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The Use of Two Clinical Staging Systems of Canine Leishmaniasis in A Clinical Setting: A Critical Evaluation

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Abstract

Objective: To evaluate the use in practice and agreement between, two classification systems: Solano-Gallego (LEISHVET SYSTEM) and Canine Leishmaniasis Working Group (CLWG) clinical staging systems in a population of dogs with leishmaniasis.

Methods: Clinicopathological data extracted from medical records of dogs previously diagnosed with leishmaniasis was evaluated using the two staging systems. Dogs that did not meet the criteria for classification were defined as unclassified. The agreement between the two staging methods was evaluated using unweighted K statistic (k) and Spearman's coefficient of rank correlation (rho). Statistical significance was $P < 0.05$.

Results: Eighty dogs met the inclusion criteria. There were 3 dogs in LEISHVET SYSTEM stage I, 52 dogs in LEISHVET SYSTEM stage II, 12 dogs in LEISHVET SYSTEM stage III, 6 dogs in LEISHVET SYSTEM stage IV and 7 dogs unclassified. No dog was in CLWG stage A or B, 56 dogs were in CLWG stage C, 23 dogs in CLWG stage D and 1 dog unclassified. k value: 0.669, rho: 0.558, with $P<0.0001$.

Clinic significance: Despite the different number of clinical stages between the two systems, the classification of dogs with or without proteinuria and renal involvement was possible with both methods. LEISHVET SYSTEM distinguishes among the different levels of proteinuria and serum creatinine concentration in the staging. CLWG system identifies a cut off value for these parameters only to formulate a prognosis. Despite the presence of discordances, there was good agreement between the two systems in the staging of CanL.

Abbreviation: A/G: albumin globulin ratio; CanL: Canine leishmaniasis; CKD: chronic renal disease; CLWG: Canine Leishmaniasis Working Group; Hb: hemoglobin; Ht: hematocrit; IFAT: indirect immunofluorescent antibody test; IgG: gamma globulin; IRIS: International Renal Interest Society; K: unweighted k statistics; PCR: polymerase chain reaction; PLT: platelet count; RBC: blood cells count; Rho: Spearman's coefficient of rank correlation; SD: standard deviation
LEISHVET SYSTEM: LeishVet Study Group Classification; TP: serum total protein; UP/UC: protein creatinine ratio in urine sample

Introduction

Canine leishmaniasis (CanL) due to Leishmania infantum is a life-threatening zoonotic disease with a wide distribution. CanL is endemic in more than 70 countries in the world. It is present in Europe, Africa, Asia and America [1] and is expanding in non-endemic regions [2-6]. Female sand flies from the genera Phlebotomus (Old World) are the principal vectors of Leishmania [7]. In dogs Leishmania infection may develop over a period of a few weeks to several months resulting in variable clinical presentations [7] ranging from subclinical/asymptomatic to full-blown disease, with a variety of laboratory findings depending on the host's immune response [9]. The most common clinical signs are generalized lymphadenomegaly, weight loss, mucous membranes pallor, exfoliative dermatitis, lethargy, splenomegaly and fever [10]. Other signs are related to deposition of soluble immune complexes in organs and tissues [11,12]. Because of this complex clinical presentation, CanL can be difficult to diagnose and the full clinical picture is often missed. Clinical staging systems group patients according to the severity of their clinical presentation. These systems are widely used in human medicine [13,14] and aid evaluation of the efficacy of different therapies, decisions on the most appropriate therapy for each patient and prognostic evaluation. Criteria used for classification must be simple, with the use of uncomplicated diagnostic methods. There are very few studies using these clinical staging systems in veterinary medicine [15,16].

