Contents lists available at ScienceDirect

Veterinary and Animal Science

Clinical characteristics of dogs presenting with vomiting as a gastrointestinal sign of chronic enteropathy

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ARTICLE INFO

ABSTRACT

Vomiting is a major gastrointestinal (GI) sign of chronic enteropathy (CE) in dogs. Previous studies have reported clinical characteristics of dogs with CE, who developed diarrhea with or without vomiting as GI signs. However, to characterize clinical features of dogs with CE appropriately, dogs presenting with vomiting without diarrhea should be included in the analysis. Thus, this study aimed to characterize clinical features and outcomes of dogs that presented with vomiting without diarrhea. Based on their presenting GI signs, we retrospectively classified 66 dogs with CE into "Vomiting", "Diarrhea", or "Vomiting and diarrhea" groups and compared clinical and histological characteristics of each group. We found that 18 of the 66 dogs with CE (27%) presented with vomiting without diarrhea as a GI sign. Compared to the other 2 groups, the Vomiting group was significantly associated with food-responsive enteropathy (FRE), Beagle, lower clinical severity scores, higher plasma albumin levels, and higher histological scores for eosinophils in the duodenal lamina propria according to the univariate analysis. The multivariate analysis revealed that FRE and higher histological scores for eosinophils in the duodenal lamina propria were significant variables in the Vomiting group. Moreover, the survival time was the longest in the Vomiting group among dogs with CE. These findings are of clinical significance as they indicate that presenting with vomiting without diarrhea may not only be helpful in differentiating FRE from the other types of CE, but also in predicting the prognosis.

Abbreviations

ARE	Antibiotic-Responsive Enteropathy
CCECAI	Canine Chronic Enteropathy Clinical Activity Index
CE	Chronic Enteropathy
FRE	Food-Responsive Enteropathy
GI	Gastrointestinal
IRE	Immunosuppressant-Responsive Enteropathy
NRE	Non-Responsive Enteropathy
PO	Per OS
WSAVA	World Small Animal Veterinary Association

1. Introduction

Chronic enteropathy (CE) is a common canine disease characterized by chronic persistent or recurrent gastrointestinal (GI) signs and mucosal inflammation of the GI tract (Allenspach, Wieland, Gröne & Gaschen, 2007; Dandrieux, 2016; Washabau et al., 2010). CE can be classified as food-responsive enteropathy (FRE), antibiotic-responsive enteropathy (ARE), immunosuppressant-responsive enteropathy (IRE), and non-responsive enteropathy (NRE), depending on the treatment response (Dandrieux, 2016). GI sings in dogs with FRE can be managed by dietary change alone, whereas those in dogs with ARE can be improved with antibiotics, such as metronidazole, tylosin, or oxytetracycline (Dandrieux, 2016; Hall, 2011; Simpson & Jergens, 2011). Dogs with IRE are not completely responsive to antibiotic or dietary treatments, and require anti-inflammatory or immunosuppressive drugs, including glucocorticoids, to control their clinical signs (Dandrieux, 2016; Simpson & Jergens, 2011). In contrast, dogs with NRE do not respond to the immunosuppressant therapy, thereby showing poor

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prognosis (Pietra et al., 2021).

Previous studies have reported clinical characteristics of dogs with CE, who developed diarrhea with or without vomiting as GI signs (Allenspach et al., 2007; Allenspach, Culverwell & Chan, 2016). However, some dogs with CE present clinical signs other than diarrhea (Dandrieux, 2016), and vomiting is a major GI sign scored by the canine chronic enteropathy clinical activity index (CCECAI) (Allenspach et al., 2007) and canine inflammatory bowel disease activity index (Jergens et al., 2003). Nevertheless, dogs presenting with vomiting without diarrhea have not been included in previous studies. For appropriate characterization of clinical features of dogs with CE, these dogs should also be included in the analysis.

Therefore, this study aimed to characterize clinical features and outcomes of dogs presenting with vomiting without diarrhea as a GI sign of CE.

