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# Clinical presentation, cardiovascular findings, etiology, and outcome of myocarditis in dogs: 64 cases with presumptive antemortem diagnosis (26 confirmed postmortem) and 137 cases with postmortem diagnosis only (2004–2017)

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## KEYWORDS

Troponin;  
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**Abstract** *Introduction:* This study describes presentation, cardiovascular abnormalities, etiology, and outcome of canine myocarditis in geographic areas not endemic for *Trypanosoma* or *Leishmania*.

*Animals:* Sixty-four (presumed antemortem diagnosis) and 137 (postmortem diagnosis only) client-owned dogs at two tertiary care facilities were included.

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Trypanosoma;  
Leishmania

**Materials and methods:** Medical records of dogs with clinical or histopathological diagnosis of myocarditis were reviewed retrospectively.

**Results:** Common examination findings in dogs with a presumed antemortem diagnosis included fever (21%) and heart murmur (19%). Median cardiac troponin I was 12.2 ng/mL (range: 0.2–808.0 ng/mL), and troponin exceeded 1.0 ng/mL in 26 of 29 (90%) dogs. Ventricular ectopy was the most common arrhythmia (54%), whereas decreased left ventricular systolic function was the most common echocardiographic abnormality (56%). An infectious etiology was diagnosed in 35 of 64 (55%) dogs. Confirmed infectious etiologies included bacterial sepsis (n = 9) or extension of endocarditis (3), toxoplasmosis or neosporosis (3), parvovirus (2), and one case each of bartonellosis, trypanosomiasis, leptospirosis, and dirofilariasis. Median survival time was 4 days (range: 0–828 days) for all dogs vs. 82 days for dogs who survived at least 2 weeks after diagnosis. Presence of pericardial effusion or azotemia was a significant predictor of non-survival. The most common inflammatory infiltrate on histopathology was neutrophilic (47%), and 20 of 137 (14.5%) dogs had concurrent bacterial endocarditis on postmortem.

**Conclusions:** Bacterial infection was the most common confirmed etiology of myocarditis in this study. Prognosis for canine myocarditis is guarded and similar to that reported for infective endocarditis. Criteria for the antemortem diagnosis of canine myocarditis are suggested.

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### Abbreviations

CBC	complete blood count
cTnl	cardiac troponin I
ECG	electrocardiogram
ISU-LVMC	Iowa State University–Lloyd Veterinary Medical Center
MST	median survival time
NCS-VH	North Carolina State Veterinary Hospital
PCR	polymerase chain reaction

## Introduction

Myocarditis is a non-specific inflammatory disease of the myocardium. Its incidence in the canine population is unknown, although a histopathologic diagnosis of myocarditis was reported in 1.5% of dogs in a retrospective necropsy study [1]. Numerous infectious and non-infectious etiologies have been associated with development of myocarditis in dogs. The most commonly reported infectious causes include trypanosomiasis [2–8], leishmaniasis [9–13], parvovirus [14–18], toxoplasmosis [19], neosporosis [19,20], borreliosis [21,22], ehrlichiosis [23], leptospirosis [24], and bartonellosis [25–27]. Other less commonly reported causes include other viral [28–30], bacterial [31], and fungal or algal [32] organisms. Reported non-infectious etiologies include

pharmacologic drugs or toxins, immune-mediated diseases, trauma, heat stroke, hemodynamic shock, and idiopathic myocarditis [1,22,33]. Literature pertaining to presentation, diagnosis, and treatment of myocarditis in canines is limited, consisting mostly of single-case reports and small case series focused on a single causative etiology. There are no large-scale studies reporting clinical features or outcome of myocarditis across multiple etiologies.

Definitive diagnosis of myocarditis is based on histopathology demonstrating myocardial inflammation, with or sometimes without myocyte necrosis; therefore, definitive antemortem diagnosis requires endomyocardial biopsy [34–36]. Although more routinely performed in humans [36,37], this procedure is rarely performed in dogs because of limited availability of expertise and specialized equipment, combined with procedural and anesthetic risk. For this reason, the antemortem diagnosis of canine myocarditis is generally presumptive and based on an individual clinician's interpretation of case presentation and clinicopathologic information. Standardized antemortem diagnostic criteria, as existing for canine endocarditis [38], would be helpful to identify dogs with suspected or possible myocarditis.

The primary objective of this study was to describe the clinical presentation, diagnostic test results, suspected etiology, treatment, and outcome of dogs with a presumptive diagnosis of myocarditis presenting to two tertiary-care

facilities. The two tertiary-care facilities were located in geographic areas not endemic to either *Trypanosoma cruzi* or *Leishmania infantum*, the two vector-borne infectious diseases most commonly linked to canine myocarditis. The second study objective was to compare clinical findings between institutions and between etiologies of myocarditis. The third study objective was to use these findings in conjunction with postmortem results in confirmed myocarditis cases to propose criteria that can be utilized for the antemortem diagnosis of canine myocarditis.

## Animals, Materials, and Methods

### Data collection

A retrospective medical record search of case summaries (antemortem study population) and necropsy reports (postmortem study population) was performed to identify dogs diagnosed with myocarditis at the Iowa State University Lloyd Veterinary Medical Center (ISU-LVMC) and the North Carolina State Veterinary Hospital (NCS-VH) between June 1, 2004, and March 31, 2017. The antemortem study population consisted of dogs with a final diagnosis of myocarditis documented in the patient's case summary, based on high clinical suspicion for myocarditis by the attending clinician. Dogs with a recent history of thoracic trauma were excluded. A minimum of history and physical examination findings were required for dogs enrolled in the antemortem aspect of the study. The postmortem study population consisted of dogs with a histopathologic diagnosis of myocarditis documented in a complete necropsy report including both gross and histopathologic findings. Dogs with a presumptive antemortem diagnosis of myocarditis that was later confirmed on postmortem were analyzed as part of both populations.

For the antemortem study population, data obtained from medical records included the following: patient signalment, history and presenting complaint(s), physical examination findings, complete blood count (CBC) data, biochemistry panel data, cardiac troponin I (cTnI) values on initial presentation and follow-up, electrocardiographic findings, echocardiographic data, additional diagnostic tests performed and test results, treatments administered during hospitalization, date and cause of death, and suspected etiology of myocarditis.

