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Research Paper

Utility of Plasma Osteopontin Levels in Management of Community-Acquired Pneumonia

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Abstract

Osteopontin (OPN) is an essential cytokine involved in immune cell recruitment and an important regulator of inflammation. The purpose of this study was to examine differences in OPN plasma levels between before and after antibiotic treatment in hospitalized adult patients with community-acquired pneumonia (CAP). OPN levels were measured in 93 patients with CAP and 54 healthy controls using a commercial enzyme-linked immunosorbent assay (ELISA). The CURB-65, Pneumonia Severity Index (PSI), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were used to determine the CAP severity in patients upon initial hospitalization. A decline in the number of white blood cells (WBCs) and neutrophils, and decreases in the levels of OPN and C-reactive protein (CRP) were observed after antibiotic treatment. Only the plasma level of OPN, but not CRP, was correlated with the severity of CAP based on the PSI (r = 0.514, p < 0.001), CURB-65 (r = 0.396, p < 0.001), and APACHE II scores (r = 0.473, p < 0.001). The OPN level also showed a significant correlation with the length of hospital stay (r = 0.210, p = 0.044). In conclusion, plasma level of OPN may act as diagnostic adjuvant biomarkers for CAP and further play a role in clinical assessment of the severity of CAP, which could potentially guide the development of treatment strategies.

Key words: Biochemical marker; Community-acquired pneumonia; Osteopontin; Pneumonia Severity Index.

Introduction

Community-acquired pneumonia (CAP) is a globally occurring infectious disease with high morbidity, mortality, and costs. In Taiwan, CAP was the fourth leading cause of death in 2014, and the crude mortality rate was 44.2 people per 100,000 population, which accounted for 10,353 deaths [1]. In addition, in the United States, CAP together with influenza was the eighth leading cause of death in 2014 [2]. Since prompt and optimized management of CAP can reduce morbidity and mortality, early diagnosis and recognition of the disease severity are essential for improving the prognosis of CAP patients [3, 4].

Osteopontin (OPN) was initially identified as a secreted protein associated with malignant transformation [5]. It is now recognized as a multifunctional phosphorylated acidic glycoprotein that functions as both an extracellular matrix molecule and a major cytokine involved in immune cell recruitment and type-1 (Th1) cytokine expression at sites of inflammation [6, 7]. OPN was found to be related to alveolar airspace enlargement with elevated mediators and neutrophilia [8] and plays important roles in cell growth, differentiation, migration, tissue fibrosis, epithelial repair, and regeneration [9-11].

OPN is expressed by a broad range of tissues and cells, for example, epithelial cells, macrophages, T cells, and fibroblast [12, 13]. In addition, it may be a

major mediator of various lung diseases, such as asthma [14], chronic obstructive pulmonary disease [7, 8], emphysema [9], human idiopathic pulmonary fibrosis [15], pulmonary granuloma formation [5], tuberculosis [16], silicosis [17], sarcoidosis [18], influenza [19, 20], and malignancy [5]. In patients suffering from diverse pulmonary diseases, OPN especially seems to be involved in lung inflammation, including interstitial pneumonia [21], sepsis [22], *Klebsiella pneumoniae*-induced pneumonia [23], eosinophilic pneumonia [24], and pneumococcal pneumonia [25]. However, to our knowledge, no cohort study has explored the prognostic value of OPN in CAP patients. Therefore, we measured plasma levels of OPN in CAP patients and healthy controls to evaluate the value of OPN in predicting the disease severity of CAP patients and to assist the management of CAP patients.

