Risk factors for respiratory failure in pneumococcal pneumonia: the importance of pneumococcal serotypes

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ABSTRACT   Pneumococcal serotypes are one of the main determinants of pneumococcal disease severity; however, data about their implication in respiratory failure are scarce.

We conducted an observational study of adults hospitalised with invasive pneumococcal pneumonia to describe the host- and pathogen-related factors associated with respiratory failure.

Of 1258 adults with invasive pneumococcal disease, 615 (48.9%) had respiratory failure at presentation. Patients with respiratory failure were older (62.1 years *versus* 55.4 years, p<0.001) and had a greater proportion of comorbid conditions. They also had a greater proportion of septic shock (41.7% *versus* 6.1%, p<0.001), required admission to the intensive care unit more often (38.4% *versus* 4.2%, p<0.001) and had a higher mortality (25.5% *versus* 3.5%, p<0.001). After adjustment, independent risk factors for respiratory failure were: age >50 years (OR 1.63, 95% CI 1.15–2.3), chronic lung disease (OR 1.54, 95% CI 1.1–2.15), chronic heart disease (OR 1.49, 95% CI 1.01–2.22) and infection caused by serotypes 3 (OR 1.97, 95% CI 1.23–3.16), 19A (OR 2.34, 95% CI 1.14–4.42) and 19F (OR 3.55, 95% CI 1.22–10.28).

In conclusion, respiratory failure is a frequent complication of pneumococcal pneumonia and causes high morbidity and mortality. Pneumococcal serotypes 3, 19A and 19F are the main risk factors for this complication.

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Introduction

Streptococcus pneumoniae is the leading cause of pneumonia worldwide. Despite the improvements in different medical aspects and critical care of patients, mortality remains unacceptably high [1]. Different factors related to the severity and mortality of pneumococcal disease have been described. Some of them are host-related, such as extremes of age, comorbidities or immunosuppressive conditions, and it is well known that they all are associated with an increased susceptibility to pneumococcal disease and also to a greater severity of the illness [2–4].

Nowadays there is increasing evidence that organism-related factors also play a key role in the clinical course of the disease. The capsular polysaccharide is probably the major virulence determinant of *S. pneumoniae*, protecting it from phagocytosis [5]. At present, more than 90 pneumococcal serotypes have been described on the basis of differences in the antigenic characteristics of capsular polysaccharides. Experimental studies in animal models have shown that pneumococcal serotypes differ in properties such as resistance to phagocytosis, ability to penetrate into tissues and capacity to activate the inflammatory response [5, 6]. Different studies have explored the relationship between serotypes and clinical presentation of pneumococcal disease, and associations with the severity of the illness and mortality have been demonstrated [4, 7–10].

The clinical spectrum of pneumococcal pneumonia is wide, from an almost asymptomatic disease in some cases to a devastating illness complicated with respiratory failure and septic shock in others. Septic shock is one of the most important factors influencing prognosis of patients with pneumococcal pneumonia. Interestingly, recent reports have suggested that infection caused by serotypes 3 and 19A are independent risk factors for this complication [10, 11]. Respiratory failure is also an important and severe complication of pneumococcal pneumonia that causes high morbidity and mortality. However, few data are available about the host- and pathogen-related factors associated with this complication. We hypothesise that specific serotypes could also play a role in the development of respiratory failure in patients with pneumococcal pneumonia.

The aim of our study was to analyse possible risk factors associated with the development of respiratory failure in adult patients with invasive pneumococcal pneumonia (IPP). We also aimed to investigate the role of any specific serotype in this severe complication.

Materials and methods

Study population and setting

Patients were enrolled as part of an ongoing observational study initiated in 1996 of all adults (aged ⩾18 years) hospitalised with IPP in two teaching hospitals from Catalonia, Spain (Hospital Universitari Vall d'Hebron and Hospital Universitari Parc Tauli). In both hospitals, all microbiological strains isolated in sterile samples are collected systematically. When *S. pneumoniae* was isolated from a sterile sample, the patient was included in the study and all the clinical and evolutive data were collected prospectively. The study was approved by the ethics board of the participating centres. The need for informed consent was waived due to the observational nature of the study.

