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ORIGINAL

Host–pathogen interactions and prognosis of critically ill immunocompetent patients with pneumococcal pneumonia: the nationwide prospective observational STREPTOGENE study

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Abstract

Purpose: To assess the relative importance of host and bacterial factors associated with hospital mortality in patients admitted to the intensive care unit (ICU) for pneumococcal community-acquired pneumonia (PCAP).

Methods: Immunocompetent Caucasian ICU patients with PCAP documented by cultures and/or pneumococcal urinary antigen (UAg Sp) test were included in this multicenter prospective study between 2008 and 2012. All pneumococcal strains were serotyped. Logistic regression analyses were performed to identify risk factors for hospital mortality.

Results: Of the 614 patients, 278 (45%) had septic shock, 270 (44%) had bacteremia, 307 (50%) required mechanical ventilation at admission, and 161 (26%) had a diagnosis based only on the UAg Sp test. No strains were penicillin-resistant, but 23% had decreased susceptibility. Of the 36 serotypes identified, 7 accounted for 72% of the isolates, with different distributions according to age. Although antibiotics were consistently appropriate and were started within 6 h after admission in 454 (74%) patients, 116 (18.9%) patients died. Independent predictors of hospital mortality in the adjusted analysis were platelets $\leq 100 \times 10^9$/L (OR, 7.7; 95% CI, 2.8–21.1), McCabe score ≥ 2 (4.58; 1.61–13), age > 65 years (2.92; 1.49–5.74), lactates > 4 mmol/L (2.41; 1.27–4.56), male gender and septic shock (2.23; 1.30–3.83 for each), invasive mechanical ventilation (1.78; 1–3.19), and bilateral pneumonia (1.59; 1.02–2.47). Women with platelets $\leq 100 \times 10^9$/L had the highest mortality risk (adjusted OR, 7.7; 2.8–21).

Conclusions: In critically ill patients with PCAP, age, gender, and organ failures at ICU admission were more strongly associated with hospital mortality than were comorbidities. Neither pneumococcal serotype nor antibiotic regimen was associated with hospital mortality.

Keywords: Pneumococcal pneumonia, Severe community-acquired pneumonia, Intensive care unit, Pneumococcal serotypes, Macrolides, Fluoroquinolones

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Introduction

Severe community-acquired pneumonia (CAP) is the most common infection requiring intensive care unit (ICU) admission and the leading cause of death from infection in Western countries [1]. *Streptococcus pneumoniae* is the main cause of severe CAP managed in the ICU, with 30% of microbiologically documented cases in adults [2]. Given the increased frequency of pneumococcal CAP (PCAP) with advancing age, the burden of severe PCAP can be expected to increase in the near future [3]. Despite the availability of antibiotics effective against *S. pneumoniae* and early ICU admission to treat organ failures, severe PCAP remains associated with high mortality rates of 15–30% [4–7].

The outcome of severe PCAP managed in the ICU depends on multiple factors including patient characteristics, pneumococcal serotype, the impact of sepsis-related organ failures, and the management strategy [8–10]. These factors interact with many confounders, making it difficult to determine the relative contribution of each [5, 11, 12].

The primary objective of this study was to assess the relative contributions of various factors to the outcome of severe PCAP in patients managed in French ICUs. We performed a multicenter prospective cohort study in a uniform population of immunocompetent Caucasian adults treated between 2008 and 2012. We assessed the strengths of the associations of various factors—including patient characteristics, pneumococcal serotypes, and antibiotic regimens—with hospital mortality. Our secondary objective was to obtain epidemiological and microbiological data on severe PCAP.

Take-home message

In immunocompetent Caucasian patients critically ill with pneumococcal pneumonia, mortality was high (18.9%). Age, gender, and organ failures at admission were more closely associated with mortality than were comorbidities, pneumococcal serotypes, and antibiotic regimens

Materials and methods

Study design

Consecutive immunocompetent Caucasians older than 18 years and admitted to multiple French ICUs in university- and nonuniversity-affiliated hospitals between 2008 and 2012 for PCAP were included in a prospective observational study. The study sponsor registered the study database with the French Data Protection Authority (*Commission Nationale Informatique et Liberté*, ENRCNIL 909234). The study project was approved by the appropriate ethics committee (*Comité de Protection des Personnes d'Ile de France*, September 9, 2008, #2008/36NICB). Each investigator undertook to conduct the study in compliance with Good Clinical Practice guidelines and with the 1964 Declaration of Helsinki and its amendments. Written informed consent was obtained before study inclusion from patients who were competent. For patients who were not competent, written informed consent was obtained from the next-of-kin then from the patients as soon as they regained competence.

Inclusion and exclusion criteria

Patients were first screened for eligibility based on the following criteria: age ≥ 18 years, Caucasian, ICU admission for CAP, and criteria for severe CAP requiring ICU admission. *S. pneumoniae* CAP was defined as the presence at hospital admission or within the next 48 h of acute respiratory manifestations with a new radiological infiltrate of unknown cause combined with a positive urinary *S. pneumoniae* antigen test (UAg Sp; in the absence of documented pneumococcal pneumonia within the past 2 months and of pneumococcal immunization within the last 2 weeks) and/or with a sputum smear, tracheal aspirate (containing < 10 epithelial cells and > 25 neutrophils per × 10 field), distal protected airway specimen, or pleural aspirate showing Gram-positive diplococci. Criteria for severe CAP requiring ICU admission were those defined by the American Thoracic Society [13], i.e., at least one of two major criteria [invasive mechanical ventilation (IMV) or septic shock] or at least three minor criteria among the following: respiratory rate > 30/min; $PaO_2/FiO_2 < 250$ or non-invasive ventilation (NIV); multilobar infiltrates; confusion or disorientation; blood urea nitrogen > 7 mmoL/L; leukocytes < 4000/mm^3; platelets < 100,000 mm^3; body temperature < 36°; hypotension requiring fluid repletion; metabolic acidosis; and high serum lactate level.