In developing a clinical staging model for CanL, Solano-Gallego, et al. [7] reviewed and focused on several aspects of CanL and proposed a system of four clinical stages (I to IV and 2 substages A and B), based on clinical signs, clinicopathological abnormalities (with evaluation of renal function according to the recommendations of the International Renal Interest Society, IRIS), and serological status. Prognosis and appropriate therapy was classified according to stage. Subsequently, in 2010, the Canine Leishmaniasis Working Group (CLWG) proposed classification of dogs with positive serological tests, or those in which the parasite had been identified via direct diagnostic methods, into 4 stages (A to D), including, unlike the previous system, asymptomatic dogs as well as those with clinical signs [8]. The proposed classification system divided dogs into groups of: exposed, infected, sick and severely sick dogs, with only two stages for dogs with clinically evident leishmaniasis. In 2013 the CLWG reviewed the classification adding stage E for dogs unresponsive to treatment or dogs with early relapse and used the staging system to formulate a prognosis and monitor subjects depending on the stage of disease [17]. The purpose of this study was to evaluate practical application of the LEISHVET SYSTEM [10] clinical staging system and the CLWG [8] classification system in a population of dogs affected by canine leishmaniasis, evaluating the agreement between these two schemes for the assessment of severity of CanL.

Materials and Methods

Study population. This study was a retrospective analysis of all dogs diagnosed with leishmaniasis and admitted to the Faculty of Veterinary Medicine University of Milan between 2000 and 2014. The following inclusion criteria were used:

a) A complete physical examination with a detailed description of signs referable to CanL at the time of diagnosis, as previously reported in the literature [10].

b) A diagnosis of leishmaniasis established by clinicopathological abnormalities, positive serology for Leishmania infantum using IFAT and cytological identification of Leishmania amastigotes or detection of parasite DNA using polymerase chain reaction (PCR) in either lymph node or bone marrow aspirate, as previously described [18].

All dogs in which concomitant infectious diseases (e.g. babesiosis, ehrlichiosis, and dirofilariasis) were diagnosed by parasitological or/and serological examinations were excluded, while concomitant neoplastic, endocrine and metabolic diseases were considered as described in stage D of CLWG classification. Subjects with incomplete information in the medical records were also excluded from the study.

Medical Records Review. Information extracted from the medical records of each dog with CanL comprised breed, sex, age, environmental history (to identify habitation or travel in endemic areas), clinical signs of CanL as classified in the literature [10], IFAT titer, cytological identification or PCR detection of Leishmania and laboratory findings [red blood cells count (RBC), hematocrit (Ht), hemoglobin (Hb), platelet count (PLT), serum total protein (TP), gamma globulin (IgG), albumin globulin ratio (A/G), creatinine serum concentration (Serum creatinine concentration was considered non pathological until 1,4 mg/dl [7]) and protein creatinine ratio in urine sample (UP/UC). Dogs were considered: non proteinuric when UP/UC value was less than 0.5 and proteinuric when UP/UC value was more than 0.5 and marked proteinuric when UP/UC value was more than 5 [7].

All dogs were retrospectively staged using the two staging systems, i.e. LEISHVET SYSTEM [10] and CLWG [17].

Statistical analysis. All statistical analyses were performed using commercial statistical software (MedCalc, v. 15.0.0, Mariakerke, Belgium). Descriptive statistics were used for demographic variables. Mean, standard deviation, median, lowest value and highest value of RBC, Ht, Hb, PLT, TP, IgG, A/G, serum creatinine and UP/UC were calculated after calculating normal distribution of data using D'Agostino-Pearson test. The agreement between the LEISHVET SYSTEM and the CLWG staging methods was evaluated using unweighted K statistic (k) with a 95% confidence interval. As the two staging systems did not have the same number of clinical stages (4 for the LEISHVET SYSTEM and 2 for CLWG) the two staging scales were adapted to calculate kappa as a measure of agreement, recording CanL severity in 3 categories. In the LEISHVET SYSTEM system stages I and II received the value 1, stages III and IV received the value 2 and unclassified dogs received the value 0 (Table 1). In the CLWG system stage C received the value 1, stage D received the value 2 and unclassified dogs received the value 0 (Table 2). The level of agreement was scored according to the following guidelines: 0: no better than chance; <0.20: poor agreement; 0.21–0.40: fair agreement; 0.41–0.60: moderate agreement; 0.61 0.80: good agreement; 0.81–1.00: very good agreement [19]. Spearman's coefficient of rank correlation (rho) was also used to determine the agreement of two methods. Statistical significance was set as $P < 0.05$.

