Original Article
Early prognostic factors of mortality in patients with severe healthcare-associated pneumonia in the intensive care unit

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Abstract: Introduction: Healthcare-associated pneumonia is a new classification of pneumonia, which is lack of studies to evaluate the predictive factors of mortality on ICU admission. We construct a model and tried to find the factors predicting mortality. Method: This was a retrospective study of prospectively collected data from all consecutive patients with severe HCAP who were admitted to the hospital through the ICU of a university hospital between May 2013 and May 2015. Results: A total number of 145 patients with severe healthcare-associated pneumonia were evaluated. Bivariate analysis of serum biomarkers showed high mortality in patients with low serum albumin and hemoglobin concentrations, as well as in patients with high AST, BUN, SCR. The other prognostic factors related to increased mortality by bivariate analysis included age, gender, respiratory rate, median CURB-65 score, co-morbid of COPD or coronary artery disease and acute heart failure, acute renal failure, and the presence of septic shock on admission. The total ICU mortality was the mortality rate was 33.8% (49 patients). Multivariate analysis of the risk factors generated a new predictive model of mortality applicable within 24 h after ICU admission. Conclusions: CURB severity score 3-5, the underlying disease of COPD or coronary artery disease, and the co-morbids of acute renal failure or the presence of septic shock during the first 24 h of ICU admission were found to be independent predictors of mortality in sever HCAP. Significantly higher AST, BUN and SCR levers, and lower ALB and HGB levels were found in non-survivors. Sever HCAP patients showed an aetiological pattern not far from the typical hospital acquired pneumonia (HAP) microbiology in China.

Keywords: Healthcare-associate pneumonia, ICU, mortality, severe pneumonia

Introduction

A new classification of pneumonia, healthcare-associated pneumonia (HCAP), was introduced by the American Thoracic Society (ATS)/ Infectious Diseases Society of America (IDSA) in 2005 [1]. The definition of HCAP includes hospitalization for two days or more within the preceding 90 days, residence in a nursing home or long-term facility, the use of home infusion therapy (including antibiotics), receipt of chronic dialysis within 30 days, home wound care and a history of infection with a multidrug-resistant pathogen in a family member. Patients with HCAP are characterized by an older age, easy to have an infection with drug-resistant pathogens and increased mortality which is independent of patient demographics and co-morbidities compared to those with community-acquired pneumonia [2-4]. Severe pneumonia remains a serious illness with important clinical impact and most of them require intensive care unit (ICU) admission. Previous studies have demonstrated that the mortality in severe community-acquired pneumonia is independent of patient demographics and co-morbidities during the first 24 h of ICU admission [5, 6]. Considering how common pneumonia is, among intensive care unit (ICU) admissions, there is a surprising lack of studies to evaluate the predictive factors of mortality in severe HCAP requiring ICU treatment. In this work, a cohort of ICU-admitted sever HCAP patients was studied. The main aim was constructing a model of predictive factors of mortality from variables evaluated during the 24 h of ICU admission.

Materials and methods

Patient study subjects

All sever hospital-associated pneumonia patients hospitalized in our ICU were prospectively

Table 1. Aetiology of severe HCAP in all patients

Microbiological aetiology	All patients (N = 145)	Non-survivors (N = 49)	Survivors (N = 96)	p value
Streptococcus pneumoniae	24 (16.6)	11 (22.4)	13 (13.5)	0.172
Pseudomonas aeruginosa	15 (10.3)	3 (6.1)	12 (12.5)	0.233
Staphylococcus aureus	13 (9)	4 (8.2)	9 (9.4)	0.809
Stenotrophomonas maltophilia	6 (4.1)	4 (8.2)	2 (2.1)	0.194
Staphylococcusepidermidis	6 (4.1)	2 (4)	4 (4.2)	0.981
Enterobacter cloacae	5 (3.4)	0 (0)	5 (5.2)	0.252
Klebsiella pneumoniae	4 (2.8)	0 (0)	4 (4.2)	0.361
Acinetobacter baumannii	4 (2.8)	2 (4.1)	2 (2.1)	0.874
Escherichia coli	3 (2.1)	1 (2.1)	2 (2.1)	0.986
Streptococcus hemolyticus	1 (0.7)	0 (0)	1 (1)	1
Fungus	7 (4.8)	2 (4)	5 (5.2)	1
Other microorganisms	15 (10.3)	4 (8.2)	7 (7.3)	0.851
Mixed infection	20 (13.8)	6 (12.2)	14 (14.6)	0.699
Unknown aetiology	72 (49.7)	28 (57.1)	44 (45.8)	0.198

