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Clinicopathologic and prognostic factors in short- and long-term surviving dogs with protein-losing enteropathy

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1 **Introduction**

2 Protein-losing enteropathy (PLE) in dogs results from severe small intestinal disease that allows leakage of protein into
3 the intestinal lumen (Dossin and Lavoue, 2011). While panhypoproteinemia associated with loss of albumin and
4 globulin is the most common clinicopathological abnormality, isolated albumin loss can also be observed (Willard et
5 al., 2000; Allenspach et al., 2007). The major causes of PLE in dogs are intestinal lymphangiectasia, inflammatory
6 bowel disease, and lymphoma (Craven et al., 2004; Dandrieux et al., 2013; Nakashima et al., 2015). Because PLE is
7 associated with decreased serum albumin and increased loss of α_1 -PI into the gastrointestinal tract, measurement of
8 serum albumin and fecal α_1 -proteinase inhibitor (α_1 -PI) should be included in the diagnostic workup (Murphy, 2003;
9 Willard, 2013). But since the α_1 -PI test is not readily available, PLE is usually diagnosed after excluding other
10 conditions associated with hypoalbuminemia and intestinal histopathology (Dossin and Lavoue, 2011; Willard, 2013).
11 As compared with chronic enteropathy (CE) with normal albumin (Craven et al., 2004; Allenspach et al., 2007;
12 Simpson and Jergens, 2011), the prognosis for PLE is usually considered guarded (Allenspach et al., 2007; Dossin and
13 Lavoue, 2011), and the response to therapy is variable (Simmerson et al., 2014).

14 Moreover, information on factors that predict outcome of PLE at diagnosis is limited and long-term follow-up data are
15 lacking. Negative prognostic indicators include medium size (11 to 20 kg), high canine IBD activity index (CIBDAI)
16 score, a history of vomiting, monocytosis, mildly increased C-reactive protein, normal serum calprotectin and S100A12
17 concentrations, clonal rearrangement of lymphocyte antigen receptor genes, and intestinal villous blunting (Simmerson
18 et al., 2014, Equilino et al., 2015; Nakashima et al., 2015). Information on the impact of serum albumin and blood urea
19 nitrogen concentrations on outcome or survival time is controversial. One study found the survival time to be
20 significantly influenced by low blood urea nitrogen concentration and severity of hypoalbuminemia (Simmerson et al.,
21 2014), two others reported that elevated blood urea nitrogen concentration and hypoalbuminemia, but not its severity,
22 were negatively correlated with outcome (Owens et al., 2011; Nakashima et al., 2015), and another found that outcome
23 or survival time were not significantly influenced by the initial serum albumin concentration (Equilino et al., 2015).

24 Finally, while many dogs with PLE secondary to CE die shortly after initiation of treatment, there are some that achieve
25 prolonged survival.

26 The aim of this study was to retrospectively evaluate the differences in clinical and clinicopathological findings
27 between short- and long-term surviving dogs with PLE secondary to CE at diagnosis and after treatment, and to identify
28 potential risk factors for poor outcome.

29 **Animals, Material and Methods**

30 *History and laboratory findings*

31 We retrospectively reviewed the medical records of dogs with PLE secondary to CE diagnosed at three different
32 hospitals between January 2009 and November 2013. Inclusion criteria were complete history and physical
33 examination findings, chronic gastrointestinal signs lasting for more than 3 weeks, hypoalbuminemia (< 2 g/dL) of
34 gastrointestinal origin with or without hypoglobulinemia, and histopathological evidence of gastrointestinal
35 inflammation on biopsies collected by endoscopy or laparotomy. Histologic examination was performed in all dogs
36 according to the histopathological standards of the World Small Animal Veterinary Association (WSAVA)
37 Gastrointestinal Standardization Group. All biopsies were retrospectively reviewed by a pathologist blinded to the
38 diagnosis. Chronic canine enteropathy clinical activity index (CCECAI) scores (Allenspach et al., 2007), complete
39 blood count, serum biochemistry and coagulation profiles, pancreas specific lipase levels, serum folate and cobalamin
40 concentrations were gleaned from the medical records. The reference ranges of the hospital laboratories were
41 substantially similar. During review of the medical records (February 2015), follow-up information was obtained by
42 telephone from the owners or referring veterinarians.

