Predictive and prognostic factors in patients with blood-culture-positive community-acquired pneumococcal pneumonia

Rosanel Amaro[1], Adamantia Liapikou[2], Catia Cilloniz[1], Albert Gabarrus[1], Francesc Marco[3,4], Jacobo Sellares[1], Eva Polverino[1], Javier Garau[5], Miquel Ferrer[1], Daniel M. Musher[6] and Antoni Torres[1]

Affiliations: [1]Dept of Pneumology, Hospital Clinic of Barcelona – Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Ciber de Enfermedades Respiratorias (CIBERES), Barcelona, Spain. [2]Respiratory Dept, Sotiria Chest Diseases Hospital, Athens, Greece. [3]Dept of Microbiology, Centre Diagnostic Biomèdic (CDB), Hospital Clinic of Barcelona, Barcelona, Spain. [4]Barcelona Institute for Global Health, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain. [5]Dept of Medicine, Hospital Universitari Mutua de Terrassa, Terrassa, Spain. [6]Dept of Medicine, Baylor College of Medicine, Houston, TX, USA.

Correspondence: Antoni Torres, Dept of Pneumology, Hospital Clinic of Barcelona, C/ Villarroel 170, 08036 Barcelona, Spain. E-mail: atorres@ub.edu

ABSTRACT In patients with pneumococcal community-acquired pneumonia (CAP), the risk factors for bacteraemia and its impact on outcomes are not fully elucidated. We aimed to compare characteristics of patients with blood-culture-positive *versus* blood-culture-negative pneumococcal CAP, and to characterise bacteraemic serotypes.

We describe a prospective, observational study on nonimmunocompromised patients with pneumococcal CAP, from 1996 to 2013. We define severe pneumonia according to American Thoracic Society/Infectious Diseases Society of America guidelines.

Of a total of 917 patients with pneumococcal CAP, 362 had blood-culture-positive pneumococcal pneumonia (BCPPP; 39%). High C-reactive protein (CRP) ($\geqslant$20 mg·dL^{-1}) (odds ratio (OR) 2.36, 95% CI 1.45–3.85), pleural effusion (OR 2.03, 95% CI 1.13–3.65) and multilobar involvement (OR 1.69, 95% CI 1.02–2.79) were independently associated with bacteraemic CAP, while nursing home resident (OR 0.12, 95% CI 0.01–1.00) was found as a protective factor. Despite the clinical differences, BCPPP showed similar outcomes to blood-culture-negative pneumococcal pneumonia (BCNPP). 14% of the serotypes (period 2006–2013) causing bacteraemia are included in pneumococcal conjugate vaccine PVC7, 74% in pneumococcal conjugate vaccine PVC13 and 83% in pneumococcal polysaccharide vaccine PPSV23.

Pleural effusion, a high level of CRP and multilobar involvement predicted an increased risk of BCPPP. Although BCPPP patients were more severely ill at admission, mortality was not significantly greater than in BCNPP patients.

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Introduction

Streptococcus pneumoniae remains the most commonly identified cause of community-acquired pneumonia (CAP), and its morbidity and mortality are still substantial despite improvements in medical practice. In the modern era, there have been very few clinical comparisons between patients with bacteraemic and blood-culture-negative nonbacteraemic pneumococcal pneumonia [1]. Bacteraemia in patients with pneumococcal pneumonia, which is estimated to occur in about 25% of cases [2], is thought to increase the raw mortality beyond that seen with pneumococcal pneumonia alone [1, 3]. Mortality of bacteraemic pneumococcal pneumonia (BPP) has been reported to vary between 15% and 26% [4].

Previous studies of all-cause CAP (not specifically CAP due to *S. pneumoniae*) have proposed several clinical variables that predict risk of bacteraemia [5, 6]. To the best of our knowledge, only a handful of small studies [7–9] have sought predictors of bacteraemia in patients with pneumococcal pneumonia. Determining which predictors may be involved in patients with BPP could be used for suspected diagnosis in these patients and enable adequate antibiotic treatment (*e.g.* combination antibiotic therapy).

However, previous investigators have presented conflicting data on the likelihood of different serotypes of *S. pneumoniae* causing invasive (bacteraemic) disease [10–13]. In these studies, serotype prevalence was variable, which may have been due to geographic and epidemiologic differences.

The purpose of this study was to investigate the predictive factors and outcomes of blood-culture-positive pneumococcal pneumonia (BCPPP) in comparison with blood-culture-negative pneumococcal pneumonia (BCNPP) in a large population of nonimmunosuppressed adult patients, and to define risk of bacteraemia *versus* nonbacteraemic disease and the role of pneumococcal serotypes in bacteraemic CAP.

Materials and methods

Study design and patients

This prospective observational study was carried out in the Hospital Clinic of Barcelona (Spain) and included all consecutive patients with CAP who visited the emergency department from November 1996 through June 2013. In the context of routine clinical follow-up of CAP and due to the observational nature of the study, informed consent was considered unnecessary. This study was approved by the Ethics Committees (Register 2013/8868) of the Hospital Clinic of Barcelona, Spain.