Eligible patients were definitely included if *S. pneumoniae* infection was diagnosed based on the presence of any of the following: positive UAg Sp and/or positive *S. pneumoniae* culture of blood or pulmonary specimens.

Exclusion criteria were non-Caucasian ethnicity, pneumococcal pneumonia related to healthcare or with onset more than 72 h after hospital admission, aspiration pneumonia in a comatose or trauma patient, and immunodeficiency (asplenia or splenectomy; chemotherapy, hematological malignancy within the past 6 months and not in complete remission, solid-organ or bone marrow transplant; neutrophils < 1000/mm^3 before the infection, HIV infection, Child C cirrhosis of the liver, or immunoglobulin deficiency).

Data collection

For each patient, the study data were recorded in an electronic case-report form. Demographic, epidemiological, clinical, bacteriological, laboratory and imaging data were collected prospectively upon admission and during the ICU stay. Details are reported in Electronic Supplementary Material (ESM1). We also recorded previous pneumococcal vaccination with the polysaccharide 23-valent vaccine, pre-admission exposure to antibiotics, time from hospital admission to the first dose of antipneumococcal antibiotic, and the nature of the antibiotics given in the ICU.

All patients were followed up until death or hospital discharge. The causes of death were recorded. After ICU discharge, patients were managed as deemed suitable by the ward physicians, who complied with French recommendations [14].

Microbiology

Susceptibility testing was performed at the French National Reference Centre for Pneumococci (FNRCP). Susceptibility to penicillin G, amoxicillin, cefotaxime, and levofloxacin was determined using the agar dilution method and susceptibility to erythromycin using the disk diffusion method. In addition, the norfloxacin screen test was used according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [15] in order to successfully discriminate wild-type pneumococcal strains from those with any acquired mechanism of resistance to fluoroquinolones [16]. The results were interpreted according to EUCAST breakpoints [15]. Antibiotics given to treat PCAP were classified as appropriate if one or more empirical antibiotics had in vitro activity against the *S. pneumoniae* strain and adequate if the antibiotic had in vitro activity and was given in recommended dosage with timing of administration < 6 h. Serotyping was performed at the FNRCP with use of latex particles sensitized with pool, group, type and factor antisera provided by the Statens Serum Institut (Copenhagen, Denmark). This panel of antisera enabled recognition of 92 known serotypes. Pneumococcal strains with known serotypes from the Statens Serum Institute and from the CNRP collection were used as internal quality controls [17].

Statistical analysis

The statistical methods are detailed in the Electronic Supplementary Material (ESM2). The primary outcome was hospital mortality. The probability of hospital mortality was estimated using the cumulative incidence function estimator [18], with discharge alive as a competing risk.

Marginal associations between single variables and hospital mortality were assessed by applying Wilcoxon's rank-sum test for quantitative variables and Fisher's exact test for categorical variables. Some of the continuous variables were categorized according to predefined cut-offs. Variables independently associated with hospital mortality were identified by multiple logistic regression using a backward stepwise selection procedure, with *P* value cutoffs of 0.20 and 0.10 for considering and retaining variables, respectively. First-order interactions between selected variables were then tested. Missing data were handled through multiple imputation. Results were pooled over imputed datasets. Model performance was evaluated based on the concordance (*c*) index and calibration curve. As internal model validation, the final model parameters and performance were corrected for over-optimism using bootstrapping. Results of the final model are reported as odds ratios (ORs) with their 95% confidence intervals (95% CIs). In addition, a nomogram for predicting the patient-specific probability of hospital death was created.

Potential associations between pneumococcal serotypes and hospital mortality were assessed in the subgroup of patients with microbiologically documented PCAP. Individual associations were determined for the serotypes found in at least ten patients, using serotype 3 as the reference, since a strong association of serotype 3 with high mortality in adults has been reported [19]. Serotypes were then grouped according to their potential for causing invasive disease, as previously described [20–23], and their case fatality rate was determined for each group as previously reported [24, 25]. To estimate the invasiveness of serotypes for which no published data were available, invasive isolates in our patients were compared to a previously characterized sample of *S. pneumoniae* isolated during the study period from healthy carriers younger than 5 years of age [20].

Both unadjusted analyses and analyses adjusted on variables independent from the pathogen (age, gender, body mass index (BMI), McCabe score, and Charlson score) were performed. When no event or a single event occurred in a category, exact logistic regression was used, and the category was excluded from the adjusted analyses.

All tests were two-sided, and analyses were performed using R statistical software version 3.0.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

We prospectively included 614 patients, including 377 (61%) males admitted to 51 French ICUs between December 2008 and February 2012. Table 1 shows that

several features differed significantly across age groups. As expected, a large proportion of patients (45.1%) were older than 65 years. The Fine score, median Sepsis-Related Organ Failure (SOFA) score, and median Simplified Acute Physiology Score version II (SAPSII) indicated that most patients had severe acute illness. Most patients met major IDSA/ATS criteria for severe CAP and many patients had multiple comorbidities (ESM 3) only 2% of patients received previous pneumococcal vaccination with the polysaccharide 23-valent vaccine.

