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Retrospective evaluation of the etiology and clinical characteristics of peripheral edema in dogs

Bradley D. Whelchel[1] | Jean-Sebastien Palerme[1] | Sandy P. Tou[2] | Jessica L. Ward[1]

[1]Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Iowa State University, Ames, Iowa, USA

[2]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina, USA

Correspondence
Jessica L. Ward, Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Iowa State University, 1809 S. Riverside Drive, Ames, IA 50010, USA.
Email: jward@iastate.edu

Abstract

Background: The prevalence and clinical characteristics of different etiologies of peripheral edema in dogs are unknown.

Hypothesis/Objectives: To determine the prevalence of different etiologies of peripheral edema, describe clinical characteristics that vary among etiologies, and report survival times.

Animals: Five hundred twenty-seven dogs with peripheral edema.

Methods: Retrospective medical record review. Differences in clinical variables among etiology groups were assessed by Kruskal-Wallis testing with post hoc pairwise Dunn's testing and Chi-square testing with Monte Carlo simulation.

Results: The most common etiologies of peripheral edema in dogs were vasculitis (n = 193, 37%), lymphatic/venous obstruction (LVO; 114, 22%), and hypoalbuminemia (94, 18%). Right-sided congestive heart failure (R-CHF) was uncommon (25, 5%). Edema was localized in 377 (72%) dogs and generalized in 142 (27%) dogs, and hypoalbuminemia was more likely to cause generalized edema compared to LVO or vasculitis ($P < .0001$). Concurrent abdominal effusion (155, 29%) was more common than pleural (77, 15%) or pericardial (12, 2%) effusion. Abdominal and pleural effusion occurred more commonly in dogs with hypoalbuminemia or R-CHF compared to LVO or vasculitis ($P < .0001$).

Conclusions and Clinical Importance: Distribution of edema, concurrent cavitary effusions, and clinicopathological data can help predict the underlying etiology of peripheral edema in dogs.

KEYWORDS
congestive heart failure, effusion, hypoalbuminemia, pitting, thrombosis, vasculitis

1 | INTRODUCTION

Peripheral edema is a physical examination finding that occurs secondary to abnormalities in plasma oncotic pressure, hydrostatic pressure, vascular integrity, or lymphatic function.[1-4] Mechanisms causing

peripheral edema are the same as those responsible for development of cavitary effusion in dogs and cats,[1-3] including decreased plasma oncotic pressure (pure transudate),[5-14] increased intravascular hydrostatic pressure (modified transudate),[15-19] increased vascular permeability (modified transudate or exudate),[20-27] and disturbances of lymphatic drainage (transudate or lymphocyte-rich effusion).[28-35] Underlying etiologies of peripheral edema include hypoproteinemia secondary to protein-losing nephropathies or enteropathies, vasculitis secondary to allergic reaction or infectious disease, right-sided congestive heart failure (R-CHF), and lymphatic obstruction secondary to neoplasia or cranial vena cava syndrome, among others.[6-8,10,15-21,23-26,28,30-35] Each of these underlying diseases is associated with different diagnostic findings and varying prognostic implications. Peripheral edema is often described as either localized or diffuse and either pitting or nonpitting,[4] though distribution and characteristics of edema have not been associated with specific underlying etiologies.

In the veterinary literature, there are several case reports and small retrospective studies describing peripheral edema caused by a single etiology.[14,27,36] However, there are no published reports describing the prevalence of these different etiologies within a larger sample of small animals with peripheral edema. Furthermore, no previous studies have compared clinical characteristics between etiologies, including such factors as location of edema, presence of concurrent cavitary effusions, and clinicopathological results. Survival differences between etiologies of peripheral edema have also not been described.

The primary objectives of this study were to report the prevalence of specific etiologies causing peripheral edema in dogs, to investigate clinical characteristics that differ between etiology groups, and to report survival times. We hypothesized that clinical and clinicopathological variables would differ between etiology groups and would prove useful for predicting the etiology of peripheral edema.

2 | MATERIALS AND METHODS

2.1 | Case selection

Dogs diagnosed with peripheral edema were enrolled in this retrospective study from the online medical record systems at Iowa State University Lloyd Veterinary Medical Center and North Carolina State Veterinary Hospital between the years of 2010 and 2020. The search terms "peripheral edema," "subcutaneous edema," and "pitting edema" were utilized to identify study subjects. Dogs of any age and sex were included if peripheral edema was documented in the medical record on either intake examination or during hospitalization. Animals were excluded from the study if peripheral edema was noted only after performing a centesis, if the animal received subcutaneous fluids before presentation, if edema developed only immediately after surgery without evidence of incision site infection, if edema was only identified on postmortem examination (not antemortem), or if peripheral edema had been present historically but resolved before presentation to the study visit.

2.2 | Data collection

For each dog, the first hospital visit during which peripheral edema was noted (either on intake examination or during hospitalization) was utilized for this study. Demographic information (age, sex, breed) and presenting complaints were recorded. Information from the intake physical examination was recorded, including weight, temperature, heart rate, respiratory rate, and cardiac auscultation abnormalities. Details regarding the edema were recorded including location (exact body areas involved), whether the peripheral edema was generalized or localized, whether edema was described as pitting, whether peripheral edema was the dog's presenting complaint, and whether edema was present on intake examination or developed later. Peripheral edema was classified as generalized if the edema met at least 2 of the following criteria: the edema was noted in more than 2 body locations, the edema occurred in the cranial and caudal half of the animal, and the edema occurred in the left and right side of the animal. The presence of concurrent cavitary effusion (peritoneal, pleural, pericardial, or retroperitoneal) was also recorded, based on findings from point-of-care ultrasound, radiographs, diagnostic abdominal ultrasound, echocardiography, or computed tomography.

Clinicopathological data performed within 24 hours of initial intake were recorded from point-of-care bloodwork (packed cell volume and total protein), complete blood counts (CBC), and serum chemistry panels. When available, fluid analysis and cytology from the peripheral edema itself or any concurrent effusion were obtained, as well as culture and sensitivity results if performed on these samples. Results of other diagnostic testing, including additional blood and urine testing, advanced imaging, surgery/endoscopy, or necropsy, were also recorded. Survival data were also collected, including the date of death or the date of last follow-up.

