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CONTENTS

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INDONESIAN JOURNAL OF
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RESEARCH

RELATIONSHIP BETWEEN D-DIMER LEVEL AND CLINICAL SEVERITY OF SEPSIS

(Hubungan antara Kadar D-dimer dan Tingkat Keparahan Klinis di Sepsis)

Yessy Puspitasari[1], Aryati[1], Arifoel Hajat[1], Bambang Pujo Semedi[2]

ABSTRAK

D-dimer merupakan tolok ukur laboratorium yang menunjukkan derajat keparahan pada sepsis. Selama tahapan sepsis terjadi aktivasi prokoagulan yang tidak diimbangi aktivitas antikoagulan (depresi protein C dan meningkatnya pelepasan Plasminogen activator inhibitor) sehingga dapat meningkatkan hasilan fibrin polimer. Fibrin polimer yang telah mengalami cross-linked akan difibrinolisis oleh plasmin membentuk formasi D-dimer. Tujuan penelitian untuk menganalisis hubungan D-dimer dengan derajat keparahan klinis dari sepsis. Metode penelitian bersifat potong lintang observasional. Sampel darah sitrat dari 52 pasien sepsis yang dirawat di IRD, ICU, ROI, Ruang penyakit dalam RSUD. Dr. Soetomo Surabaya, dikumpulkan selama Februari 2016–Juni 2016. Kadar D-dimer diukur dengan metode ELFA (Enzyme Linked Fluorescent Assay). Proses dan tafsiran data menggunakan analisis deskriptif, One sample Kolmogorov-smirnov dan uji Pearson digunakan untuk menganalisis kenasaban. Didapatkan rerata kadar D-dimer 3879,46±2800,29 ng/mL. D-dimer pada non-survivors sepsis menurut skor APACHE II dan SOFA lebih tinggi daripada survivors sepsis. Terdapat kenasaban positif yang bermakna antara kadar D-dimer dengan skor APACHE II dan skor SOFA r=0,513 dan r=0,580 (p=0,01). Berdasarkan telitian ini dapat disimpulkan D-dimer memiliki kenasaban dengan derajat keparahan klinis dari sepsis, semakin tinggi nilai D-dimer menunjukkan keparahan sepsis.

Kata kunci: *D-dimer, aktivitas prokoagulan, aktivitas antikoagulan, protein C, plasminogen activator inhibitor, fibrin polimer, cross-linked fibrin, APACHE II, SOFA, tingkat keparahan sepsis*

ABSTRACT

D-dimer is an important laboratory parameter showing coagulation severity occuring in sepsis. Procoagulant activation that was not compensated by anticoagulant (C protein depression and Plasminogen Activator Inhibitor (PAI) increased) during sepsis could increase polymerized fibrin production. Cross-linked fibrin which underwent fibrinolisis by plasmin then produce D-dimer formation. The purpose of this study was to analyze the relationship of D-dimer with clinical severity of sepsis. Processing and interpretation of the data used a Descriptive analysis, one sample Kolmogorov-smirnov and Pearson test was used in analyze correlation. This was a cross-sectional observational study conducted in February 2016–June 2016. Citrate blood samples from 52 patients treated at the Emergency Unit, ICU, ROI, Internal wards of the Dr. Soetomo Hospital were examined for D-dimer levels using Enzyme Linked Fluorescent Assay (ELFA). APACHE II and SOFA score was used to assess severity of sepsis. Mean levels of D-dimer were elevated 3.879.46±2.800.29 ng/mL. Non-survivors of sepsis patients showed APACHE II and SOFA scores higher than survivors. There was a significant positive correlation between the levels of D-dimer with APACHE II and SOFA score with r=0.513 and r=0.580 (p=0.001). Based on this study, it can be concluded that D-dimer has a correlation with the clinical severity of sepsis, more higher D-dimer levels could determine the severity of sepsis.

Key words: D-dimer, procoagulan activation, anticoagulant activation, C protein, plasminogen activation inhibitor, polymerized fibrin, cross-linked-fibrin, APACHE II, SOFA, severity of sepsis

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INTRODUCTION

Sepsis is a major health problem in the world. Currently, sepsis is still the twelfth leading cause of death in the United States. In Indonesia, from 4,776 patients at a teaching hospital in Surabaya, 504 patients were diagnosed as sepsis with a mortality rate of 70.2% in 1996. Research at a teaching hospital in Yogyakarta reported in 2007, as many as 631 cases of sepsis had a mortality rate of 48.96%.[1] The incidence of sepsis every year is between 50–95% of cases and per 100.000 increased 9% every year.

