Diagnostic utility of cardiac troponin I in cats with hypertrophic cardiomyopathy

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Background: Cardiac troponin I (cTnI) is useful for assessing hypertrophic cardiomyopathy (HCM) in cats.

Objective: To measure plasma cTnI concentrations in healthy cats and evaluate the clinical utility of cTnI in determining the severity of HCM.

Abbreviations: CHF, congestive heart failure; cTnI, cardiac troponin I; E, wave mitral early diastolic flow; HCM, hypertrophic cardiomyopathy; HF, heart failure; HOCM, hypertrophic obstructive cardiomyopathy; LAD, left atrial dilatation; LA/Ao, ratio left atrial-to-aortic diameter ratio; LVIDd, left ventricular end-diastolic internal dimensions; LVPWd, end-diastolic left ventricular posterior wall; IVSd, end-diastolic intraventricular septum
1 | INTRODUCTION

Cardiac troponin contains 3 subunits (cTnT, C, and I) and plays a regulatory role in cardiomyocyte contraction.\(^1\) In dogs, 98% of cardiac troponin is myofibril-bound and 2% is cytosolic.\(^2\) One study found that both cytosolic and myofibrillar cardiac troponins concentrations were decreased in ischemic myocardial tissue, which may precede histological evidence of necrosis.\(^3\) Circulating cardiac troponins are sensitive markers of cardiomyocyte injury, which may precede histological evidence of necrosis.\(^3\)

Although acute myocardial infarction is rare in veterinary medicine, cardiomyopathies including HCM are common types of heart disease in cats.\(^9\) Cardiomyopathies are progressive diseases associated with ongoing myocardial damage.\(^10\) Advanced cardiomyopathy can trigger congestive heart failure (CHF) and arterial thromboembolism, which is associated with a poor prognosis.\(^9,11,12\) Earlier clinical studies found that circulating cTnTs were increased in ischemic heart disease\(^4-6\) and hypertrophic cardiomyopathy (HCM)\(^7,8\) in humans.

Although some studies have reported that cTnI concentrations are increased in cats with HCM, the clinical implications of plasma cTnI concentrations at various stages of HCM remain unclear. We compared changes in plasma cTnI concentrations in cats with various stages of HCM. Our objective was to explore the sensitivity and specificity of plasma cTnI concentration in predicting HCM severity in cats.

2 | MATERIAL AND METHODS

2.1 | Cats

The study population consisted of 181 client-owned cats evaluated in a prospective multicenter manner. All cats were examined between April 2014 and March 2017. We followed the Guidelines for Institutional Laboratory Animal Care and Use of the School of Veterinary Medicine of Rakuno Gakuen University, Japan. All owners provided informed consent before their cats participated in the study. All cats underwent physical examination, indirect blood pressure measurement, echocardiography, and blood sampling. All clinical evaluations were performed without sedation in a quiet room.

Clinically healthy cats (n = 88) were identified on the basis of physical examination, blood pressure measurement, biochemical test data, serum thyroxine concentration, and echocardiography. Cats with HCM and hypertrophic obstructive cardiomyopathy (HOCM) constituted the study subjects (n = 93). Diseased cats were subdivided into 3 groups: asymptomatic cats without left atrial dilatation (ASYMP group), asymptomatic cats with left atrial dilatation (LAD group), and cats with heart failure (HF group). Left atrial dilatation was diagnosed when the left atrium-to-aorta (LA/Ao) ratio was >1.5.\(^18\) Congestive heart failure was diagnosed on the basis of radiographic evidence of pulmonary edema or pleural effusion, in addition to dyspnea. Arterial thromboembolism...
was diagnosed on the basis of acute onset limb paresis accompanied by clinical signs such as weak pulse, limb cyanosis, cold limb, or some combination of these findings or by sonographic evidence of a lack of blood flow. Cats with pulmonary edema, pleural effusion, arterial thromboembolism, or some combination of these constituted the HF group. Cats treated with cardiovascular medications chronically and those with concomitant chronic kidney disease were included.

