Mortality predictors in patients with severe community-acquired pneumonia requiring ICU admission

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Background Community-acquired pneumonia (CAP) is a major cause of mortality. This prospective study was conducted to describe patient's characteristics, mortality rate, and etiological pathogens in patients with severe CAP who required ICU admission and to determine the predictors of mortality.

Patients and methods This was a multicenter prospective observational study of 57 consecutive patients who were admitted to the ICU with diagnosis of severe CAP from October 2012 to August 2015.

Results Overall 57 patients were included in the study and the overall ICU mortality rate was 49.1%. Heart disease and chronic obstructive pulmonary disease were the most common comorbidities associated with severe CAP. Comparison between survivors and nonsurvivors revealed that mortality was associated with old age (P=0.01), low diastolic blood pressure (P=0.04), low PaO₂/FiO₂ (P=0.04), high acute physiology and chronic health evaluation II (APACHE II) score (P=0.001), (CURB-65) score (P=0.005), low hemoglobin (P=0.008), and high urea (P=0.04). The univariate analysis demonstrated that the following were the predictors of mortality: age older than 65 years (P=0.03); APACHE II score greater than 20 (P=0.007); CURB-65 of 3 or greater (0.03); total leukocyte count less than 4 or greater than $11\times10^9/(P=0.04)$; PaO₂/FiO₂ less than 250 (P=0.03); serum urea greater than 30 mg/dl (P=0.04); presence of septic shock (P=0.003); mechanical ventilation requirement (P=0.02); and bilateral or multilobar infiltrate on chest radiograph (P=0.03). Multiple regression analysis identified

high APACHE II score (>20) and septic shock as significant independent predictors of mortality in severe CAP. Microbiological identification was obtained in 52.6% of cases, with positive blood culture in 17.5%. The most frequently isolated pathogens were Streptococcus pneumonia (S. pneumonia) (19.3%) and Staphylococcus aureus (S. aureus) (15.8%).

Conclusion Mortality rate in patients with severe CAP was high as reported by most of the other studies. The presence of septic shock and high APACHE II were independent predictors of mortality. Heart disease and chronic obstructive pulmonary disease were the most common comorbidities. Microbiological identification was obtained in 52.6% of cases, and S. pneumonia and S. aureus were the most frequently isolated pathogens.

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Introduction

Community-acquired pneumonia (CAP) is a common, serious, and potentially life-threatening infection worldwide. Severe CAP is usually defined as pneumonia that requires ICU admission [1,2].

Although 2–20% of CAP patients require ICU admission [3,4], the mortality rates can be as high as 20-50% [5].

Patients with severe CAP commonly comorbidities and impaired host defenses, and invasive procedures are frequently applied [6].

The knowledge of pathogen patterns causing severe CAP (as a basis for the selection of antibiotic treatment) is crucial. The reported rates for polymicrobial etiology differ considerably between 5.7 and 38.4% [7,8].

Many studies have investigated CAP comorbidities and prognostic factors [9,10], and guidelines have been proposed by several medical societies to define the optimal management of patients with CAP [11].

This prospective study was conducted to assess clinical characteristics, etiology, outcomes, and predictors of mortality for severe CAP patients admitted to the ICU and to compare our results with those from other studies.

Patients and methods

The present study was conducted in three ICUs in Minia University Hospital (general ICU, respiratory ICU, and the ICU of Internal Medicine Department) from October 2012 to September 2015. The study included

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57 consecutive patients admitted to the ICU for severe CAP and for whom all laboratory investigations had been carried out. The study design was approved by the Ethics in Research Committee of the Institution.

CAP was defined as symptoms of an acute lower respiratory tract illness (cough and at least one other lower respiratory tract symptom - e.g. dyspnea or chest with evidence of systemic (temperature>38°C and/or the symptom of sweating, fevers, shivers, aches) and demonstrable consolidation or new radiographic shadowing on chest radiography for which there was no other explanation [1].

