Original Paper

Prognostic factors related with prolonged hospital stay in community-acquired pneumonia

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Key words:
- Community acquired pneumonia
- Length of hospital stay
- Outcomes
- Mortality

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ABSTRACT

BACKGROUND: Community-acquired pneumonia (CAP) is associated with higher morbidity, mortality and economic burden among adults. The cost of the disease increases according to the site of care (home, ward, ICU) and the length of hospital stay (LOS). The early recognition of prognostic factors for prolongs hospital stay it will be helpful to decrease the cost of CAP. **METHODS:** A prospective observational study of consecutive CAP patients was performed at Sotiria Hospital of Athens-Greece, between June 2011-July 2018. We divided the population in two groups: prolonged length of stay (PLOS) group (hospitalization equal or higher than the mean LOS) and short length of stay (SLOS) group (less than the mean LOS). **RESULTS:** Of a total 930 patients (55% men, 63.7 years (SD 18) with a mean length of hospital stay of 11 days (SD 9.6), 286 patients has PLOS of 20 days (SD 13). The patients with PLOS were older (66 y vs. 63y, p=0.023) and had received more often antibiotics before admission (53% vs. 44%, p=0.015). They presented with more severe CAP according to PSI score (115 vs. 98, p<0.001). The clinical evolution was more often complicated with systemic complications (43% vs. 19%, p<0.001) and need for ICU (14% vs. 6%, p<0.001) admission, but not with higher mortality. **CONCLUSIONS:** In the multivariate analysis, the severity of CAP (PSI class >4),previous antibiotics, hypoalbuminemia, therapy with corticosteroids, pulmonary complications and the non-adherence to guidelines are significantly related with prolonged hospitalization for CAP.
Pneumon 2019, 32(3):81-88.

INTRODUCTION

Community-acquired pneumonia (CAP) is a common cause of patient hospitalization, and its burden on health care systems is increasing in

aging societies[1,2]. Appropriate clinical management is important for reducing length of stay (LOS), health cost and mortality. Inpatient management is up to 20 times more expensive than outpatient care[3-5]. Safely reducing the number of inpatient days is cost-effective and physicians are under increasing pressure from health insurance providers and their own institutions to discharge patients from the hospital in as timely a manner as possible. In the last two decades LOS in CAP patients has continuously been declining safely and maintaining the quality of care[5,6].

Clinical practice guidelines recommend discharging patients with CAP as soon as they are clinically stable, have no other active medical problems, and have a safe environment for continued care[7]. Several studies have reported that pneumonia severity, comorbidities, and specific procedures (such as the use of mechanical ventilation) are associated with prolonged LOS in CAP patients[4,8-12]. However, there are other factors that influenced LOS such as clinicians characteristics and work efficacy, availability of beds, and social services that help patient support[13].

The aim of this study was to identify the factors independently associated with prolong LOS in hospitalized adult CAP patients during a 7-year period in a single hospital. We hypothesized that non-adherence to guidelines are significantly related with prolonged LOS in hospitalized patients with CAP.

METHODS

Ethics statement

For publication purposes, the study was approved by the Ethics Committee of our institution. Written informed consent was waived because of the non-interventional study design.

Study design and patients

This was a prospective observational study carry in an 800 - bed university tertiary-care hospital in Athens, of consecutive adult (≥18 years old) patients with diagnosis of CAP admitted to the hospital from the emergency department between June 2011 and July 2018. The exclusion criteria were: a) severe immunosuppression (AIDS, chemotherapy, immunosuppressive drugs [e.g., oral corticosteroid ≥10 mg prednisone or equivalent per day for at least two weeks]), b) active tuberculosis, d) cases with a confirmed alternate diagnosis.

Definitions

Pneumonia was defined as a new pulmonary infiltrate found on the hospital admission chest radiograph, with symptoms and signs of lower respiratory tract infection. Severe CAP was defined according when at least one major or 3 minor criteria of the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines were present[7].

Prior antibiotic treatment was defined as the use of a previous antibiotic within at least 24 hours before the admission and given for the current episode of pneumonia. LOS was defined as the time (days) spent in hospital. The LOS was dichotomized using a cut-off point of 11 days considering that the mean LOS in the entire study population was 11.0 ±4.9 days.

The appropriateness of empiric antibiotic treatment was defined according to the IDSA/ATS guidelines for managing CAP[7]. Pulmonary complications include pleural effusion, empyema, or radiological progression of pulmonary infiltrates at admission and during hospitalization. Overall mortality was defined as death from any cause during the hospitalization period.

