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# Organ Involvement Related to Death in Critically Ill Patients With Leptospirosis: Unsupervised Analysis in a French West Indies ICU

**OBJECTIVES:** To identify distinct phenotypes of critically ill leptospirosis patients upon ICU admission and their potential associations with outcome.

**DESIGN:** Retrospective observational study including all patients with biologically confirmed leptospirosis admitted to the ICU between January 2014 and December 2022. Subgroups of patients with similar clinical profiles were identified by unsupervised clustering (factor analysis for mixed data and hierarchical clustering on principal components).

**SETTING:** All patients admitted to the ICU of the University Hospital of Guadeloupe on the study period.

**PATIENTS:** One hundred thirty critically ill patients with confirmed leptospirosis were included.

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** At ICU admission, 34% of the patients had acute respiratory failure, and 26% required invasive mechanical ventilation. Shock was observed in 52% of patients, myocarditis in 41%, and neurological involvement in 20%. Unsupervised clustering identified three clusters—"Weil's Disease" (48%), "neurological leptospirosis" (20%), and "multiple organ failure" (32%)—with different ICU courses and outcomes. Myocarditis and neurological involvement were key components for cluster identification and were significantly associated with death in ICU. Other factors associated with mortality included shock, acute respiratory failure, and requiring renal replacement therapy.

**CONCLUSIONS AND RELEVANCE:** Unsupervised analysis of critically ill patients with leptospirosis revealed three patient clusters with distinct phenotypic characteristics and clinical outcomes. These patients should be carefully screened for neurological involvement and myocarditis at ICU admission.

**KEYWORDS:** encephalitis; intensive care unit; leptospirosis; multiple organ failure; myocarditis

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Leptospirosis is a zoonosis that is highly prevalent in tropical areas, which most often infects humans through exposure to water, soil, or mud contaminated with urine from infected animals (1). Although most patients are paucisymptomatic, a significant proportion (6–50%) experience severe forms that may require ICU admission (2, 3). Previous reports show that patients who require ICU admission have a 10–20% mortality rate (4–6) despite appropriate treatment. The clinical manifestations are pleomorphic (1), mimicking various bacterial diseases. The archetypal pattern is Weil's disease with liver jaundice and kidney failure (2), which predominates among hospitalized patients. Leptospirosis has also been reported to exhibit other primary organ involvement, including the brain (7–9),

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## KEY POINTS

**Question:** Which clinical and biological factors at ICU admission of critically ill leptospirosis patients help identify patients with high ICU mortality?

**Findings:** Three clusters were identified through unsupervised clustering based on clinical and biological features at ICU admission. The presence of neurologic involvement and myocarditis was associated with high mortality rates.

**Meaning:** Further studies are essential to identify the determinants of neurologic involvement and myocarditis in critically ill leptospirosis patients (i.e., potential association with specific *Leptospira* serogroups) and evaluation of adjunctive therapies for these organ involvements associated with high ICU mortality.

lung (10, 11), and heart (12–14). The pathophysiological mechanisms leading to organ damage are poorly understood (1) and involve both bacterial and immunological mechanisms. Most studies in tropical areas have focused on identifying prognostic factors during the ICU course (4–6, 10), revealing that standard severity scores are poor predictors of mortality in ICUs and hospitals (5). Analyses focused on identifying patient subgroups have yielded heterogeneous results (5, 15), and there is not yet a consensus regarding the definition of severe forms. Few studies have described the differences between clinical entities during the ICU course. Furthermore, studies of specific organ involvement (14, 16, 17) have mostly been small and not in an ICU setting.

Guadeloupe is a French Caribbean territory where leptospirosis is endemic (18, 19). In the present study, our primary objective was to identify clinical and biological phenotypes of leptospirosis at ICU admission and their potential associations with outcomes. Our secondary objective was to precisely describe the clinical features, organ involvement, and management of patients with leptospirosis in the ICU.

## METHODS

### Study Design and Data Collection

This retrospective monocentric study was conducted in the ICU of the Guadeloupe University Hospital

(Guadeloupe Island, French West Indies; 30 beds). Our study included all adult patients ( $\geq 18$  yr old) admitted between January 2014 and December 2022 with confirmed leptospirosis (3). Patients were evaluated for anti-leptospiral immunoglobulin M (IgM) using Serion IgM-enzyme-linked immunosorbent assay (Institut Virion\Serion GmbH, Würzburg, Germany) according to the manufacturer's protocol 1 (20). In case of positivity (IgM  $\geq 35$  international units/mL), the results were confirmed by microscopic agglutination test (MAT) at the National Reference Center for Leptospirosis (Institut Pasteur, Paris, France). Leptospirosis was verified by positive real-time polymerase chain reaction (PCR) findings in urine, blood, and/or cerebrospinal fluid (CSF); a positive MAT (first sample  $> 1/400$ ) performed using samples taken at ICU admission; or a four-fold rise in MAT titer between two samples taken approximately 10 days apart (21). The *Lip32* gene was used to detect *Leptospira interrogans* by PCR (20). The *Leptospira* isolates used for the microscopic agglutination assay comprised the following serogroups: Australis, Autumnalis, Ballum, Bataviae, Canicola, Celledoni, Cynopteri, Djasiman, Grippotyphosa, Hebdomadis, Icterohaemorrhagiae, Javanica, Louisiana, Mini, Panama, Pomona, Pyrogenes, Sarmin, Sejroe, Shermani, and Tarassovi.