Materials and methods

Subjects and diagnoses

Chung Shan Medical University Hospital (CSMUH) is a tertiary care university hospital in Taichung, Taiwan. This cohort study was conducted from January 2009 to December 2012 by the Department of Medical Research and the Departments of Infectious Diseases and Chest Medicine, CSMUH. The study was approved by the Institutional Review Board of CSMUH (IRB no. CS11237). We enrolled 93 CAP patients and 54 healthy controls and all subjects provided informed consent. For the healthy control group, we randomly chose 54 individuals who visited Department of Family Medicine for health examination in the same hospitals from the same geographic area. In addition, subjects with any inflammation or infectious diseases were excluded from control group. For CAP patients, the inclusion criteria consisted of patients aged > 20 years, who were definitely diagnosed by either emergency room or outpatient department, and who were admitted for treatment of CAP. Demographic characteristics, comorbidities, symptoms and signs of pneumonia, laboratory results, and previous antibiotic treatment were recorded upon admission. The diagnostic criteria for CAP were based on guidelines of the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) [26]. Guidelines for diagnosing CAP included a typical infiltration change on chest x-ray film within 1 day of symptom occurrence and at least one clinical manifestation, such as a cough, yellow thick sputum, or high fever (> 37.8 °C); or at least two minor criteria, including tachypnea, dyspnea, pleural pain, chest pain, confusion or disorientation, lung consolidation, or a WBC count of > 12,000 cells/mL. Exclusion criteria included being an outpatient; having been transferred from another hospital or having had a separate hospital admission within the previous 3 weeks for other acute conditions such as pulmonary edema, pulmonary embolism, or malignancy appearing during follow-up; pneumonia caused by tuberculosis or malignancy; being severely immunocompromised, including severe neutropenia (with a WBC count of < 10^9 cells/L); and having an organ or bone marrow transplant or human immunodeficient virus infection. All CAP patients were given empirical antimicrobial agents (e.g., moxifloxacin, levofloxacin, and amoxicillin) intravenously within the first 48 h. Thereafter, oral antibiotics were given based on established guidelines. Blood samples before treatment were collected before patients with CAP received treatment protocols, and post-treatment blood samples were obtained within 3 days after the pneumonia had resolved. The collected blood samples were placed in tubes containing EDTA, immediately centrifuged at 2500 × g, stored at -80 °C, and used to measure WBCs, neutrophils, the CRP level, and OPN plasma level. Pneumonia severity was evaluated by the PSI [27], APACHE II [28], and CURB-65 [29] tests.

Measurements of WBCs, neutrophils, and CRP levels

WBCs, neutrophils, and CRP levels were measured by clinical laboratory staff members who were unaware of the source for the samples (i.e., blinded to the study).

Quantitative analysis of plasma OPN level

The OPN levels in the plasma samples were analyzed by human osteopontin enzyme-linked immunosorbent assay (ELISA) kits (ADI-900-142, Enzo). Briefly, 100 µL of prepared standards and samples were added to appropriate wells of ELISA plate and then assayed according to the manufacturer's instructions. The absorbance was measured at 450 nm in a microtest plate spectrophotometer, and OPN levels were quantified with a calibration curve using human OPN as a standard. Each standard or sample was assayed in duplicate.

Statistical analysis

SPSS 15.0 statistical software (SPSS, Chicago, IL, USA) was used for all statistical analyses. Continuous variables are expressed as mean ± standard deviation (SD), and the number (n) is presented with percentages for categorical variables. To compare untreated patients with controls, the Mann-Whitney U-test was used for continuous variables that did not

follow a parametric distribution, and the Wilcoxon signed-rank test was used to compare categorical variables of untreated and treated patients. A linear regression analysis was applied for correlations between OPN and all clinical and laboratory variables of CAP patients. Statistical significance was defined at $p < 0.05$ in a two-tailed test.