Data collection

Demographic, epidemiological, and clinical information was systematically collected through patient interviews and medical chart abstraction. Other data were also recorded: history of cigarette smoking, alcohol abuse, asthma or chronic obstructive pulmonary disease, coronary artery disease, diabetes, dementia, hospitalization in the preceding year, and previous admissions for CAP. Initial clinical symptoms and physical signs noted were pleural pain, cough, expectoration, abrupt onset dyspnea, and the time-lapse (in days) from symptom onset. Laboratory analyses recorded leukocyte, haematocrit, plasma urea (BUN), albumin, sodium, potassium and platelet levels and blood gas measurements (arterial oxygen tension (PaO_2), arterial carbon dioxide tension, and pH) on admission.

Pneumonia severity upon hospital admission was estimated using the validated prediction rules: calculated according to the PSI and CURB65 score[9]. During hospitalization, we recorded whether the patients had complications such as, pleural effusions, demonstrated radiographic progression of pneumonia, progressive respiratory failure, acute respiratory distress syndrome (ARDS)[17], septic shock[18], or acute renal failure[19]. Further details are reported elsewhere[11].

Microbiological data were obtained from medical

charts and/or laboratory records. All patients were followed until hospital discharge.

STATISTICS

Statistical analysis was performed using SPSS software, version 18 (SPSS Inc, Chicago, Illinois. Categorical variables were described by frequencies and percentages, while continuous variables by means and standard deviations (SD), or the median and interquartile range (IQR) for data not normally distributed (Kolmogorov-Smirnov test). Categorical variables were compared with the chi-square test or Fisher's exact test where appropriate. Continuous variables were compared using the Student's t-test once normality was demonstrated; otherwise, the nonparametric Mann-Whitney U test was performed.

Univariate and multivariate logistic regression analyses were performed to identify variables predictive of PLOS (dependent variable). Multivariate logistic regression analysis was used to determine factors that independently predicted LOS using variables that had p-value <0.1 on univariate analysis. We report odds ratios (OR) and 95% confidence intervals (CI). All tests were two-tailed and significance was set at p <0.05. The Hosmer and Lemeshow goodness-of-fit test was used to evaluate the adequacy of the logistic regression models.

RESULTS

Patients' characteristics

During the study period 950 patients were hospitalized with a diagnosis of CAP. Of these, 930 (97%) adults patients were included in the analysis. Our cohort compromised 510 males (55%) and 420 females (45%), with a mean age of 64 (SD 18) years; 516 (56%) were aged >65 years. The mean duration of pneumonia symptoms at presentation was 5.33 ± 5.8 days. Forty six percent (423 patients) of the patients received previous antibiotic treatment, been the most frequent antibiotics administered β-lactams 16% (142 patients), macrolides 12% (105 patients) and quinolones 9% (79 patients). At least one comorbidity was present in 71% patients (n=663), the most frequent of which was chronic respiratory disease, present in 37% (n=346) and heart disease in 33% (n=303). Fifty nine percent (n=547) were classified as PSI IV-V and 35% (n=326) CURB65 3-5 at admission (Table 1).

Compared to patients with SLOS, those with PLOS were older, more frequently received previous antibiotic therapy, had higher PSI and CURB-65 risk, more frequently presented with confusion, dyspnea and higher CRP levels at admission.

Table 3 shows the mean LOS stratified by PSI risk class. The mean LOS increases steadily according to PSI risk class, starting from 7.8 (SD 4.5) days in patients belonging to PSI I class and reaching to 13.3 (SD 13.6) days in PSI V class patients. The mean LOS increases steadily according to PSI risk class (Figure 1).

Also patients in PLOS group presented with more tachypnea, acute respiratory failure, higher CRP level, multilobar affectation and pleural effusion. Their demographics and clinical characteristics at admission according to LOS are presented Table 1 & Table 2.

