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Acute respiratory distress syndrome in leptospirosis

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ABSTRACT

Purpose: Acute Respiratory Distress Syndrome is a major complication of leptospirosis, leading to the majority of fatalities.
Methods: Retrospective, descriptive and single-center cohort study. The primary outcome was the Standardized Mortality Ratio (SMR) for ARDS in leptospirosis based on the quartiles of the SAPS2 score in the reference population of 1683 patients hospitalized for ARDS. The second outcomes were to determine the risk factors of mortality of ARDS in leptospirosis and to describe the cases requiring Extracorporeal Membrane Oxygenation (ECMO).
Results: Of 172 leptospirosis patients from January 2004 to October 2017, 39 (23%) presented a moderate or severe ARDS with a mortality rate of 23% (9 cases). Among patients with ARDS, the SMR with regards to Simplified Acute Physiology Score II was 0.49 (CI95%: 0.21; 0.96). Risk factors associated with mortality found by bivariate analysis were Severity Acute Physiology Score II ($p = 0.01$), Sequential Organ Failure Assessment ($p = 0.01$), base excess ($p = 0.002$), kaliemia ($p = 0.004$), bilirubinemia ($p = 0.01$) and level of aspartate aminotransferase ($p = 0.01$). Eight patients underwent ECMO for refractory ARDS and six survived.
Conclusions: Leptospirosis can induce serious but transient ARDS with a better prognosis than that of other causes of ARDS. Several patients have been successfully treated with ECMO.

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1. Introduction

Leptospirosis is a common disease in French overseas territories with a high mortality rate: 8% in Reunion Island [1]. Though it is distributed worldwide, leptospirosis is more common in the tropics, where conditions for transmission are more favourable. Human infection results from direct exposure to infected urine of carrier mammals or from contamination of soil or water by wild mammals. The disease is also associated with specific occupational activities (farming, veterinary medicine, military training), recreational immersion in water, poor living conditions and seasonal rainfall in the tropics [2]. Leptospirosis produces a several array of clinical manifestations, ranging from subclinical infection to jaundice, renal failure and potentially lethal pulmonary haemorrhage [3]. Typical descriptions include a biphasic disease and a fulminating form. Moreover, leptospirosis may mimic cholangitis. Thrombocytopenia is frequent and it is associated with the occurrence of acute renal failure, which contributes in part to the hemorrhagic diathesis. Pulmonary manifestations in leptospirosis are a major complication, the most typical pulmonary involvement being intra-alveolar haemorrhage. Among a cohort of patients who underwent bronchoalveolar lavage at admission, 81.5% exhibited an alveolar haemorrhage [4].

Reunion Island is a French overseas territory located in the South-West Indian Ocean. It is one of the few world regions with a high rate of leptospirosis endemicity in which all forms of organ support are available, including Extra-Corporeal Membrane Oxygenation (ECMO) and Extra-Corporeal Life Support (ECLS). We have already demonstrated on a retrospective cohort of 134 patients that the mortality of severe leptospirosis is lower than that of other bacterial infections, provided modern resuscitation techniques are available [5]. This finding was consistent with the observational data of Indian ICUs [6] in which the mortality of tropical diseases including malaria, dengue, leptospirosis and scrub typhus, was lower than the cumulative mortality of severe sepsis and septic shock (22% *vs* 34%).

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In our practice, leptospirosis induces a severe and sudden ARDS, most often reversible within a few days. In our previously described cohort of 134 patients [5], almost all patients who died exhibited a respiratory failure. However, 28 out of 134 patients, including 7 patients who died, exhibited an ARDS, which does not allow a statistical analysis of this subgroup. Thus, we performed an ancillary study of ARDS cases of our cohort (2004–2015) with cases of leptospirosis between 2015 and 2017. Our primary endpoint was to compare the mortality of ARDS in leptospirosis with mortality in ARDS in the same ICU. A secondary outcome was to determine the ARDS risk factors of mortality in leptospirosis and to analyze the performed treatments. Finally, we describe the subgroup of patients treated with ECMO.

2. Patients and methods

2.1. Participants

Inclusion criteria were 18 years or older patients; admissions in ICU for leptospirosis; moderate or severe ARDS according to the Berlin definition [7]. Patients were identified using an electronic database. Leptospirosis cases were defined as the presence of positive urine and/or blood polymerase chain reaction (PCR) and/or serology higher than 1: 400 as measured with the Microscopic Agglutination Test (MAT) and/or the Enzyme-Linked Immunosorbent Assay (ELISA).