Results

Demographic and clinical characteristics are summarized in Table 1. Totally, 147 subjects were included in the analysis, and the age and percentage of males did not significantly differ between CAP patients and controls. Among the 93 CAP patients, the mean scores of the PSI, CURB-65, and APACHE II were 82.97 ± 37.17, 1.09 ± 0.93, and 9.94 ± 5.31, respectively. The mean hospital length of stay was 11.71 ± 17.49 days. CAP patients had significantly higher CRP levels (11.26 ± 7.30 vs. 0.46 ± 0.27 mg/dl; Table 1), WBCs (12,505.4 ± 5533.9 vs. 6280.7 ± 1814.5 cells/mm^3; Table 1), and neutrophils (9904.1 ± 5010.1 vs. 3670.9 ± 1341.7 cells/mm^3; Table 1) compared to control subjects ($p < 0.001$). Moreover, there were significant decreases in CRP levels (untreated: 11.26 ± 7.30 mg/dl; treated: 4.61 ± 4.65 mg/dl; Table 1), WBCs (untreated: 12,505.4 ± 5533.9 cells/mm^3; treated: 8752.0 ± 3673.2 cells/mm^3; Table 1), and neutrophils (untreated: 9904.1 ± 5010.1 cells/mm^3; treated: 6265.3 ± 3402.2 cells/mm^3; Table 1) after antibiotic treatment ($p < 0.001$).

Figure 1 shows plasma OPN levels in control subjects and CAP patients before and after antibiotic treatment. CAP patients presented with significantly higher OPN plasma levels compared to control subjects (controls: 9.16 ± 5.61 ng/mL; patients: 24.32 ± 14.08 ng/mL; $p < 0.001$; Figure 1). After CAP patients received antibiotic treatment, OPN levels significantly dropped (untreated: 24.32 ± 14.08 ng/mL; treated: 16.50 ± 12.01 ng/mL; $p < 0.001$; Figure 1).

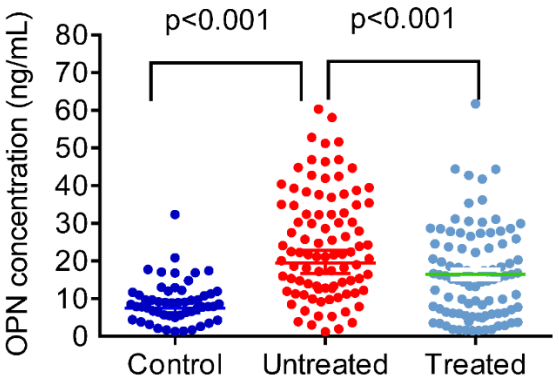

Figure 1 Plasma levels of osteopontin (OPN) in control subjects and patients with ommunity-acquired pneumonia (CAP) before and after treatment. The plasma OPN level was significantly elevated in patients with CAP before they received treatment compared with the controls ($p < 0.001$) and significantly decreased in patients with CAP after treatment ($p < 0.001$). Data were presented as the mean ± SD. Control vs Untreat: The statistical difference was analyzed by the Mann-Whitney U-test. Untreated vs Treated: The statistical difference was analyzed by the Wilcoxon signed-rank test.

To further examine the correlation between plasma OPN levels and the severity of CAP before treatment, we used the PSI, CURB-65, APACHE II, and the length of hospital stay as pneumonia severity indices. Correlations among them are shown in Table 2. There were significant correlations between OPN and the PSI (Spearman correlation coefficient r = 0.514, $p < 0.001$; Figure 2A), CURB-65 (Spearman correlation coefficient r = 0.396, $p < 0.001$; Figure 2B), APACHE II (Spearman correlation coefficient r = 0.473, $p < 0.001$; Figure 2C). Although the same trend of OPN and CRP were observed in CAP patients before and after antibiotic treatment, there was no significant correlation between OPN levels and CRP levels in CAP patients before (Figure 2D) and after (Figure 2E) antibiotic treatment.

The rule of PSI stratifies CAP patients into five classes of risk for death within 30 days of presentation. The lowest risk class (risk class I) comprises patients who are younger than 50 years of age, have none of the five important coexisting illnesses and have normal mental status and normal or only mildly abnormal vital signs at presentation. Assignment to the remaining risk classes depends on the presence or absence of a set of medical history, physical examination, and laboratory

Table 1. Laboratory data of controls and patients with community-acquired pneumonia (CAP) before and after antibiotic treatment [a, b]