Admission to ICU as a result of severe CAP were indicated when at least one major criterion or three minor criteria of the Infectious Disease Society of America/American Thoracic Society guidelines were fulfilled [1]. The major criteria are (a) a need for mechanical ventilation (MV) and (b) the presence of septic shock. The nine minor criteria are a respiratory rate of 30 or greater breaths per min, ratio of arterial oxygen tension to inspired oxygen fraction of 250 or less, multilobar infiltrates, confusion and/or disorientation, uremia (blood urea nitrogen level \geq 20 mg/dl), leukopenia (white blood cell count<4000 cells/mm³), thrombocytopenia (platelet count<100 000 cell/mm³), (core temperature < 36°C), hypothermia hypotension requiring aggressive fluid resuscitation.

Septic shock was defined as severe sepsis and sustained hypotension with a systolic blood pressure less than 90 mmHg despite intravenous fluids or the need for vasopressors [11].

Data collection

The following variables were recorded.

- (1) Age and sex.
- (2) History of risk factors for severe CAP (smoking habits, alcohol habits, chronic chest diseases such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic cardiac diseases, chronic renal failure, chronic neurologic diseases, chronic diseases, neoplasm, steroids, liver and immunosuppressive drugs).
- (3) Acute physiology and chronic health evaluation II (APACHE II) scores at ICU admission.
- (4) Signs and symptoms of CAP at admission.
- (5) Vital signs at ICU admission.
- (6) Confusion, urine output, respiratory rate, blood pressure, age more than 65 years (CURB-65) score at ICU admission [12].

- (7) Chest radiograph features at admission.
- (8) Laboratory data (complete blood count, Cprotein, reactive prothrombin time, prothrombin sodium, concentration, serum potassium, urea, creatinine, aspartate transaminase, and alanine transaminase) at ICU admission.
- (9) Arterial blood gases measurements at ICU admission.
- (10) Microbial identification procedures: culture of sputum, deep tracheal aspirate and blood, and nasopharyngeal swabs for virus PCR (when viral infection is suspected).
- (11) MV requirement and duration of MV.
- (12) Duration of ICU stay.
- (13) Overall in-ICU mortality.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 17 (SPSS for Windows, Chicago, IL). Data were expressed as mean±SD for continuous variables and as number with percentage for categorical data. Comparisons between two categorical variables were made with χ^2 . Continuous data were tested with Student's t-test. P values below 0.05 were considered statistically significant. The relative risk for outcome was defined according to the following variables: age (≤65 or >65 years), presence of one comorbidity (yes/no), number of comorbidities (≥2 or <2), APACHE II score (≤20 or >20), CURB-65 score (≥ 3 or < 3), total leukocyte count (< 4 or $>11\times10^{9}$), PaO₂/FiO₂ (<250 or \geq 250), serum sodium (<135 or≥135 mmol/l), serum urea (<30 or≥30 mg/ dl), presence of septic shock (yes/no), MV requirement (yes/no), initial MV requirement (yes/no), microbial identification (yes/no), positive blood culture (yes/no), bilateral or multilobar involvement on chest radiograph (yes/no), and length of ICU stay (≤ 10 or > 10 days). All of the variables attaining a value less than 0.05 in the univariate analysis were included in the multiple logistic regression analysis models.

Results

Patient characteristics

The present study included 57 patients who had a definitive diagnosis of CAP. The main baseline patient characteristics and underlying conditions are listed in Tables 1 and 2.

Male patients constituted 59.6% of CAP patients and the mean age was 59.0±16.8 years. The most frequent comorbidity associated with CAP was cardiac disease

Table 1 Patient characteristics and underlying conditions

Patients	57
Sex (male) [n (%)]	34 (59.6)
Age (years)	59.0±16.8
Comorbidities [n (%)]	
Cardiac disease	16 (28.1)
COPD	14 (24.6)
Diabetes mellitus	10 (17.5)
Neoplasm	8 (4.0)
Immunosuppression	7 (12.3)
Steroids	6 (10.5)
Neurologic diseases	5 (8.8)
Liver diseases	3 (5.3)
Chronic renal failure	3 (5.3)
Prognostic scores	
APACHE II score	20.9±6.8
CURB-65 score	3.1±1.3
Vital signs at ICU admission	
HR (beats/min)	123.7±29.5
Temperature (°C)	37.6±0.9
SBP (mmHg)	93.1±20.7
DBP (mmHg)	49.4±10.9
PaO ₂ /FiO ₂	146.7±80.8

