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Factors Associated with Hospital Mortality in Community-acquired Legionellosis in France

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ABSTRACT

The aims of this work are to describe the clinical, biological and radiological features of community-acquired (CA) Legionnaires' disease (LD) and identify the predictors of mortality in hospitalized patients.

Demographic data, risk factors, clinical, and biological features, medical management, complications and outcome from 540 hospitalized patients with confirmed CA LD were prospectively recorded.

8.1% of patients (44/540) died. The predictors of survival after Kaplan-Meier analysis were male gender (*P*=.01), age <60 years (*P*=.02), general symptoms (*P*=.006), intensive care unit (ICU) stay (*P*<.001), and class II-III pneumonia severity index score (*P*=.004). Six predictors of death were identified by multivariate analysis: age (per 10-year increments) (relative hazard (RH), 1.50; 95% confidence interval [95% CI], 1.21-1.87), female gender (RH, 2.00; 95% CI, 1.08-3.69), ICU admission (RH, 3.31; 95% CI, 1.67-6.56), renal failure (RH, 2.73; 95% CI, 1.42-5.27), corticosteroid therapy (RH, 2.54; 95% CI, 1.04-6.20) and C-reactive protein (CRP) >500 mg/L (RH, 2.14; 95% CI, 1.02-4.48). Appropriate antibiotic therapy was prescribed for 76.3% (292/412) of patients after admission and for 99.6% (537/538) of patients after diagnosis confirmation.

In conclusion, female gender, age, ICU stay, renal failure, corticosteroid treatment, and increased level of CRP are significant risk factors for mortality in CA LD.

INTRODUCTION

Legionnaires' disease (LD), first described in 1977 [1], is caused by a Gram-negative bacillus of the genus *Legionella. L. pneumophila* serogroup 1 (*Lp*1), observed most frequently in human disease, accounts for about 90% of cases. It is responsible for sporadic or epidemic, community-acquired (CA) or hospital-acquired (HA) cases of LD, all of which can evoke severe disease and death [2].

The suggestive clinical presentation of LD usually consists of severe acute pneumonia, with confusion, hepatic cytolysis, hyponatremia and renal failure. Risk factors for LD include smoking, male gender, chronic heart or lung disease, diabetes, end-stage renal failure, organ transplantation, immunosuppression, cancer, and age older than 50 years [2, 3]. The overall case fatality rate (CFR) is around 10-15% in France [4-6], and mortality in intensive care units (ICUs) ranges from 15 to 33% [7].

Few prospective studies have assessed the factors associated with LD outcomes, particularly death, and most of them involved a limited number of patients. These investigations were undertaken before the era of rapid diagnosis and increased use of quinolones for treatment.

The objectives of the present prospective, multicenter cohort study are to describe the clinical features and to evaluate the factors linked with in-hospital mortality in CA LD patients.

METHODS

Source of information

Reporting of LD has been mandatory in France since 1987. Physicians and microbiologists are required to report confirmed and probable cases of LD to the National Institute for Public Health Surveillance (InVS, Institut de Veille Sanitaire). The number of reported cases has increased over the years, especially since the introduction of urinary antigen tests in 1997 [8]. Surveillance sensitivity also has increased over the same time period [9]. In 2005, 1,527 reported LD cases corresponded to an estimated incidence of 2.5 per 100,000 inhabitants [4].

Definitions

Confirmed LD cases were defined as acute illness with clinical and radiographic signs of pneumonia combined with at least one of the following biological criteria:

(i) *Lp*1 isolation from clinical samples (sputum, broncho-alveolar lavage fluid, or bronchial aspirate); or (ii) the presence of soluble antigens in urine (*Lp*1-specific test). Patients with 4-fold increment of *Lp*1 antibody titers were not included.

Definite or possible HA LD cases were excluded (HA LD was defined as LD in patients hospitalized for the entire period beginning 10 days and ending 2 days before the onset of symptoms; patients hospitalized for part of that period were defined as possible HA LD [10]).

The time to appropriate treatment was defined as the number of days from onset to the administration of antibiotic therapy (at least 1 intracellular drug: macrolide, fluroroquinolone) active against *Legionella*.

The overall CFR was defined as death from any cause occurring during the first 30 days after LD diagnosis.

