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Short- and long-term prognosis of patients with community-acquired *Legionella* or pneumococcal pneumonia diagnosed by urinary antigen testing

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ABSTRACT

Objectives: To analyze the differences in short- and long-term prognosis and the predictors of survival between patients with community-acquired *Legionella* and *Streptococcus pneumoniae* pneumonia, diagnosed early by urinary antigen testing (UAT).

Methods: Prospective multicenter study conducted in immunocompetent patients hospitalized with community-acquired *Legionella* or pneumococcal pneumonia (L-CAP or P-CAP) between 2002-2020. All cases were diagnosed based on positive UAT.

Results: We included 1452 patients, 260 with community-acquired *Legionella* pneumonia (L-CAP) and 1192 with community-acquired pneumococcal pneumonia (P-CAP). The 30-day mortality was higher for L-CAP (6.2%) than for P-CAP (5%). After discharge and during the median follow-up durations of 11.4 and 8.43 years, 32.4% and 47.9% of patients with L-CAP and P-CAP died, and 82.3% and 97.4% died earlier than expected, respectively. The independent risk factors for shorter long-term survival were age >65 years, chronic obstructive pulmonary disease, cardiac arrhythmia, and congestive heart failure in L-CAP and the same first three factors plus nursing home residence, cancer, diabetes mellitus, cerebrovascular disease, altered mental status, blood urea nitrogen ≥30 mg/dl, and congestive heart failure as a cardiac complication during hospitalization in P-CAP.

Conclusion: In patients diagnosed early by UAT, the long-term survival after L-CAP or P-CAP was shorter (particularly after P-CAP) than expected, and this shorter survival was mainly associated with age and comorbidities.

Introduction

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide [1]. Traditionally, CAP has been considered an acute illness in which once the initial process has been passed, the patient fully recovers with no implications for long-term survival. In contrast, some recent studies have observed a higher risk of death after recovery from the acute episode than that in the general population [2–4].

Early identification of the CAP etiological agent allows the timely administration of an adequate antibiotic treatment and limits the development of antibiotic resistance. Urinary antigen testing (UAT) is a noninvasive, quick, low-cost method with moderate sensitivity (Sn) and high specificity (Sp) for *Streptococcus pneu-*

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moniae (Sn: 50-70% and Sp: 90-99%) [5,6] and *Legionella pneumophila* serogroup 1 (Sn: 71-85% and Sp: 99-100%) [7] and the results are obtained in less than 1 hour, enabling an early diagnosis of CAP. According to a 2019 European Centre for Disease Prevention and Control report, most human *L. pneumophila* cases (>80%) are caused solely by serogroup 1 [8]. Despite UAT being simple to perform and providing rapid results, there are some differences between countries in the criteria for using this diagnostic tool. Specifically, the guidelines from the American Thoracic Society/Infectious Diseases Society of America only recommend UAT in patients with severe CAP [9]; in contrast, the Spanish guidelines recommend UAT for all patients admitted with CAP [10].

S. pneumoniae is the most commonly identified bacterial etiology and the leading cause of hospitalization in patients with CAP [11]. Furthermore, the previous research from our group observed a reduced long-term survival after hospitalization for community-acquired pneumococcal pneumonia (P-CAP) [12]. *L. pneumophila* is also an important cause of CAP, accounting for 2-15% of patients with severe CAP requiring hospitalization [13,14]. There are few previous studies on community-acquired *Legionella* pneumonia (L-CAP); most of them include few patients and have focused on the diagnostic test [7] or the acute process during hospitalization and short-term prognosis [15–17], whereas there is a lack of data on the long-term prognosis.

The objectives of this study were to describe the clinical course and survival rate during and after hospitalization in two of the most important bacterial causes of CAP (*Legionella* and *S. pneumoniae*), both diagnosed early and easily by UAT, to analyze the between-group differences and similarities in the short- and long-term prognosis and identify the predictors of survival in each group. Our analysis of risk factors associated with long-term mortality in each type of pneumonia could guide future strategies for improving the long-term survival of these patients.

Methods

Study design and population

This is a multicenter observational study based on the analysis of prospective registries of consecutive immunocompetent adults (aged ≥18 years) hospitalized for L-CAP or P-CAP between January 2002 and December 2020 to one of the two tertiary medical centers (Cruces University Hospital or Galdakao-Usansolo Hospital) serving populations of over 400,000 and part of the Spanish national health system. This study was approved by the corresponding ethics committee (code EPA2019043) and conducted in accordance with the principles of the Declaration of Helsinki on research in humans.

The bacteriological diagnoses of L-CAP and P-CAP were based on the results of *L. pneumophila* serogroup 1 and *S. pneumoniae* UAT performed within 24 hours of presentation to hospital. The tests were performed by analyzing urine samples with an immunochromatographic membrane assay (BinaxInc; Scarborough, ME). For the purpose of the study, for P-CAP, we limited the analysis to consecutive patients who had blood cultures performed.

Patients were excluded if they had a polymicrobial infection (*Legionella* or *S. pneumoniae* and ≥ 1 other pathogen), had been hospitalized at any point in the 14 days before the diagnosis of pneumonia, had previously received a diagnosis of pneumonia in the last 3 months, or were immunocompromised.

The participants were stratified into two groups by survival status during hospitalization and long-term follow-up: (i) survivors and (ii) nonsurvivors.

