SUPAR as a Predictive Biomarker for Severe Dengue Infection in Hospitalized Children: A Diagnostic Laboratory Approach

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KEYWORDS
suPAR, pediatric, biomarker, disease severity, diagnostic laboratory, severe Dengue

ABSTRACT

Background: Dengue infection remains a major public health issue in Indonesia, particularly affecting children who are more vulnerable to severe outcomes. Identifying reliable biomarkers for predicting disease severity is crucial for improving clinical management and reducing mortality rates. The soluble urokinase-type plasminogen activator receptor (suPAR) has emerged as a promising biomarker for systemic infections due to its stable plasma levels and minimal circadian variation. This study investigates the potential of suPAR as a predictive biomarker for severe Dengue infection in hospitalized pediatric patients.

Objective: To evaluate plasma suPAR levels in children with Dengue infection, assess its correlation with disease severity, and determine its predictive value for identifying patients at higher risk of severe infection.

Methods: A cross-sectional study was conducted with 52 pediatric patients diagnosed with Dengue infection. Plasma suPAR levels were measured using enzyme-linked immunosorbent assay (ELISA). Patients were categorized based on clinical severity into Dengue Fever/Dengue Hemorrhagic Fever (DHF) Grade 1, DHF Grades 2–4, and further classified into Shock and Non-Shock groups. Statistical analyses were performed to evaluate correlations and odds ratios (OR) for severe Dengue prediction.

Results: Mean suPAR levels significantly differed between DHF Grade 1 and DHF Grade 2 ($p = 0.003$), and between DHF Grade 1 and DHF Grade 4 ($p = 0.047$). suPAR levels demonstrated a weak but significant correlation with overall disease severity ($r = 0.350$; $p = 0.011$). The odds ratio (OR) for developing DHF Grades 2–4 compared to DHF Grade 1 was 6.5 ($p = 0.001$) with a suPAR cutoff level > 6.25 ng/mL. However, no significant difference in suPAR levels was observed between Shock and Non-Shock groups.

Conclusion: suPAR shows potential as a predictive biomarker for severe Dengue infection in children, offering valuable diagnostic insights that could support early clinical interventions. Its use in laboratory diagnostics may enhance the ability to identify children at risk of severe outcomes, contributing to more effective patient management and improved prognostic outcomes in pediatric Dengue cases.

INTRODUCTION

Dengue has been a significant public health issue in Indonesia since it was first reported. Over the past five decades, the incidence of dengue infection has surged dramatically. The initial outbreak in 1968 involved 58 cases in two cities across two provinces. By 2015, the number of cases had escalated to 126,675, spanning all 34 provinces and affecting 436 cities and districts (Directorate General for Communicable Diseases Control, Ministry of Health of Indonesia, 2016). This upward trend has persisted, with more recent data from the Ministry of

Health showing an even higher incidence, reaching 354,110 cases in 2022, with a mortality rate of 0.72% (Indonesian Ministry of Health, 2023).

Several factors contribute to the increasing burden of Dengue Hemorrhagic Fever (DHF) in Indonesia, including rapid population growth, urbanization, increased human mobility, and improved transportation infrastructure. Additional drivers include changes in population density and distribution, climate change, behavioral factors, and inadequate community participation in mosquito control activities such as Mosquito Nest Eradication. Recent studies also highlight the influence of global warming on vector breeding patterns and the expansion of Aedes mosquito habitats (WHO, 2023; Haryanto, 2022). These findings underscore the urgent need for integrated vector management, public health education, and stronger community involvement to mitigate the spread of dengue.

Recently, the soluble form of the urokinase-type plasminogen activator (suPAR) has gained scientific interest, particularly in patients with sepsis. In contrast to C-reactive protein (CRP) and procalcitonin (PCT), suPAR has no diagnostic value but has the strongest prognostic value of the two biomarkers. Studies by Backes 2012 and Donadello 2014 reported that suPAR has potential as a prognostic marker in the ICU (Eugen-Olsen, 2015). Other study claimed that suPAR is different from other pro-inflammatory cytokines, as it shows a good-yielding property due to its high stability in serum samples and minimal changes in circadian rhythm in plasma concentrations (Rissbro, 2001).

