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EDITORIAL

Leptospirosis: one of the forgotten diseases

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"On a strange, acute infectious disease, accompanied by swelling of the spleen, icterus, and nephritis" Adolf Weil (1886)

Leptospirosis is a zoonosis with a worldwide distribution affecting in particular countries with tropical and subtropical climates. Even before the first description of leptospirosis by Adolf Weil in 1886, the disease was well known in different parts of the world frequently with names, some of which associated with agriculture or industrial activities [1]. Leptospira, a corkscrew shaped bacterium, was first identified in 1907, but it was only in 1915 that this bacteria was recognized as the cause of this disease by Inada and Ido in Japan [2].

Leptospires are Gram-negative aerobic bacteria from the order Spirochaetales and the family Leptospiraceae, comprising 26 serogroups and more than 260 serovars [3]. Although several mammals have been identified as potential reservoirs, the rats are the most significant one. The pathogenesis of the disease is poorly understood [4], but to develop leptospirosis the bacteria has to reach the host after contact or drinking contaminated water through small abrasions in the skin or the mucosa of the conjunctiva, oro and nasopharynx. Subsequently, it multiplies and grows spreading to virtually all organs causing a systemic infection. The disease is more frequent in tropical countries (10–100 per 100,000 inhabitants) compared to non-tropical areas (0.1–1 per 100,000 inhabitants). However, it is present in all continents with the exception of Antarctica [5, 6]. In Europe the number of reported cases was 1222 in 2015, that represents an increase in relation to the average reported cases in the 5 years before [7]. However, climate change and global warming could alter this scenario in Europe with more favorable conditions of transmission. In addition, it is clear that leptospirosis is re-emerging in some countries [4].

Leptospirosis could present itself as a very severe disease, with multiple organ dysfunction with unusual clinical phenotypes (e.g. pulmonary failure with alveolar hemorrhage or marked jaundice without liver failure). Since in non-tropical areas it is an uncommon reason of hospital admission, clinicians often miss this diagnosis. Therefore, incidence in non-endemic areas is unknown and, more clinically relevant, misdiagnosis might occur. In this issue, Miailhe et al. [8] report the largest cohort of severe leptospirosis cases requiring intensive care unit (ICU) admission in a French multicenter cohort. During a 4-year period (2012–2016), 160 patients were retrospectively identified (0.04% of all ICU admissions). Overall hospital mortality was surprisingly low (9%) if one considers the severity-of-illness score (median SAPS II of 40) and the high prevalence of organ failures (SOFA of 11, more than half on vasoactive drugs, and at least one-third on invasive mechanical ventilation or renal replacement therapy). Multiple correspondence analysis and hierarchical classification on principal components identified four clinical phenotypes, with different prevalence and clinical presentations, and more relevant, contrasting demand for organ support therapies and mortality rates. Their phenotyping is mostly welcomed because it is based on clinical characteristics readily available and highlights the heterogeneity of this disease, and might help clinicians to raise clinical suspicious and pursuit proper microbiological diagnosis as well as initiate adequate antibiotic treatment empirically.

However, we believe that one of the major strengths of this study is that it portends a relevant observation in critical care medicine: the same disease might have strikingly different mortality rates throughout the world. The authors mentioned this briefly in the

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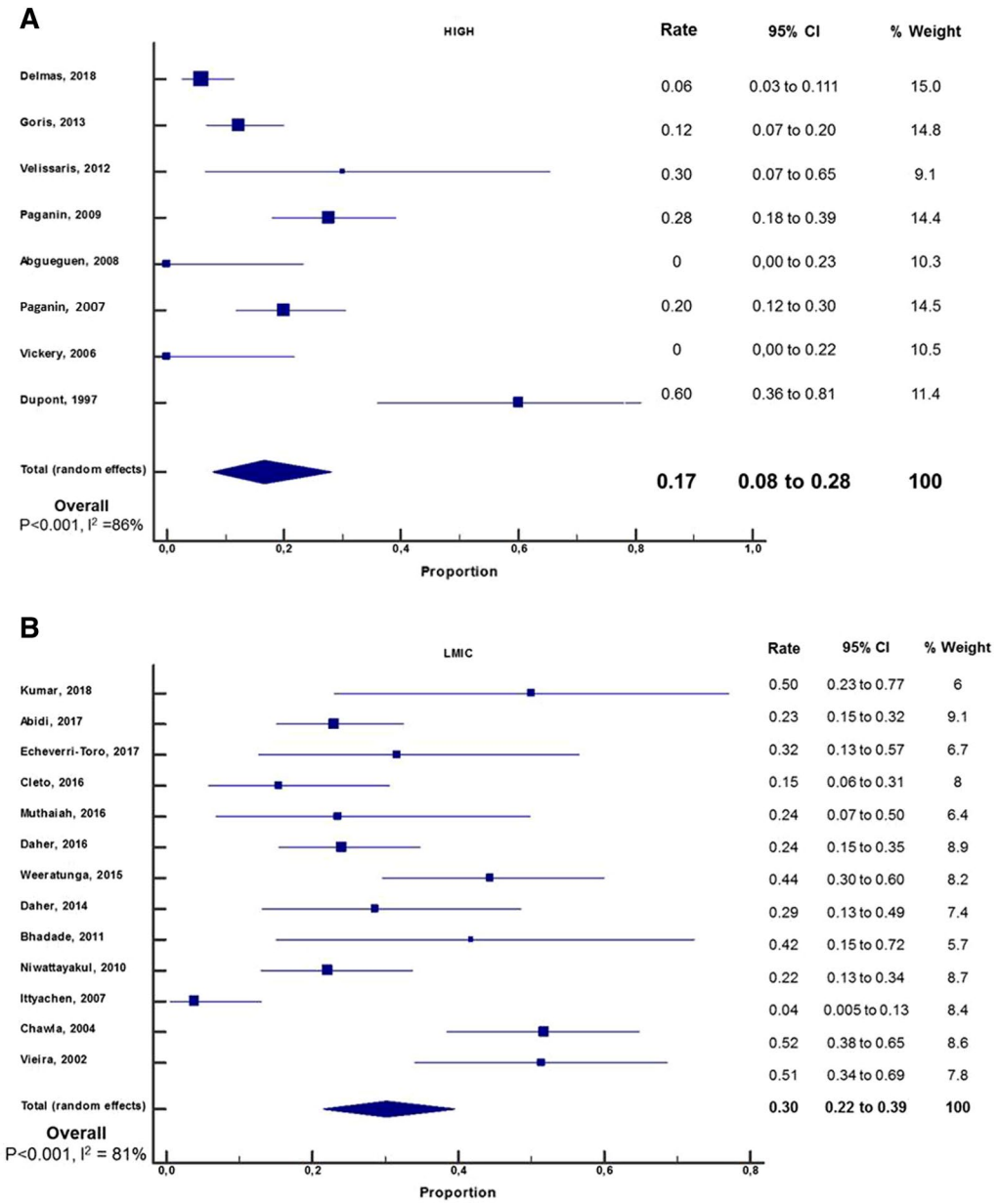