Intra-alveolar haemorrhage (IAH) was defined as a percentage of siderophages of 20% on the bronchoalveolar lavage and/or as macroscopically bloody bronchial aspirations associated with alveolar-interstitial syndrome on either chest radiography or chest-CT [8]. Collected data in the historical cohort were already described [5]. Additional data collected were: echocardiographic upon admission, pneumonia under mechanical ventilation, arterial gazometry before ECMO and the length of ECMO.

2.2. Study design

The primary objective of this study was to compare both mortalities in leptospirosis ARDS and in other causes of ARDS. For this purpose, we determined the expected mortality using a Standardized Mortality Ratio (SMR) approach based on the quartiles of the SAPS2 score (instead of age). Since leptospirosis affects mainly young healthy subjects, we have chosen the SAPSII as a standardization variable because this score integrates the age and comorbidities. A calculation of the SAPSII of 1683 cases of ARDS hospitalized during the same period and in the same ICU was performed in order to elaborate a population of reference. This reference population was constructed using the International Classification of Diseases, 10th Edition coding for patients hospitalized in our ICU (Code J80).

According to French law (L.1121–1 paragraph 1 and R1121–3 Public Health Code), neither informed consent nor approval by an ethics committee is necessary for the extraction of anonymous data or for the analysis of patients' medical files. We nonetheless received an approval (IRB 00010254–2017-013) from the Ethics and Research committee of French Society of Anesthesiology and Intensive Care (SFAR).

Our secondary objectives were (1) to determine risk factors of mortality by bivariate analysis in our ARDS cohort, (2) to compare mortality and length of ECMO on patients with leptospirosis and on other ECMO patients.

2.3. Statistical analysis

Qualitative variables were expressed as frequency and percentages with 95% confidence intervals (95% CI). Quantitative variables were expressed as mean ± standard deviation (SD) or as median and 1st and 3rd quartiles, as appropriate. Percentages were compared using the chi-square test or the Fisher's exact test, as appropriate. Quantitative variables were compared using the Mann and Whitney test. All statistical tests were conducted at the two-tailed level of 5%. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

A total of 172 patients were hospitalized for leptospirosis in our ICU from January 2004 to October 2017 (134 patients in our historical cohort and 38 patients between January 2015 and October 2017), 39 (23%) of them presented a moderate or severe ARDS. Their main characteristics were as follows: young (47 [33–58]), male (87%), severely ill (median SAPS II of 54 [43–69] and median SOFA score of 12 [10–15.5]). All cases but one were biologically confirmed by urine and/or blood PCR. None of the patients had been vaccinated against leptospirosis.

3.1. Clinical characteristics

Patient characteristics at baseline are presented in Table 1. The most frequent symptoms were fever (87%), myalgia (74%), jaundice (58%) and dyspnea (69%). The median respiratory rate at admission was 28 [22–36] per minute. Twenty patients (51%) had an haemoptysis. Laboratory findings on ICU admission and first days are summarized in

Table 1
Baseline and organ failures characteristics during ICU stay in 39 patients with ARDS and leptospirosis.

Characteristics		Median [Q1-Q3] or n (%)
Age (years)		47 [32–59]
Male sexe		34 (87%)
SAPS II		54 [42–70]
SOFA		12 [10–17]
Cardiovascular		1[0–4]
Respiratory		2 [2–3]
Renal		3 [1–4]
Liver		2.5 [1–4]
Neurologic		0 [0–0]
Coagulatory		2.5 [1–3]
Comorbidities		47 (35)
Diabetes		1 (3)
Chronic alcohol abuse		5 (13)
High blood pressure		4 (10)
Chronic respiratory failure		1 (3)
Ischemic heart disease		1 (3)
Smoking		12 (31)
Occupational Risk Factors of leptospirosis		18 (46)
Swimming or fishing in freshwater or canyoning		12 (31)
Organ failures at admission		
Cardiovascular	Catecholamine	35 (92)
	Noradrenalin	30 (77)
	Dobutamine	4 (10)
Renal	Acute kidney injury	36 (92)
Respiratory	Intra-alveolar haemorrhage	32 (82)
Neurologic	Meningo-encephalitis	1 (2)
Abdominal	Bilirubinemia >20 μmol.L^{-1}	31 (79)
	Gastrointestinal bleeding	4 (10)
Coagulatory	Thrombopenia <150 G.L^{-1}	36 (92)
	Thrombopenia <20 G.L^{-1}	3 (8)
Echocardiography	LVEF (%)	60 [50–65]
	LVOT VTI (cm)	16 [15–17]
	Inferior vena cava <15 mm	7 (54)
Time between beginning of symptoms and hospital admission (days)		4 [3–5]
Time between beginning of symptoms and antibiotic treatment (days)		4 [3–5]
Time between first medical consultation and ICU admission (days)		0 [0–3]
ICU length of stay (days)		11 [8–16]
Hospital length of stay (days)		17 [12–27]
ICU mortality		9 (23)

