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Factors affecting treatment success in community-acquired pneumonia

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Background/aim: Treatment failure in hospitalized patients with community-acquired pneumonia is a major cause of mortality. The aim of this study was to evaluate the factors affecting treatment success in community-acquired pneumonia.

Materials and methods: A total of 537 patients (mean age: 66.1 ± 15.8 years, 365 males) registered to the Turkish Thoracic Society Pneumonia Database were analyzed. Of these, clinical improvement or cure, defined as treatment success, was achieved in 477, whereas 60 patients had treatment failure and/or died.

Results: Lower numbers of neutrophils (5989.9 ± 6237.3 vs. 8495.6 ± 7279.5/mm^3), higher blood urea levels (66.1 ± 42.1 vs. 51.2 ± 38.2 mg/dL), higher Pneumonia Severity Index (PSI) scores (123.3 ± 42.6 vs. 96.3 ± 32.9), higher CURB-65 scores (2.7 ± 1.2 vs. 2.2 ± 0.9), lower PaO_2/FiO_2 ratios (216.3 ± 86.8 vs. 269.9 ± 65.6), and the presence of multilobar (33.3% vs. 16.4%) and bilateral (41.7% vs. 18.9%) radiologic infiltrates were related to treatment failure. The PSI score and PaO_2/FiO_2 ratio were independent parameters affecting treatment results in multivariate linear regression analysis ($P < 0.001$).

Conclusion: The risk of treatment failure is high in patients with severe pneumonia and with respiratory failure. Effective treatment and close monitoring are required for these cases.

Key words: Community-acquired pneumonia, treatment failure, pneumonia severity index, PaO_2/FiO_2

1. Introduction

Community-acquired pneumonia (CAP) remains a leading cause of morbidity and mortality, particularly in patients admitted to hospitals for severe disease. Although most hospitalized patients with CAP respond satisfactorily to treatment, some develop treatment failure (TF) and may experience rapidly progressive life-threatening pneumonia. The incidence of TF in CAP is 10% to 15%, and it is associated with significant increases in mortality and in cost (1). Factors associated with TF are related to the initial severity of the infection, the presence of comorbidities, the causative organism, and the antibiotic therapy administered (2).

Severity scores such as the Pneumonia Severity Index (PSI) and CURB-65 have been validated and their use has been recommended by international (3) and national (4) guidelines for identifying patients with a higher risk of poor prognosis. The PSI is a prediction rule for prognosis that objectively stratifies patients into quintiles of risk for short-term mortality on the basis of 20 demographic and clinical variables routinely available at presentation (4,5) (Table 1). The British Thoracic Society's CURB-65 score consists of 5 variables: new onset of confusion, blood urea nitrogen of >7 mmol/L, respiratory rate ≥30 breaths/min, blood pressure <90 mmHg systolic or <60 mmHg diastolic, and age ≥65 years (4,6). Each risk factor scores one point and the total score defines the risk level of the patient, as well as predicting mortality and offering a treatment approach (Table 2). However, there have been no large-scale, multicenter studies in Turkey regarding the prognostic use of these severity scoring systems and other clinical or laboratory parameters.

The aim of this study was to evaluate the factors affecting treatment success in hospitalized CAP patients using the multicenter Turkish Thoracic Society Pneumonia Database (TURCAP).

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Table 1. Pneumonia Severity Index.

Age		Laboratory findings	
Male	Age (years)	BUN ≥ 30 mg/dL	20
Female	Age (years) – 10	Na < 130 mmol/L	20
Nursing home resident	10	Glucose ≥ 250 mg/dL	10
Coexisting illnesses		Hematocrit < 30%	10
Neoplastic disease	10	Radiographic findings	
Liver disease	30	Pleural effusion	10
Congestive heart failure	20	Oxygenation	
Cerebrovascular disease	10	Arterial pH < 7.35	30
Kidney disease	10	PaO_2 < 60 mmHg	10
Physical examination findings		SaO_2 < 90%	10
Altered mental status	20		
Respiratory rate ≥ 30/min	20		
Systolic BP < 90 mmHg	20		
Temperature < 35 °C / ≥ 0 °C	15		
Pulse ≥ 125/min	10		

BP: Blood pressure; BUN: blood urea nitrogen; Na: sodium; PaO_2: partial pressure of arterial oxygen; SaO_2: oxygen saturation.
Point assignments correspond with the following risk classes: age < 50 and no neoplastic, cerebrovascular, liver or kidney disease class I; ≤70 class II; 71–90 class III; 91–130 class IV; >130 class V.

