Severe Pneumonia: Etiology and Outcome in a Tertiary Hospital in Indonesia

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Abstract

Background: Severe pneumonia represents a subset of life-threatening pneumonia. The mortality rate of patients with severe pneumonia is considerably high. This study aims to determine the etiology and outcome of severe pneumonia.

Methods: An observational prospective study was conducted from September 2017 to September 2018 on pneumonia patients in a tertiary hospital. Clinical and diagnostic evaluations were carried out to assess the severity of the disease, etiology, comorbidities, and several other factors associated with outcomes.

Results: 140 pneumonia patients were evaluated and 41 patients met the severe pneumonia criteria. A pathogen was found in 20 community-acquired pneumonia (CAP) and 13 hospital-acquired pneumonia (HAP). The most frequently isolated pathogen from the sputum culture of patients with either severe CAP or HAP was *Acinetobacter baumannii*. The mortality rate of severe HAP patients was higher than that of severe CAP patients (84% vs. 65%), but the difference was nonsignificant. Most of the subjects had comorbidities (CAP 75%, HAP 61.6%). Procalcitonin (PCT) and C-reactive protein (CRP) levels in severe CAP were higher than those in severe HAP (PCT 7.7 vs 6.0, p=0.658; CRP 163.1 vs 93.6, p=0.580), but the differences were also nonsignificant.

Conclusion: The most frequently isolated pathogens from the sputum culture of patients with severe pneumonia were Acinetobacter baumanii, which should be considered at the time of diagnosis and empirical antibiotic therapy. Severe pneumonia was often accompanied by comorbidities, inflammation responses increase in both severe CAP and HAP with a high mortality rate.

Keywords*: severe pneumonia, etiology, mortality*

Introduction

Pneumonia is defined as an infection of the pulmonary parenchyma. Causative microorganisms of severe pneumonia are one of the risk factors associated with mortality[1]. Pneumonia was caused by different microbes in different parts of the world. In the Middle East, the most frequently isolated pathogens in intensive care unit-admitted hospital-acquired pneumonia (HAP) is Streptococcus pneumoniae and for community-acquired pneumonia (CAP) is Acinetobacter baumanii[2]. In South Asia, Staphylococcus aureus and Pseudomonas aeruginosa are the most common causes of severe CAP[3]. Streptococcus pneumonia is the most common cause of severe CAP in Singapore[1]. The mortality rate in severe pneumonia (community or hospital-acquired)

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is considerably high, (30.3%)[2].

Clinically distinguishing CAP and HAP is relevant because there are distinctions in the causative pathogens and thus different therapies. In HAP, the initial illness that leads to hospitalization interferes with host defenses and can contribute to susceptibility to infections and host response disorders. This theory explains the difference in the immune responses in HAP and CAP[4]. This study aims to determine the etiology and outcome of severe pneumonia

Methodology

Population and study design :

This study is a prospective observational study of hospitalized pneumonia patients in Dr. Soetomo Academic Hospital from September 1, 2017, until September 1, 2018, who met the inclusion criteria of severe pneumonia. Of the 140 patients with pneumonia (CAP and HAP), 50 were excluded because of incomplete laboratory data, 1 was discharged against medical advice, and 11 passed away before sputum culture collection. Of the remaining 78 patients, 41 patients met the criteria for severe pneumonia; however, positive sputum culture was found only in 33 patients. All patients gave written informed consent, and this study received ethical approval from the Health Research Ethics Committee of Dr. Soetomo Hospital Surabaya (602 / Panke.KKE / X / 2017).