43 *Classification and therapy*

44 Dogs were classified as either short-term (STs) or long-term (LTs) survivors if they had died within or were still alive
45 at 6 months after diagnosis, respectively. Additionally, the medical records were searched for information about the
46 categorization of CE as food-, antibiotic-, or immunosuppressive-responsive. Dogs that showed complete remission of

47 clinical signs while on elimination diet (hydrolysed or restricted antigen diets) were categorized as having food-
48 responsive CE. Dogs that showed complete remission of clinical signs while on tylosin (15 mg/kg, PO, q 12 h) or
49 metronidazole (10 mg/kg, PO, q 12 h) were categorized as having antibiotic-responsive CE. Dogs that responded to oral
50 prednisone (1 mg/kg, twice a day for 2-3 weeks before considering dose reduction), oral azathioprine (1 or 2 mg/kg,
51 once a day), oral chlorambucil (4-6 mg/m², once a day for at least 2 weeks before considering dose reduction), or oral
52 cyclosporine (5 mg/kg, once a day) were categorized as having immunosuppressive-responsive CE. Dogs were
53 classified as immunosuppressive-unresponsive if they showed poor or no clinical response to immunosuppressives
54 (partial disappearance or persistence of clinical signs).

55 Since the medical records also reported the results of repeated exams at follow-up visits , we set T1 (1 month after
56 initiation of immunosuppressives) as the time point at which the clinical and clinicopathological information was
57 complete for the majority of the dogs.

58 *Statistical analysis*

59 Statistical analysis was performed with a commercially available statistical data analysis program (MedCalc®).
60 Assessment of data for normality was calculated using the D'Agostino-Pearson test. Continuous variables were
61 expressed as mean (\pm sd), median (minimum and maximum), percentages or both. Categorical variables were expressed
62 as normal/negative (0) or abnormal/positive (1). Fisher's exact test was used to compare between the STs and the LTs
63 the variables: sex, complaints/clinical signs (small bowel diarrhea, mixed diarrhea, decreased appetite, increased
64 appetite, vomiting, peripheral edema, ascites, pleural effusion, pruritus, polyuria and polydipsia, lethargy, and muscular
65 twitching/convulsions), results of the SNAP cPL® test, coagulation profile at T0, and treatments with different types of
66 immunosuppressives.

67 Student's t-test was used to compare between the STs and the LTs the variables: age, body weight, CCECAI scores,
68 serum albumin, folate concentrations, and lipase activity at T0 and the CCECAI scores, serum albumin and globulin
69 concentrations at T1. The Mann-Whitney test was used to compare between the STs and the LTs the variables: number

70 of monocytes and platelets, globulin, serum total protein, total cholesterol, blood urea nitrogen, magnesium, cobalamin
71 and fibrinogen concentrations at T0 and the serum total protein, magnesium and total cholesterol concentration at T1.
72 Values of $P < 0.05$ were considered significant. A receiver operating characteristic (ROC) curve was used to select the
73 optimum cut-off value of the variables at T1 to discriminate the STs from the LTs.

