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CONTENTS

RESEARCH

The Morphological Features of Erythrocytes in Stored Packed Red Cells
(Gambaran Morfologi Eritrosit di Packed Red Cells Simpan)
Dewi Sri Kartini, Rachmawati Muhiddin, Mansyur Arif .......................................................... 103–106

Correlation of Advanced Glycation End Products with Urinary Albumin Creatinin Ratio in Patients
(Kenasaban Kadar Advanced Glycation End Products dengan Rasio Air Kemih Albumin Kreatinin di
Pasien Diabetes Melitus Tipe 2)
Debie Angraini, Rismawati Yaswir, Lillah, Husni ........................................................................ 107–110

Monocyte Lymphocyte Ratio in Dengue Hemorrhagic Fever
(Monocyte Lymphocyte Ratio di Dengue Hemorrhagic Fever)
Dwi Retnoningrum, Purwanto AP .................................................................................................. 111–113

Correlation between NT-proBNP and Left Ventricular Ejection Fraction by Echocardiography in Heart
Failure Patients
(Kenasaban antara Kadar NT-proBNP dan Fraksi Ejeksi Ventrikel Kiri Secara Ekokardiografi di Pasien
Gagal Jantung)
Mutia DS, Leonita Anniwati, M. Aminuddin ............................................................................. 114–118

Detection of Mycobacterium Tuberculosis with TB Antigen Rapid Test in Pulmonary Tuberculosis
Patients with Four Types of Spctum Sample Preparation
(Deteksi Antigen Mycobacterium Tuberculosis Menggunakan TB Antigen Uji Cepat di Pasien Tuberkulosis
Paru dengan 4 Cara Preparasi Dahak)
Miftahul Ilmiah, IGAA. Putri Sri Rejeki, Betty Agustina Tambunan ........................................ 119–125

Diagnostic Test of Hematology Parameter in Patients Suspect of Malaria
(Uji Diagnostik Tolok Ukur Hematologi di Pasien Terduga Malaria)
Ira Ferawati, Hanifah Maani, Zelly Dia Rofinda, Desywar ................................................................ 126–130

Comparison Results of Analytical Profile Index and Disc Diffusion Antimicrobial Susceptibility Test to
Technical Dedicated Reasonable 300B Method
(Perbandingan Hasil Analytical Profile Index dan Uji Kepekaan Antibiotika Difusi Cakram dengan
Metode Technical Dedicated Reasonable 300B)
IG Eka Sugiartha, Bambang Pujo Semedi, Puspa Wardhani, IGAA Putri Sri Rejeki ......................... 131–137

The Agreement between Light Criteria and Serum Ascites Albumin Gradient for Distinguishing
Transudate and Exudate
(Kesesuaian Patokan Light dengan Serum Ascites Albumin Gradient dalam Membedakan Transudat dan
Eksudat)
Rike Puspasari, Lillah, Efrida ........................................................................................................ 138–140

Correlation between Serum Tissue Polypeptide Specific Antigen Level and Prostate Volume in BPH
(Kenasaban antara Kadar Tissue Polypeptide Specific Antigen Serum dan Volume Prostat di BPH)
Mahrany Graciella Bumbungan, Endang Retnowati, Wahjoe Djatisoesanto .................................. 141–145
Correlation of Antinuclear Antibody Profile with Hematologic and Renal Disorders in Systemic Lupus Erythematosus

(Chelvi Wijaya, Asvin Nurulita, Uleng Bahrun)

Identification of Dengue Virus Serotypes at the Dr. Soetomo Hospital Surabaya in 2016 and its Correlation with NS1 Antigen Detection

(Jeine Stela Akualing, Aryati Puspa Wardhani, Usman Hadi)

Correlation of Coagulation Status and Ankle Brachial Index in Diabetes Mellitus Patients with Peripheral Arterial Disease

(Lany Anggreani Hutagalung, Adi Koesema Aman, Syanti Syafril)

The Difference of Plasma D-dimer Levels in Acute Myocardial Infarction with and without ST Elevation

(Henny Elfira Yanti, Fery H Soedewo, Puspa Wardhani)

Diagnostic Test on the Fourth Generation Human Immunodeficiency Virus in HIV Suspects

(Sofitri, Ellyza Nasrul, Almurd, Erfida)

Correlation of Neutrophils/Lymphocytes Ratio and C-Reactive Protein in Sepsis Patients

(Binar R. Utami, Betty Agustina T, Suprapto Ma’at)

LITERATURE REVIEW

Glycated Hemoglobin A1c as a Biomarker Predictor for Diabetes Mellitus, Cardiovascular Disease and Inflammation

(Indranila KS)

CASE REPORT

Erythroleukemia

(Ailinda Theodora Tedja, Riadi Wirawan)

