A Retrospective Analysis of 111 Cases of Pneumococcal Pneumonia: Clinical Features and Prognostic Factors

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Abstract

Objective *Streptococcus pneumoniae* is an important and common pathogen of acute pneumonia. The urinary pneumococcal antigen test has been increasingly used for the diagnosis of pneumococcal pneumonia, but there have been few studies on pneumococcal pneumonia after this test became prevalent. The present study was conducted to characterize the clinical features of pneumococcal pneumonia after the introduction of the urinary antigen test.

Methods We retrospectively analyzed 111 cases from 105 patients with pneumococcal pneumonia in our hospital between 2007 and 2010, and collected data regarding background characteristics, laboratory data, isolated bacteria, and clinical courses.

Results The cases analysed included 77 of community-acquired pneumonia (CAP), 21 of healthcare-associated pneumonia (HCAP), and 13 of hospital-acquired pneumonia (HAP). Penicillin-resistant *Streptococcus pneumoniae* was isolated in 12.5 and 55.6% of non-HAP and HAP cases, respectively. When the cases were divided into 5 groups according to A-DROP scores (0, 1, 2, 3 and 4 points), critical events occurred at 0, 0, 8.7, 15.4, and 75.0% in groups of cases of 0, 1, 2, 3, and 4 points, respectively. Similarly, critical events occurred at 66.7, 4.7, 3.8, and 9.1% in groups of cases according to WBC counts of <4,000, 4,000-9,999, 10,000-19,999, and ≥20,000 cells/μL, respectively.

Conclusion Most of the pneumococcal pneumonia cases occurred as CAP and were treated successfully. HAP cases were frequently penicillin resistant. Elevated A-DROP scores and decreased WBC counts were found to be predictive of critical events.

Key words: A-DROP, pneumococcal pneumonia, *streptococcus pneumoniae*, urinary pneumococcal antigen

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Introduction

Although acute pneumonia can be successfully treated with effective antibiotics, it is the fourth most frequent cause of death in Japan (1) and the world (2). Acute pneumonia is still an important infectious disease. *Streptococcus pneumoniae* is the leading microorganism causing community-acquired pneumonia (CAP) (3, 4) and lethal pneumonia (5), and should be also considered as an important cause of hospital-acquired pneumonia (HAP) (6).

In recent years, the urinary pneumococcal antigen test (7-9) has been increasingly used for diagnosing pneumococcal pneumonia. However, there have been few clinical studies on pneumococcal pneumonia after this test was introduced. In addition, the A-DROP system proposed by the Japanese Respiratory Society (JRS) in 2007 was not fully evaluated for its validation. To document or identify clinical characteristics of pneumococcal pneumonia and evaluate the usefulness of A-DROP system in pneumococcal pneumonia, we conducted a retrospective analysis of 111 cases (105 patients) based on the urinary pneumococcal antigen test and

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culture results of *S. pneumoniae*. This led us to identify several important findings regarding the clinical features and prognosis of the disease.

Materials and Methods

Inclusion criteria for pneumococcal pneumonia cases

We screened 112 urinary pneumococcal antigen positive tests and 360 samples (from sputum, blood, pleural effusion, and bronchofiberscopy) that were culture-positive for *S. pneumoniae* between January 2007 and December 2010 according to our hospital database. BinaxNOW® *S. pneumoniae* (Binax, Inc, Scarborough, ME, USA) was used for the detection of urinary pneumococcal antigen. We established three diagnostic criteria: (i) bacteriological, (ii) clinical, and (iii) radiological. Bacteriological criteria required at least one factor from (a)-(d): (a) positive result for the urinary pneumococcal antigen test without pneumonia in the previous three months, (b) identification of *S. pneumoniae* cultured from sputum at $\geq 2+$ (equivalent to 10^5 CFU/mL), (c) identification of *S. pneumoniae* cultured from sputum at $\geq 1+$ (equivalent to 10^3 CFU/mL) with phagocytosed bacteria by Gram staining, and (d) identification of *S. pneumoniae* cultured from pleural effusion or blood. Clinical criteria included either fever $\geq 37.0^\circ\text{C}$, cough, elevated white blood cell (WBC) counts ($\geq 10,000$ cells/ μL), decreased WBC counts ($< 4,000$ cells/ μL), elevated CRP values (≥ 0.30 mg/dL), or progression of hypoxemia ($\text{SpO}_2 \leq 90\%$ or $\text{PaO}_2 \leq 60$ Torr). Radiological criteria retained either chest X-ray or computed tomography scans suggestive of pneumonia. The patients that met all three criteria were designated as a case of pneumococcal pneumonia. We selected 111 cases (events) from 105 patients that met the pneumococcal pneumonia criteria during the four-year study period and analyzed these cases (6 patients had a second bout of pneumococcal pneumonia).

