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Chronic enteropathy food- and immunosuppressant-responsive: comparison of clinicopathological findings and follow-up

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Introduction and objective - The term chronic enteropathy encompasses various clinical entities with similar etiology, but different therapeutic responses on the basis of which they are retrospectively subdivided. In this work two groups of italian dogs suffering from diet- (food responsive enteropathy, FRE) and immunosuppressant-responsive chronic enteropathy (steroid responsive enteropathy, IRE) were compared, respectively, with two aims: to evaluate possible associations between clinical, clinicopathological marker and diagnosis of FRE/IRE; identify possible clinical, clinicopathological findings predictive of survival and/or relapse in dogs with IRE.

Materials and Methods - Retrospective analysis of medical records of client-owned dogs with a diagnosis of FRE or IRE. Clinical and clinicopathologic findings of the two groups were compared and correlated with the survival time and relapse.

Results - Of the 81 dogs included in the study, 42 were classified as FRE and 39 as IRE. A significant association between a diagnosis of IRE and old age, high CIBDAI/CCECAI scores, small intestine diarrhea, anorexia, weight loss, ascites, hypoalbuminemia, hypoglobulinemia and hypocobalaminemia was found. In addition, a significant association between one relapse at least and death in dogs with IRE was found.

Discussion - Most of the results of this study are consistent with previous observations. The most interesting novelty, is represented by the fact that, regardless the severity of clinical presentation at diagnosis, dogs with IRE that respond to therapy are more likely to live longer.

Keywords - Food-responsive enteropathy, immunosuppressant-responsive enteropathy, relapse, survival, canine.

INTRODUCTION

Chronic enteropathy includes several clinical entities with similar chronic gastrointestinal symptoms, aetiology, clinical as well as histological alterations, but which respond differently to diet and sequential therapeutic trials, on the basis of which they are retrospectively classified.[1] In the dog, once excluded other causes of chronic vomiting and diarrhoea in view of the clinical response, the following disorders may be identified: chronic food-responsive enteropathy (FRE), antibiotic-responsive enteropathy

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(ARE) and immunosuppressant-responsive enteropathy (IRE). For the latter, however, the presence of an underlying intestinal inflammatory process must first be confirmed.[1-6]

At present, no clinicopathological markers allow the disticntion between dogs with FRE and IRE. In addition, scientific information on the prognostic value of clinical and clinicopathological parameters as predictors of survival time and/or of relapses in dogs with IRE is scarce and discordant, if not entirely absent.[2,4,7-11]

Most dogs with chronic enteropathy do not require immunosuppressive drugs but only dietary treatment.

The aim of this study was twofold: to compare two groups of dogs with respectively FRE and IRE in order to identify a possible correlation between clinical and clinicopathological factors and the phenotype, and to identify any clinical and/or clinicopathological marker predictive of survival and/or of relapse in dogs with IRE.

