Relationship between serum TNF-α, IL-6, and IL-10 levels and disease severity, and changes in the cytokines after treatment in patients with bacterial community-acquired pneumonia

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ABSTRACT

INTRODUCTION The role of some cytokines, such as interleukin (IL) and tumor necrosis factor-α (TNF-α), in serum in community-acquired pneumonia (CAP) has been mentioned. There are few results on changes in serum cytokines in patients with bacterial CAP. This study aimed at the relationship between serum TNF-α, IL-6, and IL-10 levels, disease severity, and changes in serum cytokines in patients with bacterial CAP.

METHODS A descriptive follow-up study was conducted on 78 hospitalized patients with CAP. Serum IL-6, IL-10, and TNF-α levels were measured by fluorescence covalent microbead immunosorbent assay technique. Changes in serum cytokine levels were measured on admission's first and seventh day.

RESULTS TNF-α, IL-6, and IL-10 medians were 0.76, 2.15, and 1.18 pg/mL, respectively. There was no difference in interleukin levels between the two groups, namely those aged <65 years and those aged ≥65 years (p>0.05). The levels of IL-10 in patients with Gram-positive bacteria pneumonia were significantly higher than those with Gram-negative bacteria (2.23 pg/mL vs 1.15 pg/mL, respectively, p=0.03). Logistic regression analysis revealed that IL-10 (OR=0.92; 95% CI: 0.86–0.99, p=0.03) was associated with the prognosis of disease severity. IL-6 levels decreased statistically on day 7 after treatment (1.12 pg/mL vs 2.15 pg/mL, p=0.003). The change in TNF-α and IL-10 after treatment was not significant (p>0.05).

CONCLUSIONS Serum IL-10 levels during hospitalization time are related to the prognosis of disease severity. After 7 days of treatment, IL-6 levels decreased statistically; however, TNF-α and IL-10 levels did not change.

ABBREVIATIONS APACHE: Acute Physiology And Chronic Health Evaluation, CAP: community-acquired pneumonia, CRP: c-reactive protein, CURB-65: confusion uremia respiratory rate BP age ≥65 years, IL: interleukin, TNF-α: tumor necrosis factor-α, VMMU: Vietnam Military Medical University

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INTRODUCTION

Community-acquired pneumonia (CAP) is one of the lower respiratory tract infections with high morbidity and mortality[1]. In the United States, CAP is the second leading cause of hospitalization, with 650 adults/100000 people hospitalized for the same period, equivalent to 1.5 million hospital admissions/year, and is the leading cause of death from infection[2]. A higher mortality proportion is usually found in children and the elderly[1,2].

Currently, the common cause of CAP is bacteria, in which the leading cause is typical bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*[1]. The infection's severity depends on the bacteria's pathogenicity and the protective barrier's resistance, which includes the ciliated system of the bronchial mucosa, mucus, and innate immune system. Soluble mediators of the innate immune system include complement, acute-reactive proteins, and cytokines that increase the activity of phagocytes and antibodies to eliminate pathogens from the body[3,4]. The components involved in cellular immunity include alveolar macrophages, helper T lymphocytes, and suppressor T lymphocytes. Some B lymphocytes transform into memory cells that carry immune memory, resulting in a faster and more potent immune response for the upcoming invasion of the same antigen. Suppressor and helper T cells are essential in regulating B cell antibody production; cytotoxic T cells also aid in destroying antigen-carrying cells[3,5].

