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Community-Acquired Pneumonia in the Immunocompromised Patients: An Observational Study from a Single Center, TURKEY

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Purpose: Immunocompromised hosts are underrepresented in clinical trials. The goal of the study to search for the unmet needs in the management of CAP in immunocompromised hosts.

Patients and Methods: An observational study was conducted with CAP patients documented immunocompromise or those aged over 65 who have at least one chronic visceral disease. We clinically assessed the eligible patients at the time of the presentation with a follow-up assessment on day three of admission. The data were statistically analyzed to assess the impact of variables on mortality.

Results: During a 15-month study period, 140 CAP patients were observed. The overall 30-day mortality rate was 17.8%. The mortality rate was significantly higher in patients with sputum cultures positive for Pseudomonas aeruginosa, or two bacteria (p=0.049). Tachypnea was a stronger predictor of mortality. Failure to achieve a treatment response within three days of treatment identified the population with the worst outcomes. Less than half of such patients survived past one month.

Conclusion: Dynamic response assessment emerged as potentially the strongest predictor of outcomes in CAP of susceptible hosts. We propose that immunocompromised CAP patients who fail to respond early to treatment face extremely high rates of mortality, identifying an unmet need.

Keywords: community acquired pneumonia, CAP, initial response to treatment, immunocompromised patient, impaired immunity

Introduction

The world has been challenged by a new community-acquired pneumonia (CAP) agent, SARS-CoV-2, since the end of 2019; however, we continue to encounter pneumonia cases with well-known microbiological pathogens. Despite the wide range of developments in healthcare, mortality related to pneumonia has not been reduced for four decades.[1,2] Older age and comorbid conditions are among well-defined risk factors for contracting pneumonia.[1,3] Further, the increasing number of immunocompromised patients are complicating our understanding of pneumonia.[4]

Susceptibility to an infection varies according to the severity of the immune disorder and the type of impaired immunity.[4] Common comorbid conditions such as chronic lung, kidney, or liver diseases or advanced age also impair immunity.[4] These susceptible hosts need specialized attention for diagnostic procedures and therapeutic interventions.

Reports indicate that immunosuppressive conditions are found in 20–30% of hospitalized patients with CAP.[5] However, it is worth underlining that, immunosuppressed patients are generally excluded from trials, and specific considerations for susceptible hosts are not included in CAP guidelines.[4,6–8] The unsettled debate about the definition of an immunosuppressed patient, the need for management of pneumonia in immunosuppressed patients to be individualized, and the unique distribution of causative agents in CAP of these hosts complicate their integration into clinical studies. This situation contributes to the lack of sufficient data from clinical trials of immunosuppressive patients and the inability to eliminate the adverse effects caused by comorbid factors during disease management.

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We consider that expanding the knowledge regarding the CAP of the susceptible host is valuable as they are underrepresented in many published works, their unmet needs are yet to be defined, and prospective studies involving these patients are unlikely to emerge. Therefore, we conducted this study to evaluate the characteristics and clinical course of CAP in immunocompromised patients by collecting real-life data, and to better define the risk factors and etiologic agents affecting mortality.

Material and Methods

Following Istanbul University Medical Faculty clinical trial ethics committee's approval (file number 2019/448), we conducted the study in a single center between January 2019 and April 2020. We observed patients diagnosed with pneumonia at the emergency department (ED) and documented data from file archives and digital medical records to a standard survey. Diagnostic procedures including cultures of blood, respiratory secretions, and clinical care decisions were undertaken by attending physicians, not by the researchers. We calculated Pneumonia Severity Index (PSI), CURB-65 scores, Charlson Comorbidity Index (CCI), and qSOFA (quick Sepsis-Related Organ Failure Assessment) and evaluated the correlation between those scores and mortality rates. We evaluated pulmonary imaging results, empirical antimicrobial therapy, and clinical response rates from file or digital medical records. The primary objective is to identify and evaluate risk factors for 30-day mortality. The secondary objectives are defining the spectrum and antibacterial susceptibilities of causative organisms associated with pneumonia among different patient subgroups and evaluating predictors for initial response to treatment.