Deaths caused by sepsis, were primarily due to multiorgan dysfunction syndrome. During sepsis, coagulation activation that is not offset by the anticoagulation activity can cause an accumulation of fibrin, thus contributing multiorgan dysfunction syndrome as the leading cause of death in sepsis. Increased D-dimer can be found in patients with Disseminated Intravascular Coagulation (DIC), severe sepsis, thromboembolic events, pregnancy, hepatic disease and surgery trauma. DIC is a syndrome characterized by a systemic activation of blood coagulation, which leads to increased formation of thrombin and fibrin intravascular.[2]

Elevated levels of D-dimer can indicate prognosis of sepsis patients. Some studies suggested that plasma D-dimer correlated with clinical outcomes in sepsis patients. The scoring system widely used to assess the degree of severity in this study is a scoring system Acute Physiology, Age and Chronic Health Evaluation (APACHE) II. There are some shortcomings about the assessment of the severity degree of the disease using APACHE II score system. SOFA score is used to explore the condition of the patients while in the ICU. SOFA score is used to determine the extent of organ malfunction. The average and the highest score of SOFA can be a predictor of outcome.

The purpose of this study was to analyze the relationship of D-dimer with clinical severity of sepsis. This research was an observational analytical study. Diagnosis of sepsis can established based on the North American and European Critical Care Societies Criteria of Sepsis 2001.[3]

METHODS

Citrate blood samples from 52 patients treated at the Emergency unit, ICU, ROI, Internal wards of the Dr. Soetomo Hospital, were examined for D-dimer by Enzyme Linked Fluorescent Assay (ELFA) in February 2016–June 2016. D-dimer and APACHE II score was taken on the first day, while SOFA score was assessed on 1–5 days.

RESULTS AND DISCUSSION

Blood for research subjects were collected as many as 52 samples, females were more than males. The mean age of sepsis patients were elderly around 51.31±17.64 years. A previous research, showed more male patients, this was caused by the influence of sex hormones. Androgens are immunodepressive, while estrogen increases cellular and humoral immune responses. In this study, as many as 32.7% of patients died. The incidence of sepsis patients increased at an old age. A previous study found an average of 63.8 years in sepsis patients and its incidence increased with age.[4] Dysregulation of the immune system, the potential for malnutrition, increased comorbidities, exposure to resistant pathogens in nursing homes, and increasing dependence on invasive medical devices caused them more susceptible to infections and complications that may accompany.[5] Demographic characteristics of sepsis patients can be seen in Table 1.

The mean level of D-dimer was 3,879.46±2,800.29 ng/mL with a range of 368.16 ng/mL-14.980 ng/mL. The results were consistent with a previous research that said that 91% of the 1,529 failures of the

Table 1. Characteristics of sepsis patients

Sample characteristic	Result
Gender n (%)	
Males	19 (36.5%)
Females	33 (63.5%)
Age (year) average ± SD	51.31±17.64
Alive	35 (67.3%)
Died	17 (32.7%)

Table 2. Level of D-dimer in various clinical condition

	n	D-dimer level (ng/mL) mean±SD	
Survivors (APACHE II)	29	2,510.72±1,777.37 ng/mL	p=0.001
Non-survivors (APACHE II)	23	5,605.25±2,928.21 ng/mL	p=0.001
Survivors (SOFA)	42	3,194.05±2,008 ng/mL	p=0.017
Non-survivors (SOFA)	10	6,758±3,829 ng/mL	p=0.017
Survived	35	3,383.96±2,169.12 ng/mL	p=0.064
Died	17	4,899.60±3,654.33 ng/mL	p=0.064
Total	52	3,879.46±2,800.29 ng/mL	

microcirculation of the samples showed levels above normal, with median levels of D-dimer of 3.2 mg/mL (=3.200 ng/mL) mean of 8.2±0.42 ug/mL.[6]

Non-survivor patients by APACHE II and SOFA showed D-dimer levels higher than survivor patients. Patients who died had higher levels of D-dimer than live patients. This was consistent with the theoretical framework that in patients with sepsis coagulopathy occurred ie coagulation activity with unbalanced anticoagulation activity resulting in an increase in the formation of fibrin. Fibrin which experienced cross-linkage will undergo fibrinolysis to form D-dimer.

