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Research Article

Aggregate Index of Systemic Inflammation is Correlated with Plasma Leakage Indicator in Dengue Virus Infection

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ABSTRACT

Severe dengue virus infection (DVI) is characterized by thrombocytopenia and plasma leakage (PL) due to the release of vasoactive cytokines by immune cells such as monocytes, lymphocytes, neutrophils, and platelets in response to dengue virus (DENV). This immune response triggers systemic inflammation, altering monocyte, lymphocyte, and neutrophil kinetics, which in turn affects leukocyte differentials. PL is indicated by an increase in hematocrit (Hct). This study aims to evaluate the potential use of the Aggregate Index of Systemic Inflammation (AISI) as an indicator of plasma leakage. A correlative analytical study with a cross-sectional approach was conducted on 70 pediatric DVI patients diagnosed according to the 2009 WHO criteria and confirmed by anti-DENV IgM/IgG tests. Patients with a history of malignancy, autoimmune thrombocytopenic purpura, or secondary DVI were excluded. Absolute neutrophil, monocyte, platelet, and lymphocyte counts, AISI, and Hct levels were obtained from complete blood count results using a hematology analyzer. The results showed that AISI and lymphocytes correlated with Hct, with correlation values of ($r=0.410$, $p<0.001$) and ($r=0.446$, $p<0.001$), respectively. In contrast, monocytes, neutrophils, and platelets did not correlate with Hct, with correlation values of ($r=-0.009$, $p=0.942$), ($r=-0.059$, $p=0.628$), and ($r=-0.175$, $p=0.147$), respectively. In conclusion, AISI levels in DVI were low and negatively correlated with Hct, a known indicator of PL. These findings suggest that AISI has potential as a marker for PL and disease severity in DVI.

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INTRODUCTION

Dengue virus infection (DENV) includes serotypes 1–4 and is primarily transmitted by Aedes aegypti and Aedes albopictus mosquitoes. According to the WHO, approximately 3.5 billion people reside in tropical and subtropical regions where dengue is endemic. In Indonesia, a tropical country, there were 142,294 reported cases in 2022, with 1,227 deaths. The incidence of dengue virus infection (DVI) is expected to rise due to rapid population growth, tourism, global warming, and poor sanitation and hygiene (Direktorat Jenderal Pencegahan dan Pengendalian Penyakit, 2023; World Health Organization, 2023).

DVI is often asymptomatic, with only 40% of infected individuals experiencing symptoms ranging from mild to severe. Mild cases present with flu-like fever, while severe cases are characterized by bleeding and shock due to plasma leakage (PL) (Castillo et al., 2019). PL occurs when plasma fluid shifts from blood vessels to tissues, leading to pleural effusion, ascites, hypoalbuminemia, low urine output, shock, and an increase in hematocrit (Hct) levels. Hct level correlates positively with PL. Hct elevation in dengue patients can be detected by the third day of illness due to varying degrees of PL (Talukdar et al., 2021). However, PL in DVI does not align with the WHO classification, as its criteria tend to overestimate severe DVI while underestimating PL (Rodrigo et al., 2021). This highlights the need for additional parameters to predict PL in DVI.

Multiple factors, including viral structural components and immune responses, influence PL. The DENV non-structural 1 (NS1) antigen disrupts endothelial glycocalyx integrity, altering the endothelial membrane's electrical charge and triggering PL (Teo et al., 2021). Moreover, immune responses from monocytes, neutrophils, lymphocytes, and platelets lead to cytokine production, further contributing to PL (Malathesa & Ashwini, 2014; Ostermeier et al., 2022; Srikiatkhachorn et al., 2017).