Definitions

Pneumonia

Patients fulfilling all three items listed below were considered to be afflicted by pneumonia: Diagnosed with CAP by the attending emergency physician, and Presence of a new pulmonary infiltrate on thoracic imaging (chest radiograph, computed chest tomography) evaluated by the researcher compatible with pneumonia. and At least one of the following conditions: New or increased cough with/without sputum production and purulent respiratory secretions or Body temperature (oral or rectal) $\geqslant$37.8°C or <36°C or Signs of systemic inflammation (abnormal white blood cell count (leukocytosis >10,000 cells/mm^3, band neutrophils >10% or leukopenia <4000 cells/mm^3), procalcitonin or C-reactive protein levels above the upper limit of normal.[9]

Vital Signs

Fever; body temperature (oral) $\geqslant$37.8°C. *Tachypnea*; respiratory rate (ResR)$\geqslant$22 breaths per minute, and severe tachypnea; $\geqslant$30 breaths per minute. *Hypotension*; systolic blood pressure below 90 mmHg. *Tachycardia*; radial pulse $\geqslant$100 beats per minute.

Initial Response to Treatment (IRT)

In the present study, patients responsive to initial treatment were determined according to whether clinical stabilization was achieved or not 72 hours after the first dose of antibiotics. Patients who met all the following criteria were accepted as clinically stable and having an IRT.[10–13]

Improved respiratory symptoms (improved cough and shortness of breath), Resolution of fever (below 37.8 °C) for at least 8 hours, and Reduction in leucocyte count by at least 10% from the previous day, and Improved oral intake.

In cases where laboratory data such as blood count or acute-phase reactants on the third day were missing, we evaluated treatment response by assessing the respiratory dynamics and the course of fever.

Antibacterial Treatment

Data related to antibacterial treatment was collected retrospectively for every patient from medical records. In our institute, the management of CAP patients including the decisions to hospitalize and select specific antibacterial therapy are undertaken by the department of infectious disease. The latest guidelines of Turkish Thoracic Society and IDSA/ATS for CAP, local antibacterial resistance profiles, prior culture results, recent antibacterial exposures of patients, and the

availability of the appropriate drugs are taken into consideration. After 72 hours from the initiation of empirical treatment, clinical response defined above is evaluated. Empiric treatment is revised according to the clinical response and culture results.

Immunocompromised State

The NIH defines immunocompromised as, people who have a reduced ability to fight infections and other diseases caused by certain diseases or conditions, such as AIDS, cancer, diabetes, malnutrition, COPD, certain genetic disorders, and various treatments. This definition was used as a reference to predefine the patient population with strict criteria which are explained below to improve the reproducibility of results.

Inclusion and Exclusion Criteria

Adult patients classified as pneumonia as defined above and fulfilling at least one of the following items as a classification for immunocompromised status in line with the NIH definition were included in the study: Immunosuppressed patients as defined by recipients of solid organ or hematopoietic stem cell transplantation, patients with rheumatologic/autoimmune diseases receiving immunosuppressive treatment, and patients with active malignancy[4,14] or Patients above the age of 65 who have at least one chronic visceral disease associated with an increased risk of infection (Diabetes mellitus, dementia, chronic kidney disease, neurodegenerative disease, malnutrition, neurological deficits due to stroke) or Patients with structural lung disease and/or cirrhosis and/or end-stage renal disease.[4] Pneumonia patients diagnosed at least 48 hours after hospitalization were considered hospital-acquired and excluded from the study population. Patients below age of the 18 were excluded. Patients who had no pulmonary imaging compatible with pneumonia were also excluded.

Microbiological Analysis

We collected all the available microbiologic data including bacterial, fungal cultures and viral analysis from the respiratory tract (sputum, tracheal aspirate, bronchoalveolar lavage fluid), blood, and pleural fluid. In our institute, conventional culture methods and Gram stain examinations are used to identify bacterial agents from respiratory tract specimens. Bacterial isolates not described through conventional methods are evaluated by BD Phoenix™ automated identification and susceptibility testing system. Only the specimens considered clinically relevant were taken into analysis.[15]

BD BACTEC™ (BD Diagnostic Systems) blood culture automatized instruments are used to detect bacterial growth from blood cultures. We analyzed blood culture results from medical records (coagulase-negative staphylococci were considered as contamination).