Inclusion criteria :

Adult hospitalized patients who met the criteria of severe CAP according to IDSA / ATS 2007[5] or severe HAP according to 2016 HAP guidelines[6] and did not suffer from pulmonary tuberculosis, experience an acute infection of other organs, or suffer from lung cancer were included. The severe CAP definition according to IDSA / ATS 2007 consists of minor criteria, respiratory rate > 30 breaths/min, PaO_2 /FIO_2 ≤250 mmHg, multilobar infiltrates, confusion/disorientation, uremia (BUN ≥20 mg/dl), leukopenia (WBC count < 4000 cells/mm^3), thrombocytopenia (platelet count <100.000 cells/mm^3), hypothermia (core temperature <36°C), and hypotension that requires aggressive resuscitation, and major criteria, requires invasive mechanical ventilation and septic shock with the need for a vasopressor that requires aggressive fluid resuscitation[5]. Severe HAP is defined as HAP with risk factors for mortality, i.e., the need for ventilatory therapy due to pneumonia and septic shock[6].

Examination procedure:

Sputum samples for culture were collected spontaneously (with a prior mouth rinse) in patients who were conscious and able to expectorate phlegm. Sputum suctioning with a suction catheter was performed for patients who were unable to expectorate phlegm or with an endotracheal tube. The samples were subsequently sent to the laboratory for aerobic culture examination. Sputum samples were inoculated on blood agar and MacConkey agar. The etiology of pneumonia was determined based on the pathogenic bacteria that grew on the culture medium. Inflammatory biomarker examination (PCT and CRP) was performed by withdrawing 3-5 mL of venous blood. The C-reactive protein extended range (RCRP) method based on the PETIA technique was used to measure CRP levels with a Flex reagent cartridge (Dimension, Siemens Healthcare Diagnostics Inc.). A CRP value > 10 mg/L was categorized as higher than normal. Serum procalcitonin levels were measured by VIDAS® B.R.A.H.M.S PCT® (bioMerieux SA. Marcy-I'Etoile-France).

Statistical Analysis

Descriptive statistics were analyzed using the mean ± SD for quantitative variables and frequency and percentage for qualitative variables. The chi-square test was used to evaluate differences in qualitative variables, and the t-test was used for quantitative variables. The Kaplan-Meier method and log-rank test were used for survival analysis. The results of statistical calculations were considered significant when $p < 0.05$.

Results

Clinical characteristics of severe pneumonia

The characteristics of the 33 severe pneumonia patients are shown in Table 1. Of all study subjects, 60.0% had severe CAP, and 40% had severe HAP. The mean age was 56 years old in severe CAP and 46 years old in severe HAP, and there were more patients with comorbidities than those without comorbidities. Of the 33 pneumonia patients, 26 (78.8%) were hospitalized in

intensive care, and 7 (21.2%) were hospitalized in non-intensive care. All patients have received antibiotics before sputum culture sample collection.

Table 1. Clinical characteristics and comorbidity distribution

Characteristics N (%)	**Severe CAP 20 (60.6%)**	**Severe HAP 13 (39.4%)**	**p-value**
Age [mean ± SD]	56.65 ± 18.37	46.77 ± 17.32	0.133
Sex			
Male	10 (50.0%)	9 (69.2%)	0.464
Female	10 (50.0%)	4 (30.8%)	
Clinical features			
Fever (°C) [median (min-max)]	38 (36-38.9)	38.1 (36.2-38.7)	0.605
Cough	20 (100%)	13 (100%)	
Respiration Rate	25.90±3.21	26.92±2.56	
Systolic blood pressure	111.45±24.31	120.23±23.43	0.312
Diastolic blood pressure	68.50±13.41	70.38±15.40	0.712
Comorbidity			
Without comorbidity	5 (25.0%)	5 (38.4%)	0.329
With comorbidity:	15 (75.0%)	8 (61.6%)	
Diabetes mellitus	9 (45.0%)	2 (15.4%)	0.132
Cardiovascular insufficiency	7 (35.0%)	4 (30.8%)	1.000
Stroke	2 (10.0%)	3 (23.1%)	0.360
COPD	3 (15.0%)	0 (0.0%)	0.261
Chronic kidney disease	2 (10.0%)	1 (7.7%)	1.000
Malignancy	0 (0.0%)	2 (15.4%)	0.148

Note: Results are expressed as the mean ± SD, median (min-max) or %.