Fig. 1 Forest plots showing **a** pooled mortality rate of studies from high-income countries (HIC) and **b** pooled mortality rate of studies from low-middle-income countries (LMIC)

discussion, but the tropical vs non-tropical labels do not explain the issue entirely. This geographical view hinders another relevant classification: high income (HIC) *vs* low-middle income countries (LMIC). A search in Pubmed found 21 previous publications about cases of leptospirosis in ICU (reports with at least ten patients with leptospirosis, see Supplementary Appendix for details). The pooled mortality rate was 25% (95% CI 18–33%), but higher for LMICs (30%, with 95% CI of 22–39%) compared to HIC (17%, with 95% CI of 8–28%, Fig. 1). With the present study, this discrepancy in mortality rates even increases. Although distinct serovars might explain some of these differences, certainly climate and geographic location might not. A recent publication from Reunion Island (a French department located in the Indian Ocean, a tropical area) reports in 134 ICU patients a mortality rate of 6% [9]. Healthcare resources are not different between Reunion Island and continental mainland, but probably different compared to LMICs.

Since severe leptospirosis is a cause of sepsis (i.e. infection with organ dysfunction), lower availability of treatment resources are detrimental and unfortunately common in LMICs [10, 11]. The present study from Miailhe et al. reinforce that leptospirosis, albeit uncommon in some parts of the world, can have good outcomes if properly treated, but much worse outcomes in other areas with treatment resource limitations.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05839-z) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflict of interest.

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ORIGINAL

Severe leptospirosis in non-tropical areas: a nationwide, multicentre, retrospective study in French ICUs

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Abstract

Purpose: To report the incidence, risk factors, clinical presentation, and outcome predictors of severe leptospirosis requiring intensive care unit (ICU) admission in a temperate zone.

Methods: LEPTOREA was a retrospective multicentre study conducted in 79 ICUs in metropolitan France. Consecutive adults admitted to the ICU for proven severe leptospirosis from January 2012 to September 2016 were included. Multiple correspondence analysis (MCA) and hierarchical classification on principal components (HCPC) were performed to distinguish different clinical phenotypes.

Results: The 160 included patients (0.04% of all ICU admissions) had median values of 54 years [38–65] for age, 40 [28–58] for the SAPSII, and 11 [8–14] for the SOFA score. Hospital mortality was 9% and was associated with older age; worse SOFA score and early need for endotracheal ventilation and/or renal replacement therapy; chronic alcohol abuse and worse hepatic dysfunction; confusion; and higher leucocyte count. Four phenotypes were identified: moderately severe leptospirosis ($n = 34$, 21%) with less organ failure and better outcomes; hepato-renal leptospirosis ($n = 101$, 63%) with prominent liver and kidney dysfunction; neurological leptospirosis ($n = 8$, 5%) with the most severe organ failures and highest mortality; and respiratory leptospirosis ($n = 17$, 11%) with pulmonary haemorrhage. The main risk factors for leptospirosis contamination were contact with animals, contact with river or lake water, and specific occupations.

Conclusions: Severe leptospirosis was an uncommon reason for ICU admission in metropolitan France and carried a lower mortality rate than expected based on the high severity and organ-failure scores. The identification in our population of several clinical presentations may help clinicians establish an appropriate index of suspicion for severe leptospirosis.

Keywords: Severe leptospirosis, Intensive care unit, Mortality, Outcome, Temperate zone

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Introduction

Leptospirosis is a worldwide zoonosis with a high prevalence in tropical areas [1–4]. Although many patients experience few or no symptoms [5], severe disease with organ failure and bleeding requiring intensive care unit (ICU) admission has been reported in 6–59% of cases [6]. The epidemiology, clinical course, and outcomes of severe leptospirosis have been investigated in retrospective studies [7–15]. The number of deaths due to leptospirosis has been estimated at nearly 60,000 worldwide [1]. Despite advances in elucidating the pathogenesis of leptospirosis, the factors associated with severe forms of the disease remain unclear [16, 17].

