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Factors influencing long-term survival after hospitalization with pneumococcal pneumonia

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SUMMARY

Objective: To assess survival and identify predictors of survival more than 30-days after discharge in a cohort of consecutive patients diagnosed with pneumococcal pneumonia.
Methods: Observational study including all consecutive immunocompetent adult patients surviving more than 30-days after hospitalization. The bacteriological diagnosis was based on the results of urinary antigen testing and/or blood culture. Life expectancy was calculated for each patient considering their sex, age and date of discharge.
Results: We included 1114 patients that survived more than 30- days after discharge. Of them, 431 (38.6%) died during follow-up (median follow-up of 6.7 years). Age, history of cancer, liver disease, chronic renal disease, chronic obstructive pulmonary disease, cerebrovascular disease, atrial arrhythmia and coronary disease, red cell distribution width (RDW) > 15%, positive blood culture, hematocrit < 30% and living in a nursing home were independent risk factors for reduced long-term survival after hospital discharge. Cumulative 1-, 3- and 5-year survival rates were 93.9%, 85.3% and 76%, respectively. Among non-survivors, 361 (83.8%) died earlier than expected given their life expectancy.
Conclusions: Survival after hospital discharge is mainly associated with age and comorbidities. The findings of bacteremia and elevated RDW on admission could help identify patients at high risk of long-term mortality.

Introduction

Pneumonia remains a common cause of morbidity and mortality around the world. In fact, this entity represents the leading cause of infection-related death.[1] Traditionally, pneumonia has been considered an acute process that, once resolved, has no impact on patient survival. There is growing evidence, however, of a higher risk of death after recovery from the acute episode than that the general population.[2–4] The excess mortality observed in these patients may be as high as 50% within 5 years after hospital discharge.[5]

Streptococcus pneumoniae is the most commonly identified pathogen in pneumonia, being responsible for the highest rates of hospital admission and mortality. Approximately 20% of patients diagnosed with pneumococcal pneumonia develop bloodstream infections, and this type of pneumonia has traditionally been associated with poorer outcomes during hospitalization.[6,7] By contrast, for both bacteremic and non-bacteremic pneumococcal pneumonia, there is limited information in the literature on mortality after hospitalization.[8,9] At this point, it could be speculated that the acute infectious episode acts as a trigger to create a persistent inflammatory state which, in turn, has a negative effect on host-related factors such as age or comorbidities.[2] This could be even more relevant in patients with bacteremia due to their elevated cytokine production.[10] Considering the higher incidence of invasive pneumococcal disease in older people and those with underlying conditions, together with the results of recent animal studies reporting a possible association between "cardiotoxicity" and invasive pneumococcal infection, we hypothesized that invasive pneumococcal disease, among other factors, is a marker of impaired long-term survival in these patients.[11,12]

Given this, the objectives of our study were to assess the survival rate after hospitalization in a prospective cohort of patients with pneumococcal pneumonia requiring hospital admission as well as to identify risk factors associated with outcome, to guide

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the design and implementation of future strategies for improving the long-term survival of these patients.

Methods

Study design and population

This is an observational study based on the analysis of a prospective registry of consecutive immunocompetent adults (age 18 years or more) hospitalized for pneumococcal pneumonia in two tertiary medical centers (Cruces and Galdakao Hospitals). The study was conducted between January 2002 and January 2017. The bacteriological diagnosis of pneumococcal pneumonia was based on the results of urinary antigen testing and/or blood culture within 24 h after hospital admission. For the purpose of the study, we limited the analysis to consecutive patients who had blood culture performed. Patients were excluded if they died during hospitalization or within 30- days after hospital discharge. Participants were stratified into two groups according to their survival status during follow-up: (1) survivors and (2) non-survivors.

The severity of patients' clinical condition was assessed on admission using the Pneumonia Severity Index (*PSI*) *score*.[13] A local ethic committee approved the analysis of data for this study.

Data collection

Since 2002, there has been an ongoing standardized prospective registry of all patients hospitalized for pneumonia in our two hospitals. This registry includes numerous variables characterizing patients and their pneumonia. For eligible patients, we assessed data on socio-demographic characteristics, medical comorbidities, influenza and pneumococcal vaccination status, vital signs, results of routine laboratory tests, including the pneumococcal urinary antigen test and blood cultures, and radiological findings on admission. Measures of in-hospital clinical course and outcome included: (1) admission to the intensive care unit; (2) use of invasive mechanical ventilation; (3) septic shock; and (4) in-hospital mortality. Patients were empirically treated in accordance with the National Guidelines of the Spanish Society of Pulmonology [SEPAR] at the discretion of the attending doctor.[14]

Comorbidities considered were the following diagnosed prior to hospital admission: chronic respiratory disease, diabetes mellitus, cerebrovascular disease, chronic liver disease, chronic renal disease, cancer, arterial hypertension, dyslipidemia, heart arrhythmias (atrial fibrillation or flutter), congestive heart failure and coronary disease. In addition, incident in-hospital heart complications were considered.

