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L'atteinte pulmonaire en tant que composante d'un syndrome de défaillance multiviscérale chez les chiens atteints de leptospirose

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Abstract.

Anglais : Background: The objectives of this study were to assess the frequency of pulmonary dysfunction as a component of multiple organ dysfunction syndrome (MODS) in dogs with leptospirosis and to identify risk factors associated with mortality. **Methods:** Records of 27 dogs with leptospirosis were retrospectively reviewed. Thoracic radiographs during hospitalisation were mandatory for inclusion. A MODS was defined as the dysfunction of at least two organs or functions. Pulmonary dysfunction was defined as abnormal respiratory clinical signs associated with abnormal thoracic radiographs. Survival was assessed using Kaplan-Meier product limit estimates, and differences between groups were assessed using log rank tests. **Results:** Twenty-one dogs (78%) exhibited a MODS. The median number of organ dysfunction was two. Ten dogs (37%) had a pulmonary dysfunction which was always part of a MODS. The overall mortality rate was 41%. The log-rank test showed an association between mortality and pulmonary dysfunction ($P = 0.04$), haemostatic dysfunction ($P = 0.02$), gastrointestinal dysfunction ($P = 0.002$) and with ≥ 3 organ dysfunctions ($P < 0.001$). **Conclusion:** Pulmonary dysfunction occurred in about one third of critically ill dogs with leptospirosis and was always a component of MODS. The number of organ dysfunctions, and pulmonary, gastro-intestinal, and haemostatic dysfunctions were associated with mortality.

Key-words: Leptospirosis, multiple organ dysfunction syndrome, pulmonary haemorrhages

Français : Propos : Ce travail avait pour objectif d'étudier le dysfonctionnement pulmonaire en tant que composante du syndrome de défaillance multiviscérale (SDM) chez les chiens atteints de leptospirose. **Matériel et Méthodes :** Les dossiers de 27 chiens ont été examinés rétrospectivement. L'absence de radiographies thoraciques était un critère d'exclusion. Un SDM a été défini comme le dysfonctionnement d'au moins deux organes ou fonctions. Le dysfonctionnement pulmonaire était défini par la présence de signes cliniques respiratoires associés à des radiographies thoraciques anormales. La survie a été évaluée à l'aide de courbes de Kaplan-Meier. **Résultats :** 21 chiens (78%) ont présenté un SDM. Le nombre médian de dysfonctionnements d'organes était de deux. Dix chiens (37%) avaient un dysfonctionnement pulmonaire qui faisait toujours partie d'un SDM. Le taux de mortalité était de 41%. On observait une association entre la mortalité et le dysfonctionnement pulmonaire ($P = 0,04$), hémostatique ($P = 0,02$), gastro-intestinal ($P = 0,002$) et avec ≥ 3 dysfonctionnements d'organes ($P < 0,001$). **Conclusion :** Un dysfonctionnement pulmonaire est survenu chez environ un tiers des chiens atteints de leptospirose et a

toujours été une composante du SDM. Le nombre de dysfonctionnements d'organes et les atteintes pulmonaires, gastro-intestinaux et hémostatiques étaient associés à la mortalité.

Mots-clés : leptospirose, syndrome de défaillance multiviscérale, hémorragies pulmonaires

Introduction

In human medicine, multiple organ dysfunction syndrome (MODS) has recently been defined as "an acute change in total sequential (sepsis-related) organ failure assessment (SOFA) score ≥2 points consequent to the infection" (1). In other words, MODS is clinically defined by a progressive, but potentially reversible, dysfunction of 2 or more organ systems (2). Occurrence of MODS has been reported in severe forms of leptospirosis in humans (3–6). Acute kidney injury (AKI), hepatic involvement, and pulmonary dysfunction are the most common features reported in dogs with leptospirosis (7–9). Other conditions including pancreatitis, gastroenteritis and haemostatic disorders are also encountered and could be involved in a MODS (7,9,10).

Pulmonary involvement associated with leptospirosis in dogs seems very similar to the leptospiral pulmonary haemorrhage syndrome (LPHS) described in humans (9,11), primarily in South America (12), Reunion Island (13), Iran (4,14) and Southeast Asia (15–18). Twenty-six to 80% of human patients with leptospirosis exhibit respiratory signs such as dyspnoea, coughing, haemoptysis, acute respiratory distress syndrome, chest pain and pulmonary crackles (13,15,16,19). In dogs, pulmonary involvement seems to be an emerging form of leptospirosis, especially in Europe with a prevalence of respiratory signs between 62% and 85% (9,11).

