Supplementary material

Predictive and Prognostic Factors in patients with Blood Culture Positive Community-Acquired Pneumococcal Pneumonia

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Materials and Methods

Study Design and Patients

Exclusion criteria included the following: a) severe immunosuppression, such as solid-organ or bone-marrow transplantation or human immunodeficiency virus (HIV), or receiving chemotherapy or other immunosuppressive drugs (>20 mg prednisone-equivalent per day for 2 weeks or more); b) hospitalization in the preceding 21 days; c) active tuberculosis and d) functional or anatomical asplenia. Nursing home patients were not excluded.

Data collection

The following parameters were recorded at admission to the Emergency Department: age, sex, current smoking, alcohol habits, and drug use, co-morbidities, antibiotic treatment in the previous 30 days prior to ED admission, treatment with corticosteroids, clinical symptoms and features, clinical signs, laboratory findings, arterial blood gas measurements, diagnostic procedures, empiric antibiotic therapy, need for ventilator support, pulmonary complications, and other clinical events.

Microbiologic Evaluation

Microbiologic examination was performed in all patients at admission on sputum, urine, two samples of blood and nasopharyngeal swabs. All blood cultures were taken before antibiotic treatment. In some patients blood cultures were obtained after admission but we only included those patients with blood culture drawn at admission. Pleural fluid, tracheobronchial aspirates (TBAS) and bronchoalveolar lavage (BAL) fluid, when available, were collected for Gram and Ziehl-Nielsen stains and for cultures for bacterial, fungal and mycobacterial pathogens.

Sputum and blood samples were obtained for bacterial culture before the start of antibiotic therapy in the emergency department. Urine samples for *S. pneumoniae* and *Legionella pneumophila* antigen detection were obtained within 24 hours of hospital admission.

Minimal inhibitory concentrations (MICs) were determined by a microdilution method (Sensititre, Trek Diagnostic Systems Ltd, West Sussex, England) or by E-Test (bioMérieux SA, Marcy-l'Etoile, France). Results were interpreted according to breakpoints stated in the CLSI documents[1].

As we mention in previous studies[2], isolates were defined to be penicillin non susceptible *S. pneumoniae* (MIC ≥2 mg/mL) or penicillin-resistant *S. pneumoniae* (MIC >8mg/mL).

Definitions

Pulmonary complications were defined as the presence of one or more of the following: pleural effusion, empyema, multilobar infiltrates (infiltrates involving 2 or more lobes) and respiratory distress at the initial presentation according to a previous publication by our group[3].

Severe pneumonia definition includes patients with one of the 2 major severity criteria (mechanical ventilation on septic shock) or the presence of the least 3 minor criteria (respiratory rate ≥30 breaths per minute, PO_2/FiO_2 <250, multilobar, altered mental status, leukocytes <4,000 x 10^9/L, platelets <100 x 10^9/L, temperature <36.0 ºC, systolic blood pressure <90 mmHg and creatinine ≥1.5 mg/dL) according to ATS/IDSA guidelines[4].

Prior antibiotic treatment was defined as the previous antibiotic used within 2 weeks before the admission and given for the current episode of pneumonia. The information of antibiotic therapy was given by the patient at admission.

Data on clinical outcomes were collected including mortality due to all causes, length of hospital stay, intensive-care unit (ICU) admission, need for mechanical ventilation and septic shock.

PSI score stratified according to 30-day risk mortality for CAP: risk classes I-III (≤90 points) have low mortality (range, 0%-10%) and risk class IV (91-130 points) and risk class V (>130 points) have the highest mortality (range, 10%-35%). CURB-65 score stratified according to 30-day mortality for CAP: risk classes 0-1 have low mortality (range, 1%-3%), risk class 2 has moderate mortality (7%) and risk classes 3-5 have the highest mortality (range, 14%-28%).

Appropriateness of empiric antibiotic treatment in all patients was defined according to Guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) treatment[5]. Appropriateness of empiric antimicrobial treatment in patients was defined when the isolated pathogens were susceptible in vitro to ≥1 of the antimicrobials agents administered[6].

Statistical Analysis

To identify factors associated with bacteremic pneumococcal pneumonia we used a logistic regression model. Variables were included in the multivariate model when univariate comparisons yielded a level of significance of $p<0.10$. The following variables were tested: year of occurrence of pneumonia (<2007 vs. ≥2007), age (<65 vs. ≥65 years), gender, influenza and pneumococcal vaccination, systemic and inhaled corticosteroids, prior antibiotic treatment, chronic pulmonary disease, chronic

