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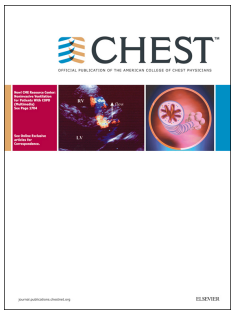

Invasive Disease versus Urinary Antigen Confirmed Pneumococcal Community-Acquired Pneumonia

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Invasive Disease versus Urinary Antigen Confirmed Pneumococcal Community-Acquired Pneumonia.

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Abbreviation List

AIDS: acquired immune deficiency syndrome

ARDS: acute respiratory distress syndrome

ATS/IDSA: American Thoracic Society/ Infectious Disease Society of American

BAL: Broncho-alveolar lavage

CAP: community- acquired pneumonia

CAPITA: Community-Acquired Pneumonia Immunization Trial in Adults

CI: confidence interval

COPD: chronic obstructive pulmonary disease

ED: emergency department

HIV: human immunodeficiency virus

IQR: interquartile range.

IPP: invasive pneumococcal pneumonia

ICU: intensive care unit

LOS: length of stay

MV: mechanical ventilation

NIPP: non-invasive pneumococcal pneumonia

PSI: pneumonia severity index

PCV 13: 13-valent pneumococcal conjugate vaccine

rt PCR: real-time polymerase chain reaction

ROC: receive operational characteristic

SEPAR: Spanish society of pulmonology and thoracic surgery

TBAS: Tracheobronchial aspirate

UAT: urinary antigen test

USA: United States of America

Abstract

Objectives: The burden of pneumococcal disease is measured only through patients with invasive pneumococcal disease. The urinary antigen test (UAT) for pneumococcus has exhibited a high sensitivity and specificity. We aimed to compare the pneumococcal pneumonias diagnosed as invasive disease with pneumococcal pneumonias defined by UAT.

Methods: Prospective observational study on consecutive non-immunosuppressed patients with community-acquired pneumonia from January 2000 to December 2014. Patients were stratified in 2 groups: Invasive pneumococcal pneumonia (IPP) defined as a positive blood culture or pleural fluid culture and non-invasive pneumococcal pneumonia (NIPP) defined as a positive UAT with blood or pleural fluid culture negative.

Results: We analyzed 779 (15%) patients out of 5,132 where 361 (46%) had IPP and 418 (54%) were NIPP. Compared with IPP cases, the NIPP cases presented more frequent chronic pulmonary disease and received previous antibiotics more frequently. IPP patients presented more severe CAP, higher inflammatory markers and worse oxygenation at admission, more pulmonary complications, greater extrapulmonary complications, longer time to clinical stability and longer length of hospital stay compared to NIPP group. Age, chronic liver disease, mechanical ventilation and acute renal failure were independent risk factors for 30-day crude mortality. Neither IPP nor NIPP were an independent risk factor for 30-day mortality.

Conclusions: A high percentage of confirmed pneumococcal pneumonia is diagnosed by UAT. Despite differences in clinical characteristics and outcomes, IPP is not an independent risk factor for 30-day mortality compared with NIPP, reinforcing the importance of NIPP for pneumococcal pneumonia.

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INTRODUCTION

Community Acquired Pneumonia (CAP) remains a leading cause of death worldwide[1,2]. *Streptococcus pneumoniae* is the most frequent pathogen in CAP involved in all settings (outpatients, patients requiring hospitalization and patients needing intensive care treatment), in all age groups and regardless of comorbidities present[3].

A definitive microbiological diagnosis of pneumococcal pneumonia is difficult to establish, and the proportion of cases attributed to pneumococcus is potentially higher than those with a definitive diagnosis[4]. Within the available techniques for pneumococcus diagnosis, sputum is unreliable due to misclassifications, contributing to uncertainty in epidemiologic studies because etiologic diagnosis can only be considered as probable, or presumptive[5,6]. In contrast, a positive culture from normally sterile body fluids is the gold standard in order to determine invasive pneumococcal disease. In lower respiratory tract infections, blood cultures are employed as the main source to establish the presence of pneumococcal disease. However, blood cultures require laboratory settings and are subject to low sensitivity[7].