The objectives of this study were (1) to assess the frequency of MODS including pulmonary dysfunction, and (2) to identify risk factors and organ dysfunctions associated with death in a population of critically ill dogs with leptospirosis in France.

Materials and Methods

Medical records

The medical records of dogs with a confirmed diagnosis of leptospirosis presented at an intensive care unit of a veterinary School between January 1st, 2010 and December 31st, 2012 were retrospectively reviewed. Dogs were eligible for inclusion if the diagnosis of leptospirosis was confirmed and if thoracic

radiographs were obtained during hospitalization. Clinical information collected for each case included signalment, history, physical signs, results of Complete Blood Count (CBC) and biochemistry panel at admission, abdominal ultrasounds, thoracic radiographs, realization of extracorporeal renal replacement therapy (ERRT) sessions and outcomes.

Leptospirosis diagnosis

Dogs were diagnosed with leptospirosis if they had one or more condition(s) consistent with the disease (AKI, glycosuria without hyperglycaemia, acute hepatitis, haemorrhagic syndrome, haemorrhagic gastro-enteritis) and if they met at least one of the three following criteria: a single micro agglutination test (MAT) titre ≥ 1:800 for non-vaccine serovars or ≥ 1:1600 for vaccine serovars for vaccinated dogs, or a single MAT titre ≥ 1:800 for any serovar for non-vaccinated dogs; a 4-fold rise in convalescent titres; or a urine or blood positive polymerase chain reaction (PCR) (7,10,20). Nineteen serovars (Australis, Bratislava, München, Autumnalis, Bim, Canicola, Grippotyphosa, Vanderhoedoni, Icterohaemorrhagiae, Copenhageni, Panama, Mangus, Pomona, Mozdok, Pyrogenes, Sejroe, Saxkoebing, Hardjo, Wolfii) representing nine serogroups (Australis, Autumnalis, Canicola, Grippotyphosa, Icterohaemorrhagiae, Panama, Pomona, Pyrogenes and Sejroe) were tested for MAT. Diagnostic analyses were realized at the French National Laboratory of Leptospira (Laboratoire des Leptospires, VetAgro Sup, Campus vétérinaire de Lyon, 1 avenue Bourgelat, 69280 Marcy L'Etoile).

Thoracic radiographs

To avoid any interpretation bias, thoracic radiographs from dogs with leptospirosis were mixed with normal thoracic radiographs (from 10 dogs) randomly selected from the facility database. These radiographs were evaluated retrospectively and blindly by two radiologists, one of whom is a board-certified clinical radiologist. In case of disagreement, the two radiologists met to find a consensus. The same reading grid was used for the analysis of all radiographs. The criteria reviewed were the presence or absence of pleural effusion, presence or absence of interstitial and alveolar patterns and, in cases with abnormalities, the lesions distribution. Abnormalities that were consistent with the age or degree of obesity of the dog were not considered.

Clinical signs (peripheral oedema, decreased skin turgor, and acute weight gain) and radiographic signs (pulmonary veins enlargement and the presence of pleural effusion) of fluid overload were recorded

to investigate the potential impact of fluid overload on radiographic lung opacity. The association between the realization of ERRT and the presence of abnormal radiographic lung opacity was also studied.

Groups and multiple organ dysfunction syndrome definition

Five groups were defined based on the presence of organ failure, each dog could be included in several groups if he had several organ failures:

1. Renal dysfunction was defined according to the criteria of azotaemia AKI of International Renal Interest Society grading system (serum creatinine concentrations >140 µmol/L) in the absence of prerenal and postrenal azotaemia (21). Prerenal azotaemia was excluded if the hydration status was adequate, and postrenal azotaemia was excluded if there was no evidence of urinary tract obstruction or rupture.

2. Hepatic dysfunction was defined as the presence of hyperbilirubinemia (> 8 µmol/L) in the absence of haemolysis (22) and the absence of bile duct obstruction.

3. Haemostatic dysfunction was defined as a prolongation of the prothrombin time (PT) and/or the activated partial thromboplastin time (aPTT) of > 25% above the upper reference limit and/or a platelet count < 100,000 $x10^9$/L (22).

4. Gastrointestinal dysfunction was defined as acute diarrhoea or vomiting associated with gastrointestinal ultrasonographic findings consistent with gastritis or enteritis.