Patient selection

From April 1, 2006 to June 30, 2007, hospitalized patients with confirmed CA LD due to *L. pneumophila* serogroup 1 in metropolitan France were prospectively identified through the mandatory notification system. Physicians who fulfilled compulsory reporting requirements were immediately asked to participate in this prospective study and to enroll cases after written, informed consent. To detect potential selection bias, enrolled cases were compared to cases reported to InVS during the same time period but not included in the present investigation.

Data collection

A standard case report form was completed at all sites to collect data on admission, during hospitalization and follow-up at 30 days. The variables collected were: (i) demographic data (birth date, gender); (ii) risk factors for LD (smoking habit, alcohol intake, diabetes mellitus, cancer, immunosuppression, corticosteroid therapy); (iii) clinical features at onset and at hospitalization, including respiratory rate, diastolic and systolic arterial blood pressure, heart rate, oxygen partial pressure (PaO_2), temperature (>38.5°C), general symptoms (chills, anorexia, myalgia), respiratory symptoms (dyspnea, cough, expectoration, hemoptysis, thoracic and pleural pain), gastrointestinal symptoms (nausea, diarrhea, abdominal pain), neurological symptoms (confusion, headache); (iv) radiological findings on admission; (v) laboratory data (serum creatinine, creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), white cell count); (vi) criteria of severity, such as the pneumonia severity index (PSI) [11] at admission, ICU admission, mechanical ventilation; (vii) time to administration of appropriate antibiotic treatment; (viii) incidence of complications (renal failure, hepatic failure) and outcome (death or recovery/discharge).

Microbiology testing

Clinical isolates were sent to the French National Reference Centre for *Legionella* for characterization by sequence-based typing (ST) and Dresden monoclonal antibody-based (mAb) subgrouping [12-14].

Statistical analysis

Continuous variables were expressed as median [range]. Categorical variables were presented as percentages of the group from which they were derived.

Patients were stratified into those who survived and those who died within the first 30 days after LD diagnosis. These 2 subgroups were compared by Fisher's exact test for categorical variables or with the non-parametric Mann-Whitney U-test for continuous variables. Patients survival was calculated from the date of diagnosis until in-hospital death and based on the Kaplan-Meier method. Follow-up was censored at 30 days. Survival distributions were compared by the log-rank test. Variables independently associated with survival were identified with a Cox regression model based on relative hazard (RH) with a 95% confidence interval (95% CI). Proportional risk assumptions were checked. The final Cox model was assessed for potential interactions and for adequacy with hypotheses of proportional risks. Variables with $P \leq 0.15$ were entered in the initial multivariate model. Backward stepwise selection was made with the Wald test to compare models. $P<0.05$ (2-tailed) was considered to indicate statistical significance. All statistical analyses were performed with a commercially-available statistical software package (SPSS, version 16.0 for Windows, SPSS Inc., Chicago, IL, USA).

Ethics

This study was approved by the French Data Protection Authority.

RESULTS

During the study period, out of 1,595 LD cases attributed to *Lp*1 and reported to the InVS, 540 patients hospitalized for CA LD (36%) were enrolled in this investigation; 395 were male and 145 female, with a mean age of 60 years (17-100 years).

All cases were confirmed in hospitals where they were included, by positive urinary antigen detection of *Lp*1 by immunochromatographic test (ICT), mainly *Now Legionella* ICT. In addition, positive cultures and seroconversion were reported in 93 (17.2%) and 66 cases (12.2%), respectively. The 93 clinical isolates were distributed among 36 genotypes (STs). About 50% of isolates were accounted for by only 4 STs, with ST23 being the most frequent (23.7%). Other common STs included ST1 (7.5%), ST146 (6.5%) and ST47 (11.8%). mAb 3/1-positive isolates were predominant (87 isolates); only 6 isolates (6.5%) did not react to mAb 3/1 (4 Olda isolates and 2 Bellingham isolates).

The main risk factors for acquiring LD were smoking (53.5%), alcohol intake (18.7%), diabetes (15.7%), cancer/malignancy (6.3%), corticosteroid therapy (5.7%), and immunosuppressive therapy (3.3%). Seventy-four percent of patients had at least 1 known risk factor of LD, regardless of age. No known risk factor was identified in the 139 remaining patients (27.7%).