APACHE II, acute physiology and chronic health evaluation II; COPD, chronic obstructive pulmonary disease; CURB-65, confusion, urine output, respiratory rate, blood pressure, age more than 65 years; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

(28.1%), followed by COPD (24.6%) and diabetes mellitus (17.5%). Bilateral or multilobar infiltrate was present in 52.6% of patients. Thirty-five patients (61.4%) required MV and another 10 patients required MV later on during the course of ICU stay. Overall mortality was 49.1%.

Prognostic factors

The overall mortality percentage was 49.1% among studied patients. The nonsurvivors had a lower mean age (P=0.01) and lower diastolic blood pressure (P=0.01). They also had higher mean APACHE II (P=0.001) and CURB-65 scores (P=0.005). They also had lower mean PaO₂/FiO₂ (P=0.04), lower mean hemoglobin (P=0.008), and higher mean urea (P=0.02). Other parameters listed in Table 3 are not significant.

Univariate analysis for in-ICU mortality showed that mortality rate was higher for patients older than 65 years (P=0.03), those with APACHE II less than 20 (P=0.007), those with CURB-65 of 3 or greater (P=0.03), those with total leukocyte count less than 4 or greater than $11\times10^9/1$ (P=0.04), those with PaO_2 / FiO_2 less than 250 (P=0.03), those with serum urea greater than 30 mg/dl (P=0.04), those with shock at admission (P=0.003), those with bilateral or multilobar

Table 2 Patient characteristics

Laboratory data at ICU admission	
Hemoglobin (g/dl)	10.1±2.3
Total leukocyte count (×10 ⁹ /l)	12.6±6.9
Platelets (×10 ⁹ /l)	220.5±133.8
C-reactive protein (mg/dl)	140.9±110.3
Serum sodium (mmol/l)	140.1±6.2
Serum potassium (mmol/l)	3.2±1.2
Serum urea (mg/dl)	11.9±9.4
Serum creatinine (mg/dl)	140.1±132.6
Bilateral/multilobar infiltrate in CXR [n (%)]	30 (52.6)
Patients with initial MV required [n (%)]	35 (61.4)
Patients with MV required [n (%)]	45 (78.9)
Duration of MV (days)	12.2±18.2
Shock at admission [n (%)]	16 (28.1)
Length of ICU stay (days)	12.2±18.2
Microbial identification [n (%)]	33 (57.9)
Positive blood culture [n (%)]	10 (17.5)
Overall mortality [n (%)]	28 (49.1)

CXR, chest X ray; MV, mechanical ventilation.

infiltrate in CXR (P=0.03), and those who needed MV (P=0.02). Other parameters listed in Table 4 are not significant.

Multiple regression analysis in Table 5 identified that high APACHE II score (P=0.03) and shock at admission (P=0.01) were significant independent factors related to mortality in severe CAP.

Microbial identification

Microbiological identification was obtained in 30 cases (52.6%). Blood cultures were positive in 10 (17.5%) cases. The most frequently isolated etiological agents were Streptococcus pneumonia (S. pneumonia) (19.3%) and Staphylococcus aureus (S. aureus) (15.8% of patients). Other microbial agents are listed in Table 6. A positive blood culture was identified in 17.5% of patients, and in 66.7% of S. aureus CAP patients and 9.1% of S. pneumonia CAP patients.

Mortality percentage was 46.7% for patients in whom microorganisms were identified. Mortality rate was 55.6% among S. aureus CAP patients and 27.3% among S. pneumonia CAP patients.

MV support was required for 88.9% of S. aureus CAP patients and for 72.7% of S. pneumonia CAP patients.

