

The Levels of Troponin T in Patients with Dengue Hemorrhagic Fever

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Abstract: Introduction: The incidence of myocarditis on Dengue Hemorrhagic Fever (DHF) is still controversial because the disease was asymptomatic and definitive diagnosis only with endocardial biopsy. More specific and sensitive examination to detect the cardiac disorder is cardiac enzyme likes the level of troponin T. Objective: This study aims to evaluate the level of troponin T in patients with dengue shock syndrome (DSS) and dengue hemorrhagic fever without shock. Methods: The research conducted a cross-sectional study at Child Health Department of Dr. Wahidin Sudirohusodo Hospital, Makassar, from July to October 2012. The population included children with DHF admitted to the hospital of Dr. Wahidin Sudirohusodo, Ibnu Sina and Faisal Islamic. Diagnosis of DHF was established based on history taking, physical and laboratory examination. Results: There were 70 samples who met the criteria, including 35 patients of DSS and 35 patients of dengue hemorrhagic fever without shock. The level of troponin T was higher on DSS group than DHF group with the cut off point of ≥ 0.007 ng/ml is the best level to distinguish between dengue shock syndrome and dengue hemorrhagic fever without shock ($p=0.000$, sensitivity 97.1%, specificity 88.6%, positive predictive value 89.5%, negative predictive value 96.9%, OR 18.7; 95% CI 15.3–1417.5). Conclusion: The level of troponin T was higher on DSS group than dengue hemorrhagic fever without shock group because on DSS occurs to stress caused by hypoperfusion. But the level of troponin T between two groups within normal limits, not found cardiac disorder such as myocarditis on DHF.

Keywords: Troponin T Levels, Dengue Hemorrhagic Fever, Children

1. Introduction

Dengue virus infection has a variable clinical manifestation, from its mildest form, dengue fever, dengue hemorrhagic fever (DHF) and dengue with shock (dengue shock syndrome (DSS)).¹⁻⁵ Although shock in DSS is thought to be caused by the decreased of intravascular volume due to plasma leakage to interstitial, some new studies reported that shock might be caused by heart disease.⁶

Pathomechanism of cardiac abnormalities in DHF is not fully understand yet, but it might occurred due to hypoperfusion, direct invasion to heart muscle, or because of cytokine produced by immunological response.⁷ In general, cytokine, especially tumor necrosis factor- α (TNF- α) and interleukin-1 lead to increased vascular permeability and shock. TNF- α and interleukin also depressed myocard function.⁸⁻¹⁰

Several studies reported the presence of cardiac

abnormalities in dengue patients.¹¹ A study carried out in New Delhi reported that in children with dengue infection who underwent echocardiography, 16.7% had left ventricular dysfunction.⁶ Cardiac abnormalities in DHF is mild and temporarily, yet potentially deadly.^{12, 13} Cardiac manifestations often reported in DHF are relative bradycardia, myocardial dysfunction, myocarditis, and cardiac conduction disorders.¹⁴⁻¹⁸ Cardiac abnormalities in DHF patients can be predicted from clinical manifestations, electrocardiography test (ECG), echocardiography and cardiac enzyme tests, such as Creatinin Kinase (CK), Isoenzim MB from CK (CK-MB), Laktat Dehidrogenase (LDH) and troponin T (TnT) within circulation.^{19, 20} Of all the tests above, the more specific and sensitive examination for myocardium abnormalities is troponin T because troponin T is a regulator protein acted in myocardial contraction.^{21, 22, 23} Troponin T will be released into the circulation if there are any myocardial damage, thus troponin T represents myocardial damage.^{21, 24} If the diagnosis is not promptly made, the damage can progress into severe

dysfunction and lead to death. Thus it is important to assess troponin T levels in DHF patients.

Research on the cardiac abnormalities in DHF through troponin T level is still showing a controversial result. Study by Gupta V K *et al.* in New Delhi reported that 42.8% DHF patients had positive troponin T serum, while Supachokchaiwattana *et al.* in Thailand observed that there was no troponin T detected in dengue fever, DHF nor DSS patients.^{6,7} Based on this controversy, more research is needed to be conducted to examine troponin levels in DHF patients, especially in South Sulawesi.