TABLE 1. Characteristics of the population

Characteristics	PLOS N=286	SLOS N=644	p-value
Age, years	66 ± 17.37	63 ± 19.2	**0.022**
>65 years old	168 (33)	348 (67)	0.183
Gender, male	163 (57)	347 (54)	0.379
Aspiration	36 (13)	60 (9)	0.130
HCAP	64 (22)	96 (15)	**0.006**
Comorbidities	215 (75)	448 (70)	0.081
Number com. ≥3	48 (17)	84 (13)	0.132
D.M.	55 (19)	132 (21)	0.657
COPD	80 (28)	165 (26)	0.435
Cardiovascular disease	101 (35)	202 (31)	0.236
Neurological dis	69 (24)	128 (20)	0.143
Smoking habit	135 (47)	267 (42)	0.101
Nonsmoker	117 (41)	278 (43)	
Ex-smoker	34 (12)	97 (15)	
Previous antibiotics	146 (53)	277 (44)	**0.015**
CURB65 ≥3	128 (45)	198 (31)	**<0.001**
PSI risk class	115 ± 39	98 ± 45	**<0.001**
Low risk	78 (28)	293 (46)	**<0.001**
High risk	205 (72)	342 (54)	**<0.001**

Data are number of patients (%), mean (SD) or median (1st quartile-3rd quartile). Percentages calculated on non-missing data.

HCAP=Health Care Associated Pneumonia; DM=Diabetes mellitus; COPD=chronic obstructive pulmonary disease; CURB-65=consciousness, urea, respiratory rate, blood pressure, 65 years old; ICU=intensive care unit; PSI=pneumonia severity index.

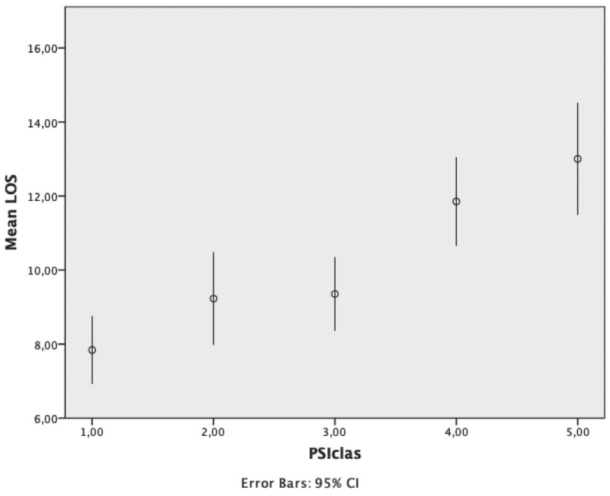

FIGURE 1. LOS according to PSI class.

TABLE 2. Clinical Presentation of CAP according to LOS

Characteristics, n (%)	PLOS N=286	SLOS N=644	p value
Confusion	94 (33)	160 (25)	**0.010**
Respiratory Rate >30/min, breaths/min	126 (44)	227 (35)	**0.011**
Insufficiency Respiratory (pO_2 <60mmHg)	193 (68)	386 (60)	**0.025**
CRP, mg/dL	18.3±13.7	15.5±11.6	**0.018**
Urea >30mg/dl	199 (70)	403 (63)	**0.045**
PLT	282539±150441	258863±112387	**0.019**
Albumin mg/dL^{-1}	3.14 ± 0.6	3.32 ± 0.6	**0.004**
Multilobar Involvement	155 (54)	252 (39)	**<0.001**
Pleural Effusion	119 (42)	112 (18)	**<0.001**
Shock	41 (14)	66 (10)	0.074

Miclobiological diagnosis

An etiologic diagnosis was obtained in 182 (20%) patients (PLOS 34% (98⁄285). The most frequent pathogen in both groups was *S. pneumoniae* (n=40, 22%). The pathogens identified most frequently in PLOS group were: *Pseud. aeruginosa* (n=12), *Klebsiella pnem.* (n=9) and *Acinetobacter baum* (n=9) and other Gram (-) s, whereas *S. pneumoniae* (n=22), atypicals (n= 8) and viruses (n=26) were more common in SLOS group.

Empiric Antibiotic Therapy

Data on empiric antibiotic treatment were available in 919 patients (Table 3). Antibiotic monotherapy had been administered to 244 patients (26%). The most frequent regimens were β-lactam plus either a macrolide (36%) or a respiratory fluoroquinolone (25%) (Table 4). PLOS patients more often received respiratory fluoroquinolones in combination (40%)compared with SLOS patients (19,5%). The empiric antibiotic treatment was inadequate in 162

TABLE 3. Duration of hospitalization in relation to initial antibiotic treatment

Antibiotic regimen	Number pts, %	LOS
B-lactams monotherapy	104 (12)	9.1 ± 6.1
Quinolone monotherapy	136 (15)	8.4 ± 6.7
Combination Macrolide	340 (37)	9.5 ± 6.5
Combination Ouinolone	231 (25)	15.09 ± 14.3

