

Factors Associated with Mortality in Immunocompetent Patients with Hospital-acquired Pneumonia

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Abstract

Aim: The aim of the study is to determine the factors associated with 28-day mortality in immunocompetent patients with hospital-acquired pneumonia (HAP). **Methods:** This was a 42-month retrospective cohort study in Chiang Kham Hospital. Patients with HAP diagnosed between January 2013 and June 2016 who did not have an immunocompromised status were recruited into the study. **Statistical Analysis Used:** Univariable and multivariable binary logistic regression analyses were performed to determine the factors associated with mortality in patients with HAP. **Results:** A total of 181 HAP patients. The most causative pathogens were nonfermenting Gram-negative bacilli. Fifty-two (28.7%) patients had died within 28 days after HAP diagnosis. Multivariable analysis demonstrated that mechanical ventilation (MV) dependency (adjusted odds ratio [OR] = 3.58, 95% confidence interval [CI] 1.53–8.37, $P = 0.003$), antibiotic duration (adjusted OR = 0.79, 95% CI 0.70–0.88, $P < 0.001$), acute kidney injury (adjusted OR = 5.93, 95% CI 1.29–27.22, $P = 0.022$), and hematologic diseases (adjusted OR = 11.45, 95% CI 1.61–81.50, $P = 0.015$) were the significant factors associated with 28-day mortality. **Conclusions:** The factors associated with mortality were MV dependency, HAP duration of treatment, acute kidney injury, and hematologic disease. Early recognition of these factors in immunocompetent patients with HAP and treatment with intensive care may improve the outcome.

Keywords: Factors, hospital-acquired pneumonia, immunocompetent, mortality, multivariable model

INTRODUCTION

Hospital-acquired pneumonia (HAP) is one of the most common nosocomial infections with high mortality and morbidity.^[1] The mortality rates range from 14.4% to 48.5%.^[2–5] Besides, HAP also often results in many health-care problems, for example, prolonged hospital stay, increased antimicrobial usage, and additional cost of treatment.^[2–3,6]

Majority of the nosocomial pneumonia studies included both HAP and ventilator-associated pneumonia (VAP). There were quite a few studies in patients with specific HAP diagnosis. Previous studies were reported that inappropriate initial antimicrobial therapy, the Simplified Acute Physiology Score (SAPS), and occurrence of multiple organ failure were associated with mortality in nosocomial pneumonia (including both HAP and VAP).^[4] A meta-analysis study exploring predictors of mortality in patients with VAP reported malignancy, Intensive

Care Unit (ICU) admission, and inappropriate initial treatment as the predictors of mortality.^[7] Nevertheless, patient-specific factors, pathogens, and other clinical factors should also be considered, while predicting mortality in patients with nosocomial pneumonia.^[8–10] In HAP patients, there were only limited data regarding factors associated with mortality. The factors reported as associated with mortality were the time from admission to pneumonia (i.e., early vs. late onset HAP), age, prior use of mechanical ventilation (MV), and neoplastic disease.^[11]

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The objective of this study was to determine the factors associated with 28-day mortality in immunocompetent HAP patients at Chiang Kham Hospital, Phayao, Thailand.

METHODS

Study design

This retrospective cohort study was conducted in the Internal Medicine Department at Chiang Kham Hospital, Phayao, Thailand. Patients admitted to the hospital between January 1, 2013 and June 30, 2016 were recruited.