Cats with severe clinical signs of urinary tract obstruction, acute systemic inflammation, gastrointestinal problems or some combination of these were excluded. Similarly, those with systemic hypertension (systolic blood pressure >180 mm Hg), diabetes mellitus (plasma glucose concentration ≥280 mg/dL) or hyperthyroidism (serum thyroxine concentration >5.2 μg/dL) also were excluded. Cats with severe clinical signs of urinary tract obstruction, acute systemic inflammation, gastrointestinal problems or some combination of these were excluded. Similarly, those with systemic hypertension (systolic blood pressure >180 mm Hg), diabetes mellitus (plasma glucose concentration ≥280 mg/dL) or hyperthyroidism (serum thyroxine concentration >5.2 μg/dL) also were excluded.12

2.2 | Echocardiography

Transthoracic echocardiography was performed by experienced echocardiographers using an ultrasonographic unit fitted with a 7.5–12 MHz probe. The LA/Ao ratio was derived and M-mode echocardiography performed using the right parasternal short-axis view. Relative wall thickness was calculated as follows: (the thickness of the end-diastolic intraventricular septum [IVSd] plus that of the end-diastolic left ventricular posterior wall [LVPWd]) divided by the end-diastolic left ventricular internal dimension (LVIDd). Using the left parasternal long-axis view, pulsed Doppler echocardiography was employed to measure transmitral flow velocity; the sample volume was that at the tips of the mitral valve leaflets. The mitral early diastolic flow (E wave) and late diastolic flow (A wave) velocities also were measured.

Diagnosis of HCM was made by reference to B-mode or M-mode echocardiographic data when the IVSd, LVPWd or both were ≥6.0 mm. Hypertrophic obstructive cardiomyopathy was diagnosed if left ventricular hypertrophy was present, combined with ≥1 of the following: systolic cranial motion of the mitral valve leaflet evident on M-mode echocardiography, mitral valve regurgitant flow and dynamic left ventricular outflow tract obstruction evident on color-flow Doppler echocardiography, and an increased peak (with the characteristic scimitar shape) in the left ventricular outflow velocity apparent on continuous-wave Doppler echocardiography.13

2.3 | Blood pressure measurements

Indirect blood pressure was recorded using a noninvasive oscillometric monitor (PetMAP graphic System; Ramsey Chemical Inc, Florida). All cats were allowed to acclimate for a minimum of 5 minutes. An appropriately sized cuff (an inflatable bladder of width approximately 0.4 × the circumference of the measurement site) was applied. All cats were positioned in sternal recumbency and the cuff was placed directly around the forelimb. Five or more readings were obtained from each cat and means were calculated. All measurements were recorded at the initial examinations.

| TABLE 1 | Intra- and inter-assay CV for cTnI measurements |
|----------|-----------------|
|          | Intra-assay     | Inter-assay     |
|          | Low  | Middle | High  | Low  | Middle | High  |
| Mean (ng/mL) | 0.011 | 0.022  | 1.897 | 0.016 | 0.032  | 1.848 |
| Standard deviation | 0.0005 | 0.0017 | 0.0618 | 0.0001 | 0.0015 | 0.0244 |
| CV (%)    | 16.6  | 7.9    | 3.3   | 14.6  | 4.8    | 1.3   |

2.4 | Blood biochemical data and cTnI measurements

Blood samples were collected from the cephalic vein at the initial visit, placed in heparinized and plain tubes, and centrifuged at 3000 rpm for 10 minutes at 4°C. Biochemical tests of plasma and serum thyroxine concentrations were performed in a commercial laboratory (FUJIFILM Monolith, Co, Ltd Tokyo, Japan). Plasma cTnI concentrations were measured using a chemiluminescent immunoassay detecting human cTnI (ADVIA Centaur CP TnI-ultra, Siemens Healthineers Japan, Tokyo, Japan). The measurement range was 0.006–50.0 ng/mL. To allow statistical analyses, blood concentrations below the detection limit were assigned values of 0.006 ng/mL.

The intra- and inter-assay coefficients of variation (CVs) for feline cTnI measurements were calculated (Table 1). Parallelism was determined by serial, 2-fold saline dilutions of plasma from a cat with HF and standard solutions (Liquichek Cardiac Markers Plus Control LT 3, BIO RAD, California), for 7 dilutions. The cat plasma cTnI concentration was 9.593 ng/mL, and the plasma was serially diluted. The final concentrations in the assay were 0.089-9.593 ng/mL. Similar effects of dilution were noted when human standards were employed (Figure 1).

2.5 | Statistical analysis

All data are described as medians (with interquartile ranges [IQR] or minima-to-maxima). The normality of the data was assessed using the

![FIGURE 1](image-url)
Kolmogorov–Smirnov test. The Mann-Whitney U-test was used to evaluate the significance of between-group differences. The Kruskal-Wallis test was employed to compare data among ≥3 groups. Post-hoc analysis was performed using the Dunn test. Correlations between plasma cTnI concentrations and other variables were explored by multiple regression analyses and betas were calculated. Receiver-operating characteristic curve analysis was used to evaluate the accuracy of plasma cTnI concentrations in terms of detecting cardiomyopathy and to derive various cutoff values for these concentrations (MedCalc version 12.2.1.0; MedCalc Software, Ostend, Belgium). A P value < .05 was considered to reflect statistical significance.