DENV-induced immune responses contribute to systemic inflammation, plasma leakage (PL), and altered leukocyte kinetics. Monocyte mobilization from bone marrow to circulation shifts their composition, with an increased proportion of intermediate monocytes as classical subsets decline (Kratofil et al., 2017; Teh et al., 2019; Lertjuthaporn et al., 2021). Some monocytes infiltrate tissues while others remain in circulation, affecting absolute monocyte count (AMC) (Rathore & St. John, 2018; Wan et al., 2018). Similarly, CD4+ and CD8+ T cell migration to tissues reduces lymphocyte count, whereas atypical B cells in circulation elevate absolute lymphocyte count (ALC) (Clarice et al., 2019; Manh et al., 2020; Rivino & Lim, 2017). Neutrophil counts increase (Chaloemwong et al., 2018) and platelet counts decrease (Thach et al., 2021), altering the Aggregate Index of Systemic Inflammation (AISI = monocyte × neutrophil × platelet/lymphocyte) (Hosseninia et al., 2023). These immunological dynamics, along with vasoactive cytokine release, contribute to PL as reflected in hematocrit (Hct) levels. Accordingly, investigating AISI as a potential indicator of PL—supported by correlations between AMC-Hct, ALC-Hct, ANC-Hct, and platelet-Hct—is justified. NLR and PLR were not included due to their inconsistent association with DVI severity (Agrawal et al., 2023; Ashma et al., 2023; Djalilah et al., 2020; Farraha et al., 2025; Pribadi et al., 2025). This study aims to evaluate the potential use of the Aggregate Index of Systemic Inflammation (AISI) as an indicator of plasma leakage

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METHODS

This study is a correlational observational analytic study with a cross-sectional design. The research was conducted at PKU Muhammadiyah Sampangan Hospital, Pasar Kliwon, Surakarta, from December 1, 2024, to February 28, 2025. The target population included all pediatric dengue virus infection (DVI) patients, while the actual population consisted of pediatric DVI patients hospitalized at PKU Sampangan Hospital, Surakarta. Inclusion criteria were patients diagnosed with DVI by a pediatric specialist according to the 2009 WHO criteria, positive anti-DENV IgM/IgG test, age < 15 years, and no history of dengue vaccination. Patients with a history of autoimmune thrombocytopenic purpura, malignancy, or who refused to participate in the study were excluded from this research.

The required sample size was calculated using a formula for correlational studies, yielding a minimum sample of 51 subjects. However, 70 patients were included in this study. Samples were collected using consecutive non-probability sampling. The study subjects were not grouped based on disease severity, considering that the WHO classification is suspected of not accurately reflecting the actual plasma leakage. Therefore, hematocrit (Hct) was preferred, as it more directly reflects plasma leakage (Rodrigo et al., 2021).

Hospitalized patients diagnosed with DVI by a pediatric specialist underwent screening based on restriction criteria. Blood samples from eligible patients who had experienced at least four days of fever were collected using an aseptic phlebotomy technique and stored in K_3EDTA anticoagulant tubes. The samples were then analyzed in the Clinical Pathology Laboratory at PKU Muhammadiyah Sampangan Hospital for a complete blood count. The results were used to calculate absolute monocyte count (AMC), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelet count, Aggregate Index of Systemic Inflammation (AISI), and hematocrit (Hct). The Calculations formula is as followed: Absolute monocyte count (AMC) = total leukocyte count × monocyte percentage, Absolute lymphocyte count (ALC) = total leukocyte count × lymphocyte percentage, Absolute neutrophil count (ANC) = total leukocyte count × neutrophil percentage, Aggregate Index of Systemic Inflammation (AISI) = (monocyte × neutrophil × platelet) / lymphocyte.

The data were analyzed using JASP software version 0.19.0.0 (Amsterdam University). A correlation coefficient (r) > 0.2 with a p-value < 0.05 was considered statistically significant. The research has been declared ethical and received an ethical clearance letter from the Health Research Ethics Commission, Faculty of Medicine, Universitas Muhammadiyah Surakarta, No. 5481A/B.1/KEPK-FKUMS/XI/2024.

RESULTS

The study was conducted to determine the correlation between inflammatory indices, including platelet count, AMC, ALC, ANC, and AISI, with hematocrit (Hct) in pediatric DVI patients. The characteristics of the study subjects are presented in Table 1.

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Table 1. Characteristics of Study Subjects

Subject Characteristics	Results
Sex	
Boys (%)	48.57
girls (%)	51.43
Age *	8.03 (7.75)
Temperature (°C) **	37.7 (1.1)
Bleeding Manifestation (%)	39.13
Epistaxis (%)	14.29
Petechiae (%)	25.71
Abdominal pain (%)	51.43
Muscle pain (%)	28.57
Disease severity	
Dengue without WS (%)	32.86
Dengue with WS (%)	57.14
Severe Dengue (%)	10
Hematocrit (%) *	38 (6.75)
Platelet mm^{-3} *	114,500 (53.250)
Leucocyte mm^{-3} *	3,290 (1602.5)
AMC mm^{-3} *	314 (76)
Monocytopenia (%)	18.57
Normal (%)	74.29
Monocytosis (%)	7.14
ALC mm^{-3} *	1,176.23 (1050.65)
Lymphocytopenia (%)	62.86
Normal (%)	35.71
Lymphocytosis (%)	1.43
ANC mm^{-3} *	2,611 (662.57)
Neutropenia (%)	28.57
Normal (%)	71.43
Neutrophilia (%)	0
AISI *	38.52 (52.39)