Antibiotic susceptibility and treatment

Of the 614 patients, 449 (73.1%) had positive cultures for *S. pneumoniae* and 270 (44%) had bacteremia. The diagnosis relied solely on the UAg Sp in 161 (26.2%) patients (Table 1). Susceptibility testing and serotyping were performed for 349 isolates, of which 56.7% were from blood, 40.9% from lung specimens, and 2.3% from pleural fluid. Of these 349 isolates, 5 were not viable and 5 were not *S. pneumoniae* strains, leaving 339 isolates for the study. Of these, 23.3, 10.0, and 2.9% exhibited decreased susceptibility to penicillin, amoxicillin, or cefotaxime, respectively. No strain was resistant to any of these antibiotics. Resistance to erythromycin was noted for 24.5% of strains and to levofloxacin for 2 (0.6%) strains. In addition, among levofloxacin-susceptible strains, one (0.3%) was detected as a topoisomerase IV first-step mutant. The proportion of isolates with a decreased susceptibility to beta-lactams declined over the 3-year study period (Electronic Supplementary Material 4).

Mean time from hospital admission to the first antibiotic dose was 6.8 ± 5.5 h (Table 1). The antibiotics were appropriate in all patients and adequate in 63.3% of patients. A beta-lactam active against *S. pneumoniae* was used alone in 22.6% of patients, with a macrolide in 36.3% of patients, and with a fluoroquinolone in 34.2% of patients (Electronic Supplementary Material 5).

Serotypes

Of the 36 capsular serotypes identified (Fig. 1), serotype 3 was the most common (23.9% of isolates), followed by serotypes 7F, 19A, 12F, 1, 6C, and 11A. These seven serotypes, each found for over 10 isolates, accounted for 72.2% of all isolates. PCV13 serotypes accounted for 69.6% of isolates overall, with a decrease from 71.8% in the first to 64.2% in the third study year. Most (84.8%) of the isolates with decreased susceptibility to penicillin had PCV13 serotypes, mainly 19A (59.5%). Among the non-PCV13 serotypes, the most prevalent was the emerging 12F serotype (6.5%), which was fully susceptible to beta-lactams (Fig. 1) and covered by the 23-valent polysaccharide vaccine.

Serotype distribution differed significantly across age groups (Electronic Supplementary Material 5). The prevalence of serotype 3 increased with age, accounting for 29% of serotypes after 65 years. Serotype 7F was found chiefly between 18 and 50 years of age and serotype 19A between 51 and 65 years of age. Serotypes known to have a highly invasive potential or associated with high mortality rates accounted for 72% and 55.5% of strains, respectively (Table 2). The frequency of these serotypes was significantly higher in the oldest group than in the younger groups ($P = 0.011$; Electronic Supplementary Material 6).

Hospital mortality

Overall, 116 (18.9%) patients died. Mortality increased with age for 27.1% in the group older than 65 years ($P < 0.0001$; Table 3). Mortality was 23.8% in patients who met major IDSA/ATS criteria at ICU admission and 31.3% in patients with septic shock. In the group of patients who died, mean age was 70 ± 15 years, mean SAPSII was 61 ± 18, mean SOFA score was 11.2 ± 4, and mean Fine score was 163 ± 35. Multiorgan failure was the main cause of death (45.7%). Of the patients who died, 32% died within the first 5 days. Day-5 mortality was similar across age groups, but differed according to ICU admission criteria ($P = 0.0008$) and presence of septic shock ($P < 0.0001$).

Factors associated with hospital mortality are reported in Table 4 (data pooled over imputed datasets) and Electronic Supplementary Material 7 (patients with no missing data). In the adjusted analysis, factors independently associated with hospital mortality were age > 65 years, male gender, McCabe score ≥ 2, higher SAPSII, platelets ≤ 100 × 10^9/L, lactates > 4 mmol/L, bilateral pneumonia, septic shock, and IMV. Interactions were found between gender and platelets: mortality was considerably higher in women with ≤ 100 × 10^9/L platelets than in women with higher platelet counts (adjusted OR, 7.70; 95% CI, 2.80–21), whereas men, regardless of their platelet count, were at greater risk for death compared to women with platelet counts > 100 × 10^9/L.

Figure 2 is the nomogram for predicting hospital death. The model was well calibrated, with a calibration curve showing no major deviations from the reference line (Electronic Supplementary Material 8) and an optimism-corrected *c* index of 0.841 (95% CI, 0.809–0.872).

After adjustment on the multivariable score predicting hospital death, no difference was found between beta-lactam therapy alone (19.4%) or with a macrolide (19.9%) or fluoroquinolone (15.1%) started within 24 h after ICU admission (Electronic Supplementary Material 4).

