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## Original Article

### **Community Acquired Pneumonia: Risk factors associated with mortality in a tertiary care hospitalized patients**

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#### **Abstract**

**Objective:** To evaluate risk factors associated with mortality in patients hospitalized with Community Acquired Pneumonia (CAP) from a developing country.

**Methods:** An observational study was conducted on adult patients admitted with a diagnosis of CAP from January 2002 to August 2003 at Aga Khan University hospital, Karachi, Pakistan. Clinical records were reviewed for demographic characteristics, clinical and laboratory features, hospital course, and risk factors associated with mortality.

**Results:** A total of 329 patients (187 males) were admitted with CAP. Two-third of patients had underlying co-morbid medical illnesses. Complications developed in 15.7% cases and the overall mortality rate was 11%. Risk factors were identified on initial clinical assessment, laboratory and radiological features and during hospital course. On admission elevated blood urea, new onset of confusion, abnormal liver function test, low serum albumin, cardiomegaly and presence of underlying malignancy were strongly associated with increased mortality. Failure to respond to therapy was associated with a high risk of mortality as depicted by complication during hospital stay (Odds Ratio= 23.3, 95% Confidence Interval= 10.3-52.8), need for mechanical ventilation (OR= 17.1, 95%CI= 7.4-39.8) and need for intensive care unit (OR= 9, 95%CI= 4.2-19.3).

**Conclusions:** Abnormal liver function test, low albumin and presence of cardiomegaly were more significant mortality risk factors than age, respiratory rate and blood pressure. Elevated blood urea and confusion remain strong risk factors on admission. Failure of response to therapy and onset of complications heralded a high risk of death (JPMA 59:448; 2009).

## Introduction

Community acquired pneumonia (CAP) is one of the leading causes of infectious death in both developed and developing countries. It is associated with a significant morbidity and mortality. In a meta-analysis of studies of prognosis, the short-term mortality in CAP ranged from 5.1% for patients treated in an ambulatory or hospital setting to 36.5% for patients treated in an intensive care unit.<sup>1</sup> Following introduction of antibiotic therapy in the 1940's the mortality rate from pneumonia decreased sharply but then the overall mortality rate has either remained stable or increased.<sup>2</sup>

Despite the high incidence of infectious diseases in developing countries, there has been little research in defining risk factors associated with mortality in adult patients with CAP. Most of the studies on respiratory tract infections have been done in the paediatric age group and cannot be used for predicting outcome in the adult population.<sup>3</sup> CURB-65 score and Pneumonia severity index (PSI) are the two widely used severity assessment tools for CAP<sup>4,5</sup> but the recommendations may not be universally applicable. The aim of this study was to define clinical characteristics, hospital course and risk factors associated with mortality in hospitalized patients with CAP being treated in a developing country.

## Patients and Methods

The study was conducted at Aga Khan University Hospital, a 450-bedded tertiary care hospital in Karachi, Pakistan. In this observational study, data was collected on adult patients (aged 16 or above) admitted between January 2002 and August 2003 with a diagnosis of CAP. Patients were identified using a computerized database of the hospital where all diseases are coded using International Classification of Diseases, 9th Revision with Clinical Modification (ICD 9CM).

The inclusion criteria for the diagnosis of CAP used were:<sup>6</sup> age 16 Years and above, acute presentation with at least one major criteria (temperature > 38°C, cough or expectoration) or at least two minor criteria (pleuritic chest pain, dyspnea, leukocytosis i.e. white cell count >12,000/mL, altered mental status, or signs of lung consolidation by clinical examination). A new infiltrate observed on Chest Radiograph (CXR).

The exclusion criteria were: patients with clinical or radiological feature strongly indicative of tuberculosis, patients transferred from another hospital, patients developing pneumonia after being hospitalized within the last 2 week for other reason and post-obstructive pneumonia.

A pre-designed structured format was used to gather data on demographic features, clinical features, co-morbid

conditions, laboratory investigations, treatment, complications and outcome.

The primary outcome measure was risk factors associated with mortality in patients with CAP.