Forty-four cases died during hospitalization, corresponding to an overall CFR of 8.1% (44/540). Four patients died within 24 hours after diagnosis. Compared to LD cases reported to the InVS but not entered in this study, those included (n=540) did not differ statistically by gender, age and geographic distribution.

Interestingly, the CFR of culture-confirmed cases (15.1%, 14/93) was greater than among patients in whom the strain was not identified (6.7%, 30/447, P=0.012).

Death was attributed solely to LD in 17/44 (38.63%) patients and to LD complications in 27/44 (61.36%) patients. Reported complications included: cardiovascular (n = 10),

respiratory (n = 8), malignancy (n = 3), shock (n = 3), multiorgan failure (n = 2), neurological (n = 2), renal (n = 1), and bacteremia (n = 1); some patients may have suffered more than one complication.

Demographic, clinical, biological and radiographic characteristics were compared between surviving and non-surviving patients; non-survivors were older ($P<0.001$), more frequently female ($P=0.02$) and more often in the PSI high-risk group at admission ($P<0.001$) (Table 1).

Corticosteroid therapy was significantly more frequent in non-survivors ($P=0.03$), whereas, surprisingly, smoking was significantly more frequent in survivors ($P<0.001$). Other potential risk factors, such as cancer/malignancy, diabetes and immunosuppression therapy, were not significantly associated with death.

Table 2 summarizes the significant differences in clinical, biological and radiological characteristics in hospital survivors *versus* non-survivors.

Non-survivors were more often confused ($P=0.02$), had dyspnea ($P=0.02$), higher respiratory and heart rates ($P=0.03$ and $P=0.02$ respectively), lower median systolic ($P<.001$) and diastolic blood pressure ($P=0.01$). More frequently, they also had serum creatinine levels >160 µmol/L ($P<0.001$), serum CRP >500 mg/L ($P=0.003$) and higher neutrophil counts (G/L) ($P=0.009$), but their lymphocyte levels (G/L) were lower ($P=0.001$). They more frequently had multilobar or bilateral infiltrates ($P=0.001$) (Table 2).

Survivors were clinically more symptomatic at admission, with a higher proportion having body temperature >38.5°C ($P=0.001$), chills ($P=0.004$), nausea ($P=0.04$), and headache ($P<0.001$).

Although only 14.4% (25/174) of patients received appropriate empirical antibiotic treatment before hospital admission (most received beta-lactams, data not reported), more than 76.3% (292/412) and virtually all patients (99.6%, 537/538) were given appropriate antibiotics upon admission (empirically) and after confirmation of LD diagnosis, respectively (Table 3). The

median time to appropriate antibiotic treatment was shorter in non-survivors (3.0 *vs* 4.0 days, P=0.1), but the difference was not significant.

ICU admission, the need for mechanical ventilation, and in-hospital complications (respiratory super-infection, renal and hepatic failure as well as decompensation of pre-existing illness) were more likely to occur in non-survivors (Table 3). As expected, patients in the high-risk group based on PSI (classes IV and V at admission) were at significantly higher risk of death (P<0.001) (Table 1).

The log-rank test indicated that the probability of patient survival during the first 30 days after LD diagnosis was associated with male gender (P=0.01), age <60 years (P=0.02), the presence of general symptoms (P=0.006) and digestive symptoms (P=0.05), whereas ICU admission (P<0.001) and PSI classes IV-V (P=0.004) were significantly associated with a lower probability of survival (Table 4 and Figure 1 A-B).

Independent factors linked with mortality in multivariate analysis (Table 5) were age (per 10-year increments (P<0.001)), female gender (P=0.03), ICU admission (P=0.001), renal failure (P=0.003), corticosteroid therapy (P=0.04) and elevated CRP level (P=0.04).

DISCUSSION

To the best of our knowledge, this study of 540 patients is the largest prospective, hospital-based investigation to describe the clinical-biological features and outcome of confirmed CA LD in our modern era. For example, the biological parameters or the proportion of in-hospital complications among LD patients have rarely been documented in such a series, and we consider our analysis to be a helpful description of sporadic LD cases. All diagnoses were confirmed by urinary antigen testing, a more reliable method than serology screening. However, reported values for pooled test sensitivity and specificity were 0.74 and 0.99 respectively in a systematic review and meta-analysis [15], and LD caused by serogroup 1 mAb 3/1-negative were significantly less frequently diagnosed by commercially-available assays [14].