Table 2. CURB-65 severity score for CAP.

1. Confusion
2. Urea > 42.8 mg/dL (or blood urea nitrogen > 20 mg/dL [7 mmol/L])
3. Respiratory rate ≥ 30/min
4. Blood pressure (systolic < 90 mmHg or diastolic ≤ 60 mmHg)
5. Age ≥ 65

The existence of each criterion corresponds to 1 point.

2. Material and methods

A retrospective study was performed in patients with CAP registered to TURCAP by four university hospitals from September 2009 to September 2013. Briefly, this is a web-based database, where several tertiary care centers register relevant clinical data of their patients diagnosed with CAP. The project was supported with a grant from the Turkish Thoracic Society. Nonimmunocompromised patients older than 18 years with the presence of a new radiographic infiltrate and at least two compatible clinical symptoms were included in the study. Patients with missing data were excluded. The study was approved by the local ethics committee.

In order to determine the predictors of treatment failure in this study population, we compared the findings of the patients in whom the initial antibiotic succeeded and failed. TF was defined as persistence or reappearance of fever (37.8 °C or higher) or radiographic progression (50% or more increase in the extent of infiltrates) including pleural effusion and/or empyema, or worsening of the clinical condition, which would necessitate change in antibiotic treatment or death. No distinction was made for early and late failure. Treatment success (TS) was defined as improvement or resolution of all symptoms and clinical and radiographic signs of pneumonia by days 10–15, without the appearance of new signs and/or symptoms

and without any need to change the antibiotic therapy.

The demographic data (age, sex, smoking history, comorbidities), admission to hospital or history of antibiotherapy in the preceding 3 months, laboratory findings including C-reactive protein, procalcitonin, culture results, and radiologic findings of the two groups were compared. Initial risk class was recorded according to CURB-65 and PSI scores.

2.1. Statistical analysis

SPSS was used for statistical analysis (SPSS Inc., Chicago, IL, USA). The t-test and chi-square test were used to conduct between-group analyses. Linear multivariate regression analysis was used for examining independent variables.

3. Results

Four tertiary care centers contributed data to this study. Out of 788 patients who were registered from these four centers, 251 patients were excluded because of missing data. Thus, 537 patients (mean age: 66.1 ± 15.8 years, 365 males) were included in the analysis. Of these, 477 (89%) patients had TS, whereas TF was documented in 60 (11%) patients. There were no significant differences between the two patient groups in demographic data including age, sex, smoking history, comorbidities, history of hospitalization, or antibiotherapy in the preceding 3 months (Table 3). Patients in whom the initial antibiotic regimen failed had lower numbers of neutrophils (5989.9 ± 6237.3 vs. 8495.6 ± 7279.5/mm^3; P = 0.019), higher blood urea levels (66.1 ± 42.1 vs. 51.2 ± 38.2 mg/dL; P = 0.006), higher procalcitonin levels (6.3 ± 17.4 vs. 26.6 ± 70.1 ng/mL; P = 0.027), higher PSI scores (123.3 ± 42.6 vs. 96.3 ± 32.9, P < 0.001) and CURB-65 scores (2.7 ± 1.2 vs. 2.2 ± 0.9, P < 0.001), and lower PaO_2/FiO_2 ratios (216.3 ± 86.8 vs. 269.9 ± 65.6, P = 0.010). They were also found to have more frequent multilobar (33.3% vs. 16.4%, P = 0.002) and bilateral (41.7% vs. 18.9%, P < 0.001) radiographic infiltrates (Table 4).

There was no difference between the two groups regarding the percentage of patients who received guideline-concordant antibiotherapy (75% vs. 68.3%, P = 0.182). A causative pathogen was identified and susceptibility tests were performed in only 67 patients (12.5%). There were too few patients to perform statistical analysis (Table 5). However, patients with more severe

Table 3. Demographic data of treatment success and failure groups.

Age (years)	65.6 ± 15.7	69.7 ± 15.8	NS
Sex, male (%)	322 (67.5)	43 (71.6)	NS
Smoking history, pack-years	40.0 ± 277	36.3 ± 15.8	NS
Comorbidity, n (%)	409 (85.7)	55 (91.7)	NS
Hospitalization in the preceding 3 months, n (%)	78 (16.4)	16 (26.7)	NS
Antibiotic use in the preceding 3 months, n (%)	100 (21.0)	15 (25.0)	NS

Table 4. Comparison of clinical and laboratory findings in treatment success and failure groups.