studied from May 2013 to May 2015 in a university and teaching hospital with 3300 bed. Pneumonia was defined as a new infiltrate on the chest roentgenogram and two out of six clinical signs of pneumonia: cough, production of sputum, signs of consolidation on respiratory auscultation, temperature >38°C or <35°C, leukocytosis (white blood cell count (WBC) >10 × 109/l) or leukopenia (WBC <4 × 109/l). Severe pneumonia was defined according to Infectious Diseases Society of America/American Thoracic Society criteria. The diagnosis criteria for HCAP are as follow: hospitalization for 2 days during the previous 90 days, antibiotic use during the previous 90 days, a non-ambulatory status, tube feeding, an immuno-compromised status or the use of gastric acid suppressive agents. The patients were included by a study protocol and the final decision on ICU patient admission was made according to clinical judgment by the physician in charge. The institutional review board and the local ethical committee for clinical research approved the study protocol. The written consent of the patient or the patient's legally authorized representative was obtained before inclusion in the study. Empirical antibiotic treatment was started following the clinical diagnosis and just after obtaining samples for culture.

Data collection

The following parameters were collected at the moment or within the first 24 hours of ICU admission. The following data were recorded upon admission: demographic (classification of pneumonia, age, gender, smoking and alcohol habits), underlying disease, co-morbid illness, vital signs (body temperature, respiratory rate, arterial systolic and diastolic pressure, sphygmus), blood biochemical indexes (blood gas analysis, blood routine, liver function, renal function, blood glucose, serum electrolyte level, CRP, BNP, PCT, D-dimer), CURB-65 scores. During the clinical process the following variables were collected: results of microbial investigation, need for mechanical ventilation and noninvasive ventilation, radiographic progression, systemic steroid treatment and length of ICU stay. Both hospital and ICU mortality were recorded.

Microbiological evaluation

Blood cultures and bronchoalveolar lavage (BAL) or non-bronchoscopic lavage (NBL) or sputum cultures obtained within 48 h of ICU admission from the emergency department were included. The threshold of quantitative cultures for BAL and NBL was 104 cfu/ml. Sputum was stained for Gram and only cultured with the presence of more than 25 granulocytes and less than 10 epithelial cells. PSB and BAL fluid samples were cultured for aerobic and anaerobic bacteria pathogens, mycobacteria and fungi. Negative bacterial cultures were discarded after 7 days. All microorganisms isolated were identified by standard laboratory methods.

Statistical analysis

Descriptive statistics of demographic and clinical variables included means and standard deviations for quantitative variables, and percentages for qualitative variables. For unadjusted comparisons between or among groups, continuous variables were compared by using Student's t test, if data are normally distribut-

Table 2. Bivariate analysis for risk factors of ICU mortality in patients with severe HCAP

