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HOW CLOSELY IS PROTEIN CARBONYL (PCO) LEVEL CORRELATED WITH SEPSIS-RELATED ORGAN FUNCTION ASSESSMENT (SOFA) SCORE?

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ABSTRACT

Objective: Sepsis remains an unsolved problem in hospitals since its mortality rate is not significantly reduced despite considerable therapy efforts. The most used prognostic tool is the Sepsis-related Organ Function (SOFA) score, which requires several clinical and laboratory examinations; our recent studies also showed that the protein carbonyl level (PCO) has prognostic value in predicting sepsis mortality.

Methods: This prospective study was designed to assess the correlation between PCO values and the SOFA score following ethical approval. Adult patients aged>18 y who met the Sepsis-3 definition were included. Exclusion criteria were patients not admitted to the intensive care unit. Dropout criteria included mortality within the 1h bundle protocol. Baseline demographic data and blood collection were measured for all subjects. Subjects were treated with the 1h bundle protocol and observed for 28 d.

Results: Fifty-nine subjects were included, with no significant differences in age, sex, diagnosis, microbiology or Charlson's Comorbidity score between survivors and non-survivors. The SOFA score was higher in non-survivors (10.90±3.38 vs 8.11±3.07; p=0.003), as was the PCO value (24.5 [14.67-81] vs 18 [15-21.33]; p<0.001). However, the correlation between PCO and SOFA score is very weak (r=0.101; p=0.45).

Conclusion: Both the PCO level and SOFA scores were higher in non-survivor septic patients. However, they have a very weak correlation and cannot be used interchangeably.

Keywords: Correlation, Mortality, Protein carbonyl, Sepsis, SOFA score

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INTRODUCTION

Sepsis remains an unsolved problem in hospitals as well as in other critical care settings such as intensive care units and emergency rooms; its morbidity and mortality rate remains high. One-third of patients who die in the hospital suffer from sepsis [1]. Sepsis is the leading cause of mortality in the ICU, with a mortality rate of 25% in uncomplicated cases and 80% in multiple organ failure cases [2]. Based on our sepsis database, the incidence of sepsis in 2017 was 30.1% and the 28-day mortality rate was 46.8%.

Despite considerable therapy efforts, the sepsis mortality rate has not been significantly reduced. The most used prognostic tool is the Sepsis-related Organ Failure Assessment (SOFA) score. Current guidelines set a SOFA score of two or more points to represent life-threatening organ dysfunctions in sepsis-related to the dysregulated host response to infection [3]. However, the score requires sequential examinations, including clinical and laboratory variables.

Many studies support the pivotal role of oxidative stress in sepsis pathogenesis [4, 5]. Oxidative stress is described as an imbalanced condition between oxidants, as produced by inflammatory cells, and antioxidants. The stress induces mitochondrial dysfunction and cytopathic dysoxia, resulting in organ damage [4, 6, 7]. Recent studies showed that protein carbonyl (PCO) has a prognostic value, more than other oxidative stress surrogates, in predicting sepsis mortality [8]. PCO is a specific surrogate of stress oxidation, in which the carbonyl group formation in the side chains affects its properties and increases its susceptibility to proteolysis [9].

Our current knowledge with respect to septic patients is still limited since no study has correlated the PCO level and the SOFA score. Our study aimed to assess the correlation between PCO values and SOFA scores in septic patients.

MATERIALS AND METHODS

Patients

This prospective study was conducted following ethical approval No. 047/kepkrsmhfkunsri/2019. The study took place in a single tertiary teaching hospital in Palembang, South Sumatera, Indonesia. The inclusion criteria were adult patients aged>18 who met the Sepsis-3 definition. The exclusion criterion was patients not admitted to the ICU. The dropout criterion included mortality within the 1h bundle protocol. Trained investigators analyzed all eligible patients.

Research protocol

Baseline demographic data and blood laboratory examinations were measured for all subjects. Demographic variables included age, sex, diagnosis classification, microbiology result, the Charlson comorbidity score, and the SOFA score. Subjects were treated with the 1h sepsis bundle protocol [10]. The blood sample was taken from a peripheral vein at a one-time point of earlier sepsis recognition. Arterial blood gas analysis was measured using Stat Profile pHOx® Series (Nova Biomedical, Waltham, U. S.). PCO levels were determined using an enzyme-linked immunosorbent assay using Bio-Rad (Bio-Rad Laboratories, California, U. S.). Patients were observed for 28 d.