Discussion

In the present study, we prospectively determined patient's characteristics, mortality percentage, mortality predictors, and etiological pathogens in

Table 3 Comparison between surviving and nonsurviving patients with severe CAP

	Nonsurvivors (N=28)	Survivors (N=29)	P
Age (years)	64.3±17.2	53.8±14.9	0.01
Vital signs at admission			
HR (beats/min)	130.5±34.1	117.3±22.7	0.09
Temperature (°C)	37.6±1.1	37.7±0.9	0.5
SBP (mmHg)	89.5±21.3	96.2±19.1	0.2
DBP (mmHg)	45.9±9.8	52.7±10.9	0.01
APACHE II score	24.1±6.2	19.6±5.8	0.001
CURB-65 score	3.5±1.1	2.6±1.4	0.005
Laboratory investigation on admission			
PaO ₂ /FiO ₂	125.4±77.4	167.2±79.9	0.04
Hemoglobin (g/dl)	9.3±2.3	10.9±2.1	0.008
Total leukocyte count (×109/l)	11.9±6.9	13.4±7.1	0.2
Platelets (×10 ⁹ /l)	191.5±148.6	248.4±113.4	0.1
CRP (mg/l)	123.1±79.2	158.1±132.9	0.2
Serum sodium (mmol/l)	141.1±6.7	139.2±5.6	0.2
Serum potassium (mmol/l)	3.9± 1.9	3.7±1.7	0.6
Serum urea (mg/dl)	14.8±10.3	9.1±7.5	0.02
Serum creatinine (mg/dl)	1.9±1.6	1.4±1.4	0.2
Duration MV (days)	12.2±12.9	12.2±22.4	0.9
Length of ICU stay (days)	13.9±15.8	17.2±24.5	0.5

Data presented as mean±SD.

APACHE II, acute physiology and chronic health evaluation II; CRP, C-reactive protein; CURB-65, confusion, urine output, respiratory rate, blood pressure, age more than 65 years; DBP, diastolic blood pressure; FiO2, fraction of inspired oxygen; HR, heart rate; MV, mechanical ventilation; PaO₂, partial pressure of oxygen in arterial blood; SBP, systolic blood pressure.

Table 4 Univariate analysis for in-ICU mortality among patients with severe CAP

	Nonsurvivors (N=28)	Survivor (N=29)	Relative risk	95% CI	Р
Age (>65 years)	17 (60.7)	9 (31.1)	0.29	0.09-0.89	0.03
Sex: male	17 (60.7)	17 (58.6)	0.92	0.32-2.64	1.00
Presence of one comorbidity	23 (82.1)	18 (62.1%)	0.36	0.12-1.21	0.14
Presence of two or more comorbidities	13 (46.4)	11 (37.9)	0.71	0.25-2.03	0.59
APACHE II score>20	21 (75.0)	11 (37.9)	0.2	0.07-0.64	0.007
CURB-65 score≥3	22 (78.6)	14 (55.2)	0.34	0.11-1.07	0.03
Total leukocyte count (<4 or >11×10 ⁹)	10 (35.7)	4 (13.8)	0.28	0.07-1.07	0.04
PaO ₂ /FiO ₂ (<250)	19 (67.8)	11 (37.9)	0.29	0.09-0.86	0.03
Serum sodium (<135 mmol/l)	6 (21.4)	7 (24.1)	1.16	0.33-4.03	1.00
Serum urea (>30 mg/dl)	4 (14.3)	0 (0)	0.45	0.34-0.61	0.04
Shock at admission	13(46.4)	3(10.3)	0.32	0.11-0.98	0.003
Bilateral or multilobar infiltrate in CXR	19 (67.9)	11 (37.9)	0.39	0.14-1.14	0.03
Microbial identification	13 (46.4)	17 (58.6)	2.5	0.86-7.56	0.43
Positive blood culture	5 (17.9)	5 (17.2)	0.95	0.25-3.75	1.00
Patients with initial MV required	20 (71.4)	15 (51.7)	0.43	0.14-1.28	0.17
Patients with MV required	26 (92.9)	19 (65.5)	0.14	0.02-0.74	0.02
Length of ICU stay (>10 days)	14 (50.0)	12 (41.4)	0.28	0.09-0.86	0.59

Data presented as n (%).

