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RESEARCH

INDEPENDENT PROGNOSTIC INDICATORS IN THE ELDERLY WITH PNEUMONIA: A SINGLE-CENTRE PROSPECTIVE OBSERVATIONAL STUDY

Abstract

Background: The goal of this study was to identify and investigate the indicators of a poor prognosis in the elderly with pneumonia.

Material-Method: In this prospective observational study, the patients with pneumonia were stratified into younger (18 to 64 years) and older (more than 65 years) groups. The poor prognostic indicators were determined and compared.

Results: A total of 184 pneumonia episodes in 151 patients were recorded. The median age was 72 (18-104) of whom 127 (69%) were more than 65 years old and 110 (59.8%) were male. A multivariate regression analysis identified three variables that could be potential independent risk factors for a poor prognosis in the elderly: 1) dyspnea at the onset (OR:5.85, CI:5.18-6.52, p=0.01), 2) use of antibiotics within the last three months (OR:2.97, CI:2.51-3.43, p=0.02) and 3) acute renal failure (OR:2.51, CI:2.06-2.96, p=0.04). A receiver operating characteristic analysis showed that the areas under the curves of procalcitonin and C-reactive protein as indicators of a poor prognosis in the elderly were 0.846 (p<0.001) and 0.650 (p=0.008). In addition, changes in mental status (p<0.001), confusion, blood urea nitrogen, respiratory rate, blood pressure, and age ≥65 years score (p<0.001) and pneumonia severity index (p<0.001) were associated with a poor prognosis.

Conclusion: Dyspnea at the onset, use of antibiotics within the last three months, acute renal failure, serum C-reactive protein and procalcitonin levels should be carefully evaluated to determine the need for hospitalization, intensive care, and initial antimicrobial therapy.

Keywords: Aging; Pneumonia; Prognosis

BACKGROUND

Pneumonia is one of the most common acute infectious conditions causing fatality at any age. Treatment of pneumonia typically commences empirically based on clinical, radiological and non-specific laboratory findings (1).

Whether acquired in the community or the hospital, pneumonia leads to more severe outcomes in the elderly than the young. The results are a significant increase in health care costs due to prolonged hospitalization and the use of multiple antibiotics (2). As a result, we must develop new clinical strategies to reduce mortality and morbidity rates in the elderly.

The purpose of this prospective study was to identify and investigate the indicators of a poor prognosis in the elderly with pneumonia. We compared the risk factors, clinical and laboratory findings, severity of the course and the treatment responses in patients with pneumonia over and under-age 65.

METHODS

This prospective observational and single-centre study included patients aged 18 years or older who were diagnosed with pneumonia by the Department of Infectious Diseases and Clinical Microbiology between January and December of 2017.

Patients with community-acquired pneumonia (CAP) requiring hospitalization or hospital-acquired pneumonia (HAP) were included in the study. Outpatients, patients with neutropenia, and ventilatory-associated or postoperative pneumonia were excluded. The diagnosis of pneumonia was made on the basis of current guidelines (3-6). A total of 184 pneumonia episodes in 155 patients were recorded.

A "recurrent episode" was defined as an episode of recurrent pneumonia at least 30 days after the initial diagnosis of pneumonia during the one-year follow-up period. Each episode of pneumonia was recorded separately.

The data on demographics, underlying diseases, immunosuppressive conditions, symptoms and findings of physical examinations, laboratory test results, radiological findings, and treatments and responses were recorded in a follow-up data sheet. The cases were divided into two groups according to their ages (over or under 65) with the comparative analyses applied.

Modified Charlson comorbidity scores were calculated for all the patients. The CURB-65 and (PSI) scores were calculated only for patients with community-acquired pneumonia.

Based on tympanic membrane measurement, fever was defined as the body temperature of 37.8 °C or greater for patients 65 or older and 38 °C or greater for patients under 65. Hypothermia was defined as a body temperature of less than 35.6 °C.

A "poor prognosis" was defined as the development of septic shock associated with infection and/or the need for intensive care and/or death within 30 days.

Dependent variables were compared with many independent variables such as demographic, clinical and laboratory parameters. The Friedman Variance Analysis was used to assess continuous and more than two dependent non-parametric groups. The Wilcoxon Signed Ranks Test was used for post-hoc analysis. Afterward, these dependent groups were reviewed one by one. Receiver operating characteristic (ROC) curves were drawn and Area Under the Curve (AUC), cut-off values and sensitivity and specificity of cut-off values were shown.