An increase in the incidence of leptospirosis in temperate areas such as Europe has been reported in recent decades [3, 13, 18–20]. In metropolitan France, a five-fold increase in the incidence of leptospirosis has been documented in recent years, to a peak of 0.9 cases per 100,000 population in 2016 [21]. The reasons for the rise in leptospirosis cases in temperate zones are obscure but may include increased opportunities for contamination during recreational or professional activities and decreased preventive efforts [22]. Another possibility is growth of the *Leptospira* reservoir due to increasing numbers of rats and other mammals including dogs, as well as to the favourable effects on bacterial proliferation of climate warming and increased rainfall [20, 22]. Finally, the introduction of highly sensitive diagnostic tools may have increased the proportion of identified cases. The rising incidence of leptospirosis is creating a need for better knowledge of the disease, notably in its most severe forms, in temperate areas. Information is scarce on the incidence, risk factors, clinical presentation, and outcomes of severe leptospirosis requiring ICU admission.

The objective of this multicentre retrospective observational study was to describe the incidence, risk factors of contamination with *Leptospira*, clinical phenotypes, treatments, and outcome predictors of severe leptospirosis in France.

Take-home message

Severe leptospirosis requiring ICU admission was less common and carried a lower hospital mortality rate (9%) in a large patient population in metropolitan France compared to previous reports from tropical regions. The identification of four clinical phenotypes (moderately severe, hepato-renal, neurological, and respiratory) may have diagnostic and prognostic value.

Patients and methods

The ethics committee of the French Intensive Care Society approved the study (#CE SRLF16-06) and waived the requirement for informed consent in compliance with French law on retrospective studies of anonymised data.

Study design

Of 95 ICUs in metropolitan France that were invited to participate in the LEPTOREA retrospective multicenter study (ClinicalTrials.gov Identifier: NCT03912506, recorded on April 11, 2019), 79 were accepted. Adults (≥ 18 years of age) admitted between January 2012 and September 2016 for documented leptospirosis were identified by searching the hospital databases for code A27 in the International Classification of Diseases-10th revision and then selecting those who required ICU admission for severe leptospirosis. Documented leptospirosis was defined as at least one positive laboratory test among the following: microscopic agglutination test (MAT), enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR) on urine or blood, and dark field microscopy. There were no exclusion criteria.

Data collection

Data collected on admission included age; gender; body mass index; chronic comorbidities (e.g., cancer, immune deficiency, diabetes mellitus, liver disease, heart failure, respiratory failure, chronic kidney disease); alcohol and tobacco use; risk factors for leptospirosis contamination (exposure to animals or to water at risk for contamination; high-risk outdoor activities such as fishing, gardening, hunting, trail running, canyoning, rafting, or river swimming; and recent travel to a high-risk area); the Simplified Acute Physiology Score (SAPS II) [23]; acute illness on ICU admission (sepsis; acute circulatory, respiratory, central nervous failure; acute hepatic dysfunction; acute kidney injury; other); the Sequential Organ Failure Assessment (SOFA) score [24]; clinical manifestations on ICU admission (debilitation; fever; myalgia, arthralgia; headache, delirium, altered consciousness, meningeal syndrome; jaundice, vomiting, diarrhoea, abdominal pain; dyspnoea, cough, chest pain; and bleeding including gastrointestinal bleeding, epistaxis, purpura, and haematuria); clinical parameters (arterial blood pressure, body temperature, respiratory rate, heart rate, and urinary output); Glasgow Coma Scale score; and routine laboratory parameters. The clinical and laboratory parameters were recorded daily for the first 7 ICU days. The following were recorded from ICU admission to discharge: leptospirosis-related complications including alveolar haemorrhage, acute respiratory distress syndrome (ARDS), meningitis, myocarditis, acute hepatitis, and acute myositis; antibiotics; and life-sustaining

therapies including invasive mechanical ventilation, non-invasive mechanical ventilation, prone positioning, vasoactive drugs, sedation, neuromuscular blocking agents, renal replacement therapy, and extracorporeal membrane oxygenation. The SOFA score was calculated based on the worst clinical and laboratory values recorded on admission, then daily during the first ICU week.

Definitions

Severe leptospirosis was defined as leptospirosis requiring ICU admission [24–26]. ARDS was defined according to the Berlin criteria [27]. Debilitation was defined as severe asthenia and anorexia reported by the patient. Incidence was the total number of ICU admissions for severe leptospirosis divided by the total number of ICU admissions during the study period.

Statistical analysis

Continuous variables were described as median [25th–75th percentiles] and categorical variables as number (%). Risk factors for hospital mortality were identified using a univariate analysis. The number of hospital deaths was too small to allow a multivariable analysis. All tests were two sided, and p values < 0.05 were considered significant.

To identify different clinical phenotypes of leptospirosis, we combined two factorial analysis techniques, multiple correspondence analysis (MCA) and hierarchical classification on principal components (HCPC). The variables used for these analyses were age and gender; alcohol and tobacco use; organs with an SOFA sub-score ≥ 2 on ICU admission; and clinical signs on ICU admission (debilitation; fever; myalgia; arthralgia; headache; delirium; altered consciousness; vomiting; diarrhoea; abdominal pain; dyspnoea; cough; and bleeding including gastrointestinal haemorrhage, epistaxis, purpura, and haematuria). Patient symptoms and baseline laboratory data were discretized using standard cutoffs (Table 1) [24, 26].