5. Pulmonary dysfunction was defined as respiratory signs at admission and/or during hospitalization and abnormal lung radio-opacity. Respiratory signs included dyspnoea, tachypnoea, cough, crackles, rapid closed-mouth breathing, open-mouth breathing, haemoptysis and cyanotic mucous membranes.

MODS was defined as a dysfunction of 2 or more organ systems among the previous ones defined (2).

Statistical analysis

The results are expressed as the median (range), and categorical variables are summarized as percentages of the total. Normality was assessed using the Shapiro Wilk normality test. Mann-Whitney *U* tests were used to compare quantitative parameters between dogs with and without pulmonary dysfunction. Qualitative data were compared using Fisher's exact test. Fluid overload signs and dialysis

requirements were also compared to test the potential association between intravenous fluid therapy or ERRT and pulmonary manifestations of leptospirosis. Survival was assessed using Kaplan-Meier product limit estimates, and differences between groups were assessed using log rank tests. Hazard Ratio (HR) associated with its 95% confidence intervals (CI) were calculated. A *P*-value less than 0.05 was considered significant. All analyses were performed using commercial software (R version 3.1.0 (https://www.r-project.org/)).

Results

Forty-three dogs were diagnosed with leptospirosis requiring intensive care during the inclusion period. Sixteen dogs were excluded because of lack of thoracic radiographs. The remaining 27 dogs were included in the study.

Epidemiological data

Twenty breeds were represented; 18 of the 27 (67%) dogs were medium or large breeds. The median weight was 29.1 kg (range, 4.8–56.9 kg). The age of the dogs ranged from 0.5 to 12 years (median, 6.5 years). Twenty dogs (74%) were male (18 intact (67%) and 2 neutered (7%)) and 7 (26%) were females (3 intact (11%) and 4 spayed (15%)). Seventeen dogs (73%) had been vaccinated against leptospirosis within the last year, all with a bivalent vaccine (Nobivac® lepto, MSD Santé Animale, Beaucouzé, France; Canigen®, Virbac France, Carros, France; Eurican®, Merial, Lyon, France). Six dogs (27%) were not vaccinated against leptospirosis. The vaccination status of 4 dogs was unknown.

Leptospirosis diagnosis

Leptospirosis was diagnosed by MAT in 14/27 (52%) dogs (single elevated MAT titres for 12/14 dogs [median of the highest titre, 1:800; range, 1:800 to 1:3200] and a 4-fold rise in convalescent titres for 2/14 dogs [median of the highest titre, 1:3200; range, 1:3200 to 1:6400]), by PCR in 5/27 (18%) dogs (positive PCR results from both blood and urine for 3/5 dogs, positive PCR results from only blood or urine for 2/5 dogs), and by the combination of MAT and PCR results in 8/27 dogs (30%). The most commonly represented serogroups were Australis, Icterohaemorrhagiae and Autumnalis (Table 1).

Thoracic radiographic findings

Thoracic radiographic findings are summarized in Table 2. All control thoracic radiographs were classified as normal. Among the 27 dogs, 16 (59%) had abnormal thoracic radiographs: 16 dogs had interstitial pattern (59%), and 6 dogs had patchy alveolar pattern (22%). All these abnormalities were bilaterally distributed in 13 dogs (48%).

Radiographic signs compatible with fluid overload were found in 7 dogs (%): 4 dogs had pleural effusion (15%), and 3 (11%) dogs had pulmonary vein enlargement. Three dogs (11%) had clinical signs consistent with fluid overload (peripheral oedema, decreased skin turgor, and acute weight gain). Among these 3 dogs, 2 dogs had pleural effusion but no pulmonary vein enlargement. The last one exhibited normal thoracic X-ray. Abnormal lung radio-opacity was not associated with clinical (P = 1) or radiographic signs (pulmonary vein enlargement (P = 1) and pleural effusion (P = 0.6)) of fluid overload.

ERRT sessions were conducted in 17 dogs (63%). Among these dogs, 10 (37%) had abnormal thoracic radiographs: 10 dogs had interstitial pattern (37%) and 7 dogs had alveolar pattern (26%). Abnormal lung radio-opacity was not associated with the realization of ERRT sessions (P = 0.7).

The presence of interstitial pattern (P = 0.4) and alveolar pattern (P = 1) were not associated with mortality rates.