Data collection

We collected the following data from the patients: background (gender, age, and comorbidities), laboratory test data at the onset of pneumonia (WBC counts, BUN levels, Cr levels, urinary pneumococcal antigen test results, results of bacterial culture, and oxygenation levels), physical examination findings (blood pressure, presence of dehydration, and level of consciousness), and clinical courses (duration of antibiotic therapy, requirement of mechanical ventilation, and mortality). The definition of CAP, healthcare-associated pneumonia (HCAP), and HAP were conformed to the ATS guideline (6). Nursing-home acquired pneumonia (NHAP) was defined as a pneumonia acquired in patients of nursing-home residence. NHAP is included by HCAP according to the ATS guideline. Resistance of isolated *S. pneumoniae* to penicillin, ceftriaxone (CTRX), ofloxacin (OFLX), and imipenem (IPM) were defined by National Committee for

Clinical Laboratory Standards (NCLLS) (10). PSSP, PISP, and PRSP were defined as $\text{MIC} \leq 0.063$, $\text{MIC} = 0.12\text{--}1.0$, and $\text{MIC} \geq 2.0$ $\mu\text{g/mL}$, respectively. CTRX, OFLX and IPM resistance were defined as $\text{MIC} \geq 4.0$ $\mu\text{g/mL}$, $\text{MIC} \geq 8.0$ $\mu\text{g/mL}$, $\text{MIC} \geq 2.0$ $\mu\text{g/mL}$, respectively. Drug sensitivity was checked by using the *S. pneumoniae* isolated before antibiotic treatment in our hospital. A-DROP scores were calculated by the sum of five risk factors (1: ≥ 70 years old for males, or ≥ 75 years old for females, 2: $\text{BUN} \geq 21$ mg/dL, or presence of dehydration, 3: $\text{SpO}_2 \leq 90\%$, or $\text{PaO}_2 \leq 60$ Torr, 4: Disturbance of consciousness, 5: Blood pressure ≤ 90 mmHg) (11). The study protocol was approved by the institutional review board of our hospital.

Statistical analysis

We compared frequencies of critical events (Table 3, 6-9, as defined by requirement of mechanical ventilation or death by pneumonia) and frequencies of penicillin-susceptible *S. pneumoniae* (PSSP), penicillin-intermediate *S. pneumoniae* (PISP), and penicillin-resistant *S. pneumoniae* (PRSP) (Table 5) with a chi-square test. We compared the duration of antibiotic therapy among the patients depending on A-DROP scores (Table 6, 8, 9) with a t-test.

Results

Six of the 105 patients developed secondary pneumococcal pneumonia, and thus 111 cases in total were analyzed in this study. As shown in Table 1, 59 cases occurred in male patients and 52 occurred in female patients. The median age was 73 years old (ranging 15 to 97 years old) with 89 cases (82%) occurring in patients over 60 years of age. Ten cases had diabetes mellitus, eight had malignancy (four of which were lung cancer), 36 had respiratory diseases other than lung cancer, and 14 had a swallowing disorder (according to medical records of our hospital during pneumonia). Nine cases were receiving systemic steroid therapy for their comorbidities, and four cases had been vaccinated for pneumococcal pneumonia.

Table 2 shows the bacteriological diagnosis in the cases of pneumococcal pneumonia. Seventy-two cases (64.9%) were diagnosed by the urinary pneumococcal antigen test, 25 (22.5%) by culture results only, and 14 (12.6%) by both methods. Sputum was cultured in 67 of the 86 cases positive for the urinary pneumococcal antigen test. *S. pneumoniae* was isolated in 22 cases (32.8%), but only 11 cases (16.4%) met the bacteriological criteria ($\geq 2+$, or $\geq 1+$ with detection of phagocytosed bacteria by Gram staining).