Non-parametric groups containing two continuous sets of data were compared, and the Mann Whitney U Test was used to determine the significant difference. The significance of the categories of dependent groups and categorical independent groups was determined using a Chi-

Table 1. The demographic characteristics of the cases in terms of age groups.

	In total		<65 years		≥65 years		p
	n	%	n	%	n	%	
Number of cases	184	100	57	44.9	127	55.1	<0,001
Mean age ±se	69.27 ±1.23		49.63 ±1.68		78.09 ±0.81		<0.001
Median age	72		53		76		
Male	110	59.8	28	49.1	82	64.6	0.048
Female	74	40.2	29	50.9	45	35.4	
CAP	145	78.8	51	89.5	94	74.3	0.561
HAP	39	21.2	6	10.5	33	26	0.019
Aspiration associated pneumonia	13	7.1	4	7	9	7.1	1.000
Underlying disease	174	94.6	50	87.7	124	97.6	0.011
COPD	58	31.5	8	14.0	50	39.4	0.001
Diabetes mellitus	61	33.2	12	21.1	49	38.6	0.020
Hypertension	99	53.8	19	33.3	80	63.0	0.000
Congestive heart failure	36	19.6	5	8.8	31	24.4	0.015
Cerebrovascular disease	16	8.7	2	3.5	14	11.0	0.155
Chronic renal failure	64	34.8	9	15.8	55	43.3	<0.001
Malignancy	51	27.7	20	35.1	31	34.4	0.135
Cystic fibrosis	1	0.5	1	1.8	0	0	-
Asthma	10	5.4	1	1.8	9	7.1	0.178
Bronchiectasis	4	2.2	4	7.0	0	0	-
Coronary artery disease	52	28.3	7	12.3	45	35.4	0.001
Dementia	22	12.0	0	0	22	17.3	<0.001
Immunosuppression	36	19.6	21	36.8	15	11.8	<0.001
Chemotherapy	16	8.7	8	14.0	8	6.3	0.096
Steroid	14	7.6	8	14.0	6	4.7	0.037
Immunosuppressive disease	9	4.9	4	7.0	5	3.9	0.462
Radiotherapy	8	4.3	3	5.3	5	3.9	0.705
History of previous tuberculosis	10	5.4	7	12.3	3	2.4	0.011
Smoking history	94	51.1	24	42.1	70	55.1	0.103
Previous antibiotic use within the last 3 months	101	54.9	30	52.6	71	55.9	0.412
Hospital stay within the last 1 year	95	51.6	32	56.1	63	49.6	0.638
ICU stay within the last 1 year	24	13.0	6	10.5	18	14.2	0.638
Cough	145	78.8	51	89.5	84	74.0	0.019
Sputum	121	65.8	42	73.7	79	62.2	0.135
Dyspnea	141	76.6	48	84.2	93	73.2	0.132
Mental disorder	25	13.6	3	5.3	22	17.3	0.035
Fever	83	45.1	29	50.9	54	42.5	0.292
Hypothermia	15	8.2	6	10.5	9	7.1	0.561
Hemoptysis	13	7.1	9	15.8	4	3.1	0.004
Acute renal failure	63	34.2	18	31.6	45	35.4	0.737
Mechanical ventilation	25	13.6	5	8.8	20	15.7	0.249
Dialysis	5	2.7	2	3.5	3	2.4	-
Intensive care need	29	15.8	7	12.3	22	17.3	0.512
Poor prognosis	55	29.9	17	29.8	38	29.9	1.000
Death	19	10.3	4	7	15	11.8	0.435

TBNA: Transbronchial Needle Aspiration; TBLB: Transbronchial Lung Biopsy; BLVR: Bronchoscopıc Lung Volume Reduction

Square Test. A Fisher's Exact Test was used in cases where n<20 or 20<n<40 and at least one expected value was less than 5. Yates was chosen when n>40 and the minimum expected value was less than 5. In all cases, except those using the Pearson Chi-Square Test, the results were accepted. A univariate and multivariate analysis was performed to define significant variables.

The results were evaluated at a 95% confidence interval with the statistical significance level defined as p<0.05. The analyses were performed using the IBM SPSS - 21 (Statistical Package for Social Sciences, Chicago, IL, USA).

RESULTS

A total of 184 pneumonia episodes in 155 patients were recorded. Of these episodes, 145 (78.8%) were CAP and 39 (21.2%) were HAP. Twenty-nine recurrent episodes were recorded during the one-year follow-up. Thirteen (7.1%) episodes were directly attributable to in-hospital pulmonary aspiration.