Organ dysfunctions and multiple organ dysfunctions

1. Renal dysfunction: Renal dysfunction was the most commonly observed organ dysfunction (25/27 (93%)). Among dogs with renal dysfunction, 11 (41%) dogs had oligo-anuria (diuresis < 0.5ml/kg/h). No dogs exhibit prerenal or postrenal azotaemia.
2. Hepatic dysfunction: 12 dogs (44%) had hepatic dysfunction. Among these dogs, 8 (30%) exhibit icteric mucous membranes.
3. Haemostatic dysfunction: 12 dogs (44%) had haemostatic dysfunction. Among them, 6 dogs (22%) had an increased PT, 12 dogs (44%) had an increased aPTT and 12 dogs (44%) had a platelet count < 100,000 $x10^9$/L. Six dogs (22%) had thrombocytopenia associated with both an increase in PT and aPTT.
4. Gastrointestinal dysfunction: 8 dogs (30%) had gastrointestinal dysfunction. All dogs exhibited diarrhoea and vomiting, and had ultrasonographic signs of gastritis and enteritis. Three dogs (11%) had haematochezia and 2 dogs (7%) had hematemesis.

5. Pulmonary dysfunction: Sixteen dogs (59%) exhibited respiratory signs, 12 dogs (44%) at admission and 4 additional dogs (15%) during hospitalization. Tachypnoea was observed in 16 dogs (59%), dyspnoea in 9 dogs (33%), crackles in 4 dogs (15%), cough, cyanotic mucous membranes and open-mouth breathing in 2 dogs (7% for each), and haemoptysis in 1 dog (4%). Mechanical ventilation was used in 1 dog with a respiratory distress associated with a decreased PaO_2/FiO_2 ratio (PaO_2/FiO_2 = 180; PaO_2: arterial O_2 partial pressure, FiO_2: fraction of inspired oxygen). In accordance with our definition, 10 dogs (37%) had a pulmonary dysfunction. There was no association between respiratory signs and radiographic abnormalities (P = 0.7). No association was found between clinical signs of fluid overload (3 dogs, 11%) and pulmonary dysfunction (P = 1). No association was found between ERRT requirements and pulmonary dysfunction (P = 0.7). No association was found between biochemical or haematological abnormalities and pulmonary dysfunction (Table 3).

MODS was observed in 21 dogs (78%). The distribution of organ dysfunctions is summarized in Table 4. The median number of organ dysfunction was 2. For the survival analysis, dogs were therefore separated into two groups: those with 1 or 2 dysfunctions and those with ≥ 3 dysfunctions. Twenty-one dogs (78%) exhibited ≥ 2 organ dysfunctions, 10 dogs (37%) exhibited ≥ 3 organ dysfunctions, 7 dogs (26%) had ≥ 4 organ dysfunctions, and 2 dogs (7%) had 5 organ dysfunctions. Pulmonary dysfunction was always associated with at least another organ dysfunction.

Survival Analysis

The overall mortality rate was 41% (11/27 dogs). Seven dogs (26%) died naturally, one of these dogs died following a severe respiratory distress episode associated with haemoptysis. Four dogs (15%) were euthanized for medical or financial reasons. The overall mortality rate in dogs with MODS was 48% (10/21). A significant difference between mortality rates as a function of the number of organ dysfunctions was observed (Fisher's exact test, P = 0.0003). The mortality rates according to the number of organ dysfunctions are reported in Table 4. The Kaplan-Meier survival curves for mortality during hospitalization are presented in Figure 1. The log-rank test showed a statistically significant association between mortality and pulmonary dysfunction (P = 0.04; HR = 3.7; 95% CI = 1.1 – 14.1), haemostatic dysfunction (P = 0.02; HR = 4.5; 95% CI = 1.3 – 16.4), gastrointestinal dysfunction (P = 0.002; HR = 10.0; 95% CI = 2.3 – 43.0) and with ≥ 3 organ dysfunctions (P < 0.001, HR = 13.0, 95% CI = 3.4 – 50.4;

Figure 1). Renal and hepatic dysfunctions were not associated with mortality (P = 0.6 and P = 0.08, respectively).

Discussion

This current retrospective study provides an investigation of MODS in canine naturally-occurring leptospirosis and the associated pulmonary dysfunction. Our results suggest that MODS is a common complication of leptospirosis in critically-ill dogs in France with a frequency of 78% in our study. The most frequent dysfunctions observed were, in order of frequency: renal dysfunction (89%), hepatic and haemostatic dysfunctions (44%), pulmonary dysfunction (37%) and gastrointestinal dysfunction (30%). The presence of a pulmonary dysfunction was always associated with another organ dysfunction, occurring always in a MODS as previously defined. Pulmonary, gastrointestinal and haemostatic dysfunctions, and the presence of at least 3 organ dysfunctions were identified as significantly associated with mortality.

