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Original Article

Serum C-reactive protein levels in severe and very severe pneumonia in children

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Abstract

Background Pneumonia is a major cause of death in children from developing countries. It is difficult to assess pneumonia severity if clinical symptoms of pneumonia are unclear, co-morbidities occur simultaneously, or there is an absence of consolidation or infiltrates on chest radiograph. Examination of C-reactive protein (CRP) levels can help to determine the severity of pneumonia.

Objective To compare serum CRP levels in severe and very severe pneumonia cases.

Methods This was a cross-sectional study on pediatric patients aged > 28 days up to 60 months with a diagnosis of severe or very severe pneumonia. Subjects were hospitalized at the Department of Child Health, Udayana University Medical School/Sanglah Hospital, Denpasar from May 2010 to January 2011. There were 30 subjects in each group, severe or very severe pneumonia. Data were analyzed using Mann-Whitney and ANCOVA tests with statistical significance set at $P < 0.05$.

Results There were significant differences in median serum CRP levels in the severe and very severe pneumonia groups. The very severe pneumonia group had a median CRP level of 54.75 mg/L (IQ range 0.22 to 216.00) and the severe pneumonia group had a median CRP level of 16.06 mg/L (IQ range 0.97 to 89.35). Serum CRP levels were influenced by the severity of pneumonia ($P = 0.002$) and the timing of the CRP examination ($P = 0.001$).

Conclusion Subjects with very severe pneumonia had significantly higher median CRP level compared to that of subjects with severe pneumonia. **[Paediatr Indones. 2012;52:161-4]**.

Keywords*: severe pneumonia, very severe pneumonia, CRP levels*

Pneumonia is a respiratory infection and a major cause of death in children living in developing countries.[1] Young children with pneumonia often exhibit no symptoms or apparent lung abnormalities. It is difficult to differentiate the severity of pneumonia when clinical symptoms are unclear, comorbidities occur simultaneously, or there is an absence of consolidation or infiltrates on chest radiographs.[2] Distinguishing the severity of pneumonia is important in order for the clinician to properly manage treatment. Measuring serum CRP level is a rapid and sensitive laboratory test. CRP levels may indicate the presence of an inflammatory process in pneumonia[3] and be used as a parameter for assessing severity of infection. Pneumonia prognosis depends on the severity of infection and proper treatment.[4,5]

Several studies have been conducted to determine the relationship between CRP levels and severity of pneumonia infection.[6-9] Various scoring parameters were used in those studies, including scoring tests

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from the American Thoracic Society (ATS),[7] the British Thoracic Society (BTS),[8] and the APACHE II.[9] We used the World Health Organization (WHO) clinical criteria for this study. We aimed to compare serum CRP levels in patients with severe and very severe pneumonia.

Methods

This study was a cross-sectional study conducted at the Respirology Division, Department of Child Health, Udayana University Medical School/Sanglah Hospital, Denpasar from May 2010 to January 2011.

Sixty subjects were included in the study, 30 with severe pneumonia and 30 with very severe pneumonia. The required sample size was calculated by numerical analytic unpaired t-test. Patients with a history of trauma, liver abnormality or infection, HIV infection, other organ infections, organ transplant, malignancy, obesity, or incomplete data were excluded. This study was approved by the Research Ethics Committee of Udayana University Medical School/Sanglah Hospital, Denpasar. Subjects' parents provided written informed consent.

Patients with severe and very severe pneumonia according to WHO criteria, aged > 28 day to 60 months who came to Sanglah Hospital during the study period were eligible for the study. Physical examinations were performed by doctors in the Emergency Department or the Outpatient Clinic.

Comparison of serum CRP levels to severity of pneumonia was analyzed by Mann-Whitney test. The ANCOVA test was used to analyze possible association of factors to serum CRP levels. Statistical significance was set at $P<0.05$.

Results

During the study period, 91 children with severe or very severe pneumonia visited the hospital. However, only 30 children with severe pneumonia and 30 children with very severe pneumonia were included. Of the 31 pneumonia patients excluded, 17 suffered from diarrhea, 3 patient had sepsis, 1 patient had acute otitis media, 3 patients had HIV, 3 patients had meningitis, and 4 patients had congenital heart disease. Characteristics of the 60 subjects are shown in **Table 1.**

CRP levels were abnormally distributed after Kolmogorov-Smirnov normality test. To normalize the data distribution, we performed a data transformation of CRP serum levels using log10 method. However, the data still did not distribute normally, so we used the Mann-Whitney test to compare CRP levels of the two groups.

We found CRP levels ranged from 0.22 to 216.00 mg/L. There was a significant difference in median serum CRP levels in the severe and very severe pneumonia groups ($P = 0.006$). Median CRP in the very severe pneumonia group was significantly higher [54.75 mg/L (0.22 to 216.00)] compared to that of the severe pneumonia group [16.06 mg/L (0.97 to 89.35)]. The median CRP levels are showed in **Table 2**.

ANCOVA test was used to analyze possible associations between CRP levels and other factors. **Table 3** shows that severity of pneumonia ($P = 0.002$) and the time of CRP examination ($P = 0.001$) was significantly associated with serum CRP levels.

