

## RESEARCH ARTICLE

## Two Serial Hematocrit Level Just After Admission to Predict Dengue Hemorrhagic Fever Severity

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### Abstract

Dengue hemorrhagic fever (DHF) is still the leading cause of hospitalization and death among children in Indonesia because of plasma leakage leading to shock syndromes. This study aimed to associate the hematocrit difference (first and second) from serial hematocrit (Hct) examination just after admission with DHF severity. A analytical cross-sectional study was involving medical records of pediatric patients with DHF admitted at the pediatric ward and the Pediatric Intensive Care Unit (PICU) of Dr. Hasan Sadikin General Hospital, Bandung in January–December 2015. The subjects excluded if other conditions also cause plasma leakage. The difference in first and second Hct ( $\Delta$ Hct) from serial Hct examination just after admission and DHF grade of severity (DHF I–IV) confirmed by a positive result in serologic tests (anti-dengue IgM/IgG), or detection of dengue virus antigen (NS1Ag test) obtained. Spearman association analysis test used for analysis. A total of 16 subjects with DHF I, 21 subjects with DHF II, 31 subjects with DHF III and two subjects with DHF IV included in this study. There was no significant correlation between positive  $\Delta$ Hct value (hemoconcentration) and DHF severity ( $r=0.247$ ,  $p=0.394$ ,  $CI=95\%$ ). In conclusion, the difference in first and second Hct from serial Hct examination just after admission has no significant association with the disease severity.

**Key words:** DHF severity, two serial hematocrit level

## Dua Nilai Hematokrit Serial Sesaat Setelah Admisi sebagai Prediktor Keparahan Demam Berdarah Dengue

### Abstrak

Demam berdarah dengue (DBD) merupakan penyebab utama hospitalisasi dan kematian anak di Indonesia disebabkan oleh kebocoran plasma yang berujung pada syok. Tujuan penelitian ini mengetahui hubungan perbedaan hematokrit pertama dan kedua pada pemeriksaan hematokrit serial sesaat setelah admisi dengan keparahan DBD. Penelitian merupakan *analytical cross-sectional study* menggunakan data sekunder berupa rekam medis pasien anak yang dirawat di ruang perawatan anak dan *Pediatric Intensive Care Unit* (PICU) RSUP Dr. Hasan Sadikin Bandung pada Januari–Desember 2015. Subjek penelitian dieksklusi apabila pada rekam medis terdapat diagnosis lain yang menyebabkan kebocoran plasma. Variabel penelitian ini adalah perbedaan hematokrit pertama dan kedua ( $\Delta$ Hct) pada pemeriksaan hematokrit serial serta diagnosis DBD (DBD I–IV) yang dikonfirmasi oleh hasil positif pada pemeriksaan serologis (IgM/IgG antidengue) atau deteksi antigen virus (NS1Ag). Terdapat 16 subjek DBD I, 21 subjek DBD II, 31 subjek DBD III, dan 2 subjek DBD IV. Dengan menggunakan Uji Analisis Spearman, tidak terdapat korelasi yang signifikan antara nilai positif  $\Delta$ Hct (hemokonsentrasi) dan tingkat keparahan DBD ( $r=0,247$ ;  $p=0,394$ ;  $CI=95\%$ ). Simpulan, perbedaan hematokrit pertama dan kedua pada pemeriksaan hematokrit serial tidak berhubungan dengan keparahan DBD.

**Kata kunci:** Dua nilai hematokrit serial, keparahan DBD

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**Introduction**

Dengue hemorrhagic fever (DHF), a mosquito-borne viral disease, is still endemic and the cause of death in children aged <15 years.<sup>1</sup> Plasma leakage that leads to shock is the leading cause of death in patients with DHF.<sup>2</sup> Early clinical laboratory examination is needed to diagnose DHF so it can identify the clinical course of the disease and prevent the shock.<sup>3</sup>

The severity of DHF had been known to be related to the clinical characteristics of the disease and laboratory findings;<sup>1</sup> therefore, plasma leakage can identify by measuring the hematocrit (Hct). Serial Hct examination had been known as a marker to identify plasma leakage if the value increased  $\geq 20\%$ .<sup>4</sup> However, this following procedure had not indicated the course of disease yet, nor DHF severity. Since DHF can be a life-threatening disease,<sup>5</sup> efficient time between serial Hct examination is critical to be studied. Therefore, a fundamental notion about early serial Hct measurement related to DHF severity is needed. This study aims to correlate the difference in first and second Hct level from serial Hct examination just after admission with the severity of DHF.

