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NACHT, LRR, and PYD domains-containing Protein 3 and LL-37: prognostic value of new biomarkers in community-acquired pneumonia

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ABSTRACT

Objective: This study aimed to determine the serum levels of NACHT, Leucine-rich repeat (LRR), and Pyrin (PYD) domains-containing Protein 3 (NLRP3) and cathelicidin LL-37, and investigate their prognostic significance in community-acquired pneumonia (CAP). **Methods:** The sample of this prospective study was composed of 76 consecutive patients with CAP. Demographic data and clinical characteristics were collected. Serum levels of NLRP3 and LL-37 were determined by ELISA. Spearman's analysis was used to evaluate the correlation between NLRP3 and LL-37. Association of NLRP3 and LL-37 with 30-day survival and mortality rates was assessed using the Kaplan-Meier curve and logistic regression analysis. **Results:** Serum NLRP3 significantly increased whereas serum LL-37 significantly decreased in patients with severe CAP. Significant correlation was observed between serum NLRP3 and LL-37 in CAP patients. Patients with higher levels of NLRP3 and lower levels of LL-37 showed lower 30-day survival rate and higher mortality compared with those with lower NLRP3 and higher LL-37 levels. **Conclusion:** Severe CAP patients tend to present higher serum NLRP3 and lower serum LL-37, which might serve as potential biomarkers for CAP prognosis.

Keywords: Community-acquired pneumonia; Prognosis; Biomarkers; Prospective study.

INTRODUCTION

Pneumonia is widely recognized as a significant public health problem, and one of the most common leading causes of hospitalization and death worldwide. It is classified into community-acquired (CAP) and hospital-acquired pneumonia according to environment where infection occurs.[1,2] Pulmonary parenchymal disease occurring outside of the hospital setting has traditionally been categorized as CAP, which still presents significant morbidity and mortality. The incidence of CAP ranges from 0.33% to 4.6% a year in the elderly population, depending on co-morbid and severity conditions.[3-5] Advances in medical care have improved survival in patients with severe CAP; however, for the majority of CAP patients, improvement in disease management is inconspicuous.[6] Therefore, it is a hotspot in which more reliable biomarkers should be sought.

To date, several serum biomarkers have been found to predict disease severity and prognosis in patients with CAP. For example, Kolditz et al.[7] conducted a prospective study and demonstrated that serum cortisol predicted mortality and critical disease in CAP patients regardless of clinical scores and inflammatory biomarkers. Angus et al.[8] found that serum high-mobility group box-1 levels were significantly higher in CAP patients than in healthy controls, and were associated with mortality. Moreover, Zhang et al.[9] identified N-Terminal pro-B-type brain natriuretic peptide (NT-pro BNP) as an effective predictor of adverse cardiac events in patients with CAP, which was positively correlated with the disease severity.

Host defense peptide LL-37, a fragment of the cathelicidin protein precursor hCAP18, has been previously identified as a potent regulator of inflammatory response.[10] In addition to its anti-infective properties, LL-37 also regulated the secretion and release of multiple inflammatory cytokines from immune cells. Jiao et al.[11] showed that LL-37 deteriorated asthma via activation of eosinophils interacting with bronchial epithelial cells. Furthermore, LL-37 has been reported to improve the survival of septic mice through inhibition of macrophage pyroptosis, inflammatory cytokine production, and bacterial growth.[12] However, the expression and clinical significance of LL-37 in the pathogenesis of CAP remains unclear.

Nod-like receptor protein 3 (NLRP3) plays an important role in the inflammation process in many diseases and bioprocesses.[13] Studies have shown NLRP3 is high in injury-induced inflammation, and activation of NLRP3 can promote pneumonia development.[14] However, few studies have focused on the clinical significance of serum

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NLRP3 in CAP patients. This study aimed to investigate the expression of LL-37 and NLRP3 in CAP patients. The present study may provide deeper insights in CAP and some new research targets for CAP treatment.