The data on respiratory viral pathogens were acquired from nasopharyngeal/oropharyngeal swab studies when available. BioFire® FilmArray® Respiratory Panel commercial kits are used in our institute, and the panel detects influenza A virus, influenza B virus, H1N1, H3N2, human metapneumovirus, rhinovirus, human parainfluenza virus type 1-4, adenovirus, bocavirus, human coronavirus HKU, NL63, and OC4 through real-time PCR (RT-PCR) method.

Statistical Analysis

Statistical analysis was performed through the SPSS software (Statistical Package for the Social Sciences, version 21.0 SSPS Inc., Chicago, IL). For parametric data following normal distribution Student's *t*-test, and independent samples with non-normal distribution, Mann–Whitney *U*-test was used. Categorical data were analysed by using Pearson's chi-square test and Fisher's exact tests. Kaplan–Meier analysis was performed to estimate survival function. Data were presented as numbers and percentages for categorical variables and as medians with interquartile ranges for continuous variables. Variables with significant differences were presented with a relative risk (RR) 95% confidence interval (CI). *P*-value <0.05 was considered statistically significant.

Results

We detected 140 CAP patients who attended the ED during the study period and evaluated every case. The selected characteristics of participants are presented in Table 1. The median age was 66.5, 58.6% of the patients were male, 53.5% were at least 65 years old.

Among the patients, 42.9% had active malignancy, and 49.3% were immunosuppressed due to malignancy or treatment applied for a malignant or an autoimmune condition. Chronic pulmonary diseases (excluding asthma) were the most common comorbidity secondary to malignancy.

The median value for PSI, CURB-65, qSOFA, and CCI were 4, 2, 1, and 5, respectively (Table 1). Imaging was consistent with lobar consolidation for 49% of the patients.

72.7% of the patients were admitted and treated as inpatients. Overall, two-thirds of patients received empirical combination antibiotherapy. Among the initial treatments were piperacillin-tazobactam (38%), quinolones (31%), macrolides (28.5%), cephalosporins (26.5%), and carbapenems (13%). Antipseudomonal antimicrobial treatment was used in 70.7% of the patients. One-third of the patients received antibiotics within one hour of admission.

Microbiological investigations were undertaken in 124 patients, including blood cultures (n:95), clinically relevant sputum cultures (n:55), nasopharyngeal swab for viral pathogen detection (n:51), bronchoalveolar lavage fluid cultures (n:7), *Legionella* urinary antigen testing (n:6), pleural aspirate cultures (n:2). Among the clinically relevant sputum samples, 60% (n:33) had positive cultures. *Pseudomonas aeruginosa* (n:15) was the most frequently identified bacterial pathogen, followed by *Haemophilus influenzae* (n:9) and *Streptococcus pneumoniae* (n:5). Viral pathogens were detected in 20 patients, most

Table 1 Selected Features of Patients (N:140)

Features	Values
Male sex, *n* (%)	82 (58.6)
Age in years, median IQR[a]	66.5 (21–95)
CCI[b], median[c] <6 points, *n* (%) ≥6 points, *n* (%)	5 89 (66.4) 45 (33.6)
CURB-65[d] score, median ≥2, *n* (%)	2 72 (51.4)
PSI[e] class, median[f] ≥3, *n* (%)	4 109 (81.9)
Comorbidities, *n* (%) Malignancy Chronic pulmonary diseases Autoimmune/rheumatologic diseases Diabetes mellitus Chronic heart diseases Transplantation Chronic kidney diseases	 60(42.9) 35 (25.0) 26 (18.5) 21 (15.0) 17 (12.1) 11 (7.0) 8 (5.0)
Immunosuppressive Condition, *n* (%)	69 (49.3)
Inpatient Care in Previous 90 Days, *n* (%)	54 (38.6)
Antibiotic Usage in Previous 90 Days, *n* (%)	73 (52.1)
30-day Mortality, *n* (%)	25 (17.8)

Notes: [a]IQR; Interquartile range, [b]CCI; Charlson comorbidity index, [c]6 missing values, [d]CURB-65 score; Confusion, urea, respiratory rate, blood pressure, [e]PSI; Pneumonia severity index, [f]7 missing values.

frequently influenza virus. Blood cultures were mostly sterile, with growth reported in only ten cases, of which seven were considered contamination. Overall, the microbiologic agent responsible for pneumonia was isolated in 38.5% (n:54) (Table 2).