In our study, thoracic radiographs have been performed at admission or during hospitalization. It remains possible that some therapeutic procedures, such as intravenous fluid therapy and ERRT treatments, or biochemical disorders such as hypoalbuminemia could have favoured the occurrence of certain radiographic abnormalities. Fluid overload can cause alveolar pattern. However, fluid overload was suspected in only three dogs in this study and pulmonary vein congestion or pleural effusion, which are common features of fluid overload (23), were not associated with abnormal lung opacity. No association was found between ERRT realisation and abnormal lung opacity and between ERRT and pulmonary dysfunction, making anticoagulation therapy used during ERRT sessions unlikely to be responsible for the radiographic pulmonary abnormalities. Finally, there was a discrepancy between respiratory clinical signs and radiographic lung lesions: some dogs had abnormal thoracic X-rays without respiratory signs and some dogs had respiratory clinical signs with normal thoracic X-rays. No correlation was found between radiographic lung lesions and respiratory clinical signs, neither in the veterinary (11) nor in the human literature (15). In a study of 118 human patients, 40% had respiratory symptoms and among them, only 56 had abnormal X-rays (16). Indeed, other extra-respiratory factors, such as pain, the stress induced by the hospitalization, or acidosis, might explain respiratory signs without parenchymal lesions. For this reason, pulmonary dysfunction was defined as the association of abnormal respiratory signs and radiographic abnormalities. Interestingly, radiographic abnormalities were not associated with

mortality rates, whereas an association between pulmonary dysfunction and mortality did exist. This observation is at least partially linked to the fact that the definition of pulmonary involvement is not only radiographic but also includes clinical criteria. Moreover, in this study, lung involvement is always associated with another organ dysfunction. This combination of organ failures could also partially explain the association between lung damage and mortality. To our knowledge, this link has not been previously questioned in the veterinary literature. The articles by Kohn et al. and Major et al. for example did not study this association (9,11). In the human literature, a statistically significant association between alveolar abnormalities and mortality has been observed (24). The absence of association in our study could be secondary to a lack of statistical power.

In the current study, most of the dogs (78%) exhibited at least two organ dysfunctions. This result is similar to that of a previous Swiss study in which 75% of 298 dogs had at least two organ dysfunctions (9). In both studies, two was the median number of organ dysfunctions. The most frequent organ dysfunctions reported in dogs with leptospirosis in the literature is renal (57 to 100%), pulmonary (0 to 85%), and hepatic (20 to 81%) (7–9,11,25–28). These observations suggest that the development of MODS may be common in leptospirosis in dogs. In humans, leptospirosis is a well-known cause of MODS (3–6,29). The most frequently described dysfunctions are renal, hepatic, pulmonary, cardiovascular and haematological (12,13,18). Although combined organ dysfunctions have been clearly described previously in canine leptospirosis (9,11), the term MODS has never been used unlike in human medicine. In the current study, leptospirosis was presented as a form of MODS. Indeed, the MODS is a syndrome characterized by an association of organ dysfunctions secondary to a systemic inflammatory syndrome. This inflammation is very often caused by sepsis (30). Several arguments show that leptospirosis can be considered as a form of sepsis. For example, clinical signs of SIRS were observed in 70% of patients in a human study (31). In addition, experimental studies in animal models and medical human studies confirm the pathophysiological similarity of inflammatory reactions secondary to leptospirosis or other forms of bacterial sepsis (32,33): leptospiral elements (i.e. lipopolysaccharide LPS) are recognized by receptors (mainly Toll Like Receptors TLRs 2 and 4) and trigger a "cytokine storm", via activation of the NF-kB pathway, associating proinflammatory cytokines (such as Interleukins: IL-1B, IL-6 or TNFα) and anti-inflammatory cytokines (such as IL-10). The anti-inflammatory response can then be at the origin of an immunoparalysis as observed in other sepsis (33,34).

In the current study, pulmonary, gastrointestinal and haemostatic dysfunctions were significantly associated with death. Major et al. (9) described relatively similar results: pulmonary, haemostatic and hepatic dysfunction were associated with mortality. Gastrointestinal dysfunction was not studied. Pulmonary dysfunction is associated with potentially massive pulmonary haemorrhages and is known to be a life-threatening form of leptospirosis in dogs (9,11) and in humans (13,17). However, all dogs with pulmonary dysfunction in our study had at least another organ dysfunction making unsure the association observed between "pulmonary dysfunction" and a high mortality rate observed in the current study to be carefully interpreted. This association of at least 2 dysfunctions can partially explain the high mortality rate. Indeed, we observe in our study that the increase in the number of dysfunctions is associated with higher mortality rate.

