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Proposal for a quantitative and multifactorial index for the evaluation of kidney injury in dogs naturally infected with *Leishmania infantum*

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Background

Dogs are the main reservoir of *Leishmania infantum*, causing canine leishmaniosis (CanL), an incurable multisystemic disease that leads to death when not treated [1]. In dogs, during the disease, kidneys are frequently affected through the deposition of antigen/antibody complexes in the renal structures and intense plasma cell inflammatory infiltrate [2]. The development of a multifactorial quantitative index using a set of biomarkers of kidney injury is desirable to assess early-stage kidney damage, as well as guiding treatment strategies and outcomes. The aim of this study was to develop a quantitative, multifactorial index that includes biomarkers of kidney injury to assess kidney damage in dogs naturally infected with *L. infantum.*

Materials and methods

A retrospective survey was carried out by analysing the medical records of 165 dogs, naturally infected with *L. infantum,* at different stages of CanL, in private veterinary clinics in Belo Horizonte, State of Minas Gerais, Brazil. The dogs were classified into five groups, considering their clinical condition (Table 1).

Table 1. Groups for classifying the dogs included in this study.

Group	Description
Control group (CG)	Dogs without clinical alterations who underwent only clinical follow-up.
Low-risk group (LRG)	Dogs that were undergoing clinical follow-up but had mild clinical changes.
Intermediate-risk group (IRG)	Dogs that required hospitalization to control moderate clinical changes.
High-risk group (HRG)	Dogs that required hospitalization to control important clinical changes.
Death group (DG)	Dogs that died within 48 hours of the tests being taken.

The Generalized Linear Model was fitted with the Poisson distribution to create the index. The quality of the models was quantified using the Akaike Information Criterion (AIC) statistic, the Pearson correlation between the observed index and the index estimated by the model and McFadden's Pseudo Coefficient of Determination (R^2). The model's fit was assessed by constructing simulated probability envelopes [3]. As these models aim to predict new cases, the cross-validation technique was also used to reduce selection bias due to the study being observational rather than experimental [4]. In this technique, the database was divided equally into four parts. Three parts were used to adjust the model and the fourth part was used only for prediction, calculating the Pearson correlation between the observed indices and the indices estimated by the model. The procedure was repeated for each of the four parts and the average of the four correlations obtained was calculated. The most parsimonious model was the one with the fewest significant variables and which had the lowest AIC value and the highest Pearson correlation and R^2 values. The model including serum urea (mg/dL), serum globulin (g/dL), determined by subtracting albumin from total protein, hematocrit (HTC) and urinary protein creatinine ratio (UPC) presented the best quality index values, being described in the mathematical modelling:

Index =exp(0.0081*UREA-0.041*HTC-0.080*UPC+0.102*GLOBULIN).

Results

The variation in the index in the five groups that considered the patient's clinical condition is displayed in Table 2.

Table 2. Main descriptive statistics indices were separated by group, considering the patient's clinical condition.

Group	Minimum	Maximum	Mean	Standard deviation
CG	0,19	0,41	0,31	0,07
LRG	0,19	0,85	0,45	0,23
IRG	0,26	3,06	1,37	0,96
HRG	1,24	11,05	3,83	3,76
DG	1,71	40,38	8,86	13,93

GC: control group; LRG: low-risk group; IRG: intermediate-risk group; HRG: high-risk group; DG: death group.

When the index was applied to the LeishVet (2011) stages, we obtained the following statistical values (Table 3).

Table 3. Main descriptive statistics indices separated by LeishVet stage (2011).

LeishVet stage	Minimum	Maximum	Mean	Standard deviation
IIA	0,19	0,63	0,33	0,17
IIB	0,54	1,2	0,91	0,52
III	0,25	2,38	0,6	0,62
IV	0,26	40,38	5.43	9,67

According to the clinical point of view and the suggested index, a dog with an index between 0 and 0.5 presents a low risk of hospitalization (6%), a moderate risk of presenting acute kidney injury (AKI) (41%) and does not present a risk of death (0%). Patients with an index between 0.51 and 1.0 have a moderate risk of hospitalization (33%), a significant risk of developing AKI (67%) and no risk of death (0%). Dogs with an index between 1.1 and 3.0 have a high possibility of requiring hospitalization and presenting AKI (100%) and a low risk of death (10%). Patients with an index between 3.1 and 5.0 are highly likely to require hospitalization and experience AKI (100%) and a moderate risk of death (50%). Dogs with an index greater than 5.0 present an imminent risk of death (Table 4).

Table 4. Percentages of hospitalizations, renal failure (RF), and deaths in the index intervals obtained in the study.

Index Intervals	Percentages	Outcomes
0 - 0,5	0%	Death
0 - 0,5	6%	Hospitalizations
0 - 0,5	41%	AKI
0,51 - 1	0%	Death
0,51 - 1	33%	Hospitalizations
0,51 - 1	67%	AKI
1,1 - 3,0	10%	Death
1,1 - 3,0	100%	Hospitalizations
1,1 - 3,0	100%	AKI
3,1 - 5,0	50%	Death
3,1 - 5,0	100%	Hospitalizations
> 5,0	100%	AKI
> 5,0	100%	Death

Conclusions

The index presented provides the basis for outcome prediction that correlates highly with AKI and death in CanL. The suggested index is simple and can be applied based on the information collected in the first hour of hospitalization. When used in conjunction with other clinical assessments, the index can provide an accurate prognostic tool to aid in deciding the initiation and/or choice of therapy. The index can be used as an objective parameter to compare disease severity between different populations.

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