For the postmortem study population, data obtained from necropsy records included gross pathologic description of the heart,

histopathologic description of the myocardium, results of tissue cultures or special stains, and suspected etiology of myocarditis. Gross pathology and histopathology examinations were performed by diplomates of the American College of Veterinary Pathology (Anatomic Pathology) or anatomic pathology residents under the supervision of board-certified diplomates.

### Statistical analysis

Statistical analysis was performed using commercially available software<sup>f,g</sup>. Normality of data was assessed using a combination of visual inspection and the Shapiro-Wilk test. Comparisons of variables between groups were performed using Student's *t*-tests for continuous normally distributed data, Mann-Whitney log-rank tests for continuous non-normally distributed data, and Fisher's exact tests for categorical variables. Univariate logistical regression analysis was performed to assess variables that were associated with survival. Parameters significant in univariate analysis were subsequently entered into a multivariate stepwise logistic regression analysis. Statistical significance was set at  $p < 0.05$  for all analyses.

## Results

### Antemortem study population

#### Animals

A total of 64 dogs with a presumptive antemortem diagnosis of myocarditis were identified, including 31 of 64 (48%) dogs from the ISU-LVMC and 33 of 64 (52%) from the NCS-VH. Cases diagnosed with myocarditis represented 0.0007% of all dogs seen at the ISU-LVMC and 0.0005% of dogs seen at the NCS-VH during the study period. The study population included 23 (36%) spayed female, six (9%) intact female, 30 (47%) castrated male, and five (8%) intact male dogs. The mean age of dogs was 7.9 years (range: 0.2–15.6 years); the median weight was 22.9 kg (range: 3.3–83.0 kg). Breeds of dogs included mixed breed ( $n = 12$ ), Labrador retriever ( $n = 10$ ), golden retriever ( $n = 5$ ), boxer ( $n = 4$ ), collie ( $n = 3$ ), bullmastiff ( $n = 2$ ), Pembroke Welsh corgi ( $n = 2$ ), pointer ( $n = 2$ ), Jack Russell terrier ( $n = 2$ ), Cavalier King Charles spaniel ( $n = 2$ ), beagle ( $n = 2$ ), and one each of 18

<sup>f</sup> GraphPad PRISM, version 7.0, GraphPad Software, La Jolla, California, USA.

<sup>g</sup> MedCalc, version 17.6, MedCalc Software, Ostend, Belgium.

additional breeds. There were no differences between institutions in terms of dog sex, age, or weight.

### History and presenting complaints

Lethargy was the most common presenting complaint, reported in 45 of 64 (70%) dogs, followed by hyporexia, reported in 44 of 64 (69%) dogs. Other frequently observed signs included weakness (23/64, 36%), gastrointestinal signs (vomiting and/or diarrhea; 20/64, 31%), and tachypnea (18/64, 28%). Clinical signs observed in less than 20% of dogs included exercise intolerance (11/64, 17%), cough (11/64, 17%), syncope (10/64, 16%), central nervous system abnormalities (10/64, 16%), lameness or orthopedic pain (7/64, 11%), panting (6/64, 9%), and polyuria/polydipsia (1/64, 2%).

### Physical examination

The mean heart rate of presenting dogs was 141 beats per minute (range: 40–310 beats per minute,  $n = 63$ ). Twelve dogs were panting during examination; the remaining 52 dogs had a mean respiratory rate of 44 breaths per minute (range: 20–80 breaths per minute). Of the 61 dogs with a recorded temperature, the mean temperature was 101.4°F (range: 96.4°–106.2° F); 13 of 61 (21%) were febrile, defined by a temperature greater than 102.5° F. The mean systolic blood pressure was 123 mmHg (range: 40–290 mmHg;  $n = 39$ ). Common physical examination abnormalities included the presence of a heart murmur (12/64, 19%), femoral pulse abnormalities (12/64, 19%), lymphadenopathy (7/64, 11%), joint abnormalities (effusion, swelling, or lameness; 6/64, 9%), pale mucous membranes and/or prolonged capillary refill time (4/64, 6%), extra heart sounds (3/64, 5%), dyspnea or tachypnea (2/64, 3%), and decreased intensity of heart sounds (2/64, 3%). Location and timing of heart murmurs were further characterized in all 12 dogs as left apical systolic ( $n = 4$ ), left basilar (3), left systolic (3), left apical (1), and right-sided diastolic (1). Intensity of heart murmurs was graded as I-II/VI ( $n = 4$ ), II-III/VI (2), and III-IV/VI (5) and not reported in 1 dog.

### Clinical pathology

Thrombocytopenia was the most frequently observed abnormality on CBC, with 29 of 51 (57%) dogs affected. Neutrophilia was noted in 28 of 52 (52%) dogs, with 15 of 49 (31%) also having a left shift as defined by bands  $> 0.5 \times 10^3/\mu\text{L}$ . Monocytosis was observed in 26 of 53 (49%) dogs, while anemia was noted in 23 of 54 (43%) dogs.

The most common abnormality on serum biochemistry was elevated ALT, occurring in 36 of 54

(67%) dogs. Elevated ALP was observed in 29 of 54 (54%) dogs. In addition, based on reference intervals established at each institution's diagnostic laboratory, 30 of 56 (54%) dogs were hypocalcemic, 25 of 56 (45%) dogs were hypoalbuminemic, and 14 of 58 (24%) dogs were azotemic.

Cardiac troponin I levels were assessed at initial evaluation in 29 dogs. The median initial cTnI was 12.2 ng/mL (range: 0.2–808.0 ng/mL); individual values exceeded the upper end of the laboratory's reference interval ( $>0.2$  ng/mL) in all cases [1,39,40]. Initial cTnI exceeded 1.0 ng/mL in 26 of 29 (90%) dogs and exceeded 1.405 ng/mL in 24 of 29 (83%) dogs [39,41]. Cardiac troponin I was retested at a subsequent recheck examination (median: 26 days later, range: 0–827 days) in 26 dogs; cTnI decreased at the recheck visit in 16 of 26 (76%) cases and increased in 5 of 26 (24%) cases.