The urokinase-type plasminogen activator (uPA) system consists of proteinases, receptors (uPAR) and inhibitors. This system plays a role in pericellular proteolysis, cell migration, and tissue remodeling with multiple actions (proteolysis, signal transduction, and chemokine-like activities). Physiologically, uPA and uPAR are widely expressed on the surface of several inflammatory cells including neutrophils, monocytes, macrophages, and activated T cells. These cells are known to play a role in cell activation, adhesion, migration, and extravasation. A form of uPAR expression is activated neutrophil cells (activated by cytokines).

Soluble urokinase-type plasminogen activator receptor (suPAR) is a membrane protein bound to a uPAR in soluble form. In recent studies, it has been defined as a valuable indicator of immune system activation. Aside from inflammation, elevated plasma suPAR levels have been found in various conditions, e.g., bacteremia with endotoxemia, human immunodeficiency virus (HIV) infection, viral infections, malaria, and rheumatoid arthritis. In healthy individuals, plasma suPAR levels appear to be stable throughout the day. It is very minimally affected by the circadian rhythm and serum freeze/thaw processes. Therefore, measurement of plasma suPAR levels in bodily fluids will be valid, independent of fasting status as well as sampling schedule (Hoenigl et al., 2013).

The varying clinical presentations of Dengue infection prompts the need for biomarkers capable of predicting disease severity. The presence of this biomarker is considered important because it acts as an "early warning sign" for severe Dengue infection, that may facilitate early management and subsequently reducing mortality.

To date, the role and profile of suPAR in Dengue infection is still unknown. In this study, we aim to determine the suPAR levels in hospitalized children with Dengue infection of varying degrees, its correlation with the disease severity, and the odds ratio (OR) for developing more severe infection.

MATERIAL & METHODS

This study employed an analytical observational design with a cross-sectional approach. Ethical approval was obtained from the Medical Research Ethical Committee of Dr. Saiful Anwar General Hospital, Malang, East Java, Indonesia (Ethical Clearance No: 400/196/K/3/302/2017). The subjects were dengue-infected pediatric patients hospitalized at

Saiful Anwar General Hospital, Malang. The inclusion criteria included hospitalized children under 18 years old with good nutritional status, who were clinically diagnosed with Dengue Fever (DF) or Dengue Hemorrhagic Fever (DHF) and had laboratory confirmation of NS-1(+), IgM(+), and/or IgG(+). Patients with comorbid conditions were excluded from the study.

Samples were collected from each subject on the first day of admission to the Emergency Room or Pediatric Outpatient Unit during clinical assessment. Based on disease severity, the subjects were categorized into four groups (DF/DHF Grades 1, 2, 3, and 4). These groups were further classified into two sub-groups: mild DHF (Grade 1) and moderate-to-severe DHF (Grades 2–4). The moderate-to-severe group was further divided into two categories: DHF cases with shock and those without shock.

The collected data were analyzed to evaluate differences and correlations between suPAR levels and disease severity, as well as to calculate the odds ratio for developing severe infections. Statistical analyses were conducted using SPSS version 20.0. The normality of the data was assessed using the Kolmogorov-Smirnov test. If the data were not normally distributed, transformations were applied. If the transformed data remained non-normal, non-parametric tests such as the Kruskal-Wallis test, Mann-Whitney U test, Chi-Square test, Spearman's correlation test, and odds ratio analysis were performed. Statistical significance was defined as a p-value < 0.05.

RESULTS

During January to March 2019, 52 children with clinical Dengue infection were enrolled in the study and classified based on the degree of severity as shown in Table 1. The study analyzed the mean plasma suPAR levels among 52 subjects, with an overall mean of 8.05 ng/mL (SD = 3.53). The distribution of suPAR levels was similar between male and female subjects, with means of 7.94 ng/mL and 8.16 ng/mL, respectively ($p = 0.61$). Age group comparisons revealed that the highest mean suPAR level (9.31 ng/mL) was observed in children aged 0–1 year, while the lowest was in those aged 1–5 years (6.74 ng/mL). However, the differences in mean suPAR levels among age groups were not statistically significant ($p = 0.19$).