The final diagnosis for the dog's disease process causing peripheral edema was recorded as documented in the medical record by the overseeing clinician or pathologist. The final diagnoses were characterized as definitive, suspect, or undetermined. Classification of the etiology of the dog's peripheral edema was then performed by the primary investigator (Bradley D. Whelchel), a small animal rotating intern, after review of the dog's entire medical record, including results of all available diagnostic tests. Etiology categories utilized in this study included hypoalbuminemia, iatrogenic fluid overload, lymphatic or venous obstruction (LVO), R-CHF, trauma, vasculitis, and venous thrombosis. For dogs for which etiology category of peripheral edema or final diagnosis were unclear, additional investigators (Jessica L. Ward and Jean-Sebastien Palerme), a board-certified veterinary cardiologist and a board-certified veterinary internist, performed independent assessments of these classifications, and final determination was determined via consensus. Dogs with insufficient data to determine cause of edema or with multiple different potential etiologies of edema were categorized as "undetermined."

2.3 | Statistical analysis

Statistical analysis was performed by commercial software (R version 4.1.1, R Foundation for Statistical Computing, Vienna, Austria).

TABLE 1 Demographic data and physical examination findings in 527 dogs diagnosed with peripheral edema, separated by etiology group

Variable	All dogs	Hypo-albuminemia	Vasculitis	LVO	Venous thrombus	R-CHF	Iatrogenic	Trauma	Undetermined
Number of dogs	527	94	193	114	28	25	10	30	33
Institution (n, % ISU)	346/527 (66%)	61/94 (65%)	132/193 (68%)	77/114 (67%)	12/28 (43%)	11/25 (44%)	4/10 (40%)	27/30 (90%)	22/33 (67%)
Age (years)	7.3 (4.8-10.0)	6.9 (5.0-9.1)	7 (3.7-10.3)	8.1 (5.9-10.6)	9.1 (7.6-11.1)	8.8 (6.2-11.6)	5.3 (2.8-8.0)	4.9 (1.1-8.1)	7.4 (4.6-9.9)
Sex (n, % male)	288/527 (55%)	52/94 (55%)	87/193 (45%)	45/114 (40%)	16/28 (57%)	8/25 (32%)	5/10 (50%)	8/30 (26%)	18/33 (55%)
Weight (kg) (n = 509)	29.3 (17.9-38.0)	23.6 (8.5-33.0)	31.0 (21.1-38.7)	33.8 (24.3-40.5)	25.7 (17.6-36.0)	25.1 (11.0-38.0)	28.6 (7.3-30.8)	24.3 (11.1-35.4)	31.2 (15.0-41.8)
Rectal temperature (F) (n = 506)	101.8 (100.9-102.7)	101.2 (100.2-102.2)	102.1 (101.2-103.9)	102.0 (101.3-102.9)	101.4 (100.7-102.1)	100.9 (100.1-101.5)	100.7 (99.8-101.4)	101.5 (100.7-102.5)	101.7 (100.6-102.6)
Fever (n, %) (n = 506)	136/506 (27%)	13/91 (14%)	67/189 (36%)	35/106 (33%)	5/27 (19%)	2/22 (9%)	0/10 (0%)	5/28 (18%)	9/33 (27%)
Heart rate (beats/min) (n = 515)	129 (108-150)	129 (109-150)	124 (100-149)	127 (110-142)	136 (113-150)	157 (131-176)	121 (98-138)	134 (110-150)	127 (110-147)
Respiratory rate (breaths/min) (n = 515)	40 (30-46)	38 (28-43)	40 (30-44)	38 (28-44)	44 (31-57)	41 (35-46)	34 (28-40)	43 (32-50)	41 (24-60)
Murmur (n, %) (n = 521)	88/521 (17%)	21/94 (22%)	21/192 (11%)	10/111 (9%)	6/28 (21%)	16/24 (67%)	3/10 (30%)	2/29 (7%)	9/33 (27%)
Arrhythmia (n, %) (n = 521)	14/521 (3%)	3/94 (3%)	3/192 (2%)	5/111 (5%)	0/28 (0%)	3/24 (13%)	0/10 (0%)	0/29 (0%)	0/33 (0%)

Note: The total number and percent occurrence are shown for categorical data, whereas the median and interquartile range are shown for continuous data. Number dogs with data are included for variables with incomplete datasets.

Abbreviations: HR, heart rate; ISU, Iowa State University; LVO, lymphatic/venous obstruction; R-CHF, right-sided congestive heart failure; RR, respiratory rate; Temp, temperature.

TABLE 2 Location and description of peripheral edema in 527 dogs diagnosed with peripheral edema, separated by etiology group

Variable	All dogs	Hypo-albuminemia	Vasculitis	LVO	Venous thrombus	R-CHF	Iatrogenic	Trauma	Undetermined
Localized (n = 519)	377/519 (73%)	46/92 (50%)	155/191 (81%)	95/114 (83%)	17/28 (61%)	12/25 (48%)	3/9 (33%)	30/30 (100%)	19/30 (6%)
Generalized (n = 519)	142/519 (27%)	46/92 (50%)	36/191 (19%)	19/114 (17%)	11/28 (39%)	13/25 (52%)	6/9 (67%)	0/30 (0%)	11/30 (37%)
Left forelimb	148/527 (28%)	30/94 (32%)	52/193 (27%)	30/114 (26%)	12/28 (43%)	8/25 (32%)	4/10 (40%)	5/30 (17%)	7/33 (21%)
Right forelimb	155/527 (30%)	32/94 (34%)	54/193 (28%)	31/114 (27%)	12/28 (43%)	9/25 (36%)	4/10 (40%)	5/30 (17%)	8/33 (24%)
Left hindlimb	233/527 (45%)	50/94 (53%)	76/193 (39%)	50/114 (44%)	16/28 (57%)	14/25 (56%)	4/10 (40%)	6/30 (20%)	17/33 (52%)
Right hindlimb	215/527 (41%)	50/94 (53%)	59/193 (31%)	43/114 (38%)	19/28 (68%)	12/25 (48%)	4/10 (40%)	10/30 (33%)	18/33 (55%)
Ventral thorax	92/527 (18%)	17/94 (18%)	28/193 (15%)	16/114 (14%)	6/28 (21%)	10/25 (40%)	3/10 (30%)	5/30 (17%)	7/33 (21%)
Ventral abdomen	108/527 (21%)	25/94 (27%)	40/193 (21%)	12/114 (11%)	7/28 (25%)	9/25 (36%)	4/10 (40%)	3/30 (10%)	8/33 (24%)
Inguinal/perianal	14/527 (3%)	4/94 (4%)	8/193 (4%)	1/114 (1%)	1/28 (4%)	0/25 (0%)	0/10 (0%)	0/30 (0%)	0/33 (0%)
Prepuce/testes/vulva	18/527 (4%)	2/94 (2%)	8/193 (4%)	2/114 (2%)	1/28 (4%)	0/25 (0%)	1/10 (10%)	2/30 (7%)	2/33 (6%)
Neck	57/527 (11%)	9/94 (10%)	12/193 (6%)	17/114 (15%)	6/28 (21%)	4/25 (16%)	3/10 (30%)	1/30 (3%)	5/33 (15%)
Face/mandible	59/527 (11%)	12/94 (13%)	18/193 (9%)	19/114 (17%)	2/28 (7%)	2/25 (8%)	2/10 (20%)	1/30 (3%)	3/33 (9%)
Pitting	389/527 (74%)	55/94 (59%)	151/193 (78%)	97/114 (85%)	20/28 (71%)	19/25 (76%)	4/10 (40%)	21/30 (70%)	22/33 (67%)
Edema was presenting complaint	159/527 (30%)	16/94 (17%)	70/193 (36%)	48/114 (42%)	12/28 (43%)	4/25 (16%)	0/10 (0%)	2/30 (7%)	7/33 (21%)
Edema present on intake	496/527 (94%)	83/94 (88%)	184/193 (95%)	112/114 (98%)	26/28 (93%)	25/25 (100%)	8/10 (80%)	30/30 (100%)	28/30 (85%)