### Cardiovascular assessment

On electrocardiogram (ECG), 29 of 54 (54%) dogs had ventricular premature complexes, 18 of 54 dogs (33%) had ventricular tachycardia, and 7 of 54 dogs (13%) had both. Other ECG abnormalities included sinus tachycardia (9/54, 17%), supraventricular tachycardia (4/54, 7%), atrioventricular block (4/54, 7%), and sinus bradycardia with or without periods of sinus arrest (2/54, 4%).

Echocardiography was performed in 45 of 64 (70%) cases; all echocardiograms were performed within 24 h of presentation to the hospital. A number of dogs had decreased left ventricular systolic function, evidenced by left ventricular fractional shortening less than 25% (24/43, 56%) [42] or left ventricular ejection fraction below 50% (21/42, 50%) [43–45]. End-diastolic and end-systolic left ventricular volume indices were each increased in 15 of 33 dogs (45%) [43–45]. Subjective heteroechoogenicity of the left ventricular myocardium was noted in 15 of 44 (34%) dogs, small-volume pericardial effusion (without cardiac tamponade) was seen in 7 of 44 (16%) dogs, and subjective focal hypokinesis of the left ventricle was recorded in 6 of 44 (14%) dogs. Only one of the dogs with pericardial effusion was diagnosed with a neoplastic cause of myocarditis. Results of other echocardiographic parameters, including left ventricular measurements normalized to body weight [46], are shown in Table 1.

### Additional diagnostic testing

Additional abdominal imaging was performed in 41 of 64 (64%) dogs, while thoracic imaging was performed in 38 of 64 (59%) dogs. Thirty-four (53%) dogs had additional infectious disease testing, including serology and polymerase chain reaction

**Table 1** Cardiovascular and echocardiographic data for dogs with a presumptive antemortem diagnosis of myocarditis.

Cardiovascular parameter	Reference range	No. of dogs	Result	N (%) increased	N (%) decreased
Murmur (n, %)	—	64	12 (19%)	—	—
Pulse abnormalities (n, %)	—	64	12 (19%)	—	—
Arrhythmia (n, %)	—	54	49 (91%)	—	—
Pericardial effusion (n, %)	—	44	7 (16%)	—	—
Heterogeneity of left ventricular myocardium (n, %)	—	44	15 (34%)	—	—
cTnI (ng/ml)	<0.2	21	12.2 (0.2–808.0)	21 (100%)	—
IVSdN	0.29–0.59	44	0.47 ± 0.12	11 (25%)	4 (9%)
IVSsN	0.43–0.79	43	0.62 ± 0.17	10 (23%)	12 (28%)
LVIDdN	1.27–1.85	44	1.56 ± 0.36	15 (34%)	10 (23%)
LVIDsN	0.71–1.26	43	1.08 ± 0.35	18 (42%)	8 (19%)
LVPWdN	0.29–0.60	44	0.51 ± 0.13	16 (36%)	4 (9%)
LVPWsN	0.48–0.87	43	0.71 ± 0.19	12 (28%)	7 (16%)
LA:Ao	<1.3	33	1.18 ± 0.46	9 (27%)	—
FS (%)	>25%	43	27.6 ± 12.5	—	24 (56%)
LVEF (%)	>50%	42	52.4 ± 18.6	—	21 (50%)
EPSS (mm)	<6	28	4.8 ± 0.5	8 (29%)	—
E/A	>1	23	1.32 ± 0.47	—	6 (26%)
EDVI	<80	33	89.3 ± 55.1	15 (45%)	—
ESVI	<30	33	40.3 ± 35.9	15 (45%)	—

The number of dogs with each measurement available is noted for variables with incomplete data sets. Continuous variables are reported as mean ± standard deviation for normally distributed data and as median (range) for non-normally distributed data. cTnI, cardiac troponin I; E/A, ratio of early to late diastolic transmitral flow velocity; EDVI, end-diastolic volume index; EPSS, E-point to interventricular septal separation; ESVI, end-systolic volume index; IVSdN, interventricular septal thickness in diastole normalized to body weight; IVSsN, interventricular septal thickness in systole normalized to body weight; LA:Ao, ratio of left atrial to aortic dimension; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVIDdN, left ventricular internal dimension at end-diastole normalized to body weight; LVIDsN, left ventricular internal dimension in systole normalized to body weight; LVPWdN, left ventricular posterior wall thickness at end-diastole normalized to body weight; LVPWsN, left ventricular posterior wall thickness in systole normalized to body weight.

(PCR) panels for vector-borne diseases (n = 26),<sup>h,i</sup> enzyme-linked immunosorbent assay for canine parvovirus (n = 2), PCR using *Bartonella* Alpha Proteobacteria Growth Medium (n = 11), antigen test for *Dirofilaria immitis* (n = 8), fecal float (n = 5), giardia fecal antigen test (n = 1), rectal scrape for prototheca (n = 2), or antibody titers specifically for *Trypanosoma*, *Neospora*, *Toxoplasma*, *Leptospira*, or *Borrelia* C6 (n = 13). Cytology of effusions, lymph node aspirates, or liver aspirates was performed in 30 of 64 (47%) dogs. Various urine tests were performed in 33 of 64 (52%) cases, including urinalysis, urine culture (n = 18), *Blastomyces* and *Histoplasma* urine antigen test, and urine protein-to-creatinine ratio. Urine cultures were positive in 4 of 18 dogs (22%),

with isolated organisms including *Staphylococcus pseudintermedius*, *Staphylococcus epidermis*, *Escherichia coli*, and a mixed culture of *Enterococcus faecalis* and *Proteus mirabilis*. Blood cultures were performed in 14 dogs and were positive in two cases (14%) for *E. coli* and *Bacillus cereus*. Culture of synovial fluid was performed in three dogs and was positive in all three cases (100%), with isolated organisms including *S. pseudintermedius*, *B. cereus*, and *Enterococcus faecium*. Bacterial culture of other fluid samples (bile or cavitory effusions) was performed in five dogs and was positive in two cases, both involving mixed infections (abdominal fluid culturing positive for *E. coli*, *E. faecalis*, and *Enterobacter* spp and thoracic fluid culturing positive for *E. coli* and *P. mirabilis*).