APACHE II, acute physiology and chronic health evaluation II; CI, confidence interval; CURB-65, confusion, urine output, respiratory rate, blood pressure, age more than 65 years; CXR, chest X-ray; FiO₂, fraction of inspired oxygen; MV, mechanical ventilation; PaO₂, partial pressure of oxygen in arterial blood.

patients with severe CAP who required ICU admission. The overall mortality in the present study was 49.1%, which is higher than that reported previous studies. Three previous reports from the Middle East region have indicated ICU mortality rates of 24.4, 25.9, and 31% [13-15]. A meta-analysis showed an average mortality of 36.5% for CAP patients admitted in the ICU, with a range of 21.7 to 57.3% [10]. Severe CAP is associated with high mortality, exceeding 60% if patients require intubation and MV [16].

Table 5 Multivariate analysis for in-ICU mortality among patients with severe CAP

	Nonsurvivors (N=28)	Survivor (N=29)	Relative risk	95% CI	Р
APACHE II>20	21 (75.0)	11 (37.9)	0.16	0.03-0.86	0.03
Shock at admission	12 (50.0)	5 (24.1)	0.11	0.02-0.64	0.01

Data presented as n (%).

APACHE II, acute physiology and chronic health evaluation II; CAP, community-acquired pneumonia; CI, confidence interval.

Table 6 Microorganisms isolated from the clinical culture specimens

Causative organisms	n (%)	Positive blood culture	Mortality rate	MV required
Identified	30 (52.6)	10 (17.5)	14 (46.7)	24 (80)
Streptococcus spp.	11 (19.3)	1 (9.1)	3 (27.3)	8 (72.7)
Staphylococcus aureus	9 (15.8)	6 (66.7)	5 (55.6)	8 (88.9)
Pseudomonas aeruginosa	3 (5.3)	1 (33.3)	2 (66.7)	2 (66.7)
Klebsiella pneumonia	3 (5.3)	1 (33.3)	2 (66.7)	3 (100)
Escherichia coli	2 (3.5)	1 (50)	0 (0)	2 (100)
Influenza A	1 (1.8)	NA	1 (100)	1 (100)
Candida spp.	1 (1.8)	NA	1 (100)	1 (100)

Data presented as n (%).

MV. mechanical ventilation: NA. not available.

The outcomes of CAP patients in the ICU seem to depend on the interactions between various factors such as comorbidities, age, genetic predisposition, host defenses, microbial virulence and toxins, bacterial load, presence of organ failure, timing of ICU admission, high severity index scores, the need for surgical drainage for empyema, adjuvant therapies, and the choice of antibiotics [17].

The mean age of patients admitted to the ICU with severe CAP varies from study to study [18]. The mean age of our patients was 59.0±16.8. In the present study, the mortality rate in patients older than 65 years was 60.7%, which was significantly higher than that in those younger than 65 years (P=0.03). In addition, the nonsurviving group was older compared with the surviving group (P=0.02). These results are in agreement with previous studies [14,17,19-22]. These results indicate that elderly patients have been reported to have a depressed immune response to infection and may be particularly at risk of acquiring overwhelming infection [23].

The present study found that the presence of one or more comorbidities had no significant effect on mortality. This result is in agreement with that reported in other previous studies [5,20,21]. However, some other studies found a significant impact of COPD, DM, neoplasm, immunosuppressive drugs, and chronic renal failure on mortality of severe CAP patients [8,24].

The present study found that APACHE II scores were significantly higher in the nonsurviving patients (P=0.001) and APACHE II score greater than 20 was associated with fatality on univariate analysis (P=0.007). Multivariate analysis demonstrated that APACHE II score was an independent factor related to mortality (P=0.03). Previous studies reported that APACHE II scores were independent predictor of mortality [8,21,25].

The present study found that nonsurviving patients had significantly higher mean CURB-65 scores (P=0.005) and that CURB-65 score of 3 or greater was associated with fatality on univariate analysis (P=0.007). A similar result was reported by previous studies [12,13,26]. We found that patients with CURB-65 score of 0-1 were at low risk for mortality (11.1%), those with a score of 2 were at intermediate risk for mortality (50%), and those with score 3 or higher were at a high risk for mortality (57.9%). Similar results were reported by Lim et al. [12] and Marrie et al. [27]. Phua et al. [28] found that Infectious Disease Society of America/American Thoracic Society minor criteria were more valuable compared with PSI and CURB-65 for predicting hospital mortality and ICU admission.