74 **Results**

75 *History, physical examination, and CCECAI scores*

76 We reviewed the medical records of 59 dogs with PLE secondary to CE diagnosed between January 1, 2009 and
77 November 30, 2013. Of these 59 dogs, 19 were classified as STs and 40 as LTs. Among the STs were dogs from 9
78 different breeds and 2 mixed-breed dogs. Fourteen were male and 5 female. The age range was from 9 months to 13.4
79 years (mean, 5.9 ± 3.3), and the weight range was from 14 to 40 kg (mean, 23.6 ± 7.3). Table 1 reports the presenting
80 complaints/clinical signs. The median duration of clinical signs prior to diagnosis was 2 months (range 1-36). The
81 median survival time was 90 days (range 31 to 180). Among the LTs were dogs from 20 different breeds and 9 mixed-
82 breed dogs. Twenty-two dogs were male and 18 female. The age range was from 1 to 11.6 years (mean, 6.5 ± 2.5),
83 and the weight range was from 1.9 to 45 kg (mean 17.4 ± 12.4). Table 1 reports the presenting complaints/clinical
84 signs. The median duration of clinical signs prior to diagnosis was 2 months (range 1-36). The median survival time
85 was 880 days (range 210 to 1,787). No statistically significant differences in sex and age between the two groups were
86 found at T0; body weight was significantly higher in the STs ($P < 0.05$). There was no difference in presenting
87 complaints/clinical signs between the STs and the LTs.

88 CCECAI scores were available for all dogs at T0, and for all dogs except 1 at T1. No significant differences in the
89 CCECAI scores between the groups were found at T0; at T1 the CCECAI score was significantly higher in the STs
90 (Figure 1).

91 *Clinicopathological findings*

92 Tables 2 and 3 present the clinicopathological findings and the number of dogs that had undergone testing, respectively.
93 At T0, no statistically significant differences between the two groups were found for: number of monocytes and
94 platelets, serum albumin, globulin, total protein, total cholesterol, magnesium, cobalamin, folate and fibrinogen
95 concentrations, lipase activity, results of the SNAP cPL® test, and coagulation profile. Blood urea nitrogen
96 concentrations were significantly higher in the STs ($P < 0.05$). At T1, albumin, serum total protein and total cholesterol
97 concentrations were significantly lower in the STs ($P < 0.01$).

98 *Gastrointestinal histopathology results*

99 Gastroduodenoscopy was performed in 58 dogs. Additional ileoscopy and colonoscopy were performed in 14 and 28
100 dogs, respectively. Laparotomy was performed in 1 dog. Tissue quality was classified as adequate in all cases.
101 Moderate to marked histopathologic abnormalities in the small intestine were found in all dogs. Lymphocytic-
102 plasmacytic inflammation (50 dogs) and lymphangiectasia (28 dogs) were the most common abnormalities. Moderate
103 to severe lymphocytic-plasmacytic colonic inflammation was found in 24 dogs.

104 *Treatment and outcome*

105 No significant differences in the treatments with different types of immunosuppressive therapies were found between
106 the two groups. Based on their response, all STs were categorized as immunosuppressive-unresponsive. Among the
107 LTs, 32 dogs were categorized as immunosuppressive, 1 and 1 each as food- and antibiotic-responsive CE,
108 respectively; 6 dogs were categorized as immunosuppressive-unresponsive.

109 Follow-up information was available for all dogs. Thirty-three dogs (55.9%; 31 with immunosuppressive-responsive
110 CE; 1 with food-responsive CE; 1 with antibiotic-responsive CE) were alive at the time of medical record review (73
111 months), and 26 (44.1%; 19/19 STs and 7/40 LTs with immunosuppressive-responsive CE) had died because of PLE-
112 related complications. The main cause of death was deterioration of clinical conditions presumably due to
113 malabsorption. A cut-off CCECAI score of > 5 at T1 was found to be the best predictor for poor outcome (Figure 2).

114 **Discussion**

115 With this retrospective multicenter study we compared the clinical and clinicopathological findings of 59 short- and
116 long-term surviving dogs with PLE secondary to CE, and investigated potential prognostic factors. Consistent with
117 previous observations, the adult dogs of any size were affected by PLE (Allenspach et al., 2007; Lecoindre et al., 2010;
118 Dossin and Lavoue, 2011; Dandrieux et al., 2013; Simmerson et al., 2014), with a predominance of males, however
119 (Kull et al., 2001; Simmerson et al., 2014). Medium size (11 to 20 kg) has recently been reported as a negative
120 prognostic indicator (Equilino et al., 2015). When we compared the two groups, we observed that body weight was
121 significantly higher among the STs. This might simply reflect the type of study population or suggest that large breed
122 dogs might be affected by more severe forms of PLE.