2. Materials and methods

2.1. Dogs and diagnostic procedure of CE

Medical records of 66 dogs diagnosed with CE, between February 2013 and October 2019, at Tokyo University of Agriculture and Technology Animal Medical Center (TUAT-AMC) and Advanced Animal Medical Center (AdAM) in Japan were retrospectively reviewed. Informed consent was obtained from the owners of dogs involved in this study. During the survey period, a total of 6,946 dogs were referred to TUAT-AMC and AdAM. CE was diagnosed based on the previous reports (Dandrieux, 2016; Hirokawa et al., 2021; Ogawa et al., 2018; Osada et al., 2017). The criteria for CE diagnosis included chronic GI signs, such as vomiting, small bowel diarrhea (melena, normal fecal frequency, and increased fecal volume), and/or large bowel diarrhea (mucus, hematochezia, tenesmus, increased frequency of defecation, and decreased fecal volume) for a duration of over 3 weeks. Other possible causes of chronic GI signs, such as metabolic diseases, infectious diseases including bacterial, viral, and parasitic diseases, exocrine pancreatic insufficiency, hepatic diseases, renal diseases, and neoplasms including alimentary lymphoma, were ruled out based on vaccination history and physical and clinical examinations, including blood tests, thoracic and abdominal radiography and ultrasounds, and fecal analysis. Pancreatitis was clinically excluded as a primary cause of vomiting based on blood tests and abdominal ultrasound results. After exclusion of other causes of chronic GI signs, endoscopic examination of the duodenum with or without the colon was performed in 57 of the 66 dogs according to the procedure described in our previous report (Hirokawa et al., 2021). For the histopathological analysis, more than 6 specimens were obtained by endoscopic biopsy from each region. To differentiate CE, FRE was first diagnosed if GI signs were completely resolved with dietary trials using hydrolyzed protein diets, such as Anallergenic (Royal Canin Japon Inc., Tokyo, Japan), Hypoallergenic (Royal Canin Japon Inc.), or z/d (Hill'-s-Colgate Ltd., Tokyo, Japan), or a novel protein diet, such as Selected Protein (Royal Canin Japon Inc.). ARE was then diagnosed if there was complete resolution of GI signs in response to antibiotic treatments with metronidazole (Flagyl; Shionogi & Co., Ltd., Osaka, Japan) (10–15 mg/kg, per os [PO], q12 h) or tylosin (Tylan; Eli Lilly Japan K.K., Kobe, Japan) (20 mg/kg, PO, q12 h). After ruling out FRE and ARE, IRE was diagnosed if there was partial or complete resolution of GI signs with prednisolone (Pfizer, Tokyo, Japan; 0.5–2.0 mg/kg, PO, q24 h). NRE was diagnosed based on poor responses to the immunosuppressant drugs, including prednisolone, budesonide (Zentacoart, Zeria Pharmaceutical Co., Ltd., Tokyo, Japan; 0.2 mg/kg, PO, q24 h), and chlorambucil (Leukeran, Aspen Pharma, Baar, Switzerland; 3.7–4.7 mg/m^2, PO, q24 h). In the 9 dogs in which endoscopic examination was not performed due to the owner's request, GI signs improved completely with dietary (7 dogs) or antibiotic (2 dogs) trials. Thus, these dogs were diagnosed with FRE or ARE.

2.2. Data collection

Data extracted from the medical records included signalment, such as breed, sex, age, and bodyweight, GI signs, clinical severity, clinico-pathological findings, and histopathological findings and severity. Based on the GI signs presented, dogs were classified into the 3 groups: Vomiting group, Diarrhea group, and Vomiting and diarrhea group. Clinical severity was scored using CCECAI (Allenspach et al., 2007). Clinicopathological findings included white blood cell count, packed cell volume, platelet count, plasma albumin level, and plasma C-reactive protein level. These parameters were selected based on the previous studies (Allenspach et al., 2016, 2007; Ohno et al., 2006). Histopathological findings and severity scores were determined according to the guideline of the World Small Animal Veterinary Association (WSAVA) international GI standardization group (Washabau et al., 2010) by a board-certified veterinary anatomic pathologist (HK). Additionally, the survival time was determined based on the medical records and telephone or letter follow-up investigations until November 2020.