Notes. SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit; ARDS, Acute Respiratory Distress Syndrome. Acute kidney injury, Creatinemia >110 μmol.L^{-1}; LVEF, left ventricular ejection fraction; LVOT VTI, left ventricular outflow tract velocity-time integral.

Table 2
Evolution of patients with Acute Respiratory Distress Syndrome and leptospirosis during ICU stay.

	Admission	Day 1	Day 2	Day 3	Day 7
SOFA score	12 (10–17)	14 (10–19)	13 (10–19)	12 (9–19)	9 (6–13)
PaO2/FiO2 Ratio	136 (77–167)	134 (77–210)	174 (110–242)	216 (84–238)	174 (80–224)
PaCO2 (mmHg)	36 (31–45)	39 (35–43)	41 (36–45)	42 (38–46)	42 (39–46)
Lactate (mmol.L^{-1})	2 (1–5)	1.5 (1–3)	1.3 (1–2.3)	1.6 (1.2–2.1)	1.1 (0.9–1.4)
urea nitrogen (mmol.L^{-1})	15 (8–23)	15 (9–20)	11 (8–18)	10 (6–13)	12 (7–15)
Creatinemia (μmol.L^{-1})	256 (162–436)	257 (138–415)	177 (130–277)	161 (90–200)	133 (77–200)
Bilirubinemia (μmol.L^{-1})	120 (29–189)	121 (27–349)	163 (28–468)	126 (33–378)	380 (23–529)
ASAT (UI.L^{-1})	114 (51–216)	116 (52–193)	96 (65–186)	76 (53–183)	69 (46–101)
ALAT (UI.L^{-1})	66 (32–99)	64 (32−112)	62 (36–109)	58 (39–102)	64 (39–82)
White blood cells (G.L^{-1})	11.9 (8–18)	11.8 (7.8–18.6)	14 (9.8–16.4)	13.6 (10.5–17.6)	21 (18–26)
Platelets (G.L^{-1})	45 (26–106)	40 (24–93)	58 (29–115)	57 (44–127)	178 (72–353)
TroponinIc (ng/mL)	0.49 (0–41)	0.4 (0−23)	1.7 (0.2–6.5)	0.3 (0.05–2.8)	ND
Number of patients alive	39	37	36	35	34

SOFA: Sequential Organ Failure Assessment. ASAT: Aspartate transaminase. ALAT: Alanine transaminase. Quantitative variables were expressed as median and 1st and 3rd quartiles.

Table 2. Despite high levels of renal impairment (median creatininemia of 256 (162–436) μmol.L^{-1}), 24 (62%) patients presented with hypokalemia (defined as kaliemia <3.5 mmol.L^{-1}) and two (5%) patients with hyperkaliemia (kalemia >5 mmol.L^{-1}). Twenty-three patients had a severe ARDS upon admission and 10 had a moderate ARDS. Three patients had PaO_2/FiO_2 ratio > 200 on admission. One rapidly worsened to severe ARDS with ECMO implantation and subsequently died. The other two presented later moderate ARDS. Of the 39 patients, 37 underwent invasive mechanical ventilation, one patient (survivor) was treated with noninvasive ventilation, one patient (survivor) was treated with high-flow nasal cannula oxygen. Echocardiography was performed on 27 patients upon admission. Five patients had an impaired systolic function of the left ventricle. A right failure with dilatation of the right ventricle or paradoxal septum was described on two patients. In contrast, 9 patients had evidence of hypovolemia. One patient (deceased) had an influenza co-infection (AH1N1pdm2009). Seven patients, including one deceased, had ventilator-associated pneumonia (*Staphylococcus aureus* one case, *Enterobacteriaceae* three cases, *Stenotrophomonas maltophila* two cases, *Pseudomonas aeruginosa* two cases, *Burkholderia cepacia* one case).

