Correlation between Serum Mid-Regional Pro-Adrenomedullin and Sequential Organ Failure Assessment (SOFA) Score in Patient with Sepsis

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Abstrak

Most sepsis will develop into multi organ failure (MOF). To assess manifestation of MOF, SOFA score that includes several laboratory parameters for each organ is used. However, this requires time and is also costly. Recently, Mid-Regional Pro-Adrenomedullin (MR proADM) biomarkers are stated to be an alternative marker of MOF in sepsis because MR proADM is secreted by endothelials that may increase in sepsis or bacterial infection. The aim of this study was to analyze the correlation between serum MR proADM levels and SOFA score. This was a cross-sectional observational analytical study conducted in Dr. Hasan Sadikin General Hospital (RSHS) Bandung from August 2017 to July 2018. This study was a part of the bigger sepsis biomarker study. Samples used in this study consisted of 50 stored serum from the Sepsis Biomarker study in which the MR proADM was measured. Analysis using Spearman's correlation test showed a moderate positive correlation between serum MR proADM level and SOFA score (r=0,582, p=0.000), showing that MR proADM serum was directly proportional to SOFA score. It is concluded that MR proADM can be considered as one of the biomarkers for multi organ failure.

Key words: Multi organ failure (MOF), MR proADM serum, sepsis, SOFA score

Korelasi Kadar *Mid Regional ProAdrenomedullin* Serum dengan Skor *Sequential Organ Failure Assessment* (SOFA) pada Penderita Sepsis

Abstract

Sebagian besar sepsis akan berlanjut menjadi *multi organ failure* (MOF). Untuk mengetahui MOF digunakan skor SOFA yang memerlukan beberapa parameter laboratorium untuk tiap-tiap organ dan membutuhkan waktu dengan biaya yang mahal. Saat ini diketahui biomarker *Mid Regional proAdrenomedullin* (MR proADM) dapat digunakan sebagai biomarker MOF pada sepsis karena MR proADM disekresi oleh endotel yang akan meningkat pada keadaan sepsis atau infeksi bakteri. Tujuan penelitian ini mengetahui korelasi kadar MR proADM serum dengan skor SOFA. Penelitian ini bersifat observasional analitik dengan rancangan potong lintang yang dilakukan di Rumah Sakit Dr. Hasan Sadikin (RSHS) Bandung pada bulan Agustus 2017 sampai Juli 2018. Penelitian ini bagian dari payung penelitian "Biomarker pada sepsis". Bahan pemeriksaan berupa bahan biologis tersimpan sebanyak 50 sampel dan dilakukan pemeriksaan MR proADM. Hasil analisis menggunakan *Spearman's correlation test* menunjukkan korelasi positif sedang antara kadar MR proADM serum dan skor SOFA (r=0,582; p=0,000). Hal ini menunjukkan semakin tinggi kadar MR proADM serum maka semakin tinggi skor SOFA. Simpulan, terdapat korelasi positif sedang dan bermakna antara MR proADM dengan skor SOFA, sehingga MR proADM dapat dipertimbangkan sebagai salah satu biomarker pada *multi organ failure.*

Kata kunci: *Multi organ failure*, MR proADM serum, sepsis, skor SOFA

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Introduction

Sepsis is a syndrome caused by disruption of host response regulation against infections which is accompanied by organ function disorders. The definition of organ function disorder according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) is organ dysfunction in patients with serious illness that needs intervention in order to maintain the homeostasis. The most common cause of organ dysfunction is infection-related sepsis. More than 90% of cases of sepsis are caused by bacterial infections while others are caused by viral, fungal, and parasitic infections.[1]

Sepsis is the leading cause of death in patients treated in the Intensive Care Unit (ICU). The incidence of sepsis in the United States is 1,650,000 cases and is the leading cause of death in this country since it contributes around 50% of deaths.[2]

According to Surviving Sepsis Campaign in 2016, indication-based blood cultures or other type of cultures are generally performed in order to identify the bacterial infections that cause sepsis. Other laboratory tests are also performed to assess organ function disorders associated with infections. However, only 20–40% of blood cultures are tested positive and culture results will also take time and may delay diagnosis and treatment of sepsis.[3]

SOFA score is an organ dysfunction assessment system that assesses the functioning abilities of six organ systems (respiratory, cardiovascular, kidney, liver, central nervous, and coagulation systems) with a score of 0–24. This score may help in identifying sepsis. This is important because prompt diagnosis of sepsis and appropriate antibiotic therapy can prevent organ dysfunction and reduce mortality from sepsis.[1]

One of the organ function disorders biomarkers that are mostly studied is the examination of mid-regional pro adrenomedullin (MR proADM). MR proADM is an adrenomedullin (ADM) prohormone produced by endothelial layer of blood vessels and endothelial tissue of other organs such as the lungs, heart, kidneys, bones, hypothalamus, and anterior pituitary. The half-life of MR proADM is longer than that of ADM since its half-life is 2–3 hours whereas the half-life of ADM is only 22 minutes.[4] When infection occurs, the endothelial layer of blood vessel is damaged. The damage to the endothelium will activate the nucleus factor kappa β (NF-kB) to synthesize ADM from MR proADM. Adrenomedullin is released into the blood vessel and will bind to calcitonin receptor like receptor (CRLR) and receptor activity modifying protein (RAMP). The binding will increase cyclic adenosine monophosphate (cAMP), and stimulate the formation of nitric oxide (NO). The formed nitric oxide will cause vasodilation of blood vessels, reduction of vascular resistance, and hypotension. Systemic hypotension will result in edema of the organs which eventually causes organ dysfunction. MR proADM level increases in serum during infection or sepsis before organ damage occurs; thus, it can be used as a biomarker for organ dysfunction in patients with sepsis.[5]

The aim of this study was to calculate the correlation between MR proADM level and SOFA score in patients with sepsis and to determine the direction and strength of the correlation.