Study variables

We recorded the patients' clinical and demographic characteristics and physical examination, laboratory, and radiologic findings on admission. To assess the severity of pneumonia, we used the Pneumonia Severity Index (PSI) [18]. The measures of in-hospital clinical course and outcome included admission to the intensive care unit (ICU); use of invasive mechanical ventilation; septic shock; cardiovascular, renal, neurological, and hematologic complications during hospitalization; and in-hospital mortality. In-hospital and medical care after discharge were determined by the patients' health care providers. No interventions were instigated as part of this study.

Definitions

Pneumonia was defined as the presence of new pulmonary infiltrate on chest X-ray, together with acute signs and symptoms, suggestive of lower respiratory tract infection.

Septic shock was defined as a systolic blood pressure <90 mm Hg and the need for vasopressors for ≥4 hours after fluid replacement therapy on admission [19]. Lymphopenia was defined as a peripheral blood lymphocyte count of <500/μl, corresponding to grade III lymphopenia, according to the Common Terminology Criteria for Adverse Events [20].

We considered a patient immunocompromised if she/he has the presence of ≥1 of the following risk factors: (i) AIDS, defined either as human immunodeficiency virus infection with clusters of differentiation 4^+ lymphocyte count <200/µl, or by the occurrence of AIDS-defining conditions; (ii) aplastic anemia; (iii) asplenia; (iv) hematologic cancer, defined as lymphoma, acute or chronic leukemia, or multiple myeloma; (v) chemotherapy during the last 3 months; (vi) neutropenia, defined as a neutrophil count <500/dl at complete blood cell count; (vii) biological drug use, prescribed during ≥6 months before hospital admission; (viii) lung transplant; (ix) chronic steroid use (>10 mg/d of prednisone or equivalent ≥3 months before hospital admission); (x) lung cancer with either neutropenia or chemotherapy; (xi) other solid tumor with either neutropenia or chemotherapy; (xii) other immunocompromise (any immunocompromised state, including congenital/genetic immunocompromise and immunosuppressive therapy due to hematologic cancer/solid organ transplant other than the lung) [21].

Outcome

The main outcome was the survival rate at 30 days and after hospital discharge during the follow-up period assessed on December 31, 2022. Survival status was assessed based on the data from the database of the Basque Health Service (Osakidetza), using the same methodology as a previous study of our group. To avoid bias due to the short-term deaths attributable to the acute episode, patients who died within 30 days after hospital discharge were excluded from the long-term mortality analysis. We compared observed and expected survival according to the life expectancy of each patient. Life expectancy was estimated using life expectancy tables for the Spanish population (2002-2022) according to sex, age, and date of discharge [22].

Statistical analysis

Bivariate tables were constructed for each group of patients. Categorical variables were expressed as frequency and percentage and continuous variables as mean (standard deviation) or median (interquartile range), depending on whether the data were normally distributed. For continuous variables, the comparisons were

performed with Student's *t*-test if the data followed a normal distribution, and the Mann-Whitney U test if otherwise. The chi-square or Fisher's exact tests were performed for comparing qualitative variables. Logistic regression models were constructed to compare the 30-day mortality in L-CAP and P-CAP. The long-term survival was analyzed using Kaplan–Meier curves and the significance of differences was tested using the log-rank test. A univariate Cox regression analysis was performed to identify factors related to patient characteristics and survival. All variables with a $P < 0.05$ were included in a multivariate Cox regression model. The 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. The proportional hazard assumption was tested. All analyses were performed with the statistical software R (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 6837 immunocompetent patients were admitted to one of our two hospitals for CAP, and UAT was performed at hospital admission in 99.4% of the cases. We assessed 1452 patients with positive UAT results (21.2%): 260 patients with L-CAP (3.8%) and 1192 with P-CAP (17.4%). After applying the exclusion criteria, 244 patients with L-CAP and 1127 with P-CAP were considered eligible for the long-term survival analysis. The flow of patients through the study is illustrated in Figure 1.

Supplementary Table 1 compares the general characteristics and in-hospital course of our patients with L-CAP or P-CAP, stratified by their survival status during hospitalization. Supplementary Table 2 reports the results of the multivariate Cox regression analyses of factors associated with in-hospital mortality for each type of pneumonia.

Supplementary Table 3 presents the results of the logistic regression models comparing the 30-day mortality between groups. The 30-day mortality was higher for L-CAP (6.2% vs 5% for P-CAP; not statistically significant). Stratifying patients with P-CAP by blood culture result, the 30-day mortality was significantly higher for L-CAP ($P = 0.034$) and for bacteremic P-CAP (7.8%) ($P < 0.001$) than for nonbacteremic P-CAP (3.5%).

Table 1 compares the general characteristics and in-hospital course of our patients with L-CAP who survived 30 days after hospitalization, stratified by their long-term survival status. The mean age of the entire cohort was 56.72 years. The patients who did not survive were older, had more comorbidities, and were classified in the higher risk classes according to PSI score ($P < 0.001$). There were no differences in the complications during hospitalization or in-hospital course between the survivors and nonsurvivors.

Table 2 summarizes the demographic and clinical data, as well as the in-hospital course of our patients with P-CAP stratified by their long-term survival status. The mean age of the cohort was 64.04 years. The patients who did not survive were older, more likely to be male and live in a nursing home, had more comorbidities, and were classified in the higher PSI risk classes ($P < 0.001$); although, the bacteriemia rate was similar in those who survived and those who died.