SD; standard deviation, CAP; community-acquired pneumonia, HAP; hospital-acquired pneumonia, COPD; Chronic obstructive pulmonary disease

Causative Pathogen

Pathogenic microbes isolated from patients with CAP were mostly gram-negative (85.0% (17/20)) and were dominated by *Acinetobacter baumannii* and *Klebsiella pneumoniae*, while Gram-positive microbes accounted for only 15.0% (3/20). In HAP patients, only Gram-negative bacteria were found (13/13=100%), the most common being *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (Table 2). All patients received antibiotics before sputum culture sample collection.

Table 2. Results of sputum culture based on the type of severe pneumonia

Pathogenic microbes	*Severe CAP n=20*	Severe HAP n=13	All severe pneumonia	Passed away	p-value
Acinetobacter baumannii	12 (60.0%)	3 (23.1%)	15 (45.4%)	11 (37.9)	0.373
Klebsiella pneumoniae ESBL+	3 (15.0%)	2 (15.4%)	5 (38.2%)	3 (10.3%)	0.533
Pseudomonas aeruginosa	1 (5.0%)	3 (20.0%)	4 (13.3%)	3 (10.3%)	0.705
Enterobacter cloacae	0 (0.0%)	2 (15.4%)	2 (6.0%)	4 (13.7%)	0.260
Staphylococcus aureus	2 (10.0%)	0 (0.0%)	0 (0.0%)	2 (6.8%)	
Enterobacter aerogenes	0 (0.0%)	1 (7.7%)	1 (2.7%)	1 (3.4%)	
Escherichia coli ESBL +	0 (0.0%)	1 (7.7%)	1 (2.7%)	1 (3.4%)	
Acinetobacter iwoffii	0 (0.0%)	1 (7.7%)	1 (2.7%)	1 (3.4%)	
Proteus mirabilis	0 (0.0%)	0 (0.0%)	1 (2.7%)	1 (3.4%)	
Streptococcus pyogenes	1 (5.0%)	0 (0.0%)	1 (2.7%)	1 (3.4%)	
Aeromonas caviae	1 (5.0%)	0 (0.0%)	1 (2.7%)	1 (3.4%)	
Total	20	13	33	23	

ESBL; Extended spectrum beta-lactamases, CAP; community-acquired pneumonia, HAP; hospital-acquired pneumonia

Inflammatory response

Total leukocyte numbers in CAP patients was higher than that in HAP patients, but the difference was not significant. Procalcitonin and CRP levels were elevated in patients with CAP and those with HAP. The mean PCT and CRP levels in CAP patients were higher than those in HAP patients, but the difference was not significant (Table 3).

Table 3. Laboratory results of severe pneumonia patients

Laboratory parameters	*Severe CAP n=20*	Severe HAP n=13	p-value
Hemoglobin (g/dL)	11.44±2.41	10.56±2.26	0.307
Leukocytes (/µL)	19.240±9.59	14.850±5.46	0.145
Thrombocytes (/µL)	258.500 (180.000-513.000)	269.000 (151.000-940.000)	0.450
Blood urea nitrogen (mg/dL)	23 (4-89)	16 (6-55)	0.672
Serum creatinine (mg/dL)	1.21 (0.52-6.29)	0.77 (0.3-2.58)	0.074
Potassium (mmol/L)	3.9 (2.1-6.1)	3.8 (2.3-7.0)	0.365
Sodium (mmol/L)	140 (122-164)	141(124-164)	0.970
CRP (mg/dL)	163.1 (8.6-315)	93.62 (4.7-316.75)	0.580
PCT (ng/mL)	7.72 (0.13-116.9)	6.08 (0.22-200)	0.658

Note: Results are described as the mean ± SD or median (min-max).

