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Usefulness of Serum C-reactive Protein for the Management of Aspiration Pneumonia in Primary Care

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Objective: C-reactive protein (CRP) is frequently used to assess infectious disease, but whether CRP is truly a "useful" marker in primary care settings is unclear. This study evaluated the usefulness of CRP as a marker for severity assessment of infectious disease in primary care and the treatment effectiveness. Additionally, we also evaluated the presence of other useful modalities.

Methods: In 32 patients (independent in activities of daily living) who visited our primary care clinic between June 2011 and December 2013 and were suspected of having aspiration pneumonia based on CT imaging, various tests including CRP were performed. The patients were classified into those who could be discharged home (recovery-group: RG) and those who died or were transferred to another facility (non-recovery-group: NRG) and compared. (The NRG included patients who were bedridden and could not be sent home). Infection severity was assessed using the A-DROP score.

Results: There were 19 patients in the RG and 13 patients in the NRG. There were no significant differences in age (RG: 79±7, NRG: 85±8 years), A-DROP score (RG: 1.9±0.8, NRG: 2.4±0.8), CRP on admission (RG: 7.8±6.1, NRG: 9.7±7.5 mg/dL), maximum CRP during hospitalization (RG: 10.3±5.6, NRG: 14.1±6.4), and days to CRP normalization (RG: 14.6±7.3, NRG: 13.5±8.2). However, hospital duration (RG: 19±15, NRG: 46±29 days, $p<0.01$), time to fever normalization (RG: 2.6±3.6, NRG: 11±10 days, $p<0.05$), and arterial blood gas (ABG) lactic acid concentrations (RG: 13±6.3, NRG: 26±16, $p<0.05$) were significantly different between the two groups.

Conclusion: Elderly patients often have serious infections despite few clinical symptoms. In the present study, the CRP level was not useful as a marker of infection severity, and was not useful in assessing therapeutic efficacy. ABGs were useful in some cases.

Key words: CRP, primary care, lactic acid, elderly patients, ADL

INTRODUCTION

C-reactive protein (CRP) was originally discovered in 1930 by Tillet et al. as a protein found in patients with pneumococcal pneumonia because it reacts with the C- polysaccharide of pneumococcal bacteria[1]. CRP is mainly synthesized in the liver in response to inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and IL-6 that are produced by activated macrophages. CRP binds to phospholipids of necrotic cells, activates the complement system, plays a role in

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biological defense, and functions to remove necrotic cells[2)~4)]. CRP is produced about 6–8 hours after the onset of inflammation when cytokine (e.g., IL-6) levels begin to rise. CRP is an inflammatory marker that increases in infections, trauma, infarctions, autoimmune disorders (e.g., connective tissue disease), and malignant tumors; thus, it is not a marker seen exclusively in infections. Therefore, some reports have refuted the usefulness of CRP in diagnosing infections[5)6)]. Meanwhile, Japan is the world's most rapidly aging society, with 1 of every 4 persons now considered elderly (September 2013). However, elderly patients with infections often have few subjective symptoms, which often makes diagnosis and treatment difficult.

This study investigated whether CRP is truly a "useful" immunological marker in primary care settings for management of infections such as aspiration pneumonia, the incidence of which is expected to increase in the future. The usefulness of CRP was evaluated from the following perspectives in patients with aspiration pneumonia at our hospital.

＊ Can CRP be used as a screening test to assess the severity of infectious disease in primary care?

＊ Can CRP be used as a marker of treatment effectiveness?

＊ Are there other useful modalities?

MATERIALS AND METHODS

This retrospective study included 32 patients (23 men, 9 women; mean age: 81.1±8.3 years) who were admitted to Aichi Medical University Hospital between June 2011 and December 2013 because of aspiration pneumonia diagnosed in the primary care clinic. All patients were independent in activities of daily living (ADLs).

The patients were classified as a recovery group (RG) and non-recovery group (NRG). The RG included patients whose aspiration pneumonia improved or resolved and who could return home with the same ADLs as before hospitalization. The NRG included patients whose overall condition worsened after aspiration pneumonia. These patients either died or were unable to return home due to being bedridden and having worse ADLs.