MCA, which belongs to a family of descriptive methods, is an extension of correspondence analysis that assesses contingency tables exploring simultaneous relationships between variables. MCA uses geometrical methods to describe correlations between variables and patients. We used MCA to build the principal components that best summarised the features of the individual patients. Each component was a linear combination of variables classified by decreasing order of contribution to the component; the variable making the greatest contribution was the best descriptor of the group of patients. Each component or dimension was chosen to account for the largest possible amount of variance within the dataset. We then subjected the MCA results to HCPC, using Ward's method to merge similar patients into clusters. The first principal components to return 95% of the total inertia were used to perform the HCPC analysis. To visualise the clusters, a plot was produced by projecting the patients and centre of gravity of each cluster, using the first two principal components. The clusters thus identified were described by comparing the frequencies of the different variables using Fisher's test for categorical variables and the Kruskal–Wallis test for quantitative variables.

SAS 9.4 (SAS Institute, Cary, NC, USA) was used for the statistical analyses and R 3.4.3 (FactoMineR package) for the HCPC analysis.

Results

The 79 participating ICUs were distributed throughout metropolitan France (Fig. 1). Over the study period, 394 patients were hospitalised for documented leptospirosis, including 160 (40%) who had severe disease requiring ICU admission. Given that 366,529 patients were admitted to the ICUs during the study period, the incidence of severe leptospirosis was 0.04%. A mean of 2 patients was admitted to each ICU over the 4-year study period. Among the participating ICUs, 26 (32.9%) admitted no patients for leptospirosis during the study period. As expected, cases were most common in August, September, and October (e-Fig. 2) [2].

Patient characteristics

Table 1 reports the main baseline features of the 160 study patients. The diagnosis was confirmed by blood PCR (53%), ELISA (40%), MAT (31%), and/or urinary PCR (11%). The microbiological findings were recovered after ICU discharge or death for 70 (43%) patients, including 45 (45/160, 28%) for whom the serogroup was determined (Table 2). Risk factors for leptospirosis were identified in 152 (95%) patients and included contact with animals in 79 (56%) patients (including rats and other rodents in 44 [31%] patients), activities at high risk for *Leptospira* contamination in 98 (65%) patients, and contact with water at risk for *Leptospira* contamination in 101 (68%) patients (including river water in 52 [35%] patients and lake or pond water in 51 [34%] patients). In addition, 18 (12%) patients had recently travelled abroad (Table 3). Median time from symptom onset to ICU admission was 5 [4–6] days.

Clinical presentation

On ICU admission, the most common clinical symptoms were fever, myalgia, debilitation, and jaundice; 118 (74%) patients had at least one organ failure and the median SOFA score was 11 [8–14]. The blood platelet count was

Table 1 Main features on ICU admission in the 160 patients with severe leptospirosis

	Median [IQR] or *n* (%)
Age[a], years	54 [38–65]
Males[a], *n* (%)	146 (91)
BMI[a], kg/m^2	25.2 [22.5–28.9]
SAPS II[b]	40 [28–58]
SOFA[c]	11 [8–14]
Smoking, *n* (%)	49 (31.2)
Chronic alcohol abuse, *n* (%)	29 (18.2)
Comorbidities[a], *n* (%)	
Diabetes mellitus	9 (6)
Liver disease	4 (3)
Cancer or immune deficiency	2 (1)
Chronic kidney disease	0
Cardiovascular disease	0
Chronic respiratory failure	0
Risk factors for contamination with *Leptospira* sp., *n* (%)	
Contact with water at risk for *Leptospira* contamination	101 (68)
Activity at risk for *Leptospira* contamination	98 (65)
Contact with animals	79 (56)
Travel abroad in the past month	18 (12)
Acute illness on ICU admission, *n* (%)	
Sepsis	40 (21.5)
Circulatory failure	33 (20.8)
Multiorgan failure	30 (18.9)
Acute kidney injury	24 (15.1)
Acute respiratory failure	14 (8.8)
Central nervous failure	9 (5.7)
Acute liver dysfunction	8 (5.0)
Other or unknown	2 (1.2)
Clinical symptoms on ICU admission, *n* (%)	
Fever	135 (84)
Myalgia	95 (59)
Debilitation	85 (53)
Jaundice	74 (46)
Vomiting	50 (31)
Headache	47 (29)
Diarrhoea	43 (27)
Dyspnoea	42 (26)
Abdominal pain	41 (26)
Arthralgia	35 (22)
Cough	35 (22)
Other clinical symptoms[d]	11 (7)
Confusion	11 (7)
Haemoptysis	11 (7)
Other bleeding[e]	11 (7)
Chest pain	6 (4)
Laboratory data on ICU admission (worst value within 24 h)	
Glucose (mmol/L)	6.80 [6–8.7]
Lactate (mEq/L)	1.7 [1.1–2.6]
Blood bilirubin (µmol/L)	80 [33–186]
Blood alanine aminotransferase (IU/L)	81 [50–128]

Table 1 (continued)

	Median [IQR] or *n* (%)
Blood aspartate aminotransferase (IU/L)	112 [64–181]
Haemoglobin (Giga/dL)	11.6 [10.0–12.7]
Platelets (Giga/L)	40 [26–76]
Leucocytes (Giga/L)	10.2 [7–14]
Serum creatinine (µmol/L)	323 [191–483]
Creatine phosphokinase (IU/L)	94 [55–192]
C-reactive protein (mg/L)	237 [166–301]

BMI, body mass index; SAPS II, Simplified Acute Physiology Score version II; SOFA score, Sequential Organ Failure Assessment Score; ICU, intensive care unit; IQR, interquartile range