Figure 2 shows the Kaplan–Meier curves for long-term survival, stratified by CAP etiological agent. The long-term mortality was higher for patients with P-CAP (47.9%) than for patients with L-CAP (32.3%), $P < 0.001$ (Figure 2a). In both types of pneumonia, the survival was lower than expected based on sex, age, and date of discharge. Stratifying patients with P-CAP by blood culture results (bacteremic vs no-bacteremic) (Figure 2b), the mortality rate was significantly lower for L-CAP than for either nonbacteremic (342/739 patients, 46.3%) or bacteremic (198/388 patients, 51.0%) patients with P-CAP ($P < 0001$). Figure 2c shows the Kaplan–Meier long-term survival curves for our patients with L-CAP stratified by PSI risk class. The survival rates were 100%, 95.7%, 83.8%, 64.1%, and 50.9% for the patients in the PSI risk classes I to V, respectively (log-rank $P < 0.001$). Figure 2d compares the Kaplan–Meier survival curves for L-CAP stratified by comorbidities compared with those expected based on sex, age, and date of discharge ($P < 0.001$; log-rank test).

The multivariate Cox regression analysis of factors associated with long-term mortality after hospitalization for L-CAP or P-CAP is reported in Table 3. In an adjusted multivariate model, the following were identified as the predictors of long-term mortality in L-CAP: age >65 years (HR 3.89; 95% CI: 2.36-6.42; $P < 0.001$), chronic obstructive pulmonary disease (COPD) (HR 2.58; 95% CI: 1.39-4.79; $P = 0.003$), congestive heart failure (HR 3.71; 95% CI: 2.22-6.21; $P < 0.001$), and cardiac arrhythmia (HR 1.98; 95% CI: 1.05-3.72; $P = 0.035$). On the other hand, in patients with P-CAP, the predictors of long-term mortality were age >65 years (HR 4.68; 95% CI: 3.71-5.91; $P < 0.001$), nursing home residence (HR 2.73; 95% CI: 1.76-4.23; $P < 0.001$), cancer (HR 2.11; 95% CI: 1.49-3.00; $P < 0.001$), COPD (HR 1.62; 95% CI: 1.34-1.97; $P < 0.001$), diabetes mellitus (HR 1.34; 95% CI: 1.09-1.63; $P = 0.005$), cerebrovascular disease (HR 1.50; 95% CI: 1.09-2.05; $P = 0.012$), cardiac arrhythmia (HR 1.45; 95% CI: 1.16-1.80; $P = 0.001$), altered mental status (HR 1.57; 95% CI: 1.20-2.06; $P < 0.001$), blood urea nitrogen ≥30 mg/dl (HR 1.29; 95% CI: 1.08-1.54; $P = 0.006$), and congestive heart failure as a cardiac complication during hospitalization (HR 1.52; 95% CI: 1.20-1.93; $P < 0.001$).

Supplementary Table 4 shows the observed and expected cumulative 1-, 3-, and 5-year survival rates for patients with L-CAP and bacteremic and nonbacteremic patients with P-CAP, stratified by the presence of comorbidities.

Discussion

In this study, we analyzed the 30-day and long-term survival in a prospective cohort of patients hospitalized for the most frequent and easily diagnosed types of bacterial CAP: L-CAP and P-CAP. The main findings were as follows: (i) although the 30-day mortality was slightly higher for L-CAP than for P-CAP with no statistically significant differences, the long-term mortality was significantly higher for patients with P-CAP. (ii) The long-term survival for patients with L-CAP or P-CAP was significantly shorter than their life expectancy based on sex, age, and year of discharge from hospital. (iii) In both types of pneumonia, the most important risk factors for long-term mortality in the multivariate analysis were advanced age and comorbidities.

The interest of this study lies in the nature of the study population; we only included patients with an etiological diagnosis obtained by noninvasive UAT performed upon admission, which gives us the *Legionella* and pneumococcal diagnoses in less than an hour. To the best of our knowledge, this is among the largest series on this topic, including data for well-defined cases of L-CAP and P-CAP collected prospectively and followed up for a mean time of more than 8 years. We consider that all these factors strengthen the clinical applicability and reproducibility of our results.

Interestingly, to the best of our knowledge, this is the first study to compare the 30-day and long-term mortality in patients with L-CAP or P-CAP diagnosed by UAT. Previous research from our group [23] demonstrated a poorer in-hospital course and prognosis for bacteremic than nonbacteremic P-CAP but no previous studies with a relatively large sample size have compared these outcomes with those in L-CAP. Hung et al. [24] analyzed the in-hospital course of both types of pneumonia in a small cohort of 55 patients, showing a higher in-hospital mortality for P-CAP (9.5%) than for L-CAP (7.7%).