Outcome

The main outcome was all-cause mortality after hospital discharge during the follow-up period. Survival status was assessed using data from the database of the Basque Health Service (Osakidetza) on 31st December 2017. In order avoid bias due to short-term deaths attributable to the acute onset, patients who died within 30- days after hospital discharge were excluded. We compared observed and expected survival according to life expectancy for each patient. Life expectancy was estimated using life expectancy tables for the Spanish population (years 2000–2017) according to sex, age and date of discharge.[15]

Definitions

Pneumonia was defined as the presence of new pulmonary infiltrate on the chest X-ray together with signs and symptoms suggestive of lower respiratory tract infection. Septic shock was defined as a systolic blood pressure of less than 90 mm Hg and a need for vasopressor drugs for at least 4 h, after fluid therapy.[16] The diagnosis of altered mental status was based on observation that the patient's mental state was not normal and that this was a new phenomenon.[13]

For the purposes of this study, cancer was defined as any solid tumor not requiring chemotherapy or radiotherapy treatment in the year prior to the onset of pneumonia. The onset of congestive heart failure and/or atrial arrhythmia (atrial fibrillation or flutter) and/or coronary disease during hospitalization in patients with no previous diagnosis of these conditions was considered an incident heart complication. New hyperglycemia was defined as hyperglycemia (>200 mg/dL) at admission in a patient without a medical diagnosis of diabetes.[17]

Statistical analysis

Descriptive analysis was undertaken, using frequencies and percentages, means and standard deviations (SDs) or medians and interquartile ranges (IQRs) depending on the distribution of the data. Comparisons were performed with chi-square or Fisher's exact tests for qualitative variables and with t tests or non-parametric Wilcoxon tests for quantitative variables. Patient survival was analyzed using the Kaplan–Meier method. The log-rank test was used to compare survival with different variables. A univariate Cox regression analysis was performed to identify factors related to patient characteristics and survival. All variables with a $p < 0.20$ were included in a multivariate Cox regression model. Variables with the highest p value were excluded one by one until all variables had a p value <0.05. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated from univariate and multivariate models. The proportional hazard assumption was tested. Statistical analysis was performed using IBM SPSS Statistics for Windows version 23.0 (Armonk, NY).

Results

The flow of patients through the study is illustrated in Fig. 1. During the study period, 1525 patients were admitted to our two hospitals with pneumococcal pneumonia. Of whom, we assessed 1190 consecutive patients who had blood cultures obtained at hospital admission. After applying the exclusion criteria, 1114 patients were considered eligible for this study.

Table 1 summarizes the demographic and clinical data of patients. The mean age of the entire cohort was 63.6 (±17.5) years, with 608 (54.6%) being ≥ 65 years. Bacteremia was identified in 479 patients. In 635 (57%) cases diagnosis was made by positive pneumococcal urinary antigen (all of them with negative blood culture). Patients who did not survive were older and had more comorbidities but were less likely to be active smokers. They were also more likely to have hypoxemia, high blood urea nitrogen, altered mental status, low hematocrit, increased red blood cell distribution width (RDW), and newly discovered hyperglycemia at hospital admission. In contrast, survivors more frequently had multilobar pneumonia and were more likely to be admitted to the intensive care unit or require invasive mechanical ventilation. They were also more likely to have positive results in pneumococcal urinary antigen testing and less likely to have bacteremia. A greater proportion of non-survivors than survivors were classified in the higher risk classes according to *PSI score* ($p < 0.001$).

Fig. 2 compares the Kaplan–Meier survival curves observed and stratified by the presence or absence of comorbidities with those expected based on sex, age and date of discharge ($p < 0.001$; log-rank test). Of the 1114 patients surviving their index hospitalization, 431 (38.6%) died during a median follow-up of 6.70 years. Cumulative 1-, 3- and 5-year survival rates were 93.9%, 85.3%, and