cardiovascular disease, chronic renal disease, chronic liver disease, diabetes mellitus, neurological disease, pneumonia in the past year, nursing home resident, cough, sputum, dyspnoea, pleuritic pain, fever, confusion, creatinine (<1.5 vs. ≥1.5 mg/dL), C-reactive protein (CRP) (<20 vs. ≥20 mg/dL), white-blood-cell count (<10 vs. ≥10 x 10^9/L), $SatO_2$ (<92 vs. ≥92%), PaO_2/FiO_2 (<250 vs. ≥250), CURB-65 (1-2 vs. 3-5), PSI risk class (I-III vs. IV-V), pulmonary and systemic complications, and need for mechanical ventilation. A backward stepwise selection (p_{in}<0.05, p_{out}<0.10) was used to determine factors predictive of bacteremia, with adjustment for 3 predefined covariates (i.e., the year of occurrence of pneumonia, the age group, and the gender). To identify the problem of collinearity, we calculated the r coefficient of two variables. If two independent variables were highly correlated (r >|±0.30|), the variable with the largest variance was excluded from the multivariate analysis[7]. The association with outcomes (i.e., ICU admission, prolonged length of hospital stay (LOS) [LOS>8 days; cut-off value the median value of LOS], and 30-day mortality) was also tested in univariate and multivariate analysis, and similar inclusion criteria were applied for the logistic regression analysis (p<0.10). The following additional variables were tested for: 1) ICU admission: antibiotic therapy, LOS, and bacteremia pneumococcal pneumonia group; 2) prolonged LOS: antibiotic therapy, site of care, and bacteremia pneumococcal pneumonia group, and 3) 30-day mortality: antibiotic therapy, site of care, LOS, and bacteremia pneumococcal pneumonia group. Receiver operating characteristic (ROC) curves were constructed to determine the best cut-off points for C-reactive protein (CRP) (see Figure E1). Youden's index[8] is defined for all points of the ROC curve, and the maximum value of the index was used as a criterion for selecting the optimum cut-off point.

Results

Etiologic Diagnosis in the BCNPP Patients

S. pneumoniae antigen was detected in the urine of 384 patients (70%) in the non-BPP group. In sputum cultures, *S. pneumoniae* was the most frequently isolated bacterium, found in 218 patients (41%). In 19 of these cases *S. pneumoniae* was predominant but another potential pathogen was isolated (18 *Haemophilus influenzae* and 1 *Staphylococcus aureus*). In addition, *S. pneumoniae* was isolated in 40 patients (9%) from bronchial aspirate samples. In 1 of these cases another potential pathogen was isolated (*Staphylococcus aureus)*. Susceptibility data are described in detail in Table E2. One hundred twenty-three of the 523 pneumococcal isolates (24%) were penicillin resistant (defined as a minimum inhibitory concentration of penicillin ≥2 mg/mL), with BCPPP patients showing a lower rate of resistance than non-bacteremic patients (20% vs. 29%, p=0.015). In BCPPP patients, we also observed a lower rate of erythromycin resistance compared to BCNPP patients (14% vs. 27%, p<0.001).

Empirical Antibiotic Therapy

Antibiotic therapy was selected by the admitting physicians in accord with their usual practice. The majority of BCPPP patients (308 [85%]) received 2 antibiotics, the most frequent of which were a β-lactam with a macrolide (164 [45%]) or a β-lactam with a quinolone (100 [28%]) (see Table E3). The combination of azithromycin with ceftriaxone was used more frequent in BCPPP than in non-BPP patients (91 [25%] vs. 92 [17%], p=0.002). In the BCNPP group, a greater number of patients received a quinolone (98 [18%]) vs. (34 [9%], p<0.001). The empiric antibiotic treatment was not

in accord with accepted guidelines in only 3 of 361 (1%) BCPPP patients and 12 of 548 (2%) non-BPP patients (p=0.12).

Predictors of BCPPP

The area under the ROC curve, the sensitivity, and the specificity of each item analyzed univariately are shown in Figures E3, E4, E5, and E6.

The area under the ROC curve was 0.69 (95% CI 0.63-0.75) for the model predictive of bacteremia (76% sensitivity, 58% specificity, 58% positive predictive value, 76% negative predictive value, 2.37 positive likelihood ratio, and 0.42 negative likelihood ratio) (see Figure E2).

Predictors from the model were used to calculate the probability of bacteremia using the following formula: Exp (β) / (1+Exp(β)) where β = -1.327 + 0.110 (if year of occurrence of pneumonia <2007) - 0.141 (if age ≥65 years) + 0.026 (in the case of women) - 2.101 (in the case of nursing home resident) + 0.523 (in the case of multilobar involvement) + 0.709 (in the case of pleural effusion) + 0.858 (if CRP ≥20 mg/dL). Using this model, the probability of pneumococcal bacteremia for patients without any of these risk factors and with the protective factors was 3%, compared to 71% for patients with all the risk factors and without the protective factors.

Outcomes and Prognostic Factors

In the subgroup of patients requiring ICU admission, the multivariate analysis showed that age ≥65 years, chronic liver disease and need for invasive mechanical ventilation were independently associated with 30-day mortality (see Table E7). Cough was found as protective factor. Bacteremia was not a factor associated with 30-day mortality in this population. The area under the ROC curve was 0.86 (0.80-0.92).