The median age was 72 (range of 18 to 104) of whom 127 (69%) were over 65 years old and 110 (59.8%) were male. Of the 127 cases, 53 (41.7%) were in the 65-74 age group, 44 (34.6%) were in the 75-84 age group, and 30 (23.6%) were more than 85 years old. The demographic characteristics of the cases are shown in Table 1. Death (20,5% vs. 7,6%, p=0,040) and the need for intensive care (37,9% vs. 18,1%, p=0,016) were more frequent in patients with HAP compared to patients with CAP.

Microbiological evidence was obtained in 37 (20.1%) cases (26 in sputum culture, one in both blood and sputum culture, four in the respiratory system using a multiplex polymerase chain reaction, two in a bronchoalveolar lavage culture, two in an endotracheal aspirate and two in a transtracheal aspirate).

Blood culture was obtained in 114 (62%) cases, and sputum culture was evaluated in 76 (41.3%) cases. Positive blood culture was observed in only one case. Of the sputum cultures, the causative microorganisms were isolated in 27 (35.5%) cases.

Pseudomonas spp. (n=11, 29.7%) was the most common agent, followed by Streptococcus pneumoniae (n=6, 16.2%). Although Pseudomonas spp. was more frequent in the elderly compared to the younger group (n=8 vs. n=3), there was no significant difference between the two groups (p=0.54). Other typical bacterial agents were Haemophilus influenzae (n=5, 13.5%), Acinetobacter spp. (n=4, 10.8%) and Staphylococcus aureus (n=4, 10.8%). Of the Staphylococcus aureus strains, 25% had methicillin resistance. The rate of carbapenem resistance was 45.4% in Pseudomonas spp. and 50% in Acinetobacter spp.

Among the atypical agents, Mycoplasma pneumoniae in one case, Influenzavirus in two cases, Metapneumovirus in one case, Human coronavirus 229E (coupled with Streptococcus pneumoniae) in one case were detected using multiplex PCR in the respiratory system.

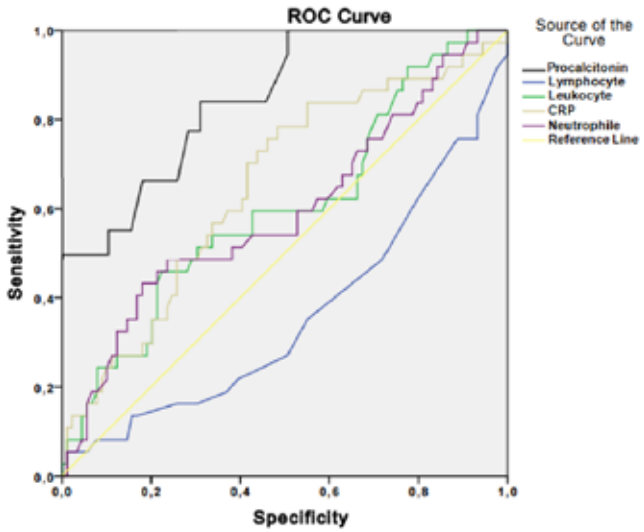
In terms of culture positivity, there was no significant difference between the elderly and the younger group. However, the availability of sputum samples was significantly lower in the elderly group (p= 0.04).

Table 2 summarizes the statistical analysis of these dependent parameters with mean and median values by age group on days D0, D3 and D7.

A ROC analysis showed that AUC of procalcitonin and CRP as indicators of a poor prognosis in the elderly were 0.846 (p<0.001) and 0.650 (p=0.008) (Figure 1). For a poor prognosis, the cut-off value of procalcitonin was 0.295 ng/mL in the elderly group with a sensitivity of 83% and a specificity of 69% (p<0.001). The cut-off value of CRP was 79 mg/L with a sensitivity of 79% and a specificity of 52% (p =0.008).

In the Chi-square test, poor prognostic

Figure 1. Receiver operating characteristic curve of procalcitonin, CRP levels, leukocyte, neutrophile and lymphocyte counts for prediction of poor prognosis of elderly with pneumonia



indicators are shown in (Table 3). There was no statistically significant relationship between body temperature and a poor prognosis (p=0.157). In addition, a recurrent episode (p=0.418) and Pseudomonas spp. (p=0.573) were not associated with a poor prognosis.