Data collected upon ICU admission included the patient's age, gender, chronic comorbidities, alcohol use, risk factors for leptospirosis contamination (agricultural work, exposure to animals or to potentially contaminated water, or high-risk outdoor activities), liver jaundice (3), and Simplified Acute Physiology Score II (SAPS II). We also recorded chest radiograph and thoracic CT scan analysis, left ventricular ejection fraction assessed by echocardiography (Biplane Simpson method), and the following biological data: platelets, blood creatinine, arterial blood lactate, bilirubinemia, troponin, and  $\text{PaO}_2$  on arterial blood gases.

### Definitions and ICU Management

Acute respiratory failure (ARF) was defined as a respiratory rate of greater than or equal to 25/min, with pulmonary infiltrates on chest radiograph or CT scan, and need for oxygen at greater than or equal to 5 L/min to maintain oxygen saturation greater than or equal to 92%. Shock was defined as a mean arterial pressure

of less than 65 mm Hg, associated with lactatemia of greater than 2 mmol/L and need for vasopressors (22). Myocarditis was defined as reversible acute nonischemic heart involvement, associated with troponin elevation ( $> 0.200$  ng/mL) and either a left ventricular ejection fraction of less than 50% without pre-load dependency, or new electrocardiographic abnormalities (23). CNS involvement was defined as either a persistent ( $> 12$  hr) altered vigilance status (Glasgow Coma Scale  $< 13$ ), status epilepticus, or meningitis, with no alternative diagnosis. Acute kidney injury (AKI) was defined as a greater than or equal to 1.5-fold increase in serum creatinine at baseline or urine output of less than 0.5 mL/kg/hr for at least 6 hours (24). ICU admission for leptospirosis was considered for patients with at least one organ failure, such as shock, myocarditis, CNS involvement, or AKI. All patients were evaluated both by a senior intensivist and the ward infectious physician before ICU admission. Final decision was made by the senior intensivist and based on the presence of severity factors (25, 26).

We also recorded instances of advanced life support therapy initiated during ICU stay, such as invasive mechanical ventilation, renal replacement therapy, and extracorporeal lung support. Finally, we recorded patients' 30-day mortality, cause of death, and length of ICU stay.

## Statistical Analysis

Analyses were performed in R (Version 4.0.4; R Foundation for Statistical Computing, Vienna, Austria) (27). Continuous variables were reported as median (25th–75th quartiles), and categorical data as percentages.

Unsupervised clustering was used to identify subgroups of patients with similar clinical and biological profiles by performing hierarchical clustering on principal components (HCPC) constructed from results of factor analysis on mixed data (FAMD). FAMD is a factorial method to explore the association between qualitative or quantitative variables and to reduce data dimensionality of a dataset into noncorrelated dimensions (principal components), which are linear combinations of the initial variables. HCPC is an algorithm using calculated principal components to partition individuals into homogeneous groups, such that the within-group similarities are large compared with

the between-group similarities. The dataset included in this clustering analysis were ARF, shock, myocarditis, CNS involvement, platelets, and bilirubinemia at ICU admission. Missing data were imputed in the missMDA package (François, AgroCampus, Rennes, France) (28). Factor analysis for mixed data was run on imputed data, and hierarchical clustering was applied to the principal components using the FactoMineR package (François Husson, AgroCampus, Rennes, France) (29) to identify patient clusters.

Clusters were compared using the Kruskal-Wallis test for continuous variables and the chi-square or Fisher exact test for categorical variables. Pairwise comparisons were performed using the Dunn post hoc test (continuous variables) and Fisher exact test (categorical variables) with Benjamini-Hochberg correction. Survivors and nonsurvivors at 30 days after ICU admission were compared using Fisher exact tests for categorical variables and the Mann-Whitney *U* test for continuous variables. Crude odds ratios (ORs) and their 95% CIs for 30-day mortality were estimated using a logistic model. Survival curves up to day 30 were computed separately for relevant parameters and were compared using log-rank tests. For all tests, results were considered significant at 5% ( $p < 0.05$ ).

