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Mortality indicators in community-acquired pneumonia requiring intensive care in Turkey

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SUMMARY

Background: Severe community-acquired pneumonia (SCAP) is a fatal disease. This study was conducted to describe an outcome analysis of the intensive care units (ICUs) of Turkey.
Methods: This study evaluated SCAP cases hospitalized in the ICUs of 19 different hospitals between October 2008 and January 2011. The cases of 413 patients admitted to the ICUs were retrospectively analyzed.

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Results: Overall 413 patients were included in the study and 129 (31.2%) died. It was found that bilateral pulmonary involvement (odds ratio (OR) 2.5, 95% confidence interval (CI) 1.1–5.7) and CAP PIRO score (OR 2, 95% CI 1.3–2.9) were independent risk factors for a higher in-ICU mortality, while arterial hypertension (OR 0.3, 95% CI 0.1–0.9) and the application of non-invasive ventilation (OR 0.2, 95% CI 0.1–0.5) decreased mortality. No culture of any kind was obtained for 90 (22%) patients during the entire course of the hospitalization. Blood, bronchoalveolar lavage, and non-bronchoscopic lavage cultures yielded enteric Gram-negatives ($n = 12$), followed by *Staphylococcus aureus* ($n = 10$), pneumococci ($n = 6$), and *Pseudomonas aeruginosa* ($n = 6$). For 22% of the patients, none of the culture methods were applied.
Conclusions: SCAP requiring ICU admission is associated with considerable mortality for ICU patients. Increased awareness appears essential for the microbiological diagnosis of this disease.

1. Introduction

Community-acquired pneumonia (CAP) is a common and serious infection worldwide. Severe CAP (SCAP) is usually defined as pneumonia that requires intensive care unit (ICU) admission. Although 2–20% of CAP patients require ICU admission,[1,2] the mortality rates can be as high as 20–50%.[3,4] These patients commonly have comorbidities and impaired host defenses, and invasive procedures are frequently applied.[5] Studies have shown that clinicians frequently either overestimate[6] or underestimate[7] the severity of CAP. Once known as the 'captain of the men of death', pneumonia is known to be one of the most fatal forms of acute infectious diseases.[8] However, mortality indicators of CAP in the ICU have not yet been detailed in Turkey, which is located at the intersection of Asia and Europe. Thus, the primary endpoint of this study was to perform an outcome analysis of CAP patients in the ICUs in this part of the world.

2. Methods

This multicenter, retrospective, cross-sectional, observational cohort study was carried out in the ICUs of different hospitals in Turkey. A total of 19 ICUs from 12 different provinces of Turkey participated in the study. Consecutive patients aged $\geq$16 years with conclusive evidence of CAP as the primary diagnosis, confirmed by chest radiography, during the period October 2008 to January 2011, were enrolled. Patients were admitted to the ICU either for mechanical ventilation or because they were judged to be in an unstable condition requiring intensive care. 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 $>38\,^{\circ}C$ or $<35\,^{\circ}C$, leukocytosis (white blood cell count (WBC) $>10 \times 10^9$/l) or leukopenia (WBC $<4 \times 10^9$/l), and more than 10% rods.[9] CAP was considered as severe (SCAP) when it required ICU admission. Shock was defined as a systolic blood pressure of $<$90 mmHg unresponsive to fluid administration, or the need for vasopressors for $>$4 h. Patients with pulmonary tuberculosis and those residing in nursing homes were excluded. Empirical antibiotic treatment was started following the clinical diagnosis and just after obtaining samples for culture. The patients were followed daily until death or complete cure. This study was approved by the local ethics committee.

2.1. Data collection

The following demographic, clinical, and laboratory data were collected for each patient with SCAP from the participating centers using a computer database: age, gender, smoking and alcohol habits, co-morbid illnesses, use of antimicrobials according to Turkish guidelines,[10] immunosuppressive drugs or systemic and inhaler corticosteroids used in the last 3 months, clinical and laboratory parameters, chest radiography findings, pneumonia severity index (PSI), CAP predisposition, insult, response, and organ dysfunction (PIRO) and CURB-65 scores, presence of septic shock, various supportive care applications, and length of hospital and ICU stays.

2.2. Microbiological investigations

Blood cultures and bronchoalveolar lavage (BAL) or non-bronchoscopic lavage (NBL) or deep tracheal aspirate (DTA) or sputum cultures obtained within 48 h of ICU admission from the emergency department were included. The culture results of patients transferred to the ICU from wards where they had been hospitalized for more than 48 h were excluded to prevent the inclusion of nosocomial isolates. Since there was ongoing debate regarding the quality of sputum cultures in various scientific platforms, and because a number of centers did not quantify DTA specimens in our study, these results were excluded. The threshold of quantitative cultures for BAL and NBL was 10^4 cfu/ml.[11,12] Only one isolate of the same species per patient was included in the study. All microorganisms isolated were identified by standard laboratory methods.