The Statistical package for social science SPSS (Release 11.0.5, standard version, copyright© SPSS) was used for data analysis. The descriptive analysis was done for demographic, clinical and laboratory data. Results were expressed as mean  $\pm$  standard deviation, and numbers (percentages). Findings potentially related with death were studied by a univariate approach using independent sample t-test, Pearson chi-square and Fisher's exact test wherever appropriate. Thereafter, a stepwise forward multiple logistic regression model was applied to the variables found to be significantly associated with death ( $p > 0.05$  was considered as statistically significant comparing survivors vs nonsurvivors. All p-values were two sided.) Multiple regressions permitted an estimate of the odds ratio of dying and a calculation of the 95% confidence interval. Patients who were transferred to another hospital were excluded from this analysis to make the outcome variable dichotomous (discharged alive vs. expired).

## Results

During the study period 712 patients were admitted with a principal diagnosis of pneumonia, but 383 were excluded (156 had aspiration pneumonia, 78 nosocomial pneumonia, 143 were transferred from another hospital and 6 failed to show a new infiltrate on CXR). Data on 329 cases, 187 (56.8%) males and 142 (43.2%) females, were analyzed in the final study group.

The mean age of the study group was  $62 \pm 16.3$  years (range: 18 to 92 years). History of tobacco smoking was given by 24.3% and alcohol use by 2.4% patients. Co-morbid medical conditions were present in 63.5% patients (Table 1).

Most patients presented within a week of onset of symptoms. The common presenting symptoms were fever (77.5%), chills (77%), and cough (72%). Other symptoms were dyspnoea (46%), chest pain (23%) and confusion (14%). Confusion was significantly more common in patients aged 65 years ( $p < 0.05$ ). On examination, lung crackles were present in 73% and bronchial breathing in 18%. Respiratory examination was normal in 34 (10.3%) patients.

Radiographic features revealed lower zones were affected more frequently than upper zones and bilateral involvement was seen in 24% of cases. Radiographic changes included consolidation (36.2%), patchy infiltrates (48.2%), pleural effusion (23.8%) and atelectasis (7.1%).

## Microbiological Specimen:

One or more microbiological specimen was sent in

**Table 1: Co-morbid medical conditions in hospitalized patients with community acquired pneumonia (n=329).**

	Frequency	Percent
<b>Cardiovascular diseases</b>	<b>150</b>	<b>45.60%</b>
Ischaemic heart disease	31	
Cardiac failure	2	
Hypertension	117	
<b>Pulmonary diseases</b>	<b>99</b>	<b>30.10%</b>
Asthma	27	
Chronic obstructive pulmonary disease	32	
Post-tuberculosis	23	
Pulmonary Fibrosis	7	
Bronchiectasis	7	
Lung Cancer	3	
<b>Diabetes Mellitus</b>	<b>98</b>	<b>29.80%</b>
<b>Neurological disease</b>	<b>31</b>	<b>9.40%</b>
<b>Malignant Neoplasm</b>	<b>24</b>	<b>7.30%</b>
<b>Chronic Renal Failure</b>	<b>17</b>	<b>5.20%</b>
<b>Chronic Liver Disease</b>	<b>12</b>	<b>3.60%</b>
<b>On corticosteroids</b>	<b>8</b>	<b>2.40%</b>

278 (84.5%) patients. These included blood cultures in 241 (86.7%), sputum in 133 (47.84%), pleural fluid in 23 (8.27%) and tracheal or bronchial aspirate in 25 (9%) patients. In about 104 cases (37.4%) both sputum and blood samples were sent. The yield from various samples included sputum 30.8% (42/133), blood culture 19.5% (47/241), pleural fluid 13.0% (3/23) and tracheal/ bronchial aspirate 60% (12/25).