Several studies in adults have demonstrated the effectiveness of the urinary antigen test (UAT) for the rapid diagnosis of pneumococcal pneumonia[8,9]. Contrasting with previous methods, urinary antigen tests have high sensitivity and specificity and can be done as a point-of-care test. Despite having these characteristics favourable for monitoring and surveillance, UAT have not been incorporated in the estimation of pneumococcal disease burden. One of the reasons for this fact could be that pneumococcal pneumonia diagnosed by a positive UAT is not considered as an "invasive disease".

An accurate and feasible method of measuring pneumococcal disease is needed, and a number of adult pneumococcal pneumonias are diagnosed and treated based on the UAT. We hypothesized that pneumococcal pneumonias diagnosed by UAT had different clinical characteristics compared to a classical “invasive disease”, but still contribute to the burden of pneumococcal disease.

For these reasons, we aimed to compare the clinical characteristics and outcomes of pneumococcal pneumonias diagnosed as a classical “invasive disease” with pneumococcal pneumonias defined by UAT.

METHODS

Study Design and Patients

We performed a prospective, observational study on consecutive CAP patients who visited the emergency department (ED) at the Hospital Clinic of Barcelona (January 2000 to December 2014).

Inclusion criteria included the following: a) adults aged ≥18 years old at diagnosis; b) CAP diagnosis confirmed by chest radiograph and consistent clinical manifestations (e.g., fever, cough, sputum production, pleuritic chest pain), C) pneumococcal etiology confirmed by UAT or blood or pleural fluid. Patients with HCAP criteria were not included, except nursing home residents since a previous study[10] from our group demonstrated a microbiological pattern similar to CAP.

Exclusion criteria were: a) previous hospital admission for ≥48 hours in the preceding 14 days; b) absence of complete clinical follow up for 4-6 weeks; d) unavailable blood culture; e) severe immunosuppression, such as in transplantation, acquired immune deficiency syndrome[11], or receiving chemotherapy or other immunosuppressive drugs (>20 mg prednisone-equivalent per day for 2 weeks or more).

Ethics Statement

The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona (Barcelona, Spain; Register: 2009/5451). Written informed consent was waived because of the non-interventional design. Patients' identification remained anonymous.

Definitions

Patients included in the study were stratified into 2 exclusive groups according to microbial etiology: invasive pneumococcal pneumonia (IPP) defined as pneumonia

with *Streptococcus pneumoniae* isolated from blood or pleural fluid (independent of the positivity of the UA) and non-invasive pneumococcal pneumonia (NIPP) defined as pneumonia with a positive urinary antigen and negative blood culture.

The patients with *S. pneumoniae* in a Gram stain or isolation only in a respiratory sample were not included in the analysis.

Severe pneumonia was defined according to ATS/IDSA guidelines[2]. Pneumonia Severity Index (PSI)[12] and CURB-65[13] scores were used to stratify cases based on severity. The Pitt score[14] was calculated for patients with bacteraemia disease.

Appropriateness of empiric antibiotic treatment in all patients was defined according to the Guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) treatment[15]. We defined pulmonary complications of CAP elsewhere[16]. Extra-pulmonary complications of CAP were also considered: septic shock and acute renal failure.

A positive blood or pleural culture was considered when *S. pneumoniae* was isolated in blood or pleural samples, respectively. UAT for pneumococcus was considered positive in accordance with the manufacturer's instructions (Alere BinaxNOW®, *Streptococcus pneumoniae* Antigen Card, Alere Inc., Waltham, MA).

Data Collection

Clinical, laboratory and radiographic characteristics were recorded on admission (see in detail in the online Supplemental Material)

The co-morbidities were registered according to medical records (see the full list of co-morbidities in the online Supplemental Material).

During hospitalization, the following data were recorded: Length of stay (LOS), admission to the intensive care unit (ICU), need for mechanical ventilation (MV) support (invasive or non-invasive), time to clinical stability[2], and mortality.

All patients discharged alive were re-examined or at least contacted by telephone within 30-40 days from hospital discharge.

