□ ORIGINAL ARTICLE □

Severe Community-acquired Pneumonia in an Intensive Care Unit: Risk Factors for Mortality

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Abstract

Objective **To evaluate severe community-acquired pneumonia (SCAP) patients in an intensive care unit (ICU) with regard to risk factors for mortality and to compare ICU patients with matched non-ICU patients to evaluate whether our judgement for ICU admission was appropriate or not.**

Materials and Methods **During a 7-year period, all patients with CAP who were admitted to the ICU were examined. They underwent clinical and radiographic evaluations, and two commonly used severity of illness scores were also calculated using the Simplified Acute Physiological Score (SAPS) and the Acute Physiology and Chronic Health Evaluation (APACHE) II methods. To detect risk factors for ICU admission using existing guidelines, each study patient was matched with two patients hospitalized in a general medical ward.**

Results **Seventy-two patients were identified during the study period. Their mean age was 72.9 years, and 35 patients (48.6%) subsequently died. For the univariate analysis, there were significant differences with the pulse rate ≥130/min, blood urea nitrogen ≥30 mg/dl, multilobar shadow, SAPS ≥13, APACHE II ≥23, and the occurrence of septic shock between the survivors and those who died. For the multivariate analysis, septic shock (p=0.0005, odds ratio of 26.6) and blood urea nitrogen ≥30 mg/dl (p=0.037, odds ratio of 5.38) were associated with mortality. Regarding the characteristics of different clinical predictions for ICU admission, the revised American Thoracic Society criteria might have been the most accurate.**

Conclusion **Septic shock was associated with high mortality, which is a more accurate and higher predictor of mortality than was physical examination, laboratory or radiographic findings.**

(Internal Medicine 44: 710–716, 2005)

Key words: severe community-acquired pneumonia, intensive care unit, septic shock

Introduction

Community-acquired pneumonia (CAP) continues to be a major cause of morbidity and mortality. Despite the availability of adequate antibiological agents to treat this illness, it has remained the fourth most common cause of death in Japan since 1975 (1), and in 2002, the mortality has risen to 69 persons out of 100,000. This rate is particularly high among the elderly, at 353 for those over 65 years, 733 for those over 75 years, and 2,036 for those over 90 years per 100,000 people (1). Recently, several guidelines for CAP have been promoted in Western countries (2–4) as well as in Japan (5) due to these high rates of morbidity and mortality.

The rate for CAP requiring treatment in an intensive care unit (ICU) is between 9–16% (6–8). Severe community-acquired pneumonia (SCAP) is a condition where severely ill patients with pneumonia who have an especially high mortality rate, ranging from 18–61% (7–18), necessitates the use of a wider spectrum of microbial chemotherapy, with potential benefits resulting from early ICU admission (2, 3). In 1993, the American Thoracic Society (ATS) defined a subset of CAP admission as being severe on the basis of specific risk factors (19), but this criteria for ICU admission is overly sensitive and non-specific (7, 8). Thus, a second ATS consensus for ICU admission was recently published (3). Other prediction rules for SCAP also exist; the British Thoracic Society (BTS) criteria (4), the Japanese Respiratory Society (JTS) severity (5), and the Pneumonia Severity Index (PSI) (6).

The decision regarding ICU admission is made according to the clinical judgement of the physician. We wanted to study a cohort of patients with CAP in which some had

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Received for publication September 7, 2004; Accepted for publication February 24, 2005

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SCAP to identify factors that may be used to predict the risk of developing SCAP. Since we did not prospectively identify a cohort of patients with CAP, we performed a case-control study. First, we evaluated SCAP patients in the ICU to determine the risk factors for mortality. Then, we compared them with matched non-ICU patients (general medical wards) using existing guidelines to evaluate whether our judgement regarding ICU admission was appropriate or not.

Patients and Methods

Selection of patients and definitions

During a 7-year period from April 1995 to March 2002, all patients over 18 years with CAP who were admitted to the ICU of Toyama City Hospital (Toyama, Japan), a 670-bed community general hospital, were retrospectively included in this study. CAP was defined by the presence of a new radiographic pulmonary infiltration on or one occurring within 24 hours of admission including at least two of the following signs; sputum production, cough, fever (temperature ≥37.8°C), and leukocytosis with a WBC count ≥12,000/μl. Patients were excluded when abnormalities observed during chest radiographic examinations were attributed to other causes, such as congestive heart failure, pulmonary infarction or obstructive pneumonia due to lung cancer.