Various pro-inflammatory and anti-inflammatory cytokines regulate the inflammatory response to infection in the lung parenchyma[4,5]. Cytokines are produced during the inflammatory response, including pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and anti-inflammatory cytokines [IL-10, IL-1 receptor antagonist (IL-1ra)]. Pro-inflammatory and anti-inflammatory cytokines are essential mediators in the host's response to infection. In contrast to the pro-inflammatory cytokines, little is known about anti-inflammatory cytokines in CAP and their relation to disease severity[6,7]. IL-6 and IL-8 are associated with APACHE and CURB-65 scores and severe clinical signs (confusion, systolic blood pressure <90 mmHg, pleural effusion, and sepsis) relating to early death[8,9]. However, the changes in serum cytokines are diverse in studies, and there are few results on changes in serum cytokines in patients with bacterial CAP[8,10]. Currently, numerous authors believe that cytokines could be used as an efficient tool for prognosis severity and monitoring treatment response[6,11]. TNF-α is an important pro-inflammatory cytokine that initiates inflammatory and bactericidal processes, increasing macrophage-derived TNF-α[12-14]. T lymphocytes, macrophages, and endothelial cells secrete IL-6. Any inflammatory stimulus can increase IL-6 levels, and it is an activator of other cytokines such as IL-1 and TNF-α[15-17]. IL-10 is an anti-inflammatory cytokine and plays the role of an important modulator in the inflammatory response. IL-10 is produced by the activation of IL-6 for immunomodulation to prevent the deleterious effects of the pro-inflammatory cascade[18-20].

Clinical rationale for the study

In Vietnam, there is a lack of national data on pneumonia epidemiology, but the proportion of hospitalization due to pneumonia ranks first among respiratory infections[21]. In addition, the role of cytokines has not yet been studied widely, especially in CAP. Therefore, this study was carried out to assess changes in serum TNF-α, IL-6, and IL-10 levels, as well as the relationship between these cytokines and patient severity in patients suffering from bacterial CAP.

METHODS

Study design and subjects

Among 178 hospitalized CAP patients, only 78 with positive sputum bacterial cultures participated in this study. Criteria for patient selection were as follows: patients were diagnosed with CAP according to the American Thoracic Society (2007) definition[22], having positive sputum bacterial culture with the CURB-65 score ≥2, and aged >18 years. Excluded patients were those who had pulmonary tuberculosis, bronchiectasis, chronic obstructive pulmonary disease, asthma, lung cancer, chronic renal disease, other infections, HIV or AIDS, any immunosuppressive treatment undergone for longer than 3 months or autoimmune diseases, and used antibiotics before admission.

A descriptive and prospective study was conducted in the Respiratory Department, Viet Tiep Hospital, Hai Phong, Vietnam, from January 2017 to December 2019.

All patients underwent clinical examination to collect information about antibiotics use history 3 months before admission, chronic diseases such as hepatobiliary disease, kidney disease, COPD, bronchial asthma, hypertension, heart failure, anemia, history of cerebrovascular accident, diabetes, cancer, stroke, fever, dyspnea, chest pain, cough, sputum production, hemoptysis, lung examination, circulation, etc. At the same time, laboratory tests including sputum quantitative bacterial culture, complete blood count, blood biochemistry, conventional chest X-ray, serum CRP level, and serum cytokine levels (TNF-α, IL-6, and IL-10) on the first and seventh day of hospitalization, were performed. Serum levels of TNF-α, IL-6, and IL-10 were measured by fluorescence covalent microbead immunosorbent assay technique, commercially available (InvitrogenR, Bender MedSystems GmbH Campus Vienna, Austria). After assessing the CAP stratification risk scores according to the CURB-65 score, patients were divided into 3 groups as follows: low risk of 30-day mortality with a score 0–1 (0.7–3.2%); intermediate risk with a score of 2 (13%), and high risk with a score 3–5 (17–57%)[22]. Evaluation of changes in serum cytokine levels and variables (CURB-65 score, the response after treatment, group of sputum bacteria). All patients received initial empiric antibiotic treatment according to the Guidelines of the British Thoracic Society (2009)[23] and adjusted according to the antibiogram results.

Statistical analysis

Data processing was performed using SPSS26.0 software.