2.3. Statistical methods

Group patient characteristics were summarized using mean (standard deviation), median (range), and number (%), as necessary. Numerical data were first tested for normality and then analyzed using the Student's *t*-test for parametric data; the Mann–Whitney *U*-test was used for variables with non-parametric data for group comparisons. Categorical data were analyzed using the Chi-square test or Fisher's exact test. Tests were two-tailed, and *p*-values of $\leq$0.05 were considered significant. Univariate analysis was used to identify the risk factors for mortality of SCAP cases, both in-hospital and in-ICU. To evaluate the independent risk factors for in-hospital and in-ICU mortality, multivariate logistic regression analysis was performed, 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 $p < 0.05$. All analyses were done using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 445 patients with SCAP were admitted to the 19 ICUs during the study period. We excluded 32 patients found to be ineligible for the study, hence a final 413 patients were included in

Table 1
Univariate analysis for in-ICU mortality among the cases with severe CAP ($N = 413$)

Variable	Non-survivors ($n = 117$)	Survivors ($n = 296$)	OR (95% CI)	p-Value
Age, years, median (range)	69 (16–95)	66 (16–91)		0.039
Male sex, n (%)	72 (61.5)	209 (70.6)	0.667 (0.425–1.043)	0.075
Predisposing factors, n (%)				
Cigarette smoking, n (%)	78 (66.7)	201 (67.9)	0.945 (0.600–1.490)	0.809
Alcohol consumption, n (%)	80 (68.4)	213 (71.9)	0.829 (0.520–1.320)	0.428
COPD, n (%)	50 (42.7)	159 (73.6)	0.643 (0.418–0.990)	0.044
Antibiotic use in last 3 months, n/N (%) ($N = 239$)	5/73 (6.8)	17/166 (10.2)	0.645 (0.228–1.819)	0.403
Systemic steroid use in last 3 months, n/N (%) ($N = 339$)	15/99 (15.2)	26/240 (10.8)	1.470 (0.742–2.913)	0.268
NIV treatment, n (%)	40 (34.2)	201 (67.9)	0.246 (0.156–0.386)	<0.0001
Intubation with IMV, n (%)	84 (71.8)	88 (29.7)	6.017 (3.747–9.661)	<0.0001
Time of IMV, days, median (range)	8 (0–48)	4 (0–39)		0.003
Comorbidities, n (%)				
Diabetes mellitus	24 (20.5)	35 (11.8)	1.924 (1.087–3.406)	0.023
Hypertension	15 (19.2)	63 (80.8)	0.544 (0.296–1.00)	0.048
Coronary artery disease	3 (2.6)	28 (9.5)	0.252 (0.075–0.845)	0.017
Chronic hepatic failure	23 (19.7)	66 (22.3)	0.853 (0.501–1.451)	0.557
Alzheimer's disease	5 (4.3)	5 (1.7)	2.598 (0.738–9.147)	0.155
Chronic renal failure	4 (3.4)	16 (5.4)	0.619 (0.203–1.893)	0.397
Pulmonary involvement, n (%)				
Bilateral pulmonary involvement	53 (45.3)	100 (33.8)	1.616 (1.041–2.507)	0.032
Multilobar pulmonary involvement	76 (30.5)	173 (69.5)	1.318 (0.845–2.056)	0.223
$PaO_2/FiO_2 \leq 250$	93 (79.5)	222 (75.0)	1.292 (0.768–2.173)	0.334
Severity of disease, n (%)				
Median PSI score (range)	151 (40–254)	125 (25–245)		0.001
Median CURB-65 score (range)	3 (0–5)	2 (0–5)		0.001
Median CAP PIRO score (range)	4 (1–8)	3 (0–7)		0.001
Presence of septic shock	50 (42.7)	31 (10.5)	6.617 (3.91–11.2)	<0.0001
Treatment data, n (%)				
Antibiotic treatment in accordance with guidelines[a]				0.136
Inadequate	52 (44.4)	133 (44.9)		
Rational	35 (29.9)	114 (38.5)		
Inadequate, *P. aeruginosa* risk (+)	6 (5.1)	8 (2.7)		
Over-treatment, *P. aeruginosa* risk (−)	24 (20.6)	41 (13.9)		
Systemic steroid treatment, n (%)	35 (29.9)	65 (21.9)	1.517 (0.937–2.456)	0.089
Length of ICU stay, days, median (range)	9 (1–48)	7 (1–44)		0.120

ICU, intensive care unit; CAP, community-acquired pneumonia; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NIV, non-invasive ventilation; IMV, intermittent mandatory ventilation; PSI, pneumonia severity index; PIRO, predisposition, insult, response, and organ dysfunction.
[a] Turkish CAP guideline.

the study. The median (range) age of the patients was 63.8 (23–80) years; 281 (68%) were males and 132 (32%) were females.