SCAP was defined as CAP requiring treatment in the ICU in this study. Patients were admitted to the ICU because they required immediate mechanical ventilation or because they were judged to be in an unstable condition requiring comprehensive medical and nursing care, such as septic shock or some neurological disturbance. Those initially hospitalized for pneumonia from home or a nursing home to a general medical ward in our hospital or another hospital who were subsequently admitted to our ICU within 72 hours were also included. If those admitted to the ICU were not treated positively, they were excluded from this study.

Overall, 72 patients were admitted to the ICU. To determine risk factors of SCAP, each study patient was matched with two patients hospitalized in a general medical ward because of CAP within 2 weeks. Decisions regarding ICU admission were made according to clinical judgement by the physician in charge. Matching according to age and comorbidity was not performed because these factors were considered potential independent risk factors. Therefore, we compared 70 ICU patients with 140 non-ICU patients with respect to risk factors for ICU admission.

Microbiological studies

Normal practice included collecting blood, sputum, bronchoalveolar lavage (BAL), and pleural effusion for investigation. Serum was examined for complement fixing antibodies against common viruses, *Chlamydia pneumoniae, Chlamydia psittaci*, *Mycoplasma pneumoniae*, and *Legionella* spp, where appropriate. Sputum data were only evaluated when a Gram stain test showed numerous leukocytes and few epithelial cells. Any organism showing heavy growth of a predominant bacterium on sputum or BAL culture was considered to be a presumptive pathogen, and was considered a definite pathogen if blood cultures or pleural fluid cultures yielded a bacterial pathogen, or when the acid-fast bacilli smear or mycobacterium cultures in sputum were positive. For serological testing, a four-fold increase in the antibody titer level between paired sera or an elevated single titer of at least 1 : 512 for viral or atypical antibodies was considered definitive.

Patient evaluation

Within 24 hours of ICU admission, all patients underwent clinical and radiographic evaluations. The following variables were recorded: age, sex, origin (home or nursing home), underlying disease, chest radiographic features (unilateral or bilateral) as well as the number of lobes involved and pleural effusion, initial vital signs including temperature, pulse, arterial blood pressure, respiratory rate, urine output, mental status, and blood pressure, and laboratory findings. Two commonly used severity of illness scores were also calculated using the Simplified Acute Physiological Score (SAPS) (20) and the Acute Physiology and Chronic Health Evaluation (APACHE) II score (21). Septic shock was defined by a systolic blood pressure lower than 90 mmHg, urine output of less than 30 ml/*l* or the need to use vasopressors for more than 4 hours after standardized fluid replacement (22).

Outcome of death

For mortalities, we distinguished pneumonia from non-pneumonia as the major cause of hospital death. Pneumonia as the major cause of death was defined by hypoxia progressing from pneumonia, septic shock, and multiple organ dysfunction syndrome caused by sepsis. Even if a patient recovered from pneumonia in the hospital, but died of sudden death due to suffocation by aspiration, sudden arrhythmia, heart disease, cerebrovascular events, etc., they were defined as non-pneumonia deaths as the major cause of hospital death. We evaluated the medical outcome of deaths between pneumonia and non-pneumonia, by length in the ICU and for the hospital stay, mortality in the ICU, and mortality within 30 and 90 days.

Statistical analyses

We compared categorical data using x^2 statistics or the Fisher exact test and continuous data using the Mann-Whitney U test. Analysis of risk factors for deaths was performed by uni- and multivariate analysis, and multivariate analysis was performed by logistic regression. We assumed statistical significance for $p<0.05$.

Results

General ICU patient characteristics

Seventy-two patients were identified during the study period, and their mean age was 72.9, and 18 (25.0%) were

female. Nineteen (26.4%) were previously healthy, and the others had at least one underlying disease (Table 1) which included pulmonary disease (29.2%), diabetes mellitus (12.5%), cerebrovascular disease (11.1%), and cardiac disease (11.1%).