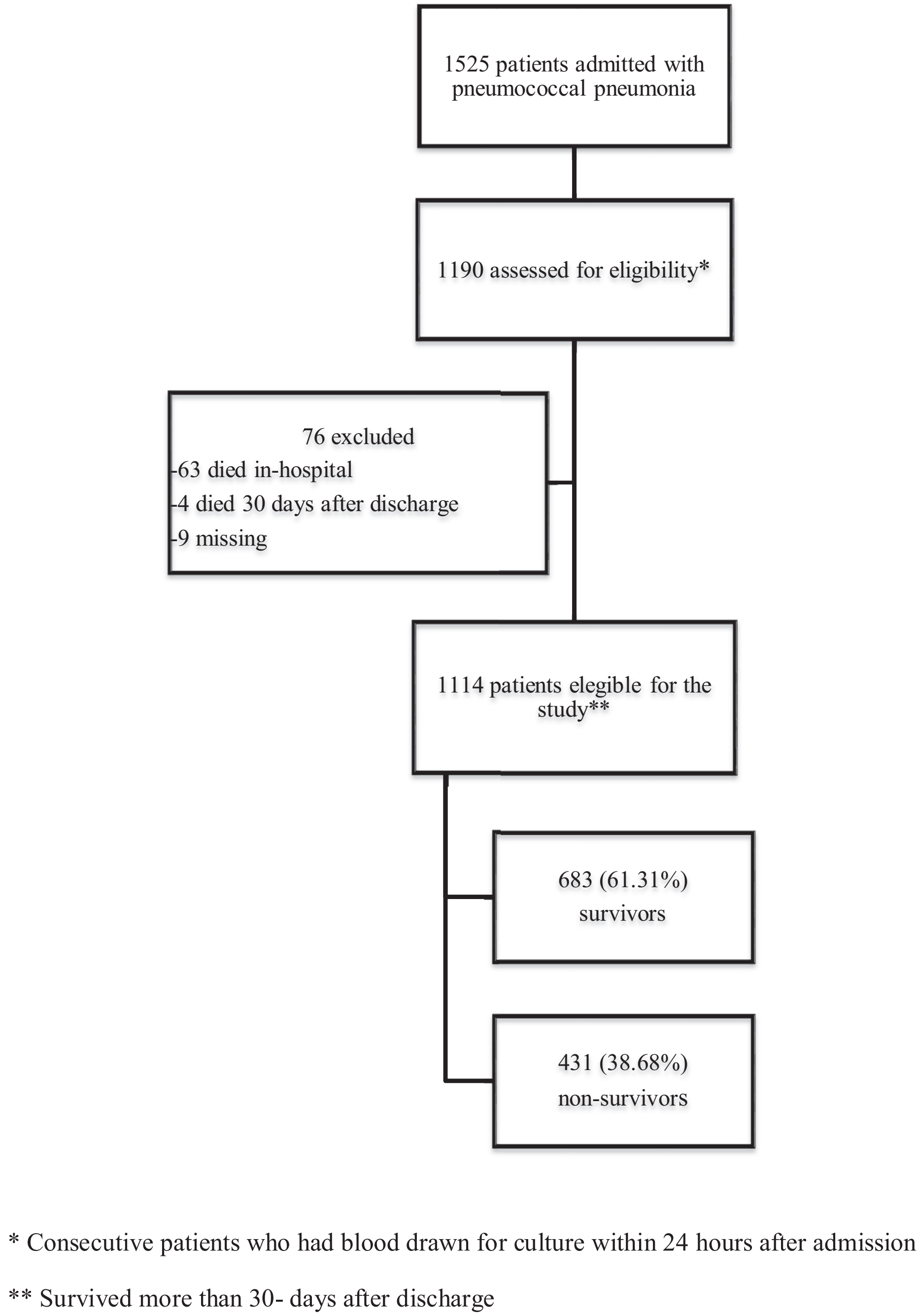


Fig. 1. Flow of patients admitted with pneumococcal pneumonia through the study.

76%, respectively. Of the 431 non-survivors, 361 (83.8%) died earlier than expected, given their life expectancy.

Fig. 3 shows Kaplan–Meier survival curves by *PSI* risk class. The survival rates were 99.3%, 94%, 81.1%, 65% and 47.6% for patients in *PSI* risk classes I to V, respectively (log rank $p < 0.001$).

The univariate and multivariate analyses of factors associated with long-term mortality after hospitalization for pneumococcal pneumonia are reported in Table 2. In an adjusted multivariate model, the following were identified as predictors of long-term mortality: age (HR 1.05; 95% CI 1.045–1.06), solid cancer (HR 2.60; 95% CI 1.81–3.73), liver disease (HR 2.02; 95% CI 1.27–3.20), chronic renal disease (HR 2.01; 95% CI 1.43–2.82), COPD (HR 1.73; 95% CI 1.38–2,14), cerebrovascular disease (HR 2.38; 95% CI 1.71–3,32), atrial arrhythmia (HR 1.42; 95% CI 1.12–1.79), coronary disease (HR 1.55; 95% CI 1.14–2.11), RDW > 15% (HR 1.89; 95% CI 1.52–2.34), bacteremia (HR 1.47; 95% CI 1.23–1.80) and living in a nursing home (HR 1.91; 95% CI 1.18–3.10). To simplify the interpretation of the results, we performed a new analysis (model 2) considering the presence of comorbidities (categorized as 0, 1 or >1). In this model, hematocrit <30% on admission (HR 1.62; 95% CI 1.04–2.52) was independently predictive of long-term mortality, no other significant differences being found compared to model 1.