Serotype 3 was the serotype associated with the highest mortality rate (23.5%). However, this rate was not

Table 1 Main baseline features of the study patients

Characteristic	All patients	Age category, years			
		18–50	51–65	> 65	*P* value
N of patients	614	143	194	277	
Age, years, median (range)	63 (19–99)	43 (19–50)	59 (51–65)	78 (66–99)	–
Gender, *n* (%)					0.54
Female	237 (38.6)	52 (36.4)	81 (41.8)	104 (37.5)	
Male	377 (61.4)	91 (63.6)	113 (58.2)	173 (62.5)	
BMI, kg/m^2, median [IQR]	24.5 [21.2–28.4]	22.9 [20.5–25.4]	24.0 [20.9–28.4]	25.7 [22.3–29.4]	< 0.0001
N missing	48	7	17	24	
Admission, *n* (%)					0.017
Direct admission to ICU	74 (12.1)	10 (7.0)	36 (18.6)	28 (10.1)	
Transfer from ER	459 (74.8)	114 (79.7)	136 (70.1)	209 (75.5)	
Transfer from another ward	81 (13.2)	19 (13.3)	22 (11.3)	40 (14.4)	
Criteria[a] for ICU admission, *n* (%)					0.12
Major	480 (78.2)	102 (71.3)	151 (77.8)	227 (81.9)	
Minor	124 (20.2)	39 (27.3)	40 (20.6)	45 (16.2)	
None	10 (1.6)	2 (1.4)	3 (1.5)	5 (1.8)	
Type of sample, *n* (%)					0.032
Blood culture (BC)	270 (44.0)	73 (51.0)	84 (43.3)	113 (40.8)	
Pulmonary specimen, no BC	183 (29.8)	31 (21.7)	69 (35.6)	83 (30.0)	
UAg Sp alone	161 (26.2)	39 (27.3)	41 (21.1)	81 (29.2)	
McCabe, *n* (%)					0.017
1	562 (91.5)	139 (97.2)	176 (90.7)	247 (89.2)	
2	51 (8.3)	4 (2.8)	18 (9.3)	29 (10.5)	
3	1 (0.2)	0 (0)	0 (0)	1 (0.4)	
Fine score, *n* (%)					< 0.0001
II	37 (6.0)	26 (18.2)	10 (5.2)	1 (0.4)	
III	63 (10.3)	36 (25.2)	20 (10.3)	7 (2.5)	
IV	191 (31.1)	55 (38.5)	75 (38.7)	61 (22.0)	
V	323 (52.6)	26 (18.2)	89 (45.9)	208 (75.1)	
SOFA, median [IQR]	7 (4–10)	6 (3–10)	8 (4–10)	7 (4–10)	0.009
SAPSII, median [IQR]	43 (32–57)	31 (23–42)	42 (32–57)	48 (39–61)	< 0.0001
Charlson index, *n* (%)					< 0.0001
0–1	101 (16.4)	90 (62.9)	9 (4.6)	2 (0.7)	
2	94 (15.3)	33 (23.1)	57 (29.4)	4 (1.4)	
3	106 (17.3)	10 (7.0)	70 (36.1)	26 (9.4)	
4+	313 (51.0)	10 (7.0)	58 (29.9)	245 (88.4)	
WBC < 4 × 10^9/L, *n* (%)	116 (19.1)	40 (28.4)	39 (20.1)	37 (13.6)	0.001
N missing	6	2	0	4	
Platelets ≤ 100 × 10^9/L, *n* (%)	90 (14.9)	28 (19.7)	34 (18.1)	28 (10.3)	0.011
N missing	11	1	6	4	
Lactates (mmol/L), *n* (%)					0.66
< 2	181 (31.7)	38 (29.0)	64 (35.6)	79 (30.4)	
2–4	249 (43.6)	58 (44.3)	72 (40.0)	119 (45.8)	
> 4	141 (24.7)	35 (26.7)	44 (24.4)	62 (23.8)	
N missing	43	12	14	17	
Shock, *n* (%)	278 (45.3)	58 (40.6)	94 (48.5)	126 (45.5)	0.35
RRT, *n* (%)	22 (3.6)	2 (1.4)	7 (3.6)	13 (4.7)	0.24
IMV, *n* (%)	307 (50.0)	64 (44.8)	110 (56.7)	133 (48.0)	0.065

Table 1 (continued)

Characteristic	All patients	Age category, years			
		18–50	51–65	> 65	*P* value
Non-invasive ventilation, *n* (%)	171 (27.9)	30 (21.0)	36 (18.6)	105 (37.9)	< 0.0001
Extent of lung infection, *n* (%)					0.35
1 lobe	216 (35.2)	43 (30.1)	65 (33.5)	108 (39.0)	
2 lobes	157 (25.6)	42 (29.4)	47 (24.2)	68 (24.5)	
Bilateral	241 (39.3)	58 (40.6)	82 (42.3)	101 (36.5)	
Pre-hospital antibiotics, *n* (%)	83 (13.5)	20 (14.0)	22 (11.3)	41 (14.8)	0.55
Time to antibiotic therapy, h					0.010
< 3	252 (48.0)	67 (52.8)	88 (55.3)	97 (40.6)	
3–6	137 (26.1)	36 (28.3)	36 (22.6)	65 (27.2)	
> 6	136 (25.9)	24 (18.9)	35 (22.0)	77 (32.2)	
N missing	89	16	35	38	
Recombinant human activated protein C, *n* (%)	48 (7.8)	6 (4.2)	20 (10.3)	22 (7.9)	0.11
Corticosteroids, *n* (%)	238 (38.8)	49 (34.3)	86 (44.3)	103 (37.2)	0.14
Protective ventilation, *n* (%)	200 (32.6)	44 (30.8)	65 (33.5)	91 (32.9)	0.86

BMI body mass index, *IQR* interquartile range, *ICU* intensive care unit, *ER* emergency room, *BC* blood culture, *UAg Sp* urinary antigen test for *S. pneumoniae*, *SOFA* Sepsis-related Organ Failure score, *SAPSII* Simplified Acute Physiology Score version II, *WBC* white blood cell count, *RRT* renal replacement therapy, *IMV* invasive mechanical ventilation

[a] IDSA/ATS (Ref. [13])