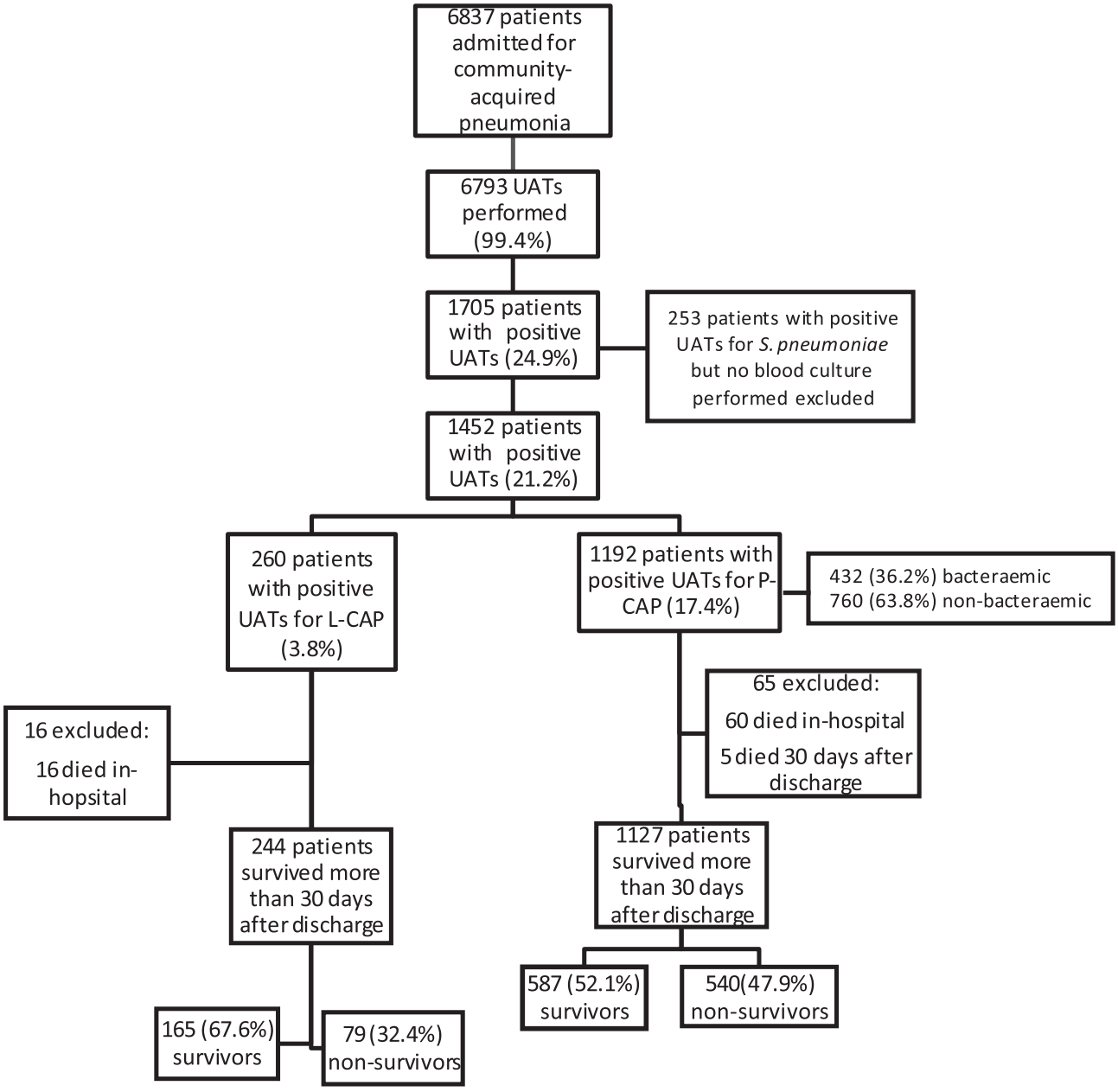

Figure 1. Flow of patients admitted with pneumonia diagnosed by positive UAT through the study. L-CAP, *Legionella* pneumonia; P-CAP, pneumococcal pneumonia; UAT, urinary antigen testing.

Regarding the long-term mortality, in our cohort, only 17.7% of the nonsurvivors after L-CAP and 2.6% of the nonsurvivors after P-CAP reached their life expectancy. Several previous studies have demonstrated a long-term negative impact of CAP on patient mortality, especially in older patients with major chronic diseases [2,25,26]. Despite several studies having analyzed the long-term mortality after pneumonia, few have taken into account the etiological agent, as we have done. In a previous study, our group found that the long-term mortality after P-CAP was higher than estimated, and compared with nonbacteremic disease, bacteremic P-CAP was associated with a shorter long-term survival [12]. On the other hand, there are few data on survival after L-CAP and none comparing it with P-CAP. Among the few studies that demonstrate a poorer quality of life after L-CAP, Lettinga et al. [27], analyzing 122 individuals with L-CAP, found that 64% had not attained their pre-illness quality of life 2 years after L-CAP, whereas Gamage et al. [28], in a 5-year follow-up of 292 patients, observed that L-CAP requiring ICU admission was associated with more subsequent hospitalizations and poorer future health.

Our findings demonstrate that patients with P-CAP (including bacteremic and nonbacteremic cases) had a shorter long-term survival than patients with L-CAP, contrasting with the pattern in the 30-day mortality. In our sample, the patients with P-CAP were older and had more comorbidities, which is very relevant for the long-term mortality, as previous studies have reported [2,26]. In L-CAP, the acute illness may often be severe, but because the patients tend to be younger and have few comorbidities, they achieve better recovery with fewer long-term adverse events. In contrast to our results, in the study published by Holter et al. [25], no significant differences were observed by microbial etiology between the long-term survivors and nonsurvivors, but the sample was smaller (259 patients), the etiology was unknown in 37.5% of the cases and the cases with an identified etiological cause did not include any patients with *Legionella*. The contribution of etiological factors to

Table 1
General characteristics and in-hospital course of patients with community-acquired *Legionella* pneumonia, surviving more than 30 days after discharge, overall and by survival during follow-up.