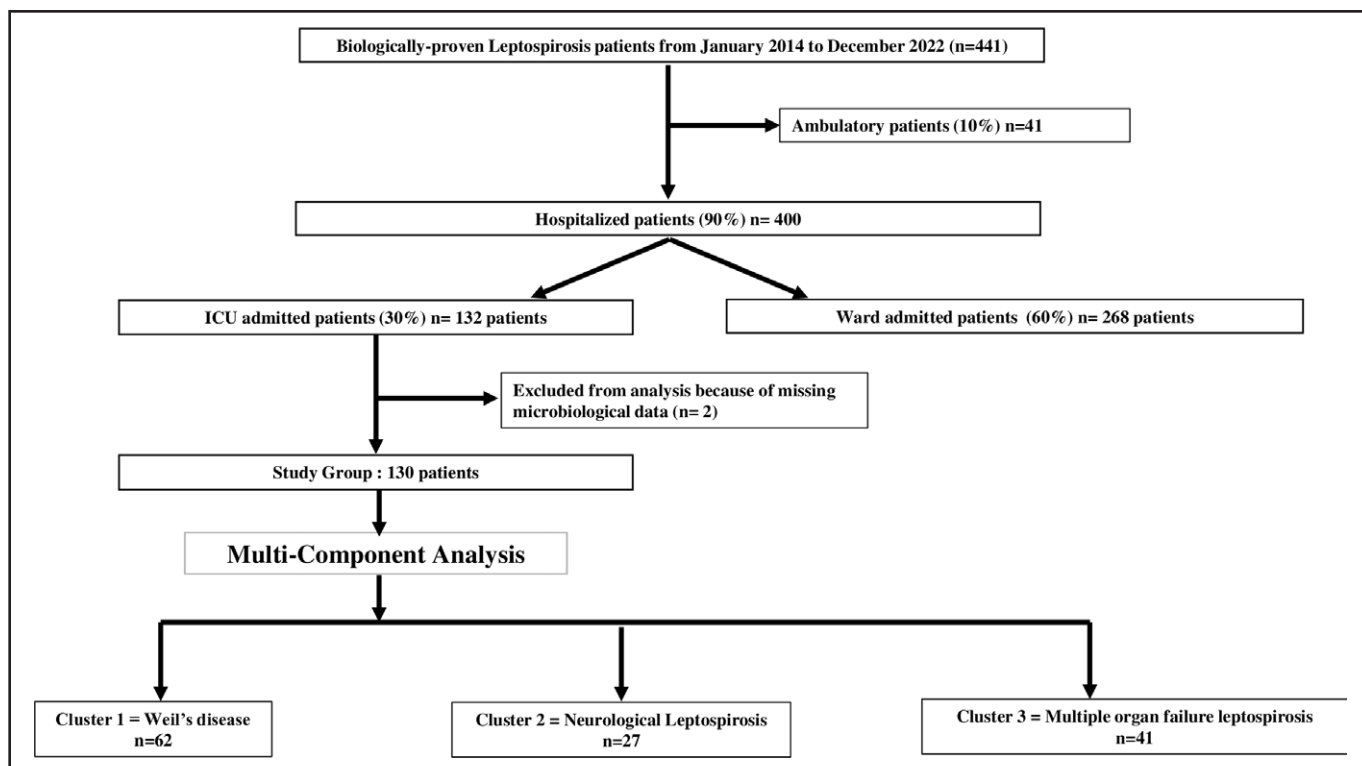
## Ethics

This study was approved by the ethical research committee of the University Hospital of Guadeloupe, in September 2021 (number reference no. 2223746 v0), and was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement. The ethical committee waived the requirement for individual consent for anonymous data collection, in accordance with French law. Procedures were conducted following the ethical standards of the national responsible committee on human experimentation and the Helsinki Declaration of 1975.

## RESULTS

### Patients' Characteristics and Management

On the study period, 441 patients had biologically confirmed Leptospirosis at the GUH (Guadeloupe University Hospital), of whom 90% ( $n = 400/441$ ) were admitted to the hospital, 30% ( $n = 130/441$ ) to the ICU and 60% ( $n = 270/441$ ) to the ward (tropical and infectious disease;



**Figure 1.** Flow chart of patients with biologically proven leptospirosis who were admitted to the Guadeloupe University Hospital between 2014 and 2022.

**Fig. 1).** Two patients were excluded due to substantial missing data. Among the 130 analyzed patients, leptospirosis was confirmed by positive blood and/or urine PCR in 69 patients (53%), positive MAT in 41 patients (32%), and positivity on both tests for 20 patients (15%). Notably, 102 patients had positive IgM serology. The serogroup was identified in 31 of 61 tested patients (51%), and *Icterohaemorrhagiae* was the main identified serogroup (11/61, 17%; **Table S1**, <http://links.lww.com/CCX/B373>).