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Rismawati Yaswir, July Kumalawati, Mansyur Arif, Rahayuningsih Dharmakoeswa, Nurhayanan Sennang Andi Nanggung, AAG. Sudewa, Ninik Sukartini, Tahono, M. Yolanda Probohoesodo
INTRODUCTION

Dengue Hemorrhagic Fever (DHF) is a disease caused by dengue virus, a virus that can be transmitted through mosquito bites. DHF is one cause of illness and death in the world, including in Asia. Approximately 500,000 cases occur each year in the world. Dengue hemorrhagic fever causes high morbidity and mortality in the world, including Asia, especially in Indonesia. The pathogenesis of DHF infection is thought to involve monocytes and lymphocytes as a result of the immune response to infection. Monocyte Lymphocyte Ratio (MLR) previously used in describing the immune response to malaria infection, tuberculosis and HIV. To determine whether there are differences between MLR in mild and severe DHF. A cross-sectional study in DHF patients at the Dr. Kariadi Hospital Semarang was done in January to December 2013. Monocyte lymphocyte ratio value was obtained from calculating the number of monocytes divided by lymphocytes from leukocyte differential count. The degree of DHF was determined in accordance to the WHO criteria, where grade I-II was considered as a mild degree and grade III-IV was considered as severe degree. Statistical analysis analyzed by Student’s t test. Group I consisted of 40 patients with mild DHF and group II consisted of 40 patients with severe DHF. The subjects consisted of 41 males (51.2%) and 39 females (48.8%). Monocyte lymphocyte ratio value range in mild DHF was from 0.03 to 0.33 (median 0.11), while the severe DHF from 0.03 to 0.59 (median 0.16). Statistical analysis showed there was no significant difference between the value of MLR group I (mild) and group II (severe) (p=0.08). There was no significant difference of MLR in mild and severe DHF.

Key words: Dengue hemorrhagic fever, monocyte lymphocyte ratio, DHF degree
severity in Southeast Asia is the most in age 13–35 years.\(^1\)

According to the WHO, there are four stages of infection DHF severity, degree I is characterized by fever accompanied by symptoms not typical and positive Rumple Leede; stage II the degree I in the presence of spontaneous bleeding in the skin or other bleeding, Grade III is characterized by circulatory failure a rapid and weak pulse and also a decrease in pulse pressure (<20 mmHg), hypotension (systolic decreased to <80 mmHg), cyanosis around the mouth, cold limbs, moist skin and the patient is agitated; while stage IV is characterized by severe shock (profound shock) that is no palpable pulse and blood pressure. Grade I and II are generally handled well, while stage III and IV are often an urgency that can lead to death.\(^2\)–\(^4\)

The pathogenesis of DHF infection allegedly involves monocytes and lymphocytes as a result of the immune response to infection.\(^2\),\(^5\) Therefore, the number in peripheral blood would describe the status of immune response to infection. The number of monocytes and lymphocytes in peripheral blood are described by Monocytes Lymphocytes Ratio (MLR). During this time MLR is proved beneficial description about of monocytes and lymphocytes immune responses.

A previous research showed that MLR described immune response to malaria infection, prediction of tuberculosis and Human Immunodeficiency Virus (HIV) severity.\(^6\)–\(^7\) Differential counts and MLR are an examination routine and easy for detecting infectious diseases including DHF. This research is aimed to know whether there were differences between MLR in mild and severe DHF.

**METHODS**

This study was a retrospective cross-sectional study. Subjects were DHF patients at the Dr. Kariadi Hospital Semarang from January to December 2013. This study used consecutive nonsampling random with inclusion and exclusion criteria. The inclusion criteria were children 1–14 years old, in order with WHO criteria for DHF diagnosis. Patients with tuberculosis (TB), HIV, malaria and typhoid fever were excluded.

Monocyte Lymphocytes Ratio (MLR) was defined as the ratio between the number of monocytes divided by lymphocytes obtained from the examination of leukocyte count. Mild DHF was grade I and II of WHO criteria in group I, while severe DHF was grade III and IV of WHO criteria in group II. Patient’s medical records were needed for history, physical examination and laboratory test results. Laboratory test results were examined by Beckman Coulter Hematology Analyzer HMX-1 (Beckman Coulter, Brea, CA) with venous blood samples. Monocyte lymphocytes ratio calculations was done manually by calculating the leukocyte count.

Data were analyzed by Student’s t test to determine the MLR in mild and severe DHF. Significance was stated at p<0.05.

**RESULTS AND DISCUSSION**

Eighty DHF patients were divided into two groups (mild and severe). Group I consisted of 40 patients with mild DHF. Group II consisted of 40 patients with severe DHF. Subject consisted of 41 males (51.2%) and 39 females (48.8%). Basic characteristic data are shown in Table 1.

