CONTENTS

RESEARCH

Proportion of Isomorphic Erythrocyte Urine in Diabetic Kidney Disease with Flow cytometry Methods
Erica Catarina, Coriejati Rita, Basti Andriyoko, Ida Parwati .................................................................................. 1 - 6

Analysis of Ret-He in Chronic Kidney Disease Patients at Dr.Wahidin Sudirohusodo Hospital, Makassar
Febrina Rovani, Asvin Nurulita, Mansyur Arif ........................................................................................................ 7 - 10

Analysis of Red Blood Cell Distribution Width Coefficient of Variation on Stroke Patient
Kartika Paramita, Agus Alim Abdullah, Mansyur Arif .................................................................................................. 11 - 15

IgA Anti-Dengue Profile in Samples with Positive Dengue PCR or NS1
M Thohirin Ramadhani, Aryati, M Vitanata Arifjanto ................................................................................................ 16 -20

The Association of Insulin Resistance and Lipid Profile Ratio in Metabolic Syndrome
Rini Rahmayani, Adi Koesoema Aman, Santi Safril ........................................................................................................ 21 - 25

Correlation of Free Hemoglobin Level and Plasma Nitric Oxide in Packed Red Cell during Blood Bank Storage Period
Ricca Fitria, Rismawati Yaswir, Zelly Dia Rofinda, Desywar ..................................................................................... 26 - 30

Correlation of Lipid Profile with Interleukin-12 in Type 2 Diabetes Mellitus
Meri Ponda Sari, Hanifah Maani, Ellyza Nasrul, Zelly Dia Rofinda ............................................................................... 31 - 34

Platelet Indices for Predicting Liver Fibrosis in Patients with Chronic Hepatitis B Infection
Shendy Sherly Soelisauwan, Darwati Muhadi, Mutmainnah ......................................................................................... 35 - 37

The Relationship Between the Level of Interleukin-6 and Procalcitonin in Severe Sepsis Patients at the Adam Malik Hospital
Sesily C Nainggolan, Adi Koesoema Aman, Achsanudin Hanafi ................................................................................... 38 - 41

Spontaneous Platelet Aggregation in Third-Trimester Pregnancy at Adam Malik Hospital, Medan
Rezqi Maulani Jusuf, Hotma Partogi Pasaribu, Herman Hariman .................................................................................. 42 - 46

Correlation between Presepsin and Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) Score as an Organ Dysfunction Marker in Sepsis
Stevi Dwiyan, Agnes Rengga Indratil, Leni Lismayanti, Adhi Kristianto S ........................................................................ 47 - 52

Correlation of Atherogenic Index of Plasma with Stenosis Level of Coronary Artery in Acute Coronary Syndrome
Ilhamifithri, Rismawati Yaswir, Eugeny Alia, Efrida .................................................................................................... 53 - 57
The Compatibility of Neutrophil to Lymphocyte Count Ratio with Serum Procalcitonin as Bacterial Infection Markers in Sepsis Patients
Elvinawaty, Hanifah Maani, Zelly Dia Rofinda, Husni ............................................................... 58 - 63

The Diagnostic Value of Troponin I Testing to Coronary Angiography with a Point of Care Testing Instrument in Patients with Acute Myocardial Infarction
Riska Anton, Sheila Febriana, Asvin Nurulita, Uleng Bahrur ....................................................... 64 - 67

Comparisons of Fibro Q Index and FIB-4 in Various Stages of Chronic B Hepatitis
Evy Adrianti, Lioong Boy Kurniawan, Ibrahim Abdul Samad ...................................................... 68 - 72

Microorganism Pattern on Nasal Cavity of End Stage Renal Disease Patients with Regular Hemodialysis and Staffs in Hemodialysis Installation Adam Malik Hospital Medan
Imelda Damayanti, Ricke Loesnihari, Syafirzlal Nasution ................................................................ 73 - 78