MATERIALS AND METHODS

A retrospective analysis of the medical records of client-owned dogs with FRE and IRE - diagnosed by the specialist service of internal medicine of the Veterinary University Hospital (OVU) of the Department of Veterinary Sciences, University of Turin, and by the Clinica Veterinaria Valdinievole, Monsummano Terme (Pistoia) - was carried out between November 2008 and January 2014. The inclusion criteria for the diagnosis of FRE were: chronic gastrointestinal symptoms (>3 weeks); negative parasites at faecal examination (intestinal helminths and Giardia cysts) on samples taken on 3 consecutive days and/or fenbendazole-based anthelmintic treatment (Panacur®, Intervet Italia, Milan) at the dosage of 50 mg/kg SID, orally, for 5 consecutive days; the exclusion of other causes of chronic gastrointestinal signs; and a positive and enduring food trial response (full resolution of symptoms within two weeks of the administration of a diet based on hydrolysed proteins or with proteins never previously taken). The inclusion criteria for the diagnosis of IRE, in addition to those listed for the diagnosis of FRE and with the exception of non-response to a food trial, were: no response to an antibiotic trial (resolution of symptoms following the administration of tylosin, 15 mg/kg BID, PO or metronidazole, 10-15 mg/kg BID, PO for at least 3 weeks);[1,4] presence of GI inflammation diagnosed by histological examination of a biopsy; and positive response to a trial with immunosuppressive drugs (prednisolone 0,5-1 mg/kg, BID, PO for 1-3 weeks before considering a reduction, either alone or in combination with azathioprine or cyclosporine; azathioprine 1-2 mg/kg, SID, PO; cyclosporine 5 mg/kg SID, PO).[1,4] The type of diet (hydrolysate proteins, new proteins), antibiotic (tylosin, metronidazole) or immunosuppressive drug (prednisolone, azathioprine, cyclosporine) were decided on a case-by-case basis. Biopsies were collected by endoscopy (gastroduodeno-, ileo- and colonoscopy) or laparotomy. Endoscopic investigations were carried out with a standard technique, using two flexible video endoscopes (XION Medical PV-SG 22, external diameter 8.9 mm, length 110 cm, working channel 2.2 mm; or XION Medical PV-SG 34L, external diameter 11 cm, length 160 cm, working channel 3.2 mm).[12] The biopsies were sent to the histopathology diagnostic laboratories of the Department of Veterinary Sciences of the Università degli Studi di Torino, Italy, or to the Texas A&M University, College Station, TX, USA, depending on in which clinic the patient was seen, and interpreted according to the WSAVA Gastrointestinal Standardization Group standards.[13]

The clinical records also contained information on the CIBDAI and CCECAI clinical scores at the time of diagnosis,[2,14] on the physical examination, laboratory tests (CBC, biochemical profile, serum levels of folates and cobalamin) and diagnostic imaging (abdominal ultrasound, endoscopy).

The study considered the clinical records of two groups of dogs with food- and immuno-responsive enteropathy.

At the time of revision of the clinical records, in January 2015, a telephone interview was made with the owners of each patient. In particular, the questions asked were: whether the dog was still alive; whether there had been at least one relapse of GI symptoms during or after the suspension of food and therapeutic trials; finally, in the case of death, when had it occurred, was it spontaneous or euthanasia, and what was the cause (GI-related disorder or other cause). In addition, CIBDAI and CCECAI clinical scores were recalculated for survivors, for relapsed and for deceased patients on the basis of the information obtained from the medical records or from the telephone interviews with the owners.

The statistical analysis of the data was performed using the "EZR" programme on R Commander.[15] Continuous quantitative variables were described using the median and the first/third quartile (Q1-Q3) while the frequency of qualitative variables was expressed with the prevalence (P) and confidence intervals of 95% (95% CI). The significance value was set for $P \leq 0.05$. Fisher's exact test allowed to assess the association between the categorical variables [symptomatology, laboratory al-

terations (hypoalbuminaemia, hypoglobulinaemia, hypoproteinaemia and hypocobalaminaemia) and diagnosis of FRE or IRE; age, sex, weight, symptomatology, laboratory abnormalities (monocytosis, thrombocytosis, thrombocytopaenia, hypoalbuminaemia, hypoglobulinaemia, hypoproteinaemia, hypocobalaminaemia, low folates, hypocalcemia), ultrasound alterations and recurrence within the group of dogs affected by IRE)]. The association between the independent categorical variables (IRE diagnosis, mortality due to gastrointestinal disorders and relapses) and the continuous dependent variables was studied using Wilcoxon (age, weight and symptoms) and Kruskal-Wallis (CIBDAI and CCECAI clinical scores) tests. The survival time was analysed using Kaplan-Meier curves.