In patients with aspiration based on evaluations including their medical history, physical examination, and swallowing function tests on admission, those with pneumonia were presumed to have aspiration pneumonia. The severity of aspiration pneumonia was evaluated using the A-DROP score based on Japanese Respiratory Society guidelines[7)]. Testing at the time of admission also included measurement of CRP as an immunological marker, hematologic and biochemical studies, arterial blood gases (ABGs), sputum cultures, and blood cultures. The extent of infiltration on plain chest X-ray examination was classified as involving $<1/3$ of one lung, 1/3 to $<2/3$ of one lung, and $>2/3$ of one lung.

ADLs were evaluated according to the "Criteria for judging independence in daily activities" used by the "Long-term care insurance system" and ranked as: J, Independent and able to go outdoors; A, Independent activities indoors; B, Able to sit independently but otherwise bedridden; and C, Completely bedridden. Dementia was assessed based on a history taken from the family and caregivers and examination findings at the time of admission. Patients with obvious dementia in social activities were judged to have dementia.

Patients with C-rank ADLs based on the "Criteria for judging independence in daily activities" used by the "Long-term care insurance

system" before their current illness and patients with a history of severe respiratory failure, aspiration pneumonitis, or on dialysis were excluded.

STATISTICAL ANALYSIS

Continuous variables are expressed as means ±standard deviation. The unpaired Student's *t*-test and chi-square test were used for comparisons between the two groups. The level of statistical significance was $p<0.05$. Cut-off values were determined using a receiver operating characteristic (ROC) curve. Furthermore, we conducted multivariable analysis by the multiplex logistic-regression analysis at the same time and judged that there was a significant difference if, $p<0.05$.

For these statistical analysis, we used 6.0 StatFlex ®ver. software (ArtechCo., Ltd, Osaka, Japan).

RESULTS

1. Clinical characteristics

Table 1 summarizes the patients' clinical characteristics. There were 19 patients in the recovery group (RG) and 13 patients in the non-recovery group (NRG). The mean age was 79 ±7 years in the RG and 85±8 years in the NRG. The mean age tended to be higher in the NRG ($p=0.05$). With regard to the sex distribution, there were 13 males (68%) in the RG and 10 males (77%) in the NRG. Two patients (11%) in the RG and 8 patients (61%) in the NRG were living in a nursing home before hospital admission; this was significantly higher in the NRG ($p<0.05$).

ADLs before hospital admission were: RG: J rank 17 patients (90%) and A rank 2 patients (11%); and NRG: J rank 12 patients (92%) and A rank 1 patient (8%) (no significant difference between the two groups). Four patients (21%) in the RG and 3 patients (23%) in the NRG had obvious dementia that impaired ADLs (no significant difference between the two groups). The patients were classified into two groups according to the number of days between disease onset (onset day) and the time of initial measurement of CRP (time of hospital admission). This was defined as "early" (day 0–4) and "late" after disease onset. (day ≥5). This time

Table 1. Baseline clinical characteristics (Demographics)

	RG	NRG	p value
Number	19	13	
Age (yrs)	79±7	85±8	p=0.05
male (%)	68	77	n.s.
Nursing home resident (%)	11	61	p<0.05
Activity of daily living (ADL)			
J rank (%)	90	92	n.s.
A rank (%)	11	8	n.s.
B rank (%)	0	0	n.s.
C rank (%)	0	0	n.s.
Onset day*	2.8±2.8	1.6±2.9	n.s.
Early on set (%)	74	85	n.s.
Late on set (%)	26	15	n.s.