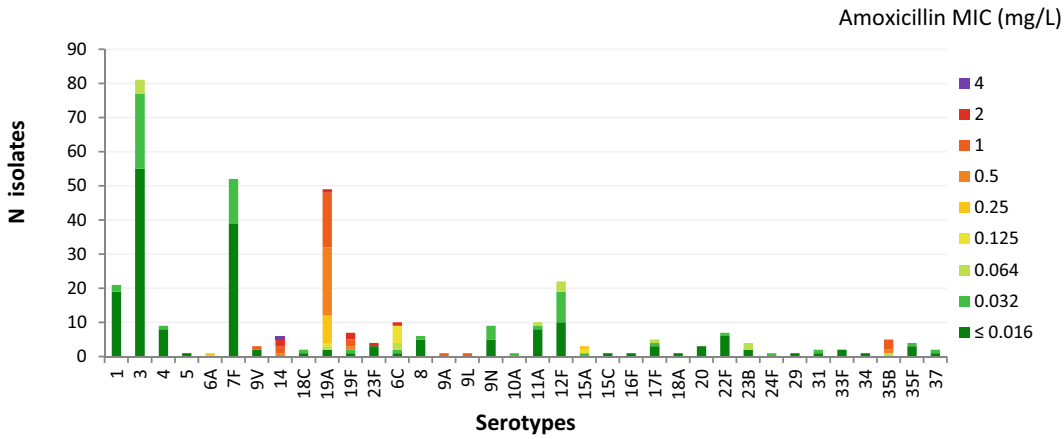

Fig. 1 Serotype distribution according to amoxicillin minimum inhibitory concentrations (MICs) for the 339 strains of *S. pneumoniae*

significantly different from the mortality rates for the other serotypes, with only the exception of serotype 12F, which was responsible for no deaths. In the unadjusted analysis, mortality was significantly higher for serotypes known to have low invasiveness and for those known to be associated with high mortality rates. However, after adjustment on host variables not affected by the pathogen, only low-invasiveness serotypes were significantly associated with higher mortality (Table 2).

Discussion

This study of a large prospective cohort of immunocompetent Caucasian adults admitted to the ICU for PCAP showed that hospital mortality was high, at nearly one in five, although all patients received appropriate antibiotics from the outset, usually within 6 h after ICU admission. The main factors assessable at admission and independently associated with hospital mortality were older age, male gender, worse McCabe score, worse SAPSII, septic shock, and markers of organ failure (serum lactate elevation, thrombocytopenia, bilateral pulmonary infiltrates,

Table 2 Hospital mortality according to serotype

Characteristic	*N* patients (column %)	*N* deaths (row %)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
N patients	339	72 (21.2)		
Serotype				
3	81 (23.9)	19 (23.5)	1	1
7F	52 (15.3)	6 (11.5)	0.43 (0.16–1.15)	0.57 (0.20–1.65)
19A	49 (14.5)	11 (22.4)	0.94 (0.41–2.20)	0.87 (0.34–2.20)
12F	22 (6.5)	0 (0)	0.10 (0.000–0.65)**	N/A
1	21 (6.2)	1 (4.8)	0.17 (0.003–1.21)**	N/A
6C	10 (2.9)	5 (50.0)	3.26 (0.85–12.5)	3.67 (0.83–16.3)
11A	10 (2.9)	2 (20.0)	0.82 (0.16–4.17)	1.04 (0.19–5.82)
Other	94 (27.7)	28 (29.8)	1.38 (0.70–2.73)	1.55 (0.74–3.24)
Serotype invasiveness[b]				
High	244 (72.0)	45 (18.4)	1	1
Low	33 (9.7)	13 (39.4)	2.87 (1.33–6.21)	2.78 (1.21–6.41)
Undetermined	62 (18.3)	14 (22.6)	1.29 (0.66–2.54)	1.23 (0.59–2.55)
Serotype case-fatality rate[c]				
Low	91 (26.8)	13 (14.3)	1	1
Intermediate	41 (12.1)	5 (12.2)	0.83 (0.28–2.51)	0.74 (0.24–2.30)
High	188 (55.5)	48 (25.5)	2.06 (1.05–4.03)	1.57 (0.76–3.24)
Other	19 (5.6)	6 (31.6)	2.77 (0.89–8.59)	1.79 (0.54–5.93)

OR odds ratio; *95% CI* 95% confidence interval; *N/A* not applicable

[a] Adjusted on age, gender, body mass index, McCabe score, and Charlson index, i.e., on variables not affected by the pathogen

[b] Serotype invasiveness: high (OR > 1, $P < 0.05$), serotypes 1, 3, 4, 5, 7F, 12F, 14, 18C, 19A, and 9L; low (OR < 1, $P < 0.05$), serotypes 6A, 6C, 10A, 11A, 15A, 15C, 23B, 24F, and 37; and undetermined (OR < 1 or OR > 1 with $P > 0.05$), serotypes 8, 9A, 9 N, 9 V, 16F, 17F, 18A, 19F, 20, 22F, 23F, 29, 31, 33F, 34, 35B, and 35F

[c] Serotype case-fatality rate: low (serotypes 1, 4, 5, 7F, and 8), intermediate (serotypes 9 V, 12F, 14, and 22F), or high (serotypes 3, 6A, 6B, 6C, 9 N, 11A, 19A, 19F, and 23F)