In the subgroup of patients with BPP, the multivariate analysis showed that confusion, respiratory distress, acute renal failure and septic shock were independently associated with 30-day mortality (see Table E8). Pleuritic pain and fever were found as protective factors. Combination antibiotic therapy was not a factor associated with 30-day mortality in BPP. The area under the ROC curve was 0.93 (0.86-1.00).

References

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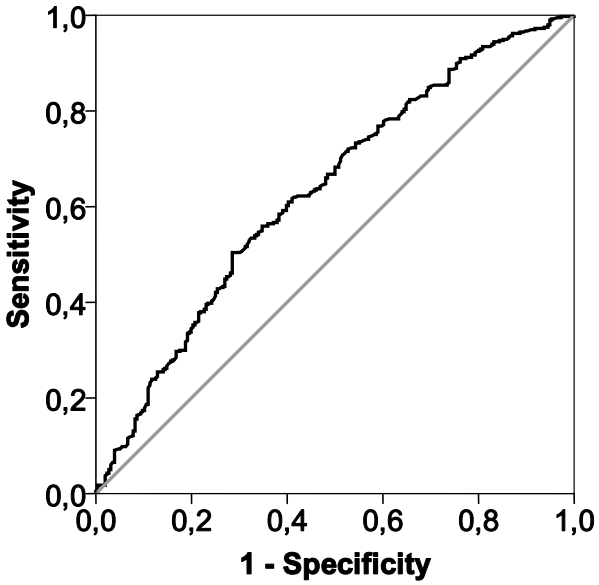
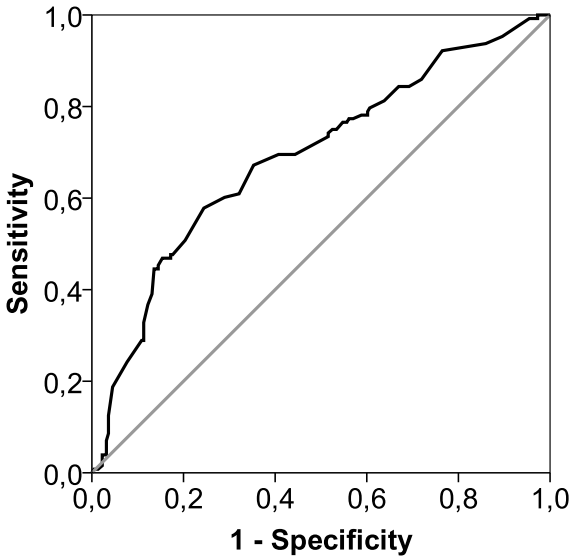
Figure E1. Receiver operating characteristic curve analysis to determine the best cut-off points for C-reactive protein for the ability to predict bacteremia



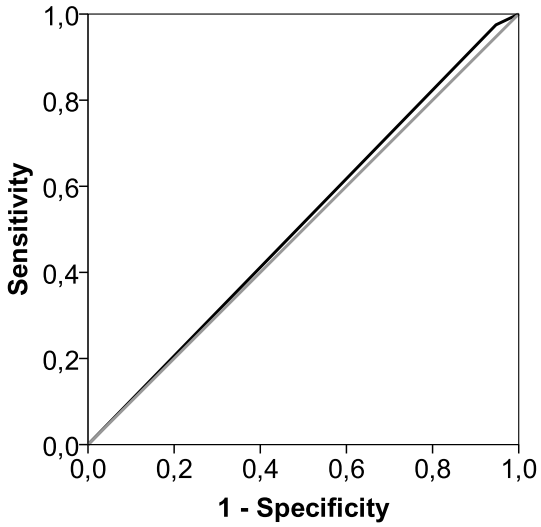
AUC 0.63, 95% CI 0.59-0.68

Figure E2. Receiver operating characteristic curve analysis of significant variables derived from the logistic regression model for the ability to predict bacteremia



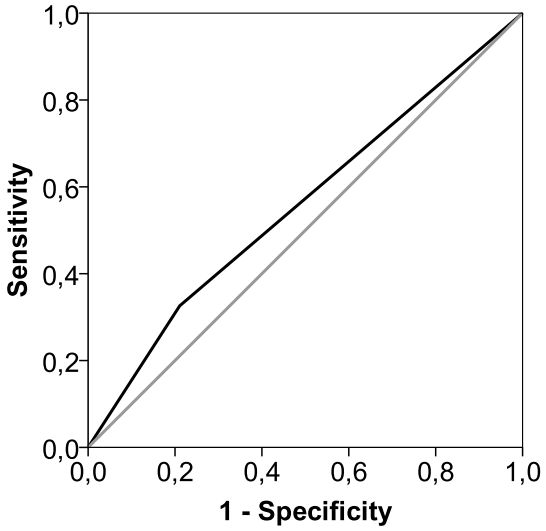
AUC 0.69, 95% CI 0.63-0.75
Sensitivity 76%, Specifity 57%