Clinical variable	Controls (n = 54)	CAP patients (n = 93)		p value	
		Before treatment	After treatment	UT/C [c]	UT/T [d]
Age (years)	59.57 ± 11.05	63.15 ± 20.98		0.247	
Gender					
Male	36 (66.7%)	56 (60.2%)		0.436	
Female	18 (33.3%)	37 (39.8%)			
CRP (mg/dl)	0.46 ± 0.27	11.26 ± 7.30	4.61 ± 4.65	< 0.001	< 0.001
WBCs (cells/mm^3)	6280.7 ± 1814.5	12,505.4 ± 5533.9	8752.0 ± 3673.2	< 0.001	< 0.001
Neutrophils (cells/mm^3)	3670.9 ± 1341.7	9904.1 ± 5010.1	6265.3 ± 3402.2	< 0.001	< 0.001
PSI score		82.97 ± 37.17			
CURB-65 score		1.09 ± 0.93			
APACHE II score		9.94 ± 5.31			
Hospital length of stay (days)		11.71 ±17.49			

CRP, C-reactive protein; WBCs, white blood cells; C, controls; UT, CAP patients before they received antibiotic treatment; T, CAP patients after they received antibiotic treatment; PSI, Pneumonia Severity Index; CURB-65, confusion, urea of > 7 mmol/l, respiratory rate of > 30/min, low systolic (< 90 mmHg) or diastolic (< 60 mmHg) blood pressure, and aged ≥ 65 years; APACHE, Acute Physiology and Chronic Health Evaluation.

[a] $p < 0.05$ was considered significant.

[b] Data were presented as the mean ± SD and n (%).

[c] The statistical difference was analyzed by the Mann-Whitney U-test.

[d] The statistical difference was analyzed by the Wilcoxon signed-rank test.

findings. Total point scores of 70 or less correspond to class II, 71 to 90 to class III, 91 to 130 to class IV, and more than 130 to class V. Mortality rates in risk classes I, II, and III are low (0.1% to 0.4% in class I and 0.9% to 2.8% in class III),with correspondingly medium and high mortality rates in risk classes IV and V, respectively [30]. In our study, we found that OPN levels in CAP patients with risk classes IV and V all significantly differed between classes I and II (Figure 3A). The OPN levels in CAP patients with medium or high mortality risk were significantly higher than patients with low mortality risk (Figure 3B). Taken together, OPN might be a potential biochemical marker to diagnose the severity of CAP and predict the mortality rate of patients with CAP.