*patients were classified into two groups according to the number of days between disease onset and Initial mesurement of CRP as follows: Early, 0–4 day: Late, ≧5 day

was 2.8±2.8 days in the RG and 1.6±2.9 days in the NRG (no significant difference between the two groups). Early and late were 14 patients (74%) and 5 patients (26%), respectively, in the RG and 11 patients (85%) and 2 patients (15%), respectively, in the NRG, with no significant difference between the two groups. Table 2 summarizes the physical examination findings. The body mass index (BMI) was 20±4 kg/m^2 in the RG and 19±3 kg/m^2 in the NRG. Systolic blood pressure was 125±27 mmHg in the RG and 124±31 mmHg in the NRG; diastolic blood pressure was 70±17 mmHg in the RG and 68±15 mmHg in the NRG. The temperature was 38±1℃ in the RG and 38±1℃ in the NRG. Heart rate was 98±19 bpm in the RG and 102±15 bpm in the NRG. The respiratory rate was 22±6/min in the RG and 25±9/min in the NRG. There were no significant differences between the two groups.

Sepsis status, including sepsis, severe sepsis, and septic shock, was compared between the two groups. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. Septic shock is defined as severe sepsis-induced hypotension persisting despite adequate fluid resuscitation. Hypotension is defined as systolic blood pressure of <90

Table 2. Baseline clinical characteristics (Physical examination findings)

	RG	NRG	p value
BMI	20±4	19±3	0.471
Blood pressure (mmHg)			
Systolic	124.7±26.5	124.3±30.9	0.963
Diastolic	69.8±17.0	68.2±15.0	0.775
Body temperature	37.7±1.03	37.6±1.2	0.751
Heart rate (bpm)	97.6±19.1	101.9±15.3	0.510
Respiratory rate	21.6±6.2	25.4±8.8	0.160
Sepsis status (%)			
Sepsis	52	46	n.s.
Severe sepsis	21	38	n.s.
Septic shock	5	15	n.s.
DisOrientation (%)	21	38	n.s.

Table 3. Baseline clinical characteristics (Main co-morbid illness)

	RG	NRG	p value
Main co-morbities (%)			
Cardiovascular disease	11	15	n.s.
Cerebrovascular disease	32	31	n.s.
Neoplastic disease (current)	11	8	n.s.
Chronic liver damage	5	8	n.s.
Chronic lung disease*	26	38	n.s.
ESRD**	0	0	n.s.
Diabetes	32	31	n.s.
Dyslipidemia	26	8	n.s.
Hypertension	26	23	n.s.
Smoking	0	15	p=0.07

*: COPD, Asthma, Old Tb, IP and Others
**: end stage renal disease

Table 4. Baseline clinical characteristics (Radiographic findings)

	RG	NRG	p value
A-DROP			
Severity of pneumonia (%)			
Mild	74	54	n.s.
Moderate	26	38	n.s.
Severe	8	8	n.s.
A-DROP score	1.9±0.8	2.4±0.8	n.s.
Extent of infiltration on the Chest X-ray examination (%)			
Less than 1/3 area of one lung is infiltrated	74	62	n.s.
Less than 2/3 1/3 or more area of one lung is infiltrated	23	38	n.s.
More than 2/3 area of one lung is infiltrated	0	0	n.s.

Table 5.

On admission Pathogens isolated (sputum culture)			
	RG (n=20)	NRG (n=17)	p value
Staphylococcus aureus* (%)	20	29	n.s.
MRSA	10	18	n.s.
MRCNS	5	6	n.s.
Psudomonas aeruginosa	0	18	P=0.05
Krebsilla pneumoniae	15	12	n.s.
Streptococcuc pneumoniae	15	6	n.s.
Candida species	5	6	n.s.
Others**	40	23	n.s.

*: including MRSA
MRSA: Methicillin -susceptible Staphylococcus aureus
MRCNS: Methicillin Resistant Coagulase Negative Staphylococci
**: including Normal pharyngeal flora

On admission Pathogens isolated (blood culture)			
	RG	NRG	p value
Staphylococcus caprae	11	0	n.s.
Staphylococcus simulans	0	8	n.s.
Staphylococcus warneri	0	8	n.s.
Streptococcus pneumoniae	5	0	n.s.
MRSA	0	8	n.s.
Positive rate (%)	16	23	n.s.