Characteristics	All N = 244	Survivors N =165	Nonsurvivors N = 79	*P*-value
Demographic characteristics				
Male sex	202 (82.8%)	132 (80%)	70 (88.6%)	0.137
Age >65 years	69 (28.3%)	26 (15.8%)	43 (54.4%)	<0.001
Nursing home resident	1 (0.41%)	0 (0%)	1 (1.27%)	0.315
Underlying conditions				
Comorbidities (yes)	106 (43.4%)	54 (32.7%)	52 (65.8%)	<0.001
Cancer	5 (2.05%)	2 (1.21%)	3 (3.80%)	0.344
Liver disease	10 (4.10%)	6 (3.64%)	4 (5.06%)	0.755
Renal disease	6 (2.46%)	2 (1.21%)	4 (5.06%)	0.094
Chronic obstructive pulmonary disease	18 (7.38%)	4 (2.42%)	14 (17.7%)	<0.001
Diabetes mellitus	39 (16.0%)	22 (13.3%)	17 (21.5%)	0.148
Cerebrovascular disease	14 (5.74%)	1 (0.61%)	13 (16.5%)	<0.001
Congestive heart disease	37 (15.2%)	9 (5.45%)	28 (35.4%)	<0.001
Cardiac arrhythmia	17 (7.17%)	3 (1.88%)	14 (18.2%)	<0.001
Coronary disease	18 (7.59%)	7 (4.38%)	11 (14.3%)	0.015
Hypertension	91 (38.4%)	55 (34.4%)	36 (46.8%)	0.091
Vaccination status				
Influenza vaccine	(1.64%)	2 (1.21%)	2 (2.53%)	0.572
Pneumococcal vaccine	34 (13.9%)	13 (7.88%)	21 (26.6%)	<0.001
Current smoker	167 (68.4%)	122 (73.9%)	45 (57.0%)	0.012
Heavy alcohol drinker	67 (27.5%)	42 (25.5%)	25 (31.6%)	0.389
Clinical characteristics at admission				
Previous antibiotic treatment	54 (22.1%)	37 (22.4%)	17 (21.5%)	1.000
Days of symptoms <3	76 (31.1%)	47 (28.5%)	29 (36.7%)	0.250
Temperature <35 or >40°C	4 (1.64%)	2 (1.21%)	2 (2.53%)	0.600
Respiratory rate ≥30 breaths/min	29 (12.2%)	19 (11.7%)	10 (13.3%)	0.878
Heart rate ≥125 beats/min	21(8.68%)	10 (6.10%)	11 (14.1%)	0.068
Altered mental status	25 (10.3%)	16 (9.70%)	9 (11.5%)	0.830
Systolic blood pressure <90 mm Hg	8 (3.42%)	6 (3.77%)	2 (2.67%)	0.718
Laboratory and radiological findings				
Blood urea nitrogen ≥30 mg/dl	48 (19.7%)	27 (16.4%)	21 (26.6%)	0.088
PaO_2 <60 mm Hg	72 (36.7%)	49 (38.3%)	23 (33.8%)	0.645
Glucose ≥250 mg/dl	23 (9.43%)	13 (7.88%)	10 (12.7%)	0.336
Hematocrit <30%	4 (1.64%)	0 (0.00%)	4 (5.06%)	0.007
Sodium <130 mmol/l	60 (24.5%)	43 (26.1%)	17 (21.5%)	0.635
Red blood cell distribution width >15%	45 (18.4%)	24 (14.5%)	21 (26.6%)	0.036
Leukocyte count <4000/µl	4 (1.64%)	3 (1.82%)	1 (1.27%)	1.000
Lymphocyte count <500/µl	42 (17.9%)	27 (17.3%)	15 (19.2%)	0.857
C-reactive protein >15 mg/dl	135 (91.2%)	107 (95.5%)	28 (77.8%)	0.003
Multilobar pneumonia	75 (30.7%)	51 (30.9%)	24 (30.4%)	1.000
Pleural effusion	8 (3.28%)	6 (3.64%)	2 (2.53%)	0.733
Severity of illness at admission				
Pneumonia Severity Index risk class IV-V	181 (74.2%)	109 (66.1%)	72 (91.1%)	<0.001
In-hospital course/Outcomes				
Intensive care admission	59 (24.2%)	45 (27.3%)	14 (17.7%)	0.141
Invasive mechanical ventilation	23 (9.43%)	17 (10.3%)	6 (7.59%)	0.658
Septic shock	17 (7.20%)	13 (8.18%)	4 (5.19%)	0.574
New cardiac arrhythmia	12 (4.92%)	8 (4.85%)	4 (5.06%)	1.000
Congestive heart failure	5 (2.11%)	2 (1.25%)	3 (3.90%)	0.348
Pulmonary embolism	1 (0.42%)	1 (0.62%)	0 (0.00%)	1.000
Neurological complications	13 (5.42%)	12 (7.36%)	1 (1.30%)	0.067
Renal complications	28 (11.7%)	20 (12.3%)	8 (10.4%)	0.835
Hematologic complications	8 (3.33%)	5 (3.07%)	3 (3.90%)	1.000

Data are given as frequency (percentage) unless otherwise stated. Percentages exclude patients with missing data.

the long-term outcomes is controversial. It has been demonstrated previously that survival is lower after discharge after admission for pneumonia, independent of the pathogen. In contrast, it is difficult to distinguish the real contribution of each pathogen because pneumococcus is the microorganism most frequently isolated in most series.