The Correlation between the Mean Platelet Volume Values with Thrombocyte Aggregation in Nephropathy Diabetic Patients
Agus Sunardi, Nadjwa Zamalek Dalimoenthe, Corieji Rita, Adhi Kristianto Sugianli ...................... 79 - 85

The Role of Platelet Concentration Transfusion on The Correlation between Platelet Number and Maximum Amplitude with Bleeding Volume Post Cardiopulmonary Bypass
Ryan Bayusantika Ristandi, Nida Suraya, Leni Lismayanti, Sylvia Rachmayati .............................. 86 - 90

The Relationship between Nitric Oxide and Glycemic Control in Controlled and Uncontrolled Type 2 Diabetes Mellitus Patients in the Adam Malik Hospital Medan
Yessy Suziarty, Ratna Akbari Ganie, Santi Syafri .............................................................. 91 - 94

Analysis of Red Blood Cell Distribution Width Value Towards Fibrotic Stage in Chronic Hepatitis B
Fatma Idris, Darwati Muhadi, Mutmainnah ........................................................................ 95 - 98

Correlation of Serum High-Density Lipoprotein Cholesterol and Homocysteine Level in Patient with Acute Myocardial Infarction
Yayie Dwina Putri, Rismawati Yaswir, Lillah, Tuty Priandani ........................................................ 99 - 103

Correlation between Galectin 3, Creatinine and Uric Acid on Stage V Chronic Renal Failure
Indranila KS, Guruhi Al, Meita H ................................................................................................. 104 - 110

LITERATURE REVIEW

Role of Delta Check in Clinical Laboratory Services
Osman Sianipar ............................................................................................................................. 111 - 114

CASE REPORT

Primary Myelofibrosis
Muhammad Irhamsyah, Darwati Muhadi, Mansyur Arif ............................................................. 115 - 120

Malignant Lymphoma with Leukemic Phase in Children
Sahriany S, Agus Alim Abdulah, Mansyur Arif ............................................................................. 121 - 128
CORRELATION BETWEEN PRESEPSIN AND SEQUENTIAL (SEPSIS-RELATED) ORGAN FAILURE ASSESSMENT (SOFA) SCORE AS AN ORGAN DYSFUNCTION MARKER IN SEPSIS

Stevi Dwiyani, Agnes Rengga Indrati, Leni Lismayanti, Adhi Kristianto S

Department of Clinical Pathology, Faculty of Medicine Padjadjaran University/Dr. Hasan Sadikin Hospital Bandung, Indonesia. E-mail: stevidwiyani@gmail.com

ABSTRACT

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The latest consensus in 2016 (Sepsis-3) identified organ dysfunction as an acute change in total SOFA score ≥ 2 points. An ideal laboratory examination is expected to detect sepsis in an early stage and correlated with the degree of infection. Presepsin or Soluble Cluster of Differentiation 14 Sub Type (sCD14-ST) is a proteolysis product of CD14 that is produced in 1-2 hour after innate immune activation during infections. The aim of this study was to determine the correlation of presepsin and SOFA score as an organ dysfunction marker in sepsis. This research was an observational, analytical cross-sectional study conducted in the Dr. Hasan Sadikin Hospital (RSHS) Bandung from September 2016 until July 2017. The subjects were 42 patients from the Emergency Department diagnosed as sepsis by clinicians using criteria of SOFA score ≥ 2 points. The serum sample was collected and measured for presepsin concentration. A correlation test was analyzed with Spearman analysis. This study showed the increasing of presepsin concentration associated with SOFA score (p=0.000; r=0.660). There was a positive correlation between presepsin and SOFA score as an organ dysfunction marker.