Our sizeable patient population, included in a limited time period, is representative of a larger group of 1.595 patients reported nation-wide during the same period, providing an accurate description of CA LD in patients hospitalized in France

The CFR of 8.1% is consistent with the mortality reported in routine national surveillance of LD in France (11%) and elsewhere. The LD fatality rate ranged from 5-25% in immunocompetent hosts [16] to 33% in severe LD [17], 8.5% in a study by Dominguez et al. [7] and 12.9% in the more recent investigation by Jespersen et al. [18].

In our study, the CFR for culture-confirmed cases was significantly higher than the global CFR, which could be related to the variability of diagnostic methods (culture of lung samples could be prescribed more often in severe cases of LD), significant dissemination of *Legionella* in more debilitated patients, or more virulent strains.

Various significant demographic risk factors for poor outcome were identified, including corticosteroid therapy and cancer/malignancy. However, diabetes, immunosuppression medication and smoking were not associated with death.

The poorer prognosis of older patients, and of those presenting with dyspnea, high respiratory rate, confusion, low blood pressure or multilobar infiltrates is consistent with the classical prognostic factors encountered in hospitalized patients with CA pneumonia [19]. Serum creatinine >160 μmol/L, and CRP >500 mg/L were significantly linked with mortality, whereas hyponatremia was not retained by multivariate analysis. Elevated CRP values have been associated with mortality in patients with community-acquired pneumonia (CAP) [20] or pneumococcal pneumonia [21].

PSI classes IV-V, ICU admission and the need for mechanical ventilation were coupled with mortality, consistent with findings in a prospective study of 84 LD patients requiring ICU admission, where variables linked with poor outcome by univariate analysis included cardiac disease, diabetes mellitus, serum creatinine ≥1.8 mg/dL, septic shock, radiographic pulmonary infiltrate extension, mechanical ventilation, hyponatremia <136 mEq/L, partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FIO_2) ratio <130, and blood urea levels ≥30 mg/dL. Acute physiology and chronic health evaluation II score >15 at admission and serum sodium levels ≤136 were the only independent factors related to death [22].

Recently, several authors have compared different CAP severity of illness (SOI) scores, such as PSI, CURB, CRB65, and observed that higher risk patients were better identified with CURB and CRB65 scores, whereas PSI better distinguished lower risk patients [23, 24]. Unfortunately, our study was not designed to compare SOI scores, and because some variables included in these scores were not collected, any retrospective calculation or comparison is impossible.

We found that symptomatic patients with body temperature >38.5°C, chills, myalgia, nausea, and headache had a better survival rate, which indicated that earlier diagnosis is facilitated by a typical clinical picture of infection and leads to better pt management. It also emphasizes the need to suspect LD in cases with an incomplete or non-typical clinical picture.

Surprisingly, outcome was poorer in females than in males. The impact of gender on mortality from infections is controversial. In an observational cohort study conducted in surgical units, mortality was significantly greater in females with lung infection [25]. Female gender independently predicted mortality in multivariate analysis of a large cohort of mechanically-ventilated patients [26]. In another large cohort of patients with severe healthcare-associated infection and hospitalized in ICUs, mortality was significantly higher among females [27]. Inversely, male gender was predictive of mortality within 90 days of hospitalization for pneumonia [28]. Finally, gender-related outcome in infectious disease studies produced inconsistent results, depending on the type of infection and the target population. However, some data converged towards increased fatality in females with pulmonary infections. Further specific investigations are needed to clarify this observation.

A short time period to appropriate antibiotic treatment is usually indicated to improve the outcome in LD patients. This has been described previously in LD patients admitted to ICUs. Administration of quinolone or erythromycin within 8 hours of arrival in the ICU has been associated with better survival [16]. Mortality may increase from 10% to 27% in patients who do not receive adequate antibiotic treatment as part of empirical therapy on admission [29]. Surprisingly, in our study, median time to appropriate treatment after the onset of clinical signs of LD was shorter (but non-statistically significant) for non-survivors.

