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## Research Article

### Correlation Analysis between Ratio of C-Reactive Protein/Albumin and Severity of Dengue Hemorrhagic Fever in Children

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#### ABSTRACT

Dengue Hemorrhagic Fever (DHF) is a dengue infection which can cause shock and leads to mortality. Hypoalbuminemia is a marker of plasma leakage in DHF and correlated with severity of inflammatory response triggered by infection, including DHF. C-Reactive Protein (CRP) is a proinflammatory marker that also increases in DHF. This study aims to determine a correlation of CRP/albumin ratio with severity of DHF. Cross sectional study on pediatric patients diagnosed as DHF at Saiful Anwar Malang Hospital was done in July-December 2016. CRP levels were examined using immunoturbidimetry method, while albumin was examined by using Bromocresol Green (BCG) method. Correlation of CRP/albumin ratio with DHF severity was analyzed by using Pearson correlation test. The result showed that there were significant differences in CRP levels and CRP/albumin ratios in the Dengue Shock Syndrome (DSS) and non-DSS group ( $p = 0.002$ ,  $p = 0.001$ ,  $\alpha < 0.05$ ). There was no significant difference in albumin level in the same group ( $p = 0.207$ ,  $\alpha < 0.05$ ). Positive correlation found in CRP and CRP/albumin ratio ( $r = 0.46$ ,  $r = 0.49$ ,  $\alpha < 0.01$ ). On the contrary the negative correlation was found in albumin ( $r = -0.21$ ,  $\alpha < 0.01$ ). This is presumably because albumin is an acute phase protein which will decrease along with the severity of infection. In contrast, CRP will increase during the critical phase of infection. It can be concluded that the CRP/albumin ratio was positively correlated with DHF severity, as well as CRP levels, but not positively correlated with albumin.

**Keywords:** Dengue Hemorrhagic Fever; Dengue Shock Syndrome; Severity; CRP/Albumin Ratio; CRP

#### ABSTRAK

Demam Berdarah Dengue (DBD) merupakan Infeksi Virus Dengue (IVD) yang dapat menyebabkan syok dan berakhir dengan kematian. Hipoalbuminemia merupakan salah satu penanda kebocoran plasma pada DBD sekaligus berkorelasi dengan intensitas respon inflamasi yang dipicu oleh infeksi, termasuk DBD. CRP juga merupakan marker inflamasi yang juga meningkat pada DBD. Penelitian ini bertujuan untuk mengetahui apakah rasio CRP/Albumin berkorelasi dengan keparahan pada DBD. Penelitian cross sectional pada pasien anak dengan diagnosis DBD dilakukan di RS Saiful Anwar Malang pada Juli-Desember 2016. Kadar CRP diperiksa menggunakan metode imunoturbidimetri, sedangkan kadar Albumin diperiksa menggunakan metode Brom Cresol Green (BCG). Korelasi Rasio CRP/albumin dengan keparahan DBD dianalisis menggunakan uji korelasi Pearson. Hasil penelitian menunjukkan terdapat perbedaan kadar CRP dan Rasio CRP/Albumin yang bermakna pada kelompok Dengue Syok Syndrome (DSS) dan non DSS ( $p = 0.002$ ,  $p = 0.001$ ,  $\alpha < 0.05$ ). Tidak didapatkan perbedaan kadar albumin yang bermakna pada kelompok yang sama ( $p = 0.207$ ,  $\alpha < 0.05$ ). Korelasi positif sedang ditunjukkan oleh CRP dan Rasio CRP/Albumin ( $r = 0.46$ ,  $r = 0.49$ ,  $\alpha < 0.01$ ). Sebaliknya korelasi negatif didapatkan pada albumin ( $r = -0.21$ ,  $\alpha < 0.01$ ). Hal ini diduga karena albumin merupakan protein fase akut yang akan turun seiring dengan beratnya infeksi. Sebaliknya, CRP akan meningkat selama fase kritis. Dapat disimpulkan

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*bahwa rasio CRP/Albumin berkorelasi positif sedang dengan keparahan DBD, demikian pula dengan kadar CRP, namun tidak berkorelasi positif dengan albumin.*

**Kata kunci:** Demam berdarah Dengue; Sindrom Syok Dengue; Keparahannya; rasio CRP/ albumin; CRP

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## INTRODUCTION

Dengue virus (DENV; family of Flaviviridae, genus Flavivirus) is transmitted by *Aedes aegypti* mosquitoes and can cause relatively mild Dengue fever (Dengue Fever-DF); or more severe form of dengue (Dengue Hemorrhagic Fever-DHF).<sup>1, 2</sup> Severe organ damage does not occur much but if it occurs, it can cause mortality because it is slowly detected. Severe organ damage is one of the leading causes of mortality besides shock.<sup>3-6</sup> Therefore, it needs a marker which can predict organ damage.