[a] Recorded on ICU admission

[b] The SAPS II was determined 24 h after ICU admission. SAPS II values can range from 0 (lowest level of critical illness) to 163 (most severe level of critical illness with 100% predicted mortality). A score of 50 predicts a 46.1% risk of death

[c] SOFA scores can range from 0 (no organ failure) to 24 (most severe level of multiorgan failure)

[d] Other clinical symptoms: angina $n=3$, meningitis syndrome $n=3$, shivering $n=2$, dysphonia $n=1$, diffuse skin rash $n=1$, diaphoresis $n=1$, knee pain $n=1$, seizure $n=1$

[e] Other bleeding: haematemesis, blood per rectum, epistaxis, thrombocytopenic purpura, blood blister

below 50 G/L in 89 (57%) patients and below 100 G/L in 138 (88.5%) patients. Blood urea nitrogen was above 15 mmol/L in 97 (61%) patients and serum bilirubin was above 150 µmol/L in 50 (32%) patients.

Antibiotic treatment

Median time from symptom onset to antibiotic initiation was 5 [4–6] days. Leptospirosis was suspected on admission in only 8 patients, but the presence of features strongly suggestive of sepsis prompted early probabilistic antibiotic treatment in 152 (95%) patients. The first antibiotic regimen prescribed in the emergency room or ICU was active against *Leptospira* in 149 (93%) patients. Third-generation cephalosporins were used in 116 (72%), amoxicillin in 17 (11%), and fluoroquinolone in 9 (5%) patients. The initial antibiotic regimen was changed after biological confirmation of the diagnosis in 39 (24%) patients, and the change was to amoxicillin in 24 (61%) patients. Median antibiotic treatment duration was 10 [8–12] days.

Outcome

Table 2 reports the main complications and life-supporting treatments. Median stay lengths were 5 [2–14] days in the ICU and 11 [2–20] days in the hospital. Of the 160 patients, 13 (8%) died in the ICU, including 6 who died on the first ICU day due to severe multiorgan failure and 1 who died in the hospital after ICU discharge, yielding a 9% hospital mortality rate. The patient who died after ICU discharge had pre-existing liver cirrhosis and died from hepatic failure. Median time from ICU admission to death was 3 days [2–20].

Factors associated with hospital mortality by univariate analysis were older age; worse SOFA score and need for invasive ventilation or renal replacement therapy within 48 h after ICU admission; chronic alcohol abuse, jaundice, and higher blood bilirubin level; confusion; and higher blood leucocyte count (Table 3).

Clinical phenotypes

MCA identified four patient clusters based on clinical features (Fig. 1 and Table 4). Cluster 1 ($n=34$, 21%) was the least severe phenotype: compared to the other clusters, this cluster had higher proportions of patients with SOFA sub-scores <2 for hepatic, renal, haemodynamic, and respiratory failure; shorter ICU and hospital stays; and a lower mortality rate (1 patient, 3%). Cluster 2 was the most common phenotype ($n=101$; 63%) and was characterised by severe hepatic, renal, and haematologic failure (with corresponding SOFA sub-scores ≥ 2) in contrast with low prevalences of respiratory and neurological failure. In cluster 2, 9/101 (9%) patients died. Cluster 3 was the rarest phenotype ($n=8$; 5%) but also the most severe, with multiorgan failure including acute central neurological failure, and a fatal outcome in 3/8 (37.5%) patients. Finally, patients in cluster 4 ($n=17$, 11%) had bleeding and respiratory failure; among them, 1/17 (6%) died.

Discussion

To our knowledge, this is the largest study to date on leptospirosis requiring ICU admission and the first study of severe leptospirosis in a non-tropical area. Severe leptospirosis requiring ICU admission was less common in