When categorized by Dengue severity, a significant increase in suPAR levels was observed as the severity progressed ($p = 0.01$). The lowest mean suPAR level (6.25 ng/mL) was found in the DF/DHF Grade 1 group, while the DHF Grade 4 group had the highest mean level (10.12 ng/mL). Notably, the variability in suPAR levels was lower in the DHF Grade 4 group (SD = 1.69) compared to the other groups, suggesting a narrower range of elevated suPAR levels in the most severe cases. This highlights the potential of suPAR as a biomarker for assessing Dengue severity.

Table 1. Mean suPAR Levels Based on Characteristics of Subjects

Parameter	Category	N	Mean suPAR (ng/mL)	SD	Min	Max	p
suPAR		52 (100%)	8.05	3.53	0.85	11.81	
Sex	Male	26 (50%)	7.94	3.58	1.65	11.81	0.61
	Female	26 (50%)	8.16	3.56	0.85	11.61	
Age	0-1 years old	10 (19.23%)	9.31	3.17	2.27	11.81	0.19
	1-5 years old	16 (30.78%)	6.74	4.16	0.85	11.61	
	5-10 years old	16 (30.78%)	8.85	3.24	2.39	11.59	
	>10 years old	10 (19.23%)	7.91	2.82	2.67	11.54	
Dengue classification	DF/DHF Grade 1	22 (42.31%)	6.25	3.79	0.85	11.61	**0.01**
	DHF Grade 2	14 (26.92%)	9.98	2.46	2.98	11.81	
	DHF Grade 3	12 (23.08)	8.41	3.10	7.76	11.46	
	DHF Grade 4	4 (7.50%)	10.12	1.69	7.76	11.46	

The study also evaluated plasma soluble urokinase-type plasminogen activator receptor (suPAR) levels across four clinical grades of Dengue infection (Table 2). The mean suPAR levels increased with the severity of the disease, ranging from 6.25 ng/mL in patients with Dengue fever (DF) or Dengue hemorrhagic fever (DHF) Grade 1 to 10.12 ng/mL in DHF Grade 4. A statistically significant difference in mean suPAR levels was observed among the groups ($p = 0.010$). Notably, DHF Grade 2 demonstrated a mean suPAR level of 9.98 ng/mL, which was similar to DHF Grade 4, suggesting a clustering of higher suPAR levels in more severe cases. These findings indicate that plasma suPAR levels correlate positively with disease severity in Dengue infection.

Table 2. Plasma suPAR levels in the 4 groups of Dengue infection

Dengue Classification	N	Mean suPAR (ng/mL)	*p*
DF/DHF Grade 1	22	6.25	
DHF Grade 2	14	9.98	
DHF Grade 3	12	8.41	**0.010**
DHF Grade 4	4	10.12	
Total	52		

The cumulative frequency distribution of plasma suPAR levels further highlights the association with disease severity. In the DF/DHF Grade 1 group, most patients had suPAR levels in the lower percentiles (below 5.74 ng/mL), while higher percentiles (≥9.16 ng/mL) were predominantly observed in DHF Grades 2 to 4. Notably, the 75th and 100th percentiles were more frequently represented in DHF Grade 2 and DHF Grade 3, with DHF Grade 4 having the highest concentration in the 75th percentile. The median plasma suPAR level was 9.16

ng/mL, aligning with increased levels in higher-grade infections, further supporting suPAR as a potential biomarker for Dengue severity (table 3 and figure 1).

Table 3. Cumulative frequency of plasma suPAR levels in the 4 groups of Dengue infection

Dengue classification	N	Percentile (Quartile)			
		25th (<5.74ng/mL)	50th (5.74-9.16 ng/mL)	75th (9.16-11.24 ng/mL	100th >11.24 ng/mL
DF/DHF Grade 1	22	**10**	5	5	3
DHF Grade 2	14	**1**	2	6	5
DHF Grade 3	12	**2**	5	1	4
DHF Grade 4	4	**-**	1	2	1