Microbial etiology of ICU patients

Of the 72 patients, 32 (44.4%) had an identifiable microbial etiology (Table 2), the most common being *Streptococcus pneumoniae* (*S. pneumoniae*, 13.9%) followed by *Pseudomonas aeruginosa* (*P. aerations*, 8.3%) and *Klebsiella pneumoniae* (*K. pneumoniae*, 6.9%). *Legionella* spp was only diagnosed in 2 patients, and pneumonia caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) accounted for 2 patients. Two organisms were identified in each of three patients, *P. aeruginosa* and *K. pneumoniae*, *P. aeruginosa* and *Stenotrophomonas maltophilia*, and *Legionella* spp and *Streptococcus milleri* group.

Clinical features and mortality of ICU patients

Thirty-five (48.6%) of the 72 patients died. The prognostic factors associated with these mortalities are shown in Table 3. Of the 37 survivors, the median age was 73 years, while for the 35 deaths, the median age was 77 years. For univariate analysis, there were significant differences in terms of the pulse rate ≥130/min (p=0.044), blood urea nitrogen ≥30 mg/dl (p=0.005), multilobar shadow (p=0.002), SAPS ≥13 (p=0.001), APACHE II ≥23 (p=0.009), and septic shock (p<0.0001) between the survivors and deaths. Multivariate analysis was performed with these six factors as independent variables for mortality, and septic shock and blood urea nitrogen ≥30 mg/dl were found to be associated with mortality (Table 4).

Characteristics and medical outcomes of deaths managed in the ICU

In the 35 deaths, 15 (42.9%) died in the ICU, while the other 20 (57.1%) died in the general medical wards. Three (8.6%) died within 24 hours and seven (20.0%) died within 72 hours of ICU admission. Overall, ten (28.6%) died of non-pneumonia, while the other 25 (71.4%) died of pneumonia. The ten non-pneumonia deaths consisted of one each with congestive heart failure, cerebral infarction, idiopathic pulmonary fibrosis, sepsis caused by catheter infection, suffocation by aspiration, as well as three with progressing renal failure, and two of sudden death of unknown origin. There were significant differences in the length of stay in the ICU (p=0.025), length of their hospital stay (p=0.0001), ICU mortality (p=0.001), mortality within 30 days (p=0.0004), and mortality within 90 days (p=0.0008) between the pneumonia deaths and non-pneumonia deaths (Table 5).

Correlation between ICU and non-ICU patients

We compared 70 ICU patients with 140 non-ICU patients in terms of risk factors for ICU admission. Two patients with *M. tuberculosis* were excluded. The characteristics and medical outcomes of the ICU and non-ICU patients examined by univariate analysis are shown in Table 6. We correlated factors necessary for individuals to decide the original ATS, revised ATS, BTS, high-risk PSI scores (PSI Risk Classes IV and V), and the JTS severity (severe). High-risk PSI scores, the original ATS criteria, revised ATS criteria, and JTS severe showed up for more than 90% of ICU admissions, and showed up for 29.9–45.5% for non-ICU admissions (Table 6). The BTS criteria showed up for 74.0% of ICU admissions, and 18.8% for non-ICU admissions (Table 6). The characteristics of different clinical predictions for ICU admission are shown in Table 7. Among the high PSI, original ATS, revised ATS, JTS (severe) and BTS criteria, the revised ATS criteria showed a sensitivity of 94.3% and specificity of 80.0%, which might have been most accurate for ICU admission.

Table 1. Underlying Disease of 72 ICU Patients

Underlying disease	Patients	Deaths
Pulmonary disease	21 (29.2%)	8 (38.1%)
Old pulmonary tuberculosis	4 (5.6%)	3 (75.0%)
Bronchiectasis	3 (4.2%)	1 (33.3%)
Interstitial pneumonia	4 (5.6%)	3 (75.0%)
Old empyema	4 (5.6%)	1 (25.0%)
Home oxygen therapy	9 (12.5%)	4 (44.4%)
Diabetes mellitus	9 (12.5%)	5 (55.6%)
Cerebrovascular disease	8 (11.1%)	5 (62.5%)
Cardiac disease	8 (11.1%)	3 (37.5%)
Renal disease	6 (8.3%)	6 (100%)
Hepatic disease	5 (6.9%)	2 (40.0%)
Malignancy	3 (4.2%)	1 (33.3%)
Previously healthy	19 (26.4%)	11 (57.9%)