Patients

Patients with ages >18 years who complied with the criteria of HAP diagnosis by following the ATS/IDSA guidelines in 2005^[12] and the Thai clinical practice guidelines for management and prevention of adults with HAP and VAP,^[13] defined as pneumonia which occurred more than 48 h after admission and has radiographic infiltrate that is new or progressive along with at least two of the following three conditions: (1) fever, (2) purulent sputum, and (3) leukocyte count $\geq 12,000$ or $< 4,000$ cells/mm³ were retrospectively reviewed. The patients were excluded if they were (1) pregnant; (2) had immunocompromised status according to the Centers for Disease Control and Prevention definition,^[14] –including neutropenia (absolute neutrophil count $< 500/\text{mm}^3$), leukemia, lymphoma, HIV, or splenectomy, or were early posttransplantation, on cytotoxic chemotherapy, or on high-dose steroids (e.g., >40 mg of prednisone or its equivalent [> 160 mg hydrocortisone and > 6 mg dexamethasone] daily) for >2 weeks; (3) had other lung infections diagnosed, for example, empyema, lung abscess, pleural effusion; (4) had positive culture for *Burkholderia pseudomallei* or been diagnosed with melioidosis; (5) had infected bronchiectasis with chronic obstructive pulmonary disease (COPD); (6) had other coinfections (e.g., septicemia, skin and soft-tissue infection, peritonitis, catheter-related infection) that used the same antibiotic as in the treatment of HAP. The choices of the initial empiric antibiotic treatment and the duration of treatment depended on the physician's judgment. This study was approved by the Ethics Committee on Human Research of Chiang Kham Hospital (register number: 02/2557, 01/2559).

Data collection and outcome measures

Patients with HAP diagnosis were retrieved from Chiang Kham Hospital database (HOSxP program), and then the data collected from their admission medical records. The data collected included age, sex, underlying diseases, comorbidity, HAP onset, severity of illness based on a SAPS II, risks of multidrug-resistant bacteria infection, type of antibiotics, and appropriateness of empirical antibiotic treatment was defined as antibiotics administered before microbiologic documentation matched the susceptibility of the pathogen, causative bacteria in sputum specimen and other sources, and number of days with MV and MV dependency was defined as patients who need MV after HAP diagnosis; number of days in ICU.

The sputum specimens were collected using a noninvasive technique. After completion of the treatment, duration of the antibiotic treatment, cost of the antibiotics administered, and length of hospital stay were recorded. Recurrence of pneumonia and death within 28 days were monitored from the hospital database on the day of follow-up and on day 28 after the initiation of antibiotic treatment for HAP.

Statistical analyses

Clinical and laboratory data were compared between the survivor and the nonsurvivor groups. The independent *t*-test or the Mann–Whitney U-test was used for comparing the continuous variables as appropriate. Fisher's exact test or the Chi-square test was used for the comparison of categorical variables. Univariate logistic regression analysis was carried out for testing the patients' clinical characteristics and outcomes. All variables with $P < 0.20$ in the univariable analysis and the factors that expert recommended were included in the multivariable model analysis using the forward stepwise (likelihood ratio) method. Statistical significance was defined as the $P < 0.05$. The data were analyzed using SPSS statistics software version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of patients

A total of 181 patients were included in this study. There were 108 (59.7%) male and 73 (40.3%) females. Most of them had late-onset HAP (61.3%); the median of HAP onset was 6 ± 7 days in both groups [Table 1]. In this study, most of the HAP patients had more than one risk factor for multidrug-resistant (MDR) infection. The risk factors of MDR infection were not statistically different between the two groups. The MDR risk factors that were frequently observed were a history of antibiotic therapy in the preceding 90 days (73.1% vs. 69.0% in the nonsurvival and the survival groups, respectively, $P = 0.587$) and length of current hospitalization being >5 days (59.6% vs. 56.6%, $P = 0.709$). The most frequently used antibiotics for empirical treatment were ceftazidime (78.8% vs. 62.0%, $P = 0.030$) and subsequently, ceftriaxone (13.5% vs. 28.7%, $P = 0.031$). The use of antibiotic treatment either by monotherapy or by combination empirical therapy was not statistically different between the two groups [Table 2]. The percentages of appropriateness of empirical treatment were observed to be 11.5% and 16.3% in the nonsurvival and the survival groups, respectively.

