ABSTRACT

Aim: to obtain: (1) the correlation between initial CRP level on admission with the decrease of albumin level during hospitalization, (2) the mean difference in initial CRP level between the groups of patients with and without decrease of albumin level during hospitalization, and (3) the risk difference of decreasing albumin level in patients with high CRP levels on the admission compared to whom with low CRP level on the admission, in hospitalized elderly patients with CAP.

Methods: a prospective cohort study were conducted on 23 hospitalized elderly patients with CAP. Subjects with diseases and conditions that could interfere with CRP and albumin level besides pneumonia infection were excluded. The patient’s CRP level was measured upon the initiation of the study, while the patient’s albumin level was measured on the first and fifth day of hospitalization to observe changes that took place during 5 days of hospitalization. Pearson’s correlation test, independent t-test, and chi-square test were used to answer the objectives of the study.

Results: we found that there were negative correlation between the initial CRP level and the percentage of albumin level decrease during 5 days of hospitalization ($r=-0.442$, $p=0.035$) and significance difference in the mean initial CRP level between patients with and without decreasing albumin level (mean difference 99.69 mg/L, 95%CI 13.25 to 186.13 mg/L; $P=0.026$). The risk difference of decreasing albumin level during hospitalization between patients with high and low initial CRP levels did not attain statistical significance (RR 2.12, 95%CI 0.26 to 29.07; $p=0.621$).

Conclusion: in hospitalized elderly patients with community-acquired pneumonia with high initial CRP levels tend to experience a decrease in albumin level during hospitalization.

Key words: CRP, albumin, community-acquired pneumonia, elderly.

INTRODUCTION

Community-acquired pneumonia (CAP) is a common health problem in elderly patients. Some study reported as well as epidemiological and clinical data demonstrate that the incidence, prevalence, and the mortality rate of CAP increase as a person gets older.\textsuperscript{1,4} One of the factors that facilitates the development of pneumonia in an elderly person and acts as a negative prognosis factor and predictor of death in persons with pneumonia, is low albumin level.\textsuperscript{5-8}

The role of hypoalbuminemia in causing a bad course of disease is by far more related to malnutrition, which is often found in an elderly.\textsuperscript{9} However, decreased albumin levels during acute infection is also directly caused by the underlying inflammation process, to some extent, could provide an illustration of the severity of infection/inflammation.\textsuperscript{10-15} Because of this characteristic during acute inflammation, albumin often mentioned as a negative acute-phase protein.\textsuperscript{16,17} At the same time the level of C-reactive protein (CRP) elevates, as a positive acute-phase protein that have been recognized and widely studied in various types of acute infection, includes pneumonia.\textsuperscript{17-20}

The relationship between albumin and CRP level in inflammation has been widely investigated, but mostly only in various chronic diseases, i.e. in patients with end-stage renal disease (ESRD) undergoing hemodialysis\textsuperscript{1,21-23} and the elderly population assumed to have various chronic inflammation.\textsuperscript{24} In patients with acute infection, especially pneumonia, there has only been one study that observed the correlation between albumin with CRP and other acute inflammatory markers at the beginning of hospitalization in hospitalized CAP patients.\textsuperscript{8} There have not been any studies that particularly investigate the relationship between initial CRP level as a representation of the severity of underlying acute infection with the decrease in albumin level during hospitalization.

Based on the result of previous studies and the
pathophysiology of changes in albumin and CRP level in acute infection, we assume that high initial CRP levels in elderly patients hospitalized with CAP is related to decreased albumin level during hospitalization.

Therefore, we designed this study, the objectives of which are to obtain: (1) the correlation between initial CRP level with the extent of decrease in albumin level during hospitalization, (2) the mean difference in initial CRP level between patients with and without decreased albumin levels during hospitalization, and (3) the increase in risk of decreasing albumin level during hospitalization in patients with high initial CRP levels compared to patients with low initial CRP levels, in hospitalized elderly patients with CAP. The results of the study are expected to increase awareness about the incidence of decrease albumin level, along with its consequences, in patients with high CRP levels at the beginning of their hospitalization.