Data collection

Clinical assessments were collected prospectively (see online supplementary material). Radiological assessments were performed by study staff physicians. Duration of treatment, length of hospital stay and 30-day mortality were recorded. We also calculated the pneumonia severity index (PSI) and CURB-65 (severity score based on consciousness, urea, respiratory rate, blood pressure and age $\geqslant$65 years) scores at admission [14, 15]. Isolates were serotyped at the Spanish Reference Laboratory for Pneumococci (Majadahonda, Madrid, Spain) by using the Quellung reaction and antisera provided by the Statens Serum Institute (Copenhagen, Denmark). Serotyping was performed only in invasive strains isolated from blood cultures during the period 2006–2013. Widespread use of pneumococcal conjugate vaccine PCV7 in the childhood immunisation schedule in Spain began in 2001 and pneumococcal conjugate vaccine PCV13 replaced PCV7 in 2010. Patients were excluded if they were immunosuppressed; the exclusion criteria, clinical definitions and microbiological diagnostic techniques are described in detail in the online supplementary material.

Definitions

Pneumonia was defined as the presence of a new infiltrate on a chest radiograph together with clinical symptoms that were suggestive of lower respiratory tract infection (*e.g.* fever, cough, sputum production, pleuritic chest pain). The definition of severe pneumonia is given in the online supplementary material.

Patients included in the study were stratified in two exclusive groups according to microbial aetiology: BCPPP defined as pneumonia with *S. pneumoniae* isolated from blood culture and BCNPP defined as pneumonia with negative blood culture, growth of *S. pneumoniae* from adequate lower respiratory specimens (sputum culture; if sputum culture yielded two or more potential pathogens, we only selected those cases in which *S. pneumoniae* predominated), tracheal bronchial aspirate, bronchoalveolar lavage (BAL), culture of pleural fluid or a positive pneumococcal urinary antigen test.

PSI and CURB-65 scores were used to stratify cases based on severity (see online supplementary material).

Patient follow-up and mortality

The 30-day survival status of hospitalised patients was evaluated and recorded in their electronic clinic history, and that of patients discharged from the hospital within 30 days was investigated by a subsequent outpatient follow-up with radiological and serological assessment.

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Statistical analysis

Data are shown as number of patients (%) for categorical variables and median (interquartile range (IQR)) for continuous variables with non-normal distribution or mean±SD for those with normal distribution. Categorical variables were compared using the Chi-squared test or Fisher exact test. Continuous variables were compared using the t-test or nonparametric Mann–Whitney test. Univariate and multivariate logistic regression analyses were performed to identify variables predictive of patients with BPP (see the full list of variables in the online supplementary material). Variables with $p<0.10$ in the univariate analyses were included in the initial logistic regression model. A backward stepwise selection ($p_{in}<0.05$, $p_{out}<0.10$) was used to determine factors predictive of bacteraemia, with adjustment for three predefined covariates (*i.e.* year of occurrence of pneumonia, age group and gender). The association with outcomes (intensive care unit (ICU) admission, prolonged length of hospital stay (LOS) (LOS >8 days; cut-off value was 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 ($p<0.10$). Two subgroup analyses examined 30-day mortality for patients admitted to the ICU and for patients with bacteraemia. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the models [16]. Internal validation of the prediction models was conducted using ordinary nonparametric bootstrapping with 1000 bootstrap samples and bias-corrected, accelerated 95% CIs. Receiver operating characteristic (ROC) curves were constructed for the ability to predict bacteraemia, ICU admission, prolonged LOS and 30-day mortality, using variables derived from the multivariate logistic regression models. The level of significance was set at 0.05 (two-tailed). All analyses were performed using SPSS Statistics version 20.0 (IBM, Armonk, New York, USA).

Results

General characteristics

Of the 5791 patients with CAP admitted during the study period, 917 were diagnosed with pneumococcal infection and included in the present study (figure 1). Out of these, 362 (39%) had documented BCPPP and 555 (61%) were classified in the BCNPP group. All patients in the BCNPP group had blood cultures performed and all of them were negative. In both groups of patients, the distribution of the pneumococcal aetiology is summarised in online supplementary table E1.

Baseline characteristics of both groups are summarised in table 1. Patients with bacteraemia were more frequently <65 years of age, had fewer chronic respiratory disorders, less use of inhaled corticoids, a lower rate of vaccination against *S. pneumoniae* and were less likely to be nursing home patients. A total of 127 patients (14%) received one antibiotic in the previous 2 weeks; this was less frequent in BCPPP patients than in patients without BCNPP (table 1).

BCPPP patients presented a higher respiratory and heart rate, more frequently manifested pleuritic pain at admission, and were more frequently hypoxaemic than BCNPP patients. They also had significantly higher levels of C-reactive protein (CRP) and creatinine at admission (table 2).