Note: Number of dogs with data is included for variables with incomplete datasets.
Abbreviations: LVO, lymphatic/venous obstruction; R-CHF, right-sided congestive heart failure.

Continuous normally-distributed data are presented as mean ± SD, continuous non-normally-distributed data are presented as median (interquartile range), and categorical data are presented as counts and percentages. Differences in continuous variables between etiology groups were assessed by Kruskal-Wallis tests with post hoc pairwise Dunn's test with a Bonferroni adjustment. Differences in categorical variables between groups were assessed by Chi-square testing with P-values computed with Monte Carlo simulation. Multinomial regression modeling was performed by LASSO to identify variables most predictive of etiology group. Group comparisons were not performed in cases with too few data points available. Survival analysis was performed for the overall data set by Kaplan-Meier curves, with Cox proportional hazards modeling used to assess survival differences between groups. P values < .05 were considered significant.

3 | RESULTS

3.1 | Study sample and clinical findings

A total of 657 dogs were identified in the initial medical record search. One hundred thirty-nine dogs were excluded from the study for the following reasons: no edema documented in the medical record (n = 93); edema only noted by the referring veterinarian before the study site visit (n = 13); edema only mentioned in a radiology report (n = 4); clinician unsure if edema was truly present (n = 8); edema only noted post-mortem (n = 6); edema only mentioned in discharge paperwork for the owner but nowhere else in the medical record (n = 4); medical record incomplete (n = 4); edema noted only after subcutaneous fluid administration (n = 3), abdominocentesis (n = 2), or chest tube placement (n = 1); or edema occurred outside of the time frame of enrollment (n = 1). A total of 527 dogs met inclusion criteria for the study.

Demographic and physical examination findings for dogs are provided in Table 1. Characteristics of the peripheral edema for dogs in the study are presented in Table 2.

Clinicopathological testing performed in dogs included CBC (72% of dogs), serum chemistry panel (73%), point-of-care-bloodwork (packed cell volume, total protein, lactate, or blood glucose; 40%), coagulation testing (prothrombin time, partial thromboplastic time, D-dimer, or fibrinogen; 16%), urinalysis (17%), and urine protein to creatinine ratio (UPCR, 8.5%). Advanced imaging included abdominal radiographs (8.9%), thoracic radiographs (18%), abdominal ultrasound (28%), echocardiography (11%), and computed tomography (5.9%).

An aspirate of the edema was obtained in 53 (10%) dogs. Most aspirates were performed blindly without ultrasound guidance and most aspirates obtained were from the vasculitis etiology group (83%). The most common cytological diagnosis obtained from the aspirates included septic inflammation (53%) or sterile inflammation (23%), with transudate (6%), hemorrhage (6%), neoplasia (6%), and lymphedema (2%) being less common; 2 samples were nondiagnostic.

Cytology of concurrent effusions (20%), other cytology or tissue biopsy with histopathology (27%), and cultures of urine, blood, effusion, edema, or tissue (21%) were also performed. Necropsies were performed in 41 dogs (16% of dogs that died). The presence of concurrent effusion and clinicopathological results for dogs are provided in Table 3.

3.2 | Etiology of peripheral edema and underlying diagnosis

Of the 527 dogs enrolled in the study, etiology of edema was categorized as vasculitis in 193 dogs (37%), LVO in 114 dogs (22%), hypoalbuminemia in 94 dogs (18%), trauma in 30 dogs (6%), venous thrombosis in 28 dogs (5%), R-CHF in 25 dogs (5%), and iatrogenic fluid overload in 10 dogs (2%); 33 dogs (6%) had an undetermined or suspected multifactorial etiology for their peripheral edema. Of the 33 dogs in the undetermined group, the suspected etiologies were: LVO or vasculitis (n = 14), hypoalbuminemia or vasculitis (n = 8), vasculitis or venous thrombosis (n = 6), hypoalbuminemia or venous thrombosis (n = 1), iatrogenic or vasculitis (n = 1), hypoalbuminemia or LVO or vasculitis (n = 1), iatrogenic or LVO or vasculitis (n = 1), and LVO or vasculitis or venous thrombosis (n = 1). A definitive diagnosis for the underlying disease causing peripheral edema was made in most dogs (71%). Definitive diagnoses were made based on results of bloodwork (hypoalbuminemia), echocardiography (R-CHF), CT or lymphangiogram (LVO), ultrasound or angiogram (venous thrombosis), or cytological evidence of infection or inflammation (vasculitis). For dogs with vasculitis, the most common underlying diseases were infection (n = 90), either local (78) or systemic (12); neoplasia (23), most commonly mast cell tumor (10) or mammary carcinoma (3); and cellulitis (20). The most common underlying diseases causing hypoalbuminemia were protein-losing enteropathy (n = 49) and protein-losing nephropathy (12). The most common underlying diseases causing LVO were neoplasia (n = 84), most commonly lymphoma (26), mast cell tumor (13), or osteosarcoma (6); other causes of LVO included unclassified space-occupying mass (8) and lymphedema (4). The most common underlying diseases causing R-CHF included pulmonary hypertension (n = 4), pulmonic stenosis (4), pericardial effusion with no identifiable mass (4), and pericardial effusion with a right atrial mass (3). The most common underlying diseases causing venous thrombosis were neoplasia (n = 7), with all 7 dogs having a different type of neoplasia diagnosed; disseminated intravascular coagulation (6); and immune-mediated hemolytic anemia (IMHA; 4). Demographic, clinical, and clinicopathological data for dogs of different etiology groups are provided in Tables 1-3. Outcome and survival data for dogs of each etiology group is shown in Table 4.