Our investigation has some limitations. Patients were selected on the basis of positive *Lp*1 testing which could have introduced a bias as we have no information on other serogroups, and because of limited sensitivity of the test, as discussed previously.

The number of deaths in the cohort was rather low, so we could only identify the most relevant risk factors. Selection bias may have prevailed because: (i) less severe cases of LD not requiring hospital care were not included, and (ii) even if the study was not designed to monitor the quality of clinical practices, physicians may have been less likely to report fatal

cases in such a study. Moreover, the survival rate did not take into account patients who may have died after the 30-day follow-up period. Pt survival was not calculated from the date of onset, but rather from the date of diagnosis. The date of onset is often difficult to obtain because of memory bias towards more severe initial symptoms. In addition, this information may be difficult to collect in patients admitted to the ICU. However, we performed multivariate analysis, including the time interval between onset and diagnosis, and found that it was not linked with survival (P=0.975), indicating that such a bias, if present, was very limited. Finally, some confounding variables may have been missed. Our analysis aimed to test a large number of variables and, consequently, increased the chances of a wrong conclusion. A lack of power could also be acknowledged for some factors, such as genotypes, obtained in a subsample of the cohort. Additional analyses are still required to better document the impact of genotype on case severity, and the time to initiation of appropriate therapy must be further explored.

In conclusion, age, female gender, ICU stay, renal failure, corticosteroid treatment, and increased CRP level were significantly associated with mortality in hospitalized CA LD patients. Less symptomatic patients had a poorer outcome. LD remains a significant cause of pneumonia, and the associated mortality can be high in weakened persons. The identification of high-risk groups in terms of mortality could increase practitioner awareness and contribute to its reduction. Specific, prospective LD studies, comparing different SOI scores, should be performed in this field.

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Table 1. Admission characteristics of survivors and non-survivors among patients hospitalized in France with Legionnaires' disease due to *L. pneumophila* serogroup 1

Characteristics	Survivors (n = 496)	Non-survivors (n = 44)	*P* value	All cases (n = 540)
Gender				
Female	126 (25.4)	19 (43.2)	.02	145 (26.9)
Male	370 (74.6)	25 (56.8)		395 (73.1)
Age, y	59 [17-95]	76 [28-100]	<.001	60 [17-100]
Weight, kg	76 [40-136]	72 [45-150]	.17	76 [40-150]
Height, cm	172 [146-197]	165 [150-185]	.008	171 [146-197]
Body mass index *	26 [16-47]	26 [18-59]	.70	26 [16-59]
Median time between hospitalization and onset of illness, days	4 [0-33]	3 [0-14]	.10	4 [0-33]
Pneumonia severity index				
Classes II-III	170 (34.3)	4 (9.1)		174 (32.2)
Classes IV-V	173 (34.9)	29 (65.9)	<.001	202 (37.4)
Risk factors †				
Smoking	277 (55.8)	12 (27.3)	<.001	289 (53.5)
Alcohol intake #	94 (19.0)	7 (15.9)	.84	101 (18.7)
Diabetes	77 (15.5)	8 (18.2)	.67	85 (15.7)
Cancer/malignancy	29 (5.8)	5 (11.4)	.18	34 (6.3)
Corticoid therapy	25 (5.0)	6 (13.6)	.03	31 (5.7)
Other immunosuppressive	14 (2.8)	4 (9.1)	.05	18 (3.3)

medication				
At least 1 risk factor	371 (74.8)	30 (68.2)	.37	401 (74.3)

Data are expressed as number (%) or as median [minimum-maximum].

* Calculated as weight in kg divided by height in m^2.

† Not mutually exclusive.

Alcohol intake: 30 or 20 grams of alcohol daily for men and women respectively for at least 1 year.