Study variables and data collection

From each patient, the following variables were recorded. 1) Sociodemographic and temporal data (age, sex, period of influenza epidemic, current tobacco smoking, long-term alcohol abuse and vaccination status with the 23-valent polysaccharide vaccine (PPV-23)); 2) underlying diseases (chronic lung disease, chronic heart disease, liver disease, cerebrovascular disease, diabetes and renal insufficiency); 3) immunosuppressive conditions (HIV infection, haematological cancer, solid cancer, solid organ or stem cell transplantation and current immunosuppressive therapy); 4) variables related to respiratory status (respiratory failure, need for mechanical ventilation and chest radiograph pattern); 5) other variables related to clinical presentation and outcome (septic shock, intensive care unit (ICU) admission, suppurative lung complications, length of hospital stay, mortality and pneumonia severity index); 6) antimicrobial therapy; and 7) microbiological data (serotype and antibiotic susceptibility).

Definitions

IPP was diagnosed when a patient had consistent clinical findings plus a new pulmonary infiltrate on chest radiography and isolation of *S. pneumoniae* in blood and/or pleural fluid cultures [10]. Respiratory failure was defined as oxygen saturation of <90% on room air or arterial oxygen tension to inspiratory oxygen fraction ratio <250 [12]. Mechanical ventilation was defined as any period of mechanically assisted ventilation *via* an endotracheal or nasotracheal tube. The radiographic examinations were performed by radiologists as routine examinations, and the extent of infiltrates was classified as lobar, bilobar or

multilobar and uni- or bilateral. For the purpose of this study, we analysed the presence of these variables at the moment of presentation in the emergency department.

An episode was considered to be within the epidemic period if it was diagnosed during the weeks of the influenza epidemic each year. The influenza epidemic was defined as a weekly incidence of >100 cases per 100 000 inhabitants in Catalonia, and information was obtained from the Catalan Public Health System [13].

Smoking status was considered when a patient had smoked >10 cigarettes per day for ⩾1 year, and alcoholism when a patient had consumed >80 g of alcohol daily for ⩾1 year preceding the study. Chronic lung disease was defined on the basis of clinical, radiological and/or functional tests and included chronic obstructive pulmonary disease, severe asthma and interstitial lung disease. Septic shock was considered when vasoactive drugs were necessary to obtain appropriate arterial pressure values after fluid replacement. A patient was considered to be vaccinated if PPV-23 had ever been administered before admission, according to hospital and primary healthcare centre records.

Microbiological procedures

S. pneumoniae strains were identified by Gram staining, optochin susceptibility testing, bile solubility testing and latex agglutination testing. Antimicrobial susceptibility was determinated using the microdilution method in accordance with Clinical and Laboratory Standards Institute procedures [14]. For the purpose of this study, we classified pneumococcal isolates according the nonmeningitis breakpoints: penicillin-susceptible (minimum inhibitory concentration (MIC) ⩽2 µg·mL^{-1}) or cefotaxime-susceptible (MIC ⩽1 µg·mL^{-1}). Serotypes were performed by Quellung reaction and/or dot-blot assay at the Spanish Reference Laboratory for Pneumococci (Instituto de Salud Carlos III, Majadahonda, Spain).

Statistical analysis

We estimated attributable risk of respiratory failure due to any specific serotype as the difference in rate between the specific serotype and serotype 8. We chose this serotype as the reference group because it represents a frequent serotype in our study and had a similar distribution in the risk of respiratory failure in the univariate analysis between the two groups (OR~1).