**Table 1** shows the patients' characteristics and management. Most patients were male ( $n = 111$ , 85%), the median age was 57 years (48–66 yr), and the median SAPS II was 48 (30–65). The main risk factors for leptospirosis were agricultural work (67%), exposure to animals or to potentially contaminated water (7%), and high-risk outdoor activities (4%). The most frequently reported comorbidities were chronic alcohol abuse, diabetes, and hypertension. At ICU admission, most patients had liver jaundice ( $n = 114$ , 88%), with a median serum total bilirubin level of 184  $\mu\text{mol/L}$  (66–296  $\mu\text{mol/L}$ ). AKI was present in 91% ( $n = 118$ ), with a median serum creatinine level of 409  $\mu\text{mol/L}$  (185–571  $\mu\text{mol/L}$ ). Within 24 hours after ICU admission, 34% of the patients ( $n = 44$ ) had ARF. Thoracic CT was abnormal in 30 patients (23%), of whom 27 displayed

interstitial syndrome and three exhibited micronodules. All patients received antibiotic therapy starting on the day of hospital admission. Most patients ( $n = 123$ , 95%) received third-generation cephalosporin, and 5% ( $n = 7$ ) received amoxicillin for 7 days.

Among the 44 patients with ARF, 26 (59%) required invasive mechanical ventilation for a median length of 7 days (4–9 d). At the onset of invasive mechanical ventilation, median  $\text{PaO}_2/\text{FiO}_2$  was 160 mm Hg (82–232 mm Hg). Six patients had prone positioning during mechanical ventilation, and three required a venovenous extracorporeal membrane oxygenator for refractory hypoxemia. Within 24 hours after admission, 52% ( $n = 67$ ) of patients were in shock, and norepinephrine were administered at a median dose of 1.25  $\mu\text{g/kg/min}$  (0.6–2.5  $\mu\text{g/kg/min}$ ). Myocarditis was present in 41% ( $n = 53$ ) of patients, and 20% ( $n = 27$ ) exhibited CNS involvement. During the ICU course, renal replacement therapy was initiated in 32% ( $n = 41$ ) of patients by continuous venovenous hemofiltration in 30 patients and intermittent hemodialysis in 11 patients.

### Cluster Analysis

Cluster analysis revealed three different clusters (**Fig. 2**). **Table 2** shows the patients' characteristics