METHODS

Study sample

This prospective study was conducted with 76 CAP patients and 50 healthy controls from the aforementioned Hospital between January 2015 and December 2016. Community-acquired pneumonia (CAP) was diagnosed based on lower respiratory tract symptoms, and confirmed by chest radiograph within 24h of hospital admission. Patients with health-care associated pneumonia and with autoimmune diseases were excluded from the survey. The pneumonia severity index (PSI) was used to categorize all patients into mild/moderate (PSI Risk Classes I-III) or severe (PSI Risk Classes IV-V) CAP, as previously described.[15] All experimental protocols were approved by the Research Ethics Committee of Jining No.1 People's Hospital. Informed consent was obtained from all subjects.

Data collection

Baseline assessment included age, gender, antimicrobial treatment prior to enrollment, clinical symptoms, laboratory data, PSI score, and mortality during a 30-day follow-up.

Laboratory test

Venous blood samples were collected within 24h of hospital admission and stored at -70 °C. White blood cell (WBC) count was determined by the hospital laboratory. ELISA was performed using commercial kits for the quantitative measurements of C-reactive protein (CRP; Roche Diagnostics, Almere, The Netherlands), NLRP3 (Shanghai Sunred Biological Technology Co., Ltd., Shanghai, China), and LL-37 (Hycult Biotechnology, Uden, The Netherlands), according to the manufacturer's protocol.

Statistical analysis

Continuous variables were presented as mean ± standard deviation if normally distributed, or as median if otherwise, and were compared using the Wilcoxon-Mann-Whitney test, whereas comparisons between groups on categorical variables were carried out using the Chi square test. Spearman's rank correlation coefficient analysis was performed to determine the relationship between serum NLRP3 and LL-37 levels. The Kaplan-Meier method was applied to estimate survival analysis. The correlation between CRP, NLRP3 and LL-37 serum levels and 30-day mortality in all patients was carried out using logistic multivariate regression analysis. A significance value of $p<0.05$ was adopted for all statistical analyses, which were processed using the SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software.

RESULTS

Patient characteristics

In total, 76 patients with CAP were included in this study, and their demographic data and clinical characteristics are shown in Table 1. There were no significant differences between mild/moderate or severe CAP patients regarding age, gender, antimicrobial treatment prior to enrollment, and clinical symptoms. Patients with severe CAP exhibited significantly increased serum CRP and NLRP3 levels and WBC counts, as well as lower serum LL-37 levels and higher rates for PSI Risk Classes IV-V and mortality during a 30-day follow-up compared with those with mild/moderate CAP (all with $p<0.05$).

Correlation analysis of serum NLRP3 and LL-37 levels

Serum levels of NLRP3 and LL-37 were further compared in CAP patients with those in the healthy controls, and the ELISA assay indicated higher serum NLRP3 and LL-37 levels in patients with CAP than in healthy controls (Figure 1A; $p<0.05$). Spearman's correlation analysis demonstrated that serum NLRP3 was negatively correlated with serum LL-37 (Figure 1B; $p<0.05$).

Relationship between NLRP3 and LL-37 and clinical parameters

To further determine clinical significance of NLRP3 and LL-37, all patients were categorized into NLRP3 or LL-37 high/low groups according to mean ± standard deviation or median values. Table 2 shows that patients with higher serum NLRP3 or lower serum LL-37 levels had higher serum CRP levels, WBC counts, and mortality rate during a 30-day follow-up than those with lower serum NLRP3 or higher serum LL-37 levels (all with $p<0.05$). In addition, more patients in PSI Risk Classes I-III (PSI ≤90 points) and IV-V (PSI >90 points) were included in patients with higher serum NLRP3 or lower serum LL-37 levels compared with those with lower serum NLRP3 or higher serum LL-37 levels (all with $p<0.05$).

Association between NLRP3 and LL-37 and 30-day survival and mortality rates

Prognostic relevance of serum NLRP3 and LL-37 levels in CAP patients was also assessed. Kaplan-Meier survival curves revealed that patients with high serum NLRP3 or LL-37 levels showed lower survival rates than those with low serum NLRP3 or LL-37 levels (all with $p<0.05$) according to the log-rank test (Figure 1C).

Multivariate logistic regression was then conducted based on the aforementioned results. As shown in Table 3, both higher serum NLRP3 and lower serum LL-37 conducted were closely associated with the 30-day mortality rate in CAP patients (Table 4).

Table 1. Basic clinical information on the study participants.