There were no differences between the two groups on admission according to the CURB-65 or PSI scores (table 3). A total of 115 BCPPP patients (42%) had severe CAP (21 patients (8%) with major criteria, 56 patients (20%) with at least three minor criteria and 38 patients (14%) with both criteria) as defined by the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) [17] compared with 135 BCNPP patients (30%) (33 patients (7%) with major criteria, 61 patients (14%) with at least three minor criteria and 41 patients (9%) with both criteria) ($p=0.002$). BCPPP patients presented more frequently

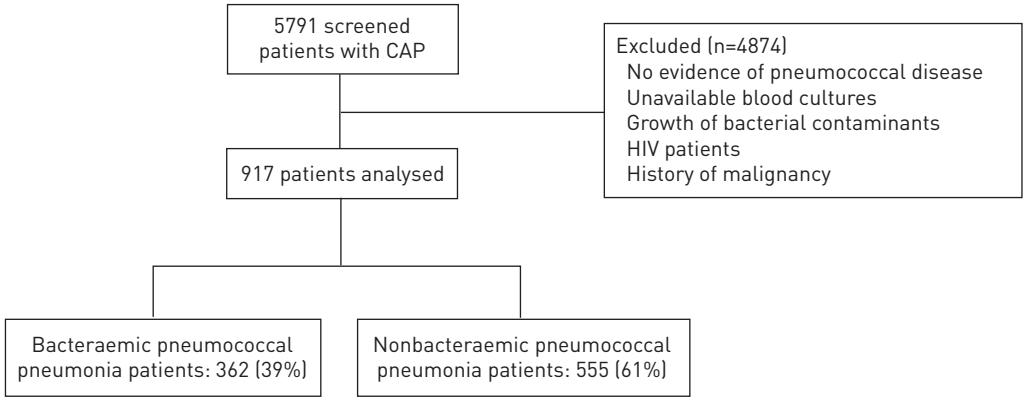

FIGURE 1 Flow diagram of the selected population. CAP: community-acquired pneumonia.

TABLE 1 Baseline characteristics of the patients

	Blood-culture-positive pneumococcal pneumonia	Blood-culture-negative pneumococcal pneumonia	p-value
Subjects	362	555	
Age years	63.4±18.8	64.5±18.4	0.32
Age ⩾65 years	187 (52)	328 (59)	0.026
Male/female	212/150	360/195	0.054
Smoking status			0.005
Never	158 (44)	190 (35)	0.004
Ex	86 (24)	179 (33)	0.005
Current	114 (32)	178 (33)	0.83
Alcohol abuse	65 (18)	116 (21)	0.28
Pneumonia in last year	43 (13)	78 (15)	0.43
Nursing home resident	9 (3)	29 (5)	0.041
Pneumococcal vaccination	23 (10)	63 (16)	0.039
Influenza vaccination	79 (34)	163 (41)	0.089
Systemic corticosteroids	15 (5)	28 (6)	0.56
Inhaled corticosteroids	47 (13)	132 (24)	<0.001
Previous antibiotics	37 (11)	90 (17)	0.011
Underlying diseases			
One or more comorbidity[#]	235 (67)	382 (70)	0.33
Chronic respiratory disease	142 (40)	286 (52)	<0.001
Chronic heart disease	41 (11)	80 (14)	0.19
Diabetes mellitus	72 (20)	84 (15)	0.052
Chronic renal disease	22 (6)	38 (7)	0.67
Chronic liver disease	33 (9)	36 (7)	0.13
Neurological disease	48 (14)	72 (13)	0.84
Site of care			0.022
Outpatient	17 (5)	44 (8)	0.052
Ward	247 (68)	393 (71)	0.32
ICU	98 (27)	114 (21)	0.025

Data are presented as n, mean±SD or n (%), unless otherwise stated. Percentages calculated on nonmissing data. ICU: intensive care unit. [#]: patients may have one or more than one comorbidity.

with pulmonary complications, in particular pleural effusion and multilobar involvement, and also had more frequent acute renal failure.

Etiologic diagnosis in the BCNPP patients is available in the online supplementary material.

Serotypes in the BCPPP patients

128 of the 362 invasive isolates (35%) were available for serotyping (period 2006–2013). The most frequent serotypes in this population were 1 (n=32, 25%), 19A (n=15, 12%), 3 (n=14, 11%), 7F (n=10, 8%) and 14 (n=7, 5%) (figure 2). Only 18 (14%) isolates were serotypes covered by the PCV7 vaccine (4, 6B, 9V, 14, 18C, 19F and 23F) and 74 (58%) were serotypes covered by the PCV13 vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F). 106 isolates (83%) were serotypes included in pneumococcal polysaccharide vaccine PPSV23 (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F). We also evaluated and compared the coverage of each vaccine per period (before (2006–2010) and after (2011–2013) the introduction of PCV13) (figure 3).

Data regarding empirical antibiotic therapy are available in the online supplementary material.