3.2. Mortality for leptospirosis ARDS

The overall mortality of this cohort was 23% (9 patients). Hospital mortality and 28-day mortality were identical. The characteristics of the reference population are shown in Table 3. Among patients hospitalized for ARDS in our ICU, the SMR of patients with leptospirosis given the SAPSII was 0.49 (CI:0.21;0.96) (Table 4). Four patients died from refractory ARDS and four from multi-organ failure. Two patients underwent therapeutic limitations. Risk factors associated with mortality found by bivariate analysis are presented in Table 5. Surprisingly enough, neither the level of hypoxemia nor haemoptysis were associated with mortality. Acute kidney failure was also not associated with mortality although its incidence was high on survivors and non-survivors. We must stress that renal replacement therapy was quickly initiated as a rule [5]. We found hypokaliemia an element of good prognosis. The nephropathy of leptospirosis is usually associated with hypokalemia and hyperkaliemia is rather a marker of severity of the renal failure. Finally, we identified not only the classic risk factors observed on ICU admission (SOFA score, SAPS II, Base excess) but also hepatic impairment with elevated Aspartate Aminotransferase and bilirubinemia, as risk factors.

3.3. Subgroup of patients with ECMO

Data of this subgroup are presented in Table 6. Eight patients underwent ECMO for ARDS. Six survived and two presented refractory shocks (Day 1 and day 11). Among survivors, the duration of ECMO was between five and thirteen days. In these patients, ARDS was mainly a consequence of intra-alveolar haemorrhage. Thrombocytopenia, the extent of intra-alveolar haemorrhage, and transfusion support made anticoagulation questionable. Only one patient was transiently anticoagulated, but the intra-alveolar haemorrhage led to stopping this anticoagulation and to use desmopressin. Despite the absence of anticoagulation, no circuit thrombosis occurred. Two patients deceased. The first patient presenting a myocarditis responsible for refractory cardiogenic shock required ECLS. It has to be noted that earlier in the course of the disease the patient presented refractory ARDS and required ECMO, then switched to ECLS when severe hemodynamic failure occurred. Surgery was complicated by hemorrhagic shock, and the patients died in the following days. The second patient presented a refractory shock upon admission and deceased despite intensive therapy. In comparison, veno-venous ECMO were performed in our ICU during the period 2010–16 for 74 patients (age 45 [35;57] years, SAPSII 48 [33;70], duration of ECMO 10 [5;15] days, mortality 46%).

Table 3
Characteristics of the study patients and of the reference population of ARDS.

Characteristics mean (SD) or n(%)	Leptospirosis-related ARDS $n = 39$	Reference population of ARDS $n = 1683$	p
Age	45.6 (17.4)	55.4 (16.5)	<0.01
Male gender	34 (87)	1168 (69)	0.02
SAPSII	57.3 (21.3)	60.6 (26.7)	0.34
ICU length of stay (days)	13.2 (9)	14.4 (19)	0.42
Invasive Mechanical Ventilation	37 (95)	1582 (94)	0.72
Length of mechanical ventilation	10 (7)	12.7 (13)	0.02
Vasoactive or inotropic support	35 (90)	1296 (77)	0.06
Renal replacement therapy	26 (67)	757 (45)	<0.01
ECMO	8 (21)	133 (8)	<0.01
ICU mortality	9 (23)	760 (45)	<0.01

Note: SD, Standart deviation; SAPS II, Simplified Acute Physiology Score II; ICU, Intensive Care Unit; ARDS, Acute Respiratory Distress Syndrome; ECMO, Extracorporeal Membrane Oxygenation.

Table 4
Standardized Mortality Ratio of patients with leptospirosis from a reference population of patients with ARDS hospitalized in the same department.

SAPSII	Number of patients in the ARDS cohort	Mortality of ARDS cohort	Number of patients in the leptospirosis cohort	Expected mortality of leptospirosis cohort	Observed mortality of leptospirosis cohort
≤ 40	408	20,34%	9	1,83	0
41–58	432	33,10%	13	4,30	3
59–79	425	47,53%	10	4,75	2
≥ 80	418	79,43%	7	5,56	3
Total	1683	45,2%	39	16,45	8

SMR = 0.49 (IC95%: 0.21–0.96)
Quartiles were defined from 1683 cases of bacterial sepsis hospitalized in our Intensive Care Unit at the same time as patients hospitalized with leptospirosis (from 2004 to 2017). The ARDS group was defined from a primary diagnosis of ARDS. SAPS: Simplified Acute Physiology Score. ARDS: Acute Respiratory Distress Syndrome.