This study identified age >65 years, COPD, congestive heart disease, and cardiac arrhythmia as the predictive factors for long-term mortality in L-CAP. The finding that both cardiovascular diseases and age increase the subsequent rate of mortality is not surprising and is in line with findings in previous studies [2,26]. Blanc et al. [3], analyzing data extracted from the medicalization program of the French information systems, showed that the short- and long-term mortality increased with age and number of comorbidities in patients with CAP. In contrast to previous studies predicting the long-term survival after CAP [25,26], in our patients with L-CAP, only age and cardiorespiratory comorbidities predict long mortality, and no biomarkers were found to be significant in the multivariate analysis, but there are no previous data on the long-term survival considering only patients with an etiological diagnosis of L-CAP.

In this study, we found that the long-term cumulative survival for our patients with L-CAP decreases with increasing severity of the disease, as measured by PSI risk class. Several previous studies have found this score to have a good accuracy for predicting the long-term survival after CAP. Specifically, Alan et al. [29] demonstrated PSI's excellent accuracy for predicting 6-year mortality, whereas Johnstone et al. [26] showed that long-term

Table 2
General characteristics and in-hospital course of patients with community-acquired pneumococcal pneumonia surviving more than 30 days after discharge, overall and by survival during follow-up.

Characteristics	All N = 1127	Survivors N = 587	Nonsurvivors N = 540	*P*-value
Demographic characteristics				
Male sex	663 (58.8%)	321 (54.7%)	342 (63.3%)	0.004
Age >65 years	589 (52.3%)	153 (26.1%)	436 (80.7%)	<0.001
Nursing home resident	24 (2.13%)	4 (0.68%)	20 (3.70%)	0.001
Underlying conditions				
Comorbidities (yes)	780 (69.2%)	310 (52.8%)	470 (87.0%)	<0.001
Cancer	48 (4.26%)	13 (2.21%)	35 (6.48%)	0.001
Liver disease	44 (3.91%)	19 (3.24%)	25 (4.64%)	0.290
Renal disease	54 (4.79%)	10 (1.70%)	44 (8.15%)	<0.001
Chronic obstructive pulmonary disease	220 (19.5%)	62 (10.6%)	158 (29.3%)	<0.001
Diabetes mellitus	191 (17.0%)	59 (10.1%)	132 (24.5%)	<0.001
Cerebrovascular disease	63 (5.59%)	16 (2.73%)	47 (8.70%)	<0.001
Congestive heart disease	109 (9.67%)	16 (2.73%)	93 (17.2%)	<0.001
Cardiac arrhythmia	170 (15.2%)	33 (5.70%)	137 (25.4%)	<0.001
Coronary disease	67 (5.99%)	24 (4.15%)	43 (7.98%)	0.010
Hypertension	450 (40.2%)	162 (28.0%)	288 (53.3%)	<0.001
Vaccination status				
Influenza vaccine	315 (29.1%)	104 (18.3%)	211 (41.1%)	<0.001
Pneumococcal vaccine	141 (13.0%)	38 (6.68%)	103 (20.0%)	<0.001
Current smoker	293 (26.1%)	207 (35.3%)	86 (16.0%)	<0.001
Heavy alcohol drinker	135 (12.4%)	77 (13.3%)	58 (11.2%)	0.335
Clinical characteristics at admission				
Previous antibiotic treatment	102 (9.24%)	59 (10.4%)	43 (8.02%)	0.210
Days of symptoms <3	595 (52.9%)	293 (50.0%)	302 (56.1%)	0.046
Temperature <35 or >40°C	5 (0.44%)	4 (0.68%)	1 (0.19%)	0.298
Respiratory rate ≥30 breaths/min	165 (14.8%)	79 (13.6%)	86 (16.0%)	0.292
Heart rate ≥125 beats/min	162 (14.4%)	101 (17.2%)	61 (11.3%)	0.006
Altered mental status	98 (8.70%)	32 (5.45%)	66 (12.2%)	<0.001
Systolic blood pressure <90 mm Hg	98 (8.70%)	65 (11.1%)	33 (6.11%)	0.004
Laboratory and radiological findings				
Blood urea nitrogen ≥30 mg/dl	407 (36.1%)	157 (26.7%)	250 (46.3%)	<0.001
PaO_2 <60 mm Hg	481 (50.6%)	209 (44.8%)	272 (56.3%)	<0.001
Glucose ≥250 mg/dl	89 (7.90%)	28 (4.77%)	61 (11.3%)	<0.001
Hematocrit <30%	39 (3.46%)	15 (2.56%)	24 (4.44%)	0.116
Sodium <130 mmol/l	94 (8.3%)	50 8.5%)	44 (8.1%)	0.134
Red blood cell distribution width >15%	228 (23.7%)	61 (13.0%)	167 (33.7%)	<0.001
Leukocyte count <4000/µl	52 (4.61%)	36 (6.13%)	16 (2.96%)	0.017
Lymphocyte count <500/µl	253 (22.8%)	141 (24.6%)	112 (21.0%)	0.177
C-reactive protein >15 mg/dl	586 (70.4%)	364 (73.7%)	222 (65.7%)	0.016
Multilobar pneumonia	334 (29.7%)	195 (33.3%)	139 (25.7%)	0.007
Pleural effusion	123 (10.9%)	69 (11.8%)	54 (10.0%)	0.396
Positive blood culture	388 (34.4%)	190 (32.4%)	198 (36.7%)	0.146
Severity of illness at admission				
Pneumonia Severity Index risk class IV-V	538 (47.7%)	163 (27.8%)	375 (69.4%)	<0.001
In-hospital course/Outcomes				
Intensive care admission	273 (24.2%)	172 (29.3%)	101 (18.7%)	<0.001
Invasive mechanical ventilation	63 (5.59%)	42 (7.16%)	21 (3.89%)	0.024
Septic shock	121 (10.7%)	71 (12.1%)	50 (9.26%)	0.150
New cardiac arrhythmia	85 (7.60%)	45 (7.77%)	40 (7.41%)	0.907
Congestive heart failure	141 (12.6%)	25 (4.32%)	116 (21.5%)	<0.001
Pulmonary embolism	10 (0.89%)	7 (1.21%)	3 (0.56%)	0.343
Neurologic complications	65 (5.77%)	21 (3.58%)	44 (8.15%)	0.002
Renal complications	169 (15.0%)	85 (14.5%)	84 (15.6%)	0.673
Hematologic complications	57 (5.13%)	44 (7.67%)	13 (2.42%)	<0.001