Fifty-two patients died within 28 days after the HAP diagnosis (nonsurvival group) and 129 patients survived. The mortality rate of HAP within 28 days was 28.7%. The mean age was 68.3 ± 11.7 years in the nonsurvival group and 68.4 ± 13.6 years in the survival group. The patients in the nonsurvival group had higher SAPS II at the time of HAP diagnosis than the ones in the survival group (32.69 ± 11.63 vs. 27.8 ± 9.38 , $P = 0.009$). The percentages of patients with MV

were 38.5% and 14.7% in the nonsurvival and the survival groups, respectively ($P < 0.001$), and the percentages of patients who required ICU transfer were 40.4% vs. 17.1% in the nonsurvival and the survival groups, respectively ($P = 0.001$). The patients in the nonsurvival group were observed to have higher incidents of acute kidney injury (17.3% vs. 3.1%, $P = 0.002$) and hematologic diseases such as anemia or thalassemia (11.5% vs. 1.6%, $P = 0.008$) than the ones in the survival group. The median times of hospital stay were 11 days and 14 days in the nonsurvival group and the survival group, respectively ($P = 0.049$).

Microbiological data

The percentages of good quality specimen were 25% and 20.9% in the nonsurvival and the survival groups, respectively. However, the quality of sputum specimen was not statistically significant between the two groups. The pathogens observed in the sputum specimens from HAP patients in both groups were similar. The most common causative organisms (27.1%) were nonfermenting Gram-negative bacilli [Table 3]. The overall number of sputum specimens of good quality was 40 (22.1%). In patients with good-quality sputum specimen, there was 10 (37.0%) with appropriate empirical treatment.

Table 1: Baseline characteristics of hospital-acquired pneumonia patients

Characteristics	Survivors (n=129)	Nonsurvivors (n=52)	P
Gender, n (%)			
Male	75 (58.1)	33 (63.5)	0.509
Female	54 (41.9)	19 (36.5)	
Age (mean±SD)	68.4±13.6	68.3±11.7	0.975
HAP onset day (median±IQR)	6±7	6±7	0.297
HAP onset			
Early	51 (19.5)	19 (38.5)	0.708
Late	78 (60.5)	33 (63.5)	
SAPS II (mean±SD)	27.8±9.38	32.69±11.63	0.009
Co-morbidity, n (%)			
Sepsis/septic shock	26 (20.2)	13 (25.0)	0.473
Acute kidney injury	4 (3.1)	9 (17.3)	0.002
COPD with AE	19 (14.7)	8 (15.4)	0.911
Co-infection	16 (12.4)	5 (9.6)	0.596
Congestive heart failure	5 (3.9)	2 (3.8)	1.000
Stroke	12 (9.3)	5 (9.6)	1.000
Electrolyte imbalance	5 (3.9)	1 (1.9)	0.675
Ischemic heart disease	3 (2.3)	1 (1.9)	1.000
Hematologic disease	2 (1.6)	6 (11.5)	0.008
Hepatic disease	7 (5.4)	4 (7.7)	0.515
Other co-morbidities	42 (32.6)	7 (13.5)	0.009
Mechanical ventilation	19 (14.7)	20 (38.5)	<0.001
ICU after HAP	22 (17.1)	21 (40.4)	0.001
Antibiotic duration (median±IQR)	10±7	6±7	<0.001
Hospital duration (median±IQR)	14±10	11±6	0.049

HAP: Hospital-acquired pneumonia, SAPS II: Simplified Acute Physiologic Score II, COPD with AE: Chronic obstructive pulmonary disease with acute exacerbation, ICU: Intensive care unit, SD: Standard deviation, IQR: Interquartile range