Note: Median (percentile 50) = 9.16 ng/mL

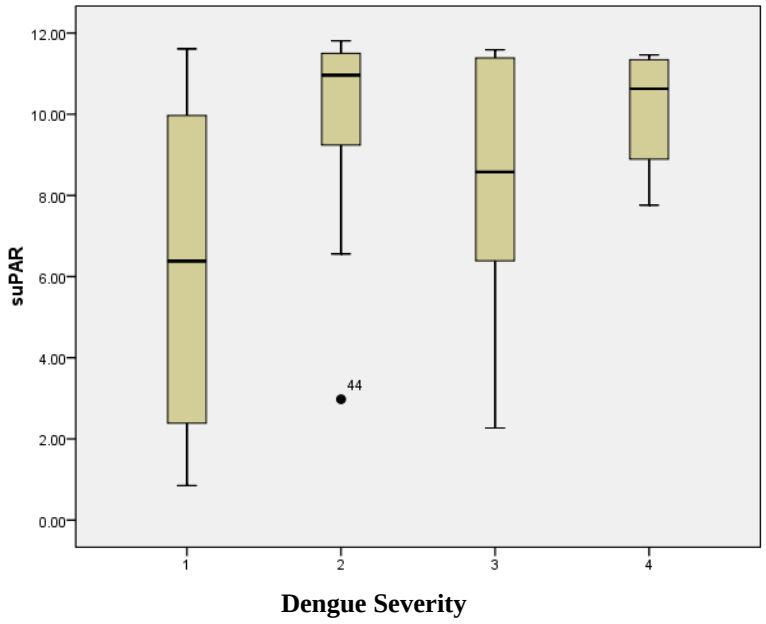

Figure 1. Difference in plasma suPAR levels in the 4 groups of Dengue infection

Mean difference test between 2 groups using Mann-Whitney U test was then performed to find out which group with significant difference in plasma suPAR levels. Results showed that mean plasma suPAR levels were significantly different between DHF Grade 1 and 2 (p=0.03) and between DHF Grade 1 and 4 (p=0.047).

The relationship between plasma suPAR levels and the severity of Dengue infection was analyzed using Spearman correlation test. The results showed that plasma suPAR levels were weakly correlated with the severity of Dengue infection (r=0.350, p=0.011).

Sub-group analysis comparing DF/DHF Grade 1 to DHF Grade 2-4 showed significant difference in mean plasma suPAR levels (p=0.001). It was then continued with cross-tabulation analysis using a cut off value of 6.25 ng/mL to produce an Odds Ratio of 6.5. This cut off value of 6.25 ng/mL is taken from the mean plasma suPAR levels in DF/DHF Grade 1.

Another sub-group analysis was performed to compare mean plasma suPAR levels between shock and non-shock cases of DHF. The four groups of DHF were regrouped into 2 subgroups, namely shock cases (DHF Grade 3 and 4) and non-shock cases (DHF Grade 1 and 2). Results showed that there was no significant difference of mean plasma suPAR levels between the two groups (p= 0.163). Cross-tabulation analysis using a cut off value of 6.25 ng/mL produced an Odds Ratio of 1.67.

DISCUSSION

Dengue Hemorrhagic Fever is an infection caused by any of the four-Dengue virus (DENV). It is an RNA virus that belongs to the family *Flaviviridae*, genus *Flavivirus*. Other viruses of the same genus are yellow fever virus, West Nile virus, St. Louis Encephalitis virus, Japanese Encephalitis virus, tick-borne encephalitis virus, Kyasanur Forest virus, and Omsk Hemorrhagic fever virus. Dengue virus is transmitted by several types of mosquitoes in the genus *Aedes*, mainly of the species *Aedes aegypti* (Heilman et al., 2014, Runge et al., 2014).

Viral infection stimulates the formation of specific antibodies which form a bond (complex) with the virus. This binding will activate complement which affects vascular endothelial cells and causes plasma leakage. Monocytes infected with Dengue virus will activate specific T lymphocyte cells and trigger the production of cytokines that cause complement activation. Specific T lymphocyte cells also cause lysis of monocytes infected with Dengue (Soedarto, 2012).