Age-dependent and independent analyses, including univariate and multivariate regression, revealed that dyspnea, use of antibiotics within the last three months and acute renal failure were associated with a poor prognosis. Table 4 shows the odds ratios (OR), confidence intervals (CI) and p values for all ages and for those 65 years or older.

DISCUSSION

In this prospective observational study of pneumonia in the elderly, patients with pneumonia were divided into younger (18 to 64 years) and older (over 65 years) groups. The indicators of a poor prognosis were determined and compared in both age groups. We identified three variables that could be potential independent risk factors for a poor prognosis in the elderly with pneumonia: 1) use of antibiotics within the last three months (OR:2.97, CI:2.51-3.43, p=0.02), 2) acute renal failure (OR:2.51, CI:2.06-2.96, p=0.04) and 3) dyspnea (OR:5.85, CI:5.18-6.52, p=0.01). Also, we found that serum procalcitonin (p<0.001) and CRP levels (p=0.008) were valuable indicators of a poor prognosis in the elderly. In addition, mental status changes, the CURB-65 score, and the pneumonia severity index (PSI) as well as the independent risk factors were associated with a poor prognosis for those 65 years and older.

Exposure to antibiotics is one of the primary reasons for increased pneumonia cases. With an increase in resistant microorganisms, that exposure leads to a lack of response to empirical antimicrobial therapies. Ruhe et al. (7) showed that previous use of antibiotics is a risk factor for infection with drug-resistant Streptococcus pneumoniae. In our study, the rate of previous antibiotic use within the last three months was high in the elderly (n=71, 55.9%) and in the younger group (n=30, 52.6%). Also, use of antibiotics within

Table 2. The analysis of five dependent laboratory parameters on D0, D3 and D7.

		D0		D3		D7	
Age		<65	≥65	<65	≥65	<65	≥65
WBC*	Mean ± se	12,761.40 ±845.07	11,971.65 ±527.41	9,575.80 ±617.70	10,215.49 ±506.77	10,209.80 ±660.69	10,297.98 ±634.44
	Median	11900	11900	9295	9200	10000	9050
	p	0.460		0.755		0.587	
Friedman p<0.001		The day which is made a significant difference was D0.					
CRP*	Mean ± se	181.68 ±15.86	118.11 ±8.34	79.47 ±11.13	79.24 ±6.85	35.51 ±6.42	47.68 ±5.40
	Median	179	92	51	56	19	31
	p	0.001		0.755		0.119	
Friedman p<0.001		All the days were made a significant difference.					
PRC*	Mean ± se	2,.05 ±0.81	1.99 ±0.88	2.36 ±1.79	1.16 ±0.45	0.20 ±0.09	0.32 ±0.07
	Median	0.24	0.25	0.16	0.18	0.07	0.16
	p	0.758		0.703		0.002	
Friedman p<0.001		All the days were made a significant difference.					
NEU*	Mean ± se	11,017.54 ±896.59	9,399.68 ± 472.05	7,176.40 ±573.02	7,513.06 ±396.74	7,655.00 ±662.25	7,345.31 ±402.12
	Median	9,300	8,600	6,350	6,800	6,300	6,400
	p	0.173		0.702		0.792	
Friedman p<0.001		The day which is made a significant difference was D0.					
LYMP*	Mean ± se	1142,10± 88.04	1,560.48 ±226.04	1,498 ±133.11	1,641.65 ±332.71	1,757.31 ±161.53	1,943.77 ±465.30
	Median	1000	1,200	1,350	1,200	1,600	1,400
	p	0.072		0.354		0.235	
Friedman p<0.001		The day which is made a significant difference was D7.					

*WBC: Leukocyte CRP:C-reactive protein PRC: Procalcitonin NEU: Neutrophile LYMP: Lymphocyte

Table 3. Chi-square test for poor prognosis.

	Age-independent			**≥65 years**		
	n	%	p	n	%	p
Number of cases	184	100		127	55.1	
Cases with poor prognosis	55/184	29.9		38/127	29.9	
Gender			0.772			1.000
Male	32	58.2		25	65.8	
Female	23	41.8		13	34.2	
Dyspnea	52	94.5	<0.001	35	92.1	0.002
Mental status changes	18	32.7	<0.001	17	44.7	<0.001
Mechanical ventilation need	25	45.5	<0.001	20	52.6	<0.001
CURB-65 class			<0.001			<0.001
Class 1	8	21.1		1	4.0	
Class 2	10	26.3		7	28.0	
Class 3	20	52.6		17	68.0	
PSI class			<0.001			<0.001
Class 1	3	7.9		0	0	
Class 2	14	36.8		7	28.0	
Class 3	21	55.3		18	72.0	
Acute renal failure	28	50.9	0.002	20	52.6	0.014
Previous antibiotic use within the last 3 months	39	70.9	0.006	27	71.1	0.032
ICU stay within the last 1 year	12	21.8	0.03	9	23.7	0.055
Malignancy	22	40.0	0.015	12	31.6	0.261
Hospital-acquired pneumonia	17	30.9	0.048	13	34.2	0.189

the last three months was an independent risk factor for a poor prognosis in both age groups.