Table 2. Microbial Etiology of 72 ICU Patients

Pathogen	Patients (%)	Deaths (%)
Streptococcus pneumoniae	10 (13.9)	1 (10.0)
Pseudomonas aeruginosa	6 (8.3)	3 (50.0)
Klebsiella pneumoniae	5 (6.9)	3 (60.0)
Staphylococcus aureus	2 (2.8)	0
Streptococcus milleri group	2 (2.8)	2 (100)
Haemophilus influenzae	2 (2.8)	1 (50.0)
Legionella spp	2 (2.8)	2 (100)
Mycobacterium tuberculosis	2 (2.8)	2 (100)
Enterobacter spp	2 (2.8)	0
Escherichia coli	1 (1.4)	1 (100)
Stenotrophomonas maltophilia	1 (1.4)	1 (100)
Pathogen known	32 (44.4)	19 (59.4)
Pathogen unknown	40 (55.6)	23 (57.5)

Discussion

The mortality rate for SCAP requiring ICU admission was

Table 3. Clinical Characteristics and Mortality in ICU Patients (Univariate Analysis)

Clinical features	Survivors (n=37)	Deaths (n=35)	p value
Demographic factor			
Age, years, median (range)	73 (36–91)	77 (31–89)	0.097
Age ≥76 years	14 (37.8%)	19 (54.3%)	0.162
Sex, male/female	30/7	24/11	0.221
Nursing home resident	4 (10.8%)	5 (8.6%)	0.749
Therapies			
Use of mechanical ventilation	22 (59.5%)	33 (94.3%)	0.0005
Physical-examination findings			
Temperature ≥38.6°C	11 (29.7%)	15 (42.9%)	0.246
Pulse ≥130/min	6 (16.2%)	13 (37.1%)	0.044
Respiratory rate ≥30/min	22 (59.5%)	23 (65.7%)	0.584
Laboratory findings			
Blood urea nitrogen ≥30 mg/dl	13 (35.1%)	24 (68.6%)	0.005
Hematocrit <30%	7 (18.9%)	12 (34.3%)	0.139
Sodium <130 mmol/*l*	1 (2.7%)	4 (11.4%)	0.146
Potassium <3.5 or ≥5.5 mmol/*l*	8 (21.6%)	9 (25.7%)	0.683
WBC count <3,000 or ≥15,000/μl	9 (24.3%)	9 (25.7%)	0.892
Arterial pH <7.35	13 (35.1%)	15 (42.9%)	0.502
Radiographic findings			
Pleural effusion	5 (13.5%)	7 (20.0%)	0.460
Bilateral involvement	22 (59.5%)	22 (62.9%)	0.768
Multilobar involvement	26 (70.3%)	34 (97.1%)	0.002
Positive blood culture	2 (5.4%)	5 (14.3%)	0.204
Septic shock	4 (10.8%)	24 (68.6%)	<0.0001
SAPS ≥13	10 (27.0%)	23 (65.7%)	0.001
APACHE II ≥23	8 (21.5%)	18 (51.4%)	0.009

Table 4. Factors Selected by Multivariate Analysis Independently Related to Mortality

Factor	Odds ratio	95% confidence interval	p value
Blood urea nitrogen ≥30 mg/dl	5.38	1.10–26.2	0.037
Septic shock	26.6	4.19–168	0.0005

Table 5. Characteristics and Medical Outcomes of Deaths (35 Patients)

Variable	Pneumonia	Non-pneumonia	p value
Number	25 (71.4%)	10 (28.6%)	
Age, years, median (range)	76 (31–89)	77 (71–87)	0.687
Age ≥76 years	13 (52.0%)	6 (60.0%)	0.668
Sex: male/female	18/7	6/4	0.490
Length in ICU stay, days median (range)	6 (1–47)	14 (3–43)	0.025
Length in hospital stay, days median (range)	12 (1–83)	72 (21–284)	0.0001
Mortality in ICU	15 (60.0%)	0	0.001
Mortality within 30 days	19 (76.0%)	1 (10.0%)	0.0004
Mortality within 90 days	25 (100%)	6 (60.0%)	0.0008

48.6%. This was higher than the overall mortality recently reported (7–11, 14–18), and only two previous reports had a higher rate than that of this study with regard to overall mortality (12, 13). Such discrepancies may be explained by varying degrees of the criteria requiring ICU admittance, the severity of illness, underlying medical conditions, and deaths unrelated to pneumonia.