**Methods**

A cross-sectional analytical study involving the clinical and laboratory medical records of pediatric patients diagnosed with DHF admitted at the pediatric ward and the Pediatric Intensive Care Unit (PICU) of Dr. Hasan Sadikin General Hospital, Bandung from January to December 2015. The diagnosis of DHF established by the

clinician in charge based on WHO criteria (Table 1).<sup>4</sup>

Data included in this study should have the diagnosis of DHF confirmed by a positive result in serologic tests (anti-dengue IgM/IgG) or detection of dengue virus antigen (NS1Ag test), and the first and second Hct measurement result. The diagnosis of DHF used in this study was the working diagnosis established by the clinician at the time the subject discharged from the hospital. Any reports in medical record data informing plasma leakage caused by other diseases or conditions, i.e. severe dehydration, burns, polycythemia vera, diabetic ketoacidosis, and lung emphysema excluded.<sup>6</sup>

The first and second measurement of Hct level obtained through serial Hct examination of each patient just after admission. The time between first to second Hct examination also recorded—the difference of Hct defined as  $\Delta Hct$ . A positive value in  $\Delta Hct$  indicated an increase in Hct confirming hemoconcentration and increased vascular permeability, while negative value indicated a decrease in Hct confirming convalescence in DHF.

Data analyzed for their correlation using SPSS version 20.0. Normally distributed data were presented as mean (standard deviation/SD), while non-normally distributed data presented as median (inter-quartile range/IQR). Spearman analysis test was used to analyze the correlation between  $\Delta Hct$  and severity of DHF.

This research has received a permit from the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran Bandung by ethics exemption letter number: 309/UN6.C.10/PN/2017.

**Table 1 WHO Classification of DHF Severity Grade**

Grades	Clinical Characteristics	Laboratory Findings
DHF I	Fever and hemorrhagic manifestation (positive tourniquet test) and evidence of plasma leakage (pleural effusion).	Thrombocytopenia <100.000/mm <sup>3</sup> and hemoconcentration $\geq 20\%$ .
DHF II	As in Grade <b>I plus</b> spontaneous bleeding.	Thrombocytopenia <100.000/mm <sup>3</sup> and hemoconcentration $\geq 20\%$ .
DHF III*	As in Grade <b>I or II plus</b> circulatory failure (weak pulse, narrow pulse pressure ( $\leq 20$ mmHg), hypotension, restlessness).	Thrombocytopenia <100.000/mm <sup>3</sup> and hemoconcentration $\geq 20\%$ .
DHF IV*	As in Grade <b>III plus</b> profound shock with undetectable blood pressure and pulse.	Thrombocytopenia <100.000/mm <sup>3</sup> and hemoconcentration $\geq 20\%$ .

\*DHF III and IV are dengue shock syndrome (DSS)

**Results**

Seventy reports of confirmed DHF diagnosis with different severity grades recorded (Table 2). In one year, the majority of subjects in Dr. Hasan Sadikin General Hospital had DHF III (31 subjects). The mean ages of pediatric patients diagnosed having DHF I until DHF IV were 6, 7, 7, and 5, respectively. The median ΔHct values of DHF I to DHF IV were -3, -1, -3, and 4, respectively. The mean time between the first and second Hct of DHF I and IV were 15 and 5.5

hours, respectively. The median time between the first and second Hct of DHF II and III were 11 and 5.5 hours, respectively.