Key words: CD14, presepsin, sepsis, SOFA score

INTRODUCTION

Sepsis strikes an estimated 20 million people annually worldwide, but only half have been appropriately treated according to the best standards, even in developed countries with proper facility and healthcare systems. Global reports show an increase in sepsis mortality in developing countries such as 56% in Brazil, 45% in other developing countries, and 30% in developed countries.¹

Sepsis develops when the host response to infection becomes amplified, and then dysregulated. Proinflammatory cytokines release will induce reactive oxygen species (ROS) and nitric oxide activity, causing vasodilatation, vascular instability leading to hypotension and edema, coagulation disorders and organ failure.² Define identification of pathogens in sepsis was only obtained in half of the cases, and the bacterial causative was found in nearly 90% of cases.³

The European Society of Intensive Care Medicine and Society of Critical Care Medicine established the latest definition of sepsis in 2016 through a third international consensus (Sepsis-3), stating that sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is represented by assessment of Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score of 2 points or more, encompass clinical and laboratory parameters related to respiratory, coagulation, liver function, cardiovascular system, nervous system, and kidney function. Septic shock is identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or higher and serum lactate level greater than 2 mmol/L (>18mg/dL) in the absence of hypovolemia.⁴

Early diagnosis and treatment are the best methods to prevent sepsis deterioration into septic shock. Early detection of sepsis is crucial so that aggressive management and initial antibiotic treatment can be done before multiple organ dysfunction occurs.⁵ Diagnosis of sepsis can be difficult to obtain because clinical signs and systemic inflammation symptoms are hard to differentiate with symptoms of non-infection inflammation. An ideal diagnostic marker is expected to detect sepsis at an early stage, sensitive, fast and correlated with the degree of infection. Clinical and laboratory parameters have been combined to diagnose sepsis. However, there is a significant lack of evidence for
biomarkers to reliably diagnose sepsis.\textsuperscript{5}

Blood culture is the gold standard to detect pathogens in sepsis, but it takes 48-72 hours to obtain the result and has a low sensitivity and a high risk of interfering factors such as insufficient blood volume, false technique or sampling time.\textsuperscript{17} Sepsis biomarkers such as Procalcitonin (PCT) and C-Reactive Protein (CRP) have been used widely for infection markers but not specific enough as a sepsis marker because PCT and CRP are found to be increased in non-infection state such as severe trauma, massive surgery, malignancy, burn injuries, severe pancreatitis, autoimmune disorders, liver and kidney dysfunction, myocardial infarction, etc.\textsuperscript{3,15}

Research of presepsin has been developed regarding the role in the pathogenesis of sepsis and is expected to be a specific marker of infection produced in an early stage of infection (1-2 hour after exposure). Presepsin does not bind to Lipopolysaccharide (LPS), and its biological function remains unknown but is found to be increased significantly in sepsis.\textsuperscript{5,6,11} The role of presepsin and sepsis can be seen in Figure 1.

Peptidoglycan and LPS released from bacterial lysis will induce the inflammation process. During the acute phase response to Gram-negative bacteria, there is an increase of lipopolysaccharide binding protein (LBP) production by hepatocytes. The LPS-LBP complex is then transferred to CD14. Immune response to Gram-positive bacteria is also mediated by CD14.\textsuperscript{12} Cluster of differentiation 14 is a pattern recognition molecule that is identified on the surface of monocytes and macrophages, found in two forms; soluble CD14 (sCD14) that can be found in blood circulation and membrane-bound CD14 (mCD14) that is attached to the membrane of monocytes, neutrophils, macrophages, hepatocytes, cornea, and epithelial cells.\textsuperscript{13} Cells with mCD14 will be activated through LPS-mCD14 complexes. Membrane CD14 (mCD14) is also a receptor to peptidoglycan. Cells without mCD14 such as endothelium and epithelium will be activated through LPS-sCD14 complexes.\textsuperscript{14}

Presepsin or Soluble Cluster of Differentiation 14 Sub Type (sCD14-ST) is a 13kDa protein, derived from proteolysis of CD14, mCD14 and sCD14.\textsuperscript{13,15} In-vitro study of human monocytes induced with LPS (10 ng/mL) showed a release of presepsin 1 hour after induction, peaked in 3 hours and decreased in 4-6 hours.\textsuperscript{15}