Predictors of BCPPP

Of the variables associated with BCPPP in univariate logistic regression analyses, CRP ⩾20 mg·dL^{-1}, pleural effusion and multilobar involvement were independently associated with increased risk of bacteraemia in the multivariate analysis. Nursing home resident was the only protective factor (table 4). Internal validation of the logistic regression model was conducted using bootstrapping with 1000 samples. All the variables included in the model demonstrated robust results, with small 95% CIs around the original coefficients, except for nursing home resident which appeared to be less reliable, with wider 95% CIs around the original coefficients (online supplementary table E4). The area under the ROC curve was 0.69 (95% CI 0.63–0.75) for the model predictive of bacteraemia (76% sensitivity, 58% specificity, 58%

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TABLE 2 Clinical and laboratory parameters

	Blood-culture-positive pneumococcal pneumonia	Blood-culture-negative pneumococcal pneumonia	p-value
Subjects	362	555	
Clinical data on admission			
Days of symptoms	4 (2–6)	4 (2–7)	0.74
Cough	301 (85)	456 (83)	0.53
Expectoration	221 (64)	389 (72)	0.008
Dyspnoea	248 (70)	397 (73)	0.41
Pleuritic pain	208 (59)	274 (50)	0.007
Fever	313 (88)	449 (81)	0.011
Confusion	83 (23)	101 (18)	0.074
Respiratory rate breaths·min^{-1}	28 (24–32)	28 (20–32)	0.014
Heart rate beats·min^{-1}	104 (92–120)	100 (87–110)	<0.001
Temperature °C	38.0 (37.5–38.7)	37.7 (36.9–38.5)	<0.001
Laboratory data on hospital admission			
Creatinine mg·dL^{-1}	1.2 (0.9–1.6)	1.1 (0.9–1.4)	0.001
Creatinine ⩾1.5 mg·dL^{-1}	113 (31)	132 (24)	0.014
C-reactive protein mg·dL^{-1}	26.4 (17.3–34)	19.8 (9.3–28.7)	<0.001
C-reactive protein$^{\#}$ ⩾20 mg·dL^{-1}	183 (71)	197 (50)	<0.001
WBC count 10^9 L^{-1}	15.3 (9.8–20.5)	14.4 (9.9–19.4)	0.25
WBC count ⩾10×10^9 L^{-1}	266 (74)	410 (75)	0.84
S_{aO_2} %	92.5 (88.1–95.0)	93.2 (90.3–95.7)	0.014
S_{aO_2} <92%	101 (43)	111 (35)	0.044
P_{aO_2}/F_{IO_2} mmHg	271.4 (228.6–302.9)	281.0 (238.1–328.6)	0.002
P_{aO_2}/F_{IO_2} <250 mmHg	109 (41)	133 (32)	0.015

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. Percentages calculated on nonmissing data. WBC: white blood cell; S_{aO_2}: arterial oxygen saturation; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction. $^{\#}$: optimal cut-off value to predict bacteraemic pneumococcal pneumonia using receiver operating characteristic curves.

positive predictive value, 76% negative predictive value, 2.37 positive likelihood ratio and 0.42 negative likelihood ratio) (online supplementary figure E2).

Outcomes and prognostic factors

Of the 362 BCPPP patients, 17 (5%) were treated as outpatients *versus* 44 of 555 (8%) non-BPP patients (p=0.052), and 247 (68%) were admitted to the ward *versus* 393 (71%) in the non-BPP group (p=0.32). A greater proportion of BCPPP patients were admitted directly to the ICU (98 (27%) *versus* 114 (21%), p=0.025). None of the patients with BCPPP treated as outpatients patients died or needed re-admission.

Both groups had similar rates of mechanical ventilation (noninvasive and invasive) (table 5). The median (IQR) LOS was greater for BCPPP *versus* BCNPP cases (9 (5–14) and 7 (4–10) days, respectively, p<0.001).

TABLE 3 Severity of community-acquired pneumonia

	Blood-culture-positive pneumococcal pneumonia	Blood-culture-negative pneumococcal pneumonia	p-value
Subjects	362	555	
PSI risk class IV–V	201 (56)	289 (52)	0.31
CURB-65 risk class 3–5	90 (25)	113 (21)	0.12
Severe pneumonia	115 (42)	135 (30)	0.002
Pulmonary complications$^{\#}$	168 (47)	167 (30)	<0.001
Pleural effusion	76 (21)	74 (13)	0.002
Multilobar involvement	118 (33)	117 (21)	<0.001
Respiratory distress	16 (5)	23 (4)	0.72
Septic shock	46 (13)	50 (9)	0.059
Acute renal failure	125 (35)	147 (27)	0.010

Data are presented as n or n (%), unless otherwise indicated. Percentages calculated on nonmissing data. CURB-65: severity score based on consciousness, urea, respiratory rate, blood pressure and age ⩾65 years; PSI: pneumonia severity index. $^{\#}$: patients may have more than one pulmonary complication.