MRSA: Methicillin -susceptible Staphylococcus aureus

mmHg or a reduction of >40 mmHg from baseline in the absence of other causes for hypotension. Sepsis was present in 52% of the RG and 46% of the NRG; severe sepsis was present in 21% in the RG and 38% in the NRG; and septic shock was present in 5% in the RG and 15% in the NRG. There were no significant differences between the two groups. Table 3 summarizes

Table 6.

On admission Laboratory Data			
	RG	NRG	p value
WBC ($\times 10^3/\mu l$)	9.5±5.1	10.6±3.4	0.524
Hb (g/dl)	11.7±1.8	111.7±2.8	0.936
PLT ($\times 10^3/\mu l$)	212±112	194±68	0.604
ALB (g/dl)	3.4±0.5	3.2±0.5	0.231
T-cho (mg/dl)	137±40	130±38	0.646
T-bil (mg/dl)	1.1±1.29	1.0±0.53	0.712
AST(U/l)	34±23	80±104	0.069
ALT (U/l)	42±87	48±70	0.826
BUN (mg/dl)	22±13	30±12	0.081
Cre (mg/dl)	0.94±0.04	1.2±0.5	0.077
e-GFR (ml/min/1.73^2)	64±24	45±16	0.019
GLU (mg/dl)	148±50	147±39	0.938
CRP (mg/dl)	7.8±6.1	9.7±7.5	0.407
On admission Blood gas analysis			
	RG	NRG	p value
pH	7.44±0.03	7.43±0.05	0.254
PCO_2 (mmHg)	36±6.3	35±7.7	0.700
PO_2 (mmHg)	75±25	75±28	0.960
$cHCO_3$ (mmol/l)	24±3.4	23±4.5	0.258
SAT (%)	92±8.3	90±8.2	0.682
ABE (mmol/l)	0.8±2.9	−1.2±4.1	0.124
AnGap (mmol/l)	12.2±2.8	14.4±3.9	0.068
Lactic acid (mg/dl)	13.2±6.31	25.5±16.4	0.006
O_2 flow (l/min)	1.1±1.6	2.0±3.7	0.302

the main comorbidities. Although these did not differ significantly between the two groups, smoking tended to be more common in the NRG.

Table 4 summarizes the radiographic findings. The A-DROP score did not differ significantly between the two groups, being 1.9±0.8 in the RG and 2.4±0.8 in the NRG. Each category for the extent of lung infiltration on plain chest X-ray also did not differ significantly between the two groups. Table 5 shows the sputum and blood culture results on admission. *Staphylococcus aureus* tended to be isolated frequently in both groups, but, most often, no specific organism was identified on cultures in both groups. The blood culture-positive rate did not differ significantly between the two groups, being 16% in the RG and 23% in the NRG. Table 6 summarizes the laboratory data and ABG results on admission. Most of the laboratory data, including WBC count and CRP level, did not differ between the two groups, but the estimated glomerular filtration rate (eGFR) was significantly lower in the NRG (45 ±16 ml/min/1.73^2) than in the RG (64±24 ml/min/1.73^2; $p<0.05$). On ABG analysis, lactic acid was significantly different between the two groups, being 13.2±6.31 mg/dl in the RG and 25.5±16.4 mg/dl in the NRG ($p<0.05$).

Table 7 shows the details of the first-line medications. Monotherapy did not differ significantly between the RG and NRG, but combi-

nation therapy (lincomycin＋fluoroquinolones) was used significantly more often in the NRG (30%) ($p<0.05$).

Table 7. Details of first line medication

	RG	NRG	p value
Monotherapy			
Carbapenemes	16	15	n.s.
Cephems	11	0	n.s.
Penicillins combined with β-lactamase inhibitor	68	54	n.s.
fluoroquinolones	5	0	n.s.
Combination therapy			
Lincomycin＋fluoroquinolones	0	30	p＜0.05

2. Clinical outcome

In the NRG, the rate of disuse syndrome was 39%, dementia 38%, other (deceased) at discharge 15%, and cerebrovascular disease 8%.