White blood cell count (cells/mm^3)	12,148.9 ± 8133.2	11,111.5 ± 6769.9	NS
Neutrophil count (cells/mm^3)	8495.6 ± 7279.5	5989.9 ± 6237.3	0.019
Urea (mg/dL)	51.2 ± 38.2	66.1 ± 42.1	0.006
Albumin (g/L)	3.4 ± 2.3	3.07 ± 0.57	NS
C - reactive protein (mg/dL)	15.6 ± 10.8	17.1 ± 11.3	NS
Procalcitonin (ng/mL)	6.3 ± 17.4	26.6 ± 70.1	0.027
PaO_2/FiO_2	269.9 ± 65.6	216.3 ± 86.8	0.01
CURB-65 score	2.2 ± 0.9	2.7 ± 1.2	<0.001
PSI score	96.3 ± 32.9	123.3 ± 42.6	<0.001
Culture (+) respiratory sample, n (%)	61 (12.8)	6 (10)	NS

Table 5. The effect of appropriate antibiotherapy on treatment outcome in patients in whom a microorganism was isolated.

Treatment success	41 (67.2%)	20 (32.8%)	61
Treatment failure	5 (83.3%)	1 (16.7%)	6
Total	46	21	67

CAP, i.e. with PSI scores higher than 90, appeared to be more frequently infected with drug-resistant bacteria (enteric gram-negative bacilli, bacteria that produced extended-spectrum beta-lactamases, *Pseudomonas*, and *Acinetobacter*) (Table 6).

Multivariate linear regression analysis showed that PSI score ($P < 0.001$) and PaO_2/FiO_2 ratio ($P < 0.001$) were the only independent parameters affecting treatment results (Table 7). Thus, inpatients with an admission PaO_2/FiO_2 ratio below 200 or a PSI score greater than 90 had significantly higher risks for treatment failure (RR: 5.2 and 3.1, respectively) (Table 8). Treatment failure rates tended to be higher in the PSI > 90 group compared to the PSI ≤ 90 group (47 vs. 11, respectively; $P < 0.001$). Mortality rate was also significantly higher in the group with PSI > 90 compared to the PSI ≤ 90 group (24 vs. 2, respectively; $P < 0.001$).

4. Discussion

This study showed that a high PSI score and a low PaO_2/FiO_2 ratio were the only independent parameters that were associated with TF. The magnitude of respiratory failure and the severity of the disease were significantly predictive particularly for $PaO_2/FiO_2 < 200$ and PSI > 90. In our study, where we aimed to define the risk factors affecting treatment response in a large population, our findings were substantially consistent with previous reports.

Since CAP is related to high mortality and morbidity, defining the predicting factors for treatment outcome is important and would help clinicians to better assess and manage their patients. Several studies have been performed with heterogeneous results. In a multicenter observational prospective study performed in 15 Spanish hospitals, TF was observed in 15.1% of the patients (1), a rate similar to our study. The factors associated with treatment failure were found to be the presence of high-risk pneumonia, liver disease, multilobar infiltrates, *Legionella* pneumonia, gram-negative pneumonia, pleural effusion, cavitation, leukopenia, and discordant antimicrobial therapy. Arancibia et al. examined the causes of antimicrobial treatment failure in CAP patients who were admitted to the hospital and had extensive microbiological investigations (7). TF was mostly due to antimicrobial resistance of the primary pathogen and acquisition of a nosocomial infection. In another Spanish study performed by Rosón et al. (8), independent factors associated with early failure were high-risk pneumonia (PSI score greater than 90), multilobar infiltrates, *Legionella* pneumonia,

Table 6. Causative bacteria in patients with less severe (PSI ≤ 90) and more severe (PSI > 90) pneumonia.

S. pneumococcus	4	7	11
H. influenzae	2	3	5
M. catarrhalis	2	0	2
Methicillin-sensitive *S. Aureus*	0	4	4
Enteric gram-negative bacilli	0	3	3
ESBL-producing *K. Pneumoniae*	1	4	5
ESBL-producing *E. coli*	1	8	9
P. aeruginosa	7	8	15
A. baumannii	3	1	4
Other	2	3	5
Total	22	41	63

Table 7. Factors associated with treatment success in a multivariate model.