Fig. 4 shows survival curves plotted as a function of bacteremia and RDW (dichotomized to ≤15% vs. >15%) and stratified by age or the presence of one or more comorbidities. Patients with both positive blood cultures and RDW >15% at admission had shorter long-term survival than other groups, the shortest survival being seen in those with comorbidities or ≥ 65 years old.

Table 1
Demographic and clinical characteristics of patients with pneumococcal pneumonia surviving more than 30-days after discharge.

Characteristics	All	Survived (n=683)	Non-survived (n=431)	*p*
Demographics				
Male sex	670 (60.1)	386 (56.5)	284 (65.9)	0.002
Age in years, mean (SD)	63.6 (17.5)	57.1 (17.3)	73.7 (12.3)	<0.001
Nursing home resident	27 (2.4)	7 (1)	20 (4.6)	<0.001
Underlying conditions				
Cancer	50 (4.5)	15 (2.2)	35 (8.1)	<0.001
Liver disease	39 (3.5)	16 (2.3)	23 (5.3)	0.008
Renal disease	58 (5.2)	16 (2.3)	42 (9.7)	<0.001
Chronic obstructive pulmonary disease	216 (19.4)	86 (12.6)	130 (30.2)	<0.001
Diabetes mellitus	194 (17.4)	79 (11.6)	115 (26.8)	<0.001
Cerebrovascular disease	63 (5.7)	20 (2.9)	43 (10.0)	<0.001
Congestive heart disease	112 (10.1)	37 (5.4)	75 (17.4)	<0.001
Cardiac arrhythmia	186 (16.7)	64 (9.4)	122 (28.3)	<0.001
Coronary disease	74 (6.6)	27 (4)	47 (10.9)	<0.001
Hypertension and/or dyslipidemia	564 (50.6)	297 (43.5)	267 (61.9)	<0.001
Incident heart complication	100 (9)	59 (8.7)	41 (9.5)	ns
Number underlying diseases				<0.001
0	539 (48.4)	445 (65.2)	94 (21.8)	
1	304 (27.3)	149 (21.8)	155 (36)	
>1	271 (24.3)	89 (13)	182 (42.2)	
Vaccination status				
Influenza vaccine	303 (27.2)	146 (22)	157 (38.9)	<0.001
Pneumococcal vaccination	141 (12.7)	69 (10.4)	72 (17.4)	0.001
Current tobacco use	306 (27.5)	227 (33.2)	79 (18.5)	<0.001
Heavy drinker (> 80 mg alcohol/day)	132 (11.8)	89 (13.4)	43 (10.5)	ns
Clinical characteristics at admission				
Body temperature <35 or >40 °C, mean (SD)	15 (1.3)	12 (1.8)	3 (0.7)	ns
Respiratory rate, mean (SD)	22.7 (6.9)	21.8 (6.5)	24 (7.4)	<0.001
Heart rate, mean (SD)	102.5 (20.5)	104.3 (20.1)	99.7 (20.8)	<0.001
Altered mental status	91 (8.2)	43 (6.3)	48 (11.1)	0.003
Systolic blood pressure < 90 mm Hg	96 (8.6)	76 (11.1)	20 (4.6)	<0.001
Laboratory and radiological findings				
Blood urea nitrogen> 30 mg/dL	431 (38.7)	214 (31.3)	217 (50.3)	<0.001
PaO_2 < 60 mm Hg	475 (42.6)	249 (45.3)	226 (56.9)	<0.001
Glucose>200 mg/dL and no diagnosis of DM	56 (5)	26 (3.8)	30 (7.0)	0.019
Hematocrit <30%	391 (3.5)	16 (2.3)	23 (5.3)	0.002
RDW >15[a]	256 (23)	97 (14.5)	159 (38.4)	<0.001
Leucocyte count <4000 ($\times 10^9$/L)	40 (3.6)	29 (4.3)	11 (2.6)	ns
Multilobar pneumonia	322 (28.9)	214 (31.3)	108 (25.1)	0.026
Pleural effusion	132 (11.8)	87 (12.7)	45 (10.4)	ns
Urinary antigen positive	959 (86)	607 (88.8)	352 (81.6)	<0.001
Positive blood culture	479 (43)	265 (38.8)	214 (49.7)	<0.001
Severity of illness at admission				
PSI risk class >3	530 (47.6)	229 (33.5)	301 (69.8)	<0.001
Outcomes				
Intensive care admission	255 (22.9)	182 (26.7)	73 (16.9)	<0.001
Invasive mechanical ventilation	57 (5.1)	42 (6.1)	15 (3.5)	0.049
Septic shock	119 (10.7)	88 (12.9)	31 (7.2)	0.003