Figure E3. Receiver operating characteristic curve analysis of nursing home resident for the ability to predict bacteremia



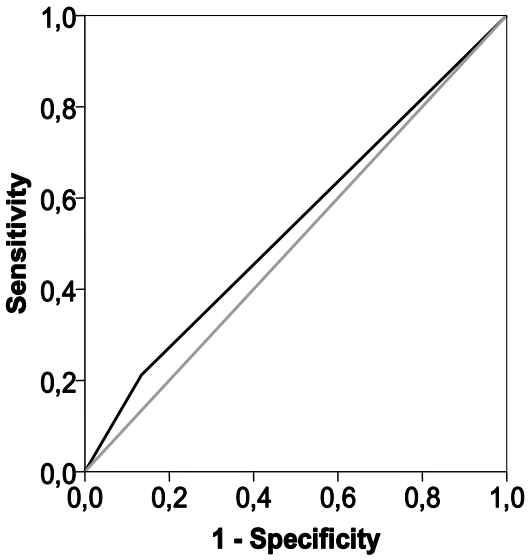
AUC 0.51, 95% CI 0.48-0.55
Sensitivity 97%, Specificity 5%

Figure E4. Receiver operating characteristic curve analysis of multilobar involvement for the ability to predict bacteremia



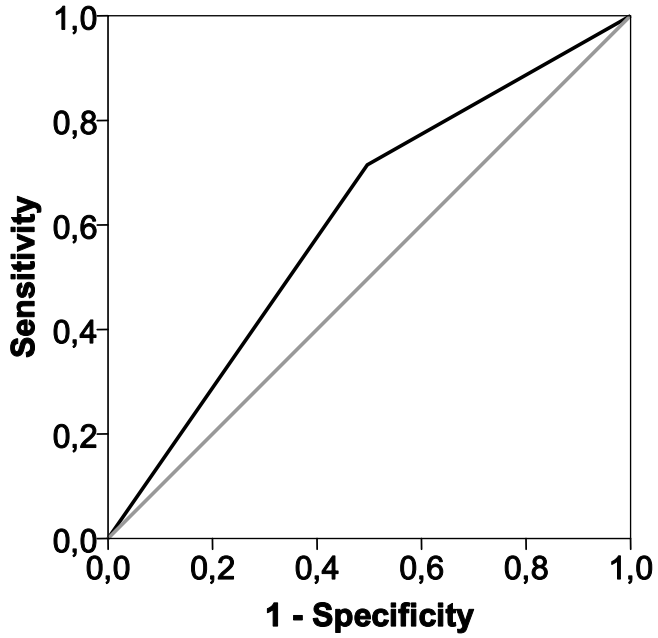
AUC 0.56, 95% CI 0.52-0.60
Sensitivity 33%, Specificity 79%

Figure E5. Receiver operating characteristic curve analysis of pleural effusion for the ability to predict bacteremia



AUC 0.54, 95% CI 0.50-0.58
Sensitivity 21%, Specificity 87%

Figure E6. Receiver operating characteristic curve analysis of C-reactive protein for the ability to predict bacteremia



AUC 0.61, 95% CI 0.57-0.65
Sensitivity 71%, Specificity 50%

Table E1. Diagnosis samples of Pneumococcal Pneumonia

	Blood culture positive pneumococcal pneumonia (n=362)	**Blood culture negative pneumococcal pneumonia (n=555)**	**Total (n=917)**
Blood culture	362/362 (100)	0/555 (0)	362/917 (39)
Sputum	52/164 (32)	199/370 (54)	251/534 (47)
T-BAS/BAL	10/35 (29)	39/70 (56)	49/105 (47)
Pleural Fluid	14/64 (22)	0/43 (0)	14/107 (13)
Urinary antigen	141/176 (80)	384/435 (88)	525/611 (86)

Data are shown as number of patients with Pneumococcal Pneumonia / number of patients for each microbiologic examination performed (%).

Table E2. Antibiotic Resistance According to Groups

		Bacteremic pneumococcal pneumonia (n=362)	Non-bacteremic pneumococcal pneumonia (n=555)	Total
Penicillin	Sensitive	266 (80)	134 (71)	400 (76)
	Intermediate	27 (8)	29 (15)	56 (11)
	Resistant	40 (12)	27 (14)	67 (13)
Erythromycin	Sensitive	278 (86)	138 (73)	416 (81)
	Intermediate	1 (0.3)	2 (1)	3 (1)
	Resistant	46 (14)	50 (26)	96 (19)
Cefotaxime	Sensitive	301 (91)	166 (88)	467 (90)
	Intermediate	22 (7)	18 (10)	40 (8)
	Resistant	6(2)	4 (2)	10 (2)
Levofloxacin	Sensitive	41 (98)	16 (94)	57 (97)
	Resistant	1 (2)	1 (6)	2 (3)

Data are shown as number of patients (%). Percentages calculated on non-missing data.