A comparison of CRP on admission (day 0), day 7, Max-CRP, and the Max-CRP/day 7 CRP ratio showed no significant differences between the RG and NRG. However, the day 7 CRP tended to be higher in the NRG (3.1±3.0) than in the RG (1.5±1.3; $p=0.05$). Max-CRP was 10.3±5.6 in the RG and 14.1±6.4 in the NRG ($p=0.09$). The CRP normalization period (days) did not differ between the two groups,

Table 8. Clinical outcome

	RG	NRG	p value
CRP (mg/dl)			
Day 0 CRP	7.8±6.1	9.7±7.5	0.407
Day 7 CRP	1.5±1.3	3.1±3.0	0.050
Max-CRP	10.3±5.6	14.1±6.4	0.099
Max-CRP/day 7 CRP ratio	10.4±6.7	8.6±8.0	0.508
WBC ($\times 10^3/\mu l$)			
Day 0 WBC	9.5±5.1	10.6±3.4	0.524
Max-WBC	11.1±5.1	12.4±3.3	0.398
Cre (mg/dl)			
Day 0 Cre	0.94±0.04	1.2±0.5	0.077
Max-Cre	1.03±0.45	1.4±0.5	0.050
CRP normalization period (day)	14.6±7.3	13.5±8.2	0.698
Fever normalization period (day)	2.6±3.6	10.8±10.7	0.006
Hospital stay (days)	18.9±14.8	45.6±28.7	0.002

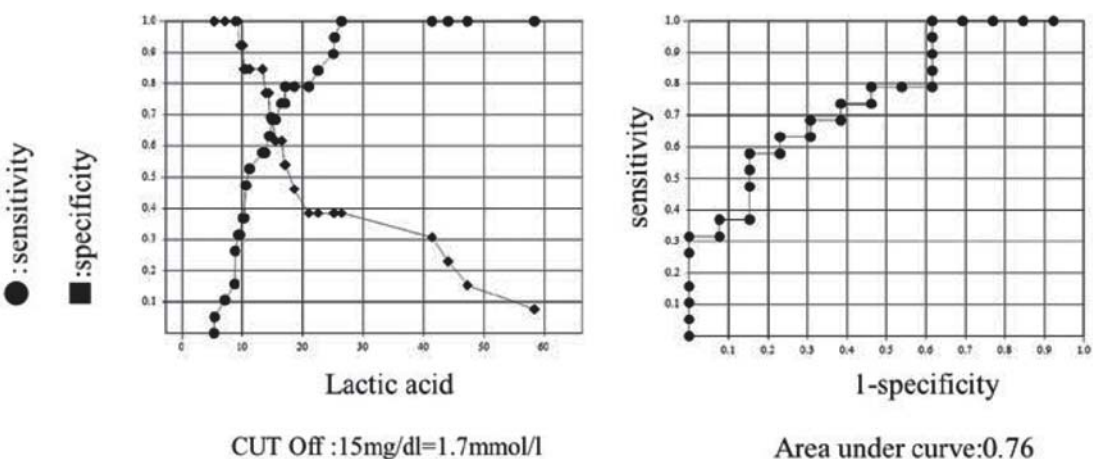

Figure 1. Receiver operating characteristics curve of lactic acid

being 14.6±7.3 in the RG and 13.5±8.2 in the NRG. In addition, the WBC count, CRP on admission (day 0), and Max-CRP did not differ significantly between the RG and NRG.

There was a significant difference the fever normalization period (days) between the two groups, (2.6±3.6 day in the RG and 10.8±10.7 day in the NRG; $p<0.05$) (Table 8). And there was a significant difference in the hospital stay (days) between the two groups (18.9±14.8 in the RG and 45.6±28.7 in the NRG; $p<0.05$) (Table 8). The cut-off value on the ROC curve for ABG lactic acid on admission in the RG and NRG was 15 mg/dL, and the area under the curve was 0.76 (Fig. 1).

By the results of the multivariable analysis of the drawing blood factor which became $p\leqq0.05$ by univariate analysis, it lactic acid level was $p=0.069$ (for a renal function index, e-GFR was an examination item) (Table 9).