Factors associated with mortality

The results showed that patients in the nonsurvival group had higher SAPS II ($P = 0.009$) and required more frequent MV ($P < 0.001$) and ICU transfer after HAP diagnosis ($P = 0.001$). These factors were included in the univariable analysis. The univariable analysis showed that factors associated with mortality within 28 days after HAP diagnosis were SAPS II, MV dependency, ICU transfer, *Acinetobacter baumannii* (MDR) or *Pseudomonas aeruginosa* infection, duration of antibiotic treatment, having acute kidney injury or hematologic diseases as comorbidities [Table 4]. Then, eight factors that were statistically significant in the univariable model as described above and two factors from the expert recommendation were included in the multivariable logistic regression analysis. The factors from the expert recommendation included sepsis/septic shock and appropriateness of empirical antibiotic treatment. The multivariable analysis demonstrated that MV dependence (adjusted odds ratio [OR] = 3.58, 95% confidence interval [CI] 1.53–8.37, $P = 0.003$), antibiotic duration (adjusted OR = 0.79, 95% CI 0.70–0.88, $P < 0.001$), acute kidney injury (adjusted OR = 5.93, 95% CI 1.29–27.22, $P = 0.022$), and hematologic diseases (adjusted OR = 11.45, 95% CI 1.61–81.50, $P = 0.015$) were the significant factors associated with 28-day mortality [Table 5]. This multivariable model had prediction capability of 79.3% according to the area under the receiver operating characteristic curve, 95% CI 0.71–0.87, $P < 0.001$ [Figure 1].

DISCUSSION

HAP is one of the important causes of prolongation of hospital stay with high morbidity and mortality.^[2,15,16] The mortality rate in the present study was 28.7%, which is in according to the previous studies that the mortality rate of nosocomial pneumonia was in the range of 9.2%–53.3%.^[2-4,6,8,15,17-19]

The univariable analysis conducted in this study demonstrated that the factors associated with mortality in 28 days were SAPS II, MV dependence, ICU transfer, a causative pathogen of either *A. baumannii* (MDR) or *P. aeruginosa*, and having

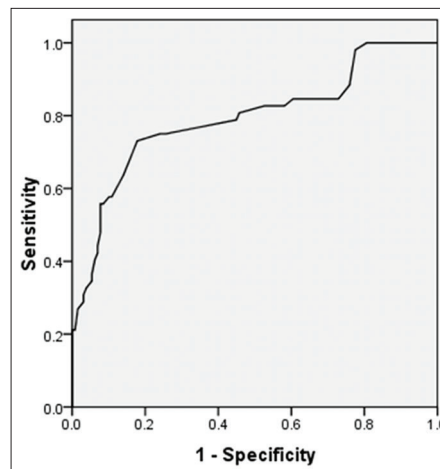


Figure 1: The ROC curve of multivariable model

Table 2: Clinical characteristics of patients with hospital-acquired pneumonia

Characteristics	Survivor (n=129)	Nonsurvivors (n=52)	P
MDR risk factor, n (%)			
Antibiotic therapy in preceding 90 days	89 (69.0)	38 (73.1)	0.587
Current hospitalization of >5 days	73 (56.6)	31 (59.6)	0.709
Admission in ICU in current visit	28 (21.7)	9 (17.3)	0.507
Chronic hemodialysis	2 (1.6)	2 (3.8)	0.325
Sputum quality			
Good	27 (20.9)	13 (25.0)	0.933
Bad	65 (50.4)	25 (48.1)	
Cannot assess	30 (23.3)	12 (23.1)	
No specimen	7 (5.4)	2 (3.8)	
Antibiotic treatment			
Monotherapy	103 (79.8)	40 (76.9)	0.662
Combination	26 (20.2)	12 (23.1)	
Type of antibiotic			
Amoxicillin/clavulanate	6 (4.7)	2 (3.8)	1.000
Cefoperazone/sulbactam	2 (1.6)	0	1.000
Ceftazidime	80 (62.0)	41 (78.8)	0.030
Ceftriaxone	37 (28.7)	7 (13.5)	0.031
Ciprofloxacin	24 (18.6)	11 (21.2)	0.694
Clindamycin	3 (2.3)	1 (1.9)	1.000
Imipenem/cilastatin	5 (3.9)	5 (9.6)	0.153
Others	8 (6.2)	2 (3.8)	0.726
Empirical therapy			
Appropriate	21 (16.3)	6 (11.5)	0.418
Inappropriate	108 (83.7)	46 (88.5)	

