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Factors associated with hospital mortality in community-acquired legionellosis in France

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ABSTRACT: The aims of this study were to describe the clinical, biological and radiological features of community-acquired (CA) Legionnaires' disease (LD) and identify the predictors of mortality in hospitalised patients.

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

8.1% of patients (44 out of 540) died. The predictors of survival after Kaplan–Meier analysis were male sex (p=0.01), age <60 yrs (p=0.02), general symptoms (p=0.006), intensive care unit (ICU) stay (p<0.001), and class II–III Pneumonia Severity Index score (p=0.004). Six predictors of death were identified by multivariate analysis: age (per 10-yr increment) (relative hazard (RH) 1.50, 95% CI 1.21–1.87), female sex (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^{-1} (RH 2.14, 95% CI 1.02–4.48). Appropriate antibiotic therapy was prescribed for 70.8% (292 out of 412) of patients after admission and for 99.8% (537 out of 538) of patients after diagnosis confirmation.

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

KEYWORDS: Community-acquired pneumonia, *Legionella pneumophila*, mortality, outcomes, risk factors

Legionnaires' disease (LD), first described in 1977 [1], is caused by a Gram-negative bacillus of the genus *Legionella*. *Legionella pneumophila* serogroup 1 (*Lp*1), observed most frequently in human disease, accounts for ~90% of cases. It is responsible for sporadic and epidemic, community-acquired (CA) and 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, hyponatraemia and renal failure. Risk factors for LD include smoking, male sex, chronic heart or lung disease, diabetes, end-stage renal failure, organ transplantation, immunosuppression, cancer, and age >50 yrs [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, multicentre cohort study were 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 (Institut de Veille Sanitaire (InVS), Saint Maurice, France). The number of reported

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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: 1) *Lp*1 isolation from clinical samples (sputum, bronchoalveolar lavage fluid or bronchial aspirate); or 2) the presence of soluble antigens in urine (*Lp*1-specific test). Patients with four-fold increment of *Lp*1 antibody titres were not included.

Definite or possible HA LD cases were excluded (HA LD was defined as LD in patients hospitalised for the entire period beginning 10 days and ending 2 days before the onset of symptoms; patients hospitalised 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 one intracellular drug, macrolide or fluoroquinolone) 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, hospitalised patients in metropolitan France with confirmed CA LD due to *Lp*1 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 enrol cases after obtaining 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 hospitalisation and at 30-day follow-up. The variables collected were: 1) demographic data (birth date and sex); 2) risk factors for LD (smoking habit, alcohol intake, diabetes mellitus, cancer, immunosuppression or corticosteroid therapy); 3) clinical features at onset and at hospitalisation, including respiratory rate, diastolic and systolic arterial blood pressure, heart rate, arterial oxygen tension (P_{a,O_2}), temperature (>38.5°C), general symptoms (chills, anorexia or myalgia), respiratory symptoms (dyspnoea, cough, expectoration, haemoptysis, or thoracic or pleural pain), gastrointestinal symptoms (nausea, diarrhoea or abdominal pain), neurological symptoms (confusion or headache); 4) radiological findings on admission; 5) laboratory data (serum creatinine, creatine phosphokinase, aspartate aminotransferase, alanine aminotransferase, C-reactive protein (CRP) and white cell count); 6) criteria of severity, such as the Pneumonia Severity Index (PSI) [11] at admission, ICU admission and mechanical ventilation; 7) time to administration of appropriate antibiotic treatment; and 8) incidence of complications (renal or hepatic failure) and outcome (death or recovery/discharge).

Microbiology testing

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

Statistical analysis

Continuous variables are presented as median (range). Categorical variables are 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 two subgroups were compared by Fisher's exact test for categorical variables or with the nonparametric Mann–Whitney U-test for continuous variables. Patient survival was calculated from the date of diagnosis until in-hospital death, 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 with a 95% confidence interval. Proportional risk assumptions were checked. The final Cox model was assessed for potential interactions and for adequacy with hypotheses of proportional risks.

Variables with $p \leqslant 0.15$ were entered in the initial multivariate model. Backward stepwise selection was made with the Wald test to compare models. A p-value <0.05 (two-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 hospitalised for CA LD (33.9%) were enrolled in this study; 395 were male and 145 female, with a mean age of 60 yrs (range 17–100 yrs).

