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■ Original Article ■

The Prognostic Factors of Pneumonia with Septic Shock in Patients Presenting to the Emergency Department

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Background: Pneumonia is the most common cause of death among patients with infectious disease in Korea. However, studies of pneumonia with septic shock in patients presenting to the emergency department are limited. The aim of this study was to investigate the prognostic factors associated with pneumonia with septic shock in patients presenting to the emergency department.
Methods: From January 2008 to September 2014, patients with pneumonia with septic shock admitted through the emergency department were retrospectively examined.
Results: Of the 561,845 patients who visited the emergency department, 398 were admitted for pneumonia with septic shock. The 28-day mortality rate in these patients was 36.4%. The independent prognostic factors were old age (>70 yrs) (odds ratio [OR], 2.42; 95%, confidence interval [CI], 1.35–4.32), Acute Physiology and Chronic Health Evaluation (APACHE) II score (OR, 1.04; 95% CI, 1.01–1.08), leukopenia (OR, 3.63; 95% CI, 1.48–8.94), prolonged PT-INR (OR, 2.53; 95% CI, 1.41–4.54), and hypoxemia (OR, 2.88; 95% CI, 1.30–6.38).
Conclusions: A poor prognosis of patients with pneumonia is associated with old age (>70 yrs), increased APACHE II score, leukopenia, prolonged PT-INR, and hypoxemia.

Key Words: mortality; outcome; pneumonia; shock, septic.

Introduction

Sepsis is one of the leading causes of death and spurs increases in socioeconomic burden around the world. According to the U.S. reports, more than 750,000 severe septic patients occur a year, and more than 500,000 septic patients presented to emergency room a year.[1-3] the short-term mortality of severe septic patients is estimated at 20-30%, and it soared to 50% when in patients with sepsis and septic shock.[4,5] Furthermore, the incidence of sepsis is rising amid growing age population.[6] In attempting to reduce mortality from sepsis, many therapeutic approach are taken in the early stage of diagnosis because early therapy is crucial, and early goal directed therapy has emerged as a promising approach.[1,7,8] Along with sepsis, pneumonia poses a significant threat to patients in intensive care units (ICUs). According to the 2013 official health statistics, pneumonia is the primary cause of death in Korea.[9,10] The number of pneumonia patients is estimated at around 4 million per year in the U.S., and one fourth of them are admitted to hospitals, 12% of them do not survive to discharge. The mortality rises to 40% when pneumonia has accompanying

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bacteremia and sepsis.[11] Pneumonia is also the second most cause of ICU admission.[12,13]

While sepsis and pneumonia became increasingly life-threatening, early therapy for these conditions has been widely explored and applied in medical research. However, prognostic factors of septic shock caused by pneumonia in the emergency department have not been well established, making evaluation of research review difficult.[14] This study therefore aimed to identify prognostic of septic shock caused by pneumonia by investigating outcomes in patients who were diagnosed with pneumonia-induced septic shock in emergency department of a hospital in Korea and the related literature.

Materials and Methods

This retrospective study was conducted in adult patients treated after being identified with septic shock caused by pneumonia in emergency department of a hospital from January 2008 to September 2014. It was a regional referral hospital receiving around 90,000 patients a year with 100 ICU beds.

The inclusion criterion was that septic shock occurred after pneumonia, which was confirmed through retrospective analysis of medical records and lab and imaging results. Pneumonia was considered definitive in patients who had one of respiratory symptoms such as coughing, sputum and breathing difficulties prior to emergency room admission and lesions shown on chest X-rays. Septic shock was considered definitive when the systolic blood pressure remained 90 mmHg due to sepsis despite adequate amounts of fluid infusion. Fluid and vasopressor agents were administered according to the Surviving Sepsis Campaign guidelines.[1] Patients were excluded if they had no symptoms of infection, if they had anaphylactic shock or asthma seizure, if they died in the emergency department and if they had obscure cause of death according medical records.