123 Small bowel diarrhea and decreased appetite were the most common historical complaints in both groups. A recent
124 retrospective study found that vomiting was a negative prognostic factor (Simmerson et al., 2014), however, we noted
125 no significant differences in the presenting complaints/clinical signs between the two groups at T0. As seen also in our
126 sample, ascites or pleural effusion are common complaints or physical examination findings in dogs with PLE
127 (Allenspach et al., 2007, Lecoindre et al., 2010) but they do not seem to be negative prognostic indicators (Simmerson
128 et al., 2014). Activity indices for assessing disease severity can also be used as prognostic markers (Jergens et al., 2003;
129 Allenspach et al., 2007). According to one study, CCECAI ≥ 12 at diagnosis predicted refractoriness to treatment and
130 euthanasia within 3 years (Allenspach et al., 2007). To the contrary, in our and in a recent study (Equilino et al., 2015),
131 outcome or survival time were not significantly influenced by activity indices at diagnosis.

132 The only significant difference in pathologic variables between the two groups at T0 was the blood urea nitrogen
133 concentration, which can be influenced by dehydration, renal failure or severe GI protein loss. But because we had no
134 information about prerenal and renal azotemia values in these PLE dogs, this result should be interpreted with caution.
135 Furthermore, the retrospective design of the present study is an additional limitation. Several variables tested at T0
136 were not available at T1 for all dogs, and treatments were not strictly standardized. That said, collectively, our results

137 may support the hypothesis that the severity of clinical signs and the majority of serum biochemistry and coagulation
138 profile findings at diagnosis do not appear to correlate with outcome.

139 The prognosis for dogs with PLE in the current veterinary literature is guarded (Allenspach et al., 2007; Dossin and
140 Lavoue, 2011). Except for a recent retrospective study (Simmerson et al., 2014), there are few reports of survival data
141 for dogs with PLE (Craven et al., 2009; Simmerson et al., 2009; Dijkstra et al., 2010; Goodwin et al., 2011; Owens et
142 al., 2011; Equilino et al., 2015). Although 32.2% of the dogs had died within 6 months of diagnosis, a greater
143 proportion (55.9%) was still alive at the time of manuscript preparation, suggesting that not only PLE-affected
144 Yorkshire Terriers, but also other PLE-affected breeds may experience remission of clinical signs and prolonged
145 survival despite severity of clinicopathologic findings at diagnosis, as recently described (Equilino et al., 2015).

146 To our knowledge, no long-term data on the follow-up of dogs with PLE exist. At T1 (6 months follow-up) the
147 CCECAI scores were higher and the albumin, total protein, and total cholesterol concentrations all lower in the STs.
148 Moreover, the dogs with a CCECAI score > 5 were more likely to die within 6 months of initial diagnosis. Since these
149 variables at T0 did not significantly influence the outcome, they might simply reflect a poor response to therapy.
150 Finally, since all STs were categorized as immunosuppressive-unresponsive, it is reasonable to assume that a poor
151 response to therapy is a poor prognostic indicator. Indeed, survival time was shorter in the dogs with high CCECAI
152 scores at T1 and that were unresponsive to therapy.

153 In conclusion, the clinical outcomes of PLE are variable, with the majority of the dogs having prolonged survival
154 despite the severity of clinicopathological findings at diagnosis.

155

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230 Table 1. List of presenting complaints/clinical signs at diagnosis (T0) in short-term (ST) and long-term (LT) survivors.