2.3. Statistical analysis

All the signalment and clinical data from the first visit were used for statistical analysis, except for histopathological findings and severity and survival time. Distribution of the dog breeds in the Vomiting, Diarrhea, and Vomiting and diarrhea groups was compared with that of the overall hospital population of TUAT-AMC and AdAM during the survey period. Categorical variables were analyzed using the chi-squared test. Continuous variables were analyzed for the normality using the Shapiro–Wilk test; these were expressed as medians and ranges. Continuous variables among the Vomiting, Diarrhea, and Vomiting and diarrhea groups were compared using one-way analysis of variance, followed by the Bonferroni test, or the Kruskal–Wallis test, followed by the Steel–Dwass test, depending on the normality. The overall survival time was analyzed using the Kaplan–Meier method and compared using the log-rank test among the groups. The significantly different parameters among the 3 groups in the univariate analysis were further evaluated by the multivariate analysis using the multinomial logistic regression model. Statistical analyses were performed using the Jamovi version 2.2 computer software (The Jamovi project, 2021). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical and histopathological characteristics of dogs with CE

The breeds of the 66 dogs diagnosed with CE included Toy Poodle ($n = 11$), Miniature Dachshund ($n = 10$), Shiba ($n = 8$), Maltese ($n = 6$), Beagle ($n = 3$), Mixed breed ($n = 3$), Pembroke Welsh Corgi ($n = 3$), Border Collie ($n = 2$), Miniature Schnauzer ($n = 2$), Papillon ($n = 2$), Pomeranian ($n = 2$), American Cocker Spaniel ($n = 1$), American Pit Bull Terrier ($n = 1$), Bichon Frise ($n = 1$), Boston Terrier ($n = 1$), Brussels Griffon ($n = 1$), Cavalier King Charles Spaniel ($n = 1$), Flat Coated Retriever ($n = 1$), French Bulldog ($n = 1$), Italian Greyhound ($n = 1$), Jack Russell Terrier ($n = 1$), Labrador Retriever ($n = 1$), Pug ($n = 1$), Shetland Sheepdog ($n = 1$), and Wire Fox Terrier ($n = 1$). The dogs consisted of 30 castrated males, 8 intact males, 20 spayed females, and 8 intact females. The median age was 7.1 years (range, 1.5–14.1 years), and the median body weight was 5.8 kg (range, 1.8–29.7 kg). Histopathological diagnoses of the duodenal specimens included lymphoplasmacytic duodenitis ($n = 45$), lymphoplasmacytic and eosinophilic duodenitis ($n = 11$), or lymphoplasmacytic, neutrophilic, and eosinophilic duodenitis ($n = 1$), while those of the colonic specimens were lymphoplasmacytic colitis ($n = 43$) or lymphoplasmacytic and eosinophilic colitis ($n = 3$).

3.2. Association between GI signs and classification of CE

Among the 66 dogs with CE, 18, 26, and 22 dogs developed vomiting, diarrhea, and vomiting and diarrhea, respectively, and 24, 9, 28, and 5 dogs were diagnosed with FRE, ARE, IRE, and NRE, respectively. Vomiting was significantly detected in dogs with FRE ($P < 0.001$), but it was significantly less common in dogs with IRE ($P < 0.001$) (Table 1). In contrast, diarrhea was significantly associated with dogs with IRE ($P = 0.011$), but it was significantly lower in dogs with FRE ($P = 0.004$) (Table 1). Further classification of diarrhea into small and large bowel diarrhea did not reveal significant associations with FRE, ARE, IRE, or NRE (Supplementary Table 1).

3.3. Breed-wise distribution

The breed-wise distribution in the Vomiting, Diarrhea, or Vomiting and diarrhea groups is shown in Table 2. There was a significant over-representation of Beagle in the Vomiting group (odds ratio = 7.2, $P = 0.037$) and of Shiba, Maltese, American Pit Bull Terrier, and Brussels Griffon in the Diarrhea group (odds ratio = 4.5, 6.4, 46, and 140, respectively; $P = 0.009, 0.015, 0.025,$ and 0.011, respectively). On the other hand, the Vomiting and diarrhea group did not show a significant predisposition for any specific breed (Table 2).

3.4. Comparison of clinical and histopathological characteristics among dogs presenting with vomiting, diarrhea, or vomiting and diarrhea

Clinical and histopathological characteristics were compared among the Vomiting, Diarrhea, and Vomiting and diarrhea groups (Table 3). Significant differences were detected in the CCECAI scores, plasma albumin levels, and WSAVA scores for eosinophils in the duodenal lamina propria among the 3 groups ($P = 0.008$, $P < 0.001$, and $P = 0.033$, respectively; Table 3). The CCECAI scores were significantly lower in the Vomiting group than in the Vomiting and diarrhea group ($P = 0.007$; Table 3). The plasma albumin levels were significantly higher in the Vomiting group and in the Vomiting and diarrhea group than in the Diarrhea group ($P < 0.001$ and $P = 0.044$, respectively; Table 3). The WSAVA scores for eosinophils in the duodenal lamina propria were significantly higher in the Vomiting group than in the Vomiting and diarrhea group ($P = 0.036$; Table 3). No significant differences were found in the other clinical and histopathological variables among the 3 groups ($P > 0.05$; Table 3).