The overall 30-day mortality rate was 17.8% (n:25), and mortality rates were even higher in patients who did not achieve initial response to treatment (7% vs 51.4%, $p<0.001$). The mortality rates were significantly higher in patients with sputum cultures positive for *P. aeruginosa* or positive for multiple bacteria (35.2%, $p=0.049$). In predicting mortality, the most efficient ResR threshold to define tachypnea at presentation was ≥22 breaths per minute. The mortality rates were significantly higher in patients who presented with tachypnea (RR=3.01, p=0.01), in patients with high scores in pneumonia severity index (RR=2.43 for PSI V, RR=3.77 for CURB-65 ≥ 2), and in patients who failed to achieve IRT at the third day of treatment (RR=6.48) (Table 3). The latter also appeared to be the strongest predictor of mortality (Figures 1 and 2).

We evaluated the initial response to treatment on the third day for 99 patients (70.7%), and 63 of them had an IRT. Age, gender, empirical antibiotic choices, and timing of antibiotics or lung involvement type did not affect the likelihood of initial treatment response. Besides that, any laboratory parameter except LDH at presentation such as leucocyte count, neutrophil, CRP, procalcitonin, lactate, or creatinine did not affect the initial treatment response rates (Table 4). Patients with malignancy had a numerically less IRT, but it was not statistically significant (57.7% vs 68.5%, $p=0.269$). Although statistically insignificant, a higher PSI class was associated with a worse IRT to treatment (PSI IV–V; p=0.076). CURB-65 score, CCI, and qSOFA score at presentation also did not discriminate patients responsive to initial treatment from those who were initially unresponsive (Table 4). Patients who received antibiotics within the first hour of admission had

Table 2 Microbiologic Data

Test	*n* (%), Patients (*n*:140)
Sputum culture obtained	72 (51.4)
Growth detected	33 (45.8)
Pseudomonas aeruginosa	11 (33.3)
Haemophilus influenzae	8 (24.2)
Streptococcus pneumoniae	4 (12.1)
MSSA	1 (3.0)
Others[a]	3 (9.0)
Polymicrobial[b]	6 (18.0)
Nasopharyngeal swab obtained	51 (36.4)
Positive[c]	20 (39.2)
Influenza virus	10 (50.0)
Rhinovirus	2 (10.0)
Blood Culture	95 (67.8)
Streptococcus pneumoniae	2 (20.0)
Pseudomonas aeruginosa	1 (10.0)
CoNS	7 (70.0)
Bronchoalveolar lavage fluid Culture	7 (5)
MTC	1 (14)
Pseudomonas aeruginosa	3 (52)
Pneumocystis jirovecii + CMV DNA	1 (14)
Pleural Fluid Culture	
MTC	1 (14)

Notes: [a] *Nocardia* spp., *Acinetobacter* spp., *Alcaligenes faecalis*. [b] *Pseudomonas aeruginosa+ Klebsiella pneumoniae; Klebsiella pneumoniae+ Streptococcus pneumoniae; MSSA+ Haemophilus influenzae; MSSA+ Pseudomonas aeruginosa+Escherichia. coli; Pseudomonas aeruginosa+ Enterobacter* spp.; *MSSA+Pseudomonas aeruginosa*. [c]Others; n:8 (40%).

Abbrviations: MSSA; Methicillin sensitive *Staphylococcus aureus*, CoNS; Coagulase negative staphylococci, MTC; *Mycobacterium tuberculosis* complex.