LPS-LBP-CD14 complex in Gram-negative bacteria infection is then transferred to Toll-Like

![Figure 1. Role of presepsin in sepsis](image-url)
Receptor 4 (TLR4) and then binds to accessory protein myeloid differentiation-2 (MD2). Lipoprotein recognition in Gram-positive bacterial infection is mediated by TLR2. LPS and or peptidoglycan complex with CD14 and TLR triggering intracellular signaling events results in proinflammation cytokine release (TNF-α, IL-1, IL-6, IL-8, interferon). Dysregulation of cytokine release leads to a massive inflammation response, activated coagulation, and fibrinolysis system, Disseminated Intravascular Coagulation (DIC), and Multiple Organ Dysfunction Syndrome (MODS).

This study aimed to assess the correlation between presepsin a SOFA score based on the theory of sepsis pathogenesis so that presepsin could be used in early detection of sepsis.

METHODS

The design of this study was cross-sectional observation, correlation analytical. Forty-two patients, age >18 years old, who met the criteria diagnosis of sepsis (infection with SOFA score ≥ 2) were recruited consecutively in the Emergency Department Hasan Sadikin Hospital Bandung, Indonesia during April 2017 to July 2017. Patients with chronic kidney disease and hemolytic, lipemic and icteric samples were excluded in this study. Venous blood samples were collected and processed into serum, aliquoted in sterile polypropylene tubes and stored at -80°C until analysis. Presepsin measurement was done in the Immunology Division, Department of Clinical Pathology, Hasan Sadikin Hospital, Bandung, Indonesia using a manual Enzyme-Linked Immunosorbent Assay (ELISA). The results were read using a spectrophotometer.

The data results were analyzed statistically using Shapiro-Wilk test and Spearman correlation test. P-value<0.05 was considered statistically significant. Data were recorded in a written form and analyzed using statistical software.

RESULTS AND DISCUSSION

There were 42 subjects met the criteria in this study. Subjects characteristic are shown in Table 1.

Correlation tests between Presepsin a SOFA score were assessed with 95% confidence interval as shown in Figure 2.

Statistical analysis using Spearman correlation test showed r=0.660; p=0.0000 (p<0.05), meaning that there was a significant correlation between presepsin and SOFA score. Correlation coefficient value (r) showed a strong positive correlation. These concluded that higher presepsin concentration would be followed with a higher SOFA score and vice versa (Figure 2).

Sepsis contributes as a major mortality cause in the hospital influenced by varied risks factors. Subjects in this study were mostly aged >60 years old. Sepsis risks were increased concomitantly with age, based on the increased degeneration processes, comorbidity, malnutrition, and usage of invasive devices such as catheters. There were functional impairment in cellular a humoral immunity such as thymus atrophy caused that causes less activity of T-cell, alteration of antigen processing function in macrophage, decreased bactericidal activity, TLR expression, and plasma cell function.

Sepsis diagnosis can be obtained by blood culture examination. There were only a few positive blood cultures in this study (19%). Antibiotic treatment before blood culture examination might be a contributing factor. There were 52.4% subjects who had been treated with antibiotics before admission and from 34 subjects with negative blood culture, 47% of subjects had received antibiotic treatment. Gram-negative sepsis is caused by endotoxin release. Antibiotic treatment, especially that works on cell membrane might affect the amount of endotoxin in circulation. Another possibility is sepsis-causing microorganisms that cannot be detected by a conventional assays such as
fastidious microorganisms, bacterial toxins, and viral sepsis.\textsuperscript{23} Presepsin has an advantage in this case because innate immune cells recognizing endotoxin through Pattern Recognition Receptor (PRR) such as CD14 so that presepsin increases due to the increase of endotoxin.\textsuperscript{24} Low blood volume and wrong storage temperature might also affect the results of blood culture.\textsuperscript{5,7}