Quantitative variables with normal distributions are given as mean and standard deviation. Quantitative variables that did not follow a normal distribution were reported as median and interquartile range (IQR: Q1–Q3). Categorical variables were reported as frequencies and percentages. We used Wilcoxon's rank sum test for qualitative variables and the Kruskal-Wallis test for variables with three or more categories. The R^2 value was used to evaluate how well the logistic model could explain the observed data. A $p<0.05$ was considered a statistically significant difference.

RESULTS

The studied patients had a median of 69 years and a high proportion of comorbidities (60.25%). All patients had a CURB-65 score ≥2, in which the proportion of patients with a CURB-65 score ≥3 accounted for 44.87%. Clinical symptoms were diverse, in which the most common was chest pain and sputum production, at 98.72% and 87.18%, respectively. The rate of complications of respiratory failure was 6.41%. Bilateral lesions were mainly found in chest X-rays (75.64%). The white blood cell count of the study patients was high, with a median of 10.9 G/L. CRP and

Table 1. General characteristics of patients

Characteristics	All (N=78) n (%)	<65 years (N=33) n (%)	≥65 years (N=45) n (%)	p
Age (year), mean ± SD Median (Q1–Q3)	67.96 ± 14.51 69 (59–79)	53.34 ± 10.58 57 (51–60)	76.6 ± 8.19 75 (70–84)	
History of intravenous antibiotics in the previous 3 months	10 (12.82)	5 (15.15)	5 (11.11)	0.735
Comorbidity	47 (60.25)	9 (27.27)	38 (84.44)	0.001
Respiratory symptoms				
Dry cough	5 (6.41)	3 (9.09)	2 (4.44)	0.645
Sputum	68 (87.18)	29 (87.88)	39 (86.67)	1.00
Hemoptysis	6 (7.69)	3 (9.09)	3 (6.67)	0.694
Chest pain	77 (98.72)	33 (100)	44 (97.78)	1.00
Dyspnea	60 (76.92)	27 (81.82)	33 (73.33)	0.451
Complications				
Pleural effusion	16 (20.51)	7 (21.21)	9 (20)	0.896
Respiratory failure	5 (6.41)	2 (6.06)	3 (6.67)	1.00
CURB-65 score				0.001
2	43 (55.13)	27 (81.82)	16 (35.56)	
≥3	35 (44.87)	6 (18.18)	29 (64.44)	
Lesions on chest X-ray				0.424
Unilateral	19 (24.36)	10 (30.30)	9 (20.00)	
Bilateral	59 (75.64)	23 (69.70)	36 (80.00)	
Measurements	Median (Q1–Q3)	Median (Q1–Q3)	Median (Q1–Q3)	
White blood cell count (G/L)	10.9 (8.1–14.3)	9.5 (5.8–15.4)	12.5 (6.2–23.8)	0.101
Neutrophil (G/L)	72.2 (63.1–80.2)	69.1 (46.9–82.6)	73.4 (54–91)	0.116
CRP (mg/dL)	127 (92.2–240.5)	112 (24.8–265)	128 (73–345)	0.085
Procalcitonin (ng/mL)	5.94 (4.85–9.32)	4.6 (1.2–11.6)	6.5 (1.2–11)	0.793
TNF-α (pg/mL)	0.76 (0.43–1.42)	0.75 (0.37–1.66)	0.77 (0.53–1.37)	0.686
IL-6 (pg/mL)	2.15 (0.79–6.98)	0.75 (0.79–7.3)	2.55 (0.88–5.7)	0.927
IL-10 (pg/mL)	1.18 (0.45–2.58)	1.03 (0.41–1.84)	1.58 (0.56–2.99)	0.199

CRP: c-reaction protein. CURB-65: confusion urea respiratory rate BP age ≥65 years. BP: blood pressure.