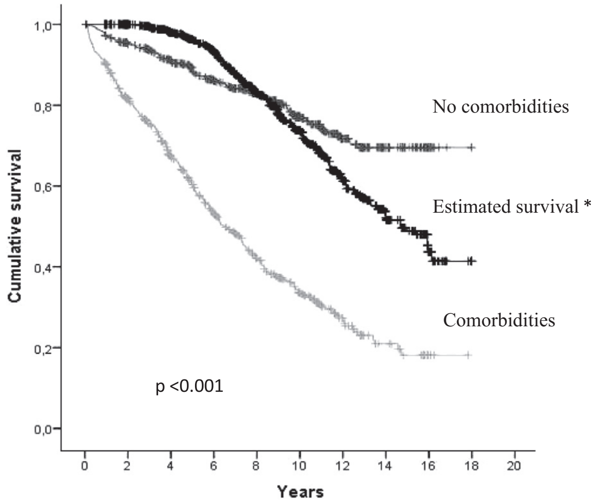
Data are given as frequency (percentage) unless otherwise stated. Percentages exclude patients with missing data. SD: Standard deviation. RDW: red blood cell distribution width. PSI: Pneumonia severity index.
[a] Reference range for RDW in our laboratory is 11% to 15%.

Discussion

In this large prospective study, we documented a significantly shorter long-term survival in patients with pneumococcal pneumonia than their life expectancy based on sex, age and year of discharge from hospital. To our knowledge, this is one of the largest series focusing on this topic including both bacteremic and non-bacteremic patients with this entity. The interest of this study lies not only in the number of patients included but also in the reproducibility of the observational design itself, which is based on the current clinical management of these patients in real life and differs from approaches based on complex biomarkers or microbiological analysis, most only available for research purposes.[18,19] We consider that these factors strengthen the clinical applicability of our results.

We have reported 1-, 3- and 5-year survival rates of 93.9%, 85.3% and 76%, respectively. At this point, beyond overall survival rates, it is interesting to consider how long these patients might live and how long they actually live. In our cohort, only 16.2% of non-survivors reached their life expectancy. Other authors have also reported this negative association between pneumonia and long-term outcome, reporting survival rates ranging from 25% to 53% at 5 years.[5, 20–23] This variability is mainly attributable to the type of population included, differences in control groups and follow-up intervals.

Similar to other studies, we have found that the presence of comorbidity and the number of comorbid conditions are both independently associated with shorter long-term survival.[23–25] This could simply be a consequence of the natural history of the underlying conditions themselves. Another factor that might be responsible for this finding, however, is a persistent inflammatory state impairing underlying conditions or even favoring the development of other health problems.[2,26,27] On the other hand, it is also possible that pneumonia itself is a surrogate marker of unknown poor health status that increases the risk of subsequent death. If so, close follow-up and optimal and more intensive management of underlying conditions might be crucial for improving the prognosis. In our series and unlike in others, neither diabetes



Survival	Comorbidities	No comorbidities	Estimated *
1 year	90.1%	97.2%	100%
3 year	75.3%	95.1%	99.9%
5 year	60.4%	89,3%	96.3%

Fig. 2. Observed and estimated *survival curves for patients with pneumococcal pneumonia stratified by the presence or absence of comorbidities and surviving more than 30 days after discharge.
*Estimated survival according to Spanish survival tables based on age, sex and date of hospital discharge.

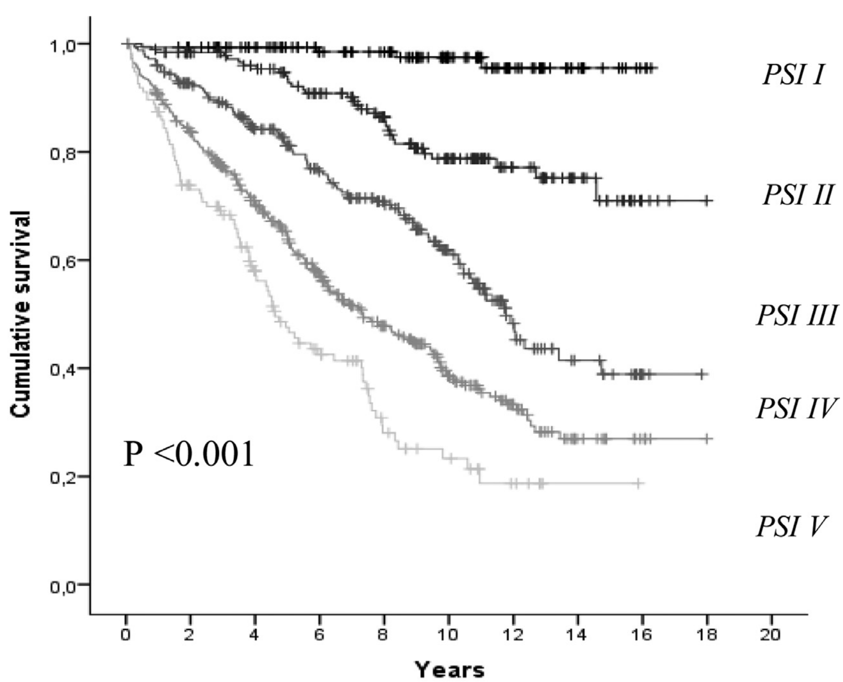
nor new hyperglycemia was associated with this poor outcome.[17] The reason for this is not clear. It is possible that diabetes and its effects on the immune system only influence the early prognosis. It might also be the case that in our study its long-term effects were masked by the statistical procedures applied to control for other comorbidities such as ischemic heart disease or renal failure.