We were able to obtain microbiological diagnoses for only 44.4% of the patients. This rate was lower than that for previously reported SCAP studies in the Western World (41–

Table 6. Characteristics and Medical Outcomes of ICU and Non-ICU Patients (Univariate Analysis)

	ICU (n=70)	Non-ICU (n=140)	p value
Age, years, median (range)	74.5 (31–92)	71 (18–92)	0.007
Death	33 (47.1%)	0	<0.0001
Physical-examination findings			
Temperature ≥38.6°C	25 (35.7%)	39 (27.9%)	0.243
Pulse ≥130/min	19 (27.1%)	21 (15.0%)	0.035
Respiratory rate ≥30/min	44 (62.9%)	30 (21.4%)	<0.0001
Systolic blood pressure <90 mmHg	26 (37.1%)	6 (4.3%)	<0.0001
Diastolic blood pressure <60 mmHg	44 (62.9%)	11 (7.9%)	<0.0001
Altered mental status	12 (17.1%)	4 (2.9%)	0.0002
Laboratory findings			
Hematocrit <30%	18 (25.7%)	17 (12.1%)	0.013
Sodium <130 mmol/*l*	5 (7.1%)	4 (2.9%)	0.148
Blood urea nitrogen ≥30 mg/dl	35 (50.0%)	13 (9.3%)	<0.0001
Arterial pH <7.35	27 (38.6%)	1 (0.7%)	<0.0001
PaO_2/FiO_2 <250	63 (90.0%)	15 (10.7%)	<0.0001
Radiographic findings			
Pleural effusion	12 (17.1%)	18 (12.9%)	0.403
Bilateral involvement	43 (61.4%)	31 (22.1%)	<0.0001
Multilobar involvement	59 (84.3%)	41 (29.3%)	<0.0001
Rapid growing	21 (31.3%, n=67)	3 (2.1%)	<0.0001
Use of mechanical ventilation	53 (75.7%)	0	<0.0001
Severity of illness (PSI)			<0.0001
Risk Class I	0	23 (16.4%)	
Risk Class II	0	24 (17.1%)	
Risk Class III	5 (7.1%)	50 (35.7%)	
Risk Class IV	24 (34.3%)	28 (20.0%)	
Risk Class V	41 (58.6%)	15 (10.7%)	
Original ATS criteria	68 (97.1%)	62 (44.3%)	<0.0001
Revised ATS criteria	66 (94.3%)	28 (20.0%)	<0.0001
BTS criteria	52 (74.3%)	24 (17.1%)	<0.0001
JTS severity			<0.0001
Mild	0	19 (13.6%)	
Moderate	1 (1.4%)	64 (45.7%)	
Severe	69 (98.6%)	57 (40.7%)	

72%) (9–11, 16, 18, 23, 24) and two previous CAP studies in Japan (25, 26). The most common organism encountered in our study was *S. pneumoniae*, but it was detected in only 13.9% of the patients. In the Western World, *S. pneumoniae* is the most common organism found in SCAP in the ICU (15–32.6%) (9–12, 15, 16, 23, 24, 27). *Legionella* spp is also an important organism (0–16%) (9, 10, 12, 16, 23, 24) which causes high mortality in the Western World (9, 12). However, in Japan, *Legionella* spp was isolated in only 1% of patients in CAP studies (25, 26) and in 2.8% in this study. In this study, *P. aeruginosa* was detected in 8.3% of the cases and *K. pneumoniae* in 6.9%, which was higher than the rates previously reported in SCAP studies in the Western World (9, 10, 15, 16, 18, 23, 24, 27) and the two previously CAP studies in Japan (25, 26). We found that 29.2% of the patients had underlying pulmonary disease and 12.5% had been receiving home oxygen therapy. Therefore gram-negative rods might have been detected at higher rates than usual. Although *M. tuberculosis* was isolated in 2 patients (2.8%), the prevalence of tuberculosis is still high in Asian countries (13).