Methods

This was a cross-sectional observational correlative analytic study on adult patients with sepsis who were also the subjects of Biomarker Sepsis study.[6-9] Sepsis was diagnosed using the Sequential Organ Failure Assessment (SOFA) criteria by the clinician in the Emergency Room of Dr. Hasan Sadikin General Hospital Bandung during the period of June 2017 to July 2017. Fifty samples of serum were obtained from stored biological materials from the subject of Sepsis Biomarker study.[6–9] Stored biological material serum was stored at the temperature of -70ºC to -80ºC for 10 months and MR proADM was measured. The inclusion criterion in this study was patients with sepsis aged 18 years or above while the exclusion criterion was patients with sepsis accompanied by a history of chronic kidney disease (CKD), acute myocardial infarction, diabetes mellitus, and hemolysis, lipemia or jaundice.

The MR proADM examination in this study was performed using micro-enzyme linked immunosorbent assay (ELISA) method and the results were read using a spectrophotometer with a wavelength of 450 nm. Serum was used as the test material. The correlation between MR proADM levels and SOFA scores was analyzed using Spearman correlation test.[10] This study was conducted under an ethical clearance from the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung with reference number of LB.04.01/A05/EC/140/V/2018.

Table Characteristics of Research Subjects

Variables	Total n(%)	Median	Min.–max.
Age (year)	50	61	19–92
SOFA score		6	2–13
MR proADM(nmol/L) level		6,9	0,74–36,6

Notes: SOFA: sequential [sepsis-related] organ failure assessment; MR proADM: mid regional proadrenomedullin

Results

The characteristics of the subjects of this study, including age, SOFA score, and MR proADM levels, were presented in Table. These characteristic data were not distributed normally.

The statistical analysis on the level of MR proADM and SOFA score was performed using Spearman correlation test and resulted in a significant positive correlation with medium correlation strength which was equal to 0.582 (95% confidence level).

Discussion

This study revealed that the level of MR proADM and SOFA scores vary in patients with sepsis and, from the results of statistical tests of this study, there was a moderately positive correlation between the level of MR proADM and SOFA score. The patients age in this study ranged from 19 to 92 years. Based on 2016 National Report Sepsis[11], sepsis can occur at various ages. According to a previous study conducted by Martin et al.[12] patients with old age are more susceptible to infection due to decreased immunity factors, comorbidities, and malnutrition. Somatic mutations throughout a person's life will cause a decrease in cell regeneration capacity, cell repair, and immunity. Increased age will result in a decrease in the cellular and humoral immune systems due to thymus atrophy and decreased bactericidal activities.

The level of MR proADM in this study ranged from 0.74 to 36.6 nmol/L. This level tends to be higher compared to the results of the study conducted by Andaluz et al.[4]. The difference in the level of MR proADM is caused by several possibilities. The first possibility is the difference in the assay used. This study used the micro-elisa method while Andaluz et al.'s research used the TRACE method (Time Resolved Amplifield Cryptat Emision) which was an automated method of immunofluorescence. The second possible cause is the difference in immune responses due to genetic factors.

The results of statistical analysis regarding the correlation between MR proADM level and organ dysfunction based on SOFA score in patients with sepsis in this study showed a significant moderate positive correlation (r= 0.582; p=0.000). Based on these results it can be concluded that the increase in MR proADM level is related to the severity of organ dysfunction that occurs; in other words, the higher the level of MR proADM, the higher the SOFA score will be. The results of this study are similar to a study conducted by Gille et al.[13] who obtained a statistically significant positive correlation between MR proADM level and SOFA score with a p value of <0.001 and r=0.61.

The strength of the correlation in this study is likely due to differences in the length of infection in each subject, the effect of antibiotics administered, the type of antibiotics administration, and the length of antibiotics administration that can affect the level of MR proADM.

Cytokine release, which can stimulate the endothelium to secrete MR proADM, may occur in infection. MR proADM level will increase as the amount of cytokine secreted increases. The duration of exposure to infection can affect the level of MR proADM. Increased MR proADM levels are caused by the presence of cytokines, tissue hypoxia, and malignancy.[14] Administration of antibiotics at the beginning of infection can reduce the MR proADM level.[15] Antibiotics can kill bacteria by utilizing various mechanisms, such as by inhibiting bacterial synthesis, damaging bacterial cell walls, and modifying or inhibiting protein synthesis. Longer duration of antibiotics administration will greatly affect the MR proADM level.

The limitation of this study is that the researchers can only obtain the information regarding the administration of antibiotics but had difficulties in tracking data regarding the time and type of antibiotics administered.

Researchers were also unable to obtain the information regarding the timing of infection and sepsis at the time of sampling.

The conclusion of this study is that there is a moderate and significant positive correlation between MR proADM level and SOFA score and that MR proADM can be considered as one of the biomarkers in multi organ failure.

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