Sixty-nine percent subjects showed presepsin concentrations $<5.00$ pg/mL. A study by Ulla\textit{ et al.} demonstrated a range of presepsin between 1.579-4.647 pg/mL in sepsis and septic shock with a cut-off value 600 pg/mL.\textsuperscript{25} A study by Liu\textit{ et al.} showed a lower cut-off value 4.49 pg/mL with a range of 2.10-2.365 pg/mL.\textsuperscript{25} Presepsin concentration in this study was lower than previous studies. There is a possibility that presepsin concentration had been decreased by the time samples were obtained. Presepsin is produced early in innate immune response, then proceeded with an adaptive immune response after 96 hours.\textsuperscript{27} An in-vitro study showed a decrease of presepsin 4-8 hours after endotoxin exposure,\textsuperscript{11} but how long presepsin could be found in circulation before sepsis symptoms were developed is still unknown.

Kidney function can also affect the concentration of presepsin. This study excluded subjects with chronic kidney disease to prevent bias by nonsepsis kidney dysfunction. Ulla\textit{ et al.} did not exclude this criteria in their study and attained higher cut-off values compared to a study by Liu\textit{ et al.}, which excluded subjects with final stage renal failure.\textsuperscript{25,26} Presepsin is filtrated in the glomerulus and catabolized in proximal tubules so that presepsin concentration can be increased in low renal clearance.\textsuperscript{28}

Genetic factors and exposure to infection in Indonesia compared to developed countries may also contribute to the presepsin level. A study by Lisciandro\textit{ et al.} compared TLR based innate immune response in children born under typical western conditions (Australia) with a traditional condition of high microbial burden (Papua Nugini/PNG). The result showed that cord blood from PNG neonates had a lower proportion of B cells, monocytes (CD14), and dendritic cells, lower response of lipoteichoic acid-induced mononuclear cells to produce IL-6 and IFN, lower response of TNF-\alpha to LPS, higher activation baseline of APC and less responsive in-vitro compared to cord blood in Australian neonates. Higher inhibition markers IL-3 and IL-4 in PNG monocytes showed that cells had been activated in utero. A higher baseline activation of APC indicate refractory to APC to chronic pathogen exposure.\textsuperscript{27} Similar results were pointed out from a study by Smolen\textit{ et al.} which compared PRR based immune response in North American, South American, European and African population and showed a lower innate immune response in the African population compared to the others.\textsuperscript{32}

A study of presepsin has been focused on bacterial infection. There were 34 samples (81\%) in this study that showed no microbial growth in blood culture so that sepsis caused by viral or bacterial toxins should be considered. Variation of microorganism causing agents in sepsis might contribute to lower presepsin concentration in this study, compared to previous studies.

This study showed a strong positive correlation between presepsin a SOFA score, similar to a study by Ulla\textit{ et al.} (p=0.008). Higher correlations were shown in this study because clinical parameters in sepsis 3 emphasized on organ dysfunction. Subjects in this study were more homogenous compared to a study by Ulla\textit{ et al.} because chronic kidney disease were excluded in this study, resulting in a better correlation.\textsuperscript{25}
CONCLUSION AND SUGESTION

There was a strong positive correlation between presepsin and SOFA score as an organ dysfunction marker in sepsis. Presepsin could be a promising marker to detect sepsis in early stage, but it is important to remember that there is multiorgan involvement in sepsis so that it should not be used as a single marker in diagnosing sepsis. Further studies are needed to determine the cut-off value in the Indonesian population and to evaluate the performance of presepsin in an early and late stage of infection.

REFERENCES

antigen-presenting cells are functionally more quiescent in children born under traditional compared with modern environmental conditions. J Allergy Clin Immunol, 2012; 130(5): 1167-74 e10.