METHODS

A prospective cohort study was conducted in elderly patients (aged 60 years or more), diagnosed with CAP and hospitalized at Cipto Mangunkusumo Hospital, Jakarta. The initial CRP level and changes in albumin level after 5 days of hospitalization were measured. Patients with diseases or conditions other than CAP that could interfere with the albumin and CRP level was excluded from the study, i.e. patients with congestive heart failure functional class III or IV according to NYHA classification, chronic renal diseases with < 30 mL/minute of creatinine clearance, severe dehydration, ascites and/or anasarca oedema, liver cirrhosis, proteinuria (of 2+ or more, or 300 mg or more in 24 hours), stadium III or IV pressure ulcers, autoimmune diseases with or without immunosuppresant therapy, terminal stage malignancy, acute myocardial infarction (STEMI and Non-STEMI), moderate or severe immobilization for more than 3 days, and the presence of infections other than community-acquired pneumonia.

CRP level was only measured upon admission, using Dade-Behring high-sensitivity CRP immunonephelometry method. Albumin level was measured twice, at the beginning of hospitalization and on the fifth day of stay, using bromcesol green method. Initial CRP level was correlated with changes in albumin level (in percent) during the five days of hospitalization, and the mean difference of initial CRP level was calculated between patients with and without decrease in albumin level during the 5 days of hospitalization (a patient is considered to have a decrease in albumin level if the albumin level decreases ≥10% from the initial albumin level). The relative risk of decrease albumin level during the 5 days of hospitalization was calculated in 2 groups of patient based on the initial CRP level (high CRP level, > 20 mg/L and low CRP level, < 20 mg/L). During hospitalization, the patients received antibiotics therapy and diet (including protein diet) as indicated, while patients who received albumin infusion during hospitalization were excluded from the study.

Analysis were conducted on the data obtained as follows: (1) Pearson correlation test on initial CRP level and percentage of changes in albumin level during hospitalization as numeric variables; (2) independent t-test on the mean difference of initial CRP level between patients with and without decrease in albumin level; and (3) chi-square test to obtain the relative risk of albumin level decrease during hospitalization in patients with high initial CRP levels compared to patients with low initial CRP levels. All descriptions and analysis were conducted using the SPSS version 10.0 for Windows® computer program. The study protocol had obtained ethical clearance from the Ethical Research Committee in Faculty of Medicine, University of Indonesia, Jakarta.

RESULTS

From March to June 2005, at Dr. Cipto Mangunkusumo Hospital, we found 26 elderly patients diagnosed with community-acquired pneumonia who fulfilled the subject selection criteria for the study, consisting of 13 male and 13 female subjects. Out of the 26 patients, only 23 patients completed the study until the fifth day of hospitalization (two patients were discharged and one patient was died before five days of observation). The three patients that did not complete the study were not calculated in cohort analysis, but the data obtained at the initiation of study are still included in the study subject characteristics. Basic laboratory test results, and the level of initial CRP and albumin level are presented in Table 1.

After five days of hospitalization, seven out of 23 patients demonstrated a 10% or more decrease in albumin level, and an overall significant decrease was found in the mean albumin level on the fifth day compared to the first day measurement (3.24 g/dL to 3.05 g/dL, P 0.004). Table 2 shows the comparison of some clinical and laboratory variables (other than CRP level) at the beginning of hospitalization between patients with and without reduced albumin level during hospitalization.

The data of the first-day CRP level from 23 patients who completed the study showed abnormal distribution. After data transformation for correlation analysis, the first-day CRP level showed negative correlation with
C-reactive Protein Levels and Decrease of Albumin Levels

DISCUSSION

This is the first study to investigate the relationship between CRP level with reduction in albumin level during acute infection in hospitalized elderly patients. Community-acquired pneumonia was chosen as a model of acute infection being studied, for two reasons: (1) the relatively high incidence, prevalence, and mortality of pneumonia in elderly population require attention to the factors that might contribute to the occurrence and course of the disease in the elderly, and (2) the severity of infection and inflammation quantified with CRP level, for the purpose of studying the effect to albumin level decrease in this study, have often been proven to be representative for pneumonia in all age groups, including the elderly.