2. Materials and Methods

This study was conducted from July to October 2012 in pediatric ward of several hospitals, such as Dr. Wahidin Sudirohusodo, Ibnu Sina and Faisal Islamic on dengue hemorrhagic fever (DHF) patients. It was a cross sectional study.

Population was all patients who were hospitalized with DHF based on WHO 1997 criteria and were confirmed by serological ELISA test. Patients were divided clinically based on the severity of the disease into 4 categories: I, II, III and IV based on WHO 1997 criteria. Furthermore the sample was then grouped into two, which were DHF (consists of grade I and II dengue) and DSS (grade III and IV dengue). There were 70 DHF patients met the inclusion criteria, which were DHF patient, age 1 to 15 years old, and agree to participate as study sample (the parents agreed to participate and signed an

informed consent), and the exclusion criteria were: infected by other virus or bacteria based on clinical examination and laboratory tests, DHF patient with history of previous heart disease, suffered from other muscle disease. Samples were grouped into 35 DHF patients and 35 DSS patients.

All patients who met the inclusion were recorded for name, age, sex, and nutritional status, vital sign (temperature, pulse, blood pressure, and respiratory rate) also fever duration. Afterward, the patients were divided into DSS and DHF group and blood sample were obtained from each patients for troponin T level examination. This study was approved by Ethics and Industry Research Committee of the hospital and Hasanuddin University.

Data were processed using SPSS 15. To evaluate relationship between sex and nutritional status of the diagnosis group (DHF and DSS), we used χ^2 (Chi square) test, while to find mean value for age, fever duration, temperature, and troponin T level of the diagnosis group (DHF and DSS) we performed Mann-Whitney test. There were three significant variables; body temperature, fever duration, and troponin T level in DHF patients. These results then continued to multivariate analyses. Furthermore, we took a cut off point in which troponin T is at its most optimal value in separating DHF and DSS. We also calculate p value, odds ratio (OR), sensitivity, specificity, positive predictive value, and negative predictive value.

3. Results

Table 1. Study characteristics.

Characteristics	Dengue Diagnosis Group		P
	DHF n (%)	DSS n (%)	
Sex			
Male	21 (30)	20 (28.6)	0.808
Female	14 (20)	15 (21.4)	
Body Mass Index			
Overweight	1 (1.4)	2 (2.9)	0.586
Well nourish	14 (20)	17 (24.3)	
Under nourished	20 (28.6)	16 (22.9)	
Age (years)			
Maximum	12.75	14.16	0.418
Minimum	1.08	1.08	
Mean	7.38	7.01	
Median	8.16	5.67	
Temperature (°C)			
Maximum	39.2	36.6	0.000
Minimum	37.8	36.3	
Mea	38.40	36.46	
Median	38.40	36.50	
Fever duration (days)			
Maximum	6	6	0.000
Minimum	4	5	
Mean	4.54	5.26	
Median	4.00	5.00	
Troponin T (ng/ml)			
Maximum	0.008	0.066	0.000
Minimum	0.003	0.006	
Mean	0.004	0.018	
Median	0.004	0.011	

DHF: dengue hemorrhagic fever, DSS: dengue shock syndrome

Table 1 displayed the samples characteristics. Total sample was 70 patients, 41 (58.6%) were male and 29 (41.4%) are female. From DSS group, 20 patients (28.6%) were male and 15 (21.4%) were female. Based on the BMI (body mass index), 3 (4.3%) patients were overweight, 31 (44.3%) were well nourish, and 36 (51.4%) under nourished. In DSS patients, there were 2 (2.9%) overweight patients, 17 (24.3%) well nourish, and 16 (22.9%) under nourished. The age range in this study was 1.08 – 14.16. Age range in DSS group was 1.08 – 14.16, mean 7.01, median 5.67 and standard deviation 3.96. In DHF group, the age range was 1.08 – 12.75, mean 7.38, median 8.16 and standard deviation 3.70, while the body temperature range from 36.3°C to 39.2°C. In DSS group it range from 36.3 – 36.6, mean 36.46, median 36.50 and standard deviation 0.08. In DHF group the range was between