Table 2. Results of sputum bacterial culture

Bacteria		n	%
Gram-positive bacteria	*Streptococcus pneumoniae*	6	7.69
	Staphylococcus aureus	4	5.13
	Stenotrophomonas maltophilia	4	5.13
	Staphylococcus haemolyticus	1	1.28
	Streptococcus anginosus	1	1.28
	Total	16	20.51
Gram-negative bacteria	*Klebsiella pneumoniae*	24	30.77
	Pseudomonas aeruginosa	19	24.36
	Acinetobacter baumannii	11	14.10
	Escherichia coli	5	6.41
	Enterobacter spp	1	1.28
	Proteus	1	1.28
	Aeromonas sp	1	1.28
	Total	62	79.49

procalcitonin concentrations were high, with median values of 127 mg/dL and 5.94 ng/mL, respectively. The median values of TNF-α, IL-6, and IL-10 levels were 0.76, 2.15, and 1.18 pg/dL, respectively. The group of patients aged ≥65 years had a significantly higher percentage of comorbidities and CURB-65 score than those aged <65 years (p=0.001). There was no difference in other characteristics between the two age groups (p>0.05) (Table 1).

Sputum culture results showed that the vast majority of bacteria were Gram-negative (79.49%), of which *Klebsiella pneumoniae* accounted for the most (30.77%), followed by *Pseudomonas aeruginosa* (24.36%) and *Acinetobacter baumannii* (14.1%). Gram-positive bacteria only accounted for 20.51%, of which *Streptococcus pneumoniae* 7.69%, *Staphylococcus aureus,* and *Stenotrophomonas maltophilia* had a low proportion (5.13%) (Table 2).

The levels of IL-10 in the patients with Gram-positive bacteria pneumonia were significantly higher than those of with Gram-negative bacteria (2.23 pg/mL vs 1.15 pg/mL, respectively, p=0.03). No significant difference was found in changes in serum TNF-α and IL-6 levels between the patients with Gram-positive and Gram-negative bacteria pneumonia (p>0.05). There was no difference in cytokine levels regarding CURB-65 score, white blood cell count, and lung injury characteristics on X-ray (p>0.05) (Table 3).

There was no correlation between TNF-α, IL-6, and IL-10

Table 3. Relationships between serum cytokine levels and CURB-65 score, sputum bacteria, white blood cells, and chest X-ray

Indices	TNF-α (pg/mL) Median (Q1–Q3)	IL-6 (pg/mL) Median (Q1–Q3)	IL-10 (pg/mL) Median (Q1–Q3)
CURB-65			
2 (n=43)	0.71 (0.25–1.29)	1.89 (0.76–14.79)	1.15 (0.41–1.99)
≥3 (n=35)	0.81 (0.53–1.45)	2.55 (0.96–5.43)	1.58 (0.51–3.22)
p	0.245	0.912	0.310
Sputum bacteria			
Gram-positive bacteria (n=16)	0.64 (0.36–3.635)	3.705 (0.73–12.85)	2.23 (0.57–3.87)
Gram-negative bacteria (n=62)	0.76 (0.43–1.35)	1.905 (0.88–6.63)	1.15 (0.41–1.99)
p	0.28	0.64	0.03
White blood cells			
Decreased (n=1)	0.71	1.99	0.19
Normal (n=31)	0.6 (0.25–1.34)	1.39 (0.79–2.66)	1.15 (0.65–1.84)
Increased (n=46)	0.75 (0.39–1.29)	2.43 (0.88–11.34)	1.31 (0.39–3.09)
p	0.204	0.312	0.353
Lesion on chest X-ray			
Bilateral (n=59)	0.77 (0.38–10.92)	3.93 (0.55–14.57)	1.10 (0.34–2.47)
Unilateral (n=19)	0.71 (0.24–1.35)	1.22 (0.70–2.31)	1.37 (0.87–3.22)
p	0.557	0.053	0.633

Table 4. Correlations between serum cytokine levels and paraclinical tests

Cytokines (pg/mL)	CRP (mg/L)		Procalcitonin (ng/mL)	
	r	p	r	p
TNF-α	-0.06	0.58	-0.08	0.48
IL-6	0.05	0.67	0.027	0.81
IL-10	0.02	0.85	-0.104	0.36