Seventy-seven of 111 cases (69.0%) were CAP and 60 of them were admitted to our hospital. Twenty-one of the cases (18.9%) were HCAP and 20 of them were admitted to our hospital. Seven of the cases (6.3%) were nursing home-acquired pneumonia (NHAP, which is included in HCAP) and all of them were admitted to our hospital. Thirteen of the cases (11.7%) were HAP and all of them continued to stay in the hospital (three were transferred to our hospital

Table 1. Characteristics of 111 Cases (105 Patients)

Characteristics	No. of cases (%)
Gender:	
Male	59 (53.2%)
Female	52 (46.8%)
Vaccination	4 cases (3.6%)
Comorbidities	
Diabetes mellitus	10 (9.0%)
Malignancy	8 (7.2%)
Steroid therapy	9 (8.1%)
Respiratory disease (other than lung cancer)	36 (32.4%)
Swallowing disorder	14 (12.6%)
Neuromuscular disease *	6 (5.4%)
Bronchotomy †	1 (0.9%)

Median age was 73 years old, ranging from 15 to 97 years old.

*Includes three cases of amyotrophic lateral sclerosis, two cases of muscular dystrophy, and one case of spinocerebellar degeneration. All six patients were bedridden due to their diseases.

†Patient received bronchotomy for amyotrophic lateral sclerosis-induced respiratory failure.

Table 2. Bacteriological Diagnosis

Method	Cases (%)
Urinary pneumococcal antigen test	72 (64.9%)
Bacterial cultures	25 (22.5%)
Both	14 (12.6%)

for pneumonia). We defined a critical event as requirement of mechanical ventilation or death by pneumonia as a critical event, and relationships between critical events and pneumonia type were analyzed (Table 3). The frequency of critical events in CAP was 3.9% (3/77). In contrast, the frequency of critical events in NHAP was elevated to 28.6% (2/7), but statistically not significant ($p = 0.05$). The frequency of deaths was significantly higher in NHAP than in CAP (1.3% in CAP vs. 28.6% in NHAP; $p = 0.02$).

Next, we investigated the frequency of mixed bacterial infection in 89 pneumococcal pneumonia cases in which sputum or bronchofiberscopic samples were obtained for bacterial culture. Using similar bacteriological criteria as pneumococcal pneumonia, we diagnosed 11 cases of mixed infection (12.4%): four cases with *Haemophilus influenzae*, three cases with *Pseudomonas aeruginosa*, three cases with *Escherichia coli*, and two cases with *Moraxella catarrhalis* (Table 4). The relationship between mixed infection and poor clinical outcome was not clear in this study because there were no critical events in the cases of mixed infection.

S. pneumoniae was isolated in 50 cases (including cases in which only a small amount of bacteria was isolated from sputum culture), and drug resistance was tested in 49 of those cases. PRSP was identified in 20.4% of the cases and the isolation was increased up to 55.6% in the cases of HAP (Table 5), which was significantly more frequent than that in non-HAP cases (12.5%, $p = 0.01$). The proportion of OFLX resistance was also higher in HAP cases than in non-HAP cases (55.6% in HAP vs. 5.7% in non-HAP, $p = 0.002$). On the other hand, the proportion of CTRX resistance (total:

6.1%, HAP: 11.1%, non-HAP: 5.7%, $p = 0.46$) and IPM resistance (there was no IPM resistant *S. pneumoniae* in this study) were lower, and there was no difference between HAP and non-HAP cases. There were no critical events in 10 cases in which PRSP was isolated; the relationship between PRSP isolation and poor clinical outcome was not shown.

We were able to evaluate A-DROP scores, which is a criterion proposed by the JRS for assessing the severity of CAP (11), in 102 cases. The frequency of critical events was increased along with A-DROP scores (critical events occurred at 8.7, 15.4, and 75.0% in cases of A-DROP scores of 2, 3, and 4 points, respectively), whereas there were no critical events in cases of A-DROP scores of 0 or 1 (Table 6). On the other hand, A-DROP scores were not correlated with the duration of therapy. We then analyzed the relationship between positive urinary pneumococcal antigen tests and A-DROP scores. There was no statistically significant difference in the incidence of positive urinary pneumococcal antigen tests among A-DROP score groups (Table 7).