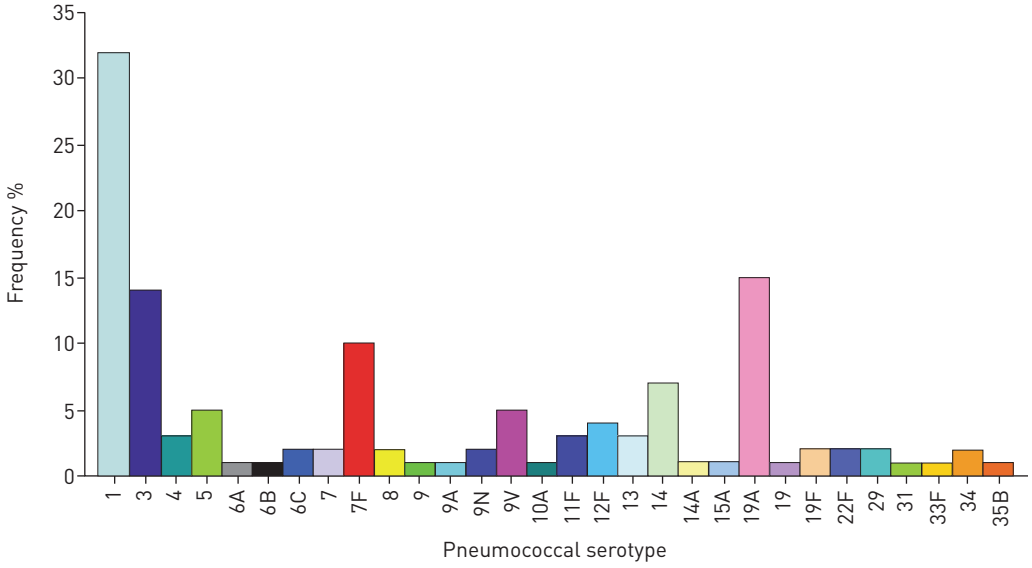

FIGURE 2 Serotype distribution of 128 *Streptococcus pneumoniae* isolates (period 2006–2013).

The overall 30-day mortality was 6%, with no significant differences between the groups (8% for BCPPP *versus* 5% for BCNPP, p=0.12). In BCPPP patients, mortality was similar when comparing the periods before (6%) and after (7%) the ATS/IDSA guidelines [17] (table 5).

We performed multivariate analyses for ICU admission, prolonged LOS (>8 days, median LOS of overall population) and 30-day mortality, but none of them showed bacteraemia to be an independently associated factor after adjustments for BCPPP and potential confounding factors (online supplementary table E5, table 6 and online supplementary table E6, respectively). The area under the ROC curve was 0.83 (95% CI 0.78–0.88) for the model predictive of ICU admission, 0.79 (95% CI 0.75–0.84) for the model predictive of prolonged LOS and 0.89 (95% CI 0.83–0.95) for the model predictive of 30-day mortality.

In the subgroup of patients requiring ICU admission, BCPPP was not a factor associated with 30-day mortality (online supplementary table E7).

Discussion

The main findings of the present study are: 1) bacteraemia is a common feature by which patients with pneumococcal pneumonia are identified (39% of all cases); 2) pleural effusion, the presence of levels of CRP $\geqslant$20 mg·dL^{-1} and multilobar involvement were identified as risk factors for bacteraemia in patients with pneumococcal pneumonia; 3) although severity and length of stay were greater in patients with BCPPP compared with those with BCNPP, the presence of bacteraemia did not affect mortality, even in

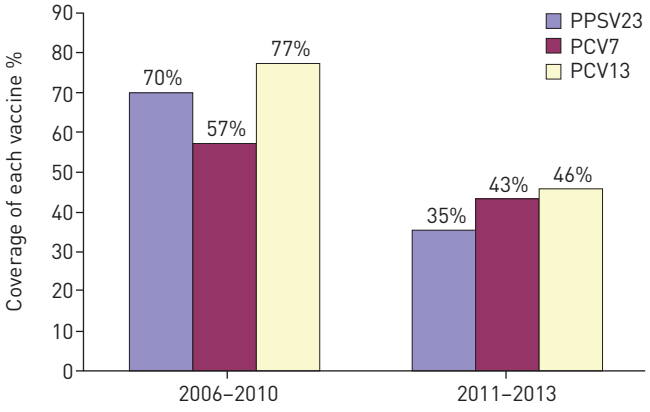

FIGURE 3 Coverage of pneumococcal vaccines per period. PPSV: pneumococcal polysaccharide vaccine; PCV: pneumococcal conjugate vaccine. The implementation of PCV13 in children in Spain started in 2010. PPSV23: p=0.018 for comparison between the groups 2006–2010 and 2011–2013. PCV7: p>0.99 for comparison between the groups 2006–2010 and 2011–2013. PCV13: p=0.11 for comparison between the groups 2006–2010 and 2011–2013.