Table E3. Empiric Antibiotic Therapy

	Bacteremic pneumococcal pneumonia (n=362)	Non-bacteremic pneumococcal pneumonia (n=555)	p-value
Known	361	551	
Monotherapy	53 (15)	143 (26)	
Quinolones	34 (9)	98 (18)	**<0.001**
ß-Lactam	16 (4)	35 (6)	0.22
Macrolide	1 (0.3)	5 (1)	0.41
Carbapenem	1 (0.3)	1 (0.2)	>0.99
Mono-β-Lactam	0 (0)	1 (0.2)	>0.99
Lincosamide	1 (0.3)	0 (0)	0.40
Glucopeptic	0 (0)	1 (0.2)	>0.99
Other	0 (0)	2 (0.4)	0.52
Combination therapy	308 (85)	408 (72)	
Macrolide + ß-Lactam	164 (45)	255 (46)	0.80
Quinolone + ß-Lactam	100 (28)	101 (18)	**0.001**
Quinolone + Macrolide	6 (2)	6 (1)	0.56
Others	38 (11)	46 (8)	0.27

Data are shown as number of patients (%). Percentages calculated on non-missing data. The percentages of antibiotics are related to the number of patients with empiric antibiotic treatment in each group.

Table E4. Internal Validation of Prediction Model for Bacteremic Pneumococcal Pneumonia Using Nonparametric Bootstrap Technique

Variable	Original	Bias	SE	95% BCa CI
Year of occurrence of pneumonia before 2007	0.110	0.017	0.253	-0.376 to 0.651
Age ≥65 years	-0.141	-0.003	0.244	-0.614 to 0.356
Women	0.026	-0.008	0.246	-0.449 to 0.519
Nursing home resident	-2.101	-6.519	9.268	-21.335 to -0.521
Multilobar involvement	0.523	0.008	0.259	0.010 to 1.020
Pleural effusion	0.709	0.016	0.309	0.122 to 1.310
C-reactive protein ≥20 mg/dL*	0.858	-0.004	0.264	0.346 to 1.375

BCa indicates adjusted bootstrap; CI, confidence interval; SE, standard error. * Optimal cut-off value to predict bacteremic CAP using ROC curves.

Table E5. Significant Univariate and Multivariate Logistic Regression Analyses for the Prediction of ICU admission

Variable	Univariate*			Multivariate#		
	OR	95% CI	p-value	OR	95% CI	p-value
Year of occurrence of pneumonia before 2007	0.45	0.33-0.61	<0.001	2.36	1.29-4.34	0.006
Age ≥65 years	0.53	0.39-0.73	<0.001	0.19	0.10-0.37	<0.001
Pneumococcal vaccination	0.49	0.26-0.92	0.027	-	-	-
Influenza vaccination	0.60	0.40-0.89	0.011	-	-	-
Previous antibiotics	0.60	0.36-1.00	0.049	-	-	-
Chronic liver disease	2.17	1.30-3.62	0.003	-	-	-
Dyspnoea	3.25	2.10-5.02	<0.001	-	-	-
Fever	0.62	0.42-0.91	0.015	-	-	-
Confusion	1.81	1.26-2.59	0.001	-	-	-
Creatinine ≥1.5 mg/dL	2.78	2.01-3.86	<0.001	-	-	-
C-reactive protein ≥20 mg/dL†	1.76	1.21-2.56	0.003	-	-	-
White-blood-cell count ≥10 x 10^9/L	0.45	0.32-0.62	<0.001	0.45	0.23-0.87	0.017
PaO_2/FiO_2 <250 mmHg	2.60	1.83-3.70	<0.001	-	-	-
$SatO_2$ <92%	1.51	1.03-2.21	0.034	-	-	-
CURB-65 risk class 3-5	2.45	1.74-3.46	<0.001	-	-	-
PSI risk class IV-V	1.75	1.28-2.41	0.001	-	-	-
Pleural effusion	2.44	1.68-3.55	<0.001	-	-	-
Multilobar involvement	3.54	2.55-4.91	<0.001	-	-	-
Respiratory distress	8.50	4.22-17.11	<0.001	-	-	-
Acute renal failure	2.77	2.00-3.82	<0.001	-	-	-
Septic shock	9.23	5.82-14.64	<0.001	4.97	1.84-13.39	0.002
Mechanical ventilation‡			<0.001	-	-	-
No	1	-	-	-	-	-
NIMV	43.45	14.84-127.24	<0.001	-	-	-
IMV	23.39	13.28-41.22	<0.001	-	-	-
LOS >8 days	6.05	4.26-8.61	<0.001	4.94	2.60-9.40	<0.001
ß-Lactam	0.34	0.13-0.88	0.025	-	-	-
Quinolone	0.27	0.14-0.52	<0.001	-	-	-
Quinolone + ß-Lactam	3.92	2.79-5.51	<0.001	2.24	1.23-4.09	0.008
Macrolide + ß-Lactam	0.52	0.38-0.72	<0.001	-	-	-
Bacteremic pneumococcal pneumonia	1.42	1.04-1.94	0.026	1.51	0.84-2.73	0.17