We performed a similar analysis for CRP levels (Table 8). The critical events occurred in 42.9% of cases with CRP levels ≥ 30 mg/dL, which was statistically significantly more frequent ($p < 0.01$) than those with CRP < 10 mg/dL (3.8%). However, the critical events also occurred in cases with CRP < 10 mg/dL and 10.0-19.9 mg/dL. We also observed a statistically significant correlation between elevated CRP levels and prolonged periods of antibiotic therapy (Table 8).

Finally, we investigated the relationship between WBC counts and the duration of therapy (Table 9). Although only three cases showed decreased WBC counts ($< 4,000$ cells/ μ L), their duration of therapy was prolonged (21.3 ± 5.8 days) and the critical events occurred at an extremely high frequency (66.7%) compared to cases with normal WBC counts (4,000-9,999 cells/ μ L). Multivariate analysis (logistic regression analysis) including A-DROP scores, decreased WBC counts, and CRP levels revealed that elevated A-

Table 3. Pneumonia Type and Outcome

Pneumonia type	Cases	CE (%) [*]	p value [†]	Death (%)	p value [‡]
CAP	77	3 (3.9%)	-	1 (1.3%)	-
HCAP	14	0 (0%)	0.45	0 (0%)	0.66
other than NHAP					
NHAP	7	2 (28.6%)	0.05	2 (28.6%)	0.02
HAP	13	1 (7.7%)	0.53	1 (7.7%)	0.15
Total	111	7 (6.3%)		4 (3.6%)	

CAP: Community-acquired pneumonia. NHAP: Nursing home-acquired pneumonia.

HAP: Hospital-acquired pneumonia. CE: critical event.

^{*}CE is defined as death or necessity for mechanical ventilation.[†]p values of CE vs. CAP group were calculated by chi-square test.[‡]p values of death vs. CAP group were calculated by chi-square test.**Table 4. Bacteria Cultured in Mixed Infections**

89 pneumococcal pneumonia cases	Cases (%)
<i>Haemophilus influenzae</i>	4 (4.5%)
<i>Pseudomonas aeruginosa</i>	3 (3.4%)
<i>Escherichia coli</i>	1 (1.1%)
<i>Escherichia coli</i> + <i>Enterococcus faecalis</i>	1 (1.1%)
<i>Moraxella catarrhalis</i>	1 (1.1%)
<i>Moraxella catarrhalis</i> + <i>Streptococcus mitis</i>	1 (1.1%)
Total	11 (12.4%)

DROP scores ($p < 0.01$) and decreased WBC counts ($p < 0.01$) were independently related to the critical events. The duration of therapy also tended to be prolonged in cases with increased WBC counts ($\geq 20,000$ cells/ μL), but the frequency of the critical events was not increased.

Discussion

In this study, we investigated the clinical features and prognostic factors of pneumococcal pneumonia not only in cases of CAP, but also in HCAP and HAP cases. The frequency of PRSP was higher in HAP than in CAP and HCAP, while the risk of death was higher in NHAP than in CAP. The A-DROP system was useful in predicting critical events, and decreased WBC counts were an independent predictor of the critical events. It is very important for successful treatment to determine the patients with a bad prognosis and drug resistance, and to treat such patients appropriately and intensively.

We confirmed that the urinary pneumococcal antigen test greatly contributed to the diagnosis of pneumococcal pneumonia in the general hospital. There were 67 urinary pneumococcal antigen positive cases in which sputum cultures were also checked. *S. pneumoniae* was not isolated in 44 cases (65.7%), and isolated in 23 cases (11 cases of which met our bacteriological criteria). This finding is consistent with a previous study reported by Gutiérrez et al (12), in which 69 of 88 urinary antigen positive cases (78%) were culture negative. There are several factors that may reduce the sensitivity of culture results, such as a preceding antibiotic therapy and quality of sputum samples. Therefore, the urinary antigen test is an important diagnostic tool for pneu-

mococcal pneumonia.