Table 9. Multivariable analysis of the drawing blood factor

	β	SE (β)	p value
e-GFR (ml/min/1.73^2)	−0.0377	0.02341	0.1077
Lactic acid (mg/dl)	0.11238	0.06195	0.0697
Day 7 CRP (mg/dl)	0.43326	0.31512	0.1692

DISCUSSION

Japan is now a super-aging society, and preventing an increase in the number of bedridden patients is an urgent issue. However, elderly patients often have serious infections despite few clinical symptoms, and the treatment they receive in primary care will have an influence on their subsequent ADLs. Prognostic factors in elderly patients with pneumonia and the usefulness of measuring CRP levels in managing pneumonia have been described in some reports, but most have examined factors related to survival rates[8)~10)]. The purpose of the present study was to investigate functional prognosis, namely, maintaining function and independence in ADLs, in older patients. In other words, in elderly patients with aspiration pneumonia, whether measurement of CRP levels on admission and during the course of treatment was useful, and whether the CRP level was a determining factor not only for survival rates, but also for whether patients could eventually be discharged with independence in ADLs, were examined. Other modalities were also examined as determining factors.

Pulliam et al. reported that CRP was valuable in detecting serious bacterial infections in neonates and young children, and that this was useful in pediatrics where establishing this by history and examination may be relatively difficult[11)]. However, there is no evidence in adults that initial CRP levels are useful in deciding indications for antibiotics and hospitalization. In the present study as well, initial CRP levels were not useful as a prognostic determinant. This is because it takes 6–8 hours before CRP levels begin to rise after inflammation develops, and the disease onset time and time until hospital evaluation differed in each patient.

In the present study, onset time was classified as early onset and late onset, and there were no differences in either between the RG and NRG. Difference of clinical course (time axis) may effect on CRP volume. This was also examined, but like other evidence, evaluation based on absolute CRP levels was difficult[3)]. This was similarly suggested by the fact that Max-CRP was not useful as an index to assess treatment effectiveness. However, in the RG, many patients did have early improvement in CRP. Therefore, treatment effectiveness based on CRP levels cannot be judged at any given time point, but rather, the changes over time (time axis) must be examined. These changes in CRP levels may reflect the clinical course

and treatment effectiveness. In addition, there were no significant differences in WBC counts. The WBC count has not previously been regarded as useful in assessing infection severity, and the present study showed similar findings.

Clinical vital signs, including temperature, pulse rate, respiratory rate, and blood pressure, also did not differ significantly between the two groups. Moreover, the systemic inflammatory response syndrome (SIRS) score, which includes the WBC count, did not differ significantly between the two groups (2.1 ± 0.95 in the RG and 2.0 ± 1.0 in the NRG). The present results reflect the fact that elderly patients often have few clinical symptoms, which makes it difficult to assess disease severity.

ABG lactic acid levels were significantly higher in the NRG than that in RG by univariate analysis. Because, it was $p=0.06$ by multivariable analysis, we could not show a clean relationship. However ABG lactic acid levels could be on index of the prognosis of infectious disease. The measurement of ABGs seems to be an useful modality when assesing elderly patients, who usually have multiple problems. ABG analysis is useful not only to assess respiratory function, but also disease severity, organ function status, hemodynamic status, and systemic energy metabolism. Therefore, while ABG analysis is a modality for individual organ assessment, it is also a modality to examine total systemic output. This is also supported by the fact that early lactate-guided therapy (ELGT) is recommended in the Surviving Sepsis Campaign Guidelines 2012 (SSCG)[12][13].

In the present study, the ROC curve cut-off value for lactic acid was 1.7 mmol/L, which is slightly higher than >1 mmol/L as a tissue perfusion variable in the SSCG 2012. One factor may be delayed hemodynamic and organ injury responses in elderly patients. The SOFA score[14] has also been used as an organ dysfunction variable in assessing disease severity. In the present study, creatinine, as an index of renal function, did not differ significantly between the two groups on admission, but the significant difference in eGFR on admission and a significant trend in the maximum creatinine do suggest that renal function during treatment of elderly patients is a prognostic factor. Therefore, in the treatment of elderly patients who often have few clinical symptoms, changes over time in CRP levels, and evaluation of lactic acid and creatinine levels as other modalities, may be useful for objective assessment.