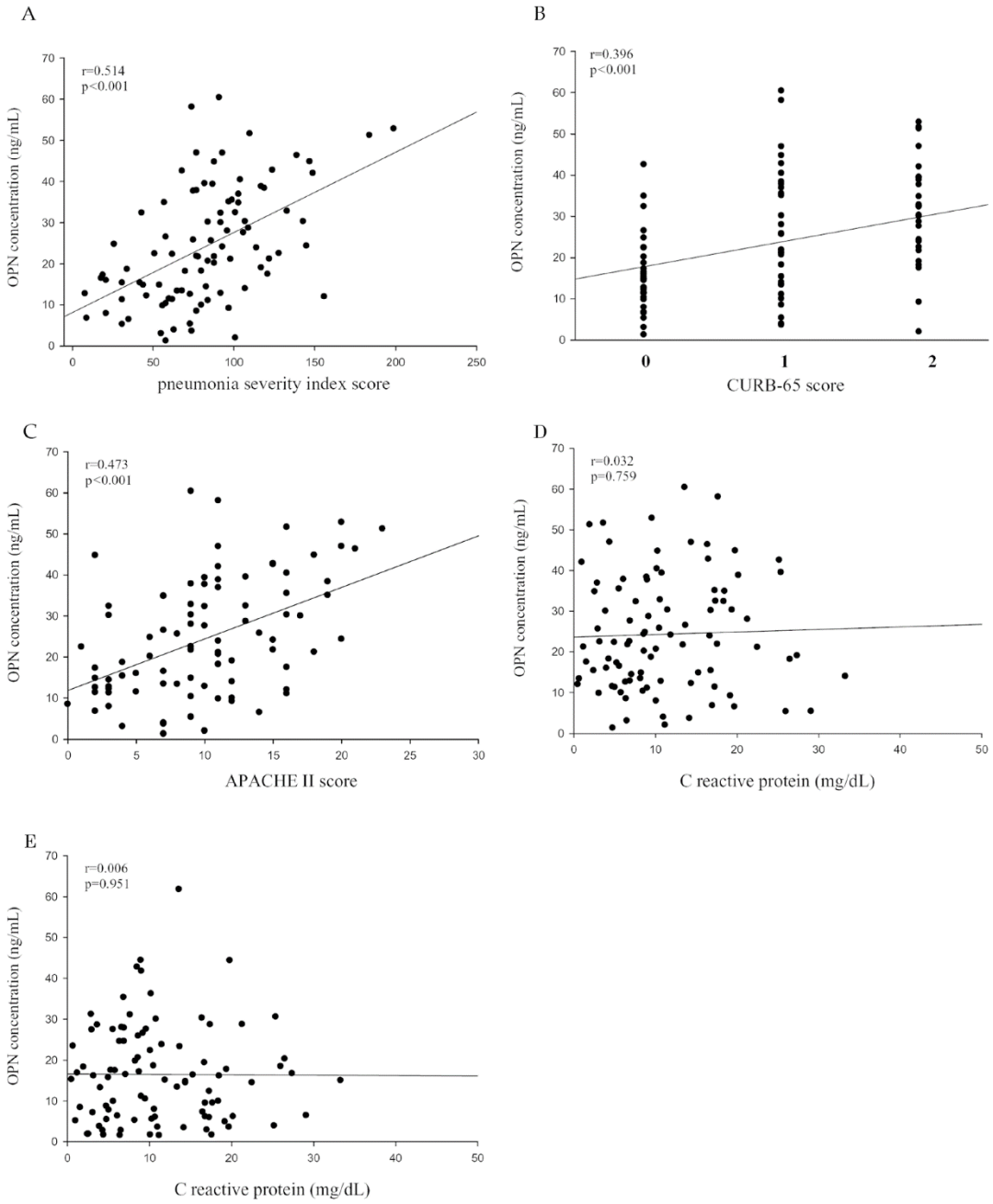

Figure 2 Correlations of plasma osteopontin (OPN) levels with the pneumonia severity index (PSI), confusion, urea level, respiratory rate, blood pressure, and age of ≥ 65 years (CURB-65), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores in 93 patients with community-acquired pneumonia (CAP). (A) A significantly positive correlation was observed between plasma OPN levels and PSI scores (Spearman's correlation coefficients: r = 0.514, p < 0.001). (B) A significantly positive correlation was observed between plasma OPN levels and CURB-65 scores (Spearman's correlation coefficients: r = 0.396, p < 0.001). (C) A significantly positive correlation was observed between plasma OPN levels and APACHE II scores (Spearman's correlation coefficients: r = 0.473, p < 0.001). (D and E) The correlation between plasma OPN levels and CRP values were insignificant before antibiotic treatment (Spearman's correlation coefficients: r = 0.032 , p = 0.759) and after antibiotic treatment (Spearman's correlation coefficients: r = 0.006 , p = 0.951). A linear regression analysis was applied for correlations between OPN and all clinical and laboratory variables of CAP patients.