Varables	Non-survivors (N = 49)	Survivors (N = 96)	Odds ratio or mean difference (95% CI)	p value
Demographic, n (%) or mean (SD)				
SCAP	20 (40.8)	51 (53.1)	1.643 (0.819, 3.298)	0.161
Age, years	71.8+16.14	65.2+17.19	6.689 (0.672, 12.75)	0.03
Male sex	38 (77.6)	55 (57.3)	2.575 (1.091, 4.485)	0.016
Cigarette smoking	22 (44.9)	36 (37.5)	0.736 (0.366, 1.480)	0.390
Alcohol consumption	20 (40.8)	30 (31.3)	0.695 (0.323, 1.347)	0.252
Vital signs, mean (SD)				
Respiratory rate	27.1+6.0	24.2+5.9	2.822 (0.770, 4.873)	0.007
Systolic pressure	118.2+21.7	126.0+25.1	-7.837 (-16.177, 0.503)	0.065
Diastolic pressure	67.7+13.1	72.4+16.4	-4.63 (-10.034, 0.774)	0.093
Sphygmus	100.67+27.6	93.36+19.0	7.309 (-0.413, 15.030)	0.091
Body temperature	36.8+1.0	37.1+1.8	-0.211 (-0.7617, 0.3408)	0.233
Coma, n (%)	21 (32.7)	16	1.984 (0.932, 4.225)	0.073
Underlying disease				
COPD	28 (57.1)	26 (27.1)	0.279 (0.135, 0.574)	0.000
Hypertension	29 (59.2)	44 (45.8)	0.749 (0.375, 1.492)	0.410
Diabetes	14 (28.6)	23 (24.0)	0.788 (0.362, 1.731)	0.547
Coronary artery disease	16 (32.7)	15 (15.6)	0.382 (0.170, 0.861)	0.018
Chronic renal disease	5 (10.2)	13 (13.5)	1.378 (0.461, 4.117)	0.564
Chronic liver disease	1 (2)	5 (5)	2.637 (0.300, 23.222)	0.642
Serebral stroke	14 (28.6)	13 (13.5)	0.392 (0.167, 0.918)	0.028
Cancer	11 (22.4)	21 (21.9)	0.967 (0.423, 2.212)	0.937
Immunosuppression	3 (6)	14 (14.6)	2.618 (0.715, 9.588)	0.134
Clinic data, n (%)				
Invasive ventilation	24 (49)	34 (35.4)	0.571 (0.284, 1.149)	0.115
Bilateral pulmonary involvement	5 (10.2)	13 (13.5)	1.378 (0.461, 4.117)	0.564
Multilobar pulmonary involvement	31 (63.3)	59 (61.5)	0.926 (0.455, 1.886)	0.832
Hydrothorax	19 (38.8)	43 (44.8)	1.281 (0.635, 2.583)	0.489
Systemic steroid treatment	18 (36.7)	38 (39.6)	1.128 (0.555, 2.296)	0.739
Co-morbids				
Acute respiratory failure	36 (73.5)	55 (57.3)	0.484 (0.228, 1.028)	0.057
Acute heart failure	31 (63.3)	33 (34.4)	0.304 (0.148, 0.623)	0.001
Acute renal failure	34 (69.4)	36 (37.5)	0.265 (0.127, 0.552)	0.000
Acute liver failure	14 (28.6)	18 (18.8)	0.577 (0.258, 1.289)	0.177
Septic shock	25 (51)	14 (14.6)	0.164 (0.074, 0.364)	0.000
Outcome				
CURB-65 score, median (range)	3 (1-5)	2 (1-4)	0.148 (0.068, 0.322)	0.000
Length of hospital stay, day, mean (SD)	13.3+10.35	21.3+9.17	-7.714 (-11.002, -4.426)	0.000
Length of ICU stay, day, mean (SD)	12.3+9.26	15.2+6.78	-2.84 (-5.511, -0.169)	0.037

ed, or Mann-Whitney *U* test for non-normally distributed data. Categorical variables were compared by using the chi-square test or Fisher's exact test where appropriate. The list of blood biomarker candidate predictors was narrowed to include those with a bivariate sig-

nificance at *P*<0.05 level. Receiver operating characteristic (ROC) curves were generated to compare the overall predictive accuracy of bio-markers for mortality, and the area under the ROC curves (aROC) was calculated. Multivariate logistic regression analysis was performed,

Table 3. Model of logistic regression analysis of early risk factors for mortality in patients with severe HCAP

Variables[1]	B	Odds ratio	95% CI	p value
COPD	-1.670	0.188	0.071-0.502	0.001
Coronary artery disease	-1.623	0.197	0.060-0.648	0.008
Acute renal failure	-1.357	0.257	0.094-0.706	0.008
Septic shock	-1.754	0.173	0.064-0.471	0.001
CURB65 score 3-5	-1.317	0.268	0.103-0.695	0.007