To identify the risk factors for respiratory failure, need for mechanical ventilation and chest radiograph pattern were compared as dichotomous variables using a Chi-squared test, and continuous variables using a t-test. To exclude variables with high co-linearity from the multivariate analysis, those significantly associated in the univariate analysis were assessed for bivariate correlation. We excluded significantly correlated variables (p<0.001) from further analysis. Clinically significant variables and those with p<0.1 in the univariate analysis were entered as covariates into a forward stepwise logistic regression analysis for respiratory failure, need for mechanical ventilation and chest radiograph pattern. Odds ratios with 95% confidence intervals are reported. The fit of the model was tested using the Hosmer–Lemeshow goodness-of-fit test. Analyses were conducted using the statistical software package SPSS (version 15.0; IBM, Armonk, NY, USA).

Results

Patient characteristics

Over the study period, 1258 consecutive adults with IPP were diagnosed: 615 (48.9%) of them had respiratory failure at admission. Clinical features and demographic characteristics of the patients are shown in table 1.

Patients with respiratory failure were significantly older and had a greater proportion of comorbid conditions. Patients were also more likely to have received prior pneumococcal vaccine than patients without respiratory failure (24.1% *versus* 17.1%, p=0.015). Regarding the severity of illness, patients with respiratory failure were more likely to have a bilateral pneumonia with multilobar involvement. As expected, they more frequently needed mechanical ventilation. They also had a greater proportion of septic shock and required ICU admission more often than patients without respiratory failure. The case fatality rate was significantly greater (25.5% *versus* 3.5%, p<0.001). In contrast, the proportion of suppurative complications was similar in both groups.

Serotype distribution and antibiotic susceptibility

Overall, 1029 (81.8%) pneumococcal strains were available for serotyping. The most frequent serotypes are shown in figure 1. Pneumococcal serotypes most commonly associated with respiratory failure were serotypes 3, 19A and 19F (respiratory failure developed in 65.8% of infections by serotype 3, in 65.5% by serotype 19A and in 81.5% by serotype 19F). The excess risks of respiratory failure attributable to each were 20.4% (95% CI 4.6–35.1%) for serotype 3, 20.1% (95% CI 1.7–36.6%) for serotype 19A and 36% (95% CI 16.3–55.7%) for serotype 19F. Serotypes 3 and 19A were the most frequently isolated in patients with

TABLE 1 Basal characteristics, clinical presentation and microbiological data of pneumococcal pneumonia patients

	Presenting with respiratory failure	Presenting without respiratory failure	p-value
Subjects n	615	643	
Sociodemographic and temporal variables			
Age years	62.13	55.42	<0.001
Male	411/615 (66.9)	388/615 (60.4)	0.019
Period of influenza epidemic	155/513 (25.2)	169/643 (26.3)	NS
Previous pneumococcal vaccination	124/513 (24.1)	96/561 (17.1)	0.015
Smoking	341/607 (56.2)	349/631 (55.3)	NS
Heavy alcohol consumption	127/605 (21)	101/629 (16.1)	0.028
Underlying disease			
Chronic lung disease	216/607 (35.6)	144/631 (22.8)	<0.001
Chronic heart disease	140/605 (23.1)	76/623 (12.2)	<0.001
Cerebrovascular disease	75/605 (12.4)	40/623 (6.4)	0.001
HIV infection	94/611 (15.4)	124/638 (19.4)	0.063
Haematological cancer	46/610 (7.5)	47/638 (7.4)	NS
Solid cancer	84/610 (13.8)	68/638 (10.3)	0.068
Clinical presentation and outcomes			
Bilateral pneumonia	210/614 (34.2)	63/643 (9.8)	<0.001
Bilobar or multilobar pneumonia	347/614 (58.2)	109/643 (17)	<0.001
Septic shock	254/609 (41.7)	39/638 (6.1)	<0.001
ICU admission	234/609 (38.4)	27/638 (4.2)	<0.001
PSI $\geqslant 4$[#]	533/609 (87.6)	328/638 (51.4)	<0.001
Mechanical ventilation	161/609 (26.1)	15/639 (2.3)	<0.001
Length of hospital stay days	17.83	10.62	<0.001
Empyema	120/615 (19.5)	120/643 (18.7)	NS
Hospital mortality	157/615 (25.5)	23/643 (3.5)	<0.001
Microbiological data			
Serotype 1	42/480 (8.8)	98/543 (18)	<0.001
Serotype 3	79/480 (16.5)	41/523 (7.6)	<0.001
Serotype 7F	27/480 (5.6)	45/523 (8.3)	0.111
Serotype 8	25/480 (5.2)	30/523 (5.4)	0.467
Serotype 19A	38/480 (7.9)	20/523 (3.7)	0.004
Serotype 19F	22/480 (4.6)	5/523 (0.9)	<0.001
Serotype 23A	2/480 (0.4)	9/523 (1.7)	0.07
Serotype 23F	5/480 (1)	16/523 (2.9)	0.045
Penicillin susceptibility[¶]	600/615 (97.5)	633/643 (98.5)	NS
Cephalosporin susceptibility[+]	601/615 (97.7)	624/643 (97)	NS