ICU: Intensive care unit, MDR: Multidrug-resistant

Table 3: Microbiological characteristics in hospital-acquired pneumonia episodes

Pathogen	Survivor (n=129)	Nonsurvivors (n=52)	P
Nonfermenting			
Gram-negative bacilli			
<i>A. baumannii</i>	10 (7.8)	3 (5.8)	0.760
<i>A. baumannii</i> (MDR)	2 (1.6)	3 (5.8)	0.144
<i>P. aeruginosa</i>	16 (12.4)	3 (5.8)	0.188
<i>P. aeruginosa</i> (MDR)	4 (3.1)	2 (3.8)	1.000
Unidentified NF-GNB	3 (2.3)	2 (3.8)	0.626
<i>S. maltophilia</i>	1 (0.8)	0	1.000
Other Gram-negative bacilli			
<i>E. coli</i>	3 (2.3)	1 (1.9)	1.000
<i>E. coli</i> (ESBL)	7 (5.4)	1 (1.9)	0.442
<i>K. pneumonia</i>	6 (4.7)	1 (1.9)	0.675
<i>K. pneumonia</i> (ESBL)	6 (4.7)	3 (5.8)	0.718
<i>Enterobacter</i> spp.	1 (0.8)	1 (1.9)	0.493
Gram-positive bacteria			
MRSA	1 (0.8)	0	1.000

MDR: Multi-drug resistant, NF-GNB: Nonfermenting Gram-negative bacilli, ESBL: Extended spectrum beta-lactamases, MRSA: Methicillin-resistant *Staphylococcus aureus*, *A. baumannii*: *Acinetobacter baumannii*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *S. maltophilia*: *Stenotrophomonas maltophilia*, *E. coli*: *Escherichia coli*, *K. pneumonia*: *Klebsiella pneumonia*

acute kidney injury or hematologic diseases as comorbidity. Two factors were included from expert recommendation, and

these were also significant factors associated with mortality, as reported by previous studies,^[7,8] that is, sepsis/septic shock and appropriateness of empirical antibiotic treatment, in the multivariable analysis. The multivariable analysis in this study revealed that the MV dependency, duration of antibiotic treatment for HAP, acute kidney injury, and hematologic diseases were the significant factors associated with 28-day mortality.

In the past, the study of attributable mortality and morbidity in HAP was reported that time from admission to pneumonia, age, prior use of MV, and having neoplastic disease were associated with mortality.^[11] The present study also confirmed that the use of MV in patients with HAP was associated with high mortality. Time from admission to pneumonia or onset of HAP was not statistically significant in this study. The median of onset of HAP in this study was 6 ± 7 days in both groups; however, in a previous study, the median of the interval from admission to the infection period was found to be 10 days.^[11] Most of the patients in this study (63.5% in the nonsurvival group vs. 60.5% in the survival group) had late-onset HAP or HAP occurring in 5 days or more after admission.

Most of the previous studies were carried out in patients with nosocomial pneumonia which included VAP and HAP together. They found that malignancy, inappropriate initial treatment, septic shock, high markers of disease severity,

Table 4: Factors associated with mortality in hospital-acquired pneumonia; univariable logistic regression analysis

Factors	Crude OR	95% CI	P
SAPS II	1.05	1.01-1.08	0.005
MV dependency	3.62	1.73-7.59	0.001
ICU transferred	3.30	1.61-6.76	0.001
<i>A. baumannii</i> (MDR)	3.89	0.63-23.98	0.144
<i>P. aeruginosa</i>	0.43	0.12-1.55	0.198
Acute kidney injury	6.54	1.91-22.33	0.003
Hematologic diseases	8.28	1.614-42.51	0.011
Duration of antibiotic treatment	0.79	0.72-0.88	0.000
Sepsis/septic shock	1.32	0.62-2.83	0.474
Appropriateness of empirical treatment	0.67	0.25-1.77	0.420