Based on medical records, lab and image results, we identified or calculated date of emergency room (ER) visit, age, sex, primary diagnosis, department name, blood pressure, heart rate, respiratory rate, temperature, onset date, admission date, main symptoms, level of consciousness during ER visit, date that the determination was made to admit, antibiotic use, duration of the first antibiotic therapy, duration from the onset of symptoms to the first antibiotic use, duration from admission to use of the first antibiotic therapy, types of antibiotics, comorbidity, underlying disease, mortality rate, length of ICU stay, total hospital stay, mechanical ventilation and its duration, vasopressor use within 24 hours, dose and types of vasopressor, central venous pressure, Acute Physiology and Chronic Health Evaluation (APACHE) II score and other lab results, including blood, arterial blood, C-reactive protein test, liver function and kidney function. The APACHE II score was based on the worst value taken during the first 24 hours after admission. Vital signs and lab values were derived from the measurements and blood test taken during ER visit, and onset was defined as the time point when patients showed a series of symptoms including coughing, sputum, fever and breathing difficulties.

The 30-day mortality was measured from admission to death, discharge or 30 days after admission.

Statistical analysis was performed using the STATA/SE 9.0 package (STATA corp., TX, USA), and p value of less than 0.05 was statistically significant. Results are expressed as mean ± standard deviation or frequencies. Patients were divided into survival group and mortality group on the basis of 30-day mortality, and the Student's t-test and chi-square test were performed to compare clinical differences between the two groups. Logistic regression analysis was performed

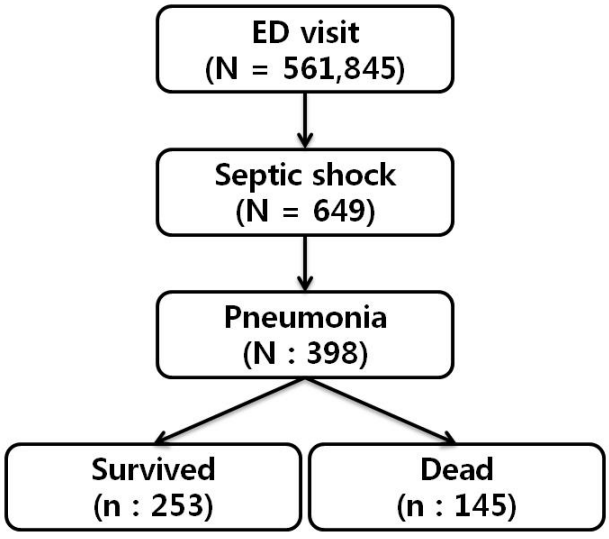

Fig. 1. Flow diagram of patients in this study. ED: emergency department.

Table 1. Characteristics, by 30-day mortality (N = 398)

	Total (N = 398)	Survived (n = 253)	Dead (n = 145)	p-value
Age (years)	69.3 ± 14.2	66.8 ± 14.6	73.6 ± 12.3	< 0.001
Sex (female)	137 (34.4)	82 (32.4)	55 (37.9)	0.265
Vital signs				
Systolic blood pressure (mmHg)	79.4 ± 15.9	81.3 ± 13.2	76.1 ± 19.5	0.002
Diastolic blood pressure (mmHg)	48.1 ± 13.8	49.8 ± 11.9	45.0 ± 16.2	< 0.001
Heart rate (/min)	101.9 ± 27.0	99.6 ± 25.5	106.0 ± 29.2	0.024
Respiratory rate (/min)	22.8 ± 6.1	22.9 ± 5.7	22.6 ± 6.7	0.646
Body temperature (°C)	36.6 ± 4.2	36.8 ± 3.5	36.3 ± 5.3	0.212
CVP (n = 305)	11.4 ± 7.2	11.2 ± 6.8	11.6 ± 7.7	0.595
APACHE II (n = 284)	24.3 ± 9.7	22.3 ± 9.5	27.2 ± 9.4	< 0.001
Laboratory results				
Hb	11.2 ± 2.5	11.4 ± 2.5	10.7 ± 2.5	0.006
WBC	13.7 ± 10.0	14.0 ± 7.8	13.2 ± 12.9	0.420
PLT	217.8 ± 121.9	224.6 ± 115.5	205.9 ± 131.9	0.140
INR	1.32 ± 0.56	1.27 ± 0.46	1.42 ± 0.69	0.009
CRP	13.9 ± 9.2	13.2 ± 9.3	15.1 ± 9.1	0.053
Cr	1.47 ± 1.10	1.42 ± 1.13	1.55 ± 1.04	0.249
AST	74.3 ± 248.6	74.1 ± 300.4	74.5 ± 111.6	0.987
ALT	45.8 ± 154.3	46.5 ± 184.8	44.5 ± 78.3	0.901
LDH	669.5 ± 846.5	610.1 ± 953.1	767.8 ± 622.7	0.086
CPK	347.9 ± 900.2	339.2 ± 945.1	362.4 ± 822.5	0.814
CK-MB (n = 317)	6.17 ± 15.11	5.47 ± 15.74	7.30 ± 14.02	0.295
Troponin-I (n = 318)	0.38 ± 2.87	0.47 ± 3.62	0.24 ± 0.51	0.506
PH	7.38 ± 0.13	7.39 ± 0.13	7.35 ± 0.15	0.003
PCO2	36.8 ± 15.7	36.2 ± 15.1	37.7 ± 16.6	0.382
PO2	67.4 ± 35.4	72.1 ± 37.6	59.1 ± 29.6	< 0.001
HCO3	21.5 ± 6.9	21.9 ± 6.4	20.7 ± 7.7	0.110
Lactate	3.3 ± 3.0	2.7 ± 2.7	4.3 ± 3.3	< 0.001
Positive culture	79 (20.0)	37 (14.7)	42 (29.2)	0.001
Comorbid disease				
Stroke	6 (1.5)	2 (0.8)	4 (2.8)	0.121
Hypertension	135 (33.9)	84 (33.2)	51 (35.2)	0.689
DM	92 (23.1)	60 (23.7)	32 (22.1)	0.708
Asthma	16 (4.0)	11 (4.4)	5 (3.5)	0.660
COPD	34 (8.5)	21 (8.3)	13 (9.0)	0.819
Tbc	57 (14.3)	31 (12.3)	26 (17.9)	0.120
AIDS	3 (0.8)	1 (0.4)	2 (1.4)	0.275
From symptom to antibiotics start, h	59.1 ± 123.0	56.3 ± 114.9	64.0 ± 136.3	0.552
From ER visit to antibiotics start, h	5.3 ± 3.3	5.3 ± 3.0	5.3 ± 3.8	0.940