3.3 | Comparison of etiology groups in dogs

Initial analyses and pairwise comparisons of the 8 separate etiology groups in dogs revealed significant differences between nearly all groups. To focus on differences of greatest clinical relevance, dogs in the "undetermined" and "trauma" groups were removed from further

TABLE 3 Location of concurrent effusion and clinicopathological data in 527 dogs diagnosed with peripheral edema, separated by etiology group.

Variable	All dogs	Hypo-albuminemia	Vasculitis	LVO	Venous thrombus	R-CHF	Iatrogenic	Trauma	Undetermined
Abdominal effusion	155/527 (29%)	71/94 (76%)	21/193 (9%)	10/114 (9%)	11/28 (39%)	22/25 (88%)	5/10 (50%)	4/30 (13%)	11/33 (34%)
Pleural effusion	77/527 (15%)	32/94 (34%)	10/193 (5%)	14/114 (12%)	5/28 (18%)	7/25 (28%)	2/10 (20%)	2/30 (7%)	5/33 (15%)
Pericardial effusion	12/527 (2%)	1/94 (1%)	1/193 (0.05%)	0/114 (0%)	1/28 (4%)	8/25 (32%)	0/10 (0%)	0/30 (0%)	1/33 (3%)
PCV (%) (n = 208)	37.7 (29.0-46.0)	38.3 (28.0-46.3)	37.9 (29.5-47.0)	36.2 (29.0-45.0)	32.3 (25.0-40.0)	39.4 (35.0-44.5)	34.8 (29.5-40.3)	43 (35.0-52.5)	35.9 (25.8-43.0)
Total protein (g/dL) (n = 374)	5.2 (4.5-6.1)	3.6 (3.0-4.4)	5.7 (4.9-6.3)	5.9 (5.2-6.5)	5.5 (5.2-6.1)	5.4 (4.5-5.8)	5.3 (4.7-5.7)	5.6 (5.0-6.3)	5.2 (4.6-5.8)
Albumin (g/dL) (n = 383)	2.4 (1.9-2.9)	1.5 (1.2-1.8)	2.6 (2.2-3.0)	2.9 (2.6-3.1)	2.7 (2.5-3.1)	3.0 (2.6-3.4)	2.5 (2.2-2.9)	2.9 (2.5-3.3)	2.4 (2.1-2.7)
Globulin (g/dL) (n = 369)	2.8 (2.2-3.3)	2.1 (1.6-2.5)	3.1 (2.5-3.4)	3.1 (2.4-3.5)	2.8 (2.2-3.2)	2.3 (1.8-2.8)	2.7 (2.3-3.2)	2.7 (2.3-2.9)	2.7 (2.2-3.2)
Glucose (mmol/L) (n = 404)	109.7 (91.0-116.0)	101.0 (86.0-110.0)	115.4 (90.0-117.0)	102.7 (90.3-109.8)	110.7 (95.5-118.0)	123.4 (107.0-141.0)	107.6 (92.5-115.0)	126.0 (104.5-135.0)	106.5 (90.8-115.3)
BUN (mg/dL) (n = 387)	26.7 (11.0-29.0)	26.2 (10.0-32.3)	23.6 (10.0-24.5)	20.4 (10.0-23.0)	34.6 (14.5-53.0)	24.3 (15.5-30.0)	78.7 (21.5-120.0)	23.3 (12.0-26.5)	39.7 (9.0-41.8)
Creatinine (mg/dL) (n = 386)	1.3 (0.6-1.2)	1.3 (0.5-1.2)	1.2 (0.6-1.2)	0.9 (0.7-1.0)	1.7 (0.5-1.8)	1.0 (0.9-1.1)	5.5 (1.1-7.9)	1.0 (0.6-1.1)	1.7 (0.6-1.9)
ALP (IU/L) (n = 371)	357.5 (57.0-350.0)	171.6 (27.0-188.5)	443.3 (93.0-354.3)	270.9 (69.0-366.0)	742.4 (109.0-1061.8)	603.9 (63.0-950.5)	196.4 (30.5-255.0)	202.4 (63.0-193.3)	469.2 (70.8-570.8)
ALT (IU/L) (n = 371)	127.4 (35.0-120.0)	123.3 (31.0-104.5)	103.8 (37.0-89.3)	73.5 (30.0-79.0)	262.1 (40.0-350.5)	133.9 (59.0-158.0)	89.9 (36.5-85.5)	327.0 (52.3-185.5)	176.8 (37.8-158.0)
Tbili (μmol/L) (n = 367)	0.6 (0.2-0.4)	0.8 (0.1-0.3)	0.6 (0.2-0.4)	0.3 (0.1-0.4)	0.9 (0.2-1.0)	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.4 (0.2-0.4)	0.8 (0.2-0.6)
Cholesterol (mg/dL) (n = 319)	213.0 (136.0-273.0)	148.2 (79.5-182.8)	242.8 (161.0-311.0)	216.0 (168.0-246.0)	268.6 (171.0-310.0)	218.6 (189.0-248.3)	214.0 (139.0-293.5)	203.4 (164.8-244.3)	223.6 (150.0-300.0)
UPCR (n = 47)	6.0 (0.6-8.1)	9.5 (0.8-10.5)	4.3 (0.61-5.5)	2.1 (0.5-5.3)	4.0 (1.2-7.8)	N/A	0.8 (0.6-1.0)	NA	7.2 (1.8-12.4)
Hematocrit (%) (n = 382)	36.6 (30.1-43.4)	36.5 (28.8-44.1)	37.0 (30.6-43.8)	38.9 (33.0-44.9)	32.7 (22.0-42.3)	37.8 (31.1-40.8)	35.2 (28.2-43.0)	35.1 (30.7-40.8)	33.2 (25.6-37.0)
WBC (×10^3/μL) (n = 382)	18.0 (10.7-22.8)	16.9 (11.6-21.5)	18.6 (11.0-24.3)	16.1 (9.2-21.7)	25.0 (10.2-30.6)	16.4 (12.7-15.4)	21.1 (13.4-34.8)	13.5 (7.9-19.2)	19.5 (7.6-28.2)
Neutrophils (×10^3/μL) (n = 381)	14.7 (8.5-18.5)	14.4 (9.9-19.3)	15.2 (8.5-19.5)	12.3 (6.8-15.6)	20.9 (8.3-25.2)	13.2 (9.2-13.6)	18.1 (11.7-28.7)	11.1 (6.6-16.9)	15.6 (5.4-22.9)
Bands (×10^3/μL) (n = 363)	0.5 (0-0.5)	0.5 (0-0.4)	0.7 (0-0.6)	0.3 (0-0.3)	1.2 (0.4-1.2)	0.01 (0-0)	0.3 (0-0.3)	0.2 (0-0.4)	0.5 (0-0.2)
Lymphocytes (×10^3/μL) (n = 381)	1.3 (0.5-1.5)	1.1 (0.4-1.1)	1.4 (0.5-1.5)	1.7 (0.4-1.4)	1.0 (0.4-1.2)	1.8 (0.8-2.8)	0.9 (0.5-1.6)	1.2 (0.8-1.6)	1.5 (0.3-2.3)
Monocytes (×10^3/μL) (n = 381)	1.1 (0.4-1.4)	0.9 (0.4-1.1)	1.1 (0.5-1.5)	0.9 (0.5-1.3)	1.4 (0.5-2.0)	1.2 (0.7-1.2)	1.6 (0.4-1.7)	0.9 (0.2-1.3)	1.4 (0.4-2.1)
Eosinophils (×10^3/μL) (n = 366)	0.4 (0-0.4)	0.2 (0-0.4)	0.3 (0-0.4)	0.7 (0-0.4)	0.3 (0-0.4)	0.1 (0-0.2)	0.2 (0-0.4)	0.2 (0-0.4)	0.5 (0-0.6)
Platelets (×10^9/L) (n = 379)	270.9 (161.0-360.0)	347.4 (142.0-514.0)	247.6 (162.3-330.8)	280.9 (179.0-338.0)	227.1 (97.0-310.0)	334.2 (224.5-412.3)	207.9 (56.5-347.5)	233.1 (184.8-308.0)	195.6 (123.8-271.3)
D-dimers (ng/dL) (n = 88)	924.0 (250.0-830.0)	850.5 (178.0-600.0)	851.7 (203.0-762.8)	280.9 (221.3-1477.0)	1180.7 (256.5-890.0)	1651.5 N/A	905.7 (250.0-2163.0)	337.0 N/A	803.1 (338.0-1312.0)