Data are given as frequency (percentage) unless otherwise stated. Percentages exclude patients with missing data.

morbidity and mortality were strongly correlated with the initial PSI class. This probably reflects the weight in the PSI of age and comorbidities, both of which our study has shown to be important risk factors for long-term mortality.

Our results demonstrate the usefulness of the UAT in patients hospitalized for CAP; this type of test allows an early etiological diagnosis to be obtained simply and rapidly and, in turn, a close follow-up of patients with P-CAP or L-CAP with surveillance of comorbidities in the short- and long-term due to their higher risk of mortality. The current American Thoracic Society/Infectious Diseases Society of America guidelines do not recommend routine UAT in patients hospitalized for CAP [9], limiting their use to patients with severe disease, but based on an analysis of 166,689 patients with CAP, Allgaier et al. [17] demonstrated that L-CAP was not more common among patients presenting with severe disease. Their results also showed that almost a quarter of patients with L-CAP did not receive adequate empirical coverage, and a positive result can guide or narrow antibiotic treatment, which makes UAT cost-effective. In contrast, a recent study published by Ito et al. [30] reported that the sensitivity of *S. pneumoniae* UAT had decreased gradually from 2001 (81.3%) to 2015 (48.7%), which should be considered to evaluate its usefulness for future research.

This study has several limitations. First, it was conducted in two hospitals in the same country and health system; therefore, it may not be appropriate to extrapolate the results to other countries. Second, this was an observational study, and the population