3 | RESULTS

The study population consisted of 88 healthy cats (43 male and 45 female) aged 0.3–16.0 years and weighing 0.9–10.5 kg. Ninety-three cats with cardiomyopathy (73 male and 20 female) aged 0.5–19.0 years and weighing 2.7–9.0 kg were enrolled as diseased cats. The most common breed was the domestic shorthair (n = 103). Other breeds studied are listed in Table 2.

In healthy cats, cTnI concentrations were distributed with a skew toward the left (lower values; Figure 2). The median concentration was 0.027 (IQR, 0.012-0.048) ng/mL. Neither sex nor age affected the cTnI concentration, but the cTnI concentrations of cats weighing >5.1 kg were significantly higher than those of cats weighing 4.1–5.0 kg (Figure 3).

In the diseased group, we included 54 HCM and 39 HOCM cats. Of these, 53 (57.0%) were in the ASYMP group, 19 (20.4%) in the LAD group, and 21 (22.6%) in the HF group; the latter group included 7 cats with arterial thromboembolism, 8 with pleural effusion, and 6 with pulmonary edema. The demographic characteristics and echocardiographic data of all cats are shown in Table 3. Cats with HF were significantly older than healthy controls. Body weight was significantly higher in the ASYMP group than in healthy controls. The plasma cTnI concentration was significantly higher in diseased cats than in healthy cats (0.027 [IQR, 0.012-0.048] ng/mL in controls versus 0.103 [IQR, 0.042-0.345] ng/mL in the ASYMP; 0.305 [IQR, 0.182-0.500] ng/mL in the LAD; and, 1.703 [IQR, 0.376-4.383] ng/mL in the HF groups; Figure 4). In addition, the plasma cTnI concentration was significantly higher in the HF group than in the ASYMP group. However, plasma cTnI concentrations overlapped significantly between the ASYMP and LAD groups.

### Table 2: Breed distributions

| Breed             | Controls | HCM |
|-------------------|----------|-----|
| Domestic Shorthair| 66       | 37  |
| Scottish Fold     | 4        | 24  |
| American Shorthair| 7        | 11  |
| Maine Coon        | 1        | 7   |
| Munchkin          | 3        | 2   |
| Norwegian Forest Cat | 0     | 4   |
| Ragdoll           | 0        | 3   |
| Russian Blue      | 2        | 0   |
| Singapura         | 1        | 1   |
| Chinchilla        | 1        | 1   |
| Other breed       | 3        | 3   |

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**FIGURE 2** The distribution of plasma cTnI concentrations in 88 healthy cats. The x-axis was truncated at 0.02 ng/mL

**FIGURE 3** Comparison of plasma cTnI concentrations by sex (A), body weight (B), and age (C) in healthy cats. A. The male group included 19 intact and 24 neutered cats, and the female group 16 intact and 29 neutered cats. B. Cats were divided into the following four groups in terms of body weight: ≤3.0 kg (n = 17), 3.1–4.0 kg (n = 26), 4.1–5.0 kg (n = 21), and ≥5.1 kg (n = 23). The weight of one cat was not recorded. †: P < .001 versus the 4.1–5.0 kg group. C. Cats were divided into the following four groups by age: ≤1.0 (n = 28), 1.1–5.0 (n = 15), 5.1–10.0 (n = 15), and ≥10.1 years (n = 29). The age of one cat was not recorded.
Multiple regression analyses showed that IVSd, LVPWd, relative wall thickness, and serum thyroxine concentration predicted the plasma cTnI concentration (r = 5.56; P < .001; Table 4).

The sensitivities and specificities of various cTnI cutoffs for detecting the severity of cardiomyopathy are shown in Table 5. To distinguish ASYMP cats or cats with more serious disease from healthy cats, a plasma concentration of 0.163 ng/mL provided sensitivity of 62.0% and specificity of 100%. To distinguish cats with LAD from those without LAD (ie, healthy and ASYMP cats), a cutoff of 0.213 ng/mL