Microbiological Evaluation

Regular sampling was taken in the first 24 hours after ED admission and included respiratory specimens (sputum, tracheobronchial aspirate (TBAS), broncho-alveolar lavage (BAL) and/or pleural fluid when available), two blood cultures, urine samples for detection of *Streptococcus pneumoniae* and *L. pneumophila* serogroup 1, and nasopharyngeal swabs for respiratory virus detection. The UAT for *Streptococcus pneumoniae* was not performed if the blood culture result had previously confirmed *Streptococcus pneumoniae*. Blood and respiratory samples were tested by Gram and Ziehl–Nielsen stains and bacterial cultures (see the online Supplemental Material).

Statistical Analysis

Data are shown as number of patients (%) for categorical variables and median (1^{st} quartile; 3rd quartile) for continuous variables with non-normal distribution or mean (standard deviation [SD]) for those with normal distribution. Categorical variables were compared using the Chi-square test or the Fisher exact test. Continuous variables were compared using the *t*-test or the nonparametric Mann-Whitney test. Logistic regression analyses were used to obtain odds ratios (OR) adjusted for potential confounding factors for the associations between the exposure type of pneumococcal pneumonia and 30-day mortality (see the full list of variables in the online Supplemental Material). In the first step, each risk factor was tested individually. In the

second step, all risk factors which showed an association in the univariate model (p<0.10) were added into the multivariate model. A backward stepwise selection (p_{in}<0.05, p_{out}<0.10) was used to determine factors associated with 30-day mortality. The OR and 95% confidence interval (CI) were calculated. The Hosmer-Lemeshow goodness-of-fit test was performed to assess the overall fit of the model[17]. Internal validation of the prediction model was conducted using ordinary nonparametric bootstrapping with 1,000 bootstrap samples and bias-corrected, accelerated 95% CIs[18]. Receiver operating characteristic (ROC) curves were constructed for the ability to predict 30-day mortality of significant variables derived from the multivariate logistic regression model. Furthermore, we calculated sensitivity and specificity, predictive values, and likelihood ratios for the model predictive of 30-day mortality. As sensitivity analysis we analyzed the clinical outcomes separating the patients with invasive disease into those with positive or negative UAT, and also the baseline characteristics and outcomes excluding cases with previous pneumococcal vaccination and pneumonia in the last year in the NIPP group. The level of significance was set at 0.05 (2-tailed). All analyses were performed using IBM SPSS Statistics version 22.0 (Armonk, New York, USA).

RESULTS

Patients' Characteristics

Of the 5,132 patients with CAP admitted during the study period, 779 (15%) were definitive pneumococcal infections and were included in the present study; we did not include 54 (1%) patients with probable pneumococcal pneumonia (Figure 1). Pneumococcal pneumonia was diagnosed by blood culture (345 [44%]) or pleural fluid (16 [2%]) in a total of 361 patients (46%) in the IPP group) and 418 (54%) were classified in the NIPP group due to a positive UAT. All patients in the NIPP group had blood cultures performed and all of them were negative, 78 (18%) of them had isolation of *S. pneumoniae* in respiratory samples and 66 (16%) had polymicrobial isolation, the most common being respiratory virus in 31 (8%) patients and *Haemophilus influenzae* in 9 (2%) patients. On the other hand, 48 (13%) patients with IPP had isolation of *S. pneumoniae* in the respiratory sample and 42 (12%) had polymicrobial isolation.

Baseline characteristics of both groups are summarized in Table 1. Compared with IPP cases, the NIPP cases had higher rates of influenza vaccination, presented more frequent chronic pulmonary disease, in particular COPD (44 patients [12%] in the IPP group vs. 81 patients [19%] in the NIPP group; p=0.006) and more frequently received prior antibiotics compared with the IPP group.

IPP patients presented more severe CAP according ATS/IDSA criteria (major and minor), although there were no significant differences regarding severity scores (PSI or CURB-65) (Table 2). 22 patients with bacteraemia (8%) presented a Pitt bacteremia score higher than 4 points. IPP patients had higher levels of creatinine and C-reactive

protein and worse oxygenation at admission. IPP patients presented more frequently with pulmonary and extra-pulmonary complications.