4. Discussion

Our main result is that the prognosis of leptospirosis-related ARDS is better in patients with leptospirosis than in other causes of ARDS. A plausible explanation is the singular pathophysiology of leptospirosis respiratory involvement. The mechanisms often considered are a direct effect of bacterial inoculum [9] or an unidentified bacterial toxin or an indirect effect mediated by host response. In humans, leptospirosis differs from of other causes of pulmonary haemorrhage with linear depositions of immunoglobulins and complement on the alveolar surface [10]. Lung endothelial cells have been suggested as targets in the lung involvement in leptospirosis through the activation of Toll-like receptor 2 or the complement system, which stimulates the release of cytokines that lead to the activation of adhesion molecules: vascular cell adhesion molecule [11], soluble *E*-selectin and soluble InterCellular Adhesion Molecule 1 [12]. Moreover, research indicates a potential role of different cytokines and enzyme expressions in blood leucocytes on the severity of the disease and occurrence of bleeding. Two subphenotypes of ARDS have been identified [13]; higher plasma levels of inflammatory biomarkers, including Interleukin-8, characterize the second phenotype. Despite its probable immunological mechanism, Interleukin-8 is not elevated in leptospirosis [14,15]. Therefore, the mechanisms of the leptospirosis ARDS seem specific and further studies are needed to decipher the innate immunity role in severity of the disease. Is the low mortality we report related to the early renal replacement therapy? We do not have biological data to document it.

Table 5
Bivariate analysis of risk factors associated with mortality for 39 patients with leptospirosis and ARDS (SAPS II, Severity Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment).

Risk factors	Non survivors ($n = 9$)	Survivors ($n = 30$)	p
Median (IQ1;IQ3) or n(%)			
Age	51.0 (47.0–66.0)	45.5 (29.0–57.0)	0.17
Male gender	7 (77.8%)	27 (90.0%)	0.57
Smoking	2 (22.2%)	10 (33.3%)	0.69
Oligoanuria	5 (62.5%)	11 (47.8%)	0.69
Haemoptysis	3 (33.3%)	17 (56.7%)	0.27
Intra-alveolar haemorrhage	6 (66.7%)	26 (86.7%)	0.32
SAPS II	67.0 (57.0–83.0)	49.0 (35.0–67.0)	0.01
SOFA	18.0 (12.0–19.0)	11.5 (9.0–14.0)	0.01
Time between beginning of symptoms and antibiotics (days)	3.5 (3.0–4.5)	4.0 (3.0–6.0)	0.37
Laboratory findings			
pH	7.3 (7.2–7.4)	7.4 (7.3–7.4)	0.13
Base excess ($mmol.L^{-1}$)	−6.0 (−17.5–4.5)	−1.5 (−4.0–0.0)	0.002
Lactate ($mmol.L^{-1}$)	8.7 (2.7–22.0)	2.0 (1.2–3.2)	0.08
Blood urea nitrogen ($mmol.L^{-1}$)	15.3 (10–23.3)	13.5 (7.7–19.2)	0.35
Creatinine ($\mu mol.L^{-1}$)	256.0 (208.0–559.0)	271.5 (162.0–402.0)	0.46
Kalemia ($mmol.L^{-1}$)	4.3 (3.7–4.9)	3.3 (3.1–3.6)	0.004
Total bilirubin ($\mu mol.L^{-1}$)	279.0 (121.0–396.0)	50.0 (27.0–169.0)	0.01
Aspartate aminotransférase	245.0 (170.0–288.0)	87.5 (37.0–158.0)	0.01
Prothrombin time	0.7 (0.4–0.8)	0.8 (0.7–0.9)	0.09
Platelets ($G.L^{-1}$)	45.5 (26.0–106.0)	38.0 (26.0–71.0)	0.62
PaO_2/FiO_2 ratio	181.5 (112.0–241.0)	105.0 (76.0–165.0)	0.15
$PaCO_2$	36.5 (23.0–54.5)	36.0 (32.5–44.0)	0.53
Therapeutics			
Vasoactive or inotropic support	9 (100%)	27 (90%)	1
Renal replacement therapy	8 (88.9%)	18 (60.0%)	0.23
Transfusion	3 (37.5%)	4 (16.7%)	0.33

Risk factors for mortality were those usually found in resuscitation studies, but also serum potassium and liver injury. Indeed, serum potassium is a classic risk factor for mortality in leptospirosis because renal damage is initially hypokaliaemic [16].