All cases were confirmed in hospitals where they were included, by positive urinary antigen detection of *Lp*1 by immunochromatographic test, mainly BinaxNOW® (Inverness Medical, Galway, Ireland). In addition, positive cultures and seroconversion were reported in 93 (17.2%) and 66 (12.2%) cases, respectively. The 93 clinical isolates were distributed among 36 genotypes (STs). About 50% of isolates were accounted for by only four 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 six (6.5%) isolates did not react to mAb 3/1 (four Olda isolates and two 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%). 74% of patients had at least one known risk

factor of LD, regardless of age. No known risk factor was identified in the 139 (27.7%) remaining patients.

44 cases died during hospitalisation, corresponding to an overall CFR of 8.1% (44 out of 540). Four patients died within 24 h of diagnosis. Compared to LD cases reported to the InVS but not entered in this study, those included (n=540) did not differ statistically by sex, age or geographic distribution.

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

Death was attributed solely to LD in 17 (38.63%) out of 44 patients and to LD complications in 27 (61.36%) out of 44 patients. Reported complications included: cardiovascular complications (n=10), respiratory complications (n=8), malignancy (n=3), shock (n=3), multiorgan failure (n=2), neurological complications (n=2), renal complications (n=1) and bacteraemia (n=1); some patients may have suffered more than one complication.

Demographic, clinical, biological and radiographic characteristics were compared between surviving and nonsurviving patients; nonsurvivors 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 nonsurvivors (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 summarises the significant differences in clinical, biological and radiological characteristics in hospital survivors *versus* nonsurvivors.

Nonsurvivors were more often confused (p=0.02), and had dyspnoea (p=0.02), higher respiratory (p=0.03) and cardiac (p=0.02) frequencies, and lower median systolic (p<0.001) and diastolic (p=0.01) blood pressure. More frequently, they also had serum creatinine levels >160 μmol·L^{-1} (p<0.001), serum CRP >500 mg·L^{-1} (p=0.003) and higher neutrophil counts (p=0.009), but their lymphocyte levels 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 out of 174) of patients received appropriate empirical antibiotic treatment before hospital admission (most received β-lactams; data not shown), more than 70.8% (292 out of 412) and virtually all patients (99.8%, 537 out of 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 nonsurvivors (3.0 *versus* 4.0 days; p=0.1), but the difference was not significant.

TABLE 1 Admission characteristics of survivors and nonsurvivors among patients hospitalised in France with Legionnaires' disease due to *Legionella pneumophila* serogroup 1

Characteristics	Survivors[#]	Nonsurvivors[¶]	p-value	All cases[+]
Sex				
Female	126 (25.4)	19 (43.2)	0.02	145 (26.9)
Male	370 (74.6)	25 (56.8)		395 (73.1)
Age yrs	59 (17–95)	76 (28–100)	<0.001	60 (17–100)
Weight kg	76 (40–136)	72 (45–150)	0.17	76 (40–150)
Height cm	172 (146–197)	165 (150–185)	0.008	171 (146–197)
Body mass index kg·m^{-2}	26 (16–47)	26 (18–59)	0.70	26 (16–59)
Time between hospitalisation and onset of illness days	4 (0–33)	3 (0–14)	0.10	4 (0–33)
PSI class				
II–III	170 (34.3)	4 (9.1)		174 (32.2)
IV–V	173 (34.9)	29 (65.9)	<0.001	202 (37.4)
Risk factors[§]				
Smoking	277 (55.8)	12 (27.3)	<0.001	289 (53.5)
Alcohol intake[f]	94 (19.0)	7 (15.9)	0.84	101 (18.7)
Diabetes	77 (15.5)	8 (18.2)	0.67	85 (15.7)
Cancer/malignancy	29 (5.8)	5 (11.4)	0.18	34 (6.3)
Corticosteroid therapy	25 (5.0)	6 (13.6)	0.03	31 (5.7)
Other immunosuppressive medication	14 (2.8)	4 (9.1)	0.05	18 (3.3)
⩾1 risk factor	371 (74.8)	30 (68.2)	0.37	401 (74.3)

Data are expressed as n (%) or median (range), unless otherwise stated. PSI: Pneumonia Severity Index. [#]: n=496; [¶]: n=44; [+]: n=540; [§]: not mutually exclusive; [f]: 30 or 20 g alcohol daily for males and females, respectively, for ⩾1 yr.