Results

The medical records of 134 dogs with CanL were reviewed, and 54 dogs were excluded. There were incomplete data for evaluation in 38 dogs, and 16 dogs had concomitant infectious diseases. Therefore a total of 80/134 dogs met the criteria for inclusion in the study. Of the 80 cases enrolled, 48 dogs (60%) were male (7 castrated) and 32 (40%) were female (18 spayed) and the mean age was 5.5years (range 7 months to 16 years). Thirty-two dogs were mixed breeds, 7 Setters, 6 Hounds, 4 German Shepherds, 4 Boxer, 4 Terriers, 3 Retrievers, 3 Spaniels, 3 Great Danes, 3 Bulldogs and the remaining 11 dogs were pure breeds representing 10 different breeds. All dogs originated from, or had previously travelled to, areas where CanL is endemic. Six dogs (7.5%) had concurrent diseases: 2 dogs had testicular neoplasia, 1 dog had a chemodectoma, 1 dog had a cutaneous plasmocytoma and 2 dogs had hyperadrenocorticism. The IFAT titer ranged from 1:80 to 1: 10240. Eight dogs had IFAT titer 1:80, 9 dogs 1:160, 18 dogs 1:320, 23 dogs 1: 640, 14 dogs 1:1280, 6 dogs 1:2560, 1 dog 1:5120 and 1 dog 1:10240.

Clinical stage	Serology	Clinical signs	Laboratory findings	Category for k test
I, mild disease	Negative to lowa positive antibody levels	Mild clinical signs such as peripheral lymphadenopathy, or papular dermatitis	No clinicopathological abnormalities	1
II, moderate disease	Low to highb positive antibody levels	Dogs, with signs of stage I, may present: diffuse or symmetrical cutaneous lesions such as exfoliative dermatitis/onicogryphosis, ulcerations, anorexia, weight loss, fever, epistaxis	Clinicopathological abnormalities such as: mild non-regenerative anemia, hypergammoglobuminemia, hypoalbuminemia, serum hyperviscosity syndrome. Substage A: creatinine <1.4 mg/dl, UP/UC<0.5 Substage B: creatinine <1.4 mg/dl, UP/UC=0.5-1	1
III, severe disease	Medium to high positive antibody levels	Dogs, with signs of stage II, may present signs originating from immune-complex lesions: vasculitis, arthritis, uveitis and glomerulonephritis	Clinicopathological abnormalities listed in stage II, chronic renal disease IRIS stage I with UP/UC >1 or IRIS stage II (creatinine 1.4-2 mg/dl)	2
IV, very severe disease	Medium to high positive antibody levels	Dogs with signs of stage III, may present with Pulmonary thromboembolism, or nephrotic syndrome and end stage renal disease	Clinicopathological abnormalities listed in stage II, chronic renal disease IRIS stage III (creatinine 2-5 mg/dl) or IRIS stage IV (creatinine >5 mg/dl); marked proteinuria UP/UC >5	2

Table 1: Clinical stage, serology, clinical signs and laboratory findings of LeishVet staging system (Solano-Gallego et al. 2009) with category assigned for k statistic.