3.5. Multivariate analysis

The multinomial logistic regression analysis revealed that among the variables significantly associated with the Vomiting group in the univariate analysis, FRE and higher WSAVA scores for eosinophils in the duodenal lamina propria were significant variables in the Vomiting group compared to the Diarrhea or Vomiting and diarrhea group (Table 4).

3.6. Clinical outcomes of FRE-associated vomiting

Of the 18 dogs in the Vomiting group, 15 were diagnosed with FRE.

Table 2
Breed-wise distribution in dogs presenting with vomiting, diarrhea, or vomiting and diarrhea.

Group	Breed	n	Dogs admitted	Odds ratio	P-value
Vomiting	Miniature Dachshund	5	927	2.5	0.081
	Toy Poodle	4	730	2.4	0.112
	Beagle	2	120	7.2	0.037
	Maltese	2	142	6.1	0.051
	American Cocker Spaniel	1	88	4.6	0.205
	Labrador Retriever	1	190	2.1	0.393
	Shiba	1	353	1.1	0.609
	Papillon	1	176	2.3	0.370
	Flat Coated Retriever	1	29	14	0.072
Diarrhea	Shiba	5	353	4.5	0.009
	Toy Poodle	4	730	1.5	0.344
	Miniature Dachshund	3	927	0.85	1.000
	Maltese	3	142	6.4	0.015
	Mixed Breed	2	643	0.81	1.000
	Pembroke Welsh Corgi	2	202	2.8	0.174
	American Pit Bull Terrier	1	7	46	0.025
	Brussels Griffon	1	3	140	0.011
	Miniature Shnauzer	1	194	1.4	0.521
	Pug	1	110	2.5	0.340
	French Bulldog	1	197	1.4	0.527
	Border Collie	1	77	3.6	0.252
	Boston Terrier	1	57	4.9	0.193
Vomiting & Diarrhea	Toy Poodle	3	730	1.3	0.498
	Miniature Dachshund	2	927	0.65	0.758
	Shiba	2	353	1.9	0.308
	Pomeranian	2	237	2.8	0.171
	Wire Fox Terrier	1	21	16	0.064
	Italian Greyhound	1	47	7.1	0.138
	Cavalier King Charles Spaniel	1	101	3.2	0.275
	Pembroke Welsh Corgi	1	202	1.6	0.478
	Shetland Sheepdog	1	114	2.9	0.305
	Jack Russell Terrier	1	99	3.3	0.271
	Miniature Shnauzer	1	194	1.7	0.464
	Papillon	1	176	1.8	0.431
	Beagle	1	120	2.7	0.318
	Bichon Frise	1	25	14	0.076
	Maltese	1	142	2.3	0.365
	Border Collie	1	77	4.3	0.217
	Mixed Breed	1	643	0.47	0.715

The median time for the resolution of FRE-associated vomiting was 1 day (range: 1–10 days) after the initiation of dietary trials. In 7 of the 15 dogs with FRE-associated vomiting, food provocation trials were performed by switching back to the original diets after the elimination diets (median period of elimination diets: 29 days, range: 15–202 days). Consequently, 3 of the 7 dogs (43%) showed relapse of vomiting after switching back to the original diets, but vomiting did not recur in the remaining 4 dogs (57%).

Table 1
Association between gastrointestinal signs and classification of chronic enteropathy.

	Vomiting			Diarrhea			Vomiting and diarrhea		
	n	Adjusted residual	P-value	n	Adjusted residual	P-value	n	Adjusted residual	P-value
FRE	15	4.9	< 0.001	4	−2.9	0.004	5	−1.6	0.103
ARE	2	−0.37	0.714	3	−0.40	0.688	4	0.76	0.446
IRE	1	−3.7	< 0.001	16	2.5	0.011	11	0.88	0.378
NRE	0	−1.4	0.154	3	0.98	0.326	2	0.33	0.742

FRE, food-responsive enteropathy; ARE, antibiotic-responsive enteropathy; IRE, immunosuppressant-responsive enteropathy; NRE, non-responsive enteropathy.