Antibiotic Treatment

Data on antibiotic treatment were available in 775 patients (99%). The initial empirical treatment was adequate in 99% of patients and not different between groups (p=0.24) (see in detail in the online Supplemental Material).

Outcomes

IPP patients had longer time to clinical stability and length of hospital stay, and higher rate of ICU admission (Table 2). 7-day and 30-day mortality did not differ between groups. Furthermore, the need for non-invasive or invasive mechanical ventilation was similar between groups

Predictors of 30-day Mortality

In the multivariate logistic regression analysis, the following risks factors were independently associated with 30-day mortality: age >74 years, chronic liver disease, mechanical ventilation requirement, and acute renal failure (Table 3). Neither IPP nor NIPP were an independent factor in the multivariate analysis. The area under the ROC curve was 0.93 (95% CI, 0.88 to 0.97) (eFigure 1) for the model predictive of 30-day mortality (88% sensitivity, 89% specificity, 27% positive predictive value, 99% negative predictive value, 8.14 positive likelihood ratio, and 0.12 negative likelihood ratio). Internal validation of the logistic regression model was conducted using bootstrapping with 1,000 samples (eTable 1). All the variables included in the model demonstrated robust results, with small 95% CIs around the original coefficients.

Sensitivity analyses

We analyzed the clinical outcomes separating the patients with invasive disease into those with positive or negative UAT. The UAT was performed on 199 patients with IPP and 156 (78%) of them were UAT positive. Only length of stay was higher in patients with UAT positive without significant differences in the other variables (eTable 2).

Also, we analyzed the baseline characteristics and outcomes excluding in the NIPP group cases with previous pneumococcal vaccination and pneumonia in the previous year (eTable 3 and 4). We observed that NIPP patients received prior antibiotics more frequently. IPP patients presented more severe CAP, and had higher serum levels of C-reactive protein and worse oxygenation at admission. IPP patients presented more frequently with pulmonary complications and higher LOS. However, no difference in mortality was observed.

DISCUSSION

In our study we found that 418 (54%) of 779 definite pneumococcal pneumonia were diagnosed by urinary antigen detection. When we compared patients with invasive pneumococcal disease to patients diagnosed only by UAT, we found clinical and evolutionary differences including a higher severity of the disease in the IPP group. However, IPP was not a factor independently associated with 30-day mortality compared with pneumococcal disease defined by a positive UAT with blood and pleural fluid culture negative.

We believe the burden of pneumococcal disease in adults should be measured by considering the pneumococcal pneumonias defined by both methods: invasive pneumococcal pneumonia and urinary antigen positive. Indeed, a recent multicenter study in the USA coincides with our results showing that 48% of the pneumococcal pneumonias could be diagnosed by systematically using UAT[19]. The urinary *S. pneumoniae* test detects capsular polysaccharide C by means of inmmunochromatography. In the case of pneumonia these soluble microbial antigens are excreted in urine and this mechanism is independent of the presence of bacteremia. Urinary detection is easy to perform and an inexpensive test that allows the diagnosis of pneumococcal pneumonia with a high sensitivity and specificity. In a recent multicenter study in Spain this technique resulted in a very high specificity (100%) indicating that in adults this test can be used very confidently used to diagnose pneumococcal pneumonia[8].

S. pneumoniae continues to be the most prevalent microorganism in CAP. In addition it is one of the causes of pneumonia that is preventable by pneumococcal vaccination[20]. For this reason it is important to adequately measure the burden of the disease in

order to conduct adequate health planning and to evaluate vaccination effects. The new UAT with additional technology can also provide information on the pneumococcal serotype causing pneumonia, as recently used in the CAPITA study (at least for the 13 serotypes included in the PCV13). When applied to clinical practice, the knowledge of serotypes from invasive strains plus those detected in urine will provide very important epidemiological information to measure the effectiveness of pneumococcal vaccination, surveillance and to guide health policy.