PaO_2/FiO_2	0.548	5.587	<0.001
PSI score	0.435	2.983	0.004
CURB-65 score	0.029	0.221	0.826
Procalcitonin	–0.022	–0.533	0.595
Urea	–0.058	–0.749	0.457
Neutrophils	0.026	0.395	0.694

gram-negative pneumonia, and discordant antimicrobial therapy. In the CAPITAL study (9), younger age, treatment with levofloxacin, and the absence of COPD and asthma were identified as significant predictors of symptom resolution in CAP. Finally, in a study on patients with severe CAP, age, CURB-65 score, presence of septic shock, acute respiratory distress syndrome, and acute renal failure during the first 24 h of ICU admission were found to be independent predictors of mortality (10).

In accordance with these studies, the findings in our study also highlight the importance of the severity of pneumonia, as indicated by high PSI scores and low PaO2/FiO_2 ratios. Besides, TF was also more frequently observed in patients with lower leukocyte counts and multilobar involvement.

It has been proposed that biological markers, including CRP and procalcitonin, may be useful in identifying patients with a higher risk of deterioration (11–14). This study showed that there was no difference in CRP levels at admission between TF and TS groups. On the other hand, patients who failed treatment were found to have higher initial procalcitonin levels, although this was not an independent predictor of treatment outcome. The study by Kruger et al. (15) also found that admission procalcitonin levels predicted the outcome of CAP as well as the CRB-65 score and with better accuracy than the CRP levels.

This study has several limitations. First, it was retrospective in nature, and a third of the patient population had to be excluded because of missing data; however, these patients were similar to those included in the study and there was no indication that the results would differ if all of the patient population was included. Second, no distinction could be made between early and late treatment failures. All participating centers were required to register their patients' data at admission and on days 3–7 of antibiotic treatment. Thus, the presented data reflect the clinical picture of this time interval. Third, and perhaps most importantly, we were not able to examine the effect of the causative pathogens and their resistance to antibiotics on the treatment outcome, as a pathogen was identified in only 12.5% of the study population. In a recent large multicenter prospective cohort study in the United States evaluating 2259 CAP patients with respiratory specimens, a pathogen was detected in 853 cases (38%) and the most common pathogens were human rhinovirus (in 9% of patients), influenza virus (in 6%), and *Streptococcus pneumoniae* (in 5%) (16). Viral pathogens could not be evaluated in our study since serological tests were not routinely performed in our retrospective study. The low rate of pathogen identification in our study possibly stems from the fact that most of the patients admitted to tertiary care centers are already treated with antimicrobials. Besides, the patients present mostly to the emergency room first, where insufficient efforts are made to obtain respiratory samples for microbiologic examinations. As there were too few patients in whom a pathogen was identified, no statistical analysis could be performed to determine whether the appropriateness of the antibiotic regimen affects treatment outcome. However, drug-resistant bacteria were more frequently isolated in patients with more severe pneumonia and further studies that include larger patient populations (and higher rates of pathogen isolation) may shed light on the effect of drug resistance and appropriateness of antibiotic regimens.

No association was found between TF and antimicrobial use that is discordant with the national guidelines. When the data were examined in detail, it was observed that discordant treatment mostly consisted of larger-spectrum regimens, possibly chosen because of failure of prior therapy. These regimens resulted in similar rates of treatment success, but were probably associated with higher costs and unfavorable effects on antimicrobial resistance.

This study showed once again that the PSI is a reliable predictor of clinical outcome in CAP and is a better tool in this respect than CURB-65. Thus, patients in PSI groups IV and V (with scores higher than 90) were found to have

Table 8. Predicted risk ratios for PaO_2/FiO_2 and PSI.

PaO_2/FiO_2	<200	27.2	5.2 (1.97–13.6)	<0.001
	<300	11.9	2.6 (0.73–9.1)	NS
PSI score	>90	13.1	3.1 (1.58–6.19)	<0.001

a 3.13-fold increased risk for treatment failure. A variety of other studies have suggested that the PSI and CURB-65 provide similar information, though the PSI is more weighted toward age and comorbidity and CURB-65 is more weighted toward acute physiological dysfunction (17). We were not able to assess the predictive value of the SMART-COP score as albumin levels were not regularly registered in the database. This latter tool has been shown to better identify CAP patients who require intensive respiratory and vasopressor support (18) and who are at higher risk of treatment failure. In the same line, we have shown that the second independent variable associated with treatment failure was the oxygenation level, as measured with the PaO2/FiO_2 ratio. Thus, risk assessment tools like SMART-COP, which put more weight on the oxygenation level of the patient, may be more sensitive in identifying at-risk patients.

In conclusion, our findings show that the risk of treatment failure is high in CAP patients with high PSI scores (>90) and with respiratory failure (PaO_2/FiO_2 < 200). Effective treatment and close monitoring are required for these cases.

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