Data are presented as mean or n/N (%), unless otherwise stated. ICU: intensive care unit; PSI: pneumonia severity index; NS: nonsignificant. [#]: PSI score $\geqslant 4$ at the moment of admission to the emergency department; [¶]: includes isolates with minimum inhibitory concentration (MIC) $\leqslant 2$ $\mu g \cdot mL^{-1}$; [+]: includes isolates with MIC $\leqslant 1$ $\mu g \cdot mL^{-1}$.

bilateral infiltrates and in those who needed of mechanical ventilation. In contrast, serotype 1 was less frequently isolated in cases of respiratory failure with an attributable risk of -15.4% (95% CI -30.6- -0.6%). Regarding antibiotic susceptibility, no differences in the rate of resistance to penicillin and cephalosporin were found between both groups.

Multivariate analysis of risk factors

The results of the multivariate analysis are shown in tables 2–4. After adjustment by age, comorbidities and pneumococcal vaccine status, independent risk factors for respiratory failure were: age >50 years (OR 1.63), chronic lung disease (OR 1.54), chronic heart disease (OR 1.49), and infection caused by serotype 3 (OR 1.97), serotype 19A (OR 2.34) and serotype 19F (OR 3.55) (Hosmer–Lemeshow p=0.96). Pneumococcal pneumonia caused by serotype 1 showed a trend to be a protective factor. In the multivariate analysis, we did not find independent associations between respiratory failure and previous pneumococcal vaccination. Because patients with underlying chronic lung disease may have chronic respiratory insufficiency, we excluded these patients from the analysis in a second model, obtaining similar results.

To assess the impact of pneumococcal serotypes in young patients, we analysed the subgroup of patients aged $\leqslant 50$ years. After adjustment, the only independent factors associated with respiratory failure were
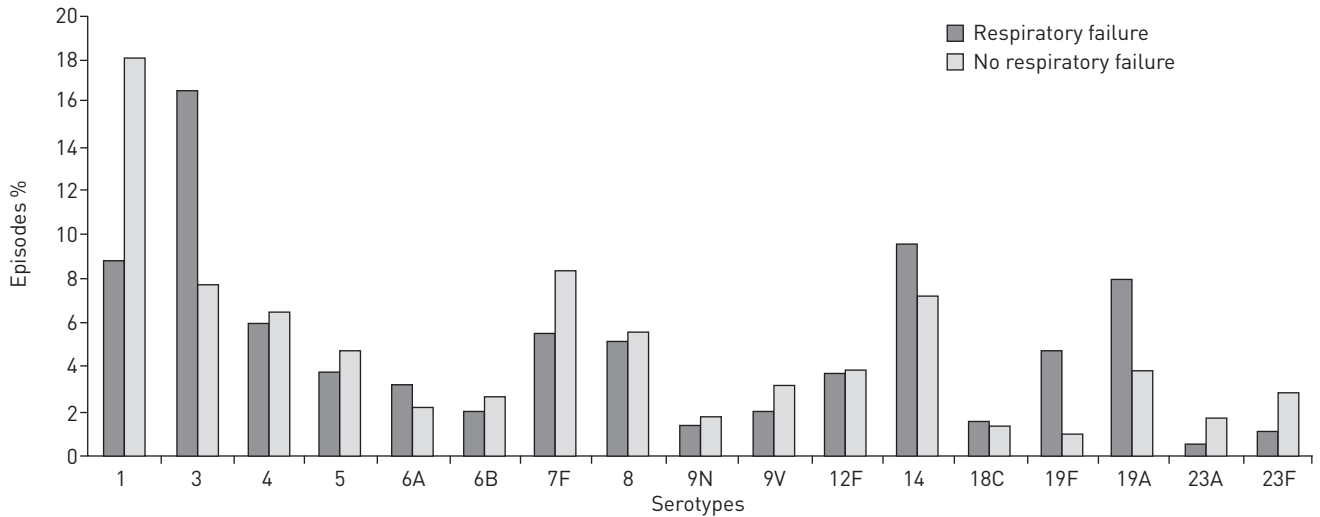
FIGURE 1 Serotypes causing invasive pneumococcal pneumonia in patients presenting with or without respiratory failure.