231

Variables	STs n/t	LTs n/t
Small bowel diarrhea	19/19	39/40
Mixed diarrhea	5/19	14/40
Decreased appetite	13/19	22/40
Increased appetite	1/19	3/40
Vomiting	9/19	24/40
Peripheral edema	1/19	5/40
Ascites	6/19	20/40
Pleural effusion	-	3/40
Pruritus	1/19	4/40
Polyuria and polydipsia	4/19	5/40
Lethargy	2/19	8/40
Muscular twitching/convulsion	1/19	4/40

232 n= number of dogs showing the complaint/clinical sign

233 t= total number of dogs

234

235

236

237 Table 2. Summary of laboratory results at diagnosis (T0) in short-term (ST) and long-term (LT) survivors

238

239

Variables	STs		LTs		Reference values
	Positive or abnormal	Mean (\pm SD)	Positive or abnormal	Mean (\pm SD)	
Albumin	-	1.49 (\pm 0.42) g/dL	-	1.45 (\pm 0.31) g/dL	2.80-3.70 g/dL ²⁴³
Globulin	-	2.08 (\pm 0.87) g/dL	-	1.88 (\pm 0.61) g/dL	2.80-4.20 g/dL ²⁴⁴
Total Protein	-	3.57 (\pm 0.97) g/dL	-	3.32 (\pm 0.75) g/dL	5.60-7.90 g/dL
Total Cholesterol	-	118 (\pm 54) mg/dL	-	122 (\pm 48) mg/dL	140-350 mg/dL ²⁴⁵
Magnesium	-	1.67 (\pm 0.86) mg/dL	-	1.88 (\pm 1.90) mg/dL	1.60-3.20 mg/dL ²⁴⁶
Blood Urea Nitrogen	-	37.62 (\pm 18.65) mg/dL	-	28.72 (\pm 17.32) mg/dL	18-55 mg/dL
Cobalamin	-	219 (\pm 128) ng/L	-	229 (\pm 107) ng/L	250-730 ng/L ²⁴⁷
Folate	-	9.95 (\pm 5.80) μ g/L	-	10.42 (\pm 5.90) μ g/L	7-17 μ g/L ²⁴⁸
Fibrinogen	-	450 (\pm 146) mg/dL	-	555 (\pm 225) mg/dL	150-450 mg/dL ²⁴⁸
Lipase	-	191 (\pm 123) U/L	-	302 (\pm 205) U/L	70-700 U/L ²⁴⁹
SNAP cPL®	2	-	3	-	-
Number of platelets	-	463,684 (\pm 218,761) cells/ μ L	-	426,056 (\pm 252,977) cells/ μ L	150,000-500,000 cells/ μ L ²⁵⁰
Number of monocytes	-	686 (\pm 482) cells/ μ L	-	634 (\pm 396) cells/ μ L	100-1400 cells/ μ L ²⁵¹
Coagulation profile	9	-	10	-	- ²⁵²

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255

256

257 Table 3. Summary of clinicopathological variables tested at diagnosis (T0) and 1 month after initiation of immunosuppressive therapy
 258 (T1) in short- term (ST) and long-term (LT) survivors.

259

Variable	T0		T1	
	STs n/t	LTs n/t	STs n/t	LTs n/t
Albumin	19/19	40/40	18/19	40/40
Globulin	19/19	40/40	18/19	39/40
Total Protein	19/19	40/40	18/19	39/40
Total Cholesterol	19/19	38/40	13/19	31/40
Magnesium	9/19	26/40	6/19	18/40
Blood Urea Nitrogen	19/19	37/40	-	-
Cobalamin	13/19	30/40	-	-
Folate	13/19	32/40	-	-
Fibrinogen	5/19	16/40	-	-
Lipase	10/19	27/40	-	-
SNAP cPL®	5/19	17/40	-	-
Number of platelets	19/19	38/40	-	-
Number of monocytes	18/19	32/40	-	-
Coagulation profile	6/19	13/40	-	-