Problems in interpreting CRP levels may arise in patients taking steroids, immunosuppressants, or biological preparations (anti-TNFα or anti-IL-6) and in patients with decreased liver function. In these cases, because CRP levels may not change or reflect disease status, other modalities such as lactic acid, as seen in the present study, may be useful. The present study did not examine other inflammatory markers such as IL-6 and procalcitonin. The test results for IL-6 require considerable time, and no consensus has yet been reached on the value of assessment with procalcitonin[15]. Measurement of CRP levels is rapid, convenient, and inexpensive from a medical cost perspective. Therefore, if the points on interpretation of CRP results are carefully taken into consideration based on the present study results, CRP may still be a useful modality compared to other inflammatory markers.

STUDY LIMITATIONS

One of the the limitation of this study is small sample size. We thought that these differences between two-groups (RG and NRG) might affect our conclusion. Herein, we con-

ducted sub-group analysis (i: 75–90-year-old patient, ii: more than 80-year-old patient). However, CRP on admission (day 0) did not different between RG and NRG. Therefore, we thought that CRP on admission did not affect the prognosis in this population.

CONCLUSION

Prognosis in elderly patients with aspiration pneumonia is difficult to assess from subjective symptoms and absolute values of inflammatory markers such as CRP and the WBC count. However, evaluation over a period of time may be useful. Other tests such as lactic acid, which indicate organ injury, are also important. Medical care in elderly patients with multiple problems is challenging. These patients require comprehensive diagnosis and careful monitoring to assess organ dysfunction. In addition, it is desirable to use objective evaluation methods such as inflammatory markers and imaging diagnosis in a complementary manner.

REFERENCES

1) Tillet WS, Francis T Jr. Serological reactions in pneumonia with a nonprotein fraction from pneumococcus. J Exp Med 1930; 52: 561–71.
2) Volanakis JE. Human C-reactive protein: expression, structure, and function. Mol immunol 2001; 38(2–3): 189–97.
3) Gabay C, Kushner I. Acute-phase proteins and other systemic responces to inflammation. N Engl J Med 1999; 340: 448–54.
4) Clyn B, Olshaker Js. The C-reactive protein. J emerg Med 1999; 17: 1019–25.
5) Van der Meer V, Arie Knuistingh Neven, Peterhans J van den Broek, Willem JJ Assendelft. Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. BMJ 2005; 331: (7507).
6) Pulliam PN, ATTia MW, Cronan KM. C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. Pediatrics 2001; 108: 1275.
7) The committee for JRS guidelines in management of respiratory infections: The JRS guidelines for the management of community-acquired pneumonia in adults. The Japanese Respiratory Society, Tokyo (2005) (in Japaneae).
8) Chalmers JD, Singanayagam A, Hoill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. Am J Med 2008; 121: 219–25.
9) Bruns AH, Oosterheert JJ, Hak E, Hoepelman AI. Usefulness of consecutive C-reactive protein measurements in follow-up severe community-acquired punmonia. Eur Respir J 2008; 32: 726-32.
10) Coelho L, Povoa P, Almeida E, Fernandes A, Mealha R, Moreira P, et al. Usefulness of C-reactive protein in monitoring the severe community-acquired pneumonia clinical course. Crit Care 2007; 11(4): R92.
11) Pulliam PN, ATTia MW, Cronan KM. C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. Pediatrics 2001; 108(6): 1275–9.
12) Dillinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Steven M, et al. Surviving sepsis campaingn: international guidelines for management of severe sepsis and septic shock: 2012. Crit care Med 2013; 41: 580–637.
13) Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. Nengl J med 2001; 345: 1368–77.
14) Vincent JL, Moreno R, Takala J, Willatts S, Mendoca ADe, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996; 22: 707–10.
15) Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections; the ProHoasp randomized controlled trial. JAMA 2009; 302: 1059–66.