heavy alcohol consumption (OR 2.26) and infections caused by serotype 19A (OR 4.32) and serotype 19F (OR 9.82) (Hosmer–Lemeshow p=0.94).

Multivariate analysis also found that age >50 years (OR 1.5), serotype 3 (OR 2.69) and serotype 19A (OR 2.75) were independent risk factors for bilateral infiltrates in the radiological pattern (Hosmer–Lemeshow p=0.86). In the same way, smoking (OR 1.99) and infections caused by serotype 3 (OR 2.97), serotype 19A (OR 2.43) and serotype 19F (OR 3.3) were identified as independent determinants of the need for mechanical ventilation (Hosmer–Lemeshow p=0.84).

Discussion

The results of this large observational study of hospitalised adults with IPP support the hypothesis that specific pneumococcal serotypes play a key role in the development of respiratory failure in patients with pneumococcal pneumonia. This observation is of particular interest in the era of conjugate vaccines, because of the continuous replacement of serotypes. In our study, serotypes 3, 19A and 19F were found to be the main risk factors for respiratory failure, bilateral involvement upon radiography and need for mechanical ventilation.

Several studies have shown that specific serotypes are associated with different clinical patterns of pneumococcal disease. BRUEGGEMANN et al. [7] classified pneumococcal serotypes according to their capacity to cause invasive disease. Serotypes 1, 5 and 7F were classified as highly invasive serotypes, and they were associated with invasive disease in younger adults; nevertheless they caused infections with low mortality rates. In contrast, serotypes 3, 19F and 23F had a low invasive potential, affecting older patients with comorbidities and causing higher case-fatality rates [7–10]. Specific serotypes have also been related with particular clinical presentations of pneumococcal disease. Thus, after the implementation of the 7-valent conjugate vaccine, an increase of suppurative complications were observed, associated with the emergence of serotypes 1 and 3 [15, 16]. In the same way, recent reports have found that septic shock in patients with pneumococcal pneumonia developed more frequently in infections caused by serotypes 3 and 19A [10, 11]. However, to our knowledge, no previous studies have addressed the relationship between pneumococcal serotypes and respiratory failure. In our study, we found that serotypes 3, 19A and 19F were the main independent risk factors for development of respiratory failure, even over the risk related to age and comorbidities. These findings are consistent with previous data that associated these serotypes with greatest severity and mortality rates of pneumococcal disease [17, 18]. Although not statistically significant, serotype 1 showed a trend to be a protective factor of the development of respiratory failure. The paradox of this serotype with a high capacity to develop invasive illness and empyema in young adults but with a lesser tendency to cause severe illness [6, 15, 16] could explain why the rates of empyema were similar in both groups.