There were two samples of D-dimer with levels <500 ng/mL, patients with type II diabetes, cholelithiasis, second attack stroke with D-dimer levels 368.16 mg/mL and patients with jaundice proevaluation suspected Weil disease with D-dimer level of 387.35 ng/mL. Possible results of D-dimer were lower due to low level involvement of organ dysfunction. This was proven with lower SOFA score in both patients, even though the criteria for sepsis was met.

Pearson analysis result showed a significant positive correlation between D-dimer with APACHE II score (r=0.513) and the SOFA score (r=0.580) (p=0.001). Plasma D-dimer was strongly correlated with the severity of disease and organ dysfunction in patients with circulatory failure or infections indicating an

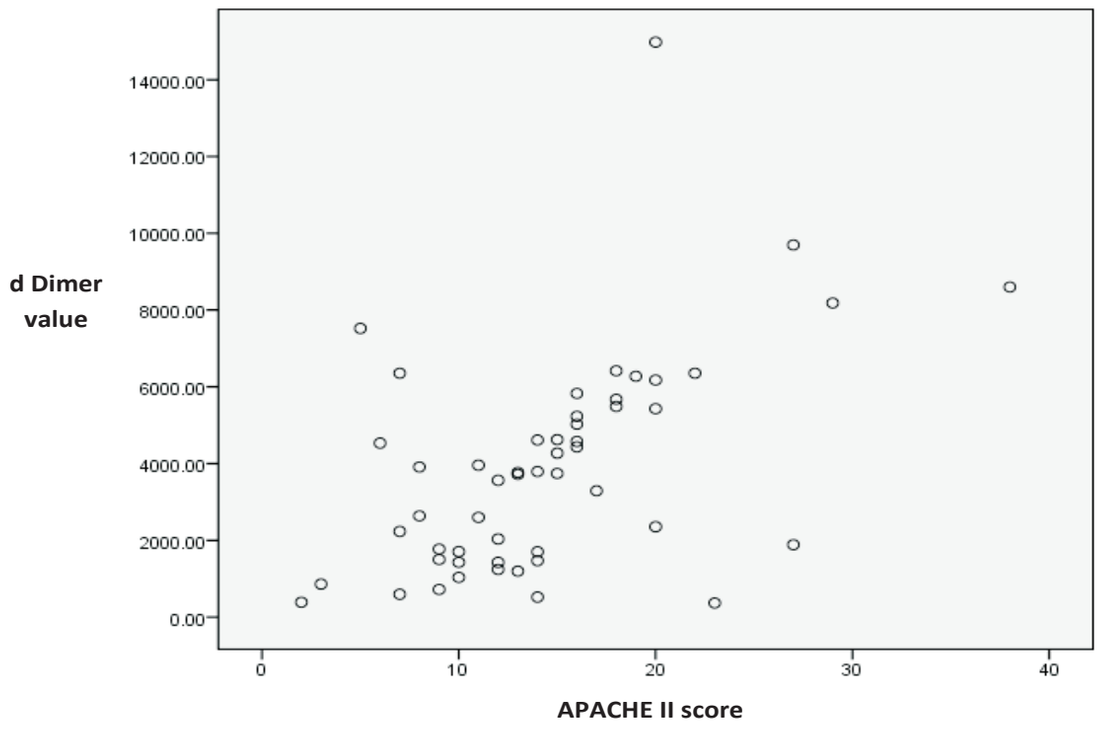

Figure 1. Correlation of D-dimer level between APACHE II

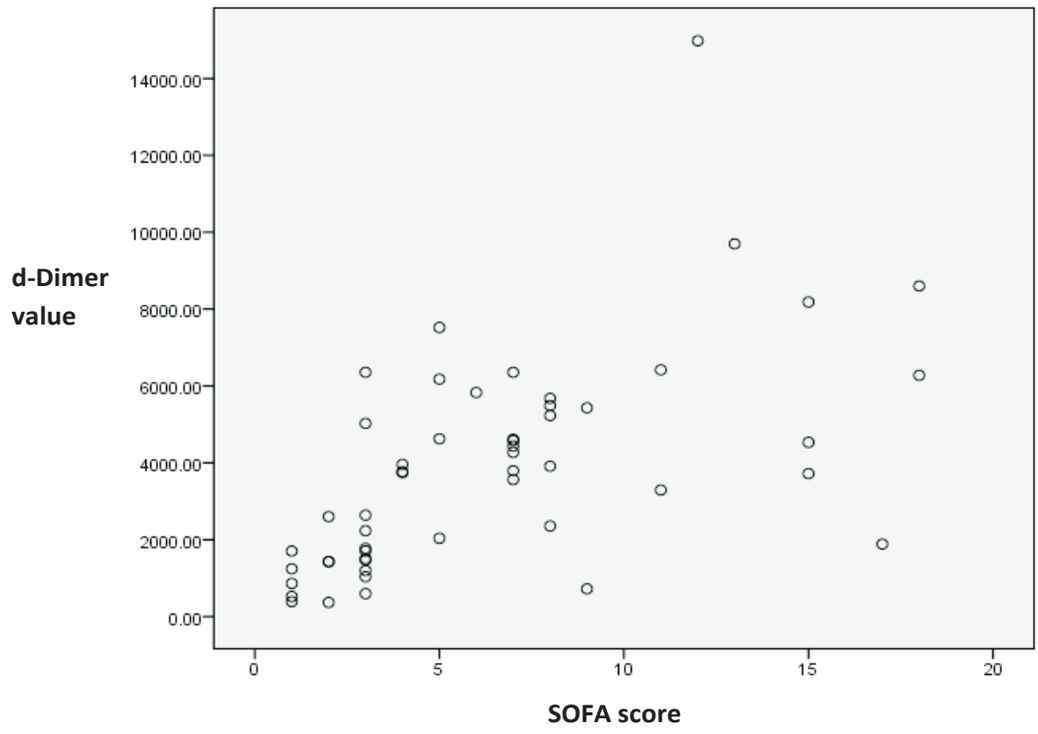

Figure 2. Correlation of D-dimer level between and SOFA score

Table 3. Clinical characteristics of sepsis patients based on severity

Variables	Sepsis n=11 (21.2%)	Severe sepsis n=28 (53.8%)	Septic shock n=13 (19.2%)	p
Ages	46.64±17.14	53.07±1.631	51.46±21.26	p>6
Sex M/F	4/7	9/19	6/7	p>0.05
APACHE II	11.82±5.382	14.07±5.185	17.38± 9.59	p>0.05
SOFA	3.27±2.57	5.93±3.88	10.31±4.69	p≤0.001
D-dimer(ng/mL)	525.46±1,405.75 ng/mL	3.890±801.39 ng/mL	848.56±3,885.70 ng/mL	p=0.004
Alive	10 (2.6%)	23 (65.7%)	2 (5.7%)	p≤0.001
Mortality in less than 48 hours	1 (12.5%)	3 (3.5%)	4 (50%)	p≤0.001
Mortality in more than 48 hours	0 (0%)	2 (22.2%)	7(77.8%)	p≤ 0.001

increase in plasma D-dimer.[6] Plasma D-dimer had a significant positive correlation with the SOFA score (r=0.625) and APACHE II (r=0.573) in sepsis patients p<0.005 in a study conducted on a total of 641 patients with different severity of sepsis and 150 patients with SIRS who were examined D-dimer during the first 24 hours in the ICU.[9]