The present study found that PaO2/FiO2 ratio was significantly higher in the surviving group (P=0.04) and that PaO₂/FiO₂ less than 250 was associated with fatality on univariate analysis (*P*=0.04). Luna *et al.* [29] reported that PaO₂/FiO₂ less than 250, aerobic gramnegative pathogen, chronic renal failure, Glasgow score less than 15, malignancy, and aspiration pneumonia were associated with fatality on multivariate analysis. There were no significant differences between the survivors and nonsurvivors with regard to PaO₂/ FiO₂ less than 250 in two studies [14,21]. Hypoxemia has been associated with impending respiratory failure, subsequent ICU admission [26], and mortality [30] in patients with CAP, reflecting the severity of primary organ impairment in this illness.

The present study found that bilateral or multilobar CXR changes are predictors of mortality on univariate analysis (P=0.03). This finding is in agreement with reports from other studies [20,25,26,31]. This is likely to be an important and valuable clinical feature in the assessment of disease severity.

In our study, univariate analysis had shown that septic shock (P=0.003) and need for MV (P=0.02) were statistically higher in survivors and nonsurvivors. Multivariate analysis demonstrated that septic shock was an independent factor related to mortality (P=0.01). These results are in agreement with other previous results [13,20,26].

The presence of shock and the need for MV have consistently been shown to be the main indications for ICU admission [27,32]. Shock is a well-known risk factor for mortality in ICU [18,33].

In the present study, serum urea was significantly higher in the surviving group (P=0.02) and serum urea greater than 30 mg/dl was associated with fatality on univariate analysis (P=0.04). These results are in agreement with those of previous studies [13,20,25,29].

In the present study, the defined microbial etiology of CAP had been established in 52.6% of patients, which is in agreement with that reported by Cillóniz et al. [31] (54%), but higher than that reported by Yoshimoto et al. [33] (44.4%) and Wilson et al. [19] (46%) and lower than that reported by Paganin et al. [20] (78.6%) and PROWESS study (60%) [34].

The present study found that *S. pneumonia* was the most frequently isolated pathogen (17.5%), followed by S. aureus (15.6%) and aerobic gram-negative organisms (14.1%). Similar results were reported by PROWESS study, which found that S. pneumonia was most common (26%), followed by S. aureus (14%) and aerobic gramnegative rods as a group (15%) [34]. Yoshimoto et al. [33] found that S. pneumonia was the most frequently isolated pathogen (13.9%), followed by Pseudomonas aeruginosa (8.3%) and Klebsiella pneumonia (6.9%). Wilson et al. [19] found that the most frequently identified cause was S. pneumonia (13.5%), followed by influenza A (9.4%), Haemophilus influenza (5.2%), and S. aureus (4.2%).

Differences in methodology and the influence of geography on etiology can contribute to these differences in percentages of identification and isolated organisms.

S. pneumonia was the most common organism in our study and in most of the previous studies [13,19,27,29,32,34,35].

S. aureus was the second most common organism in severe CAP in our study. Khawaja et al. [25] found that S. aureus was the most commonly identified pathogen causing severe CAP. Its incidence has been increasing in recent years, ranging from 12 to 22%, as reported in several patient series [9,36].

This study is limited by the small number of patients included, the lack of biochemical markers of infection (e.g. procalcitonin), and lack of availability of serological tests and quantitative PCR for the diagnosis of viral and atypical pathogens.

Conclusion

The mortality rate in the patients with severe CAP was high as reported by most of the other studies. The presence of septic shock and high APACHE II score were independent predictors of mortality. Heart disease and COPD were the most common comorbidities but we did find a significant difference between survivors and nonsurvivors with regard to associated comorbidities.

Microbiological identification was obtained in 52.6% of patients, and S. pneumonia and S. aureus were the most frequently isolated pathogens. The treating clinician should be informed of the importance of prognostic factors, laboratory data, and microbial identification in dealing with CAP patients admitted to the ICU.

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Conflicts of interest

There are no conflicts of interest.

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