The average patient age of 72.9 years was higher than that of other studies, because the Japanese population has the highest average life span in the world, and also because in Japan, with the particularly older population, the mortality rate for pneumonia is high (1). The effect of septic shock on mortality at the time of ICU admission was in agreement with other reports concerning SCAP (9–11, 15, 17). Some reports found a correlation between SCAP and the severity of the SAPS or APACHE II illness scores (9–11, 15, 24). These scores have good predictive characteristics for ICU courses and outcomes. However, for multivariate analysis, only septic shock and blood urea nitrogen ≥30 mg/dl were associated with mortality in this study.

Non-pneumonia related deaths were common, occurring at 26.2% (Table 5). In a study of 299 patients with SCAP, Leroy et al (10) mentioned that non-pneumonia related complications occurred in 55 patients and that 60% died, but they

Table 7. Characteristics of Different Clinical Predictions for ICU Admission

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Physical-examination findings				
Temperature ≥38.6°C	35.7	72.1	39.1	69.2
Pulse ≥130/min	27.1	85.0	47.5	70.0
Respiratory rate ≥30/min	62.9	78.6	59.5	80.9
Systolic blood pressure <90 mmHg	37.1	95.7	81.3	75.3
Diastolic blood pressure <60 mmHg	62.9	92.1	80.0	83.2
Altered mental status	17.1	97.1	75.0	70.1
Laboratory findings				
Hematocrit <30%	25.7	87.9	51.4	70.3
Sodium <130 mmol/*l*	7.1	97.1	55.6	67.7
Blood urea nitrogen ≥30 mg/dl	50.0	90.7	72.9	78.4
Serum creatinine ≥2.0 mg/dl	22.8	98.6	88.9	71.9
Arterial pH <7.35	38.6	99.3	96.4	77.2
PaO_2 <60 mmHg	97.1	75.7	66.7	98.1
FiO_2/FiO_2 <250	90.0	89.3	80.8	94.7
Glucose ≥250 mg/dl	20.0	94.3	63.6	70.2
Radiographic findings				
Pleural effusion	17.1	87.1	40.0	67.8
Bilateral involvement	61.4	77.9	58.1	80.1
Multilobar involvement	84.3	70.7	59.0	90.0
Rapid growing	31.3	97.9	87.5	74.9
Use of mechanical ventilation	75.7	100	100	89.2
High PSI (Risk Class IV or V)	92.9	69.3	60.2	95.1
Original ATS criteria	97.1	55.7	52.3	97.5
Revised ATS criteria	94.3	80.0	70.2	96.6
BTS criteria	74.3	82.9	68.4	86.6
JTS severity (severe)	98.6	59.3	54.8	98.8

failed to mention the rate of mortality caused by non-pneumonia. Angus et al (8) mentioned that the major cause of deaths was due to pneumonia in 73.1% of ICU cases. In this study, for non-pneumonia deaths, they recovered from pneumonia during their hospital stay, but they could not be discharged due to various reasons. Their activity might have declined because of long-term treatment for pneumonia. Some patients died of the progression of basal disease such as chronic renal failure, pulmonary fibrosis, etc., others died of suffocation by aspiration and sudden death. These deaths occurred in the general wards, and might have been avoided if managed in an ICU. The results of this study suggest that the care given in general wards is inferior to that given in an ICU, which thus leads to non-pneumonia deaths and too lengthy a hospital stay.

In this study, the high-risk PSI scores, the original ATS criteria, and JTS severity (severe) showed high sensitivity, but might have had low specificity for the ICU admissions as was true for the BTS criteria. The revised ATS criteria showed a sensitivity of 94.3% and specificity of 80.0%, which might have been most accurate for ICU admission. The JTS guidelines are widely accepted in Japan. However, in these guidelines, patients over 65 years are classified in one grade of severity, and so many patients tend to be classified as being severe.

SCAP cases requiring ICU admission in the present study had a high mortality and the average age was high. Septic shock was associated with a high mortality rate, which more accurately and more highly predicted mortality than did physical examination or laboratory or radiographic findings.

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