The mean initial CRP level in elderly patients with pneumonia in this study was greatly increased (Table 1), and this is in line with results from other studies. This increase, although also found in other bacterial infections, is a sensitive clinical marker and could be used to make diagnosis and it reflects the severity of pneumonia infection, including in the elderly. The increase in CRP level in acute infection is stimulated by interleukin-6 (IL-6) as a proinflammation mediator, and also contributes to complement activation and interacts with the humoral and cellular immune system. Experimental studies also show that CRP has protective effects on lung infection (especially the ones caused by Streptococcus pneumoniae), because it is also expressed in the alveoli.

Percentage of decrease in albumin level during 5 days of hospitalization ($r = -0.442, P = 0.035$; Figure 1).

We have mentioned above that a 10% or more decrease of albumin level was found in 7 out of 23 subjects who completed the study. When those seven patients were gathered as one group (group with albumin level decrease) and the rest were considered as one other group (group without albumin level decrease) using t-test in the independent data group, after normalization of data distribution, we found a significant difference in the mean first-day CRP levels between the two groups (mean difference 99.69 mg/L, 95% CI 13.25 to 186.13 mg/L; $P = 0.026$). The relative risk (RR) of decreasing albumin level in patients with high initial CRP level compared to patients with low initial CRP level was 2.12 (95%CI 0.26 to 29.07; $P = 0.621$).
On the other hand, a significant decrease in mean albumin level was found on the fifth day of hospitalization. Hedlud et al. found that serum albumin is decreased until the sixth day of hospitalization, and then it increases again on the ninth day, in patients with CAP. Sullivan et al. in their prospective study found lower albumin level upon patient discharge from the hospital (mean 29.1 g/L) compared to the admission (mean 36.6 g/L), in hospitalized elderly patients. Reduction in albumin level during hospitalization in patients hospitalized due to acute conditions seems to be greatly influenced by the severity of underlying infection/inflammation, although the role of nutrition could not be eliminated. This role of infection/inflammation that we investigated in this study.

From the correlation study, a negative correlation was found between high CRP level with percentage of albumin level decrease during 5 days of hospitalization, although the correlation was not too strong. (Figure 1) In other words, the higher the patient’s initial CRP level, the greater the decrease in albumin level during five days of hospitalization. Two studies that correlates CRP and albumin level at the same time showed almost similar results. The study by Hedlund et al. found weak but significant negative correlation ($r = -0.30$, $P = 0.0003$) between CRP and albumin levels at the admission in patients with hospitalized community-acquired pneumonia. A study in patients with end-stage renal disease having hemodialysis also found similar results ($r = -0.554$, $P <0.001$).

The correlation between CRP and albumin level is interesting to observe, because both are acute-phase proteins whose serum concentration changes during acute infection/inflammation. Since CRP is a positive acute-phase protein, while albumin is a negative acute-phase protein, the correlation between both is expected to be negative. This study and two other studies mentioned above showed a negative correlation, although the tendency tends to be weak. However, by considering the rate of synthesis, half life, and greatly different responses of each acute-phase proteins in an infection/inflammation process, it seems to be difficult to obtain the correlation between CRP and albumin level in parallel time. Besides, previous nutritional status influences initial albumin level to varying degrees. Therefore, the judgment to correlate initial CRP level with albumin level reduction during the first few days of hospitalization that done in this study is more acceptable, instead of just correlating CRP and albumin level at the same time.

The second finding of this study is the significant mean difference in initial CRP level between the group of patients with and without albumin level decrease during hospitalization. The first group shows significantly higher initial CRP level compared to the second group (mean difference 99.69 mg/L).