Table 3 Hamoxicillin MICospital mortality and causes of death

Characteristic	All patients	Age category, years			ICU admission criteria[a]			Shock	
		18–50	51–65	> 65	Major	Minor	None	No	Yes
N of patients	614	143	194	277	480	124	10	336	278
Day-5 mortality, *n* (%)	37 (6.0)	6 (4.2)	8 (4.1)	23 (8.3)	37 (7.7)	0 (0)	0 (0)	6 (1.8)	31 (11.2)
Hospital mortality, *n* (%)	116 (18.9)	14 (9.8)	27 (13.9)	75 (27.1)	114 (23.8)	2 (1.6)	0 (0)	29 (8.6)	87 (31.3)
Cause of death, *n* (%)									
MOF	53 (45.7)	7 (50.0)	14 (51.9)	32 (42.7)	53 (46.5)	0 (0)	–	6 (20.7)	47 (54.0)
MOF + hypoxemia	9 (7.8)	2 (14.3)	0 (0)	7 (9.3)	9 (7.9)	0 (0)	–	2 (6.9)	7 (8.0)
Hypoxemia	12 (10.3)	1 (7.1)	2 (7.4)	9 (12.0)	12 (10.5)	0 (0)	–	8 (27.6)	4 (4.6)
Shock	8 (6.9)	1 (7.1)	3 (11.1)	4 (5.3)	8 (7.0)	0 (0)	–	2 (6.9)	6 (6.9)
Neurological	7 (6.0)	2 (14.3)	2 (7.4)	3 (4.0)	7 (6.1)	0 (0)	–	0 (0)	7 (8.0)
Cardiac	3 (2.6)	0 (0)	0 (0)	3 (4.0)	3 (2.6)	0 (0)	–	1 (3.4)	2 (2.3)
Digestive	3 (2.6)	0 (0)	1 (3.7)	2 (2.7)	2 (1.8)	1 (50.0)	–	3 (10.3)	0 (0)
Other pulmonary	2 (1.7)	0 (0)	1 (3.7)	1 (1.3)	2 (1.8)	0 (0)	–	1 (3.4)	1 (1.1)
ARDS	2 (1.7)	0 (0)	0 (0)	2 (2.7)	2 (1.8)	0 (0)	–	1 (3.4)	1 (1.1)
WLST (unknown reason)	15 (12.9)	1 (7.1)	3 (11.1)	11 (14.7)	14 (12.3)	1 (50.0)	–	4 (13.8)	11 (12.6)
Unknown	2 (1.7)	0 (0)	1 (3.7)	1 (1.3)	2 (1.8)	0 (0)	–	1 (3.4)	1 (1.1)

Day-5 mortality was not significantly different across age groups ($P = 0.12$) but differed according to ICU admission criteria ($P = 0.0008$) and presence of shock ($P < 0.0001$). Hospital mortality differed across age groups, ICU admission criteria, and presence of shock ($P < 0.0001$, $P < 0.0001$, and $P < 0.0001$, respectively)

MOF multiple organ failure, *ARDS* acute respiratory distress syndrome, *WLST* withdrawal of life-sustaining therapy

[a] IDSA/ATS criteria

Table 4 Associations between baseline characteristics and hospital death

Variable	Crude OR (95% CI)	Adjusted OR (95% CI) in final model
Age, years, 51–65 vs. 18–50	1.49 (0.75–2.96)	1.15 (0.57–2.33)
Age, years, > 65 vs. 18–50	3.42 (1.86–6.31)	2.92 (1.49–5.74)
Male gender	1.84 (1.18–2.86)	2.23 (1.30–3.83)
BMI 25–30 vs. < 25	1.02 (0.62–1.68)	–
BMI > 30 vs. < 25	0.95 (0.54–1.68)	–
Blood culture vs. pulmonary specimen	1.04 (0.66–1.65)	–
UAg Sp only vs. pulmonary specimen	0.54 (0.30–0.98)	–
McCabe ≥ 2	2.27 (1.22–4.22)	4.58 (1.61–13.0)
SOFA (per unit)	1.29 (1.22–1.37)	–
SAPS II (per unit)	1.06 (1.05–1.08)	1.03 (1.02–1.05)
Charlson index 2 vs. ≤ 1	0.73 (0.27–2.01)	–
Charlson index 3 vs. ≤ 1	1.62 (0.70–3.76)	–
Charlson index ≥ 4 vs. ≤ 1	3.28 (1.63–6.61)	–
WBC < 4×10^9/L	1.77 (1.10–2.85)	–
Platelets ≤ 100×10^9/L	2.57 (1.56–4.24)	7.70 (2.80–21.1)
Lactates 2–4 vs. < 2 mmol/L	2.18 (1.17–4.04)	1.25 (0.68–2.30)
Lactates > 4 vs. < 2 mmol/L	6.06 (3.26–11.3)	2.41 (1.27–4.56)
Bilateral pulmonary infection	1.72 (1.15–2.59)	1.59 (1.02–2.47)
Time to antibiotics > 6 h	1.58 (1.00–2.50)	–
Shock	4.82 (3.05–7.62)	2.23 (1.27–3.93)
RRT	5.63 (2.37–13.4)	–
IMV	5.05 (3.11–8.18)	1.78 (1.00–3.19)
Non-invasive ventilation	1.27 (0.82–1.97)	–
Interactions		
Male gender × platelets ≤ 100×10^9/L	–	0.15 (0.045–0.49)
McCabe ≥ 2 × shock	–	0.27 (0.071–1.04)

The reported data are pooled over the imputed datasets. The final model discrimination (*c* index) was 0.841 (0.809–0.872) after correction for over-optimism

BMI body mass index, *UAg Sp* urinary antigen test for *S. pneumoniae*, *WBC* white blood cell count, *RRT* renal replacement therapy, *IMV* invasive mechanical ventilation

and IMV). Seven pneumococcal serotypes accounted for nearly three-fourths of all isolates. Serotype distribution varied significantly across age groups. Serotype was not independently associated with hospital mortality.