WS (warning sign), (°C) degrees Celsius, (mm^3) per cubic millimeter. *Data presented as median (IQR). ** Data presented as mean (SD), Categorical data are presented as percentages.

Table 2. Spearman's Rho Correlation Test

Correlation	r-value	p-value	VS-MPR
AISI-Hct	0.410*	<0.001**	112.624***
AMC-Hct	-0.009	0.942	1
ALC-Hct	-0.446*	<0.001**	367.223***
ANC-Hct	-0.059	0.628	1
Plt-Hct	-0.175	0.147	1.307

VS-MPR (Vovk-Sellke Maximum p-Ratio), *moderate correlation, **statistically significant, ***supports the alternative hypothesis

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DISCUSSION

The AISI value in this study was 38.52 (52.39), as shown in Table 1. Although there have been no research reports on AISI in dengue virus infection (DVI), the result observed in this study is significantly lower than AISI values reported in various conditions, such as open elective thoracic surgery, idiopathic pulmonary fibrosis, age-related macular degeneration, hypertension, chronic renal failure, chronic obstructive pulmonary disease, and COVID-19, which range from 176 to 4489 (Ercan et al., 2023; Hosseninia et al., 2023; Paliogiannis et al., 2018; Sannan, 2023; Xiu et al., 2023; Zinellu et al., 2021, 2023). This discrepancy occurs because dengue virus infection (DVI) is often associated with thrombocytopenia and lymphocytopenia, as shown in Table 1, where the platelet count is 114,500 (53.250), and 62.86% of patients experience lymphocytopenia. The calculation formula of AISI leads to a lower AISI value in this study.

Until now, there is no universally accepted cut-off to define a low AISI value. However, based on existing studies across various conditions, the lowest reported AISI value was 176. A low AISI value generally indicates the absence of inflammation. However, this does not apply to DVI patients, as demonstrated by the correlation results in Table 2. There is a moderate correlation between AISI and hematocrit (Hct) ($r = 0.410$; $p < 0.001$). Hct elevation is a known indicator of plasma leakage (PL) in DVI. An increase of more than 20% in Hct is considered a strong predictor of PL, although some hospitalized DVI patients experience PL without a recorded Hct change (Rodrigo et al., 2021). Since AISI reflects inflammation and Hct is an indicator of PL, this study strongly suggests that inflammation occurs in DVI patients.

AISI represents the role of both innate immunity, indicated by monocytes, neutrophils, and platelets, and adaptive immunity, represented by lymphocytes. The monocyte count in this study was 314 (76), which remains within the normal range of 200-800 (Mangaonkar et al., 2021). There was no correlation between monocyte count and Hct. However, this does not imply that monocytes are unimportant in the immune response to dengue virus (DENV). Monocyte death through necrosis, apoptosis, and pyroptosis due to DENV response leads to monocytopenia (Castillo et al., 2019; Castillo & Urcuqui-Inchima, 2018). Nevertheless, high CCL2 levels in DVI patients enhance monocyte recruitment into circulation (Jusof et al., 2022; Mentkowski et al., 2020; Patel et al., 2017, 2021; Williams et al., 2023). These opposing processes result in a stable monocyte count, consistent with our previous findings and other studies showing normal monocyte counts in DVI patients (George et al., 2023; Jatmiko et al., 2024). This stability is also linked to monocyte subset shifts, with an increase in CD14++ CD16+ and a decrease in CD14++ CD16- subsets (Kwissa et al., 2014; Lertjuthaporn et al., 2021).