It is interesting that the incidence of swallowing disorder was remarkably high as a comorbidity (12.6% of patients) (Table 1). Our survey depended on the medical records, so only evident cases were regarded as swallowing disorder. This prevalence may be influenced by definition, patient age distribution, and hospital characteristics. Accordingly more studies are needed to evaluate the relationship between swallowing disorders and pneumococcal pneumonia. El-Solh et al (13) reported that the causative agents of aspiration pneumonia include aerobic bacteria such as *S. pneumoniae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. We should not underestimate the involvement of *S. pneumoniae* when treating aspiration pneumonia.

Fuse et al (14) reported that the frequency of positive urinary pneumococcal antigen tests was not changed regardless of the A-DROP scores. In the present study, the frequency of positive urinary pneumococcal antigen tests was slightly increased in association with A-DROP scores (86.2% in the A-DROP 0 points group and 93.8% in cases with A-DROP scores ≥ 3 points, Table 6), but it was not statistically significant. Urinary pneumococcal antigen was efficiently detected, even in the mild cases.

When analyzing prognosis according to a pneumonia type, the frequency of death was significantly higher in NHAP than in CAP (Table 3). NHAP has been reported to have a poor prognosis (15), and we observed similar results in our study of pneumococcal pneumonia. The age of NHAP patients (76.7 ± 8.6 years old) was higher than that of CAP (69.3 ± 15.0 years old), but it was similar to HCAP other than NHAP (80.0 ± 7.6 years old). Therefore the reason for the poor prognosis in NHAP might reside in the decreased ability of daily life (ADL). It is possible to predict the critical events by using the A-DROP system, but pneumococcal pneumonia in nursing homes should be treated intensively in the hospital. NHAP was included in HCAP in the ATS guideline (6). The present data regarding HCAP and NHAP was limited in number, but it suggested the possibility of difference in the characteristics between NHAP and HCAP.

The incidence of resistance of *S. pneumoniae* to penicillin, one of the primarily-selected antibiotics for treating

Table 5. Susceptibility of *Streptococcus pneumoniae* Isolates to Penicillin G, Ceftriaxone, Ofloxacin, and Imipenem

	Total	HAP	Non-HAP	p value *
PSSP	17 (34.7%)	2 (22.2%)	15 (37.5%)	0.47
PISP	22 (44.9%)	2 (22.2%)	20 (50%)	0.16
PRSP	10 (20.4%)	5 (55.6%)	5 (12.5%)	0.01
CTRX resistance	3 (6.1%)	1 (11.1%)	2 (5.0%)	0.46
OFLX resistance [§]	7 (15.9%)	5 (55.6%)	2 (5.7%)	< 0.01
IPM resistance	0 (0%)	0 (0%)	0 (0%)	1.00
Total	49	9	40	

HAP: Hospital-acquired pneumonia. Non-HAP: Community-acquired pneumonia and healthcare-associated pneumonia. PSSP: Penicillin-susceptible *Streptococcus pneumoniae*. PISP: Penicillin-intermediate *Streptococcus pneumoniae*. PRSP: Penicillin-resistant *Streptococcus pneumoniae*. CTRX: ceftriaxone. OFLX: ofloxacin. IPM: imipenem.

*Frequency in HAP vs. non-HAP group compared by chi-square test.

[§]OFLX sensitivity was checked in 9 HAP cases and in 35 non-HAP cases.

Table 6. A-DROP Score and Clinical Course

A-DROP	Cases (%)	Critical events (%)	p value *	Duration of therapy (mean ± S. D.) [†]	p value ‡
0 points	34 (33.3%)	0 (0%)	-	13.3 ± 8.4 days	-
1 point	28 (27.5%)	0 (0%)	1.00	14.7 ± 8.1 days	0.53
2 points	23 (22.5%)	2 (8.7%) [§]	0.15	15.3 ± 5.9 days	0.35
3 points	13 (12.7%)	2 (15.4%) [¶]	0.07	15.7 ± 4.1 days	0.34
4 points	4 (3.9%)	3 (75.0%) [#]	< 0.01		
5 points	0 (0%)	-	-		
Total number	102 cases	7 cases		98 cases	

*p values vs. 0 points group calculated by chi-square test.