Table 3 Factors Related to 30-Day Mortality Rates

Factor	Mortality (%)	Relative Risk (RR), *p*
Charlson's Comorbidity Index[a] ≥ 6 points < 6 points	 31.1 12.6	 2.63, %95 CI: 1.22–4.96, *p*=0.010
PSI[b] Class I–IV Class V	 13.8 32.4	 2.43, %95 CI: 1.18–4.65, *p*=0.014
CURB-65 score[c] 0–1 point 2-3-4 points	 7.0 28.1	 3.77, %95 CI: 1.58–9.48, *p*= 0.004
Age in years < 65 65–80 > 80	 9.3 24.5 28.5	 0.37, %95 CI: 0.15–0.85, *p*= 0.013 (< 65 vs ≥ 65)
Initial response to treatment Yes No	 7.0 51.4	 6.48%95 CI: 2.63–15.94, *p*<0.001
Respiratory Rates (ResR) ≤ 20 vs > 20 < 22 vs ≥ 22 < 30 vs ≥ 30	 8.7 vs 25.6 8.6 vs 25.9 14.4 vs 32.2	 2.92, %95 CI: 1.16–7.32, *p*=0.02 3.01, %95 CI: 1.26–7.55, *p*=0.01 2.23, %95 CI: 1.11–4.46, *p*=0.02
Pulmonary Infiltration Lobar Atypical/Multilobar	 12.9 24.6	 *p*=0.087
Sputum Culture No Growth *PsA*+ Polymicrobial	 15.7 35.2	 2.07, %95 CI:1.04–4.82, *p*=0.049[d]
Empirical Antibiotherapy Beta-lactam monotherapy Combined antibiotic regimen[e]	 24.4 20.8	 p>0.05

Notes: [a]CCI; Charlson comorbidity index, [b]PSI; Pneumonia severity index, [c]CURB-65 score; Confusion, urea, respiratory rate, blood pressure, [d]No growth detection vs growth detected, [e]macrolide or quinolone plus beta-lactam.

an initial response rate of 54.5%, compared to 68% for others. Both subgroups had similar 30-day mortality rates. Patients who received antibiotics within one hour of admission were more likely to have high-risk qSOFA scores than others (28.5% and 13.9%, p = 0.04).

Mortality rates and IRT did not differ between patients who received beta-lactam monotherapy or combined antibiotic regimen (24.4% vs 20.8%, p>0.05) (Table 3). We found that mortality rates of patients treated in the outpatient and inpatient settings were 7% and 21.5%, respectively (p=0.054).

Discussion

We conducted this study to primarily find out 30-day mortality rates and associated risk factors in immunocompromised CAP cases. The studied condition closely resembled the entity formerly known as "Health-Care Associated Pneumonia" (HCAP) which has been underrepresented in the literature due to the omission of HCAP in the latest guidelines. We discovered that initial response to treatment was the strongest predictor of survival. Age, respiratory rate at presentation, clinical severity indices, and particular sputum culture growth were also determiners of 30-day mortality rates.