The contribution of etiological factors to long-term outcomes is controversial. In our series, cumulative survival rates were similar to those in other series including patients with different microbiological etiologies.[22] These results would seem, at first sight, to corroborate previous reports showing that survival after discharge is independent of the pathogen. It is difficult, however, to discriminate the real contribution of each of pathogen in these series due to pneumococcus being the most frequently isolated and the limitation of current procedures for identifying the causal bacteria in real-world settings. More studies are needed to clarify this issue.

Several studies have documented an association between living in a nursing home and mortality, reflecting the age, functional status and severe and multiple comorbid conditions of this population.[21,28] In our study, despite the relatively small number of patients (2.6%) who lived in a nursing home, this association was observed after adjusting for age and comorbidities. This finding could reflect a low physiological reserve or frailty in this subgroup of patients.

No classic clinical or laboratory markers for severity on admission predicted survival in this study. Similar to previous observations, severity was found to be correlated with long-term prognosis but not to be an independent risk factor for long-term mortality in the multivariate analysis.[21,23,25,29] This probably indicates that the role of severity as measured by the *PSI* may be confounded by the contribution of age or comorbidities. Notably, our findings contrast with those of another study showing severity alone or in combination with blood markers to be a predictor of long-term outcome.[19] Nevertheless, that study had some weakness regarding multivariate analysis, limiting the generalizability of the results. Further, unlike other authors, we have not found an increased risk of long-term mortality in patients requiring ICU admission and/or under IMV after adjusting for confounders. Differences in our study population, selective ICU admission criteria including the role of age as limiting factor for ICU admission, may explain these discordant results.[30–32]

In this study, we found that patients with bacteremic pneumonia have poorer long-term prognosis than those with non-



PSI: Pneumonia Severity Index

Fig. 3. Kaplan–Meier plot of long-term survival by *PSI* risk class.

Table 2
Multivariate analysis of factors associated with long-term survival more than 30 days after hospitalization.