Data were number (%) or mean ± standard deviaiton.

CVP: central venous pressure; APACHE II: acute physiology and chronic health evaluation II; Hb: hemoglobin; WBC: white blood cell; PLT: platelet; INR: international normalized ratio; CRP: C-reactive protein; Cr: creatinine; AST: aspartate aminotransferase; ALT: alanine transaminase; LDH: lactate dehydrogenase; CPK: creatine phosphokinase; CK-MB: creatine kinase MB isoenzyme; pH: power of hydrogen, PCO_2: partial pressure of carbon dioxide; PO_2: partial pressure of oxygen; HCO_3: bicarbonate; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; Tbc: tuberculosis; AIDS: acquired immune deficiency syndrome.

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with stepwise selection procedure to determine clinical factors associated with 30-day mortality. In other words, statistically significant variables $p < 0.05$ were identified in simple logistic regression, and the stepwise selection procedure was used in the model containing all variables to determine variables associated with 30-day mortality ($p < 0.05$).

Results

A total of 561,845 patients visited the ER from January 2008 to September 2014, and 715 of them were admitted to the Internal Medicine Infection or the Respiratory Internal Medicine Department because sepsis was suspected. Of those, 649 were diagnosed with sepsis, and 398 of them were diagnosed with septic shock caused by pneumonia. Of those, 145 (36.4%) died within 30 days after admission (Fig. 1). Of 398 patients, 179 developed community-acquired pneumonia and the remaining 219 developed hospital-acquired pneumonia

There was no significant difference between survival and mortality group by sex, but significant differences were found between the groups by age (66.8 ± 14.6 years old vs 73.6 ± 12.3 years old, $p < 0.001$). Vital signs showed significant differences between the two groups. Significantly lower systolic and diastolic blood pressures were found in mortality group (81.3 ± 13.2 mmHg vs 76.1 ± 19.5 mmHg, $p = 0.002$, 49.8 ± 11.9 mmHg vs 45.0 ± 16.2 mmHg, $p < 0.001$), and heart rates were also significantly higher in mortality group (99.6 ± 25.5 times/minute vs 106.0 ± 29.6 times/minute, $p = 0.024$). There was no difference in time interval from ER visit to antibiotic use between the groups (5.3 ± 3.0 hours vs 5.3 ± 3.8 hours, $p = 0.940$), but ACHE II score showed significantly lower severity in survival group (21.0 ± 9.5 vs 27.0 ± 9.8, $p < 0.001$). There was significant difference by lactic acid measured on admission (2.7 ± 2.7 vs 4.3 ± 3.3, $p < 0.001$) (Table 1).