Considering the clinical manifestations of dengue infection which vary from mild to severe and the result is difficult to predict, a predictor biomarker is needed to act as an early warning sign.<sup>7-12</sup> Suwanto in his study in 2016 has developed dengue scores to predict pleural effusion and/or ascites in adults in dengue infection. The study showed that hemoconcentration was  $\geq 15.1\%$ , albumin concentration in the critical phase was  $\leq 3.49\text{g/dL}$ , platelet count was  $\leq 49,500/\mu\text{L}$ , and high AST ratio was  $\geq 2.5$  had sensitivity and specificity above 60%.<sup>4, 5, 13</sup>

Another reliable biomarker when critical is C-reactive protein (CRP). CRP is an acute phase protein produced by hepatocytes, especially under IL-6 control which has been proven as a sensitive prognostic indicator of inflammation.<sup>14, 15</sup> Ranzani in his study (2013) on CRP shows that CRP can be used as a diagnostic tool for sepsis and for therapeutic monitoring. The measurement of CRP level can also help clinicians in making decisions whether patients need an ICU or not.<sup>16</sup> Grandner (2010) has shown that CRP level correlates with the level of inflammation at the beginning of the diseases course. Although some studies have shown that CRP level when exiting from ICU can

be a reliable marker in monitoring but no studies have focused on dengue patients.<sup>17</sup>

Not only for CRP, but serum albumin can also be an important short- and long-term marker in determining prognosis. Serum albumin is a negative acute phase protein, thus the level of hypoalbuminemia in critically ill patients correlates with the intensity of the inflammatory response triggered by infection. Therefore, CRP and serum albumin level must be inversely proportional during the critical phase. The use of CRP and albumin ratio will provide a variable which is able to combine information provided by CRP and albumin. Therefore, it can be an index which has a positive correlation with infection, a higher ratio indicates a higher inflammatory status. CRP/albumin ratio has been widely investigated in cases of malignancy. One of Liu's studies in 2015 showed that AUC was 0.625,  $p < 0.001$ , for the role of the CRP/albumin ratio as an independent prognostic marker in the preoperative of gastric cancer circumstance. The study underlines that the CRP/albumin ratio not only reflects inflammation but also the nutritional status of cancer patients.<sup>16</sup>

Based on the research background, infection is one of the strongest triggers for inflammation, we hypothesized that CRP and albumin level would be important markers of dengue severity. In addition, we also investigated whether the combination of information from CRP and albumin through the CRP/albumin ratio would improve the quality of the prognostic marker of dengue severity when compared to CRP or albumin only.

## MATERIALS AND METHODS

This study was retrospective and was conducted on all pediatric patients with a diagnosis of DHF

who were treated in the Pediatric Ward of Saiful Anwar Malang Hospital during July-December 2016. The data were obtained from medical records then the data were carried out descriptive analysis. The population of the study subjects was divided into two groups of dengue severity: dengue shock (DHF grade 3,4) and dengue non-shock (DHF grade 1,2).

The inclusion criteria in this study were DHF pediatric patients who were hospitalized with positive NS-1 laboratory results and/or IgM anti dengue immunoserology test and/or positive IgG and examined serum albumin and CRP on the same day during treatment. Another inclusion criteria is the patients who diagnosed DHF and were <18 years old. The diagnosis of DHF was based on WHO 2011 criteria. The patients who were willing to be included in this study signed informed consents. While the exclusion criteria were the subjects who suffered from another infection which could produce false positives on immunoserology dengue examination (e.g., malaria, typhoid fever). To provide sufficient power in cross sectional study, at least 32 children were needed according to the sample size formula:

$$N = \frac{Z\alpha + Z\beta}{0.5 \ln [(1+r)/(1-r)]}^2 + 3$$

$$N = \frac{1.64 + 1.28}{0.5 \ln [(1+0.5)/(1-0.5)]}^2 + 3$$

= 32 sampel

Patients who became the sample were patients who came to the Child Polyclinic and Emergency Room of Dr. Saiful Anwar Malang General Hospital, fulfilled the inclusion and exclusion criteria for clinical and laboratory examinations. The sample's inclusion and exclusion criteria were determined by history, physical examination, completely blood laboratory examination, clinical chemistry, and immunoserology. Patients' serum were collected in laboratory and then stored at -80°C. When samples collection is completed, all serum were tested CRP and albumin.