Statistical analysis

This was a prospective observational analytic study. Subjects were included in the study using consecutive sampling based on the eligibility criteria. Continuous variables (age, SOFA score, and PCO level) were expressed as mean±standard deviation for data that were normally distributed or as median (min-max) for data that were not. Categorical variables (sex, diagnosis, microbiology, and Charlson's Comorbidity score) were expressed as numbers (percentages). The differences of normally distributed continuous variables (age and

SOFA score) between non-survivors and survivors were analyzed using an independent t-test, while the not normally distributed variable (PCO level) was analyzed using the Mann-Whitney test. Categorical variables of two groups (sex and diagnosis) which met the requirement were analyzed using the X^2 test, while those variables consisting of more than two groups (microbiology and Charlson's Comorbidities score), which did not meet the requirement were analyzed using the Mann-Whitney test. The correlation between the PCO level and SOFA score was analyzed using Spearman's correlation. Significance was determined as a p-value<0.05.

RESULTS

A total of 72 subjects were recruited to the study; 13 were dropped out due to being unable to complete the sepsis bundle protocol. Fifty-nine subjects were analyzed; 40 of them died (the 28-day mortality rate was 67.8%). There were no notable differences in age, sex, diagnosis or Charlson's Comorbidity score between survivors and non-survivors. The SOFA score was higher in non-survivors (10.90±3.38 vs 8.11±3.07; *p*=0.003), as was the PCO value (27.18±11.89 vs 18.39±2.01; *p*=0.002).

Table 1: Subjects' characteristics

Variable	Total N = 59 (100%)	Non-survivor N = 40 (67.8%)	Survivor N = 19 (32.2%)	*p*
Age	50.32+14.91	51.73+14.54	47.37+15.63	0.298
Sex				
Female	29 (49.2)	18 (45.0)	11 (57.9)	0.412
Male	30 (50.8)	22 (55.0)	8 (42.1)	
Diagnosis				0.780
Medical	36 (61.0)	25 (62.5)	11 (57.9)	
Surgical	23 (39.0)	15 (37.5)	8 (42.1)	
Microbiology				0.087
Gram-negative	35 (59.3)	21 (52.5)	14 (73.7)	
Gram-positive	4 (6.8)	3 (7.5)	1 (5.3)	
Fungal	6 (10.2)	4 (10.0)	2 (10.5)	
Mixed organisms	4 (6.8)	3 (7.5)	1 (5.3)	
Other	10 (16.9)	9 (22.5)	1 (5.3)	
Charlson's Comorbidity score				
0	5 (8.5)	2 (5.0)	3 (15.8)	0.650
1-2	39 (66.1)	28 (70.0)	11 (57.9)	
3-4	7 (11.9)	5 (12.5)	2 (10.5)	
>5	8 (13.6)	5 (12.5)	3 (15.8)	
SOFA score	10.00+3.51	10.90+3.38	8.11+3.07	0.003
PCO level	20.67 (14.67-81)	24.5 (14.67-81)	18 (15-21.33)	<0.001

After analyzing the data, we found there was a positive correlation between the PCO level and the SOFA score. However, this result did not support our assumption that the PCO level might replace the SOFA score as a predictor of sepsis mortality since the correlation was very weak and insignificant (r=0.101; *p* = 0.045). The fig. below shows us that there was no linearity between PCO levels and SOFA scores in septic patients.