Twenty-eight of the 64 (44%) dogs with a presumptive antemortem diagnosis of myocarditis had postmortem examinations performed. Of these 28 dogs, 26 (92%) had the diagnosis of myocarditis confirmed on histologic examination. Myocarditis

<sup>h</sup> Canine SNAP Test Plus, IDEXX Laboratories, Westbrook, Maine, USA.

<sup>i</sup> Canine Comprehensive Vector-Borne Disease Panel, Vector Borne Disease Diagnostic Laboratory, NC State College of Veterinary Medicine, Raleigh, North Carolina, USA.

was most commonly neutrophilic (14/26, 54%); other inflammatory infiltrates included lymphoplasmacytic (5/26, 19%), necrotizing (8/26, 31%), histiocytic or lymphohistiocytic ( $n = 1$ ), granulomatous or pyogranulomatous ( $n = 1$ ), mononuclear cell ( $n = 1$ ), or unspecified ( $n = 2$ ). In two cases, antemortem diagnosis of myocarditis was not confirmed on histopathology. One of these dogs had clinically recovered from an episode of myocarditis (with recheck cTnl  $< 0.2$  ng/mL) before euthanasia. Myocardial pathology in the second dog was attributed to cholecalciferol toxicity; the predominant histologic lesion in this dog was multi-organ mineralization, including coronary arterial and myocardial mineralization, without inflammation at the time of necropsy.

### Etiology, treatment, and outcome

Of 64 dogs diagnosed with myocarditis, 35 (55%) were suspected to have an infectious etiology and 11 (17%) were suspected to have a non-infectious etiology, while the cause of myocarditis was unknown in 18 of 64 (28%) cases. Infectious etiologies included bacterial sepsis ( $n = 9$ ), extension from bacterial endocarditis ( $n = 3$ ), canine parvovirus ( $n = 2$ ), *Toxoplasma* ( $n = 2$ ), *Neospora* ( $n = 1$ ), *Trypanosoma* ( $n = 1$ ), *Leptospira* ( $n = 1$ ), *Bartonella* ( $n = 1$ ), and *Dirofilaria* ( $n = 1$ ). In 14 (22%) dogs, an infectious etiology was highly suspected based on positive response to antibiotic treatment or postmortem findings of neutrophilic inflammation, but a specific etiologic agent could not be identified. Confirmed non-infectious etiologies of myocarditis included neoplasia ( $n = 8$ ), rodenticide toxicity ( $n = 2$ ), and immune-mediated hemolytic anemia ( $n = 1$ ). For neoplastic cases with myocardial inflammation, two (25%) dogs had intracardiac tumors (hemangiosarcoma and chemodectoma), whereas six (75%) dogs had extracardiac tumors (B-cell lymphoma, T-cell lymphoma, cholangiocarcinoma, axial osteosarcoma, mediastinal thymoma plus apocrine gland anal sac adenocarcinoma, and splenic hemangiosarcoma plus adrenocortical carcinoma). Of the six extracardiac neoplastic cases, myocardial inflammation was suspected to be secondary to embolic neoplastic cells in four dogs and cardiac metastasis in two dogs, as determined by histopathologic evidence of coronary vascular thrombi or infarcts vs. presence of neoplastic cells within in the myocardium, respectively.

Antibiotics were the most commonly used treatment, prescribed in 44 of 64 (69%) dogs. The most frequently used antibiotics included doxycycline ( $n = 29$ ), beta-lactam antibiotics ( $n = 22$ ), enrofloxacin ( $n = 17$ ), clindamycin ( $n = 9$ ), and

metronidazole ( $n = 8$ ). Anti-arrhythmic medications were used in 32 of 64 (50%) dogs, including sotalol ( $n = 24$ ), lidocaine ( $n = 20$ ), mexiletine ( $n = 8$ ), procainamide ( $n = 5$ ), diltiazem ( $n = 2$ ), and magnesium sulfate ( $n = 2$ ). Other cardiac medications used to treat dogs with myocarditis included pimobendan ( $n = 14$ ), angiotensin-converting enzyme inhibitors ( $n = 13$ ), clopidogrel ( $n = 5$ ), and furosemide ( $n = 4$ ). Fifteen of the 64 (23%) dogs had been treated with an immunosuppressive medication before presentation, including prednisone, dexamethasone, or cyclosporine.

At time of manuscript preparation, 41 of the 64 (64%) dogs presented had died; 32 of these dogs were euthanized, while nine died spontaneously. The median survival time (MST) for these 41 dogs was 4 days (range: 0–828 days). Twenty-seven of the 64 (42%) dogs survived less than 2 weeks after initial presentation, while 37 of 64 (58%) survived greater than 2 weeks. The MST for dogs surviving less than 2 weeks was 2 days, whereas the MST for dogs surviving greater than 2 weeks was 82 days. Of the 41 deceased dogs, cause of death was related to myocarditis in 30 (73%) dogs. The remaining 11 (27%) dogs reportedly died or were euthanized for non-cardiac disease, although sepsis or disseminated intravascular coagulation (potentially related to myocarditis) was relevant comorbid factors in five of these cases.