CRP; C-reactive protein, PCT; procalcitonin, CAP; community-acquired pneumonia, HAP; hospital-acquired pneumonia

Table 4: Severity of illness and mortality

Variables	Severe CAP n=20	Severe HAP n=13	p-value
SOFA score	7.75	7.15	0.614
Requiring mechanical ventilation	16 (80.0%)	11 (84.6%)	1.000
Need for a vasopressor	6 (30.0%)	3 (23.1%)	1.000
CRP >100 mg/dL	13 (65.0%)	6 (46.2%)	0,478
PCT >5 ng/mL	12 (60.0%)	8 (61.5%)	1,000
ICU admission	16 (80.0%)	11 (84.6)	1.00
Blood gas analysis:			
PaO2	72.70 (31-197)	88 (36-135)	0.418
PaO2/FiO2	138.62±71.80	121.03±40.41	
PaO2/FiO2			
≥ 200 mmHg	4 (20.0%)	0 (0.0%)	0.136
< 200 mmHg	16 (80.0%)	13 (100%)	0.118

Mortality	13 (65.0%)	11 (84.0%)	0.26
ICU	10 (50.0%)	9 (69.2%)	0.261
Hospital ward	3 (15.0%)	2 (15.3%)	0.667

SOFA; The Sequential Organ Failure Assessment , CRP; C-reactive protein, PCT; procalcitonin, ICU; intensive care unit, CAP; community-acquired pneumonia, HAP; hospital-acquired pneumonia

The severity of illness and outcome

The degrees of severity of patients with severe CAP and those with severe HAP were equal, as seen in the sequential organ failure assessment (SOFA) score in Table 4. The increased SOFA score in severe CAP, pulmonary organ dysfunction (PaO_2 /FiO_2 ratio <200), and use of vasopressors were not significantly different between sCAP and sHAP. The severity of the disease affects the outcome. Overall mortality was 72.7% (n=24). Higher mortality was seen in severe HAP than in severe CAP, but the difference was not significant. Survival analysis showed that there were no differences in the survival rate between the two types of pneumonia (Figure 1).