**TABLE 1.**  
**Patients' Characteristics and Outcomes According to 30-Day Survival**

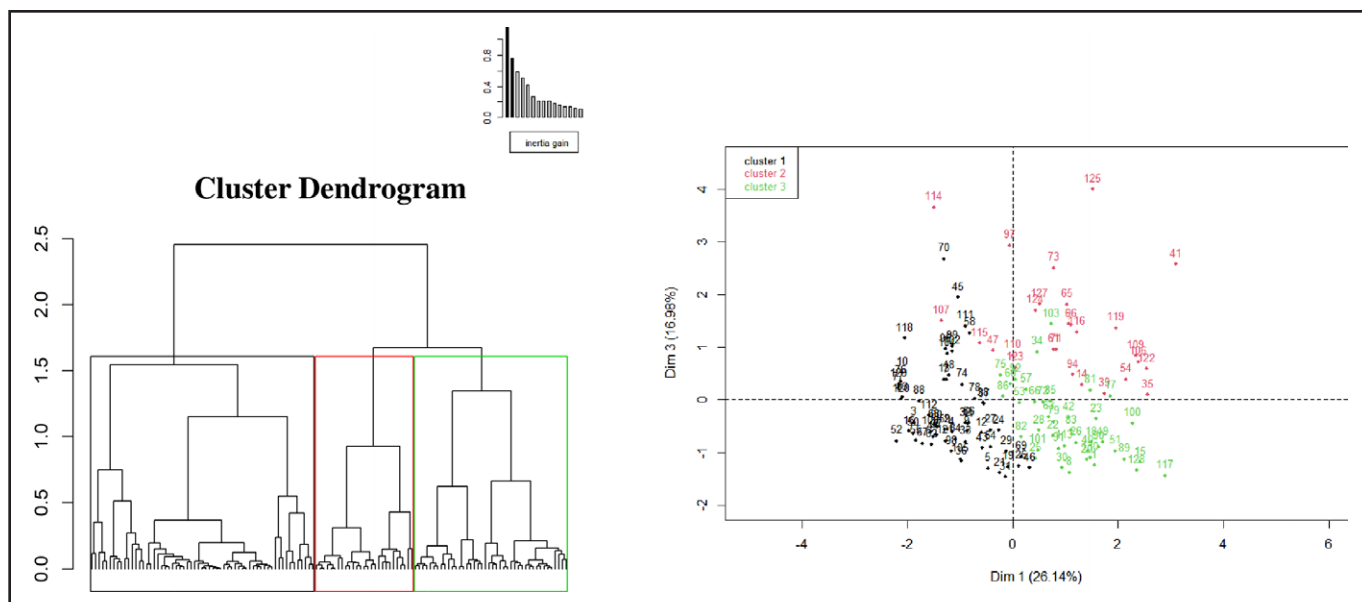
Variables	All Patients	30-d Survivors, 30-d Nonsurvivors,		Univariate Analysis	
		<i>n</i> = 112	<i>n</i> = 18	OR (95% CI)	<i>p</i>
Male, <i>n</i> (%)	111 (85)	94 (84)	17 (94)	3.3 (0.6–61)	0.3
Age, yr	57 (48–66)	56 (48–65)	62 (51–73)	1.0 (1.0–1.1)	0.13
Simplified Acute Physiology Score II	48 (30–65)	43 (30–57)	87 (70–98)	1.1 (1.1–1.2)	< 0.001
Comorbidities, <i>n</i> (%)					
Hypertension	38 (29)	31 (28)	7 (39)	1.7 (0.6–4.6)	0.3
Diabetes mellitus	19 (15)	14 (13)	5 (28)	2.7 (0.8–8.4)	0.10
Cardiopathy	7 (5)	4 (4)	3 (17)	5.4 (1.0–26.9)	0.038
Kidney insufficiency	2 (2)	2 (2)	0 (0)		> 0.9
Alcohol use	40 (31)	32 (29)	8 (44)	2.0 (0.7–5.5)	0.2
Clinical features and organ involvement, <i>n</i> (%)					
Jaundice	114 (88)	97 (87)	17 (94)	2.6 (0.5–49.1)	0.4
Acute respiratory failure	44 (34)	30 (27)	14 (78)	9.6 (3–36)	< 0.001
Shock	67 (52)	50 (45)	17 (94)	21 (4–386)	0.004
Myocarditis	53 (41)	41 (37)	12 (67)	3.5 (1.3–10.6)	0.021
CNS involvement	27 (21)	20 (18)	7 (39)	2.9 (1.0–8.4)	0.048
Acute kidney injury	118 (91)	100 (90)	18 (100)	NA	0.361
Biological and radiological data					
Lactate, mmol/L	2.3 (1.5–3.1)	2.2 (1.4–3.0)	3.5 (2.3–6.5)	1.5 (1.2–1.9)	< 0.001
Platelets, G/L	41 (26–76)	41 (27–75)	35 (18–78)	1.0 (1.0–1.0)	0.540
Creatinine, $\mu$ mol/L	409 (184–571)	338 (159–570)	488 (380–571)	1.0 (1.0–1.0)	0.2
Bilirubin, $\mu$ mol/L	184 (66–296)	158 (54–266)	244 (176–372)	1.0 (1.0–1.0)	0.013
Abnormal thoracic CT scan, <i>n</i> (%)	30 (23)	17 (15)	13 (72)	14.5 (4.8–50.4)	< 0.001
Left ventricular ejection fraction < 40%, <i>n</i> (%)	14 (11)	6 (5)	8 (44)	14.1 (4.2–51.5)	< 0.001
Advanced life support therapy, <i>n</i> (%)					
Renal replacement therapy	41 (32)	25 (22)	16 (89)	27.8 (7.3–184)	< 0.001
Mechanical ventilation	34 (26)	16 (14)	18 (100)		< 0.001
Cluster, <i>n</i> (%)					
Weil's disease	62 (48)	60 (54)	2 (11)	1	NA
Neurologic leptospirosis	27 (21)	20 (18)	7 (39)	10.5 (2.3–74.5)	0.005
Multiple organ failure	41 (32)	32 (29)	9 (50)	8.4 (2.0–57.6)	0.009

NA = not applicable, OR = odds ratio.

Results are presented as median (25th–75th quartiles) for continuous variables and *n* (%) for categorical variables.

and management according to cluster. Clusters were named based on the predominant clinical features of the patients assigned to the cluster. The clusters did not differ in comorbidities, sex ratio, or age.

Cluster 1 (the “Weil’s disease” group) was the most prevalent clinical phenotype, comprising 48% of the cases (*n* = 62/130). The predominant features in this cluster were jaundice (87%) and AKI (87%). Patients



**Figure 2.** Map showing clinical clusters of ICU-admitted patients with leptospirosis. These patients' clinical features were mapped along two dimensions by unsupervised cluster analysis. *Black* indicates cluster 1 ( $n = 62$ ), the Weil's disease group. *Red* indicates cluster 2 ( $n = 27$ ), the neurologic form. *Green* indicates cluster 3 ( $n = 41$ ), the multiple organ failure group.

in cluster 1 exhibited significantly lower rates of organ dysfunction (ARF, shock, myocarditis, and renal replacement therapy) and had the lowest 30-day mortality, significantly different from patients of the two other clusters ( $p < 0.001$ ; Table 2). No patients in cluster 1 had neurologic involvement, and 8% ( $n = 5/62$ ) had myocarditis.