The overall in-hospital mortality was 31.2% (129 patients) and in-ICU mortality was 28.3% (117 patients). Thus, 12 patients died after they were discharged from the ICUs. Three patients died of terminal lung cancer after discharge, four patients, one of whom had cystic fibrosis, experienced cardiac arrest, one died due to a cerebrovascular accident, two cases died of probable pulmonary embolism, and the reason of death was undetermined in two cases. The reasons for death were recorded for 47 patients (27.8%) in the hospital records of some of our participating centers; these centers provided 169 CAP patients hospitalized in the ICUs. For three of them (1.8%), mortality was related to reasons other than CAP. Thus, in this subgroup of patients, the attributable mortality related to CAP in the ICU was 26%. A comparison between survivors and non-survivors in the ICUs (survivors $n = 296$, non-survivors $n = 117$) is shown in Table 1. The median age, intermittent mandatory ventilation (IMV), duration of IMV, diabetes mellitus, bilateral pulmonary involvement on chest roentgenograms, median PSI score, median CURB-65 score, median CAP PIRO score, and the presence of septic shock on admission were significantly different between the two groups. There were no significant differences between the two groups regarding sex, cigarette smoking, alcohol consumption, antibiotics and steroid use in the last 3 months, chronic hepatic failure, Alzheimer's disease, chronic renal failure, the existence of multilobar pulmonary involvement on chest roentgenogram, arterial gas analysis ($PaO_2/FiO_2 \leq 250$) on admission, antibiotic treatment in accordance with the Turkish

Table 2
Multivariate logistic regression analysis for in-ICU mortality among the cases with severe CAP

	OR	95% CI	p-Value
Hypertension	0.297	0.094–0.943	0.039
Bilateral pulmonary involvement	2.461	1.062–5.704	0.036
CAP PIRO score	1.955	1.330–2.875	0.001
Non-invasive ventilation	0.192	0.079–0.466	0.001

ICU, intensive care unit; CAP, community-acquired pneumonia; OR, odds ratio; CI, confidence interval; PIRO, predisposition, insult, response, and organ dysfunction.

Table 3
Microorganisms isolated from clinical culture specimens of severe CAP

	Blood	BAL	NBL	Total
Enteric Gram-negatives				12
Klebsiella spp	2	2	1	5
Escherichia coli	1	2	1	4
Enterobacter cloacae	1	2	0	3
Staphylococcus aureus	5	5	0	10
Streptococcus pneumoniae	5	1	0	6
Pseudomonas aeruginosa	4	2	0	6
Acinetobacter spp	0	1	2	3
Moraxella catarrhalis	1	0	0	1
Stenotrophomonas maltophilia	0	1	0	1
% of recovery[a]	19/246 (7.7%)	16/78 (20.5%)	4/16 (25%)	

CAP, community-acquired pneumonia; BAL, bronchoalveolar lavage; NBL, non-bronchoscopic lavage.
[a] No. of isolated microorganisms/No. of samples obtained.

guidelines, systemic steroid treatment during ICU stay, and length of hospital stay in the ICU (Table 1).

Multivariate logistic regression analysis revealed that bilateral pulmonary involvement (OR 2.461, 95% CI 1.062–5.704) and CAP PIRO score (OR 1.955, 95% CI 1.330–2.875) were independent risk factors for a higher in-ICU mortality. Both arterial hypertension and the presence of non-invasive ventilation (NIV) appeared to decrease mortality inside the ICUs (Table 2).

In this study, no culture of any kind was obtained for 90 (22%) patients during the entire course of the hospitalization. A sputum culture was obtained for 295 (71%) cases. The Legionella urinary antigen test (UAT) was positive in one out of 18 cases, while the pneumococcal UAT was found to be negative in eight cases tested. Microorganisms isolated from blood, BAL, and NBL specimens obtained within 48 h of hospital admission are presented in Table 3.

4. Discussion

The mortality rate of CAP in patients admitted to the ICU remains high, even in immunocompetent patients, despite antibiotics and adequate supportive care.[13] Antibiotics alone do not entirely eliminate mortality in CAP patients requiring intensive care support. The overall mortality rate in our study was 31%. However, attributable mortality is a more accurate indicator,[14–16] and this was reported for a quarter of the cases in this study. These mortality rates are in accordance with rates reported from some studies,[17–19] but are lower than those of other studies.[1,20–25] The outcomes of CAP patients in the ICU reported in the literature 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.[5,26,27] According to our multivariate analysis, bilateral pulmonary involvement and increasing CAP-PIRO score were found to be independently associated with a higher mortality inside the ICUs.