Table 3

Comparison of clinical and histopathological characteristics of dogs presenting with vomiting, diarrhea, or vomiting and diarrhea.

Variables		Vomiting	*n*	Diarrhea	*n*	Vomiting and diarrhea	*n*	*P*-value	*P*-value (Post-hoc comparison)[b]			*P*-value
								(Three-group comparison[a])	Vomiting vs diarrhea	Vomiting vs Vomiting and diarrhea	Diarrhea vs Vomiting and diarrhea	
Signalment												
	Age (years)	6.2 (2.0–12.4)	18	8.0 (1.5–14.1)	26	6.9 (1.6–14.0)	22	0.276	0.335	0.892	1.000	–
	Body weight (kg)	5.3 (3.0–29.7)	18	5.8 (1.8–24.0)	26	6.5 (2.6–15.2)	22	0.631	1.000	0.692	0.678	–
	Sex (M:F)	9: 9	18	16: 10	26	13: 9	22	–	–	–	–	0.736
	Sex (Mi:Mc:Fi: Fs)	1: 8: 1: 8	18	5: 11: 4: 6	26	2: 11: 3: 6	22	–	–	–	–	0.657
Clinical severity												
	CCECAI score	5 (1–11)	18	5.5 (0–12)	26	7 (0–16)	22	0.008	0.585	0.007	0.131	–
Clinicopathological data												
	WBC (10^2/μL)	81.5 (53.0–303)	18	113 (29.0–331)	24	80.5 (44.8–295)	22	0.264	0.328	0.998	0.365	–
	PCV (%)	48.4 (28.1–58.9)	18	45.7 (23.9–60.0)	24	48.7 (27.6–59.5)	22	0.212	0.334	0.999	0.256	–
	PLT (10^4/μL)	31.7 (9.90–67.0)	18	45.0 (9.70–86.4)	24	41.8 (10.7–83.4)	22	0.074	0.071	0.450	1.000	–
	ALB (g/dL)	3.4 (1.3–4.0)	18	1.9 (1.2–3.6)	25	3.1 (1.0–3.7)	21	< 0.001	< 0.001	0.121	0.044	–
	CRP (mg/dL)	0.1 (0–18)	17	0.4 (0–2.3)	20	0.8 (0–20)	19	0.069	0.308	0.090	0.404	–
Histopathological severity and findings												
	Total WSAVA score (duodenum)	10 (7–17)	13	10 (5–17)	24	8 (2–13)	19	0.076	1.000	0.147	0.159	–
	Total WSAVA score (colon)	5.5 (5–8)	4	4.5 (1–9)	24	4.5 (1–7)	17	0.436	0.889	0.601	1.000	–
	WSAVA score for lacteal dilatation (duodenum)	1 (0–3)	13	1 (1–3)	24	1 (1–2)	19	0.836	0.831	0.893	0.988	–
	WSAVA score for lamina propria eosinophils (duodenum)	1 (0–2)	13	1 (0–2)	24	0 (0–2)	19	0.033	0.074	0.036	0.810	–
	WSAVA score for lamina propria eosinophils (colon)	0 (0–1)	4	0 (0–1)	24	0 (0–1)	17	0.107	0.112	0.119	0.993	–

Data are presented as medians (ranges).

M, male; F, female; Mi, intact male; Mc, castrated male; Fi, intact female; Fs, spayed female; CCECAI, canine chronic enteropathy clinical activity index; WBC, white blood cell; PCV, packed cell volume; PLT, platelet; ALB, albumin; CRP, C-reactive protein; WSAVA, World Small Animal Veterinary Association.

[a] Three-group comparison was performed using one-way analysis of variance or the Kruskal–Wallis test.
[b] Post-hoc analysis was performed using the Bonferroni test or Steel–Dwass test.

Table 4

Multinomial logistic regression analysis of clinical and histopathological variables associated with vomiting.