[†]Cases in which death occurred eliminated from analysis.

[‡]p values vs. 0 points group calculated by t-test.

[§]All cases were treated successfully.

[¶]Death occurred in all cases.

[#]Death occurred in two cases.

Table 7. A-DROP Score and Urinary Pneumococcal Antigen Test Results

A-DROP	Positive cases / total cases (%)	p value *
0 points	25 / 29 (86.2%)	-
1 point	23 / 25 (92.0%)	0.67
2 points	18 / 20 (90.0%)	0.96
≥ 3 points	15 / 16 (93.8%)	0.64
Total number	81 / 90 (90.0%)	

*p values vs. 0 points group calculated by chi-square test.

Five cases were eliminated from analysis because A-DROP scores could not be calculated.

pneumococcal pneumonia, was found to be 12.5% in non-HAP cases in this study, which was comparable to that reported in a previous study conducted in Japan (16). On the other hand, penicillin-resistant isolates were increased up to 55.6% in HAP cases (Table 5). Hospitalization is a risk factor of multidrug resistant bacterial pneumonia (6). Thus, pneumococcal pneumonia in hospitals should be treated as PRSP because we found that HAP cases with *S. pneumoniae* were frequently resistant to penicillin G (MIC ≥ 2 µg/dL). Recently the new criteria of penicillin resistance regarding *S. pneumoniae* was proposed by CLSI (17). The proportion of PRSP (MIC ≥ 8 µg/dL) may be reduced according

to this strict criteria, but we could not assess by this criteria, because the upper limit of MIC in our study was 2 µg/dL. To summarize Table 3 and Table 4, most pneumococcal pneumonia occurred as CAP, but the pneumococcal pneumonia in nursing-home and hospital cases possess different characteristics. NHAP is related to a bad prognosis and HAP is related to penicillin resistance.

Finally, we investigated the relationships between the critical events and A-DROP scores, CRP levels, and WBC counts. As shown in Table 5, 7, the critical events frequently occurred in patients with elevated A-DROP scores (≥ 3 points) and highly elevated CRP levels (≥ 30 mg/dL). There

Table 8. CRP Levels and Clinical Course

CRP (mg/dL)	Cases (%)	Critical events (%)	p value *	Duration of therapy (mean $\pm$ S. D.) [†]	p value [‡]
< 10	52 (47.3%)	2 (3.8%) [§]	-	11.8 $\pm$ 3.8 days	-
10-19.9	28 (25.5%)	2 (7.1%) [¶]	0.61	13.3 $\pm$ 5.7 days	0.32
20-29.9	23 (21.0%)	0 (0%)	1.00	18.2 $\pm$ 11.2 days	< 0.01
$\geq$ 30	7 (6.4%)	3 (42.9%) [#]	0.01	17.7 $\pm$ 5.4 days	< 0.01
Total	110 cases	7 cases		104 cases	

*p values vs. CRP < 10 calculated by chi-square test.

[†]Four cases in which death occurred and two cases that transferred to other hospitals before completing therapy were eliminated from analysis.[‡]p values vs. CRP < 10 calculated by t-test.[§]Death occurred in one case.[¶]Death occurred in all cases.[#]Death occurred in one case.**Table 9. WBC Counts and Clinical Course**

WBC count (cells/ μ L)	Cases (%)	Critical events (%)	p value *	Duration of therapy (mean $\pm$ S. D.) [†]	p value [‡]
< 4,000	3 (2.7%)	2 (66.7%) [§]	0.02	21.3 $\pm$ 5.8 days	< 0.01
4,000 - 9,999	43 (39.1%)	2 (4.7%) [¶]	-	12.8 $\pm$ 4.1 days	-
10,000 - 19,999	53 (48.2%)	2 (3.8%) [#]	0.76	13.6 $\pm$ 6.9 days	0.50
$\geq$ 20,000	11 (10.0%)	1 (9.1%) ^{&}	0.87	18.5 $\pm$ 13.1 days	0.02
Total	110 cases	7 cases		104 cases	