TABLE 4. Therapy & Evolution of CAP according to LOS

Variable, n (%)	PLOS N=286	SLOS N=644	p-value
Diagnosis	98 (34)	84 (13)	**0.001**
Monotherapy	55 (20)	189 (30)	**0.001**
Macrolides	80 (28)	260 (41)	**<0.001**
Quinolone monotherapy	111 (17)	25 (9)	**<0.001**
Combination			
macr + b-lactam	75 (27)	256 (40)	**<0.001**
quinol + b-lactam	113 (40)	118 (19)	**<0.001**
Guidelines Adherence	213 (76)	544 (85)	**0.001**
Cortis therapy	91 (32)	105 (16)	**<0.001**
Complications systemic	122 (43)	122 (19)	**<0.001**
Complications pulmonary	181 (64)	179 (28)	**<0.001**
ICU Admission	39 (14)	49 (8)	**0.004**
Mortality inhospital	23 (8)	56 (9)	0.74
LOS, mean days (SD)	20.4 ± 13	6.8 ± 3	**<0.001**

Data are number of patients (%), mean (SD) or median (1st quartile-3rd quartile). Percentages calculated on non-missing data. CURB-65=consciousness, urea, respiratory rate, blood pressure, 65 years old. ICU=intensive care unit. PSI=pneumonia severity index.

* Patients could have more than one comorbidity. MV: mechanical ventilation. NIV: non-invasive ventilation.

$ Patients who received initially non-invasive ventilation but needed subsequently intubation were included in the invasive mechanical ventilation group.

of all cases (17%); most often in PLOS group 69 (25%) compared with SLOS 93 (15%) (p<0.001).

Predictors of PLOS

Among the variables associated with PLOS in the univariate analysis (Table 5), the previous antibiotic therapy, high level of CRP, hypoalbouminemia, PSI class ≥4, pulmonary and systemic complications, monotherapy, therapy with corticosteroids and non-adherence to guidelines remained significant independent associated with PLOS. In the multivariate analysis (Table 5), the factors Independently related with a prolonged hospitalization was previous antibiotic therapy, hypoalbouminemia, PSI class ≥4, pulmonary complications, therapy with corticosteroids and non-adherence to guidelines. The most important variable associated with an increased LOS was the non-adherence to the guidelines (OR: 1.92).

Clinical outcomes

PLOS group had higher rate of ICU admission and needed of mechanical ventilation (invasive and non-invasive). Seventy-nine patients died giving a mortality rate of 8.5%. We did not find significant differences between groups regarding mortality (Table 4).

DISCUSSION

LOS is a major factor to consider when examining the relationship between patient severity and hospitalization costs because there is a high possibility that LOS acts both as an intermediate variable and an explanatory variable for costs. A multicenter study[19], including 20 teaching and community hospitals in Canada, showed a wide variation in LOS and the management of CAP among hospitals. The causes of this variation are not well known.

In this study we identify predictors associated with prolonged hospital stay in patients with CAP as previous antibiotic therapy, high PSI score (≥4), hypoalbuminemia, corticosteroids therapy, guidelines non-adherence and pulmonary complications.

In our study previous antibiotic use for the current episode of pneumonia was associated with prolonged hospitalization. 46% of our cohort had received antibiotics prior to admission, mainly β-lactams (15%), macrolides (11%) and quinolones (8.5%). Previous studies showed that antibiotic treatment prior to hospitalization could contribute to a reduction of ICU admissions[20], severity of pneumococcal pneumonia[21] and systemic inflammation[22]. Specifically, Amaro et al[20] reported that previous antibiotic use for pneumonia was associated with a lower incidence

TABLE 5. Factors associated with PLOS

FACTORS	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95%CI	p-value
Age, years (+1)	1.01	1.001-1.02	0.03			
Previous antbs	0.7	0.53-0.73	0.015	0.61	0.38-0.97	**0.035**
PSI high class	0.44	0.33-0.6	<0.001	0.52	0.32-0.84	**0.008**
CRP	1.02	1.003-1.035	0.020			
Hypoalbuminemia	0.58	0.39-0.87	0.008	0.57	0.357-0.908	**0.018**
Multilobar involvement	0.55	0.411-0.722	<0.001			
Pleural effusion	3.35	2.46-4.59	<0.001			
Pulmonary complications	0.22	0.16-0.3	<0.001	0.25	0.16-0.39	**<0.001**
Systemic complications	0.32	0.24-0.43	<0.001			
Guidelines adherence	1.9	1.34-2.7	<0.001	1.92	1.12-3.3	**0.018**
Monotherapy	1.8	1.3-2.5	<0.001			
Corticosteroids therapy	0.42	0.3-0.58	<0.001	0.46	0.27-0.75	**0.005**