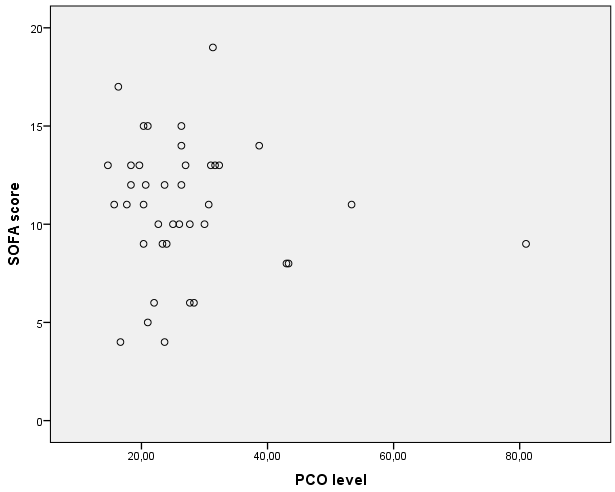

Fig. 1: Scatterplot of PCO level and SOFA score

DISCUSSION

A total of 72 subjects were included in the study, with 13 dropped out due to the inability to complete the sepsis bundle protocol. This study found that the 28-day sepsis mortality was 67.8%. Current guidelines define sepsis as life-threatening organ dysfunctions represented by a SOFA score of two or more points [3]. The dysfunctions are due to a dysregulated host response to infection [3]. The rate increases in patients suffering from multiple organ dysfunctions. The more impaired organs, the greater the increase in mortality risk. A SOFA score above 12 was an independent mortality risk factor (OR = 6.8; CI95% 1.3-37; *p*= 0.026) [11].

In this study, there were no significant differences in age, sex, diagnosis or Charlson's Comorbidity scores between survivors and non-survivors. The SOFA score was higher in non-survivors (10.90±3.38 vs 8.11±3.07; p=0.003). This result is consistent with a retrospective cohort study by Medam *et al.*, which found that the comparison in SOFA scores between the septic shock associated-mortality group compared to non-septic shock was 10±3 vs 8±2; p=0.07 [11]. Lie *et al.* also found that the SOFA score was notably higher in septic patients who did not survive (6.7±3.8 vs 4.6±2.9; p<0.001) [12].

In sepsis, oxidative stress occurs along with a high inflammatory state. Inflammatory cells produce reactive oxygen species in large quantities, which can damage biological systems [13]. Protein modification occurs due to direct oxidative attack on lysine, arginine, proline or threonine or due to secondary reactions of cysteine, histidine or lysine residues with reactive carbonyl compounds. This attack can produce PCO derivatives (reactive ketones or aldehydes), which react with 2,4-dinitrophenylhydrazine [14, 15]. Protein oxidation, including protein carbonylation, is shown to alter enzyme activity and DNA binding with transcription factors as well as to make proteins more susceptible to proteolytic degradation [16]. Abu-Zidan *et al.* found a positive correlation between proteolysis and plasma PCO (p<0.03) [17].

It is difficult to induce carbonyl, so its level indicates more severe oxidation [14]. PCO has an advantage over lipid peroxidation products (such as malondialdehyde (MDA)) as an oxidative stress surrogate because of its more stable properties [14]. It is formed earlier and circulates in the blood for a longer period [14]. Costa *et al.* found that PCO was more related to mortality in septic shock patients compared to MDA (OR 1.424 vs 1.087; CI95% 1.268-1.6 vs 0.805-1.467; p<0.001 vs 0.59) [18].

This study found that PCO values were higher in non-survivors (27.18±11.89 vs 18.39±2.01; p=0.002). This result is consistent with Abu-Zidan *et al.,* who found that PCO concentration was significantly higher in sepsis patients compared to healthy patients (p<0.0001)[17]. Andresen *et al.* found that carbonyl increased by 4.5 times in shock septic patients compared to normal values [19]. Costa *et al.* showed an association between PCO levels and mortality in septic shock patients (OR 1.424; CI95% 1.268-1.6; p<0.001) [8].

We found there was a very weak correlation between PCO levels and SOFA scores (r=0.101; p=0.45). This result means that PCO levels and SOFA scores in septic patients cannot be used interchangeably to predict mortality.

However, our study has some limitations. First, the study was conducted in a single-center, so its results cannot be generalized to other institutions. This necessitates further multi-center research. Second, PCO levels and SOFA scores, which correlated in the study were taken at one point in time. This measurement did not reflect the course of the disease. Further research is needed to correlate serial or remeasured variables.

CONCLUSION

Around two-thirds (67.8%) of septic patients in the study died. In this study, there were no differences with respect to age, sex, diagnosis classification, microbiology result or Charlson's Comorbidity scores between survivors and non-survivors among the septic patients. Both PCO levels and SOFA scores were significantly higher in non-survivors. This shows an association between life-threatening organ dysfunctions represented as SOFA scores and a high level of oxidative stress represented as PCO with respect to sepsis mortality. However, they have a very weak correlation, so they cannot be used interchangeably. The authors suggest further studies in multi-center research and elaborate serial measurements to overcome the study limitations.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

All authors have none to declare.

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