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TABLE 4 Significant univariate and multivariate logistic regression analyses of predictors for bacteraemic pneumococcal pneumonia

	Univariate[#]		Multivariate[¶]	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Year of occurrence of pneumonia <2007	1.11 (0.84–1.46)	0.48	1.11 (0.70–1.79)	0.65
Age ⩾65 years	0.74 (0.57–0.97)	0.027	0.87 (0.54–1.39)	0.56
Female	1.31 (0.99–1.71)	0.054	1.03 (0.64–1.63)	0.91
Pneumococcal vaccination	0.59 (0.35–0.98)	0.041		
Influenza vaccination	0.75 (0.53–1.05)	0.089		
Inhaled corticosteroids	0.48 (0.33–0.69)	<0.001		
Previous antibiotics	0.59 (0.39–0.89)	0.012		
Chronic respiratory disease	0.61 (0.47–0.80)	<0.001		
Diabetes mellitus	1.41 (1.00–2.00)	0.052		
Nursing home resident	0.46 (0.22–0.99)	0.046	0.12 (0.01–1.00)	0.050
Expectoration	0.68 (0.51–0.91)	0.009		
Pleuritic pain	1.45 (1.11–1.90)	0.007		
Fever	1.63 (1.11–2.39)	0.012		
Confusion	1.35 (0.97–1.87)	0.075		
Creatinine ⩾1.5 mg·dL^{-1}	1.45 (1.08–1.95)	0.014		
C-reactive protein^{+} ⩾20 mg·dL^{-1}	2.55 (1.82–3.56)	<0.001	2.36 (1.45–3.85)	0.001
$P_{a}O_2/F_{I}O_2$ <250 mmHg	1.48 (1.08–2.04)	0.015		
$S_{a}O_2$ <92%	1.43 (1.01–2.02)	0.044		
Pleural effusion	1.74 (1.22–2.47)	0.002	2.03 (1.13–3.65)	0.018
Multilobar involvement	1.81 (1.34–2.44)	<0.001	1.69 (1.02–2.79)	0.041
Acute renal failure	1.46 (1.10–1.95)	0.010		
Septic shock	1.46 (0.96–2.24)	0.078		

$P_{a}O_2$: arterial oxygen tension; $F_{I}O_2$: inspiratory oxygen fraction; $S_{a}O_2$: arterial oxygen saturation. [#]: variables analysed in the univariate analysis were year of occurrence of pneumonia (<2007 *versus*⩾2007), age (<65 *versus* ⩾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 *versus* ⩾1.5 mg·dL^{-1}), C-reactive protein (<20 *versus*⩾20 mg·dL^{-1}), WBC count (<10×10^9 *versus* ⩾10×10^9 L^{-1}), $S_{a}O_2$ (<92% *versus* ⩾92%), $P_{a}O_2/F_{I}O_2$ (<250 *versus*⩾250 mmHg), CURB-65 risk class (0–2 *versus* 3–5), PSI risk class (I–III *versus* IV–V), pleural effusion, multilobar involvement, respiratory distress, septic shock, acute renal failure, and mechanical ventilation; [¶]: Hosmer–Lemeshow goodness-of-fit test, p=0.48; [+]: optimal cut-off value to predict bacteraemic pneumococcal pneumonia using receiver operating characteristic curves.

those patients requiring ICU admission; and 4) in our series, 14% of the serotypes (period 2006–2013) causing bacteraemia are included in PVC7, 74% in PVC13 and 83% in PPSV23.

The prevalence of bacteraemia in our series of cases (39%) was similar to that reported by Palma *et al.* [18] and Lin *et al.* [7]. An older study that did not have the urine antigen test available [1] tended to have a higher proportion of bacteraemic cases, although Kang *et al.* [9], without use of the urinary antigen test, found 89% of cases to be BCNPP.

This study identified serum level of CRP ⩾20 mg·dL^{-1} as a predictive factor for the presence of bacteraemia in this cohort of patients with pneumococcal pneumonia as a simple marker that can help clinicians to identify suspect patients with a high probability of bacteraemia. In addition, multilobar involvement and pleural effusion were independent predictive variables. The presence of these three variables together might have an influence on the type of antibiotic treatment since a combination of antibiotics including macrolides has been recommended in BCPPP [19]. Importantly, the absence of these three variables in the presence of nursing home patients ruled out BCPPP (3% probability), a finding that can be useful for clinical practice.

The prediction model we have presented is the first step in establishing a more universal model. To move forward from this first step, this prediction model will need to undergo external validation with larger patient cohorts from multiple centres. We were able to apply internal validation techniques to understand how likely it is that this model will be replicable in future studies and at other centres. Bootstrapping techniques were applied and demonstrated that the coefficients obtained from this prediction model were quite robust. Nursing home resident was the one factor that the bootstrap results indicated might have

TABLE 5 Evolution of patients

	Blood-culture-positive pneumococcal pneumonia	Blood-culture-negative pneumococcal pneumonia	p-value
Subjects	362	555	
Mechanical ventilation			0.30
No	289 (86)	444 (87)	0.56
NIMV	16 (5)	14 (3)	0.12
IMV	31 (9)	50 (10)	0.77
LOS days	9 (5–14)	7 (4–10)	<0.001
ICU mortality[#]	12 (14)	20 (20)	0.27
30-day mortality	27 (8)	27 (5)	0.12
Before 2007[¶]	19 (8)	18 (5)	0.16
After 2007[+]	8 (9)	9 (6)	0.49