RESULTS

Clinical history, physical examination and CIBDAI/CCECAI scores

Eighty-one dogs met the inclusion criteria. Of these, 42 were classified as affected by FRE and 39 by IRE. Of the dogs with FRE, 25 were male and 17 were females; median age 61 months (range: 12-178) and average weight 19.7 kg (range: 2.8-53). Thirty-three dogs were of different breeds and 9 were mongrels; the German Shepherd was the most represented breed (n=9). Of the dogs with IRE, 21 were male and 18 were females; median age 81 months (range: 36-132) and average weight 18.8 kg (range: 3-45). Thirty-nine dogs were of different breeds and 10 were mongrels; the German Shepherd was the most represented breed (n=6). For dogs with FRE, the medians of both CIBDAI and CCECAI scores were 5 (range 0-11 and 0-12, respectively), while for dogs with IRE the medians of CIBDAI and CCECAI scores were 8 (range 4-15) and 11 (range 6-19), respectively. Statistically significant associations were found between high CIBDAI and CCECAI scores and small bowel diarrhoea ($P<0.05$) in dogs with FRE and IRE, respectively. Dogs with FRE were significantly younger than those with IRE ($P<0.05$) and had significantly lower CIBDAI and CCECAI scores ($P<0.0001$) (Figure 1). No significant differences emerged when comparing sex, breed and weight in the two groups. Small bowel diarrhoea ($P<0.001$), weight loss ($P<0.0001$), ascites ($P<0.01$) and anorexia ($P<0.001$) were more frequently present in dogs with IRE than in dogs with FRE. The data on symptoms, clinical findings and CIBDAI and CCECAI scores of both groups are given in Table 1.

Results show that dogs with food-responsive enteropathy tend to be young and with mild gastrointestinal symptoms while dogs with immunoresponsive enteropathy are older and with typically more severe gastrointestinal symptoms.

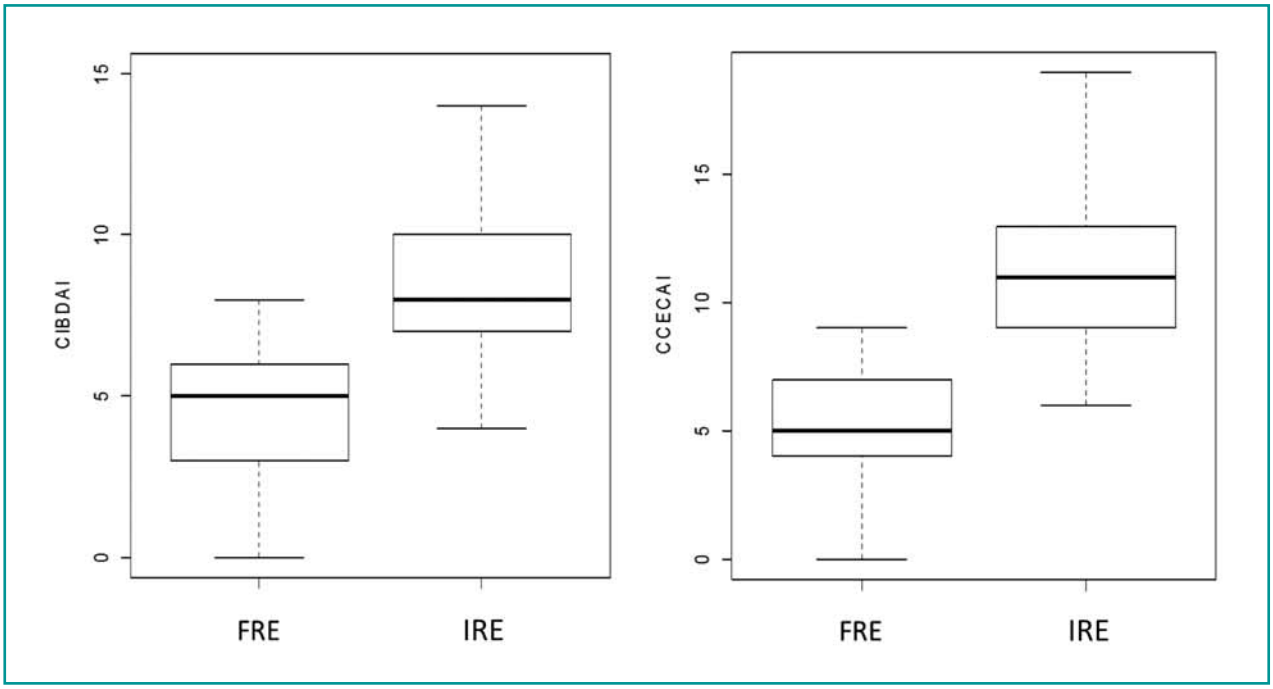

Figure 1 - Association between CIBDAI/CCECAI scores and phenotype.
FRE=Food-responsive enteropathy.
IRE=Immunosuppressant-responsive enteropathy.
CIBDAI=Canine IBD Activity Index.
CCECAI=Chronic Canine Enteropathy Clinical Activity Index.