### Population comparisons

Several clinical parameters differed between dogs presenting to the ISU-LVMC vs. NCS-VH. More dogs presenting to the NCS-VH had peripheral pulse abnormalities recorded (36% vs. 0%,  $p = 0.0002$ ) and joint abnormalities (18% vs. 0%,  $p = 0.025$ ) than those presenting to the ISU-LVMC. Compared with dogs at the ISU-LVMC, dogs at the NCS-VH had higher mean hematocrit (42% vs. 34%,  $p = 0.003$ ), albumin (3.2 vs. 2.4 g/dL,  $p \leq 0.0001$ ), and total calcium (10.1 vs. 9.5 g/dL,  $p = 0.008$ ) and lower serum creatinine (0.9 vs. 1.25 mg/dL,  $p = 0.009$ ). On echocardiogram, a higher proportion of dogs at the ISU-LVMC had pericardial effusion (38% vs. 6%,  $p = 0.015$ ), heteroechogenicity of the left ventricular myocardium (77% vs. 16%,  $p = 0.0002$ ), and increased left ventricular posterior wall thickness (77% vs. 19%,  $p = 0.0005$ ) compared with dogs at the NCS-VH. Significantly more NCS-VH dogs had infectious disease testing performed (73% vs. 33%,  $p = 0.002$ ) and were treated with sotalol (55% vs. 19%,  $p = 0.004$ ) or antibiotics (88% vs. 48%,  $p < 0.001$ ) than ISU-LVMC dogs. Survival at 2 weeks was higher for dogs at the NCS-VH than for those at the ISU-LVMC (88% vs. 26%,  $p < 0.0001$ ).

Several clinical parameters differed based on the suspected underlying etiology of myocarditis (infectious vs. non-infectious). Dogs with non-infectious myocarditis were more likely to have ventricular ectopy on ECG (69% vs. 32%,  $p = 0.012$ ) than dogs with infectious myocarditis. Dogs with infectious myocarditis had larger left ventricular size, as assessed by left ventricular internal dimension in diastole ( $p = 0.032$ ) and systole ( $p = 0.027$ ), as well as end-diastolic volume index ( $p = 0.045$ ). Infectious disease testing (48% vs. 11%,  $p = 0.0013$ ) and treatment with amoxicillin-clavulanate (59% vs. 16%,  $p = 0.0013$ ) were more commonly used in dogs diagnosed with infectious myocarditis. None of these variables were a

significant predictor of an infectious etiology of myocarditis on univariate analysis.

### Survival analysis

Clinicopathologic and treatment variables that differed significantly between dogs surviving less than vs. greater than 2 weeks are listed in Table 2. Univariate logistic regression demonstrated that the following variables were positively associated with survival: infectious disease testing ( $p = 0.0091$ ), treatment with antibiotics ( $p = 0.037$ ), treatment with doxycycline ( $p = 0.010$ ), and treatment with sotalol ( $p = 0.0044$ ). The following variables were associated with non-survival in univariate regression:

**Table 2** Clinical parameters in 64 dogs presumptively diagnosed with myocarditis (26 with diagnosis confirmed postmortem) that differed between dogs surviving greater than 2 weeks (survivor) vs. less than 2 weeks (non-survivor).

Clinical parameter	Reference interval	Survivor N = 37		Non-survivor N = 27		p-value
		Result	N (%)	Result	N (%)	
<sup>a</sup> Gonadal status (intact)	—	—	3 (8.1)	—	8 (29.6)	0.0416
Syncope	—	—	9 (24.3)	—	1 (3.7)	0.0354
Tachypnea	—	—	8 (21.6)	—	20 (74.1)	<0.0001
Lymphadenopathy	—	—	0 (0)	—	7 (25.9)	0.0041
Joint abnormalities	—	—	6 (16.2)	—	0 (0)	0.035
<sup>a</sup> Hematocrit (%)	37–55.9	42.8 (18.2–57.8)		36.2 (7.3–45.3)		<0.0001
<sup>a</sup> Anemia			9 (24.3)		18 (66.7)	0.035
<sup>a</sup> Platelet count ( $\times 10^3/\text{ul}$ )	190–500	224 (58–887)		97.5 (22–459)		0.0008
<sup>a</sup> Thrombocytopenia			17 (45.9)		20 (74.1)	0.0461
<sup>a</sup> Neutrophil count ( $\times 10^3/\text{ul}$ )	2.53–12.88	9.5 (1.0–40.4)		19.4 (4.7–41.0)		0.0188
<sup>a</sup> Neutrophilia			16 (43.2)		19 (70.3)	0.0494
<sup>a</sup> Creatinine (mg/dL)	0.5–1.5	0.9 (0.3–5.9)		1.2 (0.4–15.6)		0.044
<sup>a,b</sup> Azotemia			3 (8.1)		13 (48.1)	0.0012
Alkaline phosphatase (U/L)	16–150	119 (25–1926)	—	220 (52–3734)	—	0.0306
<sup>a</sup> Albumin (g/dL)	2.7–4.0	3.18 $\pm$ 0.7		2.39 $\pm$ 0.67		<0.0001
<sup>a</sup> Hypoalbuminemia			11 (29.7)		18 (66.7)	0.0062
Magnesium (mg/dL)	1.7–2.5	1.98 $\pm$ 0.29		2.41 $\pm$ 0.85		0.0228
<sup>a</sup> Hypermagnesemia			1 (2.7)		8 (29.6)	0.0284
<sup>a</sup> Total calcium (mg/dL)	9.4–11.4	10.3 (8.0–13.2)		9.3 (5.1–10.6)		<0.0001
<sup>a</sup> Hypocalcemia			9 (24.3)		18 (66.7)	0.0019
<sup>a,b</sup> Pericardial effusion	—	—	3 (8.1)	—	12 (44.4)	0.0216
<sup>a</sup> Left ventricular heteroechoogenicity	—	—	9 (24.3)	—	18 (66.7)	0.0425
Infectious disease testing performed	—	—	26 (70.3)	—	8 (29.6)	0.0021
<sup>a</sup> Sepsis	—	—	2 (5.4)	—	7 (25.9)	0.0291
Antibiotic treatment	—	—	30 (81.1)	—	14 (51.8)	0.016
Doxycycline treatment	—	—	23 (62.1)	—	6 (22.2)	0.0022
<sup>a,b</sup> Sotalol treatment	—	—	21 (56.7)	—	3 (11.1)	0.0002
Enalapril treatment	—	—	13 (35.1)	—	0 (0)	0.0003
Pimobendan treatment	—	—	12 (32.4)	—	2 (7.4)	0.0297

Parameters represented by both continuous and categorical variables (e.g. hematocrit as a continuous variable and anemia as a categorical variable) are shown in the same row. Results of continuous variables are shown as mean  $\pm$  SD for normally distributed data and median (range) for non-normally distributed data, whereas results of categorical variables shown as number (%) of dogs.