Cluster 2 (the “neurologic leptospirosis” group) comprised 27 patients (20%). All these patients exhibited CNS involvement at ICU admission, compared with none in the other clusters ( $p < 0.001$ ). In cluster 2, the 30-day mortality rate was 26% ( $n = 7$ ). Most patients in cluster 2 had a positive *Leptospira* antibody titer (92%) and negative PCR results (77%). When performed, PCR on CSF ( $n = 3$ ) was negative. Among the deaths in cluster 2, 43% were related to neurologic events (Table S2, <http://links.lww.com/CCX/B373>), differing from cluster 3.

Cluster 3 (the “multiple organ failure” group) comprised 41 patients (32%). These patients exhibited a higher proportion of shock and myocarditis compared with the other clusters. No patients in cluster 3 had neurologic involvement. The microbiological results did not differ from those of cluster 1. In cluster 3, the 30-day mortality rate was 22% ( $n = 9$ ), and 56% of the deaths ( $n = 5/9$ ) were secondary to refractory cardiogenic shock due to fulminant myocarditis (Table S2, <http://links.lww.com/CCX/B373>).

## Clinical Outcome

The 30-day mortality rate was 14% ( $n = 18$ ). Table 1 presents the characteristics of survivors and nonsurvivors. Univariate analysis revealed that the following factors were associated with 30-day mortality: SAPS II score (OR, 1.10; 95% CI, 1.1–1.2), ARF (OR, 9.6; 95% CI, 3–36), shock (OR, 21; 95% CI, 4–386), myocarditis (OR, 3.5; 95% CI, 1.3–10.6), CNS involvement (OR, 2.9; 95% CI, 1.0–8.4), abnormal thoracic CT scan (OR, 14.5; 95% CI, 4.8–50.4), assignment to cluster 2 (OR, 10.5; 95% CI, 2.3–74.5) or cluster 3 (OR, 8.4; 95% CI, 2.0–57.6; with cluster 1 as the reference), and hyperbilirubinemia (OR, 1.0; 95% CI, 1.0–1.0). Among the 31 patients with data available regarding serogroup, we found no association between serogroup and 30-day mortality (Table S1, <http://links.lww.com/CCX/B373>). Figure 3 shows Kaplan-Meier survival curves according to cluster (1, 2, or 3), myocarditis, and CNS involvement. Causes of death are reported in Table S2 (<http://links.lww.com/CCX/B373>).

## DISCUSSION

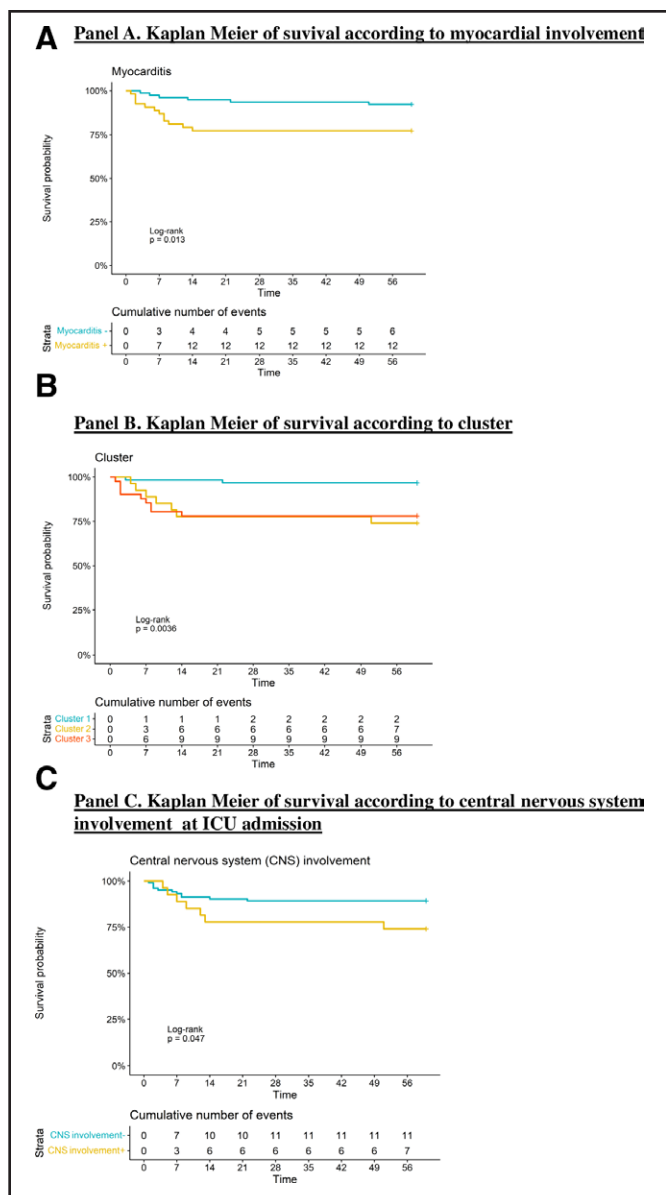
Leptospirosis is a reemerging zoonosis associated with frequent ICU admissions and a high mortality rate even with quick and appropriate treatment (4–6, 25, 30, 31). Here, we performed a retrospective study in an