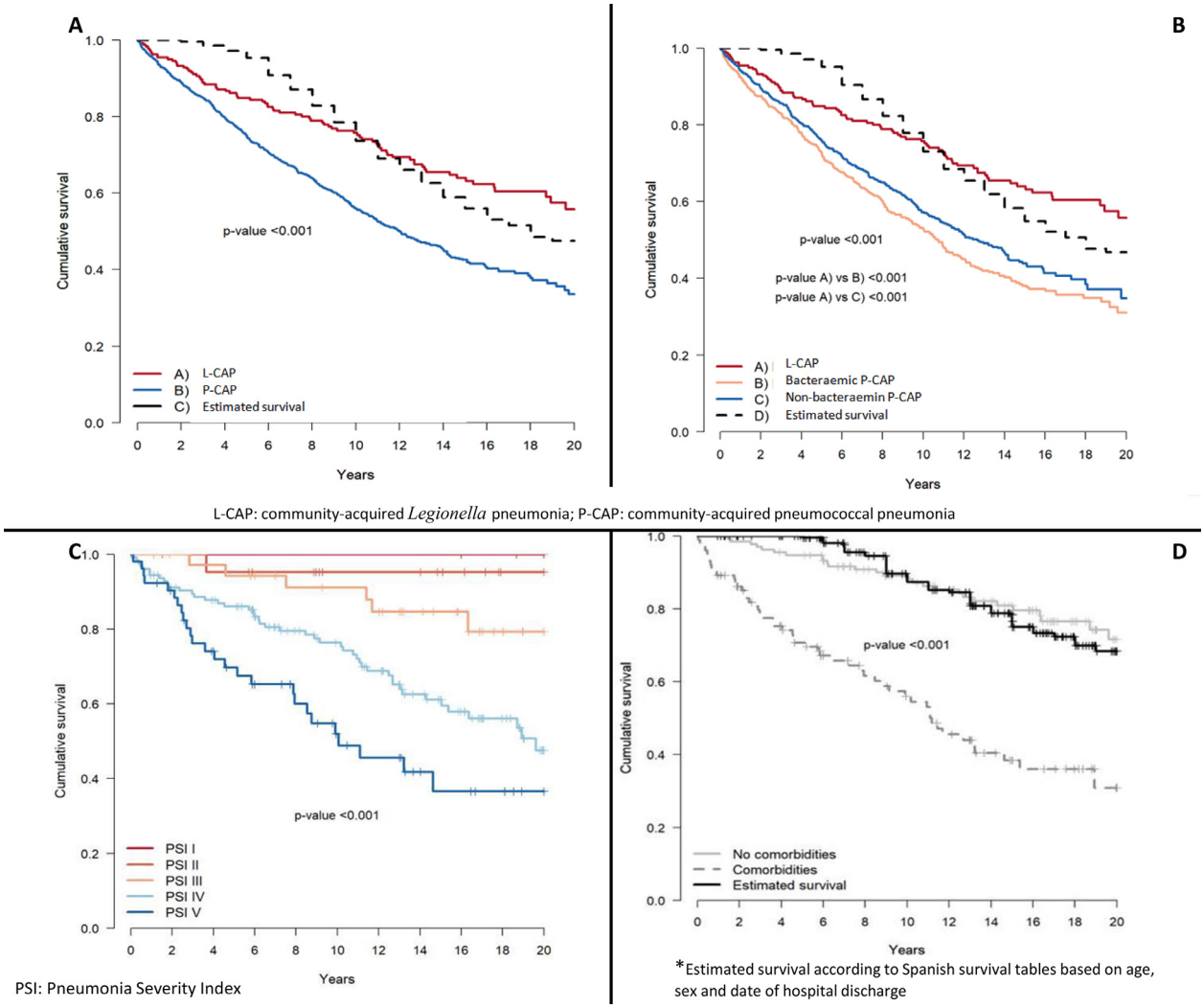

Figure 2. Kaplan–Meier curves for long-term survival stratified by etiological agent of community-acquired pneumonia (2a and 2b). Kaplan–Meier plots of long-term survival for patients with community-acquired *Legionella* pneumonia stratified b PSI risk class (2c) and comorbidities (2d). L-CAP, *Legionella* pneumonia; P-CAP, pneumococcal pneumonia; PSI, Pneumonia Severity Index.

Table 3
Multivariate Cox regression analysis of factors associated with long-term mortality after hospitalization for community-acquired *Legionella* or pneumococcal pneumonia (L-CAP or P-CAP, respectively).

L-CAP			P-CAP		
	HR 95% CI	*P*-value		HR 95% CI	*P*-value
Age >65 years	3.89 (2.36-6.42)	<0.001	Age >65 years	4.68 (3.71-5.91)	<0.001
Chronic obstructive pulmonary disease	2.58 (1.39-4.79)	0.003	Nursing home	2.73 (1.76-4.23)	<0.001
Congestive heart disease	3.71 (2.22-6.21)	<0.001	Cancer	2.11 (1.49-3.00)	<0.001
Cardiac arrhythmia	1.98 (1.05-3.72)	0.035	Chronic obstructive pulmonary disease	1.62 (1.34-1.97)	<0.001
			Diabetes mellitus	1.34 (1.09-1.63)	0.005
			Cerebrovascular disease	1.50 (1.09-2.05)	0.012
			Cardiac arrhythmia	1.45 (1.16-1.80)	0.001
			Altered mental status	1.57 (1.20-2.06)	<0.001
			Blood urea nitrogen ≥30 mg/dl	1.29 (1.08-1.54)	0.006
			Cardiac complication: Congestive heart failure	1.52 (1.20-1.93)	<0.001

CI, confidence interval; HR, hazard ratio; L-CAP, *Legionella* pneumonia; P-CAP, pneumococcal pneumonia.

was restricted to patients in whom UAT was performed on admission with a positive result for *Legionella* or *S. pneumoniae* and in the case of patients with P-CAP, those who had blood culture performed. On the other hand, the exclusion of patients with a positive UAT but no blood culture performed could be considered a strength because these restrictions allowed us to obtain a relatively homogeneous cohort and to better characterize the presence of bacteremia in the subgroup of patients with P-CAP. Third, we also excluded patients with polymicrobial pneumonia to focus the analysis on the patients with only L-CAP or P-CAP. Nevertheless, our rate of polymicrobial CAP is very low (<3%; data not published). Fourth, we were unable to obtain data on the causes of death, which might have added other factors of interest. Despite these limitations, our findings have important

implications. Clinicians should be aware of the potential impact of these CAP etiologies on the short- and long-term prognosis.

Conclusion

Our findings demonstrate a higher 30-day mortality for L-CAP than for P-CAP and a significantly shorter-than-expected long-term survival after hospitalization for L-CAP or P-CAP (most marked after P-CAP) in a large population of patients diagnosed early by positive UAT, the shorter survival principally being associated with host-related factors, particularly age and comorbidities. Our results argue in favor of the use of the UAT upon admission to obtain a rapid etiological diagnosis of both types of pneumonia, as well as underlining the need for closer monitoring after hospital discharge (especially of those with comorbid conditions) and pneumococcal vaccination as major strategies for improving survival after discharge after admission to the hospital for L-CAP or P-CAP.

Declarations of competing interests

The authors have no competing interests to declare.

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Ethical approval

This study was approved by the corresponding ethics committee (code EPA2019043) and conducted in accordance with the principles of the Declaration of Helsinki on research in humans.

Author contributions

LSF and LAR take the responsibility of the manuscript as a whole. LSF, LAR, RZJ, AGB, and PPE conceived and designed the study. AUE, BGQ, MIP, SCQ, LSF, and LAR enrolled patients and collected and compiled data. SPF performed the statistical analysis. LSF, RZJ, LAR, AGB, PPE, and MIP analyzed and interpreted the data. LSF, RZJ, and LAR wrote the manuscript. AUE, BGQ, MIP, SCQ, PPE, and AGB commented and revised the report. All authors read and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.05.065.

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