722 to 24.777	0.000
Petechiae, n(%)	18 (60)	12 (12)	30	1.758	0.729 to 4.237	0.206
Any bleeding manifestation, n(%)	13 (76)	4 (24)	17	0.646	0.194 to 2.150	0.474
Hemodynamic						
SBP, n (%)						
≤ 90 mmHg	18 (78)	5 (22)	23	1.800	0.607 to 5.335	0.285
> 90 mmHg	58 (67)	29 (33)	87			Ref
DBP, n (%)						
≤ 60 mmHg	35 (73)	13 (27)	48	1.379	0.604 to 3.149	0.445
> 60 mmHg	41 (66)	21 (34)				Ref
Pulse pressure						
≤ 65 mmHg	3 (60)	2 (40)	5	0.658	0.105 to 4.127	0.644
> 65 mmHg	73 (70)	32 (30)	105			Ref
Laboratory						
Hematocrit, n (%)						
> 50%	2 (33)	4 (67)	6	4.933	0.858 to 28.378	0.051
≤ 50%	74 (71)	30 (29)	104			Ref
Leukocyte, n (%)						
≤ 5,000/µL	53 (68)	25 (32)	78	0.830	0.335 to 2.052	0.686
> 5,000/µL	23 (72)	9 (28)	25			Ref
Platelet, n (%)						
≤ 125,000/µL	58 (64)	32 (36)	90	0.201	0.044 to 0.924	0.025
> 125,000/µL	18 (90)	2 (10)	20			Ref
Random blood glucose, n (%)						
≤ 100 mg/dL	18 (69)	8 (31)	26	1.009	0.389 to 2.615	0.986
> 100 mg/dL	58 (69)	26 (31)	34			Ref
Electrolyte						
Sodium, n (%)						
≤ 128 mmol/L	73 (75)	24 (25)	97	10.139	2.576 to 39.906	0.000
> 128 mmol/L	3 (23)	10 (77)	13			Ref
Calcium, n (%)						
≤ 1 mmol/L	70 (78)	20 (22)	90	7.000	0.603 to 81.228	0.138
> 1 mmol/L	1 (33)	2 (67)	3			Ref

to be continued

Table 4. Bivariate analysis between initial clinical data and dengue severity (continued)

Liver function test						
AST, n (%)						
> 135 units/L	5 (36)	9 (64)	14	5.112	1.564 to 15.710	0.004
≤ 135 units/L	71 (74)	25 (26)	96			Ref
ALT, n (%)						
> 135 units/L	2 (40)	3 (60)	5	3.581	0.570 to 22.493	0.170
≤ 135 units/L	74 (70)	31 (30)	105			Ref

SBP: systolic blood pressure; DBP: diastolic blood pressure; AST: aspartate transaminase; ALT: alanine transaminase

The WHO stated the warning signs of dengue: abdominal tenderness, hepatomegaly, lethargy, cold extremities, bleeding, platelet ≤ 75,000/mm^3, and hematocrit value of 50%, or a rise of more than 22% from baseline hematocrit. Initially mild dengue cases may later develop into severe dengue without any warning signs.[1] This fact warrants the search for other factors to help early prediction. Other risk factors were Caucasian race, people with AB blood group, and, extreme ages, and coexisting conditions.[1]

Several prognostic tools for dengue have been developed, e.g., the decision tree algorithm,[2] the diagnostic dengue infection severity score,[3] decision algorithms,[6] the pediatric logistic organ dysfunction score,[7] and the disseminated intravascular scoring system.[8] Previously, a dengue infection severity score developed in Thailand included age, hepatomegaly, systolic blood pressure, white cell count, and platelets as significant predictors and scoring items. Pongpan *et al*. used the scoring system to correctly classify patients into their original severity levels of DF, DHF, or DSS, with clinically acceptable over- and underestimation.[3,9]

We found age, hepatomegaly, pleural effusion, platelets > 125,000/μL, hyponatremia ≤128 mmol/L, and AST >135 units/L to be significant predictors for severe dengue. Some epidemiological studies reported that the two extremes of age (young and old) were associated with severe dengue.[1,10] This association was noted in WHO recommendations, in which infants and the elderly are included as indications for hospital referral.[11] with regards to age as a risk factor for severe dengue, Lovera et al. noted higher risk of severe dengue in children aged >5 years,[12] but Martina *et al.* reported higher risk in children <5 years old.[13] Different populations, study designs, and analyses in those studies might have affected the results. Young age was hypothesized to be related to high microvascular fragility and low vascular adaptation capacity, leading to higher risk of shock. However, in older children, i.e., > 5 years old, reinfection with different serotypes often lead to severe dengue (antibody-dependent enhancement).[13]