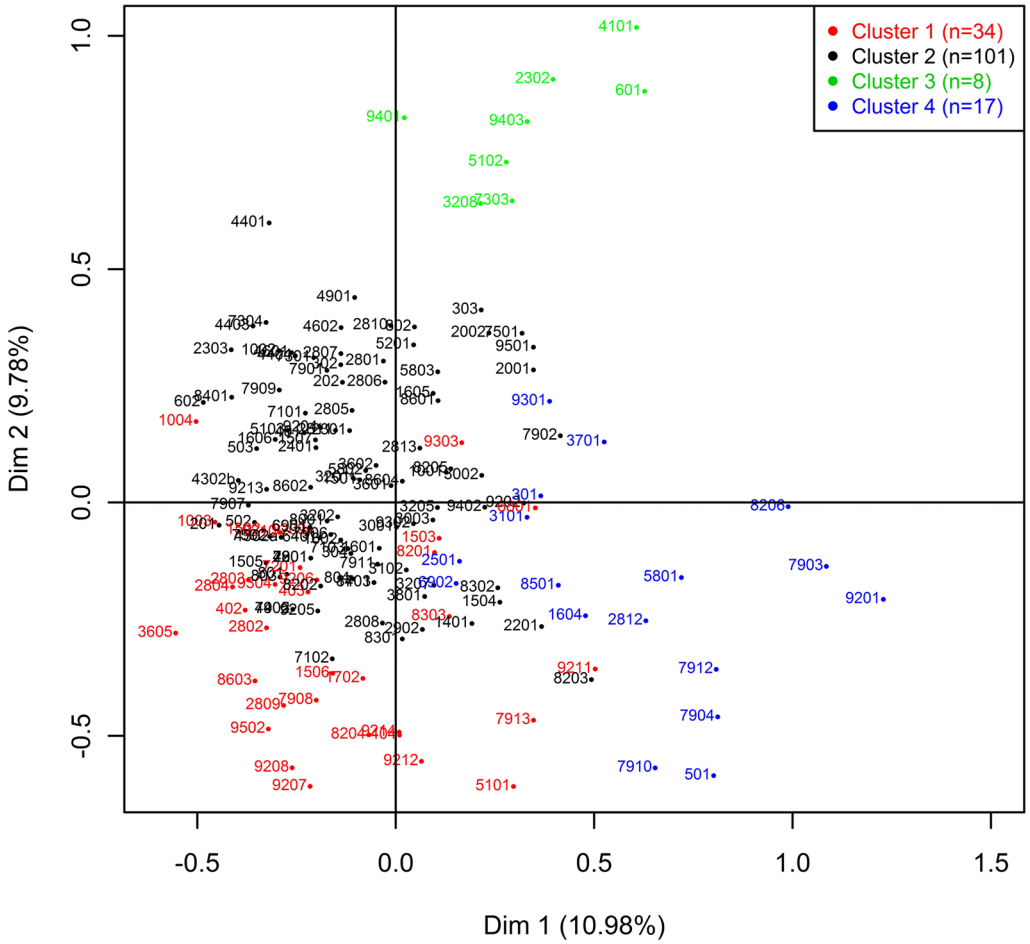

Fig. 1 Map of clinical features of severe leptospirosis. Two-dimensional distribution of clinical features of severe leptospirosis mapped along the two dimensions (dim 1 and dim 2) identified by multiple correspondence analysis. These dimensions summarise 16% of the variability in the data. The relative positions of the patients in the plane are represented by different colours reflecting the sub-types identified by cluster analysis. Cluster 1 (red; $n=34$) was the moderately severe form, cluster 2 (black; $n=101$) was a hepato-renal presentation, cluster 3 (green; $n=8$) was the neurological form, and cluster 4 (blue; $n=17$) was the respiratory form

metropolitan France compared to previous reports from tropical regions and carried a lower mortality rate than predicted by the severity and organ-failure scores. The main finding from our study is that four clinical phenotypes of severe leptospirosis were distinguished using MCA and HCPC within a single population.

The four clinical phenotypes can be described as moderately severe leptospirosis (cluster 1), hepato-renal leptospirosis (cluster 2), neurological leptospirosis (cluster 3), and respiratory leptospirosis (cluster 4). Previous observational studies separately identified similar presentations [7, 8, 12, 15, 19, 28–30]. Cluster 1 carried a better prognosis than the other three clusters in our study but should not be confused with mild leptospirosis, which may be the most common clinical presentation and does not usually require ICU admission [5]. That only a fifth of our patients were in cluster 1 suggests that many patients with this presentation may be managed outside the ICU when they have no organ failures and therefore do not require life-supporting interventions [28]. Cluster 2 predominated and was characterised by liver and kidney dysfunction but preserved neurological and respiratory function and no bleeding [6]. Cluster 2 accounted for 63% of our patients, whereas this presentation accounted for 77.5–92.7% of patients in studies from tropical and sub-tropical areas [14, 31]. This clinical presentation also predominated in a single-centre study done in metropolitan France [12]. Neurological

Table 2 Outcome of severe leptospirosis in the 160 study patients

	n (%) or median [IQR]
Complications, *n* (%)	
ARDS, any severity	58 (36)
ARDS, mild	16 (10)
ARDS, moderate	18 (11)
ARDS, severe	24 (15)
Intra-alveolar haemorrhage	23 (14)
Macrophage activation syndrome	5 (3)
Meningitis	4 (2)
Myocarditis[a]	4 (2)
Acute myositis	3 (2)
Infectious colitis	2 (1)
Acute hepatitis[b]	1 (1)
Life support, *n* (%)	
Vasoactive drug	92 (57%)
Invasive ventilation	58 (36%)
Renal replacement therapy	56 (35%)
Non-invasive ventilation	32 (20%)
Neuromuscular blockade	33 (20%)
Prone position	9 (6%)
ECMO	3 (2%)
ICU stay length, days	5 [2–10]
Hospital stay length, days	11 [8–20]
ICU mortality, *n* (%)	13 (8)
Hospital mortality, *n* (%)	14 (9)

IQR, interquartile range; ARDS, acute respiratory distress syndrome ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit

[a] One patient had cardiogenic shock and needed extra-corporeal circulation

[b] This patient had blood aspartate and alanine aminotransferase levels of 12,000 IU/L and 8400 IU/L, respectively, 24 h after ICU admission

leptospirosis (cluster 3) is rarely reported and was the least common presentation in our study. All patients had central neurological failure. Multiorgan failure and death were common in this cluster. Leptospirosis has been reported to cause meningoencephalitis, Guillain–Barré syndrome, and transverse myelitis with hemiplegia in a few patients, whose outcomes were better than those in cluster 3 in our study [6, 32]. Respiratory leptospirosis (cluster 4) was characterised by bleeding, including intra-alveolar haemorrhage with subsequent ARDS, a pattern well known to occur in patients with severe leptospirosis [15, 30]. In studies from tropical and subtropical regions, respiratory leptospirosis accounted for 25–56% of patients, compared to 11% in our population [25, 30].