The pathogenic mechanism that would explain why some specific pneumococcal serotypes might cause respiratory failure is unknown. It has been suggested that heavily encapsulated serotypes could better resist neutrophil-mediated killing [19] and induce a greater inflammatory response causing a more severe disease [17]. In fact, serotypes 3, 19F and 19A, which we identified as the main risk factors for respiratory failure, match those that have been found to be heavily encapsulated [17]. However, it is certain that other

TABLE 2 Multivariate analysis: variables associated with respiratory failure

	All adult patients#		Adults excluding patients with chronic lung disease¶		Patients aged 18–50 years+		Patients aged >50 years§	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age >50 years *versus* 18–50 years	1.63 [1.15–2.30]	0.006	1.96 [1.37–2.85]	<0.001				
Chronic lung disease	1.54 [1.10–2.15]	0.012					1.45 [1.03–2.05]	0.035
Chronic heart disease	1.49 [1.01–2.22]	0.049					1.69 [1.14–2.48]	0.008
Serotype 1	0.63 [0.40–1.01]	0.054					0.53 [0.3–0.93]	0.026
Serotype 3	1.97 [1.23–3.16]	0.005	2.52 [1.44–4.4]	0.001			2.39 [1.45–3.93]	<0.001
Serotype 19A	2.24 [1.14–4.42]	0.020	2.58 [1.14–5.82]	0.023	4.32 [1.38–13.51]	0.012		
Serotype 19F	3.55 [1.22–10.28]	0.020	3.7 [1.08–12.69]	0.037	9.82 [1.06–90.78]	0.044	3.45 [1.11–10.73]	0.032
Heavy consumption of alcohol					2.26 [1.29–12.25]	0.010		

#: odds ratios were adjusted for age, sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotype (1, 3, 19A, 19F, 23A and 23F) and comorbidities associated with respiratory failure (chronic lung disease, chronic heart disease, cerebrovascular disease, solid cancer and HIV infection); ¶: odds ratios were adjusted for age, sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotypes (1, 3, 19A, 19F, 23A and 23F) and comorbidities associated with respiratory failure (chronic heart disease, cerebrovascular disease, solid cancer and HIV infection); +: odds ratios were adjusted for sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotypes (1, 3, 19A and 19F) and comorbidities associated with respiratory failure (chronic lung disease, cerebrovascular disease and HIV infection); §: odds ratios were adjusted for sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotypes (1, 3, 19A and 19F) and comorbidities associated with respiratory failure (chronic lung disease and cerebrovascular disease).

TABLE 3 Multivariate analysis: variables associated with bilateral infiltrates

	OR (95% CI)	p-value
Age >50 years *versus* 18–50 years	1.5 (1.07–2.1)	0.018
Serotype 3	2.69 (1.74–4.14)	<0.001
Serotype 19A	2.75 (1.55–4.88)	0.001

Odds ratios were adjusted for sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotypes (1, 3, 12, 19A and 19F) and comorbidities associated with bilateral infiltrates (solid cancer and HIV infection).

serotypes with a thick capsule, such as serotype 8, are not associated with a greater risk of respiratory failure, so other factors should be involved.

Recently, SANCHEZ *et al.* [20] found that serotypes differ in their ability to adhere to the respiratory epithelium due to the expression of different adhesins, having an impact on virulence. We hypothesise that the pneumococcus requires both factors, bacterial attachment and resistance to phagocytosis, in order to persist and prevent bacterial clearance from the alveoli. This phenomenon could facilitate an excessive inflammatory response that finally leads to cellular damage and lung injury.

Other factors of the pneumococci, rather than capsular polysaccharides, are also implicated in their virulence and may affect disease severity. In this way different studies reveal an association between the amount of bacterial load of pneumococci and the risk of developing septic shock, the need for mechanical ventilation and the mortality of pneumococcal disease [21, 22]. The genetic properties of pneumococci might also play a role. The relationship between these factors and the pathogenic basis for these observations is complex and poorly understood.