This result is supports the result of the experimental studies that showed that beside increased of CRP level, increasing concentrations of proinflammation cytokines (especially IL-6) in the inflammation process inhibits albumin synthesis in the hepatocyte, as well as increases albumin catabolism and redistribution to the extravascular compartment, with the end result is reduction in circulatory albumin level. Since both are affected by increased IL-6 during acute inflammation, a decrease in albumin level occurs simultaneously with an increase in CRP level, but at a different rate. An increase in CRP level precedes a decrease in albumin level, so a high initial CRP level –as a marker for severity of infection– could serve as predictor of albumin level decreased during hospitalization (especially on the first few days of hospitalization). In addition, from data showed in Table 2, the other infection markers (leukocyte count and ESR) are higher in patients with decreased albumin level; so we can say that patients with more severe infections tend to experience significant decreased in albumin level during acute phase of infection.

Besides correlating the CRP with albumin level and comparing initial CRP level between the two groups with changes in albumin levels, the study also tried to measure the risk of albumin level reduction in patients with high initial CRP levels. The risk of albumin level reduction is higher in patients with higher initial CRP levels compared to patients with low initial CRP levels (RR = 2.12), but this was not statistically significant. However, a 2.12 times (or 112%) increase in risk could not just be ignored, because it is clinically important.

There are two things that might contribute to why the finding was, as a forementioned, not statistically significant. These are also the limitations of this study. First, the observation time of albumin level reduction is too short (5 days) in this study. It might not be enough to observe changes in albumin level as negative acute-phase protein in five days, because the half-life of albumin ranges between 19 to 21 days. Therefore, this study uses a 10% cut-off point of albumin level reduction in five days by predicting that the albumin level will reach a maximum 25% decrease during acute infection/inflammation in nine days. However, on the other hand, longer observation on albumin level decrease might be biased by nutritional factors. Second, inappropriate sample size. A cohort study to look for risk differences for albumin level reduction in patients
with high and low CRP levels needs an estimated sample size of at least 45 patients. However, due to limitations in time and costs, also considering that the number of subjects was adequate to prove the main hypothesis (to look for correlations and mean differences) without lowering the power of the study, the study was terminated after 26 patients were included. As a consequence, in a cohort study to find relative risk differences, this lack of sample affects the significance of the result obtained.

Questions are raised to whether nutritional factors—i.e. previous nutritional status and protein diet during observation—influence the incidence of albumin level reduction in this study? Two hypothetical answers maybe should be consider. First, by looking at Table 2, the initial nutritional status (the Mini Nutritional Assessment [MNA] score, body mass index [BMI], and initial albumin level) are seem similar between the two groups, so the previous nutritional factors not influence this reduction. Second, it is undoubtful that the rate of albumin synthesis is also affected by nutritional intake;28 however, considering the 21-days half-life of albumin the intake contribution to albumin level reduction in five days is very low. To prove these hypotheses, and also to correct the limitations of this study, we suggest to conduct a similar study with a larger sample size for a longer observation time, also controlling for nutritional status and protein intake as variables that could influence albumin level during hospitalization.

Considering that there were a lot of excluded conditions in this study to eliminate the interference of factors other than CAP to the CRP and albumin level, generalization of the study findings to larger populations should be done cautiously. Application to populations outside of the study subjects or to larger population could be done as long as associated diseases or conditions in the elderly are taken into account.

CONCLUSION

From the result of this study, we could conclude that in hospitalized elderly patients with CAP there were (1) a correlation is found between initial CRP level with the percentage of albumin level decrease, and (2) a tendency that high initial CRP level will cause albumin level decrease during hospitalization; however, (3) risk differences of a reduced albumin level during hospitalization between patients with high CRP levels compared to low CRP levels has not yet been obtained. The two main results of this study show that a decrease of albumin level during the first days of hospitalization in elderly patients with acute infection is associated with the severity of infection.

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