### TABLE 3  Demographic, biochemical, and echocardiographic data

|                     | Controls | ASYMP | LAD | HF |
|---------------------|----------|-------|-----|----|
| Number              | 88       | 53    | 19  | 21 |
| Sex (male/female)   | 43/45    | 42/11 | 13/6| 18/3|
| Age (years)         | 6.0 (1.0–11.4) | 4.0 (1.4–10.2) | 5.9 (3.6–8.8) | 11.0 (4.3–13.5)† |
| Body weight (kg)    | 3.9 (3.0–4.7) | 4.8 (4.0–5.5)† | 4.5 (4.1–5.4) | 4.6 (4.0–5.4) |
| Heart rate (bpm)    | 180 (163–200) | 200 (173–220) | 205 (168–217) | 170 (143–198) |
| Systolic blood pressure (mm Hg) | 130 (145–157) | 142 (132–160) | 136 (126–146) | 127 (105–146) |
| Urea nitrogen (mg/dL) | 24 (21–28) | 26 (22–29) | 26 (24–32) | 36 (31–46)‡ # |
| Creatinine (mg/dL)  | 1.3 (1.1–1.5) | 1.4 (1.2–1.7) | 1.6 (1.3–1.8) | 1.7 (1.2–2.0) |
| Thyroxine (µg/dL)   | 2.0 (1.7–2.5) | 2.0 (1.7–2.7) | 1.7 (1.5–2.7) | 0.6 (0.9–2.1)† |

**Echocardiography**

|                     | IVSd (mm) | LVIDd (mm) | LVPWd (mm) | Relative wall thickness | E wave (cm/s) |
|---------------------|----------|------------|------------|------------------------|--------------|
| Controls            | 4.1 (3.6–4.6) | 14.4 (13.0–15.9) | 4.0 (3.5–4.7) | 0.57 (0.47–0.67) | 63.9 (52.7–71.6) |
| ASYMP               | 6.5 (5.2–7.1)† | 14.3 (12.0–15.6) | 5.9 (5.1–6.6)† | 0.85 (0.74–1.09)† | 64.5 (55.2–83.0) |
| LAD                 | 6.1 (5.3–7.3)‡ | 14.4 (12.8–16.7) | 7.2 (4.9–8.2)‡ | 0.87 (0.72–1.14)‡ | 100.5 (83.1–110.2)‡ # |
| HF                  | 6.4 (5.9–7.2)‡ | 14.5 (12.4–15.7) | 7.0 (6.1–8.9)‡ | 0.93 (0.73–1.17)‡ | 84.3 (68.4–98.1)† |

Data are expressed as medians (IQR).

**Abbreviations**: ASYMP, asymptomatic cats without left atrial dilatation; E wave, mitral early diastolic flow; HF, cats with heart failure; IVSd, end-diastolic intraventricular septum; LA/Ao ratio, left atrium-to-aorta ratio; LAD, asymptomatic cats with left atrial dilatation; LVIDd, end-diastolic left ventricular internal dimension; LVPWd, end-diastolic left ventricular posterior wall.

*: P < .05 versus healthy controls, †: P < .01 versus healthy controls, ‡: P < .001 versus healthy controls, #: P < .001 versus the ASYMP group.

**FIGURE 4** Plasma cTnI concentrations in healthy control and cardiomyopathic cats. The central lines in the boxes represent the medians, and the tops and bottoms of the boxes the 75th and 25th percentiles, respectively. Abbreviations: ASYMP, asymptomatic cats without left atrial dilatation; LAD, asymptomatic cats with left atrial dilatation; LVIDd, left ventricular internal dimension; LVPWd, end-diastolic left ventricular posterior wall; b, standardized partial regression coefficient.

**TABLE 4  Results of multiple regression analyses comparing plasma cTnI concentration and other variables**

|     | B          | F value | P value |
|-----|------------|---------|---------|
| Age | -0.086     | 0.954   | 0.330   |
| Body weight | -0.016     | 0.028   | 0.867   |
| Heart rate | -0.124     | 2.206   | 0.140   |
| Systolic blood pressure | -0.094     | 1.129   | 0.290   |
| Urea nitrogen | 0.136     | 1.148   | 0.286   |
| Creatinine | -0.080     | 0.428   | 0.514   |
| Thyroxine | -0.199     | 5.384   | 0.022   |
| IVSd | 0.254     | 4.138   | 0.044   |
| LVIDd | -0.171     | 1.768   | 0.186   |
| LVPWd | 0.371     | 7.956   | 0.005   |
| Relative wall thickness | -0.563     | 9.325   | 0.003   |
| LA/Ao ratio | 0.093     | 0.878   | 0.350   |
| E wave velocity | -0.158     | 2.824   | 0.095   |