Table 2. Clinical, biological and radiographic characteristics at admission of survivors and non-survivors among patients hospitalized in France with Legionnaires' disease due to *L. pneumophila* serogroup 1

Feature *	Survivors (n = 496)	Non-survivors (n = 44)	*P* value	All cases (n = 540)
Clinical				
Temperature >38.5°C	435 (87.7)	30 (68.2)	.001	465 (86.1)
Chills	335 (67.5)	20 (45.5)	.004	355 (65.7)
Dyspnea	343 (69.2)	40 (90.9)	.002	383 (70.9)
Respiratory rate/min	25 [10-84]	28 [14-60]	.03	26 [10-84]
Heart rate/min	100 [38-183]	110 [50-180]	.02	100 [38-183]
Systolic blood pressure, mmHg	130 [70-220]	120 [60-170]	<.001	128 [60-220]
Diastolic blood pressure, mmHg	70 [30-123]	64 [30-120]	.01	70 [30-123]
Nausea	112 (22.6)	4 (9.1)	.04	116 (21.5)
Confusion	146 (29.4)	21 (47.7)	.02	167 (30.9)
Headache	136 (27.4)	2 (4.5)	<.001	138 (25.6)
Biological				
Neutrophils, G/L	9.62 [1.22-36.00]	11.70 [3.14-31.20]	.009	9.81 [1.22-36.00]
Lymphocytes, G/L	0.81 [0.02-88.80]	0.57 [0.16-2.21]	.001	0.80 [0.02-88.80]
Serum creatinine >160 µmol/L †	59 (11.9)	17 (38.6)	<.001	76 (14.1)
CRP >500 mg/L	38 (7.7)	10 (22.7)	.003	48 (8.9)
Radiological				
Unilobar infiltrate	254 (51.2)	11 (25.0)	.001	265 (49.1)
Multilobar or bilateral infiltrate	191 (38.5)	29 (65.9)	.001	220 (40.7)

***** Only features that are statistically different ($P<0.05$) between the 2 groups are reported. Data are given as median [minimum-maximum] or as number (%).

† Two times the normal value.

Non significant (NS): anorexia ($P=1$), myalgia ($P=0.13$), cough ($P=0.18$), sputum ($P=0.18$), haemoptysis ($P=0.35$), thoracic pain ($P=0.85$), pleural pain ($P=1$), diarrhea ($P=0.56$), abdominal pain ($P=0.28$), natremia <130 mmol/L ($P=0.73$), CPK >250 U/L ($P=0.72$), AST >180 IU/L ($P=0.24$), ALT >180 IU/L ($P=0.17$), PaO_2 <60 mmHg ($P=0.73$).

Abbreviations: CRP, C-reactive protein; CPK, creatine phosphokinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PaO_2, partial pressure of arterial oxygen.

Table 3. Treatment and evolution of survivors and non-survivors among patients hospitalized in France with Legionnaires' disease due to *L. pneumophila* serogroup 1

Variable	Survivors (n = 496)	Non-survivors (n = 44)	*P* value	All cases (n = 540)
Treatment				
Appropriate empirical antibiotic treatment at admission	265/375 (70.7)	27/37 (72.9)	0.851	292/412 (76.3)
Appropriate antibiotic treatment for documented LD	495/496 (99.8)	42/42 (100)	1	537/538 (99.6)
Time to appropriate treatment, median [min-max], days	4.0 [0-33]	3.0 [0-17]	.104	4.0 [0-33]
Length of hospital stay, median (min-max), days				
From date of hospitalization	10 (1-92)	6 (1-28)	<0.001	9 (1-92)
From date of diagnosis	8 (0-90)	4 (0-25)	<0.001	8 (0-90)
Intensive care unit (ICU) care				
ICU admission	118 (23.8)	30 (68.2)	<.001	148 (27.4)
Need for mechanical ventilation	47 (9.5)	28 (63.6)	<.001	75 (13.9)
In-hospital complications	171 (34.5)	34 (77.3)	<.001	205 (38.0)
Respiratory infection	28 (5.6)	11 (25.0)	<.001	39 (7.2)
Renal failure	48 (9.7)	22 (50.0)	<.001	70 (13.0)
Hepatic failure	91 (18.3)	14 (31.8)	.045	105 (19.4)
Decompensation of pre-existing illness	36 (7.3)	12 (27.3)	<.001	48 (8.9)

Table 4. Probability of survival in patients during the first 30 days after the diagnosis of Legionnaires' Disease