The entry of Dengue virus triggers activation of immune cells. When these immune cells are activated, pro-urokinase-type plasminogen activator (pro-uPA) will be converted into uPA. Urokinase-type plasminogen activator receptor (uPAR) is a membrane-bound protein found in several cell types, including immunologically active cells and endothelial cells. When urokinase has bound the three domains of uPAR (D1-D3) and activated pro-uPA, the resulting uPA can split uPAR at the binding sites between the first and second domains (D2-D3) (Hodges et al., 2015).

Soluble form of the urokinase-type plasminogen activator receptor (suPAR) is involved in several physiological pathways (regulation of atherogenesis) including pathways that activate plasminogen, regulation of cell signaling via integrins, modulation of cell adhesion, migration, proliferation, and extravasation. This protein is expressed in various immunologically active cells. High plasma suPAR have been widely demonstrated in several studies on inflammatory and infectious diseases and has been associated with increased mortality in ICU/non-ICU patients. In this study, we sequentially analyzed the difference in mean plasma suPAR levels at each degree of Dengue infection, its correlation with disease severity, and evaluated the ability of suPAR as a prognostic marker for severe Dengue infection through Odds Ratio.

A total of 52 subjects, consisting of 26 boys and 26 girls, were enrolled in this study (Table 1). There was no statistically significant difference in mean plasma suPAR levels between the two sexes. This finding is different from 1997 study by Stephens, where there was a significant difference in the mean plasma suPAR levels by sex between critically ill patients and the control group (Donadello, 2012).

Initial analysis showed that there was significant difference in the four groups of Dengue infection (p=0.01). Further analysis showed that mean plasma suPAR levels were significantly different between DHF Grade 1 and 2 (6.25 vs 9.98 ng/mL, p=0.03; Table 4) and between DHF Grade 1 and 4 (6.25 vs 10.12 ng/mL, p=0.047; Table 5). This finding is supported by the fact that mean plasma suPAR levels predominates the lowest quartile of DF/DHF Grade 1. On the other hand, mean plasma suPAR levels were not present in the lowest quartile of DHF Grade 4. Among other subgroups, the difference was found to be not statistically significant.

These results are aligned with 2010 study by Conolly, which revealed that existing relationship between plasma suPAR levels and inflammation (elevated levels in septic patients, independent association with inflammatory cytokines in multivariate linear regression analysis) does not necessarily mean that suPAR shows a proinflammatory effect. Conolly demonstrated that the uPA-uPAR interaction is required to control and reduce fibrin-mediated inflammation, particularly in the liver. This suggests that high levels of suPAR may not be harmful and may serve to reduce inflammation caused by fibrinogen (Conolly, 2010).

A study evaluating suPAR in a population of prostate cancer patients also supports our findings (Sier, 1999). Plasma suPAR concentrations were found to be inversely correlated with renal function. Furthermore, suPAR was also inversely correlated with pseudocholinesterase reflecting hepatic synthesis capacity and was directly related to parameters indicating cholestasis. Increased levels of suPAR in cholestasis could be caused by bile secretion of suPAR (Sier, 1999).

Differences in mean plasma suPAR levels between the four groups of Dengue infection was further analyzed with Spearman correlation test to assess the strength of the relationship between mean plasma suPAR levels and the severity of Dengue infection. The resulting r=0.350 revealed that plasma suPAR levels were weakly correlated with the severity of Dengue infection.

Similar results also found in other studies that measured suPAR in a population of SIRS patients with suspected infection. In this study, plasma suPAR levels was found to have a low accuracy in diagnosing bacterial infections in SIRS patients. The AUC obtained from suPAR to predict sepsis in critically ill patients admitted to the ICU is also low compared to CRP and PCT (Koefod, 2007). However, a positive correlation reflects the linearity of plasma suPAR levels with the severity of Dengue infection. Despite being weakly correlated, it can be interpreted that the increase of plasma suPAR levels suggest a more severe Dengue infection.

Plasma suPAR levels have been defined as an indicator of immune system activation and have shown to be reliable as a marker of inflammation. It is also often evaluated as a prognostic marker, particularly in sepsis, where suPAR is released from the endothelium (Conolly, 2010; Saphiro, 2010). Plasma leakage due to endothelial dysfunction is a hallmark of DHF, which is not present in Dengue fever. Therefore, it is very possible that high plasma suPAR levels reflect endothelial dysfunction, thus triggering morbidity and mortality in Dengue infection.