Neutrophils, another AISI component, play a role in the immune response to DENV. Their count is not significantly affected by stress or dehydration, making them a reliable indicator of immune response (Azab et al., 2010). Table 1 shows a neutrophil count of 2,611 (662.57), within the normal range of 1,000-8,000 (Virgo, 2021). Correlation analysis between neutrophils and Hct showed no significant relationship ($r = -0.059$, $p = 0.628$). However, this does not mean neutrophils are irrelevant in DENV immunity. DENV exposure activates neutrophils, leading to CCR7 production and increased MCL-1 expression. MCL-1 prevents neutrophil apoptosis, prolonging their lifespan, while CCR7 enhances their migration to lymph nodes (Kamsom et al., 2024). High IL-6 levels in DVI also stimulate neutrophil release

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from the bone marrow (Florentin et al., 2021; Kanwal et al., 2017). These processes maintain a stable neutrophil count, consistent with previous studies indicating normal neutrophil levels in DVI, while neutropenia is rare (Shourick et al., 2017; Thein et al., 2014). Neutrophil activation, rather than their count, plays a greater role in DVI severity (Thein et al., 2014). Activated neutrophils undergo degranulation, ROS production, and NETosis, contributing to PL (Muralidharan & Reid, 2021).

Platelets, a key AISI component, influence its value (Paliogiannis et al., 2018). The platelet count in this study was 114,500, indicating thrombocytopenia (<150,000) (Virgo, 2021). However, thrombocytopenia in DVI is often accompanied by platelet activation (Quirino-Teixeira et al., 2020; Vedpathak et al., 2025). DENV NS1 recognition by CLEC5 activates platelets, prompting extracellular vesicle (EV) release. EV interactions with CLEC5 and TLR2 on neutrophils further activate neutrophils, leading to degranulation and elastase release. Elastase damages the endothelial glycocalyx, triggering PL. Additionally, NET formation from NETosis contributes to PL (Muralidharan & Reid, 2021; Opasawatchai et al., 2019; Teo et al., 2021). Activated platelets also release mediators like PAF, which promote PL (García-Larragoiti et al., 2021; Gill et al., 2015; Jeewandara et al., 2015).

Lymphocytes play a crucial role in DENV immunity (Tian et al., 2019). The median absolute lymphocyte count (ALC) in this study was 1,176.23 (1,050.65)/mm³. Compared to the reference range of 1,500-7,000/mm³ (Virgo, 2021), this indicates lymphopenia, which is a diagnostic and severity marker of DVI (Kalabamu & Maliki, 2021; Henrina et al., 2020). However, ALC and Hct showed a moderate negative correlation ($r = -0.446$, $p < 0.001$), with VS-MPR at 367.223. This may result from various mechanisms, including DENV infection of hematopoietic progenitors, T cell activation, bone marrow stromal involvement, and lymphocyte migration to affected tissues (Henrina et al., 2020; King et al., 2020). Previous studies have reported inconsistent findings, with some noting lymphocytosis in DVI (Setiawan et al., 2023) and others reporting normal lymphocyte counts (Rai et al., 2019). These discrepancies may be due to different classification criteria and patient selection methods (George et al., 2023; Rai et al., 2019; Setiawan et al., 2023). T cells produce MIP1β, TNF-α, and IFN-γ, which contribute to PL. Additionally, activated B cells release IL-6 and TNF-α, both implicated in PL (Alsaffar et al., 2020; Imad et al., 2020; Malathesa & Ashwini, 2014; Srikiatkhachorn et al., 2017).

Table 2 shows no significant correlation between platelet count and Hct ($r = -0.175$, $p = 0.147$; VS-MPR = 1.307). This is unusual, as DVI typically involves increased Hct and decreased platelets (Salsabila et al., 2024; Oscar & Ciptono, 2023). Some studies have found a weak negative correlation (Santoso et al., 2015). However, platelet reduction in DVI is multifactorial (De Azeredo et al., 2015), and platelet count and hemoglobin levels may be more strongly associated with disease severity than platelet count and Hct (Faridah et al., 2022). Overall, AISI is a more comprehensive inflammation marker than other CBC-based indices, as it integrates multiple immune cells (Zinellu et al., 2021). Thus, AISI has potential as a marker for PL in DVI.

CONCLUSION

AISI in DVI is low and negatively correlates with Hct, an indicator of PL. There is no direct correlation between some individual components of AISI and hematocrit; however,

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considering that AISI integrates elements of innate and adaptive immunity, this index has the potential to serve as a marker of plasma leakage in dengue virus infection (DVI), thus requiring further studies and validation in larger cohorts.

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