TABLE 3 (Continued)

Variable	All dogs	Hypo-albuminemia	Vasculitis	LVO	Venous thrombus	R-CHF	Iatrogenic	Trauma	Undetermined
Fibrinogen (mg/dL) (n = 57)	387.5 (200.0-514.3)	299.2 (169.5-389.5)	403.8 (200.0-762.8)	448.8 (250.0-692.8)	495.6 (302.0-662.0)	300.0 N/A	288.0 (200.0-464.0)	715.0 N/A	220.2 (100.0-300.5)
Aspirate of edema performed	53/527 (10%)	0/94 (0%)	44/193 (23%)	5/114 (4%)	2/28 (7%)	0/25 (0%)	0/10 (0%)	0/30 (0%)	2/33 (6%)
Cytology of effusion performed	105/527 (20%)	41/94 (44%)	18/193 (9%)	12/114 (11%)	7/28 (25%)	13/25 (52%)	0/10 (0%)	2/30 (7%)	12/33 (36%)

Note: The total number and percent occurrence is included for categorical data, whereas the mean and interquartile range are included for continuous data. Number of dogs with data are included for variables with incomplete datasets.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; bands, band neutrophils; BUN, blood urea nitrogen; LVO, lymphatic/venous obstruction; PCV, packed cell volume; R-CHF, right-sided congestive heart failure; Tbili; total bilirubin; UPCR, urine protein to creatinine ratio; WBC, white blood cell.

TABLE 4 Outcome and survival in 527 dogs with peripheral edema, separated by etiology group

Variable	All dogs	Hypo-albuminemia	Vasculitis	LVO	Venous thrombus	R-CHF	Iatrogenic	Trauma	Undetermined
Definitive diagnosis	365/527 (71%)	67/94 (71%)	131/193 (68%)	85/114 (75%)	13/28 (46%)	20/25 (80%)	8/10 (80%)	26/30 (87%)	25/33 (76%)
Deceased	251/527 (48%)	51/94 (54%)	74/193 (38%)	67/114 (59%)	19/28 (68%)	13/25 (52%)	7/10 (70%)	5/30 (17%)	15/33 (46%)
Euthanized	197/251 (76%)	41/51 (80%)	59/74 (80%)	50/67 (75%)	17/19 (89%)	9/13 (69%)	5/7 (71%)	4/5 (80%)	12/15 (80%)
Died	20/251 (8%)	2/51 (4%)	7/74 (9%)	5/67 (7%)	2/19 (11%)	1/13 (8%)	2/7 (29%)	0/5 (0%)	1/15 (7%)
Survival time (days)	204 (117-427)	140 (72-735)	582 (276-1097)	31 (17-266)	21 (8-N/A)	687 (432-N/A)	9 (2-N/A)	N/A	14 (6-N/A)

Note: Number and percent of dogs is reported for categorical data. For survival data, median survival time and 95% confidence interval are reported. For groups where fewer than 50% of dogs died, the upper 95% CI is listed as N/A.

Abbreviations: LVO, lymphatic/venous obstruction; R-CHF, right-sided congestive heart failure.

TABLE 5 Variables found to be significantly different among groups in dogs with peripheral edema secondary to either hypoalbuminemia (n = 94), R-CHF and iatrogenic fluid overload (n = 35), LVO and venous thrombosis (n = 142), or vasculitis (n = 193)