<sup>a</sup> Significantly associated with survival in univariate analysis.

<sup>b</sup> Significantly associated with survival in multivariate analysis.



intact gonadal status ( $p = 0.025$ ), anemia ( $p = 0.0037$ ), thrombocytopenia ( $p = 0.040$ ), neutrophilia ( $p = 0.040$ ), azotemia ( $p = 0.0052$ ), hypoalbuminemia ( $p = 0.0092$ ), hypermagnesemia ( $p = 0.049$ ), total hypocalcemia ( $p = 0.0021$ ), presence of pericardial effusion ( $p = 0.024$ ), heteroechoogenicity on echocardiogram ( $p = 0.034$ ), and presence of sepsis ( $p = 0.041$ ). The only variables that remained significantly associated with non-survival in multivariate analysis were presence of pericardial effusion ( $p = 0.022$ , odds ratio [OR] = 12.50, 95% confidence interval [CI] = 1.45–107) and presence of azotemia ( $p = 0.045$ , OR = 10.179, 95% CI = 1.05–98), while treatment with sotalol remained predictive of survival to 2 weeks ( $p = 0.0027$ , OR = 10.66, 95% CI = 1.30–87).

### Postmortem study population

A total of 137 dogs with a postmortem diagnosis of myocarditis were identified, including 20 of 137 (14.5%) dogs from the ISU-LVMC and 117 of 137 (85.4%) from the NCS-VH. Twenty-eight of these 137 dogs (20%) were also represented in the antemortem cohort of the study. Cases diagnosed with myocarditis represented 0.01% of all dogs necropsied at the ISU-LVMC and 0.03% of dogs necropsied at the NCS-VH during this time period. Based on histopathologic examination, 81 of 137 (59.1%) dogs were suspected to have an infectious etiology of myocarditis. Of the 81 dogs with a suspected infectious etiology, 20 (25%) were diagnosed with primary infective endocarditis extending to the adjacent myocardium and resulting in secondary myocarditis. Cases with grossly visible endocarditis lesions were excluded from the remainder of the postmortem analysis.

With bacterial endocarditis excluded, the most common abnormalities on gross examination of the heart were valvular endocardiosis ( $n = 15$ ), dilation of one or more cardiac chambers ( $n = 8$ ), hypertrophy of one or more cardiac chambers ( $n = 4$ ), and unspecified cardiomegaly ( $n = 4$ ). Myocarditis was most commonly neutrophilic (55/117, 47%) or lymphoplasmacytic (33/117, 28.2%). Additional less common manifestations of myocarditis included necrotizing (33/117, 28.2%), histiocytic or lymphohistiocytic (16/117, 13.6%), granulomatous or pyogranulomatous (4/117, 3.4%), mononuclear cell (1/117, 0.8%), eosinophilic (1/117, 0.8%), or unspecified (4/117, 3.4%). Other changes seen on histopathological examination of cardiac tissue were myocardial interstitial fibrosis ( $n = 27$ ), cardiac myofiber degeneration ( $n = 15$ ) or loss ( $n = 7$ ), interstitial

hemorrhage ( $n = 5$ ), mineralization of the endocardium or coronary arteries ( $n = 3$ ), and myofiber regeneration ( $n = 2$ ). Other cardiovascular abnormalities noted on postmortem examination included presence of arteritis or vasculitis ( $n = 11$ ), thrombosis ( $n = 7$ ), myocardial infarction ( $n = 6$ ; 2 acute, 1 subacute, 1 chronic, 2 unknown duration), and presence of epicarditis or pericarditis ( $n = 3$ ). Infectious agents detected on histopathology included intralesional bacteria ( $n = 2$ ), intraluminal *Dirofilaria* ( $n = 1$ ), and disseminated blastomycosis ( $n = 1$ ). Hemangiosarcoma of the right atrium was noted in one dog.

### Discussion

The present study is the largest case series to date that reports clinical features, clinicopathologic and cardiovascular findings, treatment, and outcome in dogs with a presumptive antemortem diagnosis of myocarditis and histopathologic findings in dogs with postmortem confirmation of myocarditis. Unique features of this study were inclusion of all causes of myocarditis rather than focusing on a single etiologic agent, as well as case recruitment from geographic areas not considered endemic for the infectious diseases most commonly associated with myocarditis in dogs (*T. cruzi* or *L. infantum*). In this study, the most common cause of myocarditis was bacterial sepsis or extension of infective endocarditis (12/64 [19%] dogs in the antemortem population). Other confirmed etiologic agents, including canine parvovirus, *Toxoplasma*, *Neospora*, *Leptospira*, *Trypanosoma*, *Bartonella*, and *Dirofilaria*, were diagnosed in two or fewer cases each. Other than dirofilariasis, all of these organisms have been reported as potential causes of myocarditis in the veterinary literature, and all are regionally endemic in the United States. The single dog in this study diagnosed with Chagas disease had been recently adopted from a rescue organization in Texas. Overall, these results suggest that in geographic areas not endemic to vector-borne infections classically associated with myocarditis (such as trypanosomiasis and leishmaniasis), myocarditis may occur most commonly secondary to systemic bacterial infection and septicemia.

Previous studies have described clinical and cardiovascular findings in canine myocarditis caused by specific infectious etiologies, many of which were represented as isolated cases in the present study population. Chagas disease, caused by the hemoflagellate protozoan *T. cruzi*, is

endemic in South and Central America as well as the southern United States [2–5,7], whereas the protozoan *L. infantum* is reported as a common cause of myocarditis in the Mediterranean [9–11]. Other protozoal parasites such as *Toxoplasma gondii* and *Neospora caninum* are reported to cause myocarditis primarily in immunocompromised dogs [19,20]. One dog in the present case series was diagnosed with myocarditis secondary to parasitic infection with heartworms (*D. immitis*). Heartworm infection is most commonly associated with pulmonary endarteritis and pneumonitis, and myocarditis has not previously been reported in heartworm disease [47]; this patient had necrosuppurative myocarditis with evidence of with arteriolar thrombosis and infarction.