Table 1 - List of symptoms, clinical findings and CIBDAI and CCECAI scores in dogs with FRE and IRE

Variable	FRE		IRE	
Small bowel diarrhoea (n/t)	16/42		34/39	
Large bowel diarrhoea (n/t)	15/42		8/39	
Vomiting (n/t)	29/42		24/39	
Weight loss (n/t)	16/42		34/39	
Anorexia (n/t)	8/42		21/39	
Polyphagia (n/t)	3/42		2/39	
Ascitis/peripheral oedema (n/t)	1/42		19/39	
Pleural effusion (n/t)	-		2/39	
Polyuria/polydipsia	-		3/39	
Muscle tremors/seizures (n/t)	1/42		5/39	
Itching (n/t)	9/42		9/39	
CCECAI ≤5 CIBDAI ≤5	22/42	28/42	–	6/39
CCECAI ≤8 CIBDAI ≤8	18/42	13/42	9/39	13/39
CCECAI ≥9 ≤11 CIBDAI ≥9	1/42	1/42	15/39	18/39
CCECAI ≥12	1/42		13/39	

n = number of dogs.
t = total number of dogs.
FRE = food-responsive enteropathy.
IRE = immunosuppressant-responsive enteropathy.
CIBDAI = canine IBD activity index.
CCECAI = chronic canine enteropathy clinical activity index.

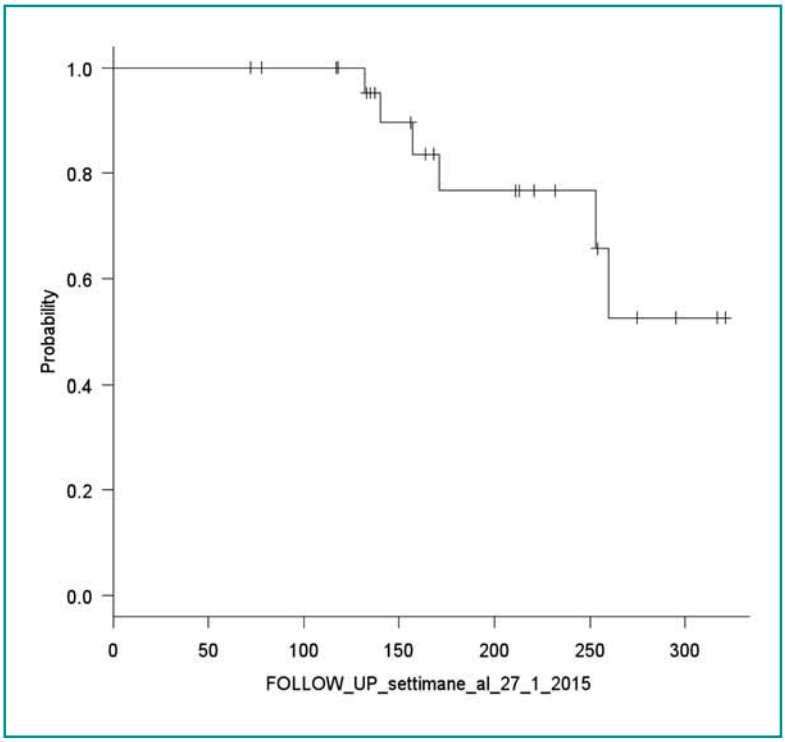

Figure 2 - Survival curves in dogs with IRE.
IRE = immunosuppressant-responsive enteropathy.