This study was approved by the local medical ethical committee with ethical clearance number 400/196/K/3/302/2017.

The data analysis consists of several tests. Shapiro-Wilk test was used to see the data normality. Mann Whitney T-test was used to see the mean differences in the two groups. Pearson test was used to determine the relationship of CRP, albumin, and CRP/albumin ratio with the severity degree of dengue infection/prognosis. ROC curve was used to see the performance of CRP single marker, albumin, and combined marker of CRP/albumin ratio.

## RESULTS

### Characteristics of Subjects

Thirty-nine pediatric patients infected with dengue virus were included in this study consist of 17 samples dengue non-shock and 22 samples dengue shock (Table I, II, III). All patients were tested albumin and CRP.

**Table I.** Characteristic of Subject Based on Age

Patients' age	Prognosis		Total
	Dengue without shock	Dengue with shock	
0-1 year	5	5	10
1-5 years old	5	6	11
5-10 years	5	8	13
11-15 years old	2	3	5
15-18 years old	-	-	-
Total	17	22	39

**Table II.** Characteristic of Subject Based on Gender

Gender	Prognosis		Total
	Dengue without shock	Dengue with shock	
Male	11	5	16
Female	6	17	23
Total	17	22	39

**Table III.** Characteristic of Subject Based on Nutritional Status

Nutritional Status (Z-score BB/TB)	Prognosis		Total
	Dengue without shock	Dengue with shock	
Very Thin (<-3SD)	1	0	1
Thin (-3SD to <-2SD)	0	3	3
Normal -2 SD to 2 SD	15	17	32
Fat > 2 SD	1	2	3
Total	17	22	39

**Data Analysis**

The normality test showed the distribution of abnormal data for age, gender, and nutritional status. The results of the post-transformation normality test data also showed the data distribution which was not normal so that the different test analysis used Mann-Whitney. The results of different test showed that there were significant differences in gender data in the shock and non-shock groups (Table IV).

**Table IV.** Difference Tests Based on Age, Gender, Nutritional Status in Shock and Non-Shock Groups (95% Confidence Interval)

Different Test	Normality test	p
Based on Age ( <i>Mann Whitney</i> )	0.004	0.136
Based on Gender ( <i>Mann Whitney</i> )	0,000	0.009
Based on Nutritional Status ( <i>Mann Whitney</i> )	0,000	0.470
CRP ( <i>T-Test</i> )	0.164	0.002
Albumin ( <i>t-Test</i> )	0.653	0.207
CRP/Albumin Ratio ( <i>t-Test</i> )	0.149	0.001

Based on the normality test it was obtained the distribution of normal data for albumin (0.653), but there is an abnormal distribution of data (<0.05) for CRP and CRP/albumin level data, so that transformation needed to be done. The Shapiro-Wilk Normality Test showed the distribution of post-transformation normal data which 0.164 for CRP and 0.149 for CRP/albumin Ratio were so that data analysis could be continued using parametric tests. The results

of different marker tests showed only CRP level which showed significant difference in the shock and non-shock groups (Table IV).

The correlation tests showed positive correlations for CRP and CRP/Albumin level, but there was a negative correlation for albumin level (Table V).

**Table V.** Pearson Correlation Test, with 99% Confidence Interval

Pearson Correlation Tests	r	p
Dengue Group and CRP Level	0.46	0.003
Dengue Group and Albumin Level	-0.21	0.199
Dengue Group and CRP/Albumin Ratio	0.49	0.002

Furthermore, the data analysis was performed with receiver operating characteristic (ROC) curve, AUC (Area Under the Curve) to see the performance of markers (Table VI, Table VII, Table VIII, Table IX, and Figure 1).