	Vomiting vs Diarrhea		Vomiting vs Vomiting and diarrhea		Diarrhea vs Vomiting and diarrhea	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
FRE	27.2 (2.06–358)	0.012	68.6 (3.79–1240)	0.004	2.53 (0.282–22.6)	0.407
Beagle	28,400 ($1.73e^{-81}$–$4.66e^{89}$)	0.918	9.55 ($2.88e^{-5}$–$3.17e^6$)	0.728	$4.08e^{-4}$ ($2.81e^{-81}$–$5.92e^{73}$)	0.931
CCECAI	0.873 (0.593–1.29)	0.493	0.697 (0.468–1.04)	0.074	0.797 (0.649–0.979)	0.031
ALB	3.25 (0.749–14.1)	0.115	0.978 (0.201–4.76)	0.978	0.300 (0.108–0.837)	0.021
EOS	10.0 (1.47–68.0)	0.018	15.4 (2.10–112)	0.007	1.54 (0.485–4.87)	0.465

CI, confidence interval; FRE, food-responsive enteropathy; CCECAI, canine chronic enteropathy clinical activity index; ALB, plasma albumin level; EOS, World Small Animal Veterinary Association score for lamina propria eosinophils in the duodenum; e: exponential notation.

3.7. Survival analysis

The median overall survival time of the Vomiting group could not be determined, because more than half of the dogs were alive at the end of the investigation. The median overall survival times of the Diarrhea group and the Vomiting and diarrhea group were 886.5 days (range, 28–3007 days) and 847 days (range, 55–2312 days), respectively. The overall survival time differed significantly among the 3 groups ($P = 0.008$) and was significantly longer in the Vomiting group than in the Diarrhea group ($P = 0.027$; Fig. 1).

4. Discussion

In the present study, we retrospectively classified dogs with CE based on their GI signs into Vomiting, Diarrhea, and Vomiting and diarrhea groups and characterized each group. Of the 66 dogs with CE, 18 dogs (27%) presented with vomiting without diarrhea as a GI sign. The univariate analysis demonstrated that the Vomiting group was significantly associated with FRE, Beagle, lower CCECAI scores, higher plasma albumin levels, and higher WSAVA scores for eosinophils in the duodenal lamina propria when compared with the other 2 groups. The multivariate analysis revealed that FRE and higher WSAVA scores for eosinophils in the duodenal lamina propria were significant variables in the Vomiting group. In addition, the survival time was the longest in the Vomiting group among the 3 groups. These findings are of clinical significance as they indicate that presenting with vomiting without diarrhea may be helpful in differentiating FRE from the other CE types and in predicting the prognosis.

In this study, 15 of the 18 dogs in the Vomiting group (83.3%) were diagnosed with FRE. The pathogenesis of FRE has not yet been elucidated fully. However, dietary changes can induce complete resolution of GI signs in dogs with FRE, suggesting that aberrant immune reactions to food antigens play a pivotal role in the pathogenesis of FRE. The main functions of the small intestine include food digestion and nutrient absorption. This study demonstrated higher WSAVA scores for eosinophils in the duodenal lamina propria in the Vomiting group. Thus, it is plausible that eosinophil-mediated mucosal inflammation, such as allergic reactions against food antigens, in the small intestine might be associated with the development of vomiting in dogs with FRE. In this study, vomiting relapsed in 43% of the dogs with FRE-associated vomiting after switching back to the original diets, suggesting the involvement of food allergy in these dogs. However, it is unclear whether food allergy was implicated in the vomiting presented by the other dogs that showed no recurrence after switching back to the original diets. Further studies are required to elucidate the mechanisms underlying FRE-associated vomiting.
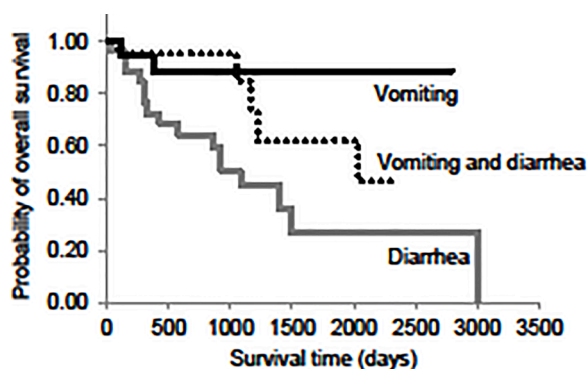

Fig. 1. Kaplan–Meier survival curves for dogs presenting with vomiting, diarrhea, or vomiting and diarrhea as gastrointestinal signs of chronic enteropathy. The survival time was compared using the log-rank test. Vomiting group vs Diarrhea group, $P = 0.027$; Vomiting group vs Vomiting and diarrhea group, $P = 1.000$; Diarrhea group vs Vomiting and diarrhea group, $P = 0.106$.