According to the severity of sepsis, 52 samples were divided into patients with sepsis, severe sepsis and septic shock. Statistically, the mean APACHE II score was not significant by increased but clinically increased, while the increase in SOFA score was significant. These results showed that APACHE II score could not be used to determine the severity of sepsis, because the APACHE II score assessed high component of chronic health problems and age of the patient too high, so APACHE II score was less accurate in assessing the severity of the patients.[10,11] It was rated that the APACHE II scores were subjectively likely to affect the statistical results. The mean level of D-dimer showed increasing results based on the severity of sepsis (p=0.004). The mean level of D-dimer was the highest in patients with septic shock. This showed that the higher D-dimer levels could determine the severity of sepsis.

CONCLUSIONS AND SUGGESTIONS

The range of D-dimer levels obtained in this study was 368.16 ng/mL–14.980 ng/mL, the mean level of D-dimer was 3,879.46±2,800.29 ng/mL. Non-survivor patients by APACHE II and SOFA scores showed that the mean D-dimer was higher (significant) compared to survivors. Patient who died had higher APACHE II and SOFA scores (significant) than patients who were still alive. There was a significant positive correlation between D-dimer levels with APACHE II and SOFA scores. APACHE II score can not be used to determine the severity of sepsis although it was clinically associated with an increase in the severity of sepsis, while the SOFA score could be used to determine the severity of sepsis. High D-dimer levels could determine the severity of sepsis.

A further research with a larger population and a larger sample is needed with the uniform state basic clinical sepsis patients as a source of infection, underlying diseases, D-dimer has to be performed serially so that it can be compared with a serially severity score, it is necessary to check the D-dimer in normal subjects or non-sepsis patients as a comparison (as a control).

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