[a] dogs with negative to medium positive antibody levels should be confirmed as infected using other diagnostic techniques such as cytology, histology/immunohistochemistry and PCR

[b] high levels are defined as three-four fold increase above a well-established laboratory reference cut-off

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Stage and definition	Diagnostic methods results	Clinical signs	Laboratory findings	Category for k test
A, exposed	Low positive antibody levels and negative cytology, histology or PCR	Clinically normal dogs or with signs associated with other diseases	No clinicopathological abnormalities	-
B, infected	Low positive antibody levels with positive cytology, histology or PCR	Clinically normal dogs or with signs associated with other diseases	No clinicopathological abnormalities	-
C, sick	Higha positive antibody levels or low level with positive cytology, histology or PCR	Clinical signs associated with leishmaniasis	Clinicopathological abnormalities suggestive of leishmaniasis	1
D, severely sick	-	Signs of chronic renal failure (IRIS stage III or IV) or proteinuric nephropathy; severe ocular disease or severe joint disease and/ or require immunosuppressive therapy; important concomitant conditions, including neoplastic, endocrine or metabolic diseases	Clinicopathological abnormalities suggestive of leishmaniasis	2
E, unresponsive to treatment or early relapse	-	Clinically unresponsive to recommended treatment – clinical relapse soon after cessation of recommended treatment	-	-

Table 2: Staging of Canine Leishmaniasis Working Group (Paltrinieri et al. 2010, Roura et al. 2013) with category assigned for k statistic.
[a]high levels are defined as ≥ four fold increase of laboratory reference value

The most common clinical signs in the 80 dogs with CanL were: peripheral lymphadenopathy (61 dogs, 76%), exfoliative dermatitis (53 dogs, 66%), weight loss (21 dogs, 26%), ulcerative dermatitis (13 dogs, 16%), anorexia (12 dogs, 15%), polyuria and polydipsia (9 dogs, 11%). The most common clinicopathological abnormalities were: hypergammaglobulinemia (80 dogs, 100%), hypoalbuminemia (76 dogs, 95%), anemia (54 dogs, 68%), elevation of UP/UC (30 dogs, 38%) and elevation of serum creatinine (19 dogs, 24%).
Table 3 shows the lowest value, highest value, mean, median, and standard deviation (SD) of laboratory findings. All data were normally distributed except for serum creatinine, UP/UC and IgG. The data from the dogs was categorized using the two staging systems and results are reported in table 2 and table 3, respectively. Dogs that did not meet the criteria for classification of one or both staging systems were defined as "unclassified".

There were 3 dogs in LEISHVET SYSTEM stage I, 52 dogs in LEISHVET SYSTEM stage II of which 41 dogs in substage A and 11 dogs in substage B, 12 dogs in LEISHVET SYSTEM stage III, 6 dogs in LEISHVET SYSTEM stage IV and 7 dogs were unclassified, Three of 7 unclassified dogs had severe clinical signs due to immune-complex lesions (uveitis and arthritis) indicating stage III, but no laboratory findings of chronic kidney disease, 3/7 dogs had high positive antibody titers (four fold increase above established laboratory reference), but no, or only mild, clinical signs, 1/7 dog had severe clinical and laboratory abnormalities, but low antibody titers. No dog was in CLWG stage A and B, 56 dogs were in CLWG stage C, 23 dogs in CLWG stage D and only 1 dog unclassified (with a very high specific antibody titer, but no clinical signs nor clinic pathological abnormalities compatible with CanL).

Parameter	Minimum value	Maximum value	Mean	Median	SD	Laboratory reference range
RBC (10^3/µL)	1880	7600	5350	5500	± 1150	5700-8800
Ht (%)	12	48.6	33.27	34.5	± 7.88	37-57
Hb (g/dl)	4.2	17.8	12.20	12.8	± 2.82	12.9-18.4
PLT (10^3/µL)	37	614	256.65	263	± 106.14	143-400
TP (g/dl)	5.5	12.1	8.30	8.2	± 1.42	6-8
Albuminemia (%)	7	56	32.77	33	± 11.06	46.3-58.5
IgG (%)	8.4	76	31.73	27.84	± 16.83	5.3-9.9
A/G	0.08	1.32	0.53	0.5	± 0.26	0.8-1.7
Serum creatinine (mg/dl)	0.3	6.1	1.19	0.9	± 0.88	< 1.2
UP/UC	0	6.6	0.83	0.3	± 1.3322	< 0.5

Table 3: Lowest value, highest value, mean, median value and standard deviation of laboratory findings included in the study.