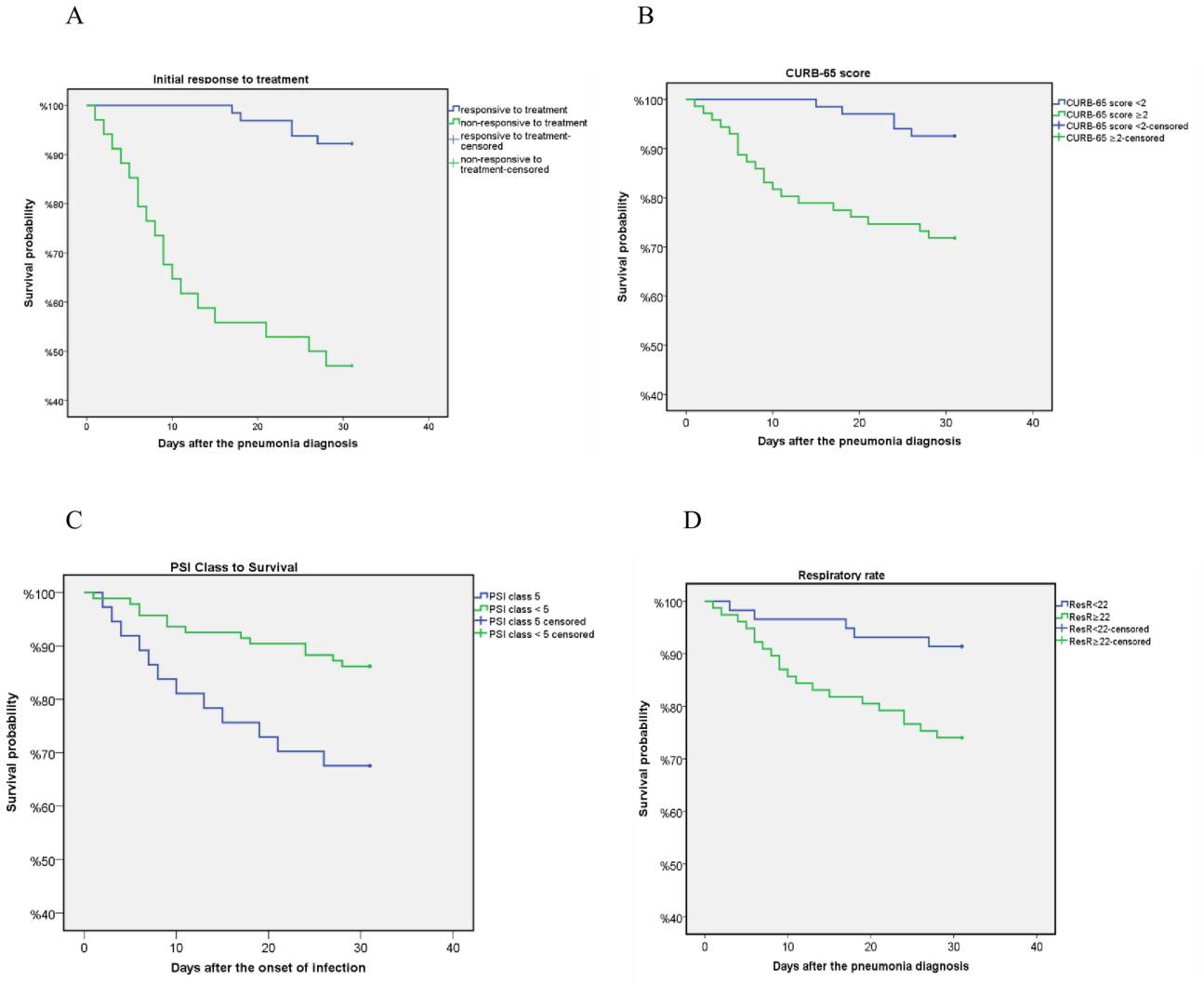

Figure 1 Survival analysis of prognostic factors. (**A**) Effect of initial response to treatment at day 3 on survival. Patients who were non-responsive to the treatment had strikingly higher mortality rates. (**B**) Effect of CURB-65 scores at the presentation on survival. Patients with CURB-65 score equal to or above 2 had more unfavorable outcome. (**C**) Effect of PSI class at the presentation on survival. Patients with PSI class 5 comparing to others had poorer prognosis. (**D**) Effect of tachypnea at the presentation on survival. Patients with respiratory rates ≥22 had more unfavorable outcome.

Across various studies, *S. pneumonia* has remained the most frequently identified bacteria in patients with CAP, and *P. aeruginosa* is responsible for CAP under specific circumstances.[16–19] The predominance of *P. aeruginosa* was remarkable in our study, and it was fourfold higher in those with chronic pulmonary diseases. Detection of *Pseudomonas aeruginosa* was also associated with increased mortality rates in the study. The added benefits of sputum collection include the opportunity to study antimicrobial susceptibility to guide antibiotherapy revisions and accumulate data to define local antimicrobial resistance patterns. Our findings highlight the importance of obtaining sputum samples in patients suspected of having CAP. This is also emphasized at the recommendations of ATS/IDSA 2019 CAP guideline.[20]

The ResR cut-off to define tachypnea differs among studies. However, it is an easy-to-measure vital sign which helps discriminate stable patients from those at risk for complications.[21] Ito et al described tachypnea (ResR>30) as a poor prognostic factor in CAP.[22] We analyzed our data to define an optimal cut-off value for tachypnea. Patients with ResR≥22 had a RR of 3.01 (p=0.01) for death and was the cut-off with the strongest significance. It was also a valuable parameter to identify patients with risk of rapid deterioration and future requirements of ICU care. Respiratory rate is one of the most neglected vital signs in patient evaluation, as our findings also emphasize that rates above the normal range should be approached with caution.[23]