In agreement with the available literature, dogs with immuno-responsive enteropathy more frequently present with small bowel diarrhoea.

Clinicopathological alterations

The list of clinicopathological variables tested and the alterations found at diagnosis in the dogs of the two groups are shown in Tables 2 and 3. Hypoproteinaemia ($P<0.01$), hypoalbuminaemia ($P<0.01$), hypoglobulinaemia ($P<0.01$) and hypocobalaminaemia ($P<0.056$) were more frequently present in dogs with IRE, compared to dogs with FRE.

In dogs with immune-responsive enteropathy, hypoalbuminaemia and hypocobalaminaemia are not associated with reduced survival or an increased likelihood of relapse during treatment.

Results of GI histology in dogs with IRE

Gastroduodenoscopy was performed in 37 dogs. In addition, ileoscopy and colonoscopy were performed in 19 dogs. Laparotomy was performed in 2 dogs. Biopsies were considered adequate in all dogs. Moderate to severe histopathological abnormalities were found in the small bowel of all dogs. The most frequent alterations encountered were lymphangectasia (19 dogs), lymphoplasmacellular infiltrate (27 dogs) and alterations of the normal microarchitecture (17 dogs). Moderate to severe colon infiltration was found in 11 dogs.

The most frequently observed microscopic alterations were lymphoplasmacellular infiltrate and lymphangectasia.

Survival and relapses

Follow-up information was available for 38/42 dogs with FRE and 28/39 dogs with IRE. At the time of revision of the clinical records, 34 dogs with FRE (81%) were still alive, while 4 had died from causes not associated with the GI disorder; 10 dogs with IRE (25.6%) were still alive and 18 (46.1%) had died, 6 of which for causes associated with the GI disorder. The presence of at least one relapse was observed in 13/39 dogs with IRE.

After 171 weeks, 76.7% of dogs with IRE were still alive (Figure 2). In the group of dogs with IRE, at follow-up survivors showed significantly higher median CIBDAI and CCECAI clinical scores (9 and 11, respectively) compared to those of deceased dogs (7.5 and 8.5). In dogs with IRE, a statistically significant association was found between deaths and age <5 years (P=0.05), between relapses and age <5 years (P=0.053) and between relapses and deaths (P<0.05).

After 3.5 years most dogs with IRE were still alive.

DISCUSSION

The multicentre retrospective study compared two groups of dogs with FRE and IRE, with two main aims: to identify a possible association between clinical and clinicopathological information and the phenotype; and, in dogs with IRE, to identify a possible association between clinical and clinicopathological information and the survival and presence of relapses.

However, in view of the unavailability of specific markers the diagnosis and classification of chronic enteropathy requires the evaluation of response to food trials, together with clinical, laboratory, endoscopic, histological and therapeutic trials; these tests are sometimes long and complex and the collaboration of both the owner and the patient is often lacking.[1]

In the study, no dog was classified as suffering from ARE. Although the use of different types of antibiotics has been reported in dogs with CE, with the exception of granulomatous colitis in Boxers and French Bulldogs the efficacy of antibiotics is still not clear and is often of short duration, making in fact the definitive diagnosis of idiopathic ARE difficult and questionable.[1,16]

In accordance with the existing veterinary literature, compared to dogs with IRE the phenotype of dogs with FRE

Table 2 - List of clinicopathological variables tested and of the alterations found at diagnosis in dogs with FRE and IRE

Variable	Phenotype	n/t	Over R.R.	Normal value	Under R.R.
Monocytes	FRE	17/42	2	15	0
	IRE	39/39	4	35	0
Platelets	FRE	17/42	0	17	0
	IRE	39/39	6	32	1
Albumins (*)	FRE	21/42	0	16	5
	IRE	39/39	0	4	35
Globulins (*)	FRE	21/42	0	13	8
	IRE	39/39	1	7	31
Total Protein (*)	FRE	22/42	0	17	5
	IRE	39/39	0	8	31
BUN	FRE	15/42	0	15	0
	IRE	13/39	0	13	0
Cholesterol	FRE	9/42	2	5	2
	IRE	37/39	0	17	20
Total calcium	FRE	8/42	0	6	2
	IRE	35/39	0	7	28
Pholates	FRE	11/42	1	7	3
	IRE	27/39	2	21	4
Cobalamine (*)	FRE	16/42	0	13	3
	IRE	26/39	1	12	13
Specific pancreatic lipase	FRE	8/42	1	7	0
	IRE	22/39	5	17	0