	LeishVet system					
CLWG system	Dogs in Stage I	Dogs in Stage II	Dogs in Stage III	Dogs in Stage IV	Unclassified dogs	TOTAL
Dogs in Stage C	3	48	1	1	3	56
Dogs in Stage D	0	4	11	5	3	23
Unclassified dogs	0	0	0	0	1	1
TOTAL	3	52	12	6	7	80

Table 4: Distribution of 80 dogs with CanL according to the 4 different clinical stages identified by SG staging system and the 2 clinical stage identified by CLWG staging system.

Six of 23 dogs categorized as D stage were included in this stage as a result of a concomitant severe condition (4 for neoplasia and 2 for hypradrenocorticism). Table 4 illustrates the conflicting results of dogs classified differently by the two staging systems.

In the reformulated categories used to calculate kappa as a measure of agreement of the between the LEISHVET SYSTEM and CWLG systems respectively, 55 dogs and 56 dogs received value 1, 18 dogs and 23 dogs received value 2 and 7 dogs and only 1 dog value 0. Unweighted K statistics demonstrated a k value of 0.669 (95% CI 0.510 to 0.827) with good agreement in the assessment of CanL stage between LEISHVET SYSTEM and CLWG systems. Spearman's coefficient of rank correlation (rho) between the LEISHVET SYSTEM and CLWG systems was 0.558 (95% CI 0.386 to 0.693), with a level of significance of $P<0.0001$.

Discussion

Clinical staging systems are very important in clinically complex and evolving diseases such as leishmaniasis, as they can contribute to prognostic information as well as to plans for therapeutic management of affected dogs [7]. To categorize patient's clinicians should be able to use a rapid, simple staging system to stage disease and to guide therapy. A validated method for clinical staging for CanL would aid comparison of different treatment protocols presented in the literature, the evaluation of potential side effects and would simplify the calculation of the most important prognostic factors. To the authors' knowledge this is the first time that 2 clinical staging systems for CanL, the LEISHVET SYSTEM and the CLWG systems, have been compared. We also evaluated the clinical application of these methods in a population of dogs with CanL in a non-endemic area and the agreement between the classifications for disease severity.

Both staging systems were found to be applicable to our heterogeneous population of dogs with CanL. Most dogs were easily classified in stage II of "moderate disease" in the LEISHVET SYSTEM system (41 dogs) and in stage C of "sick" in the CLWG system (56 dogs).