Viral myocarditis has also been described in dogs. Canine parvovirus has been recognized as a viral etiology of myocarditis in dogs since the late 1970s, classically causing lymphoplasmacytic myocarditis and sudden death in puppies after intrauterine or neonatal exposure [14–18]. West Nile virus is a more rarely reported viral etiology of myocarditis in dogs [28,29]. A recent study evaluated prevalence of viral nucleic acids in right ventricular endomyocardial biopsy specimens from dogs with unexplained myocardial and rhythm disorders [30]. Twenty of 37 (54.1%) dogs had positive PCR for nucleic acids from one or more canine viruses, including canine distemper virus, canine herpesvirus 1, canine parvovirus 2, canine coronavirus, and canine adenoviruses. While presence of viral DNA or RNA in myocardial tissue does not necessarily prove causation of myocardial disease [48], these results suggest that viral infection may be an underrecognized cause of myocarditis in dogs and may be underrecognized in the present study population; testing for viral infection was undertaken in only two dogs (serology for canine parvovirus), and endomyocardial biopsy specimens were not obtained in any patients.

Bacterial etiologies of myocarditis, including *Borrelia*, *Bartonella*, *Leptospira*, *Citrobacter*, *Staphylococcus*, and *Streptococcus*, have been described sporadically in the veterinary literature [21,22,24,26,27,31]. Bacterial sepsis has been reported to cause myocarditis or abscessation in humans, usually via extension from endocarditis lesions humans [37,49,50]. Interestingly, bacterial infection was the most common confirmed etiology of myocarditis in the present study. This suggests that bacterial septicemia may pose a greater risk of myocardial involvement than previously noted, and bacterial infection should be considered a

possible etiology of myocarditis in geographic regions not endemic to organisms known to target the myocardium specifically.

Non-infectious causes of myocardial inflammation, including pharmacologic agents, toxins, immunologic diseases, trauma, heat stroke, hemodynamic shock, and idiopathic etiologies, have been previously reported in dogs, albeit less commonly than infectious myocarditis [1,22,33]. Non-infectious myocarditis was diagnosed in 17% of dogs in the present study, including rodenticide toxicity, immune-mediated hemolytic anemia, and neoplasia. Causes of myocarditis in patients with underlying neoplasia may include peritumor inflammation (for primary cardiac tumors), cardiac metastasis (for extracardiac tumors), or paraneoplastic inflammation [39,51].

The most common presenting complaints of dogs in this study were non-specific clinical abnormalities, including lethargy and hyporexia. Common physical examination findings included fever, heart murmur, and pulse abnormalities. Most CBC and biochemistry abnormalities were consistent with non-specific inflammation (neutrophilia, left shift, monocytosis, and anemia) or decreased organ perfusion (elevated ALT and azotemia). Ventricular ectopy was common, with more than half of dogs exhibiting ventricular premature complexes and one-third of dogs experiencing ventricular tachycardia. The most commonly noted echocardiographic abnormality was decreased left ventricular systolic function, evident in more than 50% of cases. Overall, these clinical findings are consistent with previous case series describing myocarditis in dogs caused by single etiologic agents [2,9,18,19,21,23]. This suggests that cardiovascular complications and clinical signs of canine myocarditis are related to general cardiac damage, rather than specific etiologic agent.

Elevations in cTnI (>0.2 ng/ml) have been documented in dogs with infiltrative myocardial disease such as myocarditis [52,53] and myocardial neoplasia [51], as well as dogs with various congenital and acquired cardiac diseases [54–56] and bradyarrhythmias [57,58]. Common canine-acquired heart diseases typically cause only mild to moderate elevations in cTnI, with reported values up to 1.405 ng/ml (absolute maximum) [41] or 1.57 ng/ml (95% percentile) [54] because myocyte destruction is not a major feature of these diseases. There is no widely accepted cutoff for how severe cTnI elevation must be to raise clinical suspicion for an infiltrative or ischemic myocardial insult. In the present study, cTnI concentrations were >0.2 ng/ml in 100% (29/29) dogs, >1.0 ng/ml

in 90% (26/29) dogs, and >1.405 ng/ml in 83% (24/29) dogs. These results suggest that while most dogs with a clinical diagnosis of myocarditis have significantly increased cTnl, some cases may have more mild elevations, potentially related to timing of sampling in relation to myocardial injury.

Myocarditis was diagnosed much more commonly postmortem compared with antemortem at both institutions (postmortem diagnosis being 14–60 times more likely). Although this may reflect bias in terms of which cases are selected for necropsy, this disparity does suggest that myocarditis is an underdiagnosed disease. Antemortem diagnosis of myocarditis presents a challenge, given the non-specific clinical findings and difficulties related to diagnostic testing. In humans, myocarditis is diagnosed via endomyocardial biopsy samples evaluated using standardized histopathologic criteria [1,49,59,60]. While endomyocardial biopsy has been described in veterinary medicine [1], this technique is rarely performed clinically because of its invasiveness, need for specialized equipment and expertise, and requirement for general anesthesia in compromised patients.

A set of criteria to diagnose myocarditis using only non-invasive testing, as has been proposed in

humans [37], would greatly assist clinicians in increasing or decreasing antemortem index of suspicion for myocarditis. An analogous set of diagnostic criteria, the modified Duke criteria, exists for infective endocarditis [61] and has been adapted for both dogs [38] and cats [62]. The modified Duke criteria include a distinct set of 'major' and 'minor' criteria, and a definitive or possible diagnosis of endocarditis requires a certain number of major or minor criteria in combination. Based on the prevalence of clinicopathologic and cardiovascular abnormalities in the present study population, we propose a similar set of diagnostic criteria for the diagnosis of canine myocarditis (Table 3). Applying these criteria to our study population of 64 dogs with a clinical diagnosis of myocarditis, 49 (77%) dogs would be considered to have a 'definitive' diagnosis of myocarditis, including 18 of 64 dogs diagnosed via histopathology, 7 of 46 (15%) dogs would have a 'possible' diagnosis of myocarditis, and 8 of 46 (17%) would have insufficient antemortem data to apply the diagnostic criteria.