In addition to pathogen related factors, host aspects also have a significant role in the severity of the illness [2–4]. As in our study, other authors reported that older age and chronic lung disease were independent risk factors for respiratory failure [23, 24]. Interestingly, it should be noted that the serotypes, and not the underlying disease, were the main risk factors for respiratory failure in the multivariate analysis. This is best exemplified in the group of young adults without comorbidities in whom the causal serotype became the determining factor of outcome. To avoid confusion regarding the role of underlying chronic lung disease in the propensity to cause respiratory failure, we performed an analysis excluding these patients, obtaining similar results.

Nevertheless, we must keep in mind that this study did not evaluate other host factors that might also influence the risk of developing respiratory failure. Recently, specific genetic polymorphisms have been associated with a poor respiratory outcome in pneumococcal pneumonia [23, 25]. Therefore, a tendency to a particular presentation of pneumonia might also be genetically determined for the ability of the individual to respond to the infection.

There is also some debate about the beneficial effects of the prior administration of the PPV-23 improving clinical outcomes in patients with pneumonia. Some studies have observed better clinical outcomes in patients who had previously received the PPV-23 compared with unvaccinated individuals [26, 27]. We also observed this beneficial effect on the incidence of septic shock and survival in vaccinated patients with HIV infection who developed an invasive pneumococcal infection [28]. Regarding respiratory outcomes, FISMAN

TABLE 4 Multivariate analysis: variables associated with mechanical ventilation

	OR (95% CI)	p-value
Smoking	1.99 (1.34–2.94)	0.001
Solid cancer	0.42 (0.2–0.87)	0.019
Serotype 3	2.97 (1.84–4.8)	<0.001
Serotype 19A	2.43 (1.25–4.72)	0.001
Serotype 19F	3.3 (1.32–8.21)	0.010

Odds ratios were adjusted for sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotypes (1, 3, 19A, 19F and 23F) and comorbidities associated with mechanical ventilation (solid cancer).

et al. [27] found that prior receipt of pneumococcal vaccine was associated with a decreased risk of respiratory failure in a large cohort of adults with pneumonia. In our experience we have not been able to find a benefit of PPV-23 in the risk of respiratory failure. It is possible that the relatively low rates of vaccination, the limited number of patients and the confounding factors derived from the fact that patients with increased risk of respiratory complications have a stronger indication to receive PPV-23, make it difficult to establish this association.

It is known that influenza plays an important role in the incidence of pneumococcal pneumonia [29]. Moreover, animal models suggest that previous influenza infection could result in a more severe pneumococcal disease [30]. Although we do not have information regarding this viral co-infection in each patient, we analysed the risk factors of respiratory failure according to the period of influenza epidemic. The results suggest that serotypes continue to be the main risk factor for respiratory failure, irrespective of the period of influenza infection.

Some limitations of our study must be pointed out. Firstly, the study included patients with IPP, who represent only a proportion of all patients with pneumococcal pneumonia, which may cause a possible bias due to the selection of the most invasive serotypes. This therefore makes it difficult to generalise the findings to all cases of pneumococcal pneumonia. It is noteworthy that the majority of studies focused in pneumococcal serotypes are performed in patients with invasive disease. Secondly, our study presents data from only two centres, so the results might not translate to other geographical areas where specific serotype distribution could differ. Finally, and despite the adjustment for an important number of covariables, other potential factors that might modulate the clinical presentation of pneumococcal pneumonia such as genetic properties of *S. pneumoniae* strains, genetic characteristics of the host or the effect of other viral co-infections have not been evaluated in our study.

Despite these limitations, we believe that our study has shown important and novel findings about the clinical presentation of invasive pneumococcal pneumonia. We have identified pneumococcal serotypes 3, 19A and 19F as the main determinants of respiratory failure, extensive radiograph involvement and need for mechanical ventilation, after adjustment by age, comorbidities and pneumococcal vaccination. This observation is of particular interest in the era of conjugate vaccines, because of the continuous replacement of serotypes.

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