Reports of positive and negative Δhct value were distributed in each DHF severity grade (Figure). Fourteen cases of DHF had positive ΔHct value which indicated hemoconcentration confirming deterioration in DHF, while fifty cases had negative ΔHct value which indicated a decrease in hct confirming convalescence in DHF. Hemoconcentration occurred particularly in DHF II and III. Decrease in hct mostly occurred

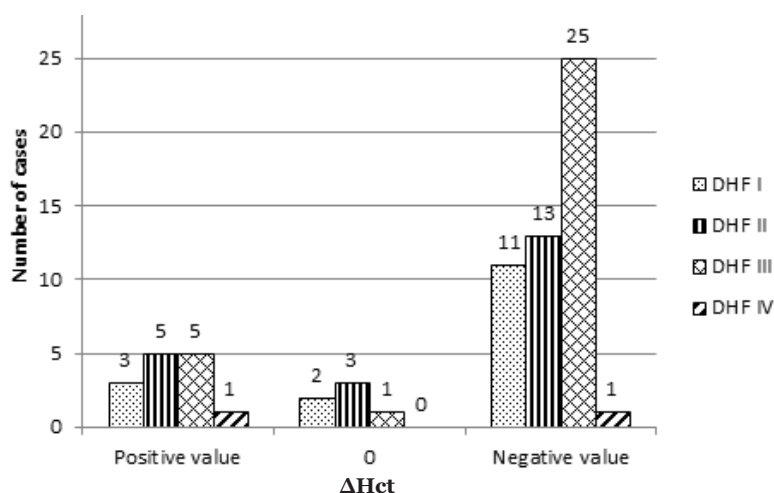
**Table 2 Distribution of Demography and ΔHct in Each DHF Severity Grade**

Variables	DHF I (n=16)	DHF II (n=21)	DHF III (n=31)	DHF IV (n=2)
Sex				
Male	6	10	12	1
Female	10	11	19	1
Age (year)	6 (3.5)*	7 (4)*	7 (3.5)*	5 (1.4)*
ΔHct	-3 (0-[-4.3])**	-1 (0-[-2])**	-3 ([-1]-[-6])**	4 (6.5-1.5)**
Time between first and second Hct (hour)	15 (6.0)*	11 (12.5-8)**	5.5 (8-4)**	5.5 (0.7)*

\*Data presented as mean (standard deviation/SD), \*\*data presented as median (inter-quartile range/IQR)

**Table 3 Correlation between Positive ΔHct Value and Severity of DHF**

	Severity of DHF		Confidence Interval (CI)
	Correlation Coefficient	p Value	
Positive ΔHct value	0.247	0.394	95%



**Figure Distribution of ΔHct Value in Each DHF Severity Grade**

in DHF III followed by DHF II and I. There was no significant correlation between positive  $\Delta$ Hct value (hemoconcentration) and severity of DHF since  $p > 0.05$  ( $r = 0.247$ ,  $p = 0.394$ ,  $CI = 95\%$ ) (Table 3).

## Discussion

Based on WHO report, Indonesia is included in the most endemic country for DHF because of its leading cause of hospitalization and death among children.<sup>4</sup> Plasma leakage that leads to shock is the leading cause of death in DHF patients.<sup>2</sup> The increased capillary permeability allows extravasation of plasma into pleural or abdominal cavity then the patient will undergo hypotension, and therefore lead it to shock and death.<sup>7</sup>

A standardized classification system for the severity of dengue virus infections is crucial for optimal communication of scientific data to improve our understanding of the pathogenesis and treatment of the disease. Incorrect disease severity classification may lead to faulty decision-making in choosing the most appropriate treatment for the individual patient.<sup>8</sup> Therefore, WHO recommended criteria for DHF diagnosis based on clinical characteristics and laboratory findings. Grading the severity of the disease has been found clinically and epidemiologically useful in DHF epidemics in children especially in Indonesia. These criteria classified DHF severity into four grades (DHF I to DHF IV).<sup>1</sup>

The percentage increase in Hct is an accurate indicator of vascular permeability and plasma leakage; thus, serial Hct examination is a laboratory parameter which need to include as part of dengue patient management.<sup>9-11</sup> Early recognition and appropriate management reduce mortality to  $< 1\%$ , but if left untreated may rise to as high as  $20\%$ .<sup>10</sup> Previous studies reported that hemoconcentration correlate with DHF severity.<sup>12,13</sup> This study aims to correlate the difference in first and second Hct level from serial Hct examination just after admission with DHF severity. If there is a significant correlation, it would be a predictor for the clinician to establish the severity of DHF and to treat the patients based on its severity as soon as possible.