Variable		Time since diagnosis			
		2 days	**10 days**	**30 days**	***P* value***
Total population		0.99	0.94	0.81	
Number of patients remaining at risk		535	259	41	
Gender	**Male**	1.00	0.96	0.86	.01
	Female	0.98	0.89	0.68	
Age	**≥60 years**	0.99	0.92	0.78	.02
	<60 years	1.00	0.96	0.85	
Digestive symptoms *	**yes**	1.00	0.96	0.92	.05
	no	0.99	0.93	0.76	
General symptoms †	**yes**	1.00	0.95	0.81	.006
	no	0.94	0.77	0.70	
Respiratory symptoms #	**yes**	0.99	0.93	0.79	.12
	no	1. 00	0.98	0.98	
Neurological symptoms ¶	**yes**	1.00	0.94	0.85	.47
	no	0.99	0.94	0.76	
Intensive care unit admission	**yes**	0.99	0.85	0.75	<.001
	no	1.00	0.98	0.78	
Pneumonia severity index	**Classes II-III**	1. 00	0.98	0.98	.004
	Classes IV-V	0.99	0.90	0.78	

* Digestive symptoms: abdominal pain, diarrhea, nausea, vomiting

† General symptoms: temperature >38.5°C, chills, myalgia, loss of weight, anorexia

Respiratory symptoms: dyspnea, cough, sputum, thoracic and pleural pain, hemoptysis

¶ Neurological symptoms: headache, confusion

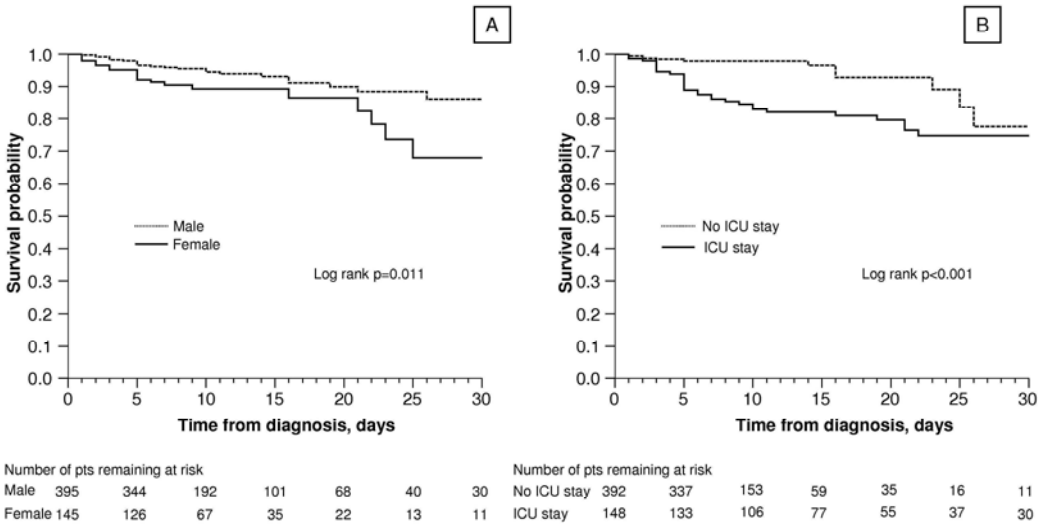
Table 5. Independent factors associated with mortality. Multivariate analysis

Variable *	Relative hazard (95% confidence interval)	*P* value
Age (per 10-year increments) †	1.50 [1.21-1.87]	<.001
Female gender	2.00 [1.08-3.69]	.03
Intensive care unit admission	3.31 [1.67-6.56]	.001
Renal failure	2.73 [1.42-5.27]	.003
Corticosteroid therapy	2.54 [1.04-6.20]	.04
CRP >500 mg/L	2.14 [1.02-4.48]	.04

***** Variables significant on univariate analysis.

† Age was included in the model as a continuous variable on a 10-year scale.

Figure 1


A
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
Time from diagnosis, days
Male
Female
Log rank p=0.011
Number of pts remaining at risk
Male 395 344 192 101 68 40 30
Female 145 126 67 35 22 13 11
B
Survival probability
Time from diagnosis, days
No ICU stay
ICU stay
Log rank p<0.001
Number of pts remaining at risk
No ICU stay 392 337 153 59 35 16 11
ICU stay 148 133 106 77 55 37 30