	Unadjusted HR (95% CI)	Model 1 Adjusted HR (95% CI)	P	Model 2 Adjusted HR (95% CI)	p
Sex male	1.35 (1.11–1.65)				
Age, years	1.06 (1.05–1.06)	1.05 (1.04–1.06)	<0.0001	1.04 (1.03–1.05)	<0.0001
Age≥65 years	6.03 (4.68–7.78)				
Nursing home resident	2,92 (1.86–4.58)	1.91 (1.18–3.10)	0.008	1.94 (1.21–3.08)	0.005
Solid cancer	2.94 (2.08–4.17)	2.60 (1.81–3.73)	<0.0001		
Liver disease	2.42 (1.58–3.69)	2.02 (1.27–3.20)	0.003		
Renal disease	2.91 (2.11–4.01)	2.01 (1.43–2.82)	<0.0001		
Chronic obstructive pulmonary disease	2.21 (1.80–2.72)	1.72 (1.38–2.14)	<0.0001		
Diabetes mellitus	2.09 (1.68–2.59)				
Cerebrovascular disease	2,99 (2.17–4.10)	2.38 (1.71–3.32)	<0.0001		
Congestive heart disease	2.88 (2.24–3.70)				
Atrial arrhythmia	3.12 (2.52–3.86)	1.42 (1.12–1.79)	0.003		
Coronary disease	2.48 (1.83–3.37)	1.55 (1.14–2.11)	0.005		
Arterial hypertension and/or dyslipidemia	1.96 (1.61–2.38)				
Incident heart complication	1.37 (0.93–1.89)				
Number underlying diseases					
1	3.95 (3.06–5.11)			2.24 (1.71–2.94)	<0.0001
>1	6.89 (5.35–8.87)			3.12 (2.37–4.10)	<0.0001
Influenza vaccine	2.13 (1.74–2.61)				
Pneumococcal vaccination	1.49 (1.15–1.93)				
Current tobacco use	0.50 (0.39–0.64)				
Heavy drinker	0.81 (0.59–1.11)				
Body temperature ≤35 or ≥40 °C	0.45 (0.14–1.42)				
Respiratory rate	1.03 (1.02–1.04)				
Heart rate	0.99 (0.98–0.99)				
Altered mental status	1.75 (1.29–2.36)				
Systolic blood pressure <90 mm Hg	0.51 (0.32–0.79)				
Blood urea nitrogen ≥ 30 mg/dL	2.02 (1.68–2.45)				
PaO_2 <60 mm Hg	1.58 (1.30–1.93)				
Glucose >200 mg/dL and no diagnosis of diabetes	1.58 (1.09–2.29)				
Hematocrit <30%	2.18 (1.43–3.33)			1.62 (1.04–2.52)	0.030
RDW >15%	2.92 (2.39–3.57)	1.89 (1.52–2.34)	<0.0001	1.98 (1.61–2.43)	<0.0001
Leucocyte count <4000 ($\times 10^9$/L)	1.27 (0.70–2.32)				
Multilobar pneumonia	0.83 (0.67–1.04)				
Pleural effusion	0.73 (0.54–1)				
Urinary antigen positive	0.73 (0.57–0.98)				
Positive blood culture	1.25 (1.04–1.52)	1.47 (1.21–1.80)	<0.0001	1.45 (1.19–1.76)	<0.0001
PSI risk class >3	3.82 (3.10–4.70)				
Intensive care admission	0.72 (0.56–0.92)				
Invasive mechanical ventilation	0.66 (0.39–1.05)				
Septic shock	0.73 (0.51–1.06)				

RDW: red blood cell distribution width. *PSI:* Pneumonia severity index. HR: Hazard ratios. CI: confidence interval.

bacteremic pneumonia with positive urinary antigen test results. It is probable that the higher inflammatory state worsens underlying conditions or acts as a trigger of other subclinical conditions. Other authors have not reported any differences between these two groups.[9] This could be largely explained by the type of population included, as reflected in the high 30-day mortality rates (similar in both groups), and the methodology of the study itself (blood cultures being obtained depending on the severity of the infection).

Recent observations suggesting a potential cardiotoxicity of pneumococcus infection raise some concerns about its possible role in the prognosis of these patients.[11,12] The presence of cardiac lesions during the acute pneumococcal infection together with production of pneumolysin seems to play a role, with other factors, in the genesis of cardiac complications.[33] Nevertheless, the long-term impact of this effect has yet to be studied. In this study, we have not found an association between in-hospital development of an incident cardiac complication and shorter survival, though this could be due to the small number of events. Studies involving more patients are needed to test this hypothesis.

Red blood cell distribution width is a laboratory parameter used for the differential diagnosis of microcytic anemia. Significantly, in this study, we have found that RDW >15% is an independent factor in long-term mortality after controlling for confounding factor such as hematocrit and comorbidities. Several studies have previously reported an association between this parameter and complicated hospitalization or mortality in community-acquired pneumonia and other conditions.[34–36] To our knowledge, however, this is the first time that this association with long-term mortality is shown in patients with pneumococcal pneumonia. The reason for this poorer outcome is not clear. It is possible that RDW is a marker of low-grade inflammation and oxidative stress.[36] Further studies are needed to evaluate this hypothesis. From a practical perspective, the interest of this finding is that RDW is routinely calculated by all hematology analyzers, and hence, its determination does not imply additional costs.

Anemia is a common complication of chronic underlying conditions with prognostic implications. A hematocrit level of <30% on admission is a classical component of the *PSI*. In this study, we have observed that anemia is also a predictor of survival independent of age and other comorbid conditions. This observation also documented by other authors is not easy to explain.[23] It is possible that it could reflect an exaggerated effect of inflammatory cytokines on subclinical not well-functioning red cell progenitors during acute onset of the disease.