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. Percentages calculated on nonmissing data. NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; LOS: length of hospital stay; ICU: intensive care unit. [#]: 88 patients in the bacteraemic pneumococcal pneumonia group and 102 patients in the nonbacteraemic pneumococcal pneumonia group were used to calculate the percentages; [¶]: percentages calculated for patients included before 2007 (240 patients in the bacteraemic pneumococcal pneumonia group, and 353 patients in the nonbacteraemic pneumococcal pneumonia group); [+]: percentages calculated for patients included after 2007 (93 patients in the bacteraemic pneumococcal pneumonia group and 144 patients in the nonbacteraemic pneumococcal pneumonia group).

limited repeatability in future work. Removal of nursing home resident from the model did not change which factors were significant predictors of bacteraemia. However, because of the importance surrounding nursing home resident, this variable was kept as a factor in this model despite some statistical limitations.

Pneumococcal bacteraemia was associated with significantly higher lactate, CRP and procalcitonin values as demonstrated by Pereira *et al.* [20] A study performed by Marrie *et al.* [21] compared nursing-home-acquired pneumonia, CAP and nursing home patients without pneumonia, and found that bacteraemic rates were similar in all groups, but there was a trend toward higher rates of pneumococcal bacteraemia in the CAP group. Lin *et al.* [7] analysed outcomes of hospitalised patients with BPP and non-BPP. Multivariate analysis showed that pneumococcal bacteraemia was correlated with extrapulmonary involvement (empyema and meningitis). In the study by Kang *et al.* [9], immunosuppressant use, younger age (<65 years) and diabetes mellitus were independent risk factors associated with bacteraemia in patients with pneumococcal pneumonia.

As has been shown previously, pneumococci isolated from patients with BCPPP showed less penicillin and erythromycin resistance than those isolated with non-BCNPP [18, 22, 23].

Of the serotypes causing invasive CAP from 2006 to 2013, only 14% were covered by the PCV7 vaccine, compared with 74% by the PCV13 vaccine and 83% by the PPSV23 vaccine. The low incidence of serotypes contained in PCV7 in patients with pneumococcal pneumonia reflects the herd protection resulting from widespread vaccination of children. However, a high numbers serotypes detected (74%) are included in the PCV13 vaccine which confirms the potential benefit of this conjugated vaccine [24]. After analysing the coverage of vaccines per period, we only observe statistically significant differences with PPSV23 in the coverage of serotypes present in the period 2006–2010 when compared with the period 2011–2013.

The case mortality rate for BPP varies in different parts of the world: 20% in the USA and Spain, 13% in the UK, 8% in Sweden and 6% in Canada, according to one study [25]. In our population the mortality rate was only 8%, and we found no association between bacteraemia and mortality. This rate is low compared with other studies. Musher *et al.* [1] and Kang *et al.* [9] found a 30-day mortality rate of about 29%, probably due to the nature of the population they studied and enrolment; in both of these studies, as well as that by Lin *et al.* [7], the mortality rate was substantially greater among BCPPP than BCNPP patients. In contrast, Palma *et al.* [18] found no significant differences when comparing BCPPP and BCNPP patients in terms of overall mortality and length of hospital stay. Furthermore, in the study by Pereira *et al.* [20] and in a subanalysis of the CAPO (Community-Acquired Pneumonia Organization) database by Bordon *et al.* [26], pneumococcal bacteraemia was reported not to have a negative effect on clinical outcomes of patients with CAP. Differences in study design, consecutive or nonconsecutive inclusion of patients and inclusion of immunosuppressed patients may explain these differing results.

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TABLE 6 Significant univariate and multivariate logistic regression analyses for the prediction of 30-day mortality

	Univariate[#]		Multivariate[¶]	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Year of occurrence of pneumonia <2007	0.86 (0.47–1.56)	0.62	0.51 (0.21–1.26)	0.14
Age ⩾65 years	2.95 (1.53–5.69)	0.001		
Chronic heart disease	1.95 (0.99–3.84)	0.052		
Chronic renal disease	2.70 (1.20–6.04)	0.016		
Chronic liver disease	3.35 (1.64–6.87)	0.001		
Neurological disease	2.63 (1.37–5.03)	0.004	2.76 (1.04–7.31)	0.041
Cough	0.32 (0.17–0.60)	<0.001		
Expectoration	0.36 (0.20–0.63)	<0.001		
Dyspnoea	3.44 (1.45–8.15)	0.005	6.50 (1.38–30.65)	0.018
Pleuritic pain	0.38 (0.21–0.69)	0.001	0.33 (0.14–0.80)	0.015
Fever	0.24 (0.13–0.43)	<0.001	0.27 (0.11–0.66)	0.004
Confusion	5.03 (2.86–8.85)	<0.001	3.33 (1.43–7.73)	0.005
Creatinine ⩾1.5 mg·dL^{-1}	5.11 (2.87–9.09)	<0.001		
WBC ⩾10×10^9 L^{-1}	0.41 (0.23–0.73)	0.002		
P_{aO_2}/F_{IO_2} <250 mmHg	5.02 (2.72–9.28)	<0.001		
S_{aO_2} <92%	2.43 (1.26–4.67)	0.008		
CURB-65 risk class 3–5	7.45 (4.11–13.50)	<0.001		
PSI risk class IV–V	9.31 (3.67–23.61)	<0.001		
Multilobar involvement	3.03 (1.74–5.29)	<0.001		
Respiratory distress	8.37 (3.93–17.84)	<0.001		
Acute renal failure	7.57 (4.04–14.20)	<0.001	3.47 (1.45–8.29)	0.005
Septic shock	10.86 (6.02–19.61)	<0.001	4.44 (1.77–11.17)	0.002
Site of care[+]		<0.001		
Outpatient				
Ward	1			
ICU	5.17 (2.92–9.16)	<0.001		
Mechanical ventilation[§]		<0.001		
No	1			
NIMV	7.55 (2.34–24.39)	0.001		
IMV	21.41 (10.94–41.90)	<0.001		
LOS >8 days	2.85 (1.58–5.11)	<0.001		
Quinolone	0.11 (0.02–0.81)	0.030		
Quinolone+β-lactam	1.98 (1.09–3.58)	0.024		
Bacteraemic pneumococcal pneumonia	1.54 (0.89–2.68)	0.12	1.29 (0.55–3.05)	0.56