*R.R.: reference range; FRE: food responsive enteropathy; IRE: immunosuppressant-responsive enteropathy; n, number of dogs; t, total number of dogs; (*)**significantly different values between FRE and IRE**.*

Table 3 - List of alterations detected during ultrasound examination of the abdomen in dogs with FRE and IRE

Abdominal ultrasound: ultrasound alteration	FRE (20/42)	IRE (39/39)
	n/t	n/t
Altered stratification	1/20	3/39
GI wall thickening	5/20	13/39
Lymphadenomegaly	7/20	6/39
Altered mucosal ecogenicity	1/20	7/39

FRE, food-responsive enteropathy;
IRE, immunosuppressant-responsive enteropathy;
n, number of dogst; t, total number of dogs;

found in the study is characteristic of a young subject.[2,7,17,18] In particular, the median age of dogs with IRE was 7 years, versus 5 years in dogs with FRE.[9,18]
Small and medium-large size dogs were present in both groups, both purebreds and mongrels, in line with previous reports.[2,6-8,19-21] Weimaraner, Rottweiler, German Shepherd, Border collie and Boxer dogs are predisposed to the development of chronic enteropathy.[22] Although breed predisposition was not among the aims of the study, also in our case in both groups German Shepherd dogs were numerically superior to subjects of other breeds.
A comparison of symptomatology and clinical findings showed that dogs with IRE presented more frequently ascites, anorexia, small bowel diarrhoea and weight loss compared to dogs with FRE, in accordance with what reported in the literature.[2,23] No significant difference was instead found for vomiting.
CIBDAI and CCECAI clinical scores can be used as indices of clinical severity.[2,14]

Dogs with FRE tend to be young and show milder symptoms compared to dogs with IRE, which tend to develop ascites and more commonly present anorexia, weight loss and small bowel diarrhoea.

In agreement with current information available in the veterinary literature, dogs with FRE had lower CIBDAI and CCECAI clinical scores compared to dogs with IRE.[2,17,24] However, in dogs with FRE and IRE with small bowel diarrhoea, CIBDAI and CCECAI scores were significantly higher than in those with other symptoms. Although it is not possible to compare such results with similar data in the literature, as they are not available, it may be hypothesised that diarrhoea, when present, is a more severe symptom than other symptoms.
As for the clinicopathological variables, dogs with IRE presented a significantly more severe malabsorption than dogs with FRE. In fact, while the percentage of dogs with hypoalbuminaemia and hypocobalaminaemia in the FRE group and hypocobalaminaemia in the IRE group were similar to those recently reported,[2,7,11,25] the percentage of dogs with hypoalbuminaemia in the IRE group was much higher.[2,7,11]
The more frequently found histopathological alterations were lymphoplasmacellular inflammation and lymphangectasia. In dogs with lymphoplasmacellular enteritis it has recently been observed that structural alterations of villi and lymphatic vessels correlate with the severity of hypoalbuminaemia and hypocholesterolaemia.[26] The prognostic value of histology was not considered in view of the retrospective nature of the study and the lack of rigorous standardization in diagnostic procedures. Future studies should however take histology into account, not only in view of its prognostic value but also for the therapeutic implications that might derive.
The Kaplan-Meier curve, used previously in the evaluation of survival in dogs with chronic enteropathy, showed that after about 3 years, 76.7% of dogs with IRE were still alive, in agreement with what previously reported.[2,11] Markedly lower survival rates are instead reported in other studies;[8,10] it should however be mentioned that these studies considered purebred dog populations, in which the enteropathy is particularly severe (Shiba), or in dogs affected by PLE (Yorkshire terrier), a disease with a poor prognosis.[21]
According to some authors, CIBDAI and CCECAI clinical scores may also be used as prognostic markers.[2,14] However, opinions in the literature are discordant. Some studies, in fact, report CIBDAI and CCECAI scores as a negative prognostic factor in dogs with IRE,[2,9,27] while in others the same scores are not associated with reduced survival.[7,9] In particular, in our study, in the dogs deceased from GI-related disorders the median of both scores was lower than in the one of survivors.
This could signify that there is indeed no association between the severity of clinical symptoms at diagnosis (and hence of CIBDAI and CCECAI scores) and deaths. However, an alternative hypothesis could be the low statistical power of the numerically small sample examined.
Although in dogs with IRE advanced age is reported in the literature as a negative prognostic factor,[10,27] in our study most of the deceased dogs were under 5 years old. It can therefore be hypothesized that variables other than age influence the prognosis.
In dogs with IRE some studies include hypoalbuminaemia and hypocobalaminaemia among the negative prognostic factors.[2,8,11] However, this association has not emerged in either a recent study on dogs with PLE[7] or in the present study.
Also interesting, although intuitable, is the significant association within the IRE group between relapses and survival. In fact, of the 13 dogs with at least one relapse, 6 died; on the contrary, in the dogs without a relapse no deaths were recorded. As a result, it can be said that regardless of the severity of clinical symptoms at diagnosis (and hence of the CIBDAI and CCECAI clinical scores) dogs with IRE that respond to therapy live longer. Since dogs who develop at least one relapse are more frequently at risk of death, the significant association between relapses and the clinical and clinicopathological parameters was similar to the one obtained by comparing survival with the same parameters. In fact, both CIBDAI and CCECAI clinical scores and age were lower in dogs with relapses and reduced survival compared to those