CI=confidence interval. CURB-65=consciousness. urea, respiratory rate, blood pressure, 65 years old. ICU=intensive care unit. OR=odds ratio. PSI=pneumonia severity index.

* Hosmer-Lemeshow goodness-of-fit test, p=0.32.

$ Patients who received initially non-invasive ventilation but needed subsequently intubation were included in the invasive mechanical ventilation group.

Note: CI = confidence interval; OR = odds ratio.

of CAP caused by *S. pneumoniae* and higher incidence of atypical and *S. aureus* pneumonia.

Previously different predictors for LOS have been reported[4,10,12,23]. In line, with our results, authors encountered several factors that correlated (positively or negatively) with the LOS and which corresponded to the initial severity of the illness (PSI, or risk class of Fine), characteristics of the patients and initial antibiotic treatment. Our predictors at admission related with the severity of pneumonia (PSI >4) and patients' acute disease condition, as hypoalbuminemia. The influence of the PSI score on this period was rather straightforward, with more seriously ill patients or those with more comorbidities taking longer to recover, for whom the factor of clinical stability may not be sensitive enough. Several studies have shown that albumin is a marker of nutritional status and is associated with mortality risk and recovery time of the patient. In the study of Menendez et al[4], observed that in low-risk patients, LOS is determined mainly by the level of hypoxemia and pleural effusion, while in the higher risk classes, additional factors, such as multi-lobe involvement, diastolic blood pressure and the albumin concentration, also become significant[4]. They did not find an association between therapy and length of hospitalization, as we did.

Logistic regression identified that appropriate use of antibiotic, corticoids therapy and pulmonary complications as key independent predictors of LOS. We found that appropriate initial selection of antibiotics according to guidelines[7,24] was associated with a shorter length of stay in univariate and multivariate analyses. These findings are similar to observations made by Capelastegui et al[6] and Battleman et al[25] and suggest that quality improvement targeted at antibiotic use may reduce LOS and save costs.

The influence of guideline compliant antibiotic treatment can be explained by the severity of pneumonia and the compliance of the clinicians of our hospital. Previous studies that analyzed the influence of treatment on the duration of hospitalization obtained discordant results[4,26-28]. Equally, the antibiotic therapy itself appears to be a cause for delayed discharge. Possible solutions may be improvements in the switch from intravenous to oral antibiotics or an increased use of outpatient parenteral antibiotic therapy for eligible patients.

With respect to the initial antibiotic regimen employed, univariate analysis indicated that there was a shorter LOS in those patients treated with quinolone monotherapy. However, this variable was not subsequently selected in the multivariate model.

The addition of corticosteroids in therapy of pneumonia resulted in prolonged hospitalization (15 days vs. 10 days, $p<0.001$) comparing to the other patients. In our population we don't know exactly the date of start of corticosteroids, neither the reason for this therapy (complication, exacerbation, respiratory failure). It is for sure associated with the presence of COPD and asthma comorbidity.

On the contrary, studies had proved that adjunctive corticosteroids treatment for patients hospitalized with CAP can reduce time to clinical stability and LOS by approximately 1 day without a significant effect on overall mortality, according to a recent meta-analysis[29,30]. But it has to be determined, in which patients with pneumonia, what dose of corticosteroids and for how long?

Pulmonary complications are a cause of PLOS and an indicator of treatment failure in many studies[6,23,31,32]. Specifically, Menendez et al[31] reported that complications appearing before 72 h were associated with prolonged hospitalization.

Furthermore, Suter- Widmer et al[23] identified several factors on admission and during follow-up, which were independently associated with longer LOS in patients with CAP. Integrated them into a clinical prediction rule, accurately estimated LOS in CAP patients.

However, LOS is influenced by various other factors, such as clinicians' practice style, availability of beds, and the availability of social services such as long-term care facilities for placement of those who can no longer care for themselves[12]. In another study, early mobilization of patients with CAP led to a reduction in LOS: 6.9 days for those who received the usual mobilization versus 5.8 days for those who received early mobilization[33].