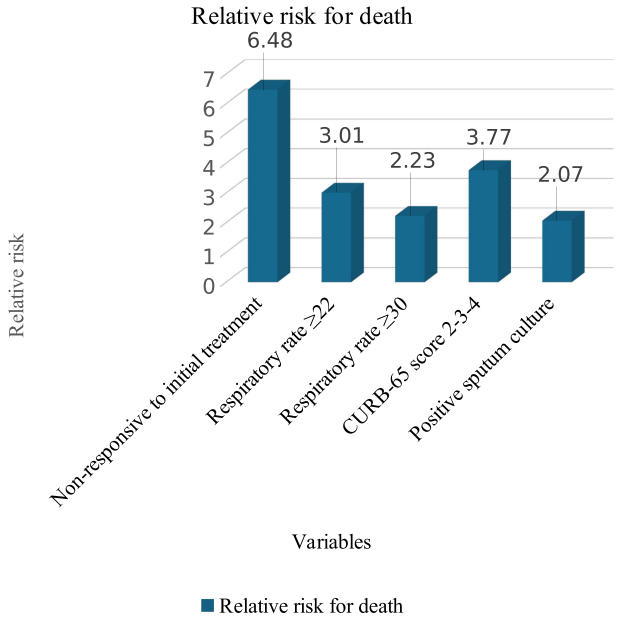

Figure 2 Relative risk analysis for 30-day mortality according to prognostic factors. Tachypnea, sputum culture positivity and non-responsiveness to the initial treatment are all negative indicators which are responsible for increase in 30-day mortality.

CURB-65 and PSI has been validated in immunocompetent patients with CAP and their prognostic accuracy in immunocompromised patients is unknown.[24–26] Carrabba et al showed that both scoring systems were a poor predictor of mortality in immunosuppressed healthcare-associated pneumonia patients.[14] In our study population, 30-day mortality was increased in higher PSI class and CURB-65 scores. Although the respiratory rate threshold used in both scoring

Table 4 Initial Response to Treatment and Related Factors

	Responder n:63, %	Non-Responder n:36, %	*p*	*t* test
Male sex	37 (58.7)	27 (75.0)	0.103	
PSI[a] class				*t* (97)=−1.94, *p*=0.045
I	2 (5.0)	0	-	
II	12 (32.4)	4 (11.1)	0.302	
III	11 (29.7)	4 (11.1)	0.396	
IV	23 (62.1)	15 (41.6)	0.611	
V	15 (40.5)	13 (36.1)	0.191	
CURB-65[b] score				*t* (97)=−1.15, *p*=0.256
0	13 (20.6)	6 (16.6)	0.629	
1	16 (25.3)	8 (22.2)	0.722	
2	23 (36.5)	12 (33.3)	0.750	
3	8 (12.6)	6 (16.6)	0.585	
4	3 (4.0)	4 (11.1)	0.235	
5	-	-		
CCI[c]				*t* (97)=−1.30, *p*=0.232
≥ 6 points	17[d] (28.3)	15 (41.6)	0.179	
Age in years ≥ 65	29 (46.0)	20 (55.5)	0.361	*t* (97)=−0.16, *p*=0.871
Respiratory Rate			0.041	*t* (96)=−2.04, *p*=0.043

(*Continued*)

Table 4 (Continued).

	Responder n:63, %	Non-Responder n:36, %	*p*	*t* test
Empirical Antibiotherapy				
B-lactam	27 (42.8)	11 (30.5)	0.256	
B-lactam+Macrolide	15 (23.8)	11 (30.5)	0.415	
B-lactam+FQ[e]	15 (23.8)	10 (27.7)	0.608	
FQ	4 (6.0)	2 (5.0)	0.896	
Time to initial antibiotic administration (first hour)	18 (27.6)	15 (41.6)	0.185	
CRP[f] (mg/L)			0.991	t (97)=0.12, p=0.991
Procalcitonin (ng/mL)			0.115	t (81)=−0.99, p=0.921
Leucocyte (cells/mm^3)			0.534	t (97)=−0.59, p=0.555
LDH[g]			0.008	t (89)=−2.82, p=0.006

Notes: [a]PSI; Pneumonia severity index, [b]CURB-65; Confusion, urea, respiratory rate, blood pressure, [c]CCI; Charlson's Comorbidity Index, [d]3 missing data, [e]FQ; Fluoroquinolone, [f]CRP; C-reactive peptide, [g]LDH; Lactate dehydrogenase.

systems is ≥30 breaths per minute, our findings yielded that defining threshold of 22 alone was as powerful as PSI or CURB-65 to predict mortality.