TABLE 2 Clinical, biological and radiographic characteristics at admission of survivors and nonsurvivors among patients hospitalised in France with Legionnaires' disease due to *Legionella pneumophila* serogroup 1

Feature[#]	Survivors[¶]	Non-survivors[+]	p-value	All cases[§]
Clinical				
Temperature >38.5°C	435 (87.7)	30 (68.2)	0.001	465 (86.1)
Chills	335 (67.5)	20 (45.5)	0.004	355 (65.7)
Dyspnoea	343 (69.2)	40 (90.9)	0.002	383 (70.9)
*f*R breaths·min^{-1}	25 (10–84)	28 (14–60)	0.03	26 (10–84)
*f*C beats·min^{-1}	100 (38–183)	110 (50–180)	0.02	100 (38–183)
Blood pressure mmHg				
Systolic	130 (70–220)	120 (60–170)	<0.001	128 (60–220)
Diastolic	70 (30–123)	64 (30–120)	0.01	70 (30–123)
Nausea	112 (22.6)	4 (9.1)	0.04	116 (21.5)
Confusion	146 (29.4)	21 (47.7)	0.02	167 (30.9)
Headache	136 (27.4)	2 (4.5)	<0.001	138 (25.6)
Biological				
Neutrophils $\times 10^9$ cells·L^{-1}	9.62 (1.22–36.00)	11.70 (3.14–31.20)	0.009	9.81 (1.22–36.00)
Lymphocytes $\times 10^9$ cells·L^{-1}	0.81 (0.02–88.80)	0.57 (0.16–2.21)	0.001	0.80 (0.02–88.80)
Serum creatinine >160 μmol·L^{-1}[ƒ]	59 (11.9)	17 (38.6)	<0.001	76 (14.1)
CRP >500 mg·L^{-1}	38 (7.7)	10 (22.7)	0.003	48 (8.9)
Radiological				
Unilobar infiltrate	254 (51.2)	11 (25.0)	0.001	265 (49.1)
Multilobar or bilateral infiltrate	191 (38.5)	29 (65.9)	0.001	220 (40.7)

Data are presented as n (%) or median (range), unless otherwise stated. *f*R: respiratory frequency; *f*C: cardiac frequency; CRP: C-reactive protein. [#]: only features that were statistically different ($p<0.05$) between the two groups are reported (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 ($p=1$), diarrhoea ($p=0.56$), abdominal pain ($p=0.28$), serum sodium <130 mmol·L^{-1} ($p=0.73$), creatine phosphokinase >250 U·L^{-1} ($p=0.72$), aspartate aminotransferase >180 IU·L^{-1} ($p=0.24$), alanine aminotransferase >180 IU·L^{-1} ($p=0.17$), arterial oxygen tension <60 mmHg ($p=0.73$) were nonsignificant); [¶]: n=496; [+]: n=44; [§]: n=540; [ƒ]: twice the normal value.

ICU admission, the need for mechanical ventilation and in-hospital complications (respiratory superinfection, renal and hepatic failure, and decompensation of pre-existing illness) were more likely to occur in nonsurvivors (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).

TABLE 3 Treatment and evolution of survivors and nonsurvivors among patients hospitalised in France with Legionnaires' disease (LD) due to *Legionella pneumophila* serogroup 1

Variable	Survivors[#]	Nonsurvivors[¶]	p-value	All cases[+]
Treatment				
Appropriate empirical antibiotic treatment				
At admission	265/375 (70.7)	27/37 (72.9)	0.851	292/412 (70.8)
For documented LD	495/496 (99.8)	42/42 (100)	1	537/538 (99.8)
Time to appropriate treatment days	4.0 (0–33)	3.0 (0–17)	0.104	4.0 (0–33)
Length of hospital stay days				
From date of hospitalisation	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)
ICU care				
ICU admission	118 (23.8)	30 (68.2)	<0.001	148 (27.4)
Need for mechanical ventilation	47 (9.5)	28 (63.6)	<0.001	75 (13.9)
In-hospital complications	171 (34.5)	34 (77.3)	<0.001	205 (38.0)
Respiratory infection	28 (5.6)	11 (25.0)	<0.001	39 (7.2)
Renal failure	48 (9.7)	22 (50.0)	<0.001	70 (13.0)
Hepatic failure	91 (18.3)	14 (31.8)	0.045	105 (19.4)
Decompensation of pre-existing illness	36 (7.3)	12 (27.3)	<0.001	48 (8.9)

Data are presented as n/N (%), n (%) or median (range), unless otherwise stated. ICU: intensive care unit. [#]: n=496; [¶]: n=44; [+]: n=540.