[1]Models were adjusted for age, gender, respiratory rate, median CURB-65 score, co-morbid of COPD or coronary artery disease and acute heart failure, acute renal failure, the presence of septic shock and CURB65 score 3-5 on admission; Dependent variable was mortality in patients with severe HCAP.

incorporating all factors that obtained p-values of <0.05 in the univariate analyses. Results of the analysis are presented as p-values, odds ratios (OR), and 95% confidence intervals (CI). Statistical significance was set at P<0.05. Statistical analyses were performed using SPSS17.0.

Results

Baseline features

During the period from 2013 to 2015, a total of 145 patients with severe HCAP were prospectively collected. The mean (SD) age of the patients was 71.8+16.14 years; 93 (63.3%) were males and 52 (36.7%) were females. Considering underlying disease, 54 patients (37.2%) had previous COPD diagnosis, 73 patients (50.3%) had hypertension, and 37 patients (25.5%) had diabetes mellitus, 18 patients (12.4) had chronic renal disease, 27 patients (18.6%) had cerebral stroke, 33 patients (22.8%) had a kind of cancer, 17 patients (11.7%) had some immunosuppression (steroid therapy, chemotherapy for malignant diseases, disease-modifying anti-rheumatic drug therapy, anti-cytokine therapy) and only 6 patients (4%) had chronic liver disease. Upon ICU admission, patient severity median (range) by CURB65 was 2 (1-5). During the first 24 h, 101 patients (69.7%) showed some level of respiratory failure that required ventilation support, and 90 patients (62.1%) displayed involvement of multiplelobes and radiographic progression. Average ICU stay was 14.2±7.79 days, and the ICU mortality rate was 33.8%. Average hospital stay was 18.4±10.12 days, and the hospital mortality rate was 37.2%.

Microbiological severe pneumonia aetiology

Microbiological aetiology could be determined in 73 out of 145 (50.3%) patients. The most frequent pathogen was *streptococcus pneumoniae* (16.6% of all patients). The second and third most common pathogens were *pseudomonas aeruginosa* and *staphylococcus aureus*. *Acinetobacter baumannii* was also isolated in 4 patients (2.8%), 4.8% (7 patients) were found by fungus and 13.8% (20 patients) were isolated with two or more kinds of pathogen. No difference in microbiological aetiology was found between survivor and non-survivor patients. See **Table 1**.

Risk factors of ICU mortality

A comparison between survivors and non-survivors in the ICU (survivors n = 96, non-survivors n = 49) is shown in **Table 2**. The mean age, gender, respiratory rate, median CURB-65 score, co-morbid of COPD or coronary artery disease and acute heart failure, acute renal failure, and the presence of septic shock on admission were significantly different between the two groups by univariate analysis for in ICU mortality. There were no significant differences between the two groups regarding sex, cigarette smoking, alcohol consumption, blood pressure, consciousness, body temperature, underlying disease (hypertension, diabetes, chronic renal disease, chronic liver disease, cancer, immunosuppression), clinic data (invasive ventilation, the existence of bilateral and multilobar pulmonary involvement on chest roentgenogram pulmonary involvement, hydrothorax, systemic steroid treatment), co-morbids (acute liver failure) on admission.

Multivariate logistic regression analysis revealed that CURB65 score 3-5 (OR 1.955, 95% CI 1.330-2.875) were independent risk factors for a higher in ICU mortality. The underlying disease of COPD or coronary artery disease, and the co-morbids of acute renal failure or the presence of septic shock appeared to increase mortality inside the ICU (**Table 3**).