Table 5. Logistic regression analysis of the dependent variable is the prognosis of severe disease with the independent variables

Independent variables	Prognosis of severe disease		
	OR	95% CI	p
TNF-α (pg/mL)	1.01	0.94–1.06	0.85
IL-6 (pg/mL)	1.12	0.85–1.48	0.418
IL-10 (pg/mL)	0.92	0.86–0.99	0.03
White blood cell (increase=1, no increase=0)	0.15	0.01–2.81	0.204
CRP (mg/L)	0.96	0.93–0.99	0.014
Procalcitonin (ng/mL)	3.23	1.02–10.25	0.047
Pleural effusion (Yes=1, No=0)	2.31	1.01–25.87	0.049

Table 6. Changes in serum cytokines levels after treatment (N=78)

Cytokines (pg/mL)	Day 1 Median (Q1–Q3)	Day 7 Median (Q1–Q3)	p
TNF-α	0.76 (0.43–1.42)	1.01 (0.55–2.37)	0.107
IL-6	2.15 (0.79–6.98)	1.12 (0.70–2.66)	0.003
IL-10	1.18 (0.45–2.58)	1.11 (0.74–1.91)	0.084

levels with serum CRP and procalcitonin levels on day 1 of admission (p>0.05) (Table 4).

Logistic regression analysis revealed that the prognosis of disease severity was associated with IL-10 levels (OR=0.92; 95% CI: 0.86–0.99, p=0.03), CRP (OR=0.96; 95% CI: 0.93–0.99, p=0.014), procalcitonin (OR=3.23; 95% CI: 1.02–10.25, p=0.047) and pleural effusion (OR=2.31; 95% CI: 1.21–25.87, p=0.049). Serum TNF-α and IL-6 levels were not associated with the prognosis of disease severity (p>0.05) (Table 5).

Compared to the first day of admission, IL-6 levels decreased significantly on day 7 (1.12 pg/mL vs 2.15 pg/mL, respectively, p=0.003). The change in TNF-α and IL-10 levels after treatment was not significant (p>0.05) (Table 6).

DISCUSSION

In this study, the patients were all aged >40 years, with a mean age of 67.96 ± 14.51 years, in which there were 45 patients aged ≥65 years, accounting for 57.69%, with the proportion of comorbidity being 60.25%. The results show that the majority of patients were elderly males with multiple respiratory symptoms and comorbidities. These characteristics were recognized as risk factors of severe CAP, especially in patients with a CURB-65 score ≥2. Kensuke et al.[21] found that the prevalence of CAP in central Vietnam among patients aged 65 years was 4.6/1000 persons/ year (95% CI: 3.8–5.5), ten times higher than that in younger groups[21]. In a study in Hong Kong on 1193 CAP patients, patients aged >65 years accounted for 73.4%[24]. In our study, the patients had high white blood cell count, CRP, and procalcitonin levels. These results showed that biomarkers increased in CAP patients, which was proved in many previous studies in which white blood cells, CRP, and procalcitonin were used as valuable biomarkers in bacterial infection and prognosis in CAP[4]. Clinical features, lung lesions on X-rays, and changes in inflammatory markers and

cytokines were independent of the patient's age, which is consistent with previous studies[9,18].