In this study, an association was observed between haemostatic dysfunction and mortality. Haemostatic dysfunction as previously defined in the current study is associated with an hypocoagulable state. A previous study reported that a hypocoagulable thromboelastometric profile was significantly correlated with haemorrhagic diathesis and higher mortality rate in dogs with leptospirosis (10). It has been hypothesised that haemostasis would favour immunity by allowing the compartmentalization of the infection and activating immune cells (35).Thus, an hypocoagulable state would favour the dissemination of bacteria and as a consequence the progression of MODS and death.

One of the original features of our study is the description of gastrointestinal dysfunction. This failure seems to be of paramount importance in the pathophysiology of MODS (30) and is associated with high morbidity and mortality (36). Gastrointestinal dysfunction is often reported but has no consensual definition (30). As for pulmonary dysfunction, we decided to define gastrointestinal dysfunction as the association of compatible clinical signs and ultrasonographic changes revealing the presence of lesions. Pathophysiology of gastrointestinal dysfunction is probably multifactorial. Inflammation caused by the pathogen, renal dysfunction, and associated pancreatitis or hepatitis could be involved (7). In our study, gastrointestinal dysfunction was the dysfunction associated with the highest risk of death. This result could be explained by the role of gastrointestinal mucosal permeability impairment in the progression of MODS, triggered by inflammation, hypoxia and oxidative stress. The alterations of digestive permeability may induce intestinal translocation of endogenous bacteria or endotoxins, which could stimulate the immune response participating to the pathophysiology of MODS. This mechanism can

be exacerbated during liver failure (which can be observed during leptospirosis, due to the lack of elimination of pathogens by Kupffer cells (30).

Surprisingly, hepatic and renal dysfunctions were not associated with mortality in our study. Hepatic involvement is usually considered to worsen prognosis (9). Given the relatively low P-value concerning the association between mortality and hepatic dysfunction (P = 0.08), it is likely that an association could have been demonstrated with a larger population. The lack of association between renal failure and mortality is probably linked to a lack of statistical power. Indeed, only two dogs did not have AKI. This small size of the population reduces the power of survival analysis.

In the current study, the number of dysfunctions was correlated with mortality, as reported in two studies of humans with leptospirosis (12,18). In the first study, non-survivors had more organ dysfunctions than survivors (12). In the second study, the mortality rate increased with the incrementing number of organ dysfunctions, reaching 83% for people with 4 organ dysfunctions (18). The correlation between the number of organs failure and the mortality rate was also described in other causes of sepsis in dogs (22) and in humans (1).

One major limitation of this study is its retrospective nature leading to a heterogeneity in the population studied. All eligible dogs with chest radiographs were included without considering the time of realization and the reason for them. During the inclusion period, thoracic radiographs have been performed on the discretion of the clinician. Consequently, it remains highly likely that global frequency of dogs with leptospirosis having pulmonary dysfunction was overestimated. In addition, some dogs arriving in severe respiratory distress died promptly, not allowing X-rays to be performed. These dogs could not be included in the study. Prospective studies in which thoracic radiographs will be systematically performed in a timely manner are warranted to better evaluate the frequency of pulmonary dysfunction. Another limitation is the small sample size, which decreased the power of the statistical tests. Moreover, there is no consensus to define most of organ dysfunctions. It remains unclear whether definitions adopted in this study, particularly the definition of pulmonary and gastrointestinal dysfunctions, could have underestimate or overestimate the frequencies of some organ dysfunctions.

Conclusion

in this study, MODS was documented with a high frequency (78%) in critically ill dogs with leptospirosis. Pulmonary dysfunction appeared as a component of MODS and was always associated with at least another organ dysfunction. The number of organ dysfunctions was significantly associated with mortality as well as the presence of pulmonary, gastro-intestinal, or haemostatic dysfunctions. Considering the clinical and pathophysiological similarities between leptospirosis and other causes of sepsis, the authors propose to consider leptospirosis as a sepsis that may be the cause of MODS. In the same way, canine leptospirosis could be used and studied as a spontaneous model for MODS in dogs.