An important finding from our study is that leptospirosis requiring hospital admission in a temperate area was sufficiently severe to require ICU admission in 40% of cases. The SAPS II and SOFA score on ICU admission were high; and vasoactive drugs, invasive mechanical ventilation, and renal replacement therapy were required in 57%, 37%, and 36% of patients, respectively. The 9% mortality rate was far lower than predicted by these data and was also lower than in previous studies of severe leptospirosis or of other infections responsible for organ failure [7, 10, 13, 25, 26]. Patients with leptospirosis are often younger and have fewer comorbidities than do patients with other severe infections. A recent study from the Reunion Island also found that mortality was lower than predicted by the severity scores and that a need for early mechanical ventilation was associated with poorer outcomes [9]. The Reunion Island is part of France and has similar healthcare resources to the mainland. Differences in healthcare resources may contribute to explain the lower mortality in our study compared to previous reports from Asia, Africa, Latin America, and Oceania [2, 3, 6, 7, 9]. Differences in *Leptospira* subgroup distribution may also be involved. However, the serogroup was determined only for a minority of patients both in our study and in previous work from tropical areas.

Our study indicates that severe leptospirosis requiring ICU admission remains uncommon in metropolitan France. Thus, 32.9% of the participating ICUs admitted no patients for leptospirosis during the study period. Importantly, previous studies [15] indicate major underestimation of leptospirosis cases, whose reporting varies according to national surveillance systems and to physician training about, and awareness of, the disease. Underreporting may be particularly common in countries where leptospirosis is rare, such as France [3, 18]. However, France has a surveillance system supported by the Ministry of Health, which has shown an increase in the incidence of diagnosed leptospirosis over the last few decades [21]. A similar increase had been documented in other European countries [18, 20, 21]. Moreover, reporting bias may also occur in tropical and sub-tropical areas. Nevertheless, the incidence of severe leptospirosis requiring ICU admission in our study suggests that leptospirosis may still be far less common in temperate areas than in tropical and subtropical areas.

The main limitation of our study is its retrospective design. This design was required by the low incidence of severe leptospirosis managed in ICUs in metropolitan

Table 3 Univariate analysis to identify risk factors for hospital mortality in patients with severe leptospirosis

	Alive ($n = 146$)	Dead ($n = 14$)	OR [95% CI]	p value
Age[a], years	52 [38–65]	65 [38–65]	1.09 [1.04–1.15]	0.0011
Male sex[a], *n* (%)	134 (92%)	12 (86%)	0.53 [0.1–2.70]	0.4493
BMI[a], kg/m^2	24.8 [22.5–28.4] (19)[c]	28.4 [21.7–31.6] (3)[c]	1.10 [0.97–1.24]	0.1209
SOFA[b]	11 [8–13]	16 [15–19]	1.77 [1.37–2.28]	< 0.001
Smoking[a]	46 (32%) (3)[c]	3 (21%) (0)[c]	0.58 [0.15–2.16]	0.4128
Chronic alcohol abuse[a]	23 (16%) (1)[c]	6 (43%) (0)[c]	3.98 [1.26–12.54]	0.0184
Diabetes mellitus[a]	7 (5%)	2 (14%)	3.31 [0.62–17.73]	0.1623
Clinical symptoms on ICU admission, *n* (%)				
Fever	125 (86%)	10 (71%)	0.42 [0.12–1.46]	0.1731
Myalgia	90 (62%)	5 (36%)	0.35 [0.11–1.08]	0.0685
Debilitation	76 (52%)	9 (64%)	1.66 [0.53–5.19]	0.3849
Jaundice	63 (43%)	11 (79%)	4.83 [1.29–18.05]	0.0192
Vomiting	47 (32%)	3 (21%)	0.57 [0.15–2.16]	0.4115
Diarrhoea	42 (29%)	1 (7%)	0.19 [0.02–1.50]	0.1156
Dyspnoea	39 (27%)	3 (21%)	0.75 [0.20–2.82]	0.6688
Abdominal pain	37 (25%)	4 (29%)	1.18 [0.35–3.98]	0.7917
Arthralgia	33 (23%)	2 (14%)	0.57 [0.12–2.68]	0.4772
Cough	34 (23%)	1 (7%)	0.25 [0.03–2.01]	0.1936
Confusion	8 (5%)	4 (29%)	6.90 [1.77–26.91]	0.0054
Haemoptysis	11 (8%)	1 (7%)	0.94 [0.11–7.90]	0.9576
Chest pain	4 (3%)	2 (14%)	5.92 [0.98–35.68]	0.0525
Laboratory data on ICU admission (worst value within 24 h)				
Blood bilirubin (µmol/L) (by 50 µmol/L increase)	71 [31–173] (4)[c]	251 [120–373] (0)[c]	1.41 [1.18–1.70]	0.0002
Blood alanine aminotransferase (IU/L) (by IU/L increase)	81 [50–123] (3)[c]	118 [48–165] (0)[c]	1.00 [0.95–1.05]	0.9113
Blood aspartate aminotransferase (IU/L) (by 50 IU/L increase)	108 [63–175] (4)[c]	163[70–434] (0)[c]	1 [0.98–1.03]	0.8469
Haemoglobin (Giga/dL)	11.6 [10–13] (2)[c]	11.7 [10–13] (0)[c]	1.16 [0.86–1.57]	0.3343
Platelets (Giga/L) (by 10 Giga/L increase)	41[26–83] (3)[c]	30[20–40] (0)[c]	0.87 [0.73–1.04]	0.1290
Leucocytes (Giga/L) (by 5 Giga/L increase)	9.8 [6.5–13.7] (2)[c]	15.7 [13–20] (0)[c]	1.37 [1.04–1.80]	0.0252
Serum creatinine (µmol/L)[d]	292 [187–482] (2)[c]	437 [371–512] (0)[c]	1.75 [0.68–4.48]	0.2338
Creatine phosphokinase (IU/L) (by 100 IU/L increase)	572[177–1848] (45)[c]	674[547–7600] (7)[c]	1.02 [1.00–1.03]	0.0695
C-reactive protein (mg/L) (by 50 mg/L increase)	239 [166–301] (54)[c]	216 [105–301] (6)[c]	0.83 [0.58–1.19]	0.3082
Life support				
Vasoactive drug within 48 h after ICU admission	63 (45%) (5)[c]	10 (71%) (0)[c]	3.10 [0.93–10.34]	0.0664
Invasive ventilation within 48 h after ICU admission	33 (23%) (1)[c]	13 (93%) (0)[c]	44.12 [5.56–349.84]	0.0003
Renal replacement therapy within 48 h after ICU admission	29 (20%) (2)[c]	7 (50%) (0)[c]	3.97 [1.29–12.20]	0.0163