The CAP PIRO (predisposition, insult, response, and organ dysfunction) score is a severity index, which includes comorbidities (chronic obstructive pulmonary disease (COPD) and immunocompromise), age >70 years, multilobar opacities on chest radiograph, shock, severe hypoxemia, acute renal failure, bacteremia, and acute respiratory distress syndrome. The PIRO score for the assessment of SCAP patients is a relatively new concept.[28] An initial study reported that the mean PIRO score of CAP patients in the ICUs was significantly higher in non-survivors than in survivors.[29] According to our data, an increase in the PIRO score by one digit is associated with a 1.9-fold increase in the in-ICU mortality. Thus, since the PIRO score integrates key signs and symptoms of clinical sepsis and of major CAP risk factors, it may provide a better means of predicting SCAP. On the other hand, bilateral pulmonary involvement is a recognized parameter, which is known to worsen the prognosis in this group of patients.[30,31]

Arterial hypertension and NIV seem to be correlated with a lower mortality in the ICUs. To the best of our knowledge, a connection between arterial hypertension and fatality has not been shown. Although further studies are necessary on this issue, antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors are known to have anti-inflammatory and immunomodulatory effects. The use of ACE inhibitors was shown to decrease mortality in pneumonia patients in a population-based study from the UK.[32] In addition, a meta-analysis reported that ACE inhibitors are associated with lower risks of pneumonia development and of pneumonia-related mortality.[33] On the other hand, it is known that CAP patients with chronic pulmonary diseases or cardiac comorbid diseases have a greater chance of survival if they have a good response to NIV.[34] However, the efficacy of NIV in reducing intubation and mortality rates in CAP is still controversial. Several studies have reported the effectiveness of NIV in pneumonia patients, particularly those with COPD.[35] Almost half of our patients had COPD; this rate is higher than the rates of most previous SCAP studies.[1,36–38] Therefore, the high rate of COPD patients might partly explain the contribution of NIV to better survival. It has been reported that NIV eliminates the risks of endotracheal intubation and provides better clinical improvement in select cases than IMV, which may cause serious complications.[39,40]

Streptococcus pneumoniae, *Legionella spp*, and Gram-negative bacilli represent the most common causative organisms of SCAP in the Western countries.[1,41,42] However there may be variations in the etiological agents in different geographical areas. For instance, pulmonary tuberculosis and *Burkholderia pseudomallei* have been reported as the most significant causes of SCAP in Singapore.[23] In a retrospective study in South Africa, Feldman et al. reported different microbial profiles in patients with SCAP admitted to the ICU, with a very low incidence of *Legionella pneumophila*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*, but high levels of *Klebsiella pneumoniae*.[25] A small study from Turkey revealed *S. pneumoniae* and *Mycobacterium tuberculosis* to be the most significant microorganisms in SCAP cases.[43] In the present study, the most common organisms were enteric Gram-negatives, followed by *S. aureus*, pneumococci, and *P. aeruginosa*.

According to Turkish, European, and American guidelines, blood and sputum cultures, Legionella and pneumococcal UATs, and if the patients are intubated, endotracheal aspirate, and possibly bronchoscopy or non-bronchoscopic BAL are recommended for all CAP patients admitted to the ICU.[10,44,45] Since we excluded the sputum culture data and we did not include the culture results of those patients transferred from the wards to the ICUs, due to the fact that cultures would have been obtained more than 48 h after hospital admission in this circumstance, our microbiological data are limited. Our aim was to disclose the true community-acquired isolates and to exclude colonizers. On the other hand, no culture of any kind was obtained for a fifth of our CAP patients in the ICUs, and both pneumococcal and Legionella UATs were performed in a small portion of the cases. Thus, the compliance of the clinicians to microbiological diagnostic techniques appears to be low. Blood cultures disclosed the pathogen in a tenth of cases, BAL in a fifth, and NBL recovered the infecting agent in a quarter of the cases. Thus, the importance of the use of diagnostic microbiological tests should be underlined for this fatal disease, along with the establishment of urgent postgraduate training programs.

There are some limitations to our study. First, it was designed retrospectively, and second, this study was conducted mainly in respiratory ICUs. Therefore, the patient characteristics of this study should be interpreted in that context. Third, we were able to provide the actual cause of death in order to estimate the attributable mortality for only a subgroup of patients. We have now modified our database and in the future we will be able to report the exact attributable mortality rate of CAP patients in the ICUs. This study also has an important strength when compared to the other studies in the literature: a large number of cases were enrolled from 19 hospitals located in various parts of Turkey.

In conclusion, CAP requiring ICU admission is associated with considerable mortality. The treating clinician should be informed of the importance of laboratory data and the prognostic factors related to CAP patients admitted to the ICU.

Conflict of interest: No conflict of interest to declare.

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