We found some clinical differences when comparing the two populations of pneumococcal disease. For example, in the IPP group we found less chronic respiratory diseases, a lower rate of influenza vaccination, higher levels of creatinine and particularly C-reactive protein, and more severe respiratory failure. Very interestingly, the use of prior antibiotics in the previous two months was more frequent in the UAT group. Despite the scores of pneumonia severity being very similar, we found higher clinical severity of pneumonia in the IPP group. This was confirmed by a higher rate of pulmonary complications, longer length of stay and longer time to clinical stability. To our knowledge this is the first report in the literature comparing two large pneumococcal disease populations, defined as invasive disease or those with only a positive UAT. Zalacain et al.[21] have compared bacteremic pneumococcal pneumonias with and without UAT positive. They found worse outcomes including treatment failure in those that were bacteremic and had a positive UAT. We performed a sensitivity analysis and only length of stay was different when comparing IPP with or without UAT positive.

An interesting point that should be highlighted is the differences observed about influenza vaccination. We observed a lower rate of influenza vaccination in the

population with invasive disease; further studies should be conducted to evaluate this finding .

When we analyzed mortality, we found a strong trend to higher crude rates in the invasive group. However, this effect disappeared in the multivariate analysis when adjusting for potential confounders, in which invasive disease was not associated with a higher mortality. In the overall population we found that the elderly (>75 years old), chronic liver disease at baseline, mechanical ventilation requirement and acute renal failure were the factors independently associated with a higher mortality. Regarding 30-day mortality, there are controversial data when comparing bacteraemic pneumococcal pneumonia with UAT confirmed pneumococcal pneumonia. Van Mens et al.[22] found a non-significant association with mortality for bacteraemia (OR 2.21, 95 % CI 0.94 to 5.21, *p*=0.07). However, the study by Capelastegui et al.[23] found a significant association of bacteraemia with mortality (OR, 2.7; 95% CI, 1.5 to 5; *p*=0.002). Both studies only included patients with positive blood culture and did not include patients with positive pleural fluid culture.

Given the possibility of false positive results in patients with previous pneumonia or prior pneumococcal vaccination, we conducted a sensitivity analysis excluding these patients in NIPP group. We only observed differences in the rate of chronic respiratory disease (maybe due a bias selection) and mortality. The UAT may give false positive results in patients with previous pneumococcal infection, especially in patients with COPD for up to one year after pneumococcal infections[24–26]. Also, patients with previous vaccination may have false positive results in the early days after vaccination[27,28].

In our study we excluded cases diagnosed by a respiratory sample alone. This decision was based on the fact that respiratory samples cannot offer a high sensitivity and specificity[7,29,30]. In addition, these types of samples cannot be obtained from everybody with CAP. For example, only 30% of sputum samples are of good quality and are very difficult to obtain in the elderly, patients with dehydration or with impaired consciousness[31]. Due to these drawbacks we chose to have a very homogeneous population in which blood and urine were easy to obtain. In the near future we are sure that the measured burden of the disease will increase because, in addition to using blood cultures and urinary antigens, we will see implementation of PCR techniques such as quantitative lytA real-time PCR in nasopharyngeal or in sputum[32] , which are more sensitive techniques than blood cultures or UAT.

The main limitation of this study is that it was performed in a single center and the results have to be confirmed by others. The strength of our study is the inclusion of a relatively high number of patients with definite pneumococcal pneumonia.

CONCLUSION

We believe that the burden of hospitalized pneumococcal pneumonia can be appreciated by combining cases diagnosed by invasive samples with those who had negative blood cultures but a positive UAT. Since these populations seem to be different, the burden of the disease should be reported separating both.

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Author contributions: Study concept and design: AT; data collection: AC, CC, RA, EPo, EPr, CGV, EMC, RM and JPBC; statistical analysis: AG, analysis and interpretation of data: AC, CC, RA, EPo, EPr, CGV, EMC, CM, IC, RM and JPBC; drafting of the manuscript: AC; critical revision of the manuscript for important intellectual content: CC, EPo, Epr, CM, IC, RM, MN and AT; and study supervision: AT. AT had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Baseline Characteristics