**Table VI.** Area Under the Curve

Test variable	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower limit	Upper limit
CRP	0.218	0.075	0.003	0.071	0.365
Albumin	0.616	0.092	0.218	0.435	0.797
CRP/Albumin Ratio	0.203	0.072	0.002	0.061	0.345

**Table VII.** CRP Prognostic Test

	Shock	Non-Shock	Total
> 0.5 mg/dL	15	5	20
≤ 0.5 mg/dL	7	12	19
Total:	22	17	39
Sensitivity:	68.18%		
Specificity:	70.59%		
PPV (Positive Predictive Value):	75%		
NPV (Negative Predictive Value):	63.16%		
RR (Relative Risk):	2.02		

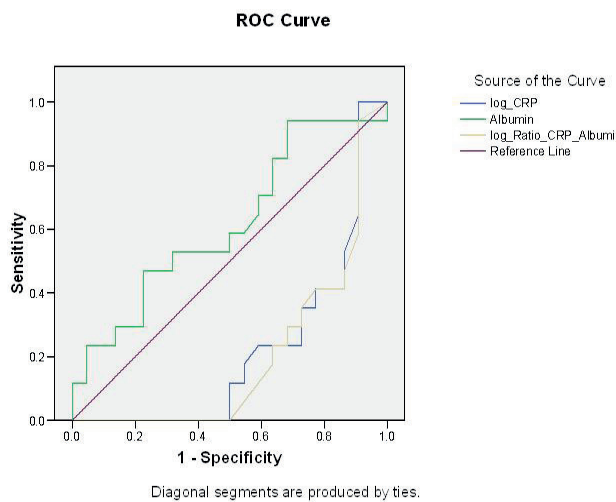


**Table VIII.** Albumin Prognostic Test

	Shock	Non-Shock	total
≤ 2.7 mg/dL	5	0	5
> 2.7 mg/dL	17	17	34
Total:	22	17	39
Sensitivity:	22.73%		
Specificity:	100%		
PPV (Positive Predictive Value):	100%		
NPV (Negative Predictive Value):	50%		
RR (Relative Risk):	2		

**Table IX.** Prognostic Test for CRP/Albumin Ratio

	Shock	Non-Shock	total
≥ 0.2	14	5	19
<0.2	8	12	20
Total:	22	17	39
Sensitivity:	63.64%		
Specificity:	70.59%		
PPV (Positive Predictive Value):	73.68%		
NPV (Negative Predictive Value):	60%		
RR (Relative Risk):	1.83		



**Figure 1.** ROC Curve of Prognostic Test of CRP, Albumin, CRP/Albumin Ratio against Severity Degree of Dengue Infection

**DISCUSSION**

In the baseline data, there were significant differences in different tests based on gender. In this case the female patients were significantly (n=17)

more than male patients (n=5) in the dengue group with shock. This is not the same as Lovera’s study in 2016 which found that there was no gender preference in severe dengue manifestation.<sup>18</sup> Also this is not the same as Anker’s study in 2011 in which his study looked at the incidence of dengue infection in children in Asia, the data showed that the number of male cases was significant in the age ≥ 15 years group. This difference based on gender was indeed not supported by specific pathophysiological mechanisms. The difference possibility related to gender in dengue fever was due to difference in exposure in the adolescent age group. The results of this study in Asia were different from those in South America, where there was a similar proportion of male and female patients in dengue fever cases or conversely the proportion of female cases were greater. The reason for this difference of incidence based on gender needs to be explored further.<sup>19</sup>

Furthermore, there were no significant difference based on age and nutritional status. Although most of the samples were form age 5 – 10 year old group which is similar to Lam et al. study.<sup>20</sup> Our nutritional status was analyzed by Z-score: weight/height (BB/TB). Based on previous studies, moderate/severe malnutrition was associated with a significant reduction in cell-mediated immunity, as indicated by a reduction in the number of CD4<sup>+</sup>T cells, and a decrease in the CD4<sup>+</sup>/CD8<sup>+</sup> ratio. There was also a decrease in secretory IgA antibody production and various component supplements (C3, C4, and factor B) and decreased phagocytosis. The production of certain cytokines such as IL-2 and TNF also decreases.<sup>21</sup> The study done by Kalayanarooj in 2005 study concluded that malnourished children had a lower risk of dengue infection, but if they were infected with dengue they had a high risk of DSS. Obese children had a higher risk of contracting dengue fever with a more unusual presentation; encephalopathy, related infections and complications of excess fluid.<sup>22</sup> Widiyati’s study mentioned that obesity is not a risk factor for children with dengue infection to get DSS.<sup>23</sup>

Furthermore, in this study there was no significant difference in the different albumin tests (unpaired T test) 0.207, whereas for CRP

and CRP/Albumin ratios there were significant differences, 0.002, 0.001 respectively.