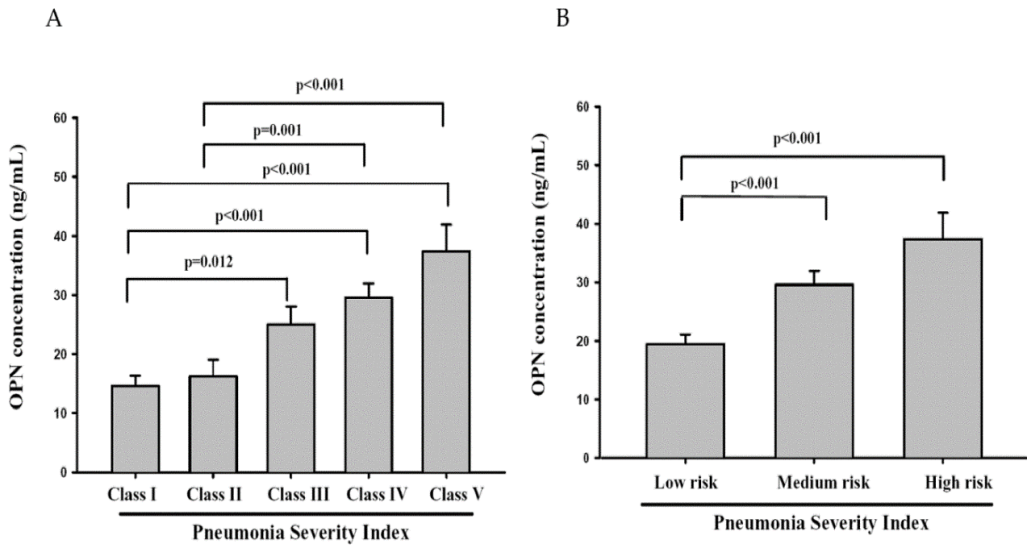

Figure 3 Plasma osteopontin (OPN) levels of community-acquired pneumonia (CAP) patients with each Pneumonia Severity Index (PSI) class (class I, n = 16; II, n = 16; III, n = 23; IV, n = 29; V, n = 9) and different mortality risk (low, n = 55; medium, n = 29; and high, n = 9). Data were presented as the mean ± SD. The statistical difference was analyzed by the Mann-Whitney U-test.

In contrast to OPN, neither CRP levels nor WBC counts correlated with the CAP severity in patients, as evidenced from the statistically nonsignificant correlations among PSI, CURB-65, and APACHE II scores and CRP levels (p = 0.755, 0.606, and 0.741, respectively) and WBC counts (p = 0.921, 0.514, and 0.922, respectively; Table 2). In addition, we also found that only OPN levels, but not CRP levels and WBC counts correlated significantly with the length of hospital stay (Spearman correlation coefficient r = 0.210, p = 0.044; Table 2).

Table 2. Correlation of white blood cells (WBCs), C-reactive protein (CRP), and osteopontin (OPN) with clinical pathological features of CAP patients.

Variables	WBC (n = 93)		CRP (n = 93)		OPN (n = 93)	
	r	p	r	p	r	p
PSI score	- 0.010	0.921	- 0.033	0.755	0.514	< 0.001
CURB-65 score	0.069	0.514	0.054	0.606	0.396	< 0.001
APACHE II score	- 0.010	0.922	0.035	0.741	0.473	< 0.001
Length of hospital stay	- 0.033	0.754	0.023	0.825	0.210	0.044

PSI, Pneumonia Severity Index; CURB-65, confusion, urea of > 7 mmol/l, respiratory rate of > 30/min, low systolic (< 90 mmHg) or diastolic (< 60 mmHg) blood pressure, and aged ≥ 65 years; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Discussion

Our results revealed that: (I) plasma OPN levels in patients with CAP were higher compared to those of healthy controls and significantly declined in the same patients after antibiotic treatment; (II) OPN levels were significantly correlated with disease severity indices; and (III) OPN levels presented a significant relation with the length of hospital stay for CAP.

Significantly higher values of CRP levels, WBCs, and neutrophils in CAP patients before antibiotic treatment, compared to the control group, significantly declined after antibiotic treatment in CAP patients, which reveals their traditional roles in CAP diagnoses. However, some other studies have indicated that elevated WBC counts and CRP levels in patients with CAP have no prognostic relevance [31, 32]. For example, in pneumococcal CAP patients, despite having a high bacterial burden, there were relatively weak CRP responses in the majority of severe cases of pneumonia [33]. CRP levels or WBCs were not significantly related to a change in the clinical classification or mortality of patients with pneumonia [31-34].