37.8 to 39.2, mean 38.40, median 38.40, and standard deviation 0.35, while the fever duration range from 4 – 6 days. In DSS group, the duration range from 5 – 6, mean 5.26, median 5.00, and standard deviation 0.443. In DHF group, it ranges from 4 – 6, mean 4.54, median 4.00, and standard deviation 0.611. The Troponin T level (ng/ml) in this study is range from 0.003 – 0.066. In DSS group it range is 0.006 – 0.066, mean 0.018, median 0.011 and standard deviation 0.015. In DHF it was 0.003 – 0.008, mean 0.004, median 0.004, and standard deviation 0.002.

Table 2 showed sensitivity, specificity, positive predictive value and negative predictive value on each cut off point of troponin T level in DHF group. Cut off point troponin T ≥ 0.007 ng/ml as diagnostic for shock had 97.1% sensitivity and 88.6% specificity, PPV 89.5% and NPV 96.9%.

Table 2. Sensitivity, specificity, positive predictive value and negative predictive value of each cut off point of troponin T level.

Troponin T levels	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (%)	P
0.005	97.1	60	70.8	95.5	0.814	0.000
0.006	100	74.3	79.5	100	0.871	0.000
0.007	97.1	88.6	89.5	96.9	0.929	0.000
0.008	88.6	94.2	93.9	89.1	0.914	0.000
0.009	71.4	100	100	77.8	0.857	0.000
0.010	60	100	100	71.4	0.800	0.000
0.011	60	100	100	71.4	0.800	0.000
0.012	48	100	100	66	0.743	0.000
0.013	45.7	100	100	64.8	0.729	0.000

PPV: positive predictive value, NPV: negative predictive value

Table 3 showed multivariate analyses troponin T level on both group (DHF and DSS). Troponin T ≥ 0.007 ng/ml had

greater risk of 18.7 times more likely to progress into shock, with $p = 0.000$ and IC 95% 15.3 – 1417.5.

Table 3. Multivariate analyses correlation variable on dengue diagnosis group.

No.	Variable	B	S.E	df	Sig	Wald	95%CI
1.	Troponin T	4.992	1.155	1	0.000	18.67	15.3 – 1417.5
2.	Temperature	19.65	10377.780	1	0.998	0.000	

B: Regression Coefficient, SE: Standard error

4. Discussion

This study showed that troponin T level is higher in DSS compared to DHF patients. Analyses were performed on sex, age, body mass index, temperature and DHF group to troponin T level. The comparison of sex to both diagnostic group did not show any significant differences, with $p = 0.808$ ($p > 0.05$). This means that sex has no influence on both groups. This is because there is no difference in cytokine production neither in male nor in female. No significant differences between DHF and DSS group means that sex does not contribute any bias to analyses of troponin T between DSS and DHF group.⁶

The body mass index in this study was divided into overweight, well nourishes and under nourished. The incidence of shock in overweight patient was higher (66.7%) than in well nourish (54.8%) and under nourished (44.4%)

patients. But, from statistical analyses on BMI to diagnosis group there were no significant differences were observed with $p = 0.586$ ($p > 0.05$), which means, overweight, well nourish and under nourished, all are had the same immune response to dengue virus which triggered the production of TNF- α followed by expression of adhesion molecule (ICAM-1, VCAM-1, selectin, integrin) and causing the increased vascular permeability and plasma leakage on dengue patients. There were no malnourished patients in this study. This is thought to be caused by the strong relation between immunological response and dengue infection, and in malnourished patients, the immune response is compromised.^{6, 7, 8, 9} BMI will not contribute any bias in the analyses of troponin T level on diagnostic group because no significant differences were found in both group regarding the status.

In this study, there were no significant difference in correlation between age on both diagnostic group, with $p =$

0.418 which means that age has no influence on both diagnostic group, so we can conclude that age will not become a bias in analyzing troponin T level.

Mean body temperature in sample showed that there were significant difference between DHF and DSS, with $p = 0.000$ ($p < 0.01$). This is because in shock, or in DSS group, body temperature decreased, and hypothermia often occurred as the result of hypoperfusion. After multivariate analyses was performed, it appeared that body temperature was insignificant in diagnosis dengue group, with $p = 0.998$. Therefore we can conclude that temperature didn't contribute any bias in level troponin T analyses between DHF and DSS group.