Variables	Mild/moderate CAP, n=41	Severe CAP, n=35
Mean age (years)	59.3 ± 10.1	61.7 ± 12.6
Gender (male:female)	24:17	20:15
Antibiotics received before treatment; n (%)	21 (52.5)	16 (45.7)
Symptoms; n (%)		
Fever	19 (46.3)	18 (51.4)
Cough	15 (36.6)	15 (42.8)
Sputum	13 (31.7)	12 (34.2)
Shortness of breath	9 (21.9)	9 (25.7)
Chest pain	6 (14.6)	7 (20.0)
Laboratory		
CRP (mg/L)	63 (25~180)	130.5 (81~235)*
WBC (10^9/mL)	9.3 (7.1~14.4)	13.1 (10.2~17.5)*
NLRP3 (ng/mL)	31 (20~45)	49 (38~60*
LL-37 (ng/mL)	132 (87~195)	86 (39~124)*
PSI; n (%)		
PSI Risk Classes I-III	41 (100)	0 (0)
PSI Risk Classes IV-V	0 (0)	35 (100)*
Mortality during a 30-day follow-up; n (%)	7 (17.0)	12 (34.2)*

*$p<0.05$.

Table 2. Clinical outcomes in CAP patients with high/low serum LL-37 or NLRP3 levels.

Variables	Low LL-37; n=39	High LL-37; n=37	Low NLRP3; n=38	High NLRP3; n=38
Mean age (years)	59.6 ± 10.5	61.5 ± 11.8	60.3 ± 11.2	61.1 ± 12.3
Gender (male:female)	23: 16	21: 16	23:15	21:17
Antibiotics received before treatment; n (%)	19 (48.7)	18 (48.6)	18 (47.4)	19 (50.0)
Symptoms; n (%)				
Fever	20 (51.3)	17 (45.9)	17 (44.8)	20 (52.6)
Cough	14 (35.9)	16 (43.2)	14 (436.8)	16 (42.1)
Sputum	13 (33.3)	12 (32.4)	12 (31.2)	13 (34.2)
Shortness of breath	8 (20.5)	10 (27.0)	8 (21.1)	10 (26.3)
Chest pain	7 (17.9)	6 (16.2)	5 (13.2)	8 (21.1)
Laboratory				
CRP (mg/L)	137 (83~235)	68 (25~174)*	60 (25~169)	135 (84~235)#
WBC (10^9/mL)	12.9 (11.2~17.5)	9.3 (7.1~14.5)*	8.7 (7.1~13.8)	13.5 (11.0~17.5)#
NLRP3 (ng/mL)	50 (40~60)	30 (20~43)*	142 (90~195)	73 (39~120)#
PSI; n (%)				
PSI Risk Classes I-III	11(28.2)	30(81.1)*	32 (84.2)	9 (23.6)#
PSI Risk Classes IV-V	28 (71.8)	7(18.9)*	6 (15.8)	29 (76.3)#
Mortality during a 30-day follow-up; n (%)	13 (33.3)	6 (16.2)*	5 (13.2)	14 (36.8)#

*$p<0.05$, compared with the low LL-37 group; #$p<0.05$, compared with the low NLRP3 group.

Table 3. Correlation between serum NLRP3 and LL-37 levels with 30-day mortality for CAP patients by logistic multivariate regression analysis.

	Wald	Odds ratio	95% CI	*p* value
CRP	1.037	1.014	(0.852~1.243)	0.174
NLRP3	13.970	1.146	(1.067~1.231)	<0.001
LL-37	14.600	0.947	(0.921~0.974)	<0.001
PSI	0.765	1.574	(0.687~2.039)	0.421

CI: confidence index.