Variable	Overall comparison	H vs LVO + T	H vs RCHF + I	H vs V	LVO + T vs RCHF + I	LVO + T vs V	RCHF + I vs V
Institution	.04*	1	.17	1	.22	1	.04*
Age	.0019*	.0042*	.42	1	1	.0027*	.61
Weight	<.0001*	<.0001*	1	.04*	.00031*	1	.12
Heart rate	.008*	1	.02*	.04*	1	.51	.0020*
Temperature	<.0001*	.0017*	.23	<.0001*	<.0001*	.71	<.0001*
Fever	.0015*	.06	1	.0013*	.03*	1	.0042*
Murmur	.00050*	.18	.0030*	.08	<.0001*	1	<.0001*
Right hindlimb	.0020*	.86	1	.0027*	1	.17	.71
Ventral abdomen	.0040*	.04*	1	.80	.01*	.62	.17
Generalized edema	.00050*	<.0001*	1	<.0001*	.0011*	1	.00010*
Pitting	.001*	.00051*	1	.0041*	.23	1	.73
Edema as presenting complaint	.00050*	.00035*	1	.0055*	.0040*	1	.02*
Abdominal effusion	.00050*	<.0001*	1	<.0001*	<.0001*	1	<.0001*
Pleural effusion	.00050*	.0019*	1	<.0001*	.70	.062	.0032*
Pericardial effusion	.00050*	1	.00067*	1	<.0001*	1	<.0001*
Total protein	<.0001*	<.0001*	<.0001*	.17	<.0001*	1	.31
Albumin	<.0001*	<.0001*	<.0001*	1	<.0001*	.02*	.36
Globulins	<.0001*	<.0001*	.14	.03*	<.0001*	1	.23
Glucose	.0036*	.27	.0029*	.07	.02*	1	.23
BUN	.0028*	1	.0032*	.0037*	1	1	.00060*
Creatinine	.00055*	1	.00011*	.0097*	.35	1	.0027*
ALP	<.0001*	<.0001*	.14	.99	<.0001*	1	.53
Total bilirubin	.00038*	.08	.57	1	<.0001*	.19	1
Cholesterol	<.0001*	<.0001*	.0011*	1	<.0001*	1	1
Bands	.0041*	1	.16	.66	.11	.26	.00030*
Monocytes	.02*	.03*	.07	1	.04*	1	1
Platelets	.01*	.51	.80	1	.0037*	1	1

Note: Differences in continuous variables between etiology groups were assessed by Kruskal-Wallis tests with post hoc pairwise Dunn's test with a Bonferroni adjustment. Differences in categorical variables between groups were assessed by Chi-square testing. *P*-values are provided for overall group comparison, as well as adjusted *P*-values for post hoc pairwise comparisons. Significant differences between groups (P < .05) are denoted in bold with an asterisk (*).

Abbreviations: ALP, alkaline phosphatase; bands, band neutrophils; BUN, blood urea nitrogen; H, hypoalbuminemia; I, iatrogenic; LVO, lymphatic/venous obstruction; R-CHF, right-sided congestive heart failure; T, venous thrombosis; V, vasculitis.

analysis, because their etiology of edema was either unknown (undetermined) or clearly obvious based on history (trauma). There were no statistically significant differences between the R-CHF and iatrogenic groups, so these groups were combined for further analysis. Similarly, the only significant differences between LVO and venous thrombosis were abdominal effusion being more common with venous thrombosis as compared to LVO (39% vs 9%, P = .01) and ALT being higher in venous thrombosis (262 [40-351] IU/L) as compared to LVO (74 [30-79] IU/L, P = .02), so these groups were also combined to facilitate meaningful comparisons.

The final groups considered for analysis were hypoalbuminemia, vasculitis, the combination of LVO and venous thrombosis, and the

combination of R-CHF and iatrogenic fluid overload. Variables that showed statistically significant differences between these revised group combinations are shown in Table 5. For variables showing statistically significant differences between groups, diagnostic accuracy (sensitivity, specificity, area under the curve, and 95% confidence interval for area under the curve) of each variable for predicting an individual etiology group is shown in Table 6.

Compared to other etiology groups, the hypoalbuminemia group had numerous continuous and categorical data with high sensitivities and specificities for predicting this group; therefore, a second round of analysis was performed with the hypoalbuminemia group removed (see Table S1).

TABLE 6 Diagnostic accuracy of clinical and clinicopathological variables for predicting individual etiology groups in 464 dogs with peripheral edema, having excluded dogs with undetermined or traumatic causes of peripheral edema

Variable	Group to predict	Cutoff	Sensitivity	Specificity	Area under the curve	95% confidence interval
Age	Iatrogenic	<9 years	100%	37%	0.69	0.56-0.82
	Venous thrombosis		96%	40%	0.65	0.58-0.73
Weight	Hypoalbuminemia	<26.9 kg	63%	61%	0.64	0.58-0.71
Temperature	Iatrogenic	<101.5 F	90%	61%	0.74	0.64-0.85
Fever	Vasculitis	Present	35%	78%	N/A	N/A
Heart rate	R-CHF	>130 beats/min	83%	56%	0.75	0.67-0.83
Murmur	R-CHF	Present	67%	86%	N/A	N/A
Generalized	Hypoalbuminemia	Present	50%	77%	N/A	N/A
	Iatrogenic		67%	72%		
	R-CHF		52%	73%		
Right hindlimb	Venous thrombosis	Present	69%	62%	N/A	N/A
Ventral abdomen	Hypoalbuminemia	Present	28%	81%	N/A	N/A
	Idiopathic		40%	80%		
	R-CHF		36%	80%		
Pitting edema	LVO	Present	86%	29%	N/A	N/A
Edema as presenting complaint	LVO	Present	42%	71%	N/A	N/A
Abdominal effusion	Hypoalbuminemia	Present	76%	81%	N/A	N/A
	R-CHF		88%	73%		
Pleural effusion	Hypoalbuminemia	Present	34%	90%	N/A	N/A
	R-CHF		28%	86%		
Pericardial effusion	R-CHF	Present	32%	99%	N/A	N/A
Total protein	Hypoalbuminemia	<4.65 mg/dL	84%	89%	0.93	0.90-0.96
Albumin	Hypoalbuminemia	<2.05 mg/dL	87%	87%	0.94	0.92-0.97
Globulins	Hypoalbuminemia	<2.15 mg/dL	61%	89%	0.80	0.74-0.86
Glucose	R-CHF	>101 mmol/L	93%	48%	0.74	0.62-0.85
BUN	Iatrogenic	>68 mg/dL	27%	79%	0.82	0.65-0.99
Creatinine	Iatrogenic	>49 mg/dL	40%	77%	0.89	0.80-0.99
ALP	Hypoalbuminemia	<68 IU/L	58%	79%	0.71	0.64-0.77
ALT	R-CHF	>64.5 IU/L	77%	61%	0.66	0.50-0.81
Tbili	Hypoalbuminemia	>0.205 mmol/L	67%	59%	0.64	0.57-0.71
Cholesterol	Hypoalbuminemia	<111.5 mg/dL	61%	96%	0.78	0.71-0.86
Bands	R-CHF	<0.147 × 10³/μL	100%	43%	0.73	0.66-0.79
Platelets	R-CHF	>355 000 × 10³/μL	60%	72%	0.65	0.51-0.79

Note: Results and cutoffs reflect diagnostic accuracy for predicting an individual etiology group compared to all other dogs. The area under the curve and 95% confidence intervals for area under the curve are reported for continuous variables.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; bands, band neutrophils; BUN, blood urea nitrogen; LVO, lymphatic/venous obstruction; R-CHF, right-sided congestive heart failure; Tbili; total bilirubin.