Table 1. Characteristics of subjects with severe or very severe pneumonia

Characteristics	Very severe pneumonia (n=30)	Severe pneumonia (n=30)
Sex, n,		
males	16	19
females	14	11
Age, n		
<2 years	26	24
≥2 years	4	6
Nutritional status, n		
no malnutrition	16	18
malnutrition	14	12
Prior antibiotics used		
yes	16	11
no	14	19
Time of CRP examination, n		
≤4 days of symptoms	24	21
>4 days of symptoms	6	9
Exclusive breastfeeding, n		
yes	15	14
no	15	16
Low birth weight, n		
yes	6	2
no	24	28
Passive smoking, n		
yes	23	22
no	7	8

Table 2. Median CRP levels in severe and very severe pneumonia.

Variable	Very severe pneumonia	Severe pneumonia	Z	P
Median CRP, mg/L (IQ range)	54.75 (0.22-216.00)	16.06 (0.97-89.35)	-2.75	0.006*

*Mann-Whitney test; IQ = interquartile (25^{th}-50^{th} percentile)

Table 3. Factors possibly associated with CRP levels

Variables	P
Age(ref 1= <2 years)	0.309
Diagnosis (ref 1= very severe pneumonia)	0.002
Prior antibiotic use (ref 1= used antibiotic)	0.422
Low birth weight (ref 1 = yes)	0.602
Timing of CRP examination (ref 1 ≤ 4 days)	0.001

ANCOVA test

Discussion

An elevated CRP concentration in blood is an indicator of infection, tissue damage, inflammation, and/or malignancy. Some infectious diseases such as diarrhea, meningitis, urinary tract infection, sepsis, otitis media, as well as immunodeficiency, may lead to increased CRP levels. In pneumonia, lung parenchyma may be damaged by the bacterial or viral infection, causing both local and systemic inflammatory responses. Lung parenchyma damage induces the release of various inflammatory cytokines into peripheral circulation. These cytokines will stimulate hepatocytes to produce CRP.[9,10] In our study, we excluded patients with pneumonia who also had other infections, in order to be sure that the elevated CRP levels were caused only by pneumonia, and not by other infections.

A study of adult patients with pneumonia used two types of scoring to determine disease severity, i.e. the pneumonia severity index (PSI) and the Missouri study index. Their results showed a positive weak correlation between CRP levels and infection severity with the PSI (r = 0.445, P<0.001), but the Missouri study index showed no correlation (r = 0.315, P<0.001).[11] Another study of 384 patients with pneumonia assessed the severity of pneumonia and complications by comparing CRP levels. CRP measurements were performed twice, at baseline, and after four days of antibiotic treatment. An increase of 50 mg/L CRP on admission was associated with a 1.22-fold odds for the patient to be in PSI classes III-V, as compared with classes I and II.[12]

We used the WHO 2005 clinical criteria to determine the severity of pneumonia in our subjects. This study is one of the first to investigate the relationship between CRP levels and pneumonia severity using the WHO 2005 criteria. We observed that the very severe pneumonia group had a significantly higher median CRP 54.75 mg/L (0.22 to 216.00) compared to that of the severe pneumonia group [median CRP 16.06 mg/L (0.97 to 89.35)], (P = 0.006).

CRP and IL-6 levels are known to increase within 20 hours after bacterial inoculation, and decrease within 24 hours of antibiotic therapy.[13] A prior study showed that appropriate antibiotic treatment for pneumonia decreased CRP levels more than 60% within 3 days.[14] We found that prior use of antibiotics showed no significant difference (P = 0.422) in CRP levels. In this study, CRP examination was performed only once, and other causes of CRP levels were unclear.

After the acute phase stimulus, CRP levels may increase up to 10,000-fold, and peak within 48 hours. When the stimulus is completely stopped, CRP rapidly decreases.[11,12] Another study also showed that CRP levels increased in 48-72 hours and decreased after 3-4 days.[5] This result is similar to previous theories that CRP levels increase within a few hours to 72 hours after the stimulus, and decline after 3-4 days.[15] We found CRP measurements performed at ≤4 days showed a statistically significant difference (P = 0.001).

Differences in CRP levels in males and females are usually accounted for by hormonal status, and become apparent after puberty. However, there has been no clear explanation for how sex hormones and/or chromosomes affect the immune system. A previous study showed no differences in gender and CRP levels in healthy adults. There was no difference

in median CRP concentration for males and females (P = 0.2) in that study.[16] We also found that CRP levels were not significantly associated with gender (P = 0.309).

There have been few studies on the association of low birth weight and CRP levels in children. One such study showed that low birth weight was not associated with higher levels of CRP in children aged 3-17 years (P = 0.157).[17] Similarly, we found low birth weight to not be associated with CRP levels (P = 0.602).

A limitation of our study was difficulty in determining the time of initial pneumonia symptom onset. Thus, we could not accurately confirm how many days after onset that our CRP measurements were done. Furthermore, we did not assess CRP levels on the mild severity pneumonia based on WHO clinical criteria.

In conclusion, subjects with very severe pneumonia had a significantly higher median CRP level compared to those with severe pneumonia. Pneumonia severity and timing of CRP examination also contributed to CRP levels.

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