AuROC: Area under the Receiver Operating Characteristic curve, SAPS II: Simplified Acute Physiologic Score II, MV: Mechanical ventilation, ICU: Intensive care unit, MDR: Multi-drug resistant, OR: Odds ratio, CI: Confidence interval, *A. baumannii*: *Acinetobacter baumannii*, *P. aeruginosa*: *Pseudomonas aeruginosa*

Table 5: Factors associated with mortality in hospital-acquired pneumonia; multivariable logistic regression analysis

Factors	Adjusted OR	95% CI	P
MV dependency	3.58	1.53-8.37	0.003
Acute kidney injury	5.93	1.29-27.22	0.022
Hematologic disease	11.45	1.61-81.50	0.015
Duration of antibiotic treatment	0.79	0.70-0.88	<0.001

MV: Mechanical ventilation, OR: Odds ratio, CI: Confidence interval

isolation of nonfermenting Gram-negative bacilli, and MV dependency were associated with high mortality.^[4,7,8,10,20,21] In the present study, it was also found that high markers of severity of illness assessed by SAPS II and MV dependency were associated with mortality in univariable analysis. In this study, isolation of *A. baumannii* (MDR) or *P. aeruginosa* from sputum specimens was associated with high mortality, and this is also in agreement with previous studies.^[4,8,10,20] Inappropriateness of empirical treatment has been reported to be a factor associated with high mortality by previous studies;^[2,4,8] however, it was not found to be significant in this study. This may be due to the present study had many poor quality sputum specimens because of the technique of specimen collection and because some of the patients had died before the results of the culture and sensitivity were reported. However, in the subgroup analysis for patients with true sputum versus low quality of sputum, the result was not different. Two comorbidities associated with death in this study were acute kidney injury and hematologic diseases such as anemia and thalassemia. The comorbidities reported in the previous studies were malignancy and shock,^[7,8] as mentioned above. The present study did not find shock to be significantly associated with death. This may be because of the limited number of patients with shock in this present study. There were only 13 patients (25%) and 26 patients (20.2%)

with sepsis or septic shock in the nonsurvival and the survival groups, respectively. The underlying diseases of the HAP patients were not statistically significant factors in the same way as in a previous study.^[4] The significant factors associated with 28-day mortality in the multivariable analysis of the present study were MV dependence, duration of antibiotic treatment, having acute kidney injury, or hematologic diseases as comorbidities. Duration of antibiotic treatment was not reported as a significant factor associated with death in VAP.^[10] However, in this study, it was found that it was a significant factor associated with mortality. This may be because this study had some patients who had discharge against advice in a few days after HAP onset, and they were not excluded from the study, so the duration of antibiotic treatment in the nonsurvival group was shorter. The medians of antibiotic duration were 6 ± 7 days and 10 ± 7 days in the nonsurvival and the survival groups, respectively.

This study had some limitations. First, the study was performed in a single center (a general hospital at secondary care level in Thailand) and had a limited number of HAP samples following the inclusion and exclusion criteria. Immunocompromised patients following CDC definitions^[14] were excluded; also excluded patients with other coinfections of lung, for example, empyema, lung abscess, and pleural effusion. Thus, generalization of the study results should be done with concern. Second, the sputum sampling technique for culture was mostly derived from patients producing cough, so the samples could be contaminated easily and the data on low-quality sputum was highly reported; also, some data of appropriateness of empirical treatment could not be assessed. Third, with the retrospective study design, some data such as cause of discharge against advice, time from doctor's order to first dose of antibiotic administration, and cause of modification of antibiotic treatment were incomplete. Nevertheless, future studies with prospective design in multicenter with larger sample sizes are required.

CONCLUSIONS

It can be stated that early recognition of the factors associated with mortality in immunocompetent patients with HAP and treatment with intensive care may improve outcomes.

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Conflicts of interest

There are no conflicts of interest.

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