The results of sputum bacteria cultures showed that the percentage of Gram-negative bacteria accounted for the majority (79.49%), of which *K. pneumoniae* accounted for the most (30.77%), followed by *P. aeruginosa* and *A. baumannii*. Gram-positive bacteria made up 20.51%, with 7.69% for *S. pneumoniae,* followed by *S. aureus*. The characteristics of microbiological etiology, mainly Gram-negative bacteria, are also consistent with the characteristics of elevation of PCT concentrations in our study. Previous studies in Europe, the United States, Latin America, and Asia-Pacific show that the most common cause of CAP is *S. pneumoniae* (54.8–62%), followed by *H. influenzae. S. aureus, P. aeruginosa,* and *Enterobacteriaceae* accounted for the minority[25–27]. The results of sputum bacteria culture in our study's patients differed from previous studies. Of note, various studies showed a low positive culture rate, hence, the etiological character of the microbiome in this study is not specific to the epidemiological situation of pneumonia in Vietnam. One of the reasons for this difference may be due to the patients in our study being mainly elderly with comorbidities. Besides, suspicion patients admitted to the hospital were immediately treated with antibiotics according to BTS guidelines[23], with antibiotics initially effective on Gram-positive bacteria, leading to some patients with Gram-positive infection being negative in sputum culture, then being excluded from the study. These factors affect the number of patients in this study. The rate of positive bacterial cultures in the CAP group in the study of Takahashi et al[21]. was low (15%), with Gram-negative bacteria accounting for a high percentage (15/22), followed by *S. pneumoniae* (4/22) and *S. aureus* (3/22). Therefore, the results of the sputum culture in the study were mainly positive for Gram-negative bacteria, although the study patients had CAP.

The results of our study showed that in patients with a CURB-65 score ≥3, the means of serum TNF-α, IL-6, and IL-10 levels were lower than those in patients with a CURB-65 score of 2, but the difference was not significant (p>0.05). Some previous studies have shown a relation between IL-6 and pneumonia severity. Yandiola et al.[28] suggested that CURB-65 is not a good predictor of mortality in pneumonia patients. Zobel et al.[17] found that serum IL-6 and IL-10 levels were highest in patients with CRB-65 scores 3–4, and serum IL-6 level was significantly higher for patients with a severe course of CAP than for those who did not. We have not found a difference between the levels of cytokines according to the CURB-65 score. This result may be related to the characteristics of the patients in the study, with the majority being elderly patients with multiple comorbidities. Thus, the immune response to the inflammatory response is reduced.

Our study showed that changes in serum TNF-α and IL-6 levels were not significantly different between the patients with Gram-positive and Gram-negative bacteria pneumonia (p>0.05). The mean of IL-10 in the patients with Gram-

positive bacteria pneumonia was significantly higher than those with Gram-positive bacteria (p<0.05). Zobel et al.[17] found that serum cytokine levels were higher in patients with typical bacterial pneumonia than those with virus and atypical bacterial pneumonia. Martinez et al.[10] suggested that serum IL-6 is elevated in pneumococcal pneumonia because IL-6 reacts strongly to lobar pneumococcal aggression, resulting in the systemic release of antigens and cytokines. Fernández-Serrano et al.[29] found that in bacterial pneumonia, after 24 hours, serum IL-6, IL-8, and IL-10 levels increased in patients with pneumococcal pneumonia, but cytokine levels did not increase in patients with *Legionella pneumonia*[29]. During the inflammatory response, IL-6 is secreted by various cells, such as T lymphocytes, macrophages, endothelial cells, and epithelial cells[16]. IL-10 is an anti-inflammatory cytokine produced mainly by mononuclear white blood cells, inhibits the synthesis of pro-inflammatory cytokines and blocks antigen presentation; IL-10 inhibits the secretion of TNF *in vivo* and protects the immune system, protecting against endotoxin toxicity in septic shock[18,30]. TNF is secreted mainly by activating macrophages, monocytes, and T lymphocytes, causing damage to neighboring cells by direct contact[31]. There are two types of TNF molecules, TNF-α and TNF-β, which play a vital role in the immune mechanism against bacterial and fungal invasion, significantly increased in pneumonia caused by *S. pneumoniae, K. pneumoniae, P. aeruginosa, L. pneumophila, Cryptococcus neoformans, Aspergillus fumigatus,* and *Pneumocystis carinii*[13,32,33]. Thus, changes in serum cytokine tend to be increased in bacterial pneumonia and relate to the microbiology etiology, due to endotoxins of bacteria.