Mean fever duration in this study showed a very significant differences between DHF and DSS group, with $p = 0.000$ ($p < 0.01$). This is because shock is also induced by the release of inflammatory mediator in large amount which occurred in day 5 or more. After multivariate analyses, the role of fever is no longer prominent; this means fever didn't cause bias in troponin T analyses in group DSS and DHF.^{12, 13, 14}

From the results above, in this study, either sex, BMI, age, body temperature and fever duration did not contribute any bias in troponin T level analyses for dengue group.

Mean troponin T in DSS group was higher compared to DHF group. In DSS mean level is 0.018 ng/ml and in DHF 0.005 ng/ml. The mean statistical analyses of troponin T in both group has $p = 0.000$ ($p < 0.01$). It is concluded that there were significant differences between DSS and DHF group. This is because in DSS, inflammatory mediator release is greater than in DHF. Dengue virus infection and hypoxia in shock also induce inflammatory mediator release. The release of TNF- α in such a large amount could cause decrease in blood pressure or shock and hypoperfusion.²² In hypoperfusion, troponin T cytosol will be release about 6-8%. In hypoperfusion, the loss of cell membrane integrity will occur, and this will release free troponin T. If shock was treated, and hypoperfusion no longer occur, membrane cell back to normal and so the troponin T will still be within normal limit.²³ Of 70 DHF patients participated in this study, all were discharged and fully recovered.

When hypoperfusion was severe and prolonged, the cell then lysis and cell membrane broke and lactate intracell increased due to glycolysis thus decreased in PH occurred, followed by the release and activation of lysosom proteolytic enzymes further cause intracellular structure disintegration and troponin complex degradation. This event induces increased troponin T (more than normal) in the circulation as a result of massive release of troponin T.

Although there are significant difference of troponin T between DHF group and DSS group, the level in both group are still within normal limit (< 0.1 ng/ml.). Therefore we determined cut off point for troponin T.

Highest cut off point in 95th percentile for troponin T in DHF is 0.005 ng/ml and the lowest in 5th percentile for troponin T in DSS is 0.013, then the ROC graph showed that the value of area under the curve (AUC) is at its greatest 0.007 ng/dl with 97.1% sensitivity and 88.6% specificity,

PPV 89.5% and NPV 96.9%. Troponin T limit ≥ 0.007 ng/ml had $p = 0.000$ ($p < 0.01$). A 97.1% sensitivity means that troponin T ≥ 0.007 ng/ml is able to detect 97.1% shock, and 88.6% specificity means troponin T < 0.007 ng/ml could detect 88.6% are not shock. PPV of 89.5% means troponin T ≥ 0.007 ng/dl then the probability of shock is 89.5% and NPV 96.9% means that if troponin T < 0.007 ng/ml then the probability for not having shock is 96.9%.

In multivariate analyses, troponin T ≥ 0.007 ng/ml in DSS had $p = 0.000$ ($p < 0.01$), Odds Ratio (OR) 18.7; 95% CI (15.3 – 1417.5), which means troponin T ≥ 0.007 ng/ml had the risk is 18.7 times more likely to have shock in DHF patient.

This result is similar with a study in 2005 conducted by Supachokchaiwattana P. et al in Thailand which observed that troponin T level in 10 DHF patients (2 are dengue fever, 6 are DHF and 2 are DSS) were still in normal limit.⁷

Based on this study, it is concluded that troponin T level in DSS is higher than in DHF, yet, the troponin T level in both group is still within normal limit. Cut off point of troponin T ≥ 0.007 ng/ml is the best point to predict the occurrence of shock, with 97.1% sensitivity and 88.6% specificity, PPV 89.5%, and NPV 96.9 with OR 18.7; 95% CI (15.3 – 1417.5).

From this study, further study using a better method (cohort) is required to see troponin T level in dengue patient before and after shock, and the more complex scope of dengue grade (dengue grade I – IV) so it is possible to get a higher level of troponin T and the strong correlation between dengue grade and troponin T.

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