The severity of clinical symptoms at the time of diagnosis is not associated with reduced survival both in dogs with food-responsive enteropathy and in those with immune-responsive enteropathy; in addition, dogs with fewer relapses while undergoing therapy live longer.

without relapses and with a longer survival. Finally, no statistically significant association was found between dogs with IRE that relapsed and the presence of a concomitant hypoalbuminaemia or hypocobalaminaemia at diagnosis. Unfortunately, as similar data are not available in the veterinary literature it is currently not possible to compare such results with other studies.

The main limitations of this study are its retrospective nature, with the consequent lack of rigorous standardization of all diagnostic procedures and of follow-up collection, and the reduced sample size of the subgroups studied (deaths and relapses), which may have influenced the absence of statistically significant associations that might have otherwise been detectable.

In conclusion, within the Italian dog population considered it can be stated that a young patient with large bowel diarrhoea and mild clinical symptoms is more likely affected by FRE, while an elderly patient with small bowel diarrhoea, anorexia or weight loss, high CIBDAI and CCECAI clinical scores, panhypoproteinaemia and hypocobalaminaemia is affected by IRE. Nevertheless, the severity of the clinical symptomatology and of clinicopathological alterations does not seem to be associated with reduced survival, while the absence of relapses, and hence a good response to the therapy established at the time of diagnosis, allows for a longer survival.

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KEY POINTS

- Based on the response to sequential trials, chronic enteropathies can be subdivided retrospectively into: food-responsive enteropathy (FRE), antibiotic-responsive enteropathy (ARE), immuno-responsive enteropathy (IRE)
- In this study, two groups of Italian dogs with FRE and IRE were compared, retrospectively
- Young dogs of any size and with large bowel diarrhoea are more likely to be affected by FRE
- Adult-elderly dogs of any size with small bowel diarrhoea, weight loss and anorexia are more likely to be affected by IRE
- Regardless of the diagnosis of FRE or IRE, the presence of small bowel diarrhoea is associated with higher CIBDAI/CCECAI clinical scores
- In dogs with IRE, neither the severity of symptoms at diagnosis (and therefore of high CIBDAI/CCECAI clinical scores) nor the presence of hypoalbuminaemia/hypocobalaminaemia are associated with reduced survival or a greater probability of developing relapses.

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