The log-rank test indicated that the probability of patient survival during the first 30 days after LD diagnosis was associated with male sex (p=0.01), age <60 yrs (p=0.02), and the presence of general (p=0.006) and digestive (p=0.05) symptoms, whereas ICU admission (p<0.001) and PSI class IV–V (p=0.004) were significantly associated with a lower probability of survival (table 4 and fig. 1).

Independent factors linked with mortality in multivariate analysis (table 5) were age (per 10-yr increment; p<0.001), female sex (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 and 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 case 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 serological 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 mAb 3/1-negative *Lp*1 were significantly less frequently diagnosed by commercially available assays [14].

TABLE 4 Probability of survival in patients during the first 30 days after the diagnosis of Legionnaires' disease

Variable	Time from diagnosis days			p-value
	2	10	30	
Total population	0.99	0.94	0.81	
Patients remaining at risk n	535	259	41	
Sex				
Male	1.00	0.96	0.86	0.01
Female	0.98	0.89	0.68	
Age yrs				
⩾60	0.99	0.92	0.78	0.02
<60	1.00	0.96	0.85	
Digestive symptoms#				
Yes	1.00	0.96	0.92	0.05
No	0.99	0.93	0.76	
General symptoms¶				
Yes	1.00	0.95	0.81	0.006
No	0.94	0.77	0.70	
Respiratory symptoms+				
Yes	0.99	0.93	0.79	0.12
No	1.00	0.98	0.98	
Neurological symptoms§				
Yes	1.00	0.94	0.85	0.47
No	0.99	0.94	0.76	
ICU admission				
Yes	0.99	0.85	0.75	<0.001
No	1.00	0.98	0.78	
PSI class				
II–III	1. 00	0.98	0.98	0.004
IV–V	0.99	0.90	0.78	

Data are presented as survival probabilities, unless otherwise stated. ICU: intensive care unit; PSI: Pneumonia Severity Index. #: abdominal pain, diarrhoea, nausea and vomiting; ¶: temperature >38.5°C, chills, myalgia, loss of weight and anorexia; +: dyspnoea, cough, sputum, thoracic and pleural pain, and haemoptysis; §: headache and confusion.

Our sizeable patient population, enrolled over a limited time period, is representative of a larger group of 1,595 patients reported nationwide during the same period, providing an accurate description of CA LD in patients hospitalised 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 dyspnoea, high respiratory frequency, confusion, low blood pressure or multilobar infiltrates is consistent with the classical prognostic factors encountered in hospitalised patients with CA pneumonia (CAP) [19]. Serum creatinine >160 μmol·L^{-1} and CRP >500 mg·L^{-1} were significantly linked with mortality, whereas hyponatraemia was not retained by multivariate analysis. Elevated CRP values have been associated with mortality in patients with CAP [20] or pneumococcal pneumonia [21].

PSI class 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^{-1}, septic shock, radiographic pulmonary infiltrate extension, mechanical ventilation, hyponatraemia (serum sodium <136 mEq·L^{-1}), P_{a,O_2}/inspiratory oxygen fraction ratio <130 and blood urea levels ⩾30 mg·dL^{-1}. Acute Physiology and Chronic Health Evaluation II score >15 at admission and serum sodium levels ⩽136 mEq·L^{-1} 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-65 (confusion, urea >7 mmol·L^{-1}, respiratory frequency ⩾30 breaths·min^{-1}, systolic