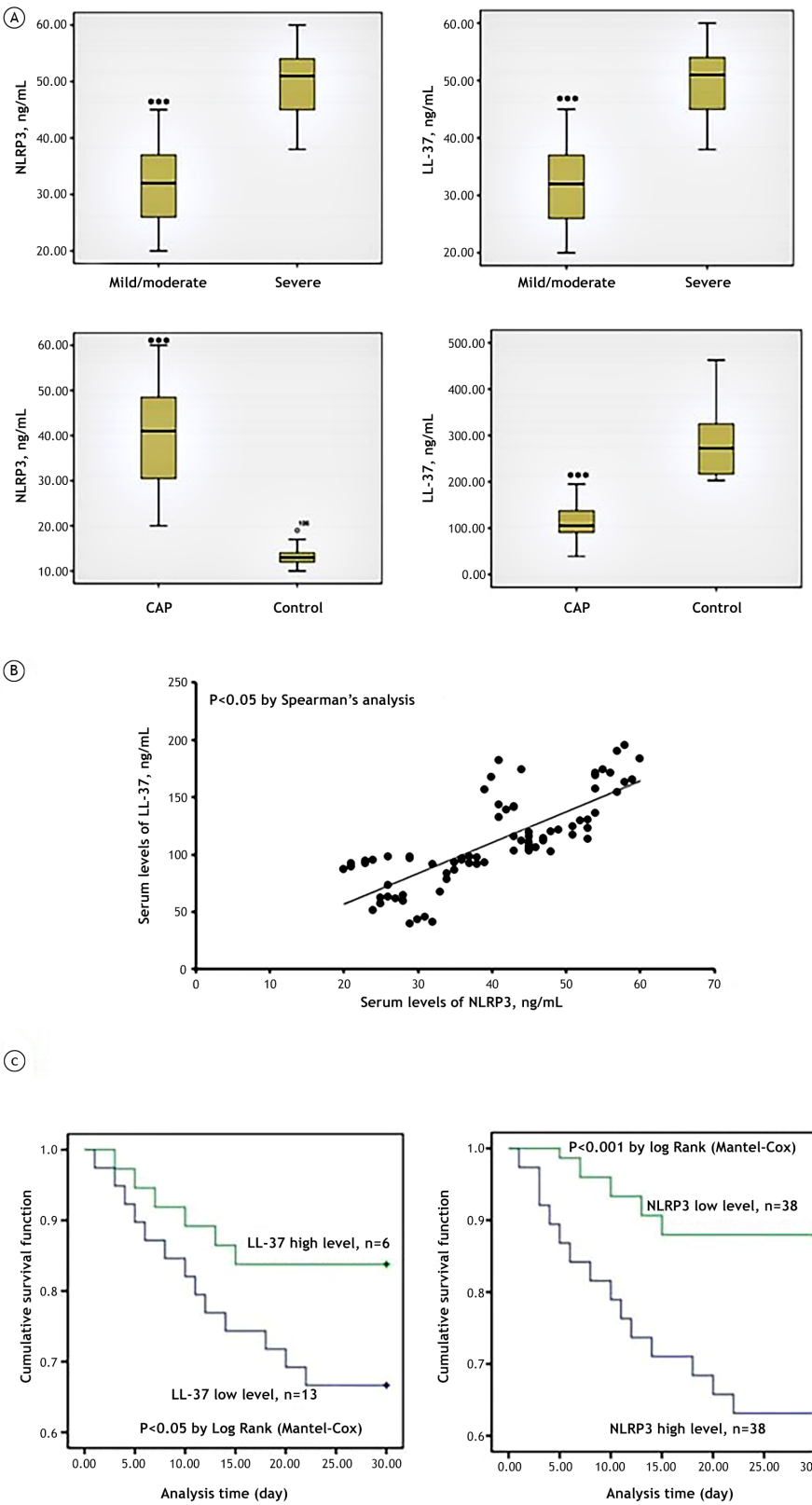

Figure 1. (A) Serum NLRP3 and LL-37 levels in patients with CAP (n=76) and healthy controls (n=50) and levels in patients with mild/moderate (n=41) or severe (n=35) CAP patients determined by ELISA. *$p<0.05$ *vs.* control group; (B) Correlation analysis between NLRP3 and LL-37 in CAP patients using Spearman's correlation analysis; (C) Kaplan-Meier survival curve of CAP patients with low or high serum NLRP3 or LL-37 levels.

Table 4. Clinic outcomes in CAP patients with high/low serum NLRP3.