OR, odds ratio; 95% CI, 95% confidence interval; ICU, intensive care unit

[a] Recorded on ICU admission

[b] SOFA scores can range from 0 (no organ failure) to 24 (most severe level of multiorgan failure)

[c] Missing values (raw numbers)

[d] Because serum creatinine values were not linear, we applied a natural log transformation

France. However, the large number of participating ICUs and their distribution throughout the country produced a reliable picture of severe leptospirosis in a temperate European country.

Conclusion

This is the first large multicentre study of severe leptospirosis in a temperate country and the world's largest cohort study of severe leptospirosis managed in the ICU. Severe leptospirosis was uncommon and was less

Table 4 The four clinical phenotypes identified in the study population: characteristics on ICU admission and outcomes

	Cluster 1 Moderately severe leptospirosis *N* = 34	Cluster 2 Hepato-renal leptospirosis *N* = 101	Cluster 3 Neurological leptospirosis *N* = 8	Cluster 4 Respiratory leptospirosis *N* = 17	*p* value
Features on ICU admission, *n* (%)					
Age > 65 years	10 (29)	29 (29)	1 (13)	3 (18)	0.680
Male sex	24 (71)	97 (96)	8 (100)	17 (100)	< 0.001
Smoking	8 (24)	30 (31)	4 (50)	7 (41)	0.359
Chronic alcohol abuse	1 (3)	18 (18)	6 (75)	4 (24)	< 0.001
Fever	30 (88)	84 (83)	5 (63)	16 (94)	0.216
Myalgia	18 (53)	66 (65)	1 (13)	10 (59)	0.024
Arthralgia	9 (27)	22 (22)	0 (0)	4 (24)	0.476
Headache	14 (41)	30 (30)	1 (13)	2 (12)	0.124
Confusion	4 (12)	4 (4)	2 (25)	2 (12)	0.041
Other bleeding[a]	0 (0)	0 (0)	0 (0)	15 (88)	< 0.001
Debilitation	13 (38)	59 (58)	6 (75)	7 (41)	0.083
Diarrhoea	13 (38)	26 (26)	0 (0)	4 (24)	0.151
Vomiting	11 (32)	31 (31)	2 (25)	6 (35)	0.960
Abdominal pain	3 (9)	34 (34)	3 (38)	1 (6)	0.003
Dyspnoea	10 (29)	19 (19)	4 (50)	9 (53)	0.008
Cough	12 (35)	13 (13)	0 (0)	10 (59)	< 0.001
Haemoptysis	1 (3)	0 (0)	0 (0)	11 (65)	< 0.001
SOFA sub-scores ≥ 2[b], *n* (%)					
Haemodynamic ≥ 2	11 (32)	61 (60)	7 (88)	11 (65)	0.003
Renal ≥ 2	10 (29)	84 (86)	6 (75)	11 (73)	< 0.001
Hepatic ≥ 2	4 (12)	95 (94)	7 (88)	13 (87)	< 0.001
Platelets ≥ 2	22 (65)	90 (89)	6 (75)	15 (100)	0.002
Respiratory ≥ 2	11 (32)	40 (40)	6 (75)	12 (80)	0.003
Neurological ≥ 2	0 (0)	0 (0)	8 (100)	0 (0)	< 0.001
Outcomes					
In-hospital deaths, *n* (%)	1 (3)	9 (9)	3 (38)	1 (6)	0.046
ICU stay length, days, median [IQR]	3 [2, 3]	5 [2–11]	8 [7–15]	8 [6–13]	< 0.001
Total hospital stay length, median [IQR]	8 [5–10]	11 [8–21]	44 [33–64]	14.5 [12–19]	< 0.001
Life support, *n* (%)					
Invasive ventilation	5 (15)	35 (35)	7 (88)	10 (59)	< 0.001
Vasoactive drug	11 (32)	61 (60)	7 (88)	13 (77)	0.002
Renal replacement therapy	3 (9)	41 (41)	5 (63)	7 (42)	< 0.001
Non-invasive ventilation	6 (18)	17 (17)	3 (38)	6 (38)	0.135

ICU, intensive care unit; SOFA score [24], Sequential Organ Failure Assessment score; IQR, interquartile range

[a] Other bleeding: haematemesis, blood per rectum, epistaxis, thrombocytopenic purpura, blood blister

[b] SOFA scores can range from 0 (no organ failure) to 24 (most severe level of multi-organ failure)

often fatal than expected, despite considerable acute illness severity. Our identification of four clinical presentations of severe leptospirosis may help clinicians recognise situations consistent with leptospirosis, while also providing prognostic orientation.

Electronic supplementary material

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