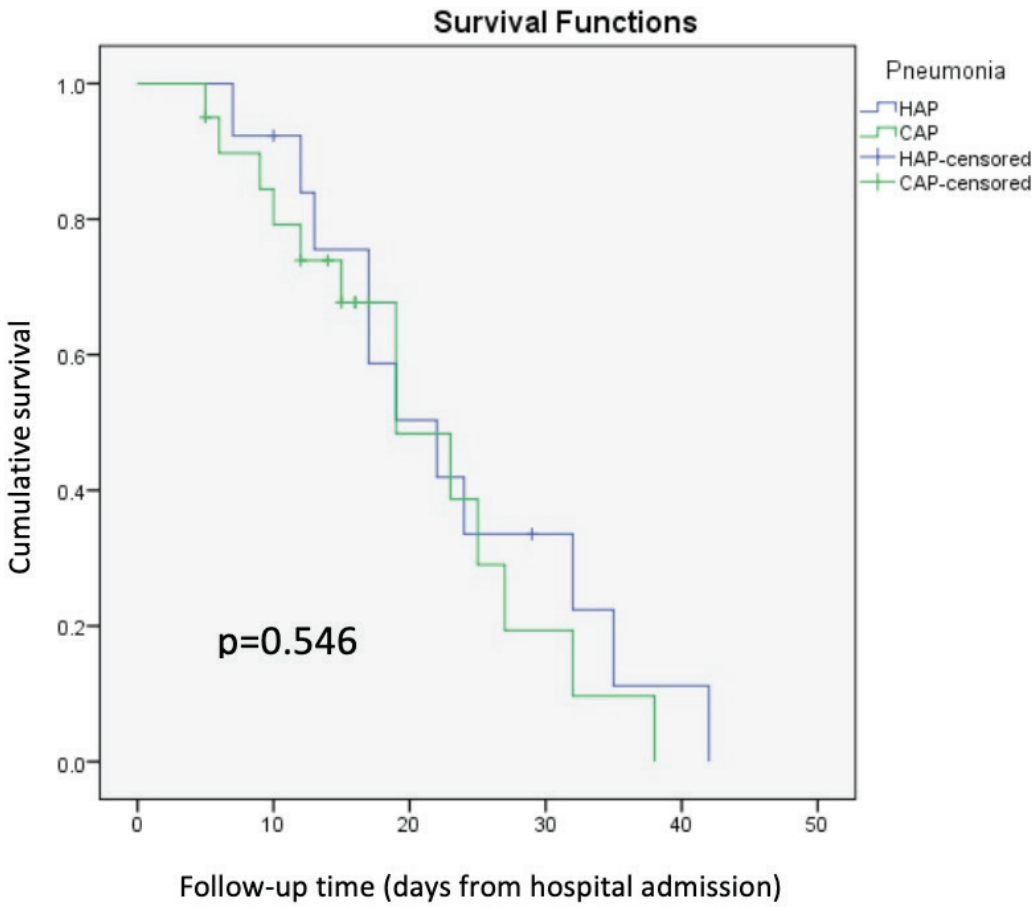

Figure 1. Kaplan-Meier survival curves in severe CAP and severe HAP.

Survival analysis of cumulative survival and follow-up time revealed that there were no differences in the survival rate between the two types of pneumonia

In this study, the most common microbes that caused severe CAP confirmed by sputum culture were Gram-negative bacteria (*Acinetobacter baumannii* and *Klebsiella pneumoniae*), followed by gram-positive bacteria (*Staphylococcus aureus*). Acinetobacter

baumanii has become the emerging cause of severe CAP in the Asia-Pacific region. In Australia, a reported 21% incidence of Acinetobacter baumanii from gram-negative bacterial pneumonia in the 1990s[7]. In the last few decades, severe CAP has been reported caused by A baumanii. The majority of cases were reported from Northern Australia and Asia, such as Thailand, Singapore, Hong Kong, Taiwan[8,9,10]. In this study, Acinetobacter baumanii sputum isolates were found in 60% of sCAP cases. Clinical characteristics of these cases were acute, severe with respiratory failure and septic shock, leading to a high mortality rate[8,11,12]. Several conditions, such as elderly patients, alcoholism, malignancy, diabetes, kidney disease, and liver cirrhosis are associated with Acinetobacter baumanii infection[8,9]. In this study, 75% of cases had an underlying disease but apart from alcoholism and cancer. Antibiotics administration might play a role as all patients have been given antibiotics from the referring hospital.

Patients` immune system is disrupted by the initial illness that leads to hospitalization and this immune disruption may contribute to susceptibility to infection[4]. Acinetobacter baumanii has become a potential pathogen of HAP in critically ill patients[13]. Acinetobacter baumanii sputum was the most common isolate found in HAP patients in this study (23.1%) as seen in HAP patients in Iranian ICU (73.9%) and 37% in Saudi Arabia[2,14]. In this study, 61.6% of HAP patients presented with comorbidities, similarly, Farid et al reported that 57.9% of patients with HAP had comorbidities[14]. This data is important in considering diagnosis and initial administration of antibiotics for severe HAP