	Invasive pneumococcal pneumonia (n=361)	**Non-invasive pneumococcal pneumonia (n=418)**	***p*-value**
Age, median (IQR), years	63 (48; 78)	69 (49; 79)	0.21
Age, n (%)			0.11
18-49 years	99 (27)	107 (26)	
50-64 years	88 (24)	78 (19)	
65-74 years	55 (15)	83 (20)	
>74 years	119 (33)	150 (36)	
Male sex, n (%)	213 (59)	244 (58)	0.86
Systemic steroids, n (%)	16 (5)	27 (7)	0.21
Pneumococcal vaccine, n (%)			0.21
No	251 (89)	303 (84)	
<6 months	13 (5)	24 (7)	
>6 months	18 (6)	33 (9)	
Influenza vaccine, n (%)			**0.015**
No	197 (69)	212 (59)	
<6 months	63 (22)	103 (28)	
>6 months	24 (8)	47 (13)	
Chronic pulmonary disease, n (%)	128 (36)	186 (45)	**0.016**
Heart failure, n (%)	36 (10)	61 (15)	0.061
Chronic renal failure, n (%)	22 (6)	27 (6)	0.88
Hepatic disease, n (%)	27 (8)	33 (8)	0.87
Diabetes mellitus, n (%)	66 (19)	61 (15)	0.13
HIV infection, n (%)	29 (8)	28 (7)	0.47
Neurological disease, n (%)	47 (14)	64 (16)	0.45

Previous neoplasia, n (%)	26 (7)	34 (8)	0.68
Tobacco, n (%)			0.41
Non smoker	158 (45)	168 (41)	
Former smoker	89 (25)	119 (29)	
Current smoker	106 (30)	127 (31)	
Alcohol consumption, n (%)			0.43
No alcohol	276 (78)	319 (77)	
Ex-alcohol addiction	18 (5)	23 (6)	
Active alcohol consumption (<80 gr/day)	52 (15)	68 (16)	
Active alcohol consumption (>80 gr/day)	7 (2)	3 (1)	
Previous pneumonia, n (%)	45 (13)	63 (15)	0.42
Nursing home, n (%)	11 (3)	23 (6)	0.10
Previous antibiotic therapy (last 2 months), n (%)	39 (11)	71 (17)	**0.022**
Previous antibiotic therapy (last 48 hours), n (%)	10 (3)	27 (7)	**0.019**
Creatinine, median (IQR), mg/dL	1.2 (0.9; 1.6)	1.1 (0.9; 1.5)	**0.005**
C-reactive protein, median (IQR), mg/dL	26.6 (17.1; 32.1)	21 (10.7; 28.9)	**<0.001**
White blood cell count, median (IQR), $\times 10^9$/L	14.7 (9.3; 20.7)	14.2 (9.5; 19.4)	0.36
PaO_2/FiO_2, median (IQR), mmHg	271 (229; 302)	290 (243; 333)	**<0.001**

Percentages calculated on non-missing data. Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.

Table 2. Clinical Characteristics and Outcomes

	Invasive pneumococcal pneumonia (n=361)	**Non-invasive pneumococcal pneumonia (n=418)**	***p*-value**
CURB-65 risk classes 3-5, n (%)	70 (21)	74 (19)	0.49
PSI score, median (IQR)	99 (73; 124)	94 (70; 115)	0.17
PSI risk classes IV-V, n (%)	150 (56)	166 (52)	0.34
Site of care, n (%)			0.062
Outpatients	21 (6)	30 (7)	NS
Ward	243 (67)	305 (73)	NS
ICU admission	97 (27)	83 (20)	**0.021**
Severe CAP, n (%)	103 (38)	93 (29)	**0.019**
Pulmonary complications, n (%)	170 (48)	135 (32)	**<0.001**
ARDS	13 (4)	14 (3)	0.75
Multilobar involvement	113 (31)	95 (23)	**0.007**
Pleural effusion	83 (23)	58 (14)	**0.001**
Extra-pulmonary complications, n (%)	137 (39)	127 (31)	**0.025**
Septic shock	38 (11)	27 (7)	**0.040**
Acute renal failure	125 (35)	114 (28)	**0.020**
Mechanical ventilation, n (%)[a]			0.16