In 2007, Schneider found that HIV-positive patients with low CD4 cell counts (<200 cells/µl) had significantly high levels of plasma suPAR, which was also significantly associated with increased mortality. Antiviral therapy was then recommended in patients with low CD4 counts and maximum plasma suPAR levels of 6 ng/mL. This cut-off value was considered as high risk (Schneider, 2007), like the cut-off value identified in this study (6.25 ng/mL). This study also explained that suPAR had better predictive value compared to routine biomarkers of organ dysfunction and inflammation, both in the ICU morbidity group and overall survival of critically ill patients (Schneider, 2007).

To date, the prognostic role of suPAR is still being investigated (Ostrowski, 2006). In this study, the prognostic role of suPAR was analyzed by calculating the Odds Ratio for developing more severe Dengue infection. To evaluate this, we performed sub-group analysis comparing subjects within DF/DHF Grade 1 group to combined DHF Grade 2-4 group.

Significant difference in mean plasma suPAR levels was found between the mild sub-group (DF/DHF Grade 1) and the more severe group (DHF Grade 2-4). Using a cut-off value of 6.25 ng/mL, the odds ratio was found to be 6.5. It can be interpreted that the risk of developing more severe Dengue infection is 6.5 times higher in subjects with plasma suPAR levels of more than 6.25 ng/mL (Table 8).

Another sub-group analysis was performed to compare mean plasma suPAR levels between shock and non-shock cases of DHF. Mean plasma suPAR levels were 7.7 ng/mL in non-shock cases (DHF Grade 1 and 2) and 8.84 ng/mL in shock cases (DHF Grade 3 and 4). Results showed that there was no significant difference of mean plasma suPAR levels between the two groups (p= 0.163; Table 9). Using the same cut-off value of 6.25 ng/mL, the Odds Ratio was 1.67 (Table 10). However, this result was not statistically significant. In this study, lack of data on treatment history received before sampling may bias the study results. Ostrowski in 2006 showed that effective treatment for infectious diseases and cancer can result in a proportional decrease in plasma suPAR levels to normal after recovery (Ostrowski, 2006).

Results from various studies revealed that suPAR levels were not always linear with the severity of Dengue infection. This emphasizes that suPAR is not the only marker that can predict the disease severity. However, it is still considered as a potential biomarker due to its stable plasma concentration and very minimally affected by circadian rhythm (Rissbro, 2001).

In this study we found that there was significant difference in the mean plasma suPAR levels between the DF/DHF Grade 1 and 2, and the DF/DHF Grade 1 and 4. However, the plasma suPAR levels were weakly correlated with the severity of Dengue infection. Moreover, subjects in DF/DHF Grade 1 group with plasma suPAR levels of more than 6.25 ng/mL were 6. 5 times higher to become DHF Grade 2, 3, 4. Although, there was no difference in the mean plasma suPAR levels between shock and non-shock cases of DHF.

Limitations

Due to the long sampling time on fever days (fever days 1-4), the results obtained were not optimal. It is recommended that the sampling time is taken in the early period of fever. Furthermore, despite meeting the minimum number of samples, the number of subjects in DHF Grade 4 was very few (only 4 subjects), so it was not proportional compared to the number of subjects in other groups. Ideally, the number of subjects should be approximately similar in each sub-group.

It is necessary to homogenize the sampling time in the initial period of fever (1-2 days of fever). The number of subjects should be approximately the same in each sub-group. Treatment and medication history as well as the shape of suPAR molecule measured should be considered. It is necessary to compare plasma suPAR levels with conventional routine prognostic markers in a prospective cohort study.

ACKNOWLEDGEMENTS

We would like to thank all of physicians and staffs of Clinical Pathology Department of Brawijaya University.

CONFLICT OF INTEREST

Agustin Iskandar, Yuyun Norwahyuni, Siti Fatonah and Andrea Aprilia declare there are no conflict of interest for this research.

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