Streptococcus pneumonia was the commonest organism identified in 23 (8.3%). Gram-negative organisms included pseudomonas in 11 (4%), Acinetobacter in 7 (2.5%), E. coli in 5 (1.8%) and Klebsiella pneumonia in 4 (1.4%) cases. Other common organisms were staphylococcus aureus

**Table 2: Risk factors associated with mortality in hospitalized patients with community acquired pneumonia (n=319).**

Risk Factor	Odds Ratio	95% Confidenc Interval
Initial clinic assessment		
Age (>65 years)	2.2	1.1-4.5
Underlying malignancy	3.8	1.3-11.1
Dyspnoea	2.4	1.2-4.5
Confusion	4	1.8-8.9
Respiratory Rate $\geq$ 28/min	2.2	1.1-4.4
O2 saturation <90%	2.9	1.3-6.4
Laboratory features		
Blood urea nitrogen >20 mg/dl	8.6	3.2-23.1
Abnormal liver function test	4	1.5-10.6
Serum Albumin <2.2 gm/dL	3.3	1.2-9.0
Infection with gram negative organisms	2.9	1.2-7.4
Radiological features		
Bilateral Involvement	2.7	1.3-5.7
Cardiomegaly	3.9	1.3-12.1
Hospital Course		
Complication during hospital stay	23.3	10.3-52.8
Intensive care unit stay required	9	4.2-19.3
Ventilatory support Required	17.1	7.4-39.8

in 7 (2.5%), hemophilus influenza in 5 (1.8%) and moraxella catarhalis in 3 (1.1%). No organism could be isolated in 186 cases (66.91%).

### Complications:

Complications during their hospital stay developed in 55 (16.7%) cases. These included parapneumonic effusion in 22 (6.7%), multiple system organ failure in 19 (5.8%), respiratory failure in 18 (5.5%), septic shock in 17 (5.2%), adult respiratory distress syndrome in 9 (2.7%), empyema in 6 (1.8%), and nosocomial infections in 3 (1%) cases. Mechanical ventilation was required in 31 (9.4%) of cases, of these 15 (48.3%) died.

The overall mortality was 36 (11%), 283 patients were discharged (86%) and 10 (3%) patients were transferred to another hospital.

Using univariate analysis multiple risk factors were identified at the time of admission and during hospital course. Independent risk factors associated with mortality in logistic regression analysis are presented in Table-2. These have been grouped together so that risk assessment can be performed at the initial clinical assessment, as laboratory results become available and during course of hospital stay.

### Discussion

Our study has defined the risk factors associated with mortality in patients hospitalized with community acquired pneumonia in a developing country. British Thoracic Society (BTS) recommends CURB-65 score to evaluate severity of CAP (Table-3). Patients with low score (0-2) are likely to be

**Table 3: CURB 65 score to evaluate severity of community acquired pneumonia.**

Score 1 point for each feature present.
◆ Confusion (of new onset)
◆ Urea >42 mg/dl
◆ Respiratory rate $\geq$ 30/min
◆ Blood pressure (SBP <90mmHg or DBP $\leq$ 60mmHg)
◆ Age $\geq$ 65 years

suitable for home treatment, as the expected mortality is low. Higher scores (3-5) are associated with increasing mortality and admission to hospital is recommended.<sup>7</sup> Patients should be assessed for intensive care unit if the score is 4 or 5. Our study confirmed that on initial assessment confusion, elevated urea, elevated respiratory rate and age >65 years were significant risk factors but blood pressure was not an independent risk factor for mortality. In a similar study from a Malaysian university hospital, BTS severity assessment criteria for CAP fared poorly in their patients.<sup>8</sup>

Pneumonia severity index (PSI) is a more detailed assessment tool that takes into account age, co-morbid

conditions, physical signs, laboratory and radiological findings. It is more complex but has been validated on over 50,000 patients.<sup>5</sup> Both of these validated tools (PSI and CURB-65) are from developed countries. They are good for predicting mortality<sup>9</sup> only. Our study and Malaysian study highlights that due to differences in patient population such as the nutritional status and other co-morbid conditions, severity criteria validated in western countries may not be universally applicable.