Multivariable modeling with LASSO further characterized the predictive value of specific variables. Coefficients for each variable, indicating power for predicting each individual etiology group, can be found in Table S2. These models excluded the "undetermined" and "trauma" groups, similar to the pairwise comparison analyses. The variables found to be most predictive of the vasculitis group were the presence of abdominal effusion, pleural effusion, ventral abdominal edema, and right hindlimb edema. Variables found to be most predictive of the hypoalbuminemia etiology group were lower albumin, lower total protein, presence of abdominal effusion, and presence of generalized edema. Variables found to be most predictive of the LVO group were the absence of a heart murmur, the absence of abdominal or pericardial effusion, and the presence of pitting edema. Variables found to be most predictive of the R-CHF group were the presence of abdominal or pericardial effusion and the presence of a heart murmur. Higher creatinine and lower cholesterol were found to

be predictive of the iatrogenic fluid overload group. For the venous thrombosis group, only the presence of right hindlimb edema was predictive in this multivariable modeling.

3.4 | Survival data

The median survival time (MST) for all dogs (n = 507), of which 251 had died by the time of medical record review, was 204 days (95% CI 117-427 days). Of the 251 dogs that died, 197 were euthanized and 20 died spontaneously, whereas this information was not recorded for 34 dogs. For the remainder of survival analyses performed, the undetermined and trauma groups were removed from the analysis. The MST of this group (n = 447, of which 214 died) was 186 days (95% CI 103-406 days). The MST for dogs living more than 14 days (n = 221, of which 90 died) was 687 days (95% CI 504-1097 days). The MST for dogs living more than 6 months (n = 101, 41 of which died) was 1158 days (lower 95% CI limit, 895 days). Outcome and survival data for dogs of each etiology group is shown in Table 4.

Considering differences in survival by etiology group, dogs in the vasculitis group (MST 582 days, 95% CI 276-1097 days) had a longer survival time than both dogs in the LVO group (MST 31 days, 95% CI 17-266 days; P = .00049) or the venous thrombosis group (MST 21 days, 95% CI 8-N/A days, P = .001).

4 | DISCUSSION

This is the first study to assess the prevalence and outcome of different etiologies of peripheral edema in dogs and to identify clinical variables predictive of edema etiology. The most common etiologies of peripheral edema in dogs were vasculitis (37%), LVO (22%), and hypoalbuminemia (18%). The prevalence of these etiologies in cases of peripheral edema is not surprising, as peripheral edema has been commonly reported in these groups and is logical from a pathophysiological perspective.[1,4-6,10,22,32,34] R-CHF was much less common (5%) as compared to other etiology groups, which is also consistent with previous reports in dogs.[37,38] However, this contrasts with other animals (such as cows) as well as humans, where peripheral edema appears to be more frequently documented in R-CHF.[39-41]

Our study identified several physical examination findings that were associated with a specific etiology of peripheral edema, although the predictive power of these variables was generally low. Fever was found to be predictive of vasculitis, consistent with the pathophysiology of inflammation and previous studies of vasculitis in dogs.[22,24] A heart rate >130 beats per minute and the presence of a heart murmur were predictive of R-CHF, also consistent with expected pathophysiology and previous reports.[37,38] Lastly, younger age was found to be predictive of venous thrombosis. This was somewhat of an unexpected finding as the most common underlying disease noted within this etiology group was neoplasia; however, the average age of patients with venous thrombosis in our study closely matched that

reported in a case series of dogs with portal vein thrombosis.[42] The significance of age within this etiology group may also be because of the relatively older age of the overall dog sample in this study.

In terms of the location of the edema, generalized edema was more commonly associated with hypoalbuminemia, R-CHF, or iatrogenic fluid overload compared to other etiologies. Specific classifications of peripheral edema location have not been examined or noted in past studies in dogs and the mechanism of edema formation in these etiologies predicts a generalized distribution.[1,2,4,39] Whereas most specific individual locations of peripheral edema were not associated with particular etiologies, ventral abdominal edema was found to be predictive of R-CHF, and peripheral edema in the right hind limb was predictive of venous thrombosis. Even though this has not been specifically reported in R-CHF in dogs, ventral abdominal edema is a common manifestation of R-CHF in large animals and humans,[40,41] which in large animals could be because of the gravity-dependent location. The significance of the location of the right hind limb for the venous thrombosis etiology group is unknown, and could be a spurious result given the relatively low predictive power of this variable. No past studies in animals or humans have reported an increase in occurrence within this specific region for underlying diseases within this etiology group. Interestingly, the opposite was found in elderly humans where peripheral edema in the left pelvic limb was commonly seen with iliac compression syndrome.[43] In addition, a low number of dogs had aspirates of their edema performed, but the most common cytological finding of the edema was inflammation (either septic or sterile). Whereas it is unclear from this study if cytological analysis of the peripheral edema is helpful in aiding a diagnosis or determining the specific etiology of edema, given the most common etiology group to have an aspirate of their edema performed was vasculitis, cytology of the peripheral edema may be helpful in this specific etiology group to determine if there is either local or systemic infection causing the edema.

Description of the edema as "pitting" was found to be predictive of LVO as compared to other etiologies. The difference between pitting edema and nonpitting edema is described as the presence of an indentation of tissue after pressing upon and releasing the tissue.[44] In human literature, the differentiation of pitting versus nonpitting edema can be helpful to determine the etiology of edema. Pitting edema tends to be caused by an increase in hydrostatic pressure or decreased oncotic pressure, whereas chronic lymphedema, myxedema, vasculitis, and trauma to the blood vessel tend to cause nonpitting edema.[44,45] In contrast, our study found that LVO was the only etiology group associated with pitting edema. However, the lack of "pitting" description for other etiology groups such as R-CHF and hypoalbuminemia may not reflect a true pathophysiologic difference but simply an incomplete physical examination description, given that peripheral edema is overall uncommon in small animals and clinicians may not habitually describe or characterize the pitting nature.

Concurrent cavitary effusion was most commonly associated with either hypoalbuminemia or R-CHF in our study sample. Abdominal effusion and pleural effusion were noted with either hypoalbuminemia or R-CHF, whereas pericardial effusion was mostly seen with

R-CHF. Occurrence of cavitary effusion is expected in both etiologies and distribution of cavitary effusion has been variably reported.[5,6,37,46,47] In humans, hypoalbuminemia has been associated with pleural effusion and abdominal effusion, whereas R-CHF can be associated with all 3 types of effusion.[48-51] The presence of concurrent effusions in dogs with hypoalbuminemia or R-CHF is therefore an expected finding that can increase index of suspicion for these disease etiologies.