This study showed that the majority of subjects had DHF III. This data is relevant since Dr. Hasan Sadikin General Hospital is the top referral hospital in West Java province, so there were more DHF severe cases admitted in this hospital

rather than non-serious cases. We noted that there was no statistically significant difference in gender among different DHF grades. The mean age range of pediatric patients with different DHF grades was 5–7 years. This data is relevant to the previous study that stated the maximum number of cases seen in the age group of 5–10 years.<sup>14</sup>

In this study, 50 cases of DHF had negative  $\Delta$ Hct value which confirmed the convalescence in DHF. This data is irrelevant with the natural course of DHF which stated that there should be deterioration in severity due to plasma leakage.<sup>1</sup> It is likely due to early fluid intervention that would have changed the natural course of the illness. It also reported in the previous study that in some cases the plasma leakage does not achieve a high degree hemoconcentration even if the patient is in shock.<sup>15</sup>

It also can be said that the hemoconcentration which is an indicator of plasma leakage did not occur in the first and second Hct of serial Hct examination. It is probably due to the lack of this study since we only collected the first and second Hct from serial Hct examination, of which the patient underwent this examination when he/she admitted to the hospital, not earlier when the patient got the symptoms for the first time. Therefore, the same study should be in primary health care facilities where the patients check their conditions for the first time they get the symptoms. Another limitation of this study includes a lack of clinical data such as bleeding, ascites, pleural effusion, and hepatomegaly that may potentially influence the predictors of plasma leakage.

The median  $\Delta$ Hct value in DHF III-diagnosed group was  $-3$ . This negative  $\Delta$ Hct value indicated a decrease in Hct confirming convalescence in DHF. While in DHF IV-diagnosed group, which were more severe cases, the median  $\Delta$ Hct value was  $4$ . This positive  $\Delta$ Hct value indicated hemoconcentration which is an indicator of plasma leakage in DHF if the value  $\geq 20\%$ . In this study, however, we found no significant correlation between positive  $\Delta$ Hct value (hemoconcentration) and DHF severity. This result is incompatible with the previous study that reported that hemoconcentration correlate with DHF severity.<sup>16</sup> The results probably due to the small sample size since we only found 14 cases with hemoconcentration from the total of 70 DHF cases in one year. The previous study showed that Bandung city was one of the hyperendemic

cities in West Java with fluctuated cases number especially in the year 2009, 2012, and 2013.<sup>18</sup> Our study result originated from DHF cases distributed in 2015, which is most likely to be the reason of small sample size. This notion provides evidence of compliance in DHF reporting system. Other than that, the increased capacity of health workers in detecting dengue symptoms and the availability of treatment in the primary health facilities would probably decrease the number of dengue hemorrhagic fever fatality rate. Besides, Dr. Hasan Sadikin General Hospital is a teaching hospital; thus, the clinician established the working diagnosis of the patient step by step and recorded in the medical record at the time the patient discharged from the hospital. Probably hemoconcentration had not been occurring when the clinician established the working diagnosis. The limitation of this study was since we used the variable of working diagnosis instead of initial diagnosis (at the time of admission). Besides, the grading of DHF severity has been noted to have limitations regarding its complexity and applicability, particularly in patients with severe symptoms.<sup>12,17</sup>

The time between first to second Hct examinations in each subject was different and had many variations from 3–24 hours. We noted that in Dr. Hasan Sadikin General Hospital, patients with DHF I and II had clinical signs that were not specific to DHF; thus, the patients were being less monitored and not adequately treated based on WHO guideline.<sup>4</sup> Meanwhile, patients with DHF III and IV had clinical signs that were specific to DHF; thus, the patients monitored and treated based on WHO guideline.

Considering the importance of close monitoring of patients with DHF, the difference in two serial hematocrit level measurements just after admission has no significant association with the disease severity; thus, it cannot be used to predict the severity of DHF. Therefore, serologic confirmation provides crucial consideration in the management for DHF patients.

## Conclusion

Hematocrit difference (first and second) from serial Hct examination just after admission has no significant association with the disease severity.

## Conflict of Interest

There was no conflict of interests declared.

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