Using a logistic regression model based on calculated independent variables, our initial results showed that IL-10, CRP, procalcitonin, and pleural effusion on admission are risk factors for aggravation of the disease, valuable in predicting treatment outcomes. The model was tested for goodness of fit at 42% and p<0.05. The relationship between changes in cytokine levels with clinical outcome was mentioned in previous studies with different results: Martinez et al.[10] found that high TNF-α and IL-6 levels at the time of admission predict severe progression of the disease. Fernández-Serrano et al.[29] found that the relationship between cytokines and clinical outcomes in pneumonia remains unclear, probably due to the complexity of the cytokine network and the different variables involved in clinical studies: the timing of cytokine measurements in relation to the onset of infection; the effect of antibiotic therapy on cytokine production; and the compartmentalization of the inflammatory response within the lungs, which makes difficult the close monitoring of these phenomena[29]. Therefore, serum IL-10 levels at hospitalization time are related to the prognosis of disease severity.

The levels of cytokines of the study patients on day 7 tended to be lower than on day 1, with the difference being most evident in the results of IL-6 (p<0.05). The results

of this study are similar to previous studies, with cytokine levels decreasing after treatment, in which IL-6 decreased most markedly. de Brito et al.[34] conducted a study on 25 CAP patients and quantified IL-6 levels on days 1 and 8 of the disease. As a result, IL-6 levels significantly reduced from 44.07 and 19.98 pg/mL (day 1) to 8.41 and 4.94 pg/mL (day 8) with p values of 0.001 and 0.041 in severe and non-sever CAP[34], respectively. Bacci et al.[8] also found that serum IL-6 levels in pneumonia patients significantly decreased after treatment, with the mean level of IL-6 decreasing from 24 pg/mL on day 1 to 8 pg/mL on day 7, while TNF-α levels did not decreased (p=0.016)[8]. Similarly, the study by Méndez et al.[35] showed that IL-6 levels decreased after 3 days of treatment. According to Kellum et al.[36], the inflammatory response is longer than the clinical symptoms, so the change in serum cytokine levels is slower than in the clinical course. Thus, IL-6 decreased earlier than both IL-10 and TNF-α after treatment.

Limitations
First, we conducted a study with a small sample size, regarding the selection criterion as a positive culture test, since various studies showed a low positive culture rate, the etiological character of the microbiome of pneumonia in this study is not specific to the epidemiological situation of pneumonia in Vietnam. Besides, characteristics of bacterial etiologies were used for the local area, relating to selection criteria. This study should further be carried out in outpatients to find out exactly the classification of CAP bacterial etiologies.

Implications
The results of this study showed that serum IL-10 levels at the time of hospitalization are associated with a risk of severe progression of CAP, which is valuable in predicting the outcome of treatment. Moreover, IL-6 levels changed earlier than IL-10 and TNF-α after treatment for CAP. Therefore, serum IL-10 levels at hospitalization may have a prognosis of severe disease in patients with CAP. In addition, IL-6 levels can be used to monitor early outcomes for CAP treatment.

CONCLUSIONS
Serum IL-10 levels at hospitalization time are related to the prognosis of disease severity. After 7 days of treatment, while IL-6 levels decreased significantly statistically, TNF-α and IL-10 levels did not change.

CONFLICTS OF INTEREST
The authors have completed and submitted to ICMJE for Disclosure of Potential Conflicts of Interest and none was reported.

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ETHICAL APPROVAL AND INFORMED CONSENT
Ethical approval was obtained from the Ethics Committee of the Vietnam Military Medical University (Approval number: 57/2014/VMMU-IRB; Date: 18 December 2014). Participants provide informed consent. All patients were treated according to the same regimen according to the guidelines of the Ministry of Health of Vietnam.

DATA AVAILABILITY
The data supporting this research are available from the authors upon reasonable request.

PROVENANCE AND PEER REVIEW
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