Biomarkers

The biomarkers of ALB, HGB, AST, BUN, SCR were significantly different between two groups

Table 4. Biomarkers' discrimination power for ICU mortality (univariate analysis) for patients with severe HCAP

Biomarkers	Non-survivors (N = 49), median (IQR)	Survivors (N = 96), median (IQR)	p value	AUC	Sensitivity	Specificity	Cutoff value	95% CI
ALB (g/L)	27.6 (24.5, 30.7)	31.6 (27.2, 37.1)	0.000	0.70	87.7	47.9	31.8	0.625-0.779
HGB (g/L)	103 (81, 122.5)	111 (99, 123.5)	0.040	0.60	36.7	86.4	90.9	0.523-0.687
AST (U/L)	37 (25.5, 64.5)	26 (19, 41.5)	0.005	0.63	71.4	53.1	28.0	0.550-0.712
BUN (umol/L)	13.2 (7.78, 20.8)	7.2 (4.93, 10.9)	0.000	0.73	51.0	90.6	13.1	0.623-0.803
SCR (umol/L)	101.3 (72.65, 223.6)	76.4 (55.2, 111.6)	0.002	0.66	42.8	86.4	123.9	0.573-0.733

in univariate analysis. Non-survivors had significantly lower levels of median HGB (103 [IQR, 81-122.5] g/L vs 111 [IQR, 99-123.5] g/L; P = 0.0040), ALB (27.6 [IQR, 24.5-30.7] g/L vs 31.6 [IQR, 27.2-37.1] g/L; P<0.001), Non-survivors had significantly higher levels of median BUN (13.2 [IQR, 2.78-20.78] umol/L vs 7.2 [IQR, 4.9-10.9] umol/L; P<0.001), AST (37 [IQR, 25.5-64.5] U/L vs 26 [IQR, 19-41.5] U/L; P = 0.005), SCR (101.3 [IQR, 72.7-223.6] umol/L vs 76.4 [IQR, 55.2-111.6] umol/L; P = 0.002) than survivors. We also compared other blood biochemical indexes in both group, such as blood gas analysis, blood routine, liver function, renal function, blood glucose, serum electrolyte level, CRP, BNP, PCT, D-dimer and no significant differences were observed. To assess the overall discriminatory ability of these biomarkers, ROC curves were calculated (**Table 4**). BUN was the best marker of mortality with a good discriminatory power (AUC, 0.73; 95% CI, 0.623-0.803; P<0.001). At the best diagnostic cutoff point of 13.1 umol/L, BUN showed a sensitivity of 51%, a specificity of 90.6%. AST, SCR and HGB presented moderate discrimination ability for mortality in patients with severe HAP, with an aROC of approximately 0.60. ALB presented a higher discrimination ability (AUC = 0.70), while the Specificity was very low (Specificity = 47.9).

Discussion

In our work, we constructed a model of predictive factors of mortality from variables evaluated during the 24 h of ICU admission. In bivariate analysis, elderly male patients with a high CURB-65 score, or high respiratory rate, or with COPD or coronary artery disease, or having acute heart failure, acute renal failure, or the presence of septic shock on admission showed the highest mortality risk. These results agree with those reported elsewhere to some degree

in patients with CAP [5, 7, 8]. However, according to multiple logistic regression analysis, the length of ICU stay, CURB65 score 3-5, the underlying disease of COPD or coronary artery disease, and the co-morbids of acute renal failure or the presence of septic shock were independent risk factors for a higher in ICU mortality. Several previous studies on COPD patients found that community-acquired pneumonia was associated with admission to the intensive care unit and higher mortality [8, 9]. A recent study in COPD patients with pneumonia found that prior cardiovascular disease was independently associated with mortality when compared to no prior cardiovascular disease [10]. Acute coronary syndromes, heart failure and stroke are associated with higher rates of short-term and long-term mortality among CAP patients [11-13]. Outcome of our patients also tended to be poor. In the previous study, patients with more severe CAP requiring hospitalization had a higher incidence of acute cardiac event, which increased their overall morbidity, mortality, duration of stay in the hospital [7]. In our present study, acute heart failure shows no significance in multiple logistic regression analysis but a higher mortality risk in bivariate analysis. Previous studies showed that community-acquired pneumonia with shock, acute renal failure and APACHE II score were independently associated with mortality in the assessment of ICU admission [14, 15]. In our study, we use CURB65 to assess the severity of HCAP, and we found CURB65 score 3-5 may have a higher mortality during the first 24 h of ICU admission, however, clearly interact in the statistical model with septic shock and acute renal failure but would be used quickly in first instance in the emergency department as a parameter to predict mortality in these patients. This early assessment allows the intensivist to start appropriate antibiotic treatment and use fast support techniques, like, for

example or early renal replacement therapy [14, 16].