In our study, acute renal failure was an indicator of a poor prognosis in 52.6% of the elderly. Acute renal failure was also an independent risk factor for a poor prognosis. In a study by Murugan et al. (8), acute renal failure was associated increased mortality risk. Further, an increased severity of acute renal failure was correlated with the increased mortality rates.

In this study, dyspnea was found to be an independent risk factor for a poor prognosis. The diagnosis of pneumonia in the elderly is delayed because the signs and symptoms are infrequent (9). Although dyspnea was seen as less frequent in the elderly, it is vital for the prognostic evaluation. However, due to weak compensating mechanisms, multiple organ failure and changes in mental status develop more easily in the elderly (1). In our study, mental status changes were found to be more frequent in the elderly (p=0.035). This finding was consistent with other studies (9-10). That is why changes in mental status should be considered one of the most important indicators in the early diagnosis of pneumonia in the elderly. Also, a change in mental status may be the first clue leading to the diagnosis of pneumonia in this group.

In our study, fever and hypothermia were less frequent in the elderly group than in the younger

group. We know that fever is less frequent in the elderly population because of reduced host immune response. In this reduced response, the decrease in the production of endogenous pyrogens such as interleukin-1, interleukin-6, the tumour necrosis factor and the reduced response to these pyrogens has been thought to play a role. In addition, hypothalamic changes occurring in the aging process and changes in thermogenic brown fat tissue may also play a role in a decreased fever response to infections observed in the elderly (11-13).

In our study, sputum culture positivity was 40.4% in the elderly group and 25.8% in the younger group. In a study by Saltoglu et al. (14), microbiological evidence was obtained in 44% of the cases. In Gutierrez's study (15), the rate was high (50.7%). In contrast, microbiological evidence was obtained in 20.1% of the cases in our study. The rate at which the sputum sample was obtained in elderly patients was significantly lower than in the younger group (p=0.037). The reasons for the lower rates include use of antibiotics before inpatient treatment, and problems with sputum production and collection in the elderly.

In our study, Pseudomonas spp. that was isolated from clinical specimens were significantly higher compared to the other isolates. This may be because of previous antibiotic use and multiple comorbid diseases. Among cases with Pseudomonas spp., the rate of previous antibiotic use and multiple comorbid diseases (≥ 2 chronic comorbidities) were 81.8% and 63.6% respectively. von Baum et al. (16) reported that over age 65, congestive heart failure and cerebrovascular disease were indicators of Enterobacteriacea. Also, chronic respiratory disease and enteral tube feeding were indicators of Pseudomonas

Table 4. Univariate and multivariate analysis for poor prognosis

	Age-independent univariate analysis			**≥ 65 years univariate analysis**			**Age-independent multivariate analysis**			**≥ 65 years multivariate analysis**		
	OR	CI	p	OR	CI	p	OR	CI	p	OR	CI	p
Dyspnea	7.80	7.18-8.42	<0.01	8.97	8.32-9.62	<0.01	6.24	5.60-6.88	<0.01	5.85	5.18-6.52	<0.01
Hypothermia	2.21	1.66-2.76	0.15	3.23	2.57-3.89	0.07	1.98	1.28-2.68	0.33	2.97	2.13-3.81	0.19
Previous antibiotic use within the last 3 months	2.63	2.28-2.98	<0.01	2.95	2.57-3.33	<0.01	2.51	2.09-2.93	0.03	2.97	2.51-3.43	0.02
Acute renal failure	2.79	2.45-3.13	<0.01	3.07	2.69-3.45	0.01	2.84	2.44-3.24	<0.01	2.51	2.06-2.96	0.04
Modified Charlson class 1	1.30	0.78-1.82	0.95	0.84	0.29-1.39	0.79	2.00	1.11-2.89	0.44	2.08	1.14-3.02	0.43
Modified Charlson class 2	1.29	0.81-1.77	0.59	1.45	0.93-1.97	0.48	1.69	0.84-2.54	0.54	2.45	1.55-3.35	0.53
Modified Charlson class 3	1.94	1.48-2.04	0.15	1.88	1.36-2.40	0.22	2.40	1.56-3.24	0.30	2.45	1.45-3.35	0.32

aeruginosa. In our study, there was no significant relationship between Pseudomonas spp. as a causative agent and a poor prognosis (p=0.573). The rates of carbapenem resistance were also quite high in Pseudomonas spp. (45.4%) and in Acinetobacter spp. (50%). And 25% of Staphylococcus aureus strains were resistant to methicillin.