Non	283 (87)	335 (89)	
Non-invasive	19 (6)	11 (3)	
Invasive	23 (7)	29 (8)	
Time to clinical stability, median (IQR), days	6 (3; 9)	5 (3; 7)	**0.026**
Length of hospital stay, median (IQR), days	9 (5; 14)	7 (5; 10)	**<0.001**
7-day mortality, n (%)	9 (3)	5 (1)	0.17
30-day mortality, n (%)	25 (7)	16 (4)	0.052

Percentages calculated on non-missing data. Abbreviations: ARDS, acute respiratory distress syndrome; CAP, community acquired pneumonia; CURB-65, confusion, blood-urea nitrogen, respiratory rate, blood pressure, age >65; ICU, intensive care unit; NS, not significant; PSI, pneumonia severity index.

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

Table 3. Significant Univariate and Multivariate Logistic Regression Analyses for the Prediction of 30-day Mortality

Variable	Univariate[a]			Multivariate[b]			
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age[c]			<0.001			**0.003**
18-49 years	1	-	-	1	-	-
50-64 years	0.12	0.04 to 0.41	0.001	1.09	0.09 to 14.04	0.94
65-74 years	0.15	0.05 to 0.51	0.002	3.79	0.35 to 40.88	0.27
>74 years	0.38	0.15 to 0.93	0.034	13.33	1.59 to 111.99	**0.003**
Chronic renal failure	2.73	1.09 to 6.84	0.032	-	-	-
Chronic liver disease	2.62	1.11 to 6.20	0.028	4.55	1.29 to 16.04	**0.018**
Neurologic disease	2.73	1.34 to 5.57	0.006	-	-	-
Previous neoplasia	2.66	1.12 to 6.29	0.026	-	-	-
Mechanical ventilation[d]			<0.001		-	**<0.001**
Non	1	-	-	1	-	-
Non-invasive	14.14	5.16 to 38.78	<0.001	15.46	3.85 to 62.09	**<0.001**
Invasive	15.49	6.73 to 35.67	<0.001	17.71	5.49 to 57.10	**<0.001**
ARDS	8.83	3.59 to 21.69	<0.001	-	-	-
Acute renal failure	7.13	3.41 to 14.88	<0.001	9.13	2.90 to 28.71	**<0.001**
Septic shock	7.40	3.63 to 15.11	<0.001	-	-	-
Antibiotic treatment[e]			0.002	-	-	-
Quinolone	0.24	0.04 to 1.35	0.11	-	-	-
Betalactamic plus Quinolone	1.72	0.57 to 5.22	0.34	-	-	-
Batalactamic plus Macrolide	0.46	0.14 to 1.55	0.21	-	-	-
Other	1	- -	-	-	-	-
Invasive pneumococcal pneumonia	1.88	0.99 to 3.57	0.056	1.71	0.64 to 4.56	0.28
Year of admission	1.04	0.96 to 1.12	0.34	1.02	0.90 to 1.15	0.76

Abbreviations: ARDS, Acute respiratory distress syndrome; CI, confidence interval; OR: odds ratio. [a] The variables analyzed in the univariate analysis were age, gender, influenza and pneumococcal vaccination, chronic pulmonary disease, chronic heart failure, chronic renal disease, chronic liver disease, diabetes mellitus, HIV infection,

neurological disease, previous neoplasia, tobacco, alcohol consumption, C-reactive protein, ARDS, pleural effusion acute renal failure septic shock, mechanical ventilation, antibiotic treatment, appropriate empiric treatment, invasive pneumococcal pneumonia, and year of admission. [b] Hosmer-Lemeshow goodness-of-fit test, p=0.70. [c] The p-value corresponds to differences between the four groups (18-49 years of age, 50-64 years of age, 65-74 years of age, or >74 years of age). [d] The p-value corresponds to differences between the three groups (non-mechanical ventilation, non-invasive mechanical ventilation, or invasive ventilation). [e] The p-value corresponds to differences between the four groups (quinolone, betalactamic plus quinolone, betalactamic plus macrolide, or other antibiotic treatment).

Figure 1. Flow Diagram of the Selected Population

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