According to the findings of multivariate analysis, the following factors were independently and significantly related to death: age of 70 years or over (odds ratio [OR], 2.42;

Table 2. Factors related to 30-day mortality from pneumonia septic shock

	Univariate		Stepwise multivariate*	
	OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Elderly (> 70 years)	2.14 (1.40–3.26)	< 0.001	2.42 (1.35–4.32)	0.003
Vital sign				
SBP < 80 mmHg	1.64 (1.05–2.55)	0.030		
DBP < 50 mmHg	1.62 (1.06–2.46)	0.026		
HR > 100/min	1.65 (1.09–2.50)	0.017		
Increased APACHE II (per 1 point)	1.06 (1.03–1.08)	< 0.001	1.04 (1.01–1.08)	0.005
Longer time to anti start at ER (> 4 h)	0.61 (0.40–0.92)	0.019		
Laboratory finding				
Leukopenia (WBC < 4000)	3.66 (1.80–7.44)	< 0.001	3.63 (1.48–8.94)	0.005
Prolonged PT-INR (> 1.2)	1.93 (1.27–2.93)	0.002	2.53 (1.41–4.54)	0.002
LDH > 485	1.77 (1.16–2.70)	0.008		
Acidosis (PH < 7.35)	2.48 (1.61–3.82)	< 0.001		
Hypoxemia (PO2 < 83)	1.78 (1.04–3.04)	0.036	2.88 (1.30–6.38)	0.009
Acidosis (HCO3 < 18)	1.69 (1.08–2.65)	0.021		
Lactate (> 4.0 mmol/L)	3.55 (2.22–5.66)	< 0.001		
Positive culture	2.39 (1.45–3.95)	0.001		

All presented variables are significant ($p < 0.05$).

*Included significant variables in the univariate analysis ($p < 0.05$).

OR: odds ratio; CI: confidence interval; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; APACHE II: acute physiology and chronic health evaluation II; ER: emergency room; WBC: white blood cell; PT: prothrombin time; INR: international normalized ratio; LDH: lactate dehydrogenase.

95% confidence interval [CI], 1.35–4.32), APACHE II score (OR, 1.04; 95% CI, 1.01–1.08), leukopenia (white blood cells < 4000/mm) (OR, 3.63; 95% CI, 1.48–8.94), elevated International Normalized Ratio (INR) (OR, 2.53; 95% CI, 1.41–4.54) and hypoxia(PO2 < 83 mmHg) (OR, 2.88; 95% CI, 1.30–6.38) (Table 2).

Discussion

This study aimed to identify prognostic factors affecting the survival in patients who developed pneumonia-induced septic shock after ER visit by investigating their vital signs, lab results and medical records and comparing survival and mortality groups.

Pneumonia causes more death than any other infectious diseases.[9] There have been numerous studies investigating effects of treatment and prognostic factors to improve survival rate in patients with pneumonia at home and abroad. Laterre et al.[15] asserted that early initiation is an important factor affecting the survival in pneumonia patients with accompanying bacteremia in consideration of severity and high mortality rate. Lee et al.[16] reported the following factors affecting mortality and ICU stay in patients hospitalized due to pneumonia: age, pulse rate, hypoalbuminemia, total cholesterol, blood pigment, blood urea nitrogen, prothrom bin time and activated partial thromboplastin time. Park et al.[17] suggested pulse rate, respiratory rate, systolic pressure, arterial oxygen tension, etc. as independent prognostic factors. In this study, there were significant differences in age, systolic pressure, heart rate, APACHE II score, hemoglobin, INR etc. between survival and mortality groups, and age of 70 years or over, leukopenia, elevated INR, hypoxia were identified as independent prognostic factors.