A strength of the study is the high percentage of microbiological confirmation in healthcare-associated pneumonia on admission. The HCAP aetiology was elucidated in a higher percentage of our patients, possibly could be that microbiological samples were taken for all patients early on admission to the ICU. We followed a strict protocol for collecting respiratory specimens as described in 'Materials and methods' section. The main etiologic micro-organism was *Streptococcus pneumonia*, similar to previous studies in other countries [17]. *Pseudomonas aeruginosa and Staphylococcus aureus are also the common* pathogens which provides meaningful information for clinicians-patients with severe HCAP admitted into ICU should always consider drug resistant pathogens and empirical regimens should cover resistant pathogens. We also found some multidrug-resistant bacteria such as acinetobacter baumannii, which is the most common pathogens in patients with HAP and it independently associated with higher mortality rates in nosocomial pneumonia [18]. Concerning aetiology, however, no differences were observed in micro-organisms between survivors and non-survivors patients. Predictive rules thought to accurately identify HCAP patients who are likely to have or not have drug-resistant pathogens should be developed. Further analyses of the subgroups of HCAP may be necessary for this purpose. Finally, the microbiological investigation demonstrated that due to the abuse of antibiotics before the sever pneumonia episode, a known risk factor for MDR infection, sever HCAP patients showed the pathogens recovered more closely resembling those seen in the typical HAP microbiology.

With regard to serum biomarkers predicting ICU mortality, we found that higher serum levels of BUN, AST and SCR and lower serum album and HGB concentrations in Non-survivors. We found no significant differences between survivors and non-survivors in biomarkers of CRP, which is different from other studies [19, 20]. However, several studies have shown that serum C-reactive protein levels on admission have little predictive value for mortality, which is consistent with our study [21, 22]. Some previous report demonstrated that lower serum albumin concentrations could have been caused by on-going inflammation, poor health status, and malnutrition; these factors have also been shown to be associated with low muscle mass or accelerated muscle loss [23, 24]. Low levels of protein and albumin was a important prognostic factors in patients with pneumonia [25]. The biomarkers study suggests that clinicians should be cautious about the potential adverse outcomes in severe HCAP patients with initial level more than 13.1 mM and a presentation of malnutrition. A earlier continuous renal replacement therapy (CRRT) or supplementation of albumin or plasma may contribute to decrease mortality in patients with severe pneumonia.

Our conclusions are hereby presented, yet they have some limitations. First, this is a large observational study on a severe HCAP patients cohort treated in one only centre. Therefore, a second study is needed to validate our multi-variate model within the 24 h of ICU admission. Second, although a strict protocol and robust statistical analysis were followed in the present study, results come from our hospital and, therefore, our model may need external validation. Furthermore, these concerns are valid risk factors for sever HCAP caused by bacteria and fungus, but not for sever HCAP caused by the virus such as influenza A/H1N1 that has a different clinical profile.

Conclusions

In this study, CURB 3-5 score, COPD, coronary artery disease, septic shock, and acute renal failure during the first 24 h of ICU admission, were independent predictive factors of mortality in SCAP patients. No factors described are probably amenable to medical intervention, but may help to identify, upon admission, subjects at higher risk. Significantly higher AST, BUN and SCR levers, and lower ALB and HGB levels were found in non-survivors. Sever HCAP patients showed an aetiological pattern not far from the typical hospital acquired pneumonia (HAP) microbiology in China.

Disclosure of conflict of interest

None.

Authors' contribution

Lianjiu Su (now working at Wuhan PuAi Hospital) analyzed the data and prepared the manuscript

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