Normality test result showed that the MLR data distribution was not normal, after transformation process, MLR data was normally distributed. Monocyte lymphocytes ratio value for mild DHF was 0.03 to 0.33 (median 0.11), while MLR value in severe DHF was 0.03 to 0.59 (median 0.16). Statistical analysis showed that there were no significance of MLR between group I and group II (p=0.08) (Table 2).

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>%</th>
<th>Mean±SD</th>
<th>Median (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (48.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>41 (52.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td></td>
<td>6.5 (1–14)</td>
<td></td>
</tr>
<tr>
<td>Hb (gr/dL)</td>
<td></td>
<td>12.38 (2.83)</td>
<td></td>
</tr>
<tr>
<td>Ht (%)</td>
<td></td>
<td>38.2 (9.7–58.2)</td>
<td></td>
</tr>
<tr>
<td>Leucocyte count (103/µL)</td>
<td></td>
<td>5.1 (1.25–23.9)</td>
<td></td>
</tr>
<tr>
<td>Thrombocyte count (103/µL)</td>
<td></td>
<td>49,950 (4,300–165,000)</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td></td>
<td>41.46 (15.48)</td>
<td></td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td></td>
<td>5 (1–22)</td>
<td></td>
</tr>
<tr>
<td>MLR</td>
<td></td>
<td>0.126 (0.03–0.59)</td>
<td></td>
</tr>
</tbody>
</table>
Monocytes and lymphocytes are an immune system, that monocytes act as APC (antigen presenting cells) and produce cytokines in response to infection. Mature monocytes would change into macrophages in tissues. Mononuclear phagocytic cells are monocytes, macrophages, histiocytes and Kupffer cells which are the main site of dengue virus replication.\(^6,^7\) IL-1, IL-6 and TNF-\(\alpha\) that were produced by monocytes can induce fever, otherwise, monocytes also play a role in remodeling and repairing tissue. The lymphocytes plays a role in immunologic processes and helps phagocytes cell.\(^10,^11\)

Monocyte lymphocytes ratio value was previously used for tuberculosis, HIV and malaria predictors. Marimwe et al.\(^6\), reported that MLR value described the immune response to malaria infection.\(^6\) Narahbhai et al.\(^7\), reported that the MLR was connected as a prediction of disease severity tuberculosis and HIV infection.\(^7\)

In this study, the value of MLR in mild and severe DHF infections showed no significant difference (\(p=0.08\)). This was consistent with Jameel et al.\(^11\), who reported that there was no change in the number of monocytes in DHF infection and the observation of DHF infection with and without shock there did not found differences in leukocyte counts and concentration.\(^11\) Passos et al.\(^12\), also reported that lymphocyte counts between dengue and non dengue there was not found significantly different (\(p=0.08\)).\(^12\) The MLR value was not significant in this study due to the possibility of different infection pathophysiology of DHF.

In addition to the theory of dengue infection in monocytes and macrophages, there were several theories explaining the dengue virus infection, such as genetics theory that HLA-A1, HLA-B, HLA-CW1 and HLA-A29 were more exposed to DHF. Other studies mentioned that the loci HLA B35, AW-33, CW4 and DR7 was found in many cases of shock, while BW 51, BW 62 and DRA was common in cases of DHF without shock.\(^2\) Complement theory showed that antigen-antibody complex would activate complement, activation of the complement thus increasing the production of C3a and C5a which increases capillary permeability, resulting in leakage of plasma, hypovolemia, hemoconcentration and shock. Another theory was the theory of secondary infections showing that the second DHF infection with other types of viruses would cause more severe clinical manifestations. In addition, there was a virulence theory of the virus, the infection of the more virulent serotype virus could cause more severe DHF compared to avirulent virus. DEN-3 serotype was more the cause of death than the others serotypes.\(^2\)

Limitation of this study was a cross sectional study design that could not clearly describe when the change of leukocyte counts occurred. In addition, in this study the subjects of unknown status of primary or secondary infection were not investigated.

**CONCLUSION AND SUGGESTION**

The conclusion of this study was that no difference of MLR in mild and severe DHF infection was found. The suggestion is that further studies with larger result and considering the type of infection, whether it is primary or secondary dengue infection are needed.

### REFERENCE


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**Table 2. Statistical analysis of MLR in mild and severe DHF**

<table>
<thead>
<tr>
<th>Description</th>
<th>Mild DHF</th>
<th>Severe DHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (min-max)</td>
<td>0.11(0.03;0.33)</td>
<td>0.16(0.03;0.59)</td>
</tr>
<tr>
<td>p</td>
<td>0.08*</td>
<td>0.08*</td>
</tr>
</tbody>
</table>

* Student t test