In consistent with previous studies, our study showed that no significant correlation was observed between the CRP levels or WBC counts and CAP severity indices (PSI, CURB-65, and APACHE II). In contrast to CRP, results presented here show that plasma OPN levels were higher in patients with CAP compared to those of healthy controls and significantly decreased in the same patients after they received antibiotic treatment. High OPN values were associated with several variables (PSI, CURB-65, and APACHE II) indicative of the disease severity. Several previous reports also suggested that CRP and the disease severity is correlated [35, 36]. This controversial role of CRP in management of CAP could probably relate to the recruited population size, race, sex, and so on in different studies. Moreover, our study showed that there was no significant correlation

between OPN levels and CRP levels before and after antibiotic treatment, even if the same trend of CRP and OPN were observed in CAP patients before and after antibiotic treatment. This result suggested that OPN might play a different role with CRP in management of CAP. In addition to disease severity, PSI has been categorized into five risk classes which associate with low (classes I~III), medium (class IV), and high (class V) mortality rate of CAP patients [30]. The significant difference between OPN values in CAP patients with medium or high mortality rate and patients with low mortality rate in this study suggests that OPN might be a potential biochemical marker to predict the mortality rate of patients with CAP. Actually, a previous report indicated that OPN serum levels can predict mortality in critically ill patients during the early course of intensive care unit (ICU) treatment [37]. Although both CRP and OPN can be induced by proinflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor-α [38, 39], CRP is almost exclusively synthesized by hepatocytes under stimulation by inflammatory cytokines [40]. However, OPN especially seems to be involved in lung inflammation, as patients suffering from diverse pulmonary diseases, including interstitial pneumonia [41], tuberculosis, silicosis [17], and acute respiratory distress syndrome [42], have shown enhanced OPN expression in their lungs, whereas patients with idiopathic pulmonary fibrosis have shown increased OPN levels in bronchoalveolar lavage fluid [43]. We suggest that OPN acts as a more direct reflective marker than does CRP with respect to the response to an inflammatory stimulus in lung tissues and also as a more specific marker of the diagnosis and clinical assessment of CAP severity in Taiwanese populations.

Clinical guidelines for managing CAP patients suggest using a severity-based approach for guiding therapeutic options, such as the need for hospital or ICU admission, suitability for ambulatory care, and choice of antimicrobial agents. Although we have found that OPN might be a potential biomarker for predicting the severity and mortality of CAP, but whether OPN can selectively recognize different types of pathogens remains unclear. Identifying the etiology of CAP is clinically difficult because single clinical, radiological, or laboratory parameters have limited value for predicting the infectious organism [44], and no rapid test has been standardized for diagnosing atypical or viral pathogens. Therefore, a type of empirical broad-spectrum antibiotic therapy is typically selected [45]. A previous report indicated that OPN levels were associated with *Streptococcus pneumoniae*-induced pneumonia in mice [25]. However, the limitation of this study is a lack of more-detailed clinical data, such as information on comorbid diseases and microbial pathogens. Some comorbidities might interfere with plasma OPN levels, and different pathogens might have different impacts on CAP severity. For example, OPN can impair host defense during *Streptococcus pneumoniae*-induced pneumonia, but promote the host defense during *Klebsiella pneumoniae*-induced pneumonia [23, 25]. Future studies are necessary to validate the precise correlation between plasma OPN levels and CAP due to different microbial pathogens. In addition, almost all the CAP patients we recruited in this study were not diagnosed as having severe CAP requiring intensive care unit admission. We can't get the information about survival data (only four patients died in our recruited patients). We will further investigate the correlation between the OPN levels and survival rate in patients with severe CAP in the future.

In conclusion, plasma OPN levels can be used in Taiwanese populations to predict the severity and mortality of CAP with higher sensitivity compared to CRP and is associated with the effect of antibiotic treatment and the length of hospital stay. In this study, we reported that measuring plasma levels of OPN can be beneficial for clinical decision making in CAP management.

Acknowledgments

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Conflict of Interest

The authors stated that there are no conflicts of interest regarding the publication of this article.

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