Albumin synthesis experienced significant changes in the critical phase. As acute responses to trauma, inflammation, and sepsis, it would improve the transcription process of acute phase proteins such as CRP and would reduce transcription of albumin mRNA and albumin synthesis. Both IL-6 and TNF- $\alpha$  could reduce gene transcription. Based on Liao's study in 1986, the induction of inflammation in mice was done to see changes in albumin levels. The study showed the lowest albumin levels were obtained at 36 hours and then rose again. A sustained inflammatory response in critical illness could result in a long barrier to albumin synthesis as well.<sup>24</sup>

The Fairclough's study in 2009 mentions low albumin levels were most often associated with chronic diseases, also often associated with malnutrition.<sup>25</sup> Napoleon-Tatura et al. found that low albumin levels can help predict shock in pediatric dengue.<sup>26</sup> This study included an acute case study so that not all critical patients showed a decrease in serum albumin during treatment. Fever days when samples taken, and nutritional status also varied so that the results obtained did not match the theory.

Based on the Pearson correlation test, the same correlation was found between the relationship between CRP ( $r = 0.46$ ) and CRP/Albumin Ratio with the friction of Dengue infection ( $r = 0.49$ ). This means there was a weak relationship. In accordance with the Liao's in 1986 that the day when sampling taken was very influential, and in the study indeed the data of the sampling taken was not homogeneous.<sup>24</sup>

While the correlation of the relationship between albumin and severity of dengue infection was  $r = -0.21$ . It is according to the theory that albumin is an acute phase protein that will decrease along with the severity of infection/inflammation. But in this study a weak correlation was also found for albumin. Based on Fairclough's study in 2009, nutritional status was very influential on albumin levels, while the nutritional status in this study was not homogeneous either.<sup>25</sup>

Based on the prognostic test, the results were almost the same, both the sensitivity and specificity between CRP and CRP/albumin ratio were 68% and 70% respectively for CRP performance; and 63% and 70% for CRP/albumin performance ratio. CRP was at the cut off  $> 0.5\text{mg/dL}$  and the CRP/albumin ratio was at the cut off  $> 0.2$ . The CRP and CRP/albumin ratio had similar AUC (0.218; 0.203) with  $p < 0.05$ , whereas AUC albumin was not significant.

Menon's study in 2005 using cut-off CRP  $> 3 \text{ mg/L}$  could be an independent marker of mortality risk factor in cardiovascular disease. The previous study on CRP/Albumin ratio used quite varied cut-offs.<sup>27</sup> Wei's study in 2015 used cut-off  $> 0.095$  which was associated with the size of esophageal tumor (squamous cell carcinoma).<sup>28</sup> While Xie's study in 2011 used cut-off  $> 0.42$  this was associated with mortality in AKI patients.<sup>29</sup> Liu et al found that patients with pancreatic cancer that have CRP/albumin ratio  $\geq 0.18$  have worse prognosis than those with CRP/albumin ratio  $< 0.18$ .<sup>30</sup> Based on this study both CRP and CRP/albumin ratio were as good at predicting the severity of dengue infection.

Whereas serum albumin of cut-off  $< 2.7\text{mg/dL}$  showed a low sensitivity of 22%, so it could not be used as a single marker of initial screening predictor of dengue infection severity. However, for the cut off, serum albumin had a specificity of 100% which could specifically direct the severity that occurs in patients with dengue infection.

Based on this study the best relative risk (RR) was in CRP (RR = 2.02) and albumin markers (RR = 2), in which the values were almost the same, followed by CRP/albumin ratio (RR = 1.83). However, all markers had a value of RR  $> 1$  so that they could be used to see the probability of dengue prognosis.

From ROC curve, only albumin that has good performance with AUC 0.616 and  $p = 0.218$ , while CRP and CRP/albumin ratio has AUC = 0.218 and AUC = 0.203 with  $p = 0.003$  and  $p = 0.002$  respectively (Figure 1).

This study had limitations that must be considered. This study was conducted on patients without comorbidity, the sampling done on the varied fever days, the nutritional status was not

homogeneous. It was better if it was tested in populations with comorbidities, especially in people with comorbidities having potential to affect the levels/concentrations of predictive variables, such as kidney disease and liver disease. It was also best to do homogenization of sampling days and nutritional status.

## CONCLUSION

Both CRP and CRP/albumin ratio are independent prognostic markers of the severity of dengue infection. The use of this ratio is easy, inexpensive, and has sufficient availability, so it is very helpful for clinicians to identify high-risk dengue patients. Single serum albumin cannot be used as a screening marker for the severity of dengue infection.

Further studies to predict the severity of dengue infection should include a population with comorbid kidney disease and liver disease, and collect more samples, including the participation of adult patients. Hopefully the best predictor markers can be found.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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