CI indicates confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of hospital stay; NIMV, non-invasive mechanical ventilation; OR, odds ratio. * The variables analyzed in the univariate analysis were year of occurrence of pneumonia (<2007 vs. ≥2007), age (<65 years vs. ≥65 years), gender, systemic and inhaled corticosteroids, influenza and pneumococcal vaccination, prior antibiotic treatment, chronic pulmonary disease, chronic cardiovascular disease, chronic renal disease, chronic liver disease, diabetes mellitus, neurological disease, pneumonia in the past year, nursing home resident, cough, expectoration, dyspnoea, pleuritic pain, fever, confusion, creatinine (<1.5 mg/dL vs. ≥1.5 mg/dL), C-reactive protein (<20 mg/dL vs. ≥20 mg/dL), white-blood-cell count (<10 $x10^9$ cell/L vs. ≥10 $x10^9$ cell/L), $SatO_2$ (<92% vs. ≥92%), PaO_2/FiO_2 (<250 mmHg vs. ≥250 mmHg), CURB-65 risk class (0-2 vs. 3-5), PSI risk class (I-III vs. IV-V), pleural effusion, multilobar involvement, respiratory distress, septic shock, acute renal failure, mechanical ventilation, LOS (≤8 vs. >8 days), antibiotic treatment, and bacteremic pneumococcal pneumonia. [#] Hosmer-Lemeshow goodness-of-fit test, p=0.083. [†] Optimal cut-off value to predict bacteremic pneumococcal pneumonia using ROC curves. [‡] The p-value corresponds to differences between the three groups (no mechanical ventilation, NIMV, or IMV).

Table E6. Significant Univariate and Multivariate Logistic Regression Analyses for the Prediction of prolonged LOS

Variable	Univariate*			Multivariate#		
	OR	95% CI	p-value	OR	95% CI	p-value
Year of occurrence of pneumonia before 2007	0.66	0.50-0.87	0.003	1.41	0.83-2.40	0.20
Age ≥65 years	1.27	0.97-1.66	0.078	1.85	1.08-3.18	0.025
Pneumococcal vaccination	0.65	0.40-1.06	0.083	-	-	-
Chronic renal disease	1.79	1.05-3.04	0.033	-	-	-
Chronic liver disease	1.97	1.20-3.25	0.007	-	-	-
Neurological disease	1.98	1.34-2.94	0.001	-	-	-
Nursing home resident	3.86	1.85-8.09	<0.001	14.03	1.61-122.20	0.017
Cough	0.66	0.46-0.95	0.024	-	-	-
Expectoration	0.70	0.52-0.93	0.015	-	-	-
Dyspnoea	2.01	1.47-2.74	<0.001	-	-	-
Fever	0.64	0.45-0.91	0.014	0.29	0.13-0.67	0.003
Confusion	2.04	1.46-2.83	<0.001	-	-	-
Creatinine ≥1.5 mg/dL	2.91	2.14-3.95	<0.001	-	-	-
C-reactive protein ≥20 mg/dL†	1.81	1.31-2.50	<0.001	-	-	-
White-blood-cell count ≥10 x 10^9/L	0.59	0.43-0.79	0.001	-	-	-
PaO_2/FiO_2 <250 mmHg	2.73	1.97-3.78	<0.001	-	-	-
$SatO_2$ <92%	2.01	1.41-2.85	<0.001	-	-	-
CURB-65 risk class 3-5	2.49	1.80-3.43	<0.001	-	-	-
PSI risk class IV-V	2.60	1.97-3.42	<0.001	-	-	-
Pleural effusion	3.37	2.32-4.90	<0.001	4.68	2.33-9.43	<0.001
Multilobar involvement	3.03	2.22-4.14	<0.001	-	-	-
Respiratory distress	3.74	1.84-7.62	<0.001	-	-	-
Acute renal failure	2.93	2.18-3.94	<0.001	-	-	-
Septic shock	4.37	2.70-7.05	<0.001	3.70	1.29-10.65	0.015
Mechanical ventilation‡			<0.001	-	-	-
No	1	-	-	-	-	-
NIMV	49.94	6.75-369.70	<0.001	-	-	-
IMV	7.51	4.26-13.26	<0.001	-	-	-
Site of care†			<0.001	-	-	-
Outpatient	-	-	-	-	-	-