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Tables

Table 1. Distribution of serogroups and serovars identified by microagglutination test (MAT) in 27 dogs with leptospirosis based on admission single MAT titres ≥1: 1600 for vaccine serovars (from the serogroups Icterohaemorrhagiae and Canicola) or ≥1: 800 for nonvaccine serovars

Serogroup	Serovar	All dogs (*n* = 22)	With 1 OD[a] (*n* = 6)	With 2 ODs[a] (*n* = 10)	With 3 ODs[a] (*n* = 1)	With 4 ODs[a] (*n* = 4)	With 5 ODs[a] (*n* = 1)
Icterohemorragiae	Icterohemorragiae	4	0	2	0	2	0
	Copenhageni	7	2	2	0	2	1
Australis	Australis	13	4	6	0	2	1
	Bratislava	12	2	6	1	2	1
	Munchen	17	4	9	1	2	1
Autumnalis	Autumnalis	0	0	0	0	0	0
	Bim	7	4	1	0	1	1
Ballum	Castellonis	0	0	0	0	0	0
Bataviae	Bataviae	0	0	0	0	0	0
Canicola	Canicola	1	0	1	0	0	0
Grippotyphosa	Grippotyphosa	3	0	2	1	0	0
	Vanderhoedoni	2	1	1	0	0	0
Hebdomadis	Hebdomadis	0	0	0	0	0	0
	Kremastos	0	0	0	0	0	0
Panama	Mangus	7	3	2	0	1	1
	Panama	1	0	1	0	0	0
Pomona	Mozdok	0	0	0	0	0	0
	Pomona	1	1	0	0	0	0
Pyrogenes	Pyrogenes	0	0	0	0	0	0
Sejroe	Sejroe	1	0	1	0	0	0
	Saxkoebing	1	0	1	0	0	0
	Hardjo	1	0	1	0	0	0
Tarassovi	Tarassovi	0	0	0	0	0	0

[a] OD, organ dysfunction

Table 2. Results of thoracic radiographic findings in 27 dogs with leptospirosis and comparison between dogs with and without respiratory clinical signs.

	All dogs (*n* = 27)	Dogs without respiratory clinical signs (*n* = 11)	Dogs with respiratory clinical signs (*n* = 16)
Radiological abnormalities	16 (59%)	6 (55%)	10 (63%)
Interstitial pattern	16 (59%)	6/6 (100%)	10/10 (100%)
Patchy alveolar pattern	6 (22%)	1/6 (17%)	5/10 (50%)
Bilateral distribution	13 (48%)	5/6 (83%)	8/10 (80%)
Pulmonary vein enlargement	3 (11%)	2/6 (33%)	1/10 (10%)
Pleural effusion	4 (15%)	1/6 (17%)	3/10 (30%)

Table 3. Results of biochemical and haematological parameters (median (range)) in 27 dogs with leptospirosis and comparison between dogs with and without pulmonary dysfunction

Blood parameters	All dogs (*n* = 27)	Dogs with pulmonary dysfunction (*n* = 10)	Dogs without pulmonary dysfunction (*n* = 17)	*P*
Glucose (mmol/L)	6.0 (3.2 – 10.7)	6.2 (4.7 – 10.7)	5.8 (3.2 – 8.4)	0.3
Urea (mmol/L)	52.4 (2.1 – 107.0)	54.6 (20.0 – 107.0)	49.6 (2.1 – 98.8)	0.4
Creatinine (µmol/L)	811.5 (69.0 – 1374.0)	887.5 (211.0 – 1096.0)	750.5 (69.0 – 1374.0)	0.6
AlkP[a] (U/L)	159.0 (12.0 – 2508.0)	159.0 (12.0 – 958.0)	159.0 (38.0 – 2508.0)	0.9
ALT[b] (U/L)	84.0 (13.0 – 566.0)	105.0 (13.0 – 265.0)	71.0 (21.0 – 566.0)	0.4
Bilirubin (µmol/L)	12.5 (2.9 – 477.0)	170.0 (5.6 – 337.0)	4.7 (2.9 – 477.0)	0.2
Total proteins (g/L)	60.5 (26.0 – 81.0)	58.5 (26.0 – 70.0)	62.5 (33.0 – 81.0)	0.5
Albumin (g/L)	22.5 (12.0 – 31.0)	21.0 (12.0 – 28.0)	23.0 (17.0 – 31.0)	0.3
Red blood cells ($x10^{12}$/L)	4.6 (1.4 – 8.3)	4.4 (1.4 – 8.3)	4.6 (3.1 – 7.8)	0.6
Haemoglobin (g/dL)	11.4 (3.6 – 19.4)	10.4 (3.6 – 18.5)	12.2 (7.3 – 19.4)	0.4
Haematocrit (%)	32.5 (9.1 – 53.7)	30.0 (9.1 – 53.2)	32.5 (21.5 – 53.7)	0.5
Leucocytes ($x10^9$/L)	17.0 (6.3 – 49.9)	21.6 (7.5 – 50.0)	16.8 (6.3 – 31.8)	0.6
Platelets ($x10^9$/L)	156.0 (43.0 – 422.0)	200.5 (43.0 – 362.0)	153.6 (48.0 – 422.0)	0.6