Both severe CAP or HAP showed identical severity and outcome[15]. The mortality of severe pneumonia cases is considerably high. Several factors are associated with the mortality of patients with severe pneumonia. The causative pathogen, comorbidity, and host response are factors that influence intensive care outcomes. In the Middle East, the mortality rate of severe CAP patients admitted to the intensive care unit (ICU) was 46.6%[16]. A 2005 study in Japan reported that the mortality rate of severe CAP patients requiring intensive care reached 48.6%[17]. A noticeably high mortality rate (89%) was seen in cases caused by *Pseudomonas aeruginosa*[3]. Quah et al. reported that respiratory viruses that coexisted with bacteria in mixed viral-bacterial coinfection were associated with an increased risk of death[1]. In this severe pneumonia study, the results of sputum culture showed that Gram-negative bacteria, especially *Acinetobacter baumannii*, were the most frequently isolated microbes, with mortality reaching 65%. After suffering a critical condition, patients with few comorbidities tend to have a superior clinical outcome[18]. A study with a large number of CAP and HAP patients admitted to the ICU with a comparable number of comorbidities (69.7% CAP, 65.4% HAP), age, and severity index showed similar host responses[3]. Patients in this study who presented with prevalent comorbidities and a severe disease index (SOFA score > 7.0) had a high mortality rate.

Procalcitonin is a calcitonin peptide precursor released by the cell parenchyma in response to bacterial toxins. Procalcitonin not only is an inflammatory biomarker but also is used in the diagnosis of bacterial pneumonia[19]. Furthermore, the PCT level is also related to the severity of pneumonia[20]. Some studies reported that PCT levels were related to the severity of pneumonia, and patients who had an increase in PCT levels showed a tendency to pass away[21,22]. Procalcitonin is a useful predictor of pneumonia severity and mortality risk. A study reported that the level of PCT >1.1 ng/mL can be a guide to identify groups of ICU patients who are at high risk of suffering multiorgan failure and mortality[24]. Another study reported that high PCT levels (>10 ng/mL) increased mortality risk[23]. In this study, the mean levels of PCT were 7 ng/mL and 6 ng/mL in CAP and HAP, respectively, but the differences were not significant. A similar result was reported by Bloos et al.[20], showing that the initial PCT level in CAP was nonsignificantly different from that in HAP, albeit at a lower level (2.4 vs 2.2).

C-reactive protein is an alternative inflammatory marker to aid in the diagnosis of bacterial pneumonia and a predictor of pneumonia severity despite being less accurate than PCT[24]. It has been reported that higher accuracy was seen when CRP was used in combination with PCT than when it was used alone[25]. In this study, PCT (>5 ng/mL) and CRP (>100 mg/dL) elevation were found in 50% of severe CAP and severe HAP patients, although the difference was not significant. The clinical condition indicates that both severe CAP and severe HAP have comparable disease severity, as it was

evident that there was no difference in mortality.

In this study, the most common clinical features were cough, fever, and dyspnea in both severe CAP and HAP. In a study by Elshamly, the most frequent clinical features were fever, cough, dyspnea, and hypoxemia in patients with CAP[29], while Aya et al. reported that 72.2% of pneumonia patients complained of fever, 89.9% cough, 66.6% spasms and 35.11% pleuritic pain. The patients with HAP were dominated by elderly people and male sex, and they complained of less cough, sputum, and dyspnea than younger patients[27]. In this study, the PaO_2 of severe CAP patients was lower than that of severe HAP patients but not significantly different, and comorbidities were more common in severe CAP than in severe HAP (75% vs 61.6%). Diabetes mellitus (DM) was the most common comorbidity in severe CAP, while cardiovascular insufficiency was the most common comorbidity in severe HAP. A study of severe CAP stated that 51.85% of CAP patients had comorbidities, and the most common comorbidities were DM and hypertension[26].

A limitation of this study was that only routine aerobic cultures of sputum were performed, so other possible causes of severe pneumonia, such as viruses and atypical pathogens, were not detected.

Conclusion

The causative pathogens of severe pneumonia were dominated by gram-negative bacterias, mainly Acinetobacter baumanii. Underlying disease was an important risk factor for severe pneumonia. Severe CAP and HAP had identical clinical characteristics, disease severity, and high mortality rate.

Disclosure: All authors declare no conflicts of interest.

Acknowledgment: We would like to thank Muhammad Miftahussurur, M.D., Ph.D. for his support in this publication and Atika, S.Si. for her help in data analysis.

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