Despite the fact the CLWG dedicates only two clinical stages to the sick subjects and LEISHVET SYSTEM has 4 clinical stages and two sub stages with detailed definition of creatinine serum concentration and proteinuria according to IRIS classification, the classification of dogs with or without proteinuria and renal involvement was simple with both systems. During CanL, one of the most important factor-influencing prognosis is the severity of any renal damage [10], so a precise categorization of clinical cases allows a more focused evaluation of therapeutic and prognostic factors [7]. LEISVET SYSTEM records the degree of proteinuria in each stage, and this makes the practical application of the score system slightly stiff. During CanL monitoring UP/UC value is very important because proteinuria is an early indicator of renal involvement often presents in the absence of an alteration in serum creatinine [18]. Furthermore quantitative measurement of proteinuria plays also a major role in the follow-up during treatment [7,20,21]. CLWG on the other end, affects the prognosis of the ill dogs as "favourable" or "guarded", depending on the serum creatinine concentration and proteinuria value. This data provides to the practitioner an objective tool to communicate with the owner. Using the LEISHVET SYSTEM 7 dogs could not be classified, mainly because of discrepancies between the antibody titer and clinical signs. The LEISHVET SYSTEM classification system allocates medium to high titers in the latter stages of the disease and low or negative titers in mild or moderate stages. Although the LEISHVET SYSTEM, provides detailed classification of leishmaniotic dogs, it has the limitation of not allowing classification of dogs without a direct correlation between IFAT titer and clinical signs [18]. In this study there were 3 dogs with high antibody levels, but few or no clinical signs, and one dog with severe clinical signs (eg asthenia, anemia), but low antibody titers. Three other cases had clinical abnormalities caused by immune complex deposition in eyes or joints as required for stage III, but they did not have renal abnormalities in laboratory parameters, as required by the LEISHVET SYSTEM to allocate them in stage III. Many of the clinical manifestations of CanL are related with host immune response and are associated with deposition of soluble immune complexes in tissues [7]. Several studies have described the levels of Leishmania IgG in sick, asymptomatic, and treated dogs, sometimes with conflicting results [18,12,22,23]. The varying immune response of affected animals with different clinical presentations makes the precise classification of clinical cases sometimes difficult and could explain the presence of "unclassified" dogs with the LEISHVET SYSTEM.

Staging of clinical cases with CLWG is less detailed and schematic, so that it is easier to allocate ill dogs in different stages. In fact the definition of "sick dog", allows inclusion of dogs with significant clinical signs or laboratory abnormalities regardless of serology. These features allow the clinician to apply the CLWG staging system even in presence of conflicting results. In this study, only one case could not be classified using the CLWG system: this dog had a high IFAT titer (1: 5120), but no clinical or laboratory abnormalities, (as required for stage C of sick animal). Unlike LEISHVET SYSTEM, CLWG system does not distinguish among the levels above the normal value of proteinuria and serum creatinine concentration in the staging but identifies a cut off value for these parameters only to formulate a prognosis.

Despite the different clinical approach, there was good agreement between the two classification systems ($k = 0.669$) with a significant level of association ($P < 0.0001$), supporting the clinical use of both systems in the staging of CanL. The comparison of two or more staging systems is widely used in human medicine to assess their effectiveness and to select the most comprehensive and reliable system [14,24]. As in this study the comparison of staging systems with many different stages is complex [13,25] and it may be difficult to define the best classification system, rather advantageous features are identified in each evaluated system [14]. As most cases of CanL are diagnosed and treated by veterinary practitioners, the main purpose of this study was to evaluate whether there were difficulties with the application of the two staging systems in clinical practice. A possible limitation of our study is the case history load, which was typical of a non-endemic area, with the majority of dogs with mild or moderate disease. This, unfortunately, allowed only a precise evaluation of LEISHVET SYSTEM stage II and CLWG stage C of classification systems. Another possible limitation is the decision to merge some clinical stages of the LEISHVET SYSTEM system to perform the k test. This decision was based on similar studies in human literature [26]. Future studies should include the assessment of the prognostic potential of the two staging systems, using survival calculations. This would require a broader review of medical records, beyond the time of diagnosis.

Conclusion

In conclusion, our results show that the LEISHVET SYSTEM clinical staging system and the CLWG staging system are simple and clinically useful methods for classifying dogs with CanL, and that there was a good agreement between the two systems. LEISHVET SYSTEM has 4 clinical stages and two sub stages with detailed definition of creatinine serum concentration and proteinuria according to IRIS classification. Its correlation of antibody titer and clinical symptoms/clinicopathological abnormalities for each stage make difficult to classifying a larger number of dogs than with CLWG system. CLWG system does not distinguish among the different levels of proteinuria and serum creatinine concentration in the staging but identifies a cut off value for these parameters only to formulate a prognosis. CLWG is less detailed and schematic than LEISHVET SYSTEM, so that it is easier to allocate the cases in different stages.

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