**TABLE 2.**  
**Clinical and Biological Characteristics of the Three Patient Clusters**

Variables	Cluster 1: "Weil's Disease," n = 62	Cluster 2: "Neurologic Leptospirosis," n = 27	Cluster 3: "Multiple Organ Failure," n = 41	p
Male, n (%)	50 (81)	23 (85)	38 (93)	0.240
Age, yr	54 (46–66)	63 (55–73)	56 (46–62)	0.005
Simplified Acute Physiology Score II	35 (25–47)	65 (46–82)	58 (45–75)	< 0.001
Positive blood and/or urine polymerase chain reaction, n (%)	46 (77)	6 (23)	35 (88)	< 0.001
Positive <i>Leptospira</i> antibody titer, n (%)	48 (80)	24 (92)	30 (77)	0.266
Comorbidities, n (%)				
Hypertension	13 (21)	11 (41)	14 (34)	0.119
Diabetes mellitus	8 (13)	6 (22)	5 (12)	0.444
Cardiopathy	2 (3)	1 (4)	4 (10)	0.360
Kidney insufficiency	0 (0)	2 (7)	0 (0)	0.042
Alcohol use	15 (24)	10 (37)	15 (37)	0.300
Clinical features and organ involvement at ICU admission, n (%)				
Jaundice	54 (87)	24 (89)	36 (88)	1.0
Acute respiratory failure	5 (8)	12 (44)	27 (66)	< 0.001
Shock	17 (27)	14 (52)	36 (88)	< 0.001
Myocarditis	5 (8)	15 (56)	33 (80)	< 0.001
CNS involvement	0 (0)	27 (100)	0 (0)	< 0.001
Acute renal injury	54 (87)	25 (96)	39 (95)	0.317
Biological and radiological data at ICU admission				
Lactate, mmol/L	1.8 (1.0–2.5)	2.3 (1.5–4.4)	3.0 (2.3–3.9)	< 0.001
Platelets, G/L	38 (26–66)	53 (34–100)	41 (26–70)	0.230
Creatinine, μmol/L	245 (138–514)	486 (360–600)	481 (325–571)	0.007
Bilirubin, μmol/L	130 (56–223)	254 (69–360)	211 (116–367)	0.014
Abnormal thoracic CT scan, n (%)	4 (7)	8 (30)	18 (44)	< 0.001
Left ventricular ejection fraction < 40%, n (%)	0 (0)	4 (15)	10 (24)	< 0.001
Advanced life support therapy in ICU, n (%)				
Renal replacement therapy	8 (13)	14 (52)	19 (46)	< 0.001
Mechanical ventilation	2 (3)	13 (48)	19 (46)	< 0.001
Outcome				
Duration of mechanical ventilation, d	4 (4–4)	7 (4–10)	8 (2–9)	0.563
30-d mortality, n (%)	2 (3)	7 (26)	9 (22)	0.002

Results are presented as median (25th–75th quartiles) for continuous variables and n (%) for categorical variables.





**Figure 3.** Kaplan-Meier survival curves according to myocardial involvement at ICU admission (A), cluster (B), and CNS involvement at ICU admission (C).

ICU in a tropical area with a high standard of care and endemic leptospirosis, which is, to our knowledge, one of the largest such studies reported (4–6).

In contrast with previous clustering studies (5, 15), our main finding was the identification of only three clinical clusters that we named: “the Weil’s disease” group (cluster 1), the “neurologic leptospirosis” group (cluster 2), and the “multiple organ failure” group (cluster 3). These clinical phenotypes are associated with different ICU outcomes.

Among critically ill patients with leptospirosis, key components of our cluster identification are

myocarditis and neurologic involvement, factors statistically associated with death in the ICU.

As previously reported (4, 18, 30, 32), we found a significantly higher leptospirosis incidence among male patients, which is likely related to occupation and exposure bias. The organ involvement and ICU management in our study were similar to those reported in other large ICU cohorts (4–6, 18).

The “neurologic leptospirosis” phenotype was the rarest, which is consistent with previous data (5, 15, 33), and significantly differed from the two other groups by including CNS involvement at ICU admission. Notably, this group did not significantly differ from the “multiple organ failure” group in terms of the need for mechanical ventilation, shock, or rate of renal replacement therapy during the ICU course (Table 2). Neurologic patients exhibited a high prevalence of positive *Leptospira* serology (92%), with mainly negative PCR results in blood and urine (77%). These findings differed from the two other clusters and suggested that most patients with the neurologic phenotype had an early post-infectious immunological phase of the disease (1, 34). The mechanism of neurologic involvement in leptospirosis is probably multiple, including bacterial damage and immunological response (9). Neurotropism of *Leptospira* in the brain of animal reservoir hosts has previously been described (35), and positive CSF *Leptospira* PCR findings have been reported in patients with predominant CSF infection in Southeast Asia (36), suggesting a direct neuroinvasive mechanism. In the Caribbean area, neurologic leptospirosis was diagnosed in 6.5% of patients with CNS infections (according to blood/urine PCR or MAT), although *Leptospira* PCR results in CSF were always negative (37). Neurologic involvement in a large cohort of critically ill patients with leptospirosis has been associated with high mortality (5) (26% in our cohort) despite appropriate antibiotic therapy and maximal intensive care support. The potential immunological mechanism leading to this organ damage (1, 34) may suggest the value of examining adjunctive immunomodulatory or immunosuppressive therapies in such cases, although a previous trial of steroid treatment in leptospirosis (irrespective of CNS involvement) showed poor results (38). Further studies are needed to deepen our understanding of the physiopathology of neurologic disorders, particularly considering the immunological mechanism.