Bilirubinemia was found also to be a risk factor for mortality. Former studies have found hyperbilirubinemia to be a risk factor for mortality in ARDS [17,18]. Even though the links between ARDS and liver impairment are tenuous, the latter results from hypoperfusion, acute hypoxia and passive liver congestion. Furthermore, high-level concentration of bilirubin is known to contribute to the development of respiratory failure. As cellular lyses of erythrocytes increases, the oxidative stress observed in hyperbilirubinemia reduces cell survival, favours apoptosis and contributes to the inflammatory syndrome [19,20]. Thus, whether it is a cause or a consequence of ARDS in leptospirosis, hyperbilirubinemia seems to be a predictive factor for mortality.

To our knowledge, this is the largest case series of patients treated with ECMO for leptospirosis. However, these eight cases do not allow us to reach a statistical conclusion. The interest of this technique remains difficult to demonstrate [21]. Mortality appears to be lower than that on other ECMO indications. Empirical evidence is that leptospirosis is a good indication of ECMO because respiratory failure is profound, but not durable, and because, in our experience, leptospirosis doesn't lead to pulmonary fibrosis.

One of the major limitations of this study is related to the retrospective and monocentric model. However, the monocentric nature of the study allows describing a cohort with homogeneous care. Our management is characterized by early renal replacement therapy (hemofiltration) and the use of ECMO, which is not available in other centres in Reunion Island. Moreover, our admission criteria are broad with regards to this pathology that affects young and active people with a risk of rapid aggravation. Another limitation is the construction of the reference population. The patients in this population were defined on the basis of their ICD10 score and not with the Berlin criteria. On the one hand, the Berlin criteria were not defined at the time of hospitalization for a majority of patients and the quality of medical procedures quotations may have varied between 2004 and 2017. It is

Table 6
Characteristics of 8 patients requiring Extracorporeal Membrane Oxygenation (ECMO) for leptospirosis.

Patient	1	2[a]	3	4	5	6	7	8
SAPS II	67	91	70	34	30	83	35	59
Type ECMO	VV-ECMO then central ECLS	VV- ECMO	VV- ECMO	VV- ECMO	VV- ECMO	VV-ECMO	VV- ECMO	VV-ECMO
Length of mechanical ventilation before ECMO	< 6 h	9 h	2 h	6 h	1 day	6 h	34 h	21 h
pH before ECMO	7.17	6.93	7.33	6.98	7.32	6.88	7.3	7.25
PaO2/FiO2 ratio before ECMO	37	56	41	56	56	63	70	82
PaCO2 before ECMO	60	89	44	50	43	43	50	32
Use or not of anticoagulation	no	No	No	No	Yes[b]	No	No	No
Duration of ECMO (day)	11	6	13	5	7	1	11	6
Total time of mechanical ventilation	11	17	15	10	9	1	13	9
ICU and hospital outcome.	No survival	Survival	Survival	Survival	Survival	No survival	Survival	Survival
Replacement Renal therapy	1	1	1	1	0	1	0	0
Pump flow (L.min-1)	5.5	6.5	7	4	4.5	4	5	4.4
Desmopressine	0	0	1	0	1	0	1	1

[a] This case was described in [22].
[b] But transient arrest for hemoptysis and addition of desmopressin.

therefore likely that some patients fulfilling the Berlin criteria were not included in our reference population. Of 39 patients with leptospirosis and ARDS fulfilling the Berlin criteria, only 6 patients were not defined initially as ARDS. They have been added to the reference population. By standardizing on SAPSII, it is likely that this lack of completeness on the reference population does not affect the result. Another limitation is that the low mortality rate (<10 cases) did not allow performing a multivariate analysis, but a bivariate analysis. Finally, in fourteen years, the management of the ARDS has evolved and now combines curarization, prone position, ECMO (Annex 1). These changes modified our practice but also affected patients with leptospirosis and those with another disease, allowing us to compare by SMR.

In conclusion, leptospirosis can induce serious but transient ARDS. The pathophysiology of leptospirosis-related ARDS is not well understood, but its prognosis is better than for other causes. ECMO seems an effective treatment in case of very severe ARDS.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.02.018.

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