The main strength of our study lies in the study population itself. Specifically, we only included patients with pneumococcal pneumonia, all of them with blood culture and urinary antigen test results. Further, the strict data collection process has allowed us to control for confounding effects in the multivariate analysis. We

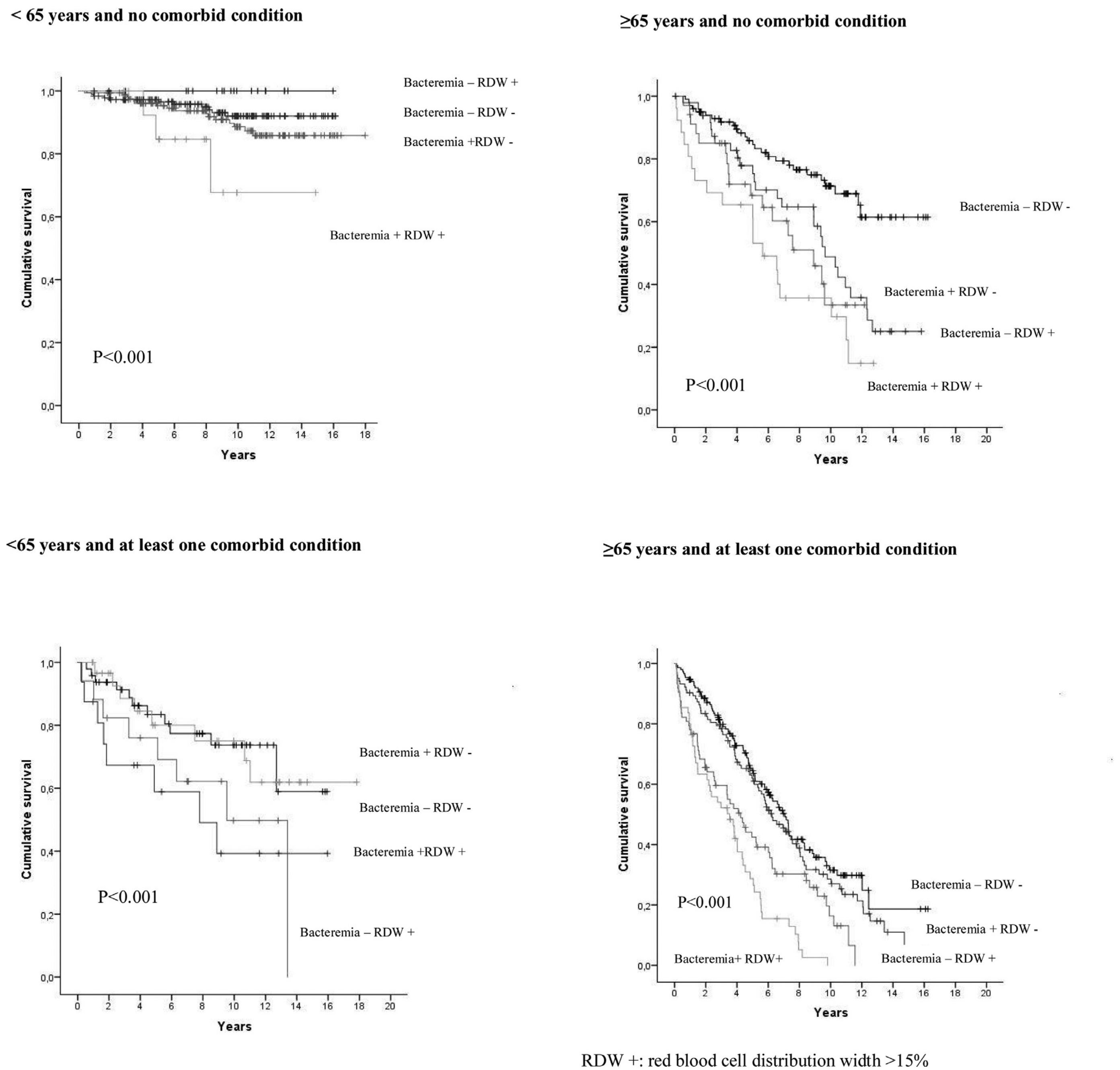


Fig. 4. Kaplan–Meier curves showing the survival probability stratified by age and presence of comorbidities.

recognize, however, that our study also has some limitations. (1) It was conducted in two hospitals in the same geographical area and health system, and hence, it may not be possible to extrapolate the results to other areas. (2) The low rate of pneumococcal immunization in our area could limit its potential beneficial effect on survival. (3) We were unable to obtain data on the causes of death, which could have added important additional information. (4) Finally, we did not evaluate the role of inflammatory markers such us C-reactive protein, because that was not routinely requested during the first years of this study.

To summarize, this study demonstrates a significant decrease in long-term survival compared with individuals' life expectancy in a large population of patients diagnosed with pneumococcal pneumonia. This is mainly associated with host-related factors such as age and presence of comorbidities. Interestingly, the finding of bacteremia and elevated RDW on admission also could help identify a group of patients at high risk of long-term mortality. Future multicenter studies are required to confirm these results. Our results could argue in favor of strengthening efforts to widen pneumococcal vaccination coverage especially in aged patients and/or those with chronic comorbid conditions, as well as improving the clinical control of underlying disease, as main strategies for improving survival after hospital discharge.

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Declaration of Competing Interest

The authors declare no conflicts of interest

CRediT authorship contribution statement

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