*p values vs. WBC counts of 4000 – 9999 cells/ μ L calculated by chi-square test.[†]Four cases in which death occurred and two cases that transferred to other hospitals before completing therapy were eliminated from analysis.[‡]p values vs. WBC counts of 4000 – 9999 cells/ μ L calculated by t-test.[§]All cases treated successfully.[¶]Death occurred in one case.[#]Death occurred in all cases.[&]Death occurred in one case.

were no critical events in the low A-DROP score groups (0 or 1 points), but a few critical events were observed in the low CRP groups (<10 mg/dL and 10.0-19.9 mg/dL). Therefore, A-DROP scores are considered to be a better predictor of the critical events than CRP levels. We additionally performed multivariate analysis between five A-DROP consisting factors and the critical event. Only hypoxemia ($p < 0.01$) and disturbance of consciousness ($p < 0.01$) were extracted as independent factors that were related to the onset of critical event, but we should not deny the meaning of other factors (age, dehydration and hypopressure) in predicting the onset of critical event from this study. Further studies including pathogens other than pneumococcal pneumonia are needed to check the validity of A-DROP scores. In addition, decreased WBC counts (<4,000 cells/ μ L) can be regarded as a risk factor for the critical events because the incidence of the critical events was observed to be extremely high in this group (66.6%, Table 9) though they were limited in number. There was a statistically significant correlation of prolonged periods of antibiotic therapy with CRP elevation (Table 8), but not with A-DROP scores. These observations suggest that the duration of therapy may be determined by CRP level rather than the disease severity, and that the duration of antibiotic therapy may not accurately reflect the disease severity. The duration of antimicrobial treatment seemed

long, even in the group of A-DROP 0 points (13.3 ± 8.4 days, Table 6). In most cases, antimicrobial treatment was ceased after normalization of CRP. Patient's age and comorbidity, such as preexisting respiratory disease (32.4%, Table 1), might affect the duration of therapy.

We analyzed the content of initial antibiotic therapy after visiting our hospital. Penicillin, cephalosporin, carbapenem, new quinolone, macrolide, and combination of carbapenem plus new quinolone were used in 45, 27, 19, 13, 1, 2 cases, respectively. Critical events occurred at 1 (2.2%), 1 (3.7%), 3 (15.8%), 1 (7.7%), 0 (0%), 1 (50.0%) case in penicillin, cephalosporin, carbapenem, new quinolone, macrolide, and combination of carbapenem plus new quinolone treated groups, respectively. The elevated incidence of critical events in the carbapenem-treated group was not likely due to the selection of antibiotics, because none of isolated *S. pneumoniae* in this study was IPM resistant (Table 5). It is not easy to discuss the regimen of antibiotics from this retrospective study.

In conclusion, we confirmed that A-DROP scores are useful for predicting the critical events in cases of pneumococcal pneumonia. Additionally our findings suggest that decreased WBC counts may be used as a prognostic factor since they were significantly correlated with the critical events despite the limited number of cases. CRP was not

helpful for predicting the critical events, when compared to A-DROP scores. Furthermore, cross-sectional analysis of all pneumococcal pneumonia cases revealed that NHAP cases were at high risk for the critical events, and that PRSP was frequently isolated in HAP cases. These findings were obtained from retrospective analysis of 111 cases of pneumococcal pneumonia and provide important information in the management of patients with pneumococcal pneumonia. To assess our findings from the present study, prospective studies will be warranted not only for pneumococcal pneumonia, but also for pneumonia caused by other pathogens.

The authors state that they have no Conflict of Interest (COI).

Author contributions: S. Ikegame performed data collection and statistical analyses. K. Wakamatsu and H. Kumazoe participated in data collection. M. Kawasaki, M. Fujita, Y. Nakanishi, M. Harada, and A. Kajiki contributed to study organization.

Summary at a glance: We conducted a retrospective analysis of pneumococcal pneumonia cases. Critical events occurred more frequently in nursing home-acquired cases while hospital-acquired cases frequently developed penicillin resistance. Decreased WBC counts and elevated A-DROP scores were predictive of critical events. Future treatment of pneumococcal pneumonia should be modified based on these factors.

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