The current study also revealed that diarrhea was frequently observed in dogs with IRE. The pathogenesis of IRE involves multiple factors including genetic predispositions, intestinal barrier dysfunction, dysbiosis, and inappropriate reactions to dietary components (German, Hall & Day, 2003; Washabau et al., 2010). A combination of these factors is related to chronic mucosal inflammation in the small and large intestines of dogs with IRE. These findings imply that dysregulation of the mucosal immune responses in the small and large intestines might be associated with the development of diarrhea in dogs with IRE.

The plasma albumin levels were significantly higher in the Vomiting and the Vomiting and diarrhea groups than in the Diarrhea group. However, there were no significant differences among the 3 groups in the WSAVA scores for lacteal dilatation in the duodenal and colonic mucosae. Therefore, it is assumed that in addition to lacteal dilatation, malnutrition due to chronic mucosal inflammation might have been also involved in the decreased plasma albumin levels in the Diarrhea group.

The survival time was longer in the Vomiting group than in the Diarrhea group. Furthermore, the present study revealed that vomiting was frequently observed in dogs with FRE; therefore, the long-term survival of the Vomiting group may be reflected by the good outcomes in dogs with FRE, as reported previously (Allenspach et al., 2016, 2007). In this study, dogs with FRE responded to diet trails, and GI signs of FRE were well controlled by diet regulation. Thus, long-term management of vomiting can be accomplished using appropriate diets, such as hydrolyzed or novel protein diets.

Clinical information of this study was extracted from dogs with CE in Japan, where toy-, small-, and medium-breed dogs are popular (Inoue, Hasegawa, Hosoi, & Sugiura, 2015a,b; Inoue, Kwan & Sugiura, 2018). In Japan, it is reported that Shiba dogs are predisposed to CE (Ohmi et al., 2017, 2011; Ohno et al., 2006; Okanishi, Sano, Yamaya, Kagawa & Watari, 2013), and eight Shiba dogs were included in this study. A previous study revealed that German shepherd dog, Boxer, Rottweiler, Border Collie, and Weimaraner were high-risk canine breeds for CE in the UK (Kathrani, Werling & Allenspach, 2011). However, these breeds are not popular in Japan, and none of these dog breeds, except for two Border Collies, were included in this study. Genetic predisposition is an important factor for the development of CE in dogs (Allenspach & Mochel, 2022). Therefore, clinical features of the CE dogs in this study might differ from those of the CE dogs in other countries, where medium- or large-breed dogs are predominant.

In this study, we detected an overrepresentation of Beagle in the Vomiting group and of Shiba, Maltese, American Pit Bull Terrier, and Brussels Griffon in the Diarrhea group. However, due to the small number of dogs of each breed, clinical and genetic significance of these breeds in the type of GI signs needs to be carefully evaluated using a larger population of CE dogs.

The CCECAI scores were significantly lower in the Vomiting group than in the Vomiting and diarrhea group. This result is reasonable considering the lack of CCECAI scores related to diarrhea, such as stool consistency and frequency, in the Vomiting group. Thus, the CCECAI score may not be a significant factor in characterizing dogs that present with vomiting, diarrhea, or vomiting and diarrhea.

This study has two major limitations. First, the number of dogs with CE analyzed in this study was relatively small. Second, the dogs were evaluated retrospectively. Thus, a prospective study characterizing a larger population of dogs with CE would provide more information on clinical features of dogs presenting with vomiting, diarrhea, or vomiting and diarrhea as GI signs of CE.

5. Conclusions

The present study demonstrated that the GI sign of vomiting without diarrhea in dogs with CE was significantly associated with FRE. In addition, the prognosis was best in the Vomiting group among dogs with CE. Thus, vomiting is considered a key clinical feature for the differentiation and prognosis of CE. To further determine the clinical

significance of vomiting in dogs with CE, future prospective studies are warranted. Nevertheless, the findings of this study highlight the clinical importance of vomiting as a GI sign of CE.

Ethical approval

This study was approved by the Research Ethics Committee of Tokyo University of Agriculture and Technology. Informed consent was obtained from the owners of the dogs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.vas.2022.100255.

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