Our mortality rate of 18.9% is high. Several ICU studies found mortality rates of 16–20%, but included patients with immunodeficiencies [5–7, 11]. However, a study of two prospective databases of patients managed in 2001–2008 found a higher hospital mortality rate of 29% [4]. The introduction in recent years of care protocols for septic shock has led to a steady decrease in mortality throughout the world [26]. Nevertheless, septic shock was an independent risk factor for death in our study. The 31% hospital mortality rate in our subgroup with septic shock is lower than the 40–50% rates reported in the past [8, 9], but higher than in recent studies [6, 10]. These discrepancies are probably due to differences in case mix and treatment strategies. Day-5 mortality was very high, at 43%, in the youngest age group and was 35.7% in the subgroup with septic shock, perhaps due to a massive and deleterious proinflammatory response in these specific populations [12].

Mortality was very low in the subgroup admitted to the ICU with minor but no major IDSA/ATS criteria, in keeping with earlier data [27]. These patients may have been admitted earlier in the course of their disease then benefited from the close monitoring provided in the ICU. Minor criteria do not seem to be strong risk factors for death and may deserve to be used only as an aid to clinical judgment when making ICU admission decisions [28].

Mortality increased with age in our study, in keeping with earlier data [5, 29], an effect probably ascribable to immunosenescence. Age older than 65 years was an independent risk factor for death. The lower mortality in patients aged 18–50 years might be ascribable to herd immunity provided by childhood vaccination with pneumococcal conjugate vaccines (PCVs) [30]. Males predominated in our population, and male gender was

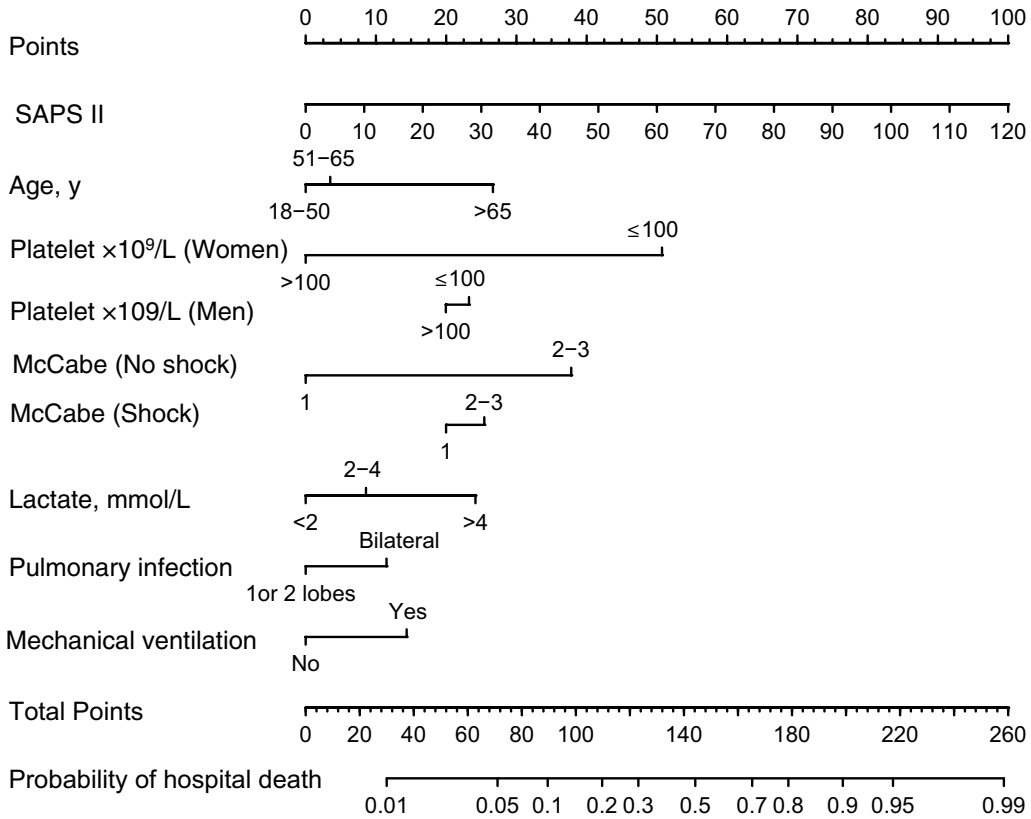

Fig. 2 Nomogram for predicting hospital death. The nomogram provides an estimate of the probability of death according to patient characteristics. For each characteristic listed, locate the relevant value on the horizontal line, and draw the vertical line from that value to the points line at the top of the figure. Sum the points for each characteristic and locate this number on the total points line at the bottom of the figure. Draw a straight line down from the number on the total points line to the probability of hospital death line just below it