The initial response to treatment as a parameter to predict outcomes of CAP with simple clinical criteria was evaluated in multiple studies. Aliberti et al showed that once a clinically stable state is reached, deterioration is a rare event.[27,28] Blasi et al conducted a study with 2039 hospitalized CAP patients.[29] Time to clinical stability was evaluated using Halm's criteria, and they found that 332 of the patients had an early response, 253 of the cohort had not, remaining patients were not assessed for early response. They showed that patients without an early response needed more treatment modification (31.8% vs 14.2%), had higher admission rates to ICU (15.6% vs 3.3%), and had higher mortality (8.5% vs 0.6%) compared to those with an early response.[29] Rosón et al conducted a prospective study with 1383 non-immunosuppressed hospitalized adults with CAP and revealed that patients with early treatment failure had significantly higher rates of complications (58% vs 24% $p < 0.001$) and overall mortality (27% vs 4%, $P < 0.001$).[30] Adding to these other studies, we came upon the lack of response to treatment at day 3 as the strongest parameter to distinguish patients with an excessively high 30-day mortality from those who performed relatively well (51.4% vs 7%, RR 6.48, $p<0.001$). Initial response to treatment rates did not differ according to age, comorbidities, empirical antimicrobial therapy (beta-lactam monotherapy or beta-lactam plus macrolide or quinolone), and time to first antibiotic dose. In multivariate analysis, among the clinical features at the presentation, high LDH levels, high PSI class, and presence of tachypnea were correlated with poor response to initial treatment. Our finding of excessively high mortality rate in CAP patients without an early treatment response exposes an unmet need. Clinical assessment for response at day three may be effective in relatively early identification of immunocompromised CAP patients who are most likely to benefit from experimental approaches by inclusion into clinical trials.

The findings may also be significant in terms of reevaluating the potential clinical significance of the former pneumonia category the HCAP which had been purposefully excluded from the latest pneumonia guidelines as it underperformed in identifying drug-resistant pathogens. However, the population that was addressed in this study as non-nosocomial pneumonia cases among patients with chronic diseases resembles that of the former HCAP population demonstrating certain unique and adverse features to other CAP cases.

Our study has several limitations. First, the study design was observational, and the study population was gathered from a single center for a predetermined period that limited the number of patients included. Antibiotic susceptibility results of microbiological cultures were not available for nearly half of the study population. This prevented us from making clear comments for drug resistance and the appropriateness of empirical antibiotics. As a result of the non-interventional design of the study, we had missing data which reduced the number of patients where certain parameters could be analysed including the initial response to treatment, PSI, and time to first antibiotic dose. The non-interventional design also impaired the homogeneity in timing and selection of the laboratory examinations (testing for respiratory

viruses) and imaging. These limitations should be considered while interpreting the data of this study and conclusions should be drawn with caution.

Conclusions

As a result, we observed that sputum culture results predict the prognosis of CAP patients sustaining the importance of the effort to obtain sputum specimens in susceptible hosts. The study supports using the PSI and CURB-65 scores to risk-stratify the immunocompromised CAP patients. Moreover, the ideal threshold defining tachypnea was 22 to predict poor prognosis for the study population. Most strikingly, the presence or absence of an initial treatment response emerged as the strongest predictor of mortality with more than half of patients without an initial treatment response succumbing in the first month. While needing validation in future studies, the dismal outlook in the initially unresponsive patients indicates an unmet need in the management of CAP effecting the susceptible host. We consider that the assessment of the initial treatment response is a potential method to identify the group of immunocompromised patients who may benefit from experimental approaches through controlled clinical studies.

Statement of Ethical Compliance

The study was approved by the Istanbul University Ethical Board on 29.03.2019 with the approval number 2019/448. All authors agreed and gave signature for the conduct of this study in compliance with the principles of the Declaration of Helsinki. All patient data was anonymized in the pre-analytic stage and the manuscript does not contain any individual patient data that could contain identifiers of any potential. Informed consent for the anonymized use of data for research purposes was not considered necessary for retrospective clinical research by the ethical committee in accordance with the regulations governing clinical research in Turkey (Official Newspaper number: 28617 (April 13, 2013)). Anonymized use of retrospective medical data was clearly stated in the ethical board application without an attached consent form. All patients with the compatible diagnosis within the research period were included consecutively regardless of clinical severity, to ensure unbiased analysis.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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