Our rationale for evaluating serum albumin was to correlate the nutritional status of patients with mortality from CAP. In this study, low serum albumin <2.2 g/l was found to be significantly associated with mortality. Abnormal liver function test was also associated with increased mortality. Low albumin level may relate to high prevalence of chronic ill health secondary to undiagnosed chronic liver disease or other diseases. Risk association of low albumin and/or abnormal liver function is in keeping with the finding of other smaller studies where patients with a low albumin or raised ALT were significantly more likely to die from their disease or had prolonged hospital stay.<sup>10,11</sup> We recommend liver function and serum albumin to be checked routinely during severity assessment of patients hospitalized with CAP in developing countries.

Bedside evaluation of history and physical signs supplemented by a chest radiograph would remain the cornerstone of initial clinical assessment at most treatment facilities in resource-limited countries. In our study, dyspnea and bilateral lung involvement on presentation were associated with a higher mortality. Additionally features of old age, confusion, underlying malignancy, rapid respiratory rate and low oxygen saturation should alert the physician for a more intensive management strategy. Medical centers admitting patients with CAP should have facility to monitor blood oxygen saturation using a pulse oximeter as oxygen saturation <90 % is associated with a worse prognosis.<sup>12,13</sup>

Knowledge about the causative organisms and their drug sensitivity pattern has important bearing on the course of the disease. *Streptococcus pneumoniae* was the organism most commonly identified in our study as has been in other studies worldwide.<sup>14,15</sup> Additionally, presence of gram-negative organisms was associated with a higher mortality. Other studies, have also shown that Gram-negative organisms are associated with a higher mortality.<sup>15,16</sup> The initial selection of antibiotics should take account of local factors that indicate risk of drug resistance or likelihood of gram-negative infection.<sup>17</sup>

In clinical practice culture results are not available before 48 hours and therefore the initial treatment has to be empiric. A sound analysis of patient factors and initial

assessment of CAP severity would help physicians to choose an appropriate antibiotic regimen. The yield of respiratory secretions was high but this should be interpreted with caution. Yield from blood culture was lower but a positive blood culture represents bacteraemia and has been shown to be an independent risk factor for mortality.<sup>14</sup> In many resource limited countries facilities for reliable blood culture are sparse and physicians would have to rely on other parameters of treatment response. Atypical pathogens (e.g. *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*) may account for up to 40% of cases of CAP and co-infection may occur in 16% cases.<sup>18</sup> We did not have facilities for serological testing at the time of the study.

In one study on 260 patients, 80 (31%) had early clinical failure in response to therapy assessed at day 3.<sup>19</sup> Failure to respond was defined as death, a need for mechanical ventilation, respiratory rate >25/min, PaO<sub>2</sub> <55 mm Hg, oxygen saturation <90%, haemodynamic instability, temperature >38°C or confusion. Patients who failed to respond had a higher 28-day mortality rate and a longer hospital stay. In our study, failure to respond to therapy and development of complications was associated with increased mortality.

The overall mortality in our study population was 11% and was comparable to that reported in previous studies.<sup>1,15</sup> In a large outcome meta-analysis, the overall mortality rate in patients with CAP was 13.7%.<sup>1</sup> In a study of pneumonia related death within 90 days of presentation, the overall mortality was 9%. Of these 53% deaths were assessed to be pneumonia related and the remaining pneumonia unrelated.<sup>12</sup> Factors independently associated with pneumonia-related mortality included hypothermia, altered mental state, increased serum urea nitrogen levels, chronic liver disease, leucopenia, and hypoxaemia. Increasing age and evidence of aspiration were independent predictors of both types of mortality.<sup>12</sup>

The main weakness of this study is its retrospective design. Collection of some data was therefore, incomplete. Other limitations are the higher frequency of elderly patients; this may not reflect the reality of CAP in our population; relatively low percentage of positive bacterial culture and failure to perform serological tests for atypical organisms.

In summary risk factors associated with mortality in CAP can be identified at the initial assessment and continue to evolve during hospital course. Greatest risks are associated with development of complications and need for mechanical ventilation. This study defines the tools for risk assessment in a developing country through focused clinical evaluation and basic investigations. Onset of complications represents failure of response to therapy and poor prognosis.

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