The main strengths of the present study were the large sample size, the large number of variables collected from the clinical records. Our study has several limitations, also. First, the study was conducted in a single geographic area and thus may reflect a single standard of practice. However, "Sotiria" as a Chest diseases hospital is a reference hospital of central Greece. Second, time to first antibiotic dose and time to clinical stability was not assessed that which may influence LOS. So, we did not evaluate the relationships between initial variables and clinical stability and/or clinical response-to therapy separate from the LOS. Third, we don't have data about the functional status of patients or the disability level (frailty) and the mobilization time of every patient to correlate it with LOS.

In our study we identify factors that increase LOS in patients with CAP and those factors that can be modified is an important responsibility for physicians as well as for administrators. Currently, several useful interventions can be suggested for shortening LOS: (i) Using Fine's PSI

risk classes, the number of hospital admissions could be reduced by dealing with patients of class I and II in outpatient departments, (ii) the implementation of ATS or ERS guidelines advising rapid antibiotic initiation, an appropriate antibiotic selection and (iii) the addition of corticosteroids only in selected patients with high inflammatory response and severe pneumonia[29].

CONCLUSIONS

Within this study we identified different baseline and follow-up characteristics to be strong and independent predictors for LOS. A better understanding of the factors influencing hospital stay should lead to measures to reduce LOS.

ΠΕΡΙΛΗΨΗ

Προγνωστικοί παράγοντες που σχετίζονται με την παρατεταμένη διάρκεια νοσηλείας σε πνευμονία της κοινότητας

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Η πνευμονία της κοινότητας (ΠΚ) συνδέεται με υψηλή νοσηρότητα, θνησιμότητα και υψηλό κόστος. Το κόστος της ασθένειας αυξάνεται ανάλογα με τον τόπο φροντίδας (σπίτι, κλινική, ΜΕΘ) και τη διάρκεια της νοσηλείας (LOS). Η έγκαιρη αναγνώριση των προγνωστικών παραγόντων για παρατεταμένη παραμονή στο νοσοκομείο θα βοηθήσει στη μείωση του κόστους της ΠΚ. Σε δύο πνευμονολογικές κλινικές του νοσοκομείου Σωτηρία, διεξήχθη μια μελέτη παρατήρησης διαδοχικών ασθενών με ΠΚ από τον Ιούνιο 2011 έως τον Ιούλιο του 2018. Διαχωρίσαμε τον πληθυσμό σε δύο ομάδες: ομάδα παρατεταμένης νοσηλείας (PLOS) (νοσηλεία ίση ή μεγαλύτερη από τη μέση τιμή LOS) και (SLOS) (μικρότερη από τη μέση τιμή LOS). ***Αποτελέσματα:*** *Από συνολικά 930 ασθενείς (55% άνδρες, 63,7 έτη (SD 18) με μέση διάρκεια διαμονής 11 ημερών (SD 9, 6), 286 ασθενείς είχαν PLOS 20 ημερών (SD 13). Οι ασθενείς με PLOS ήταν μεγαλύτεροι (66 έτη έναντι 63 ετών, p = 0,023) και είχαν λάβει συχνότερα αντιβιοτικά πριν από την εισαγωγή τους (53% έναντι 44%, p = 0,015). Η πνευμονία τους κατά την εισαγωγή ήταν βαρύτερη με βάση το PSI σκορ και εμφάνισαν συχνότερα συστηματικές επιπλοκές (43% έναντι 19%, p <0,001) και την ανάγκη για εισαγωγή στη ΜΕΘ (14% έναντι 6%, p <0,001). Παρόλα αυτά η θνητότητα δε διέφερε μεταξύ των δύο ομάδων. Προγνωστικοί παράγοντες παρατεταμένης νοσηλείας σε ασθενείς με ΠΚ αποτελούν η σοβαρότητα της πνευμονίας (PSI class >4), η λήψη αντιβιοτικών προ νοσηλείας, η υποαλβουμιναιμία, η θεραπεία με κορτικοστεροειδή, οι πνευμονικές επιπλοκές και η μη τήρηση των θεραπευτικών οδηγιών.*

Πνεύμων 2019, 32(3):81-88.

Λέξεις - Κλειδιά: *Πνευμονία της κοινότητας, Διάρκεια νοσηλείας, Θνησιμότητα*

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