[a] alkaline phosphatase, [b] alanine aminotransferase, All variables are expressed as median (range)

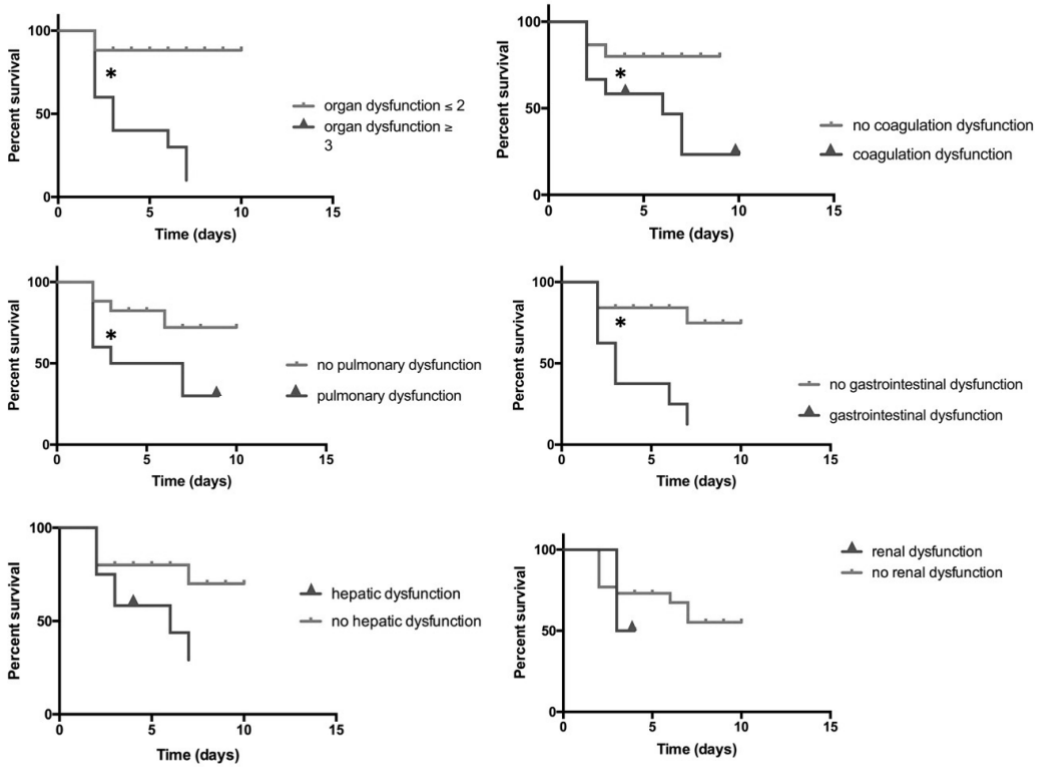
Table 4. Distribution of organ dysfunctions associated with their mortality rates in 27 dogs with leptospirosis

Number of organ dysfunctions	Number of dogs (%)	Organ dysfunctions (number of dogs)	Mortality rates (%, number of dogs)
1	6 (22%)	R (6)	17% (1)
2	11 (41%)	R + H (4)	9% (1)
		R + C (2)	
		R + P (3)	
		R + G (1)	
		H + C (1)	
3	3 (11%)	H + G + C (1)	67% (2)
		R + G + C (1)	
		R + P + C (1)	
4	5 (19%)	R + P + H + G (1)	100% (5)
		R + P + H + C (2)	
		R + P + G + C (1)	
		R + H + G + C (1)	
5	2 (7%)	R + P + H + G + C (2)	100% (2)

R, renal dysfunction; H, hepatic dysfunction; C, coagulation dysfunction; *P*, pulmonary dysfunction; G, gastro-intestinal dysfunction

Figures

Figure 1: Kaplan Meier survival curves.



On the plot, small vertical tick-marks indicate dogs withdrawn from the study (dogs discharged alive). The declining horizontal steps represent the death of dogs. * Indicate a statistically significant difference between curves.