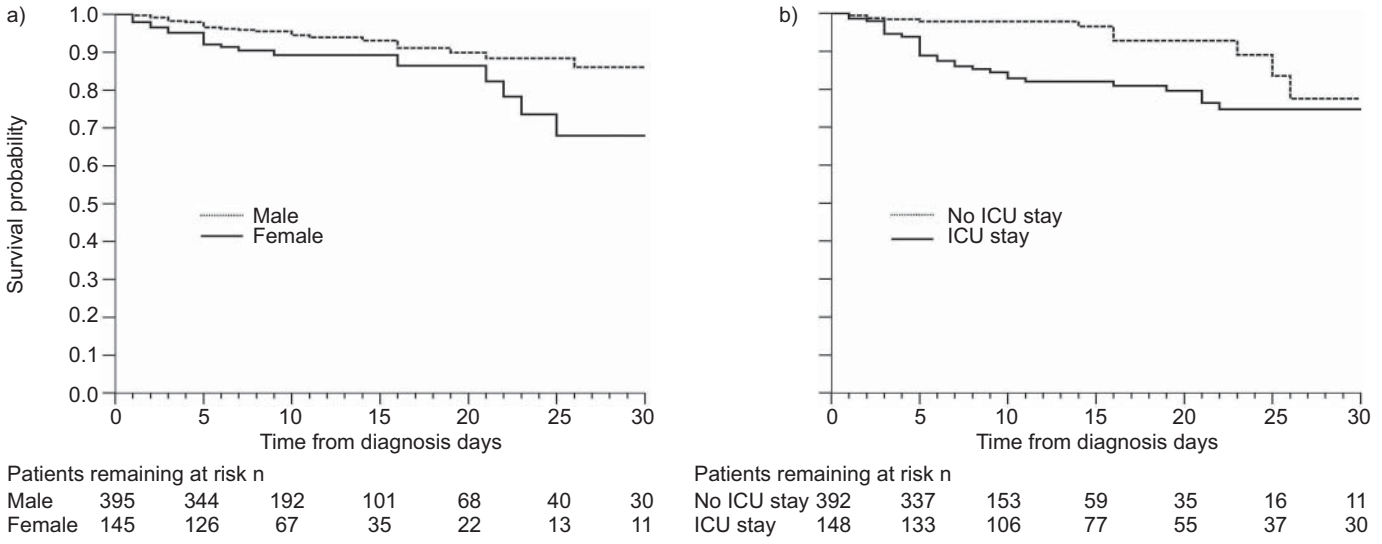

FIGURE 1. Kaplan–Meier survival curves in patients with Legionnaires' disease (LD) hospitalised in France (from April 1, 2006 to June 30, 2007). Survival was calculated from the time at which diagnosis of LD was confirmed until 30 days of hospitalisation. Survival according to a) sex (log-rank p=0.011) and b) intensive care unit (ICU) stay (log-rank p<0.001) is shown.

blood pressure <90 mmHg or diastolic blood pressure ⩽60 mmHg, and age ⩾65 yrs), CRB-65 (confusion, respiratory frequency ⩾30 breaths·min^{-1}, systolic blood pressure <90 mmHg or diastolic blood pressure ⩽60 mmHg, and age ⩾65 yrs), and observed that higher risk patients were better identified with CURB-65 and CRB-65 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 patient management. It also emphasises the need to suspect LD in cases with an incomplete or atypical clinical picture.

Surprisingly, outcome was poorer in females than in males. The impact of sex on mortality from infections is controversial.

TABLE 5 Independent factors associated with mortality[#]

Variable[¶]	RH (95% CI)	p-value
Age, per 10-yr increments[+]	1.50 (1.21–1.87)	<0.001
Female sex	2.00 (1.08–3.69)	0.03
ICU admission	3.31 (1.67–6.56)	0.001
Renal failure	2.73 (1.42–5.27)	0.003
Corticosteroid therapy	2.54 (1.04–6.20)	0.04
CRP >500 mg·L^{-1}	2.14 (1.02–4.48)	0.04

RH: relative hazard; ICU: intensive care unit; CRP: C-reactive protein. [#]: multivariate analysis; [¶]: variables significant on univariate analysis; [+]: age was included in the model as a continuous variable on a 10-yr scale.

In an observational cohort study conducted in surgical units, mortality was significantly greater in females with lung infection [25]. Female sex 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 who were hospitalised in ICUs, mortality was significantly higher among females [27]. Inversely, male sex was predictive of mortality within 90 days of hospitalisation for pneumonia [28]. Finally, sex-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 h 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 not statistically significant) for nonsurvivors.

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: 1) less severe cases of LD not requiring hospital care were not included; and 2) 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. Patient 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 sex, ICU stay, renal failure, corticosteroid treatment and increased CRP level were significantly associated with mortality in hospitalised 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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STATEMENT OF INTEREST

None declared.

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