Leptospirosis-related myocarditis is a well-known phenomenon (13, 39), with rare cases of fulminant myocarditis (39). However, the extent of cardiac involvement in leptospirosis has been scarcely described, even though specific endocardial inflammation is observed in 96% of autopsied patients (13). Myocardial involvement is probably underdiagnosed in most leptospirosis patients (14) and occurs due to unclear mechanisms (bacterial damage and immunological response). In our study, myocarditis was frequently present at ICU admission, significantly associated with poor outcomes and was one of the discriminant variables for cluster identification. These results are consistent with the findings of previous studies, although of small size and not conducted in ICU settings (32, 39). In our series, secondary evolution toward refractory cardiogenic shock was the leading cause of death in cluster 3, which included the highest prevalence of myocarditis. Therefore, we suggest that all critically ill leptospirosis patients should be systematically examined for myocarditis at ICU admission and carefully followed during their ICU course.

In our study, ARF was frequent (affecting 34% of our patients), and thoracic CT showed predominantly interstitial pulmonary lesions. Lung involvement in leptospirosis has been well described (10, 17, 40) but is probably underestimated (17). The clinical pattern is pleomorphic, and the only specific entity described is an association between ARF and hemoptysis due to alveolar hemorrhage, defined as “severe pulmonary hemorrhagic leptospirosis” and characterized by a grim outcome (16), which seems to be rare. In our analysis, despite the frequency of ARF, we did not identify a specific respiratory cluster, in contrast with previous studies (5, 15). Notably, the presence of interstitial lesions on pulmonary CT was associated with 30-day mortality in our study (Table 1), as previously described (4, 5, 15).

The 30-day mortality rate in our study (14%) was consistent with rates reported in previous ICU cohorts (4, 5) despite the severity of the cases (i.e., the high rate of mechanical organ replacement and high SAPS II). It appears that mortality was related to the presence of specific organ involvement (lung, myocardium, and neurologic). The burdens of hemodynamic, renal failure and mechanical ventilation have been previously reported (2, 26, 30). Our present results confirmed that neurologic involvement and myocarditis

were related to death in the ICU, which warrants further studies of *Leptospira* involvement in these organs.

Results of our unsupervised analysis (clusters features and factors related with death in ICU) differ slightly from previous similar studies (5, 15, 33). Several hypotheses could be discussed to explain these differences: 1) *Leptospira* serovar geographical variation leading to different clinical features, 2) biases due to data collection in our center, and/or 3) differences in the statistical models. In the recent multicenter MCA analysis comparing nontropical and tropical critically ill leptospirosis (33), there was no significant difference in-between geographical area in the prevalence or features of the clinical phenotypes. Second, previous studies were also retrospective with similar design biases. Therefore, the only major difference in our unsupervised analysis seems to be the variables used in the statistical model (mainly myocardial involvement). Careful cardiac monitoring for all critically ill leptospirosis patients upon admission and during their ICU course in our center allowed us to use these data.

The strengths of our study are its large size and the systematic management of our patients. Our study also has several limitations. First, we could not perform multivariate analysis to predict mortality-related variables on day 30 due to the low mortality rate. Second, since this is a monocentric study, our data should be confirmed by other studies.

## CONCLUSIONS

Leptospirosis is an endemic tropical zoonosis associated with severe manifestations and frequent organ failure. Mortality in the ICU remains high, even with quick and appropriate antibiotic treatment. The physiopathology of leptospirosis organ damage is multiple (respiratory, cardiac, and neurologic), and death is most often associated with uncommon organ involvement, differing from the classical Weil’s disease form. In our study, we identified a potential association of the neurologic phenotype with a later immune phase of the disease, which could indicate the provision of specific care. We also found that leptospirosis-related myocarditis predominantly occurred in the two phenotypes with the highest mortality in the ICU—“neurologic leptospirosis” and “multiple organ failure”—and was predictive of poor outcome during the ICU course. Systematic cardiac monitoring in critically ill patients

with leptospirosis, and further clinical studies on myocardial involvement, are warranted.

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