Variable	Low NLRP3, n=38	High NLRP3, n=38
Mean age, years	60.3 ± 11.2	61.1 ± 12.3
Gender, male: female	23: 15	21: 17
Antibiotics received before treatment, n (%)	18 (47.4)	19 (50.0)
Symptoms, n (%)		
Fever	17 (44.8)	20 (52.6)
Cough	14 (436.8)	16 (42.1)
Sputum	12 (31.2)	13 (34.2)
Shortness of breath	8 (21.1)	10 (26.3)
Chest pain	5 (13.2)	8 (21.1)
Laboratory		
CRP, mg/L	60 (25~169)	135 (84~235)*
WBC, 10^9/mL	8.7 (7.1~13.8)	13.5 (11.0~17.5)*
LL-37, ng/mL	142 (90~195)	73 (39~120)*
PSI, n (%)		
I-III	32 (84.2)	9 (23.6)*
IV-V	6 (15.8)	29 (76.3)*
Mortality during 30 days follow-up, n (%)	5 (13.2)	14 (36.8)*

*$p<0.05$, compared with the low cortisol group.

DISCUSSION

Community-acquired pneumonia (CAP) is a common infectious disease associated with significant morbidity and mortality that poses a major threat to human health worldwide.[16] Despite the major mortality rate observed,[4,17] at present, initial diagnosis of CAP mainly includes respiratory symptoms and general signs, which cannot accurately reflect the disease condition. Although invisible pulmonary lesions can be accurately localized by fluoroscopy, the current widely used chest CT and radiography are radioactive and relatively expensive.[18] Thus, there is an urgent need to discover and validate new serum biomarkers for CAP.

C-reactive protein (CRP) is an acute-phase protein produced by hepatic cells that is widely involved in various inflammatory processes.[19] Serum CRP levels are generally low in healthy people, whereas stress stimulations such as infection and organ and tissue damage can trigger significant increase in serum CRP, which is typically not susceptible to antibiotics, malnutrition, glucocorticoids, or immunosuppressant drugs.[20] CRP is the most commonly used biomarker in the diagnosis and treatment of CAP due to its inexpensive price and high sensitivity to inflammation.[21,22] In the present study, serum CRP levels were highly expressed in severe CAP patients compared with mild/moderate CAP patients.

The role of Nod-like receptor protein 3 (NLRP3) in inflammatory processes, including pneumonia, has been demonstrated in many studies. Van Lieshout et al.[23] showed the NLRP3 inflammasome impaired host defense during lethal pneumonia in mice. It was also found that *staphylococcus aureus* α-hemolysin could mediate virulence by activating the NLRP3 inflammasome in a murine model of severe pneumonia.[24] Nevertheless, few studies have demonstrated the clinical significance of NLRP3 in CAP patients. Finding of the present study revealed, for the first time, that serum NLRP3 was significantly up-regulated in CAP patients compared with healthy controls, as well as in patients with severe CAP compared with mild/moderate CAP patients. Further investigation elucidated that patients with higher serum NLRP3 levels had higher serum CRP and lower LL-37 levels, and higher WBC counts and 30-day mortality rate.

Antimicrobial peptide LL-37 is the only member of cathelicidin family in human innate immune system that is cleaved from a cationic antimicrobial polypeptide of 18-kDa. In addition to its broad antimicrobial activity, LL-37 plays a vital role in immune modulation, angiogenesis, wound healing, and anti-tumor.[25,26] It has been shown that LL-37 was significantly down-regulated in children with pneumonia.[27] Hou et al.[28] also found that LL-37 could inhibit LTA-induced inflammation and suppress the development of pneumonia in a mice model.However, whether serum LL-37 levels were associated with prognosis of CAP patients is unclear. Findings of the present study showed that serum LL-37 levels in CAP patients, especially in patients with severe CAP, were also significantly down-regulated, and that patients with lower serum LL-37 showed lower survival rates. Nevertheless, the present study also has some limitations: first, the study sample is limited; second, the underlying mechanisms for how NLRP3 and LL-37 affected CAP are unknown. These issues need to be confirmed in further studies.

In conclusion, a prospective study was conducted to investigate the clinical significance of NLRP3 and LL-37 in CAP patients. Results showed that NLRP3 was significantly high, whereas LL-37 was significant down-regulated in CAP patients, and that both NLRP3

and LL-37 were significantly correlated with prognosis for CAP patients. This study may provide more clinical evidence and deeper understanding regarding role of NLRP3 and LL-37 in CAP.

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