Variable	Univariate*			Multivariate#		
	OR	95% CI	p-value	OR	95% CI	p-value
Ward	1	-	-	-	-	-
UCI	5.38	3.78-7.66	<0.001	-	-	-
Quinolone	0.29	0.18-0.46	<0.001	-	-	-
Quinolone + ß-Lactam	3.37	2.41-4.71	<0.001	4.67	2.64-8.25	<0.001
Macrolide + ß-Lactam	0.63	0.49-0.83	0.001	-	-	-
Bacteremic pneumococcal pneumonia	1.91	1.45-2.50	<0.001	1.30	0.75-2.26	0.35

CI indicates confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of hospital stay; NIMV, non-invasive mechanical ventilation; OR, odds ratio. * The variables analyzed in the univariate analysis were year of occurrence of pneumonia (<2007 vs. ≥2007), age (<65 years vs. ≥65 years), gender, systemic and inhaled corticosteroids, influenza and pneumococcal vaccination, prior antibiotic treatment, chronic pulmonary disease, chronic cardiovascular disease, chronic renal disease, chronic liver disease, diabetes mellitus, neurological disease, pneumonia in the past year, nursing home resident, cough, expectoration, dyspnoea, pleuritic pain, fever, confusion, creatinine (<1.5 mg/dL vs. ≥1.5 mg/dL), C-reactive protein (<20 mg/dL vs. ≥20 mg/dL), white-blood-cell count (<10 $x10^9$ cell/L vs. ≥10 $x10^9$ cell/L), $SatO_2$ (<92% vs. ≥92%), PaO_2/FiO_2 (<250 mmHg vs. ≥250 mmHg), CURB-65 risk class (0-2 vs. 3-5), PSI risk class (I-III vs. IV-V), pleural effusion, multilobar involvement, respiratory distress, septic shock, acute renal failure, mechanical ventilation, site of care, antibiotic treatment, and bacteremic pneumococcal pneumonia. # Hosmer-Lemeshow goodness-of-fit test, p=0.95. † Optimal cut-off value to predict bacteremic pneumococcal pneumonia using ROC curves. ‡ The p-value corresponds to differences between the three groups (no mechanical ventilation, NIMV, or IMV).

Table E7. Significant Univariate and Multivariate Logistic Regression for the Prediction of 30-day Mortality of the ICU Population

Variable	Univariate*			Multivariate#		
	OR	95%CI	p-value	OR	95%CI	p-value
Year of occurrence of pneumonia before 2007	1.89	0.84-4.25	0.12	1.23	0.32-4.80	0.76
Age ≥65 years	2.21	1.01-4.82	0.047	3.43	1.10-10.69	0.034
Chronic liver disease	3.45	1.36-8.72	0.009	4.31	1.23-15.12	0.023
Diabetes mellitus	2.17	0.90-5.25	0.086	-	-	-
Cough	0.27	0.11-0.64	0.003	0.20	0.06-0.66	0.008
Expectoration	0.29	0.13-0.66	0.003	-	-	-
Pleuritic pain	0.31	0.13-0.72	0.006	-	-	-
Fever	0.23	0.10-0.52	<0.001	-	-	-
Confusion	3.58	1.63-7.84	0.001	-	-	-
Creatinine >1.5 mg/dL	1.96	0.91-4.25	0.087	-	-	-
PaO_2/FiO_2 <250	3.49	1.40-8.71	0.007	-	-	-
CURB-65 risk class 3-5	2.84	1.30-6.19	0.009	-	-	-
PSI risk class IV-V	2.96	1.08-8.13	0.035	-	-	-
Respiratory distress	3.18	1.26-8.01	0.014	-	-	-
Acute renal failure	2.73	1.22-6.15	0.015	-	-	-
Septic shock	3.52	1.61-7.70	0.002	-	-	-
Mechanical ventilation†			<0.001			<0.001
No	1	-	-	1	-	-
NIV	1.72	0.31-9.51	0.53	3.94	0.55-28.16	0.17
IMV	9.96	3.51-28.27	<0.001	14.17	3.73-53.84	<0.001
Bacteremic pneumococcal pneumonia	0.65	0.30-1.41	0.28	0.89	0.31-2.58	0.83

CI indicates confidence interval; CURB-65, consciousness, urea, respiratory rate, blood pressure, 65 years old; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, Non-invasive mechanical ventilation; PSI, pneumonia severity index; OR, odds ratio. * The variables analyzed in the univariate analysis were year of occurrence of pneumonia (<2007 vs. ≥2007), age (<65 years vs. ≥65 years), gender, systemic and inhaled corticosteroids, influenza and pneumococcal vaccination, prior antibiotic treatment, chronic pulmonary disease, chronic cardiovascular disease, chronic renal disease, chronic liver disease, diabetes mellitus, neurological disease, pneumonia in the past year, nursing home resident, cough, expectoration, dyspnoea, pleuritic pain, fever, confusion, creatinine (<1.5 mg/dL vs. ≥1.5 mg/dL), C-reactive protein (<20 mg/dL vs. ≥20 mg/dL), white-blood-cell count (<10 $x10^9$ cell/L vs. ≥10 $x10^9$ cell/L), $SatO_2$ (<92% vs. ≥92%), PaO_2/FiO_2 (<250 mmHg vs. ≥250 mmHg), CURB-65 risk class (0-2 vs. 3-5), PSI risk class (I-III vs. IV-V), pleural effusion, multilobar involvement, respiratory distress,