WBC: white blood cell; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; S_{aO_2}: arterial oxygen saturation; CURB-65: severity score based on consciousness, urea, respiratory rate, blood pressure and age ⩾65 years; PSI: pneumonia severity index; ICU: intensive care unit; NIMV: noninvasive mechanical ventilation; IMV, invasive mechanical ventilation; LOS: length of hospital stay. [#]: variables analysed in the univariate analysis were year of occurrence of pneumonia (<2007 *versus* ⩾2007), age (<65 *versus* ⩾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 *versus* ⩾1.5 mg·dL^{-1}), C-reactive protein (<20 *versus*⩾20 mg·dL^{-1}), WBC count (<10×10^9 *versus* ⩾10×10^9 L^{-1}), S_{aO_2} (<92% *versus* ⩾92%), P_{aO_2}/F_{IO_2} (<250 *versus*⩾250 mmHg), CURB-65 risk class (0–2 *versus* 3–5), PSI risk class (I–III *versus* IV–V), pleural effusion, multilobar involvement, respiratory distress, septic shock, acute renal failure, site of care, mechanical ventilation, LOS (⩽8 *versus* >8 days), antibiotic treatment, and bacteraemic pneumococcal pneumonia. [¶]: Hosmer–Lemeshow goodness-of-fit test, p=0.40; [+]: p-value corresponds to differences between the three groups (outpatient, ward or ICU); [§]: p-value corresponds to differences between the three groups (no mechanical ventilation, NIMV or IMV).

The low mortality rates in our study can be explained by our exclusion of immunosuppressed patients and the very high rate with which initial treatment was in accordance with ATS/IDSA recommendations [17] and the prompt initiation of antibiotic therapy. However, we looked at mortality rates before and after the 2007 ATS/IDSA recommendations [17], and we did not find differences in mortality. Overall, 98% of antibiotic selection was concordant with recommendations and, by policy, the initial dose is given within 6 h of presentation. Garnacho-Montero *et al.* [27] found that early treatment is the most important

variable associate with mortality in BPP. Another possible explanation for the low mortality is that most of our BCPPP patients received combination therapy [28, 29], a factor found to be associated with a better survival in some studies, although we did not find that combination therapy was a protective factor for mortality in the BCPPP population.

In our study, 30-day mortality in the specific population of BCPPP patients was positively associated with four independent factors: confusion, respiratory distress, acute renal failure and the presence of septic shock. Lujan *et al.* [30] previously reported altered mental status to be a significant risk factor for death in patients with BCPPP. In contrast with other studies (mainly retrospective) [31, 32] we did not find that combination antibiotic therapy was protective for mortality in BCPPP patients.

The strengths of our study are a very large population of consecutive patients with documented pneumococcal pneumonia. Limitations include that it is a single-centre study over a long period of time and that we did not record the time to the first dose of antibiotic in many patients, which is a factor that is clearly associated with mortality. However, our policy from many years has been to administer the first dose of antibiotics within 6 h after arrival in the emergency department. A further two limitations are the lack of power calculation for mortality and the lack of external validation. Our results have to be confirmed in external cohorts.

Finally, as previously discussed, the inclusion of nursing home resident in the prediction model introduced ambiguity regarding the reproducibility of the effect of nursing home resident in future prediction models.

In summary, the present study shows that certain factors detectable at the time of admission indicate a group of patients who are at high risk of bacteraemia and who, therefore, merit more intense therapy. These factors include pleural effusion, multilobar involvement and CRP $\geqslant$20 mg·dL^{-1}. Importantly, the absence of these factors practically rules out BCPPP. These factors could be an easy way to help clinicians to distinguish these patients; however, an external cohort is needed it to validate these results. Supporting some earlier reports, but at odds with others, bacteraemia was not, by itself, a predictor of increased mortality.

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