In this study, we found that serum procalcitonin and CRP levels were valuable indicators of a poor prognosis in the elderly. There are various studies showing the contribution of a complete blood count, CRP and procalcitonin in the diagnosis and follow-up of pneumonia. However, there are fewer studies evaluating elderly patients with pneumonia in relation to these parameters (17, 18). In our study, the mean CRP value on D0 was 181.68 ± 15.86 mg/L in the younger group and 118.11 ± 8.34 mg/L in the elderly (p=0.001). The difference between the older and younger group showed that the initial CRP values on D0 may be lower in the elderly group than in the younger group. In order to evaluate the potential for a poor prognosis, the optimal cut-off value of CRP on D0 was set at 91.5 mg/L in the age-independent group, and at 79 mg/L in the elderly group. In a study by Zhang et al. (18), CRP predicted a poor prognosis at least as accurately as procalcitonin. They found that the cut-off values were 74.2 mg/L for CRP, 78% for sensitivity and 75% for specificity.

In our study, procalcitonin was found to be the best prognostic indicator in the ROC curve in both the age-independent and elderly groups. In a meta-analysis by Liu et al. (19), the prognostic cut-off value of procalcitonin was less than 0.5 ng/mL in only two studies. However, our study was consistent with the studies showing that procalcitonin is a reliable prognostic indicator (20, 21). On the other hand, in 667 cases evaluated by Akagi et al. (17) procalcitonin was not an independent predictor of mortality in either the elderly or the young group, but was associated with the severity of pneumonia. Yazici et al. (22) showed that CRP and procalcitonin were not important for prediction of mortality in respiratory intensive care patients.

In the elderly, the immune response to infections is reduced due to immunosenescence, and a chronic, low-grade systemic inflammation occurs. Subclinical inflammation caused by exposure to various antigens in elderly patients manifests with relatively lower CRP and procalcitonin release. However, decreased procalcitonin levels in elderly patients can also be due to various etiologies of pneumonia with varying cytokine release patterns (17).

The modified Charlson comorbidity score was not correlated with poor prognosis in both age

groups. These findings suggest that the CURB-65 and the PSI are still superior to the modified Charlson comorbidity classification in accurately predicting the prognosis. Various studies have demonstrated that mortality rates are high in the elderly population (17,23). In our study, the 30-day mortality rates were found to be higher in the elderly group (11.8%) compared to the younger group (7%). However, they were not statistically significant (p=0.435). In a study by Saltoglu et al. (14), the mortality rate of 130 patients with CAP was 3% and the mean age was 40±13.6 years. The high mortality rate in our study may stem from the high mean age of the patients (69.27±1.23) and the inclusion of HAP with severe infection. The mean age of the younger group was also relatively high (49.63±1.68).

Our study had several limitations. First, it was conducted in a single centre. Second, the rate of microbiologically confirmed cases was low and we did not consider the causative pathogens other than Pseudomonas spp. as a risk factor. Our study has also several strengths. First, it is a prospective study. Second, multiple comorbidities and different types of variables were included in the multivariate regression analysis.

CONCLUSION

CRP and procalcitonin should be included in the diagnostic and prognostic work-up of elderly patients because the classic symptoms and signs of pneumonia are less common in this group. Dyspnea and acute renal failure at the onset should be considered along with the PSI and the CURB-65 scores to evaluate the need for hospitalization and intensive care. In addition, the use of antibiotics within the last three months and current rates of resistance to common causative microorganisms should be evaluated to determine the most effective initial antimicrobial therapy.

Ethics approval and consent to participate

This study was conducted in compliance with relevant laws and guidelines and in accordance with the ethical standards of the Declaration of Helsinki. It was approved by the Clinical Research Ethics Committee of Istanbul University Cerrahpasa Medical Faculty (approval number: 83045809-604.01.02-52675). All patients (or their authorized legal representatives) gave written informed consent to be included in the study.

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