Numerous clinicopathological variables were associated with specific etiologies of peripheral edema in our study. As expected, all markers of hypoproteinemia, as well as low cholesterol, were predictive of hypoalbuminemia. This is consistent with reports of the 2 most common underlying diseases, protein-losing enteropathies and protein-losing nephropathies, where hypoalbuminemia is common in both diseases and hypoglobulinemia is common in protein-losing enteropathies.[10,47] Likewise, hypocholesterolemia is frequently seen in dogs with protein-losing enteropathies,[9,10,47,52] though cholesterol can be increased in patients with nephrotic syndrome.[6,53] Surprisingly, an increased UPCR was not found to be associated with hypoalbuminemia despite protein-losing nephropathies being the second most common underlying diagnosis for hypoalbuminemia (12 dogs diagnosed with a PLN out of the 94 dogs in the hypoalbuminemia etiology group). Whereas an increased UPCR is noted in patients with hypoalbuminemia secondary to a PLN,[6,53] the lack of an association of a UPCR to hypoalbuminemia or other etiology groups may have been attributed to the low number of UPCRs performed in the study sample.

After excluding the hypoalbuminemia and iatrogenic groups, clinicopathological variables predictive of R-CHF included a lower level of band neutrophils and higher number of platelets, though these variables were still generally found to be within reference range for most patients and predictive power of these variables was low. However, increased alanine transaminase, creatinine, and blood urea nitrogen were also predictive of R-CHF. These clinicopathological findings are consistent with a previous study of dogs with R-CHF wherein increased liver enzyme activities were seen in 26% of patients and increased blood urea nitrogen and creatinine were seen in 52% of patients.[54] Increase in liver enzymes are likely secondary to reactive hypoxia (decreased blood flow to the liver secondary to a combination of hepatic congestion and decreased cardiac output), whereas the increase in kidney values could be because of decreased renal blood flow from either decreased cardiac output secondary to their congestive heart failure or medication administration (diuretics and/or angiotensin-converting enzyme inhibitors).

Also, after the exclusion of hypoalbuminemia and iatrogenic groups, low cholesterol was predictive of LVO, and increased alkaline phosphatase (ALP) was predictive of venous thrombosis, though again predictive power of these variables was quite low. These findings are most likely attributed to the most common underlying diseases in these groups. For dogs with LVO, the most common underlying disease was neoplasia. A retrospective study in dogs found that neoplasia and infection were the most common underlying disease categories associated with hypocholesterolemia.[55] Within the venous thrombosis etiology group, the most common underlying disease processes were neoplasia, disseminated intravascular coagulation, and IMHA. All 3 of these diseases have a known association with increased ALP levels in dogs, particularly in dogs where a venous thrombus is identified.[28,32,56-60] Of note, a study analyzing the prevalence of thromboembolism in dogs with IMHA found that dogs have a higher risk of thromboembolism with increasing ALP levels.[60]

There were no patients in our study sample confirmed to have peripheral edema secondary to specific therapies (such as medications, blood products, etc.) that led to suspected or known drug-induced allergic reactions.[36,61] The only known iatrogenic treatment causing peripheral edema in our study was IV fluid administration, causing peripheral edema because of increased intravascular hydrostatic pressure. One dog in our study was suspected to have vasculitis and nonpitting peripheral edema secondary to leflunomide, but this could not be confirmed. This may be because of a combination of factors: the relative infrequency of medication reactions, the possibility that a dog with a suspected allergic reaction may not present to a tertiary referral hospital, or different descriptor terms used for allergic reactions in a medical record that might not be captured via the terminology used in this study.

The data from our study sample could help clinicians utilize clinical and clinicopathological variables to prioritize differential diagnoses for the etiology of peripheral edema in dogs. An initial history can be used to identify edema that is traumatic (ie, a history of trauma) or iatrogenic (ie, a history of intravenous fluid administration). The findings of hypoalbuminemia, hypoglobulinemia, hypoproteinemia, and hypocholesterolemia are consistent with hypoalbuminemia as their underlying etiology. The presence of right hind limb edema, younger age, and increased ALP might suggest venous thrombosis as a potential etiology. The presence of edema on intake examination, pitting edema, or lower cholesterol might prompt suspicious for LVO. A temperature greater than 102.5°F raises index of suspicion for vasculitis (either secondary to infection or neoplasia). Finally, the presence of a heart murmur, ventral abdominal or generalized edema, and any combination of abdominal, pleural, or pericardial effusion might suggest R-CHF as the most likely etiology. However, a prospective dataset would be required to validate these findings, and our findings should be interpreted cautiously given the inherent limitations of a retrospective study. Additionally, whereas many variables were found to be statistically significant predictors of etiology groups in this study, the predictive power of many variables was relatively low, which could limit the clinical applicability of these results.

This retrospective study had several limitations, including the lack of confirmed etiology of peripheral edema for some cases. Because this was a retrospective medical record review, terminology used to describe edema in the physical examination was not standardized. For example, not all physical examination descriptions included the words "pitting" or "nonpitting." Another limitation is that diagnoses were based on information available in the medical record and the opinion of the overseeing clinician at the time of patient visit; there was no standardization of what diagnostics were performed for each dog, and some cases may have been misdiagnosed or miscategorized. Dogs

lacking a definitive etiologic diagnosis for their peripheral edema (including dogs with multiple potential mechanisms of edema formation) were included in the study for descriptive purposes but not included in statistical analyses of group differences, which might have limited the statistical power of some group comparisons. Survival data was also lacking for some patients, limiting the utility of comparative survival analysis. The only significant finding from the survival data was the better prognosis for dogs with vasculitis, most likely because of most dogs underlying disease being local infection or cellulitis that is more commonly and easily treatable (versus neoplasia or systemic disease being more common in other etiology groups). Given the large number of etiology groups and candidate clinicopathological variables assessed in this exploratory study, discretion was used in structuring our statistical analyses (combining or excluding certain etiology groups) to focus on the most clinically meaningful comparisons. We acknowledge the subjectivity of such decision-making and the possibility that results might have differed had we chosen different combinations of etiology groups to analyze.

Our results suggest that the most common etiologies of peripheral edema in dogs are vasculitis, LVO, and venous thrombosis, with R-CHF being uncommon. Physical examination findings, location of edema, presence of concurrent effusion, and clinicopathological data can be helpful to predict the underlying etiology of a patient's peripheral edema. Future prospective studies are needed to confirm the findings of this study.

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CONFLICT OF INTEREST DECLARATION
Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION
Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION
Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION
Authors declare human ethics approval was not needed for this study.

ORCID
Jessica L. Ward https://orcid.org/0000-0002-9153-7916

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.