In clinical settings, APACHE II score, CURB-65 (Confusion, Blood Urea Nitrogen, Respiratory Rate, Blood Pressure, age ≥ 65) and Pneumonia Severity Index (PSI) are used to measure disease severity and the need for inpatient care. High scores of these measurements are considered risk factors of death even when early detection and antibiotic therapy are provided.[18] In this study, APACHE II was used for measuring severity of illness. APACHE II scores range from 0-71, with higher scores indicating poorer prognosis.[19,20] Effectiveness of APACHE II as an independent prognostic factor was proven in patients with septic shock caused by pneumonia in this study. Although APACHE II scoring system is still used on ICU admission, depending on the hospital, CURB-65 and PSI are more widely used as scoring systems for pneumonia patients on recent trends. It is also true that APACHE II has limitations to be used for patients in ER. However, APACHI II scores were effective for predicting prognosis and assessing mortality risk in this study. Further study is necessary to verify effectiveness of CURB-65 and PSI scores as prognostic factors in patients with septic shock caused by pneumonia.

As mentioned earlier, the incidence of sepsis continues to increase in aged population.[2,6] These findings underscores the influence of age. Age is therefore assessed by severity scoring systems. Martin et al.[21] identified age as an independent prognostic factor in septic patients. In this study, age of 70 years or over was found to be independent factor predicting worse prognosis in patients with pneumonia-induced septic shock. The elderly patients are vulnerable to infection as a result of reduced inflammatory response, coagulation process and immune response, increasing risk of death.[22,23]

In assessing the severity of pneumonia, main criteria include mechanical ventilation, vasopressor use and septic shock while minor criteria include tachypnea of more than 30 times, low consciousness, hypothermia, low blood pressure in need of fluid infusion, low platelet count and leukopenia.[24] Dellinger et al.[1] suggested leukopenia as a variable present in inflammatory response and elevated INR as a predictor of organ failure. While leukopenia and elevated INR are deemed as reliable diagnostic criteria, it has been unclear whether lab findings are effective as independent predictive factors of pneumonia induced septic shock due to a lack of evidence. This study however found leukopenia and elevated INR as independent prognostic factors of pneumonia-induced septic shock. These factors can be also interpreted as byproducts of the progression to septic shock. Thus, this study provides novel evidence of effectiveness of leukopenia and elevated as factors predicting worse prognosis of septic shock caused by pneumonia and indicates the need for attentive monitoring these factors when establishing treatment strategies. In addition, the findings support the established claims that leukopenia is related to inflammatory response and severity of pneumonia.[24]

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ProCESS Investigators et al.[25] were not confident about EGDT when comparing it with standard care in their study. However, Gu et al.[26] claimed that EGDT effectively reduced the overall mortality rate in their study using meta-analysis. In Korea, Shin et al.[27] also found significant effects of EGDT in patients who developed septic shock after ER visits. In this study there were no differences in the time interval from ER visit to the first antibiotic therapy and central venous pressure between the two groups (Table 1). A recent study reported that antibiotic therapy performed in patients with severe sepsis or septic shock within 1 hour or at 5 hours after ER admission had no effect on mortality.[28] Also, there was no significant difference in duration of antibiotic therapy in this study, although it is generally considered an important factor in treatment for sepsis. Along with EGDT, antibiotic duration appear to have mixed research findings. Given that EGDT is widely used for the treatment of sepsis as part of standard medical therapy, its widespread use appears to imply its proven effectiveness in improving prognosis of septic patients.[26,29] However, age, severity of illness, inflammation-associated tissue hypoxia may be more useful to predict patient outcome. While antibiotic duration was found to have no effect on mortality in both grounds in this study, the mean duration was more than 5 hours in both groups although one hour is recommended for septic shock. This finding needs to be further investigated.

In this study, hypoxia was defined as PaO_2 of less than 83 mmHg to make it consistent with the level of blood oxygen that ER commonly uses to determine hypoxia. Although PaO2 levels can vary with age and FiO_2, the level needs to be specific and consistent to use in emergency situations like ER. However, further studies are necessary to identify better approaches to defining hypoxia in a prompt and easy way.

This study has the following limitations: first, data were obtained retrospectively by medical record review. Secondly, the study was conducted in a single institution. For the completeness of data, a prospective cohort study involving several hospitals is necessary. Thirdly, EGDT was not applied to all patients at the same time in the same manner although this study indicates otherwise.

However, this study has yielded meaningful data on old age, APACHE II, leukocytes and, elevated INR by newly finding that these factors affect mortality in patients with pneumonia-induced septic shock in addition to sepsis, which were previously known. This study proposes attentive monitoring, early recognition and aggressive therapy of these factors in the management of septic shock caused by pneumonia, but a prospective, multicenter study is necessary to validate these conclusions.

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