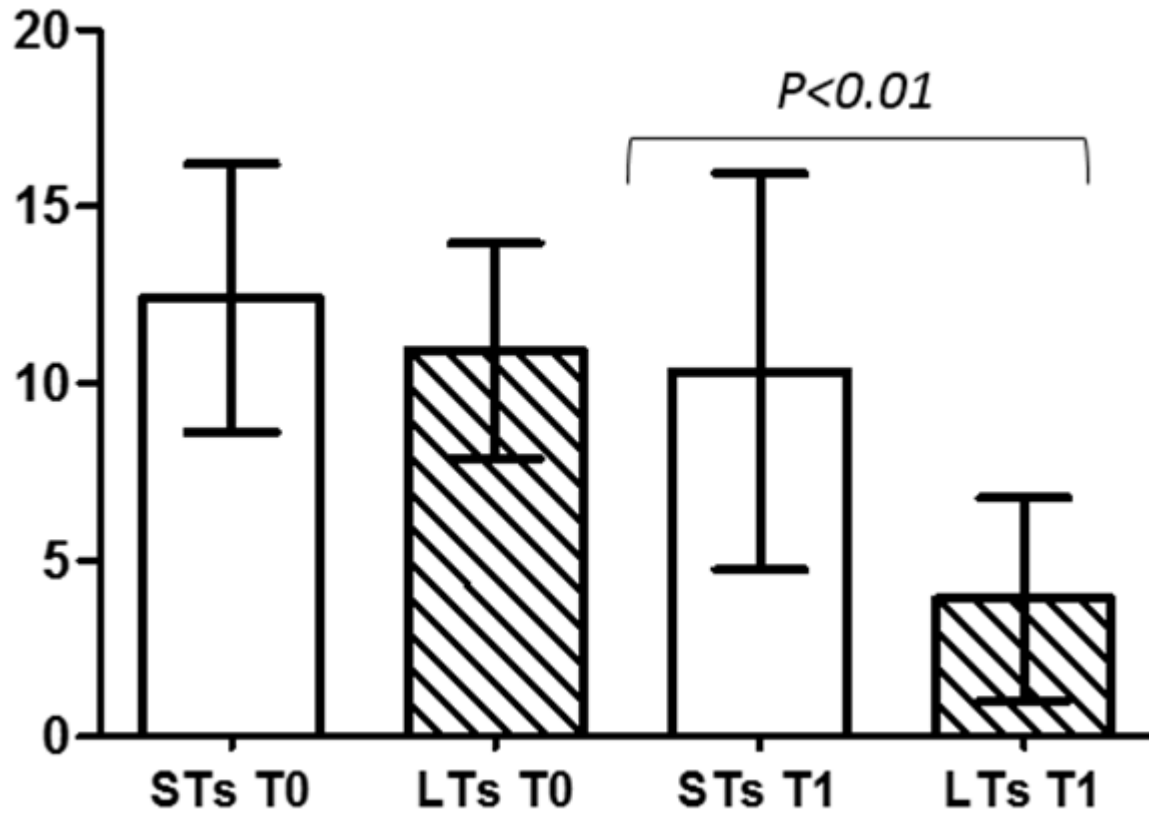
260 n=number of dogs in which the variable was measured

261 t=total number of dogs

262

263 Figure 1. Comparison of canine chronic enteropathy activity scoring index (CCECAI) between short-term (ST) and long-term (LT)
264 survivors at T0 and T1.

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269 Figure 2. The receiver operating characteristic (ROC) curve used to select the optimum cut-off value of the variable CCECAI associated
270 with survival to discriminate between short-term (ST) and long-term (LT) survivors.

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272 Sensitivity: 77.8

273 Specificity: 87.5

274 Criterion: >5

275 Area under the ROC curve: 0.828

276 Standard error: 0.0672

277 95% Confidence interval: 0.706 to 0.914

278 Z statistic: 4.878

279 Significance level $P < 0.0001$