Treatment of myocarditis can be challenging because of difficulty obtaining a definitive diagnosis antemortem, and this study did not attempt to evaluate safety or efficacy of particular myocarditis

**Table 3** Proposed major and minor criteria for the antemortem diagnosis of myocarditis in dogs.

- I. Major criteria
  - A. Cardiac troponin I > 1.0 ng/mL
  - B. Positive culture of blood or other bodily fluid for typical bacteria OR positive infectious disease testing (PCR, antibody serology, antigen serology, virus isolation, or microscopic visualization) for other organisms reported to cause myocarditis in dogs:
    - a) Viral: parvovirus, distemper, herpesvirus, West Nile virus, coronavirus
    - b) Atypical bacterial: *Bartonella*, *Leptospira*, *Borrelia*, *Rickettsia*, *Ehrlichia*
    - c) Protozoal: *Trypanosoma*, *Toxoplasma*, *Neospora*, *Leishmania*, *Babesia*, *Hepatozoon*
    - d) Fungal/algal: *Blastomyces*, *Coccidioides*, *Cryptococcus*, *Aspergillus*, *Prototheca*
- II. Minor criteria
  - A. Fever >102.5° F
  - B. New or worsening heart murmur
  - C. Inflammatory leukogram (neutrophilia and/or left shift > 0.5 × 10<sup>3</sup>/UL), anemia, thrombocytopenia, or hypoalbuminemia
  - D. Ventricular arrhythmias
  - E. Decreased left ventricular systolic function (FS < 25%, LVEF < 50%, ESVI > 30, or focal hypokinesis)
  - F. Heteroechoogenicity of left ventricular myocardium
  - G. Pericardial effusion
- I. Definitive diagnosis of myocarditis:
  - A. Histopathologic confirmation of myocardial inflammation on endomyocardial biopsy specimen
  - B. Two major criteria
  - C. One major and three minor criteria
- II. Possible diagnosis of myocarditis:
  - A. One major and two minor criteria
  - B. Four minor criteria

ESVI, end-systolic volume index; FS, fractional shortening; PCR, polymerase chain reaction; LVEF, left ventricular ejection fraction.

treatments. Treatment plan was not standardized and generally reflected clinician preference in the context of suspected etiology. When comparing dogs who survived greater than vs. less than 2 weeks, there were a number of drugs given more commonly to survivors than to non-survivors; however, this likely simply reflected that the survivors lived long enough to receive such treatments.

Prognosis for dogs diagnosed with myocarditis in this study was poor to grave, with an overall MST of 4 days. This is similar to reported MST for bacterial endocarditis [38]. Given the high incidence of bacterial sepsis in our patient population, this prognosis likely reflects the overall poor prognosis for septicemia complicated by multi-organ dysfunction [63], rather than outcomes specific to myocardial inflammation. Of dogs who were euthanized or died during hospitalization, 30 of 41 (73%) deaths were attributed to a cardiovascular cause (congestive heart failure, arrhythmias, or hemodynamic instability). Prognosis for dogs who survived at least 2 weeks after diagnosis was more encouraging, with the MST of 82 days, and some dogs surviving over 2 years. Negative prognostic indicators in this study included presence of pericardial effusion and azotemia. Given that the most common cause of myocarditis in this study was bacterial sepsis, it is possible that azotemia in this patient population may have reflected severity of systemic inflammatory response and multi-organ dysfunction rather than severity of myocardial inflammation itself.

This study had several limitations because of its retrospective nature. First, not all data were available for all cases, and records were not uniform from case to case. There were disparities in data between the two institutions that likely reflected differences in patient demographics, clinician preferences, and medical record-keeping practices. The wide date range of the study (2004–2017) presents another limitation because changes in infectious disease testing or case management over time could have affected diagnoses or outcomes.

A number of antemortem cases (36/64, 56%) were included based on strong clinical suspicion of myocarditis rather than histopathologic diagnosis; furthermore, of dogs diagnosed with a suspected infectious etiology of myocarditis, only 21 of 35 (60%) dogs had a definitive etiologic agent diagnosed with infectious disease testing. Therefore, this study population may have included some dogs without histopathologic evidence of myocarditis, and the 'infectious' group may have included some dogs with sterile inflammation. However, post-mortem data demonstrate that histopathologic

myocarditis is more common than clinical antemortem diagnosis of myocarditis, suggesting that myocarditis is likely underdiagnosed, rather than overdiagnosed, in the clinical setting. Furthermore, incidence of infectious myocarditis was similar in the antemortem group (35/64, 55%) compared with the postmortem group (59% infectious), making it unlikely that infectious myocarditis was overdiagnosed clinically.

Finally, the method used to generate antemortem diagnostic criteria in this study was inherently limited by the fact that such criteria do not yet exist. The authors examined a population of dogs with high clinical suspicion of myocarditis, identified features common in these cases, developed diagnostic criteria based on these features, and then re-evaluated these criteria within the original population of dogs. Ideally, criteria for an antemortem diagnosis of myocarditis would be developed from a population of dogs with both full antemortem clinical workup and histopathologically confirmed myocarditis, and the criteria would then be tested on a separate population with similarly complete information. In the absence of complete antemortem and postmortem data sets, the proposed criteria can be considered as a tool to aid clinicians with diagnostic and prognostic decision-making.

## Conclusions

In a population of dogs with presumed myocarditis from geographic regions not endemic to *Trypanosoma* or *Leishmania*, sepsis or extension of bacterial endocarditis predominated as infectious etiologies. Clinical findings were generally non-specific indicators of systemic inflammation or decreased perfusion. Ventricular ectopy was the most common ECG abnormality, whereas decreased left ventricular systolic function was most commonly noted on echocardiogram. Cardiac troponin I concentrations >1.0 ng/ml can support a diagnosis of myocarditis in conjunction with other proposed diagnostic criteria. Prognosis for dogs with presumed myocarditis in this study was poor to grave, with negative prognostic indicators including pericardial effusion and azotemia.

## Conflicts of Interest Statement

The authors declare no conflict of interest related to this study.

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