independently associated with death, as reported previously [29–32]. The poorer prognosis in males versus females has been ascribed to differences in hormonal status and in inflammatory and immune responses, as well as to the higher prevalence of cardiovascular disease and exposure to toxic agents among males [33]. A recent study in a mouse model of pneumococcal infection also found that mortality was higher in males than in females (stronger proinflammatory response, faster rate of bacterial proliferation, slower clearance of lung bacteria) [34]. In contrast, in a vast retrospective study of patients with CAP managed in 17 countries between 2001 and 2011, after adjustment on a propensity score, 28-day mortality was higher in females [35]. However, the difference was small (absolute difference with males, 5%; hazard ratio, 1.15; 95% CI, 1.02–1.30) and the study was not confined to ICU patients. Thrombocytopenia was an independent risk factor for death in our study and in earlier work in an ICU population [36]. In a mouse model of pneumococcal pneumonia with bacteremia, induced thrombocytopenia was followed by decreased survival [37]. *S. pneumoniae* can bind to type 2 toll-like receptors on platelets, thereby inducing platelet activation and thrombocytopenia, which contributes to thrombosis, bleeding, and excessive inflammation in patients with severe PCAP [38]). The platelet count showed a strong interaction with gender in our study. Mortality was highest in women with thrombocytopenia, whereas the higher mortality rate in males versus females was independent from the platelet count. The platelet serotonin content is higher and is metabolized more slowly in females [39, 40]. Thrombocytopenia during PCAP is accompanied with the release of serotonin in the bloodstream. Serotonin not only exerts multiple vascular and hemodynamic effects, but also has major effects on immune cells [41]. However, it remains unclear why thrombocytopenia was associated with mortality in females but not in males in our study.

An unexpected finding from our study was that a longer than 6-h time from ICU admission to initiation of appropriate antibiotics was not associated with hospital mortality in the adjusted analyses, in contrast with an old study [6]. This finding may be ascribable to the small

proportion of patients (26%) who did not receive antibiotics within 6 h. In other observational studies in critically ill patients with pneumonia due to various microorganisms, antibiotic therapy within 4–8 h was associated with survival [42, 43]. In non-randomized studies, adding a macrolide to a beta-lactam was associated with lower mortality [5, 42], although this result was not replicated in other work [12, 43–45], and all these studies had methodological weaknesses. In a mouse model of pneumococcal pneumonia, macrolides modulated the inflammatory response, as well as *S. pneumoniae* virulence [46]. Mortality was not lower in the patients given macrolides in our study. Similarly, in a recent cluster-randomized crossover trial in patients with severe CAP, after adjustment on a multivariable mortality prediction score, beta-lactam therapy alone was not inferior to beta-lactam therapy with a macrolide in terms of 90-day mortality [47]. Conceivably, the antiinflammatory effect of macrolides may be insufficient to induce clinical benefits in patients with the most severe forms of PCAP [45].

We found a broad diversity of pneumococcal serotypes reflecting the indirect herd effect of universal childhood immunization with PCV7 starting in 2005 then PCV13 starting in 2010 in France. Most of the patients enrolled during the first 2 study years had replacement serotypes such as 3, 7F, and 19A, whereas after the introduction of PCV13, the main serotypes were 3, 12F, 19A, and 7F, in descending order, with a decrease in the last two serotypes. The decline in the proportion of *S. pneumoniae* strains with decreased beta-lactam susceptibility over the 3-year study period is ascribable to the decrease in PCV13 vaccine serotypes, mainly 19A, combined with an increase in serotype 12F. In our study, serotypes 1 and 12F, which are known to be highly invasive [20–22, 42], were more common in younger patients and were associated with lower mortality, as reported previously [24, 25]. Although PCV13 includes serotype 3, the frequency of this serotype did not decrease during the study, suggesting absence of a herd effect [48]. Serotypes 3 and 19A have been reported to be associated with respiratory failure and mortality [10, 49], as well as to cause severe pneumonia in the elderly more often than serotypes 1, 7F, and 12F [24, 25]. However, in our study, serotypes 3 and 19A were not associated with hospital mortality. In the analyses adjusted for factors independent from the pathogen, no serotype was associated with hospital mortality. Thus, in patients with severe PCAP, host-related factors or other *S. pneumoniae*-related factors affecting virulence may have a greater effect on the risk of death compared to capsular polysaccharides, as suggested by a study in a murine model [50].

One limitation of our study is that, despite the large number of patients, only 349 isolates were serotyped, possibly limiting our ability to detect associations between serotype and mortality. The nomogram for predicting the risk of hospital mortality 24 h after ICU admission needs to be validated in large prospective studies of other cohorts of severe PCAP. Potential associations with viral co-infections and biomarkers such as *C*-reactive protein and procalcitonin were not assessed. Finally, we did not record mortality after hospital discharge, which has been reported to be about 40% after 1 year due, in particular, to a cardiovascular risk increase in the oldest patients [51].

In conclusion, in a large population of immunocompetent Caucasian adults managed in the ICU for severe PCAP, hospital mortality remained high, particularly in the oldest patients, although appropriate antibiotic therapy was consistently given, usually within 6 h after ICU admission. Older age, male gender, and organ failures at admission were more strongly associated with hospital mortality than were comorbidities, pneumococcal serotypes, and antibiotic regimens. Improvements in our understanding of interactions between host factors and *S. pneumoniae* virulence factors are needed to improve survival. New pneumococcal vaccines targets should be designed to match the continuous changes in pneumococcal serotypes and provide much broader and longer protective coverage.

Electronic supplementary material

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Author contributions
JPB, EV and JPM are the study guarantors and designed the study; EV and RP extracted and managed the data; RP performed the statistical analysis; and JPB, EV, RP, and JPM wrote the manuscript. All authors included more than 10 patients in the study. All authors read and approved the final version of the manuscript.

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Compliance with ethical standards

Conflicts of interest
None of the authors have any conflicts of interest to declare.

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