Hepatomegaly is a well-known physical finding in dengue. Moderate liver enlargement is a normal response to dengue infection. Several studies found a correlation between hepatomegaly, increased ALT, and dengue severity.[14,15] Clinically, hepatomegaly is one of the causes of abdominal pain, which is included in the WHO warning signs. In our study, risk of developing shock was two times higher in patients with hepatomegaly than those without hepatomegaly. A previous meta-analysis found the risk to be up to five times higher.[16] However, it should be kept in mind that physical examination to determine hepatomegaly in children is operator-dependent and requires appropriate skill.

Yacoub et al. noted that clinical plasma leakage, i.e., pleural effusion, ascites, and gall bladder wall edema were correlated with disease severity.[10] Even though gall bladder wall edema was known to precede the development of ascites and effusion, abdominal ultrasonography to detect such findings was not routinely performed in the febrile phase.

Thrombocytopenia is an important laboratory finding and one of the diagnostic criteria for dengue infection. Severity of thrombocytopenia was correlated with plasma viral load and the extent of plasma leakage. Several previous studies noted different cut-off platelet counts to predict the development of shock.[12,13] We found a significant correlation with development of severe dengue using a platelet count cut-off of ≤ 125,000/μL. This cut-off was not as low as in previous studies,[3,17] and, moreover, did not fulfill the minimum WHO diagnostic criteria (i.e., < 100,000/μL), but it could be considered as a sensitive predictor for severe dengue.

Hyponatremia and high AST showed the highest

odds ratio (approximately 10 and 5, respectively), but analysis of those two variables used mean value to fill the missing data. We preferred to consider hyponatremia and AST >135 units/L as potential predictors for severe dengue, but further studies are needed. Based on several previous studies, hyponatremia was the most common electrolyte disturbance in dengue (61% of DF patients and 72% of DHF patients). Low sodium levels are related to complications, such as central nervous system disturbance and bleeding.[18,19] The AST elevation was usually higher than ALT, probably due to involvement of myocytes in dengue patients. Several studies stated that AST was associated with severity of infection, but they did not discriminate between non-severe and severe dengue.[20,21] Liver enzymes are known to peak late in the course of dengue (day 6-7), therefore, their usefulness as prognostic markers was limited.[10]

Hematocrit is in the WHO diagnostic criteria. Increased hematocrit is one of the warning signs for progression to shock. Our analysis with a 50% cut-off value had a nearly significant P value; if the sample size had been larger, the P value may have been significant, indicating that hematocrit level >50% at initial presentation could be a predictive parameter for dengue progression to shock. Hematocrit level is a common method to identify and monitor plasma leakage. However, this method might be rather insensitive (particularly if patients had received parenteral fluid) and limited by the fact that an individual's baseline value was usually not known.[10]

Hemodynamic parameters were found to not be predictive of severe dengue. However, the parameters used in the analysis were the findings at the initial patient presentation (which mostly presented in the fever stage) and any patients with hemodynamic disturbance were excluded as subjects. As such, abnormalities in hemodynamic parameters were one of the severe dengue criteria (dengue shock syndrome), therefore, it could not be used as predictor.

There were several limitations in our study. This study was retrospective in design and based on medical records, with potential bias of incomplete documentation and variations in skills of examining physicians. We also did not take other potential parameters into account, such as laboratory bleeding parameters and other hepatic function tests. Despite the limitations, our findings suggested several risk factors that may be useful for predicting severe dengue early at the time of patient presentation. Further studies with a larger number of subjects and a randomized, prospective design are needed.

In conclusion, initial clinical findings related to impending severe dengue were age older than 5 years old, hepatomegaly, pleural effusion, platelets > 125,000/μL, hyponatremia, and AST more than three times the upper normal limit. Physicians need to be cautious if dengue patients present with one or more of these findings.

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Conflict of Interest

None declared.

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