septic shock, acute renal failure, mechanical ventilation, LOS (≤8 vs. >8 days), antibiotic treatment, and bacteremic pneumococcal pneumonia. [#] Hosmer-Lemeshow goodness-of-fit test, p=0.97. [†] The p-value corresponds to differences between the three groups (no mechanical ventilation, NIV, or IMV).

Table E8. Significant Univariate and Multivariate Logistic Regression for the Prediction of 30-day Mortality in the Bacteremic Population

Variable	Univariate*			Multivariate#		
	OR	95% CI	p-value	OR	95% CI	p-value
Year of occurrence of pneumonia before 2007	0.91	0.39-2.17	0.84	1.02	0.23-4.56	0.98
Age ≥65 years	3.59	1.41-9.15	0.007	-	-	-
Chronic renal failure	3.36	1.03-10.96	0.044	-	-	-
Chronic liver disease	3.07	1.14-8.27	0.027	-	-	-
Neurological disease	3.12	1.27-7.69	0.013	-	-	-
Cough	0.42	0.17-1.06	0.067	-	-	-
Expectoration	0.44	0.19-1.02	0.055	-	-	-
Pleuritic pain	0.34	0.15-0.80	0.013	0.15	0.03-0.72	0.017
Fever	0.21	0.09-0.52	0.001	0.17	0.04-0.75	0.020
Confusion	5.23	2.33-11.77	<0.001	6.46	1.45-28.71	0.014
Creatinine >1.5 mg/dL	6.15	2.59-14.57	<0.001	-	-	-
$SatO_2$ <92%	3.44	1.27-9.33	0.015	-	-	-
PaO_2/FiO_2 <250	2.90	1.23-6.85	0.015	-	-	-
CURB-65 risk class 3-5	7.78	3.24-18.66	<0.001	-	-	-
Multilobar involvement	3.83	1.69-8.69	0.001	-	-	-
Respiratory distress	15.22	5.12-45.27	<0.001	14.00	1.65-118.72	0.016
Acute renal failure	9.98	3.67-27.17	<0.001	11.61	2.12-63.72	0.005
Septic shock	10.25	4.40-23.89	<0.001	5.36	1.36-21.07	0.016
Site of care†			0.14	-	-	-
Outpatient	-	-	-	-	-	-
Ward	1	-	-	-	-	-
UCI	2.25	1.01-5.03	0.047	-	-	-
Mechanical ventilation‡			<0.001	-	-	-
No	1	-	-	-	-	-
NIV	1.82	0.22-15.17	0.58	-	-	-
IMV	14.56	5.73-36.96	<0.001	-	-	-
Quinolone + ß-Lactam	2.04	0.91-4.60	0.083	-	-	-

CI indicates confidence interval; CURB-65, consciousness, urea, respiratory rate, blood pressure, 65 years old; IMV, invasive mechanical ventilation; NIV, Non-invasive mechanical ventilation; OR, odds ratio. * The variables analyzed in the univariate analysis were year of occurrence of pneumonia (<2007 vs. ≥2007), age (<65 years vs. ≥65 years), gender, systemic and inhaled corticosteroids, influenza and pneumococcal

vaccination, prior antibiotic treatment, chronic pulmonary disease, chronic cardiovascular disease, chronic renal disease, chronic liver disease, diabetes mellitus, neurological disease, pneumonia in the past year, nursing home resident, cough, expectoration, dyspnoea, pleuritic pain, fever, confusion, creatinine (<1.5 mg/dL vs. ≥1.5 mg/dL), C-reactive protein (<20 mg/dL vs. ≥20 mg/dL), white-blood-cell count (<10 x10^9 cell/L vs. ≥10 x10^9 cell/L), $SatO_2$ (<92% vs. ≥92%), PaO_2/FiO_2 (<250 mmHg vs. ≥250 mmHg), CURB-65 risk class (0-2 vs. 3-5), PSI risk class (I-III vs. IV-V), pleural effusion, multilobar involvement, respiratory distress, septic shock, acute renal failure, mechanical ventilation, site of care, LOS (≤8 vs. >8 days), and antibiotic treatment. [#] Hosmer-Lemeshow goodness-of-fit test, p=0.40. [†] The p-value corresponds to differences between the three groups (outpatient, ward, or ICU). [‡] The p-value corresponds to differences between the three groups (no mechanical ventilation, NIV, or IMV).