**Abbreviations**: E wave, mitral early diastolic flow; IVSd, end-diastolic intraventricular septum; LAD, asymptomatic cats with left atrial dilatation; LVIDd, end-diastolic left ventricular internal dimension; LVPWd, end-diastolic left ventricular posterior wall; b, standardized partial regression coefficient.
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TABLE 5  Receiver-operating curve analyses for detection of cats with HCM

|        | ASYMP | LAD   | HF    |
|--------|-------|-------|-------|
| Cutoff value (ng/mL) | 0.163 | 0.213 | 0.234 |
| AUC    | 0.85  | 0.86  | 0.93  |
| 95% confidence interval | 0.79-0.90 | 0.80-0.91 | 0.88-0.96 |
| Sensitivity (%) | 62.0 | 846. | 95.0 |
| Specificity (%) | 100 | 84.9 | 77.8 |
| FPR (%) | 0.0 | 15.1 | 22.2 |
| FNR (%) | 38.0 | 15.4 | 5.0 |
| PPV (%) | 100.0 | 61.1 | 35.2 |
| NPV (%) | 71.1 | 95.2 | 99.2 |

Abbreviations: ASYMP, asymptomatic cats without left atrial dilatation; AUC, area under the receiver-operating characteristic curve; FNR, false negative ratio; FPR, false positive ratio; HF, cats with heart failure; LAD, asymptomatic cats with left atrial dilatation; NPV, negative predictive value; PPV, positive predictive value.

provided sensitivity of 84.6% and specificity of 84.9%. To distinguish cats with HF from those without HF, a cutoff of 0.234 ng/mL provided sensitivity of 95.0% and specificity of 77.8%. The areas under the receiver-operating characteristic curves were 0.85, 0.86, and 0.93, respectively.

4 | DISCUSSION

We confirmed that a chemiluminescent immunoassay for human cTnI is applicable for cats; the median plasma cTnI concentration was 0.027 (IQR, 0.012-0.048) ng/mL in healthy cats. The plasma cTnI concentration reflects the severity of HCM in cats, including the severity of HOCM. If other causes of cardiac injury are ruled out, a plasma cTnI concentration reflects the severity of HCM in cats, including the severity of CHF.31,32 One study found that plasma cTnI concentrations were significantly increased in cats with CHF (n = 6) were significantly higher than those in cats without CHF (n = 3).13 However, another study reported no difference (6 cats with CHF and 10 without CHF).13 These studies enrolled small numbers of animals, and the clinical implications of cTnI for assessing HCM severity remain controversial. We found that plasma cTnI concentrations were significantly increased in cats with HCM (including HOCM) compared with healthy controls, and concentrations in the HF group were significantly higher than in the ASYMP and LAD groups. These results suggest that plasma cTnI concentrations reflect HCM severity, especially HF, in cats.

Increased cTnI concentrations are thought to be useful for evaluating HCM disease severity, especially in cats with CHF.28,31 One study found that a plasma cTnI concentration >0.157 ng/mL provided 85% sensitivity and 97% specificity when used to diagnose HCM, regardless of disease severity.14 In addition, a high plasma cTnI concentration (>0.7 ng/mL) predicted poor prognosis in cats with HCM, independent of the presence of HF or LAD.33 Although these studies measured cTnI concentrations using a conventional method, the diagnostic utility of the current assay at various stages of HCM in cats has been unclear. We found that a plasma cTnI concentration >0.163 ng/mL identified ASYMP cats with low sensitivity, but a concentration ≤0.163 ng/mL served as an excellent cutoff to exclude HCM. Asymptomatic HCM diagnosed by echocardiography may include pseudohypertrophy such as changes associated with dehydration and tachycardia. In addition, because some cats in the ASYMP group had normal cTnI concentrations, caution should be taken when diagnosing early stage HCM based on the cTnI concentration alone. In contrast, the use of plasma cTnI concentrations >0.213 and 0.234 ng/mL to identify HCM accompanied by LAD and HF provided high sensitivity and specificity, respectively. A plasma cTnI concentration >0.234 ng/mL may be a useful cutoff for predicting cats with severe HCM.

Other types of heart disease may affect cTnI concentrations.31,34 Increased cTnI concentrations have been reported in dogs with mitral valve disease, cardiomyopathy, and cardiac hemangiosarcoma.27,30,35 The cTnI concentration may support echocardiographic data but may be attributable to variations in the plasma and sera tested, different populations or both.

Regarding the distribution of cTnI in healthy cats, a previous study found that neither sex nor age significantly affected the cTnI concentration in 35 healthy cats; also, the concentration was not affected by breed (British Shorthairs, Maine Coons, and Norwegian Forest Cats).17

We studied a large population of healthy cats and found that the cTnI concentration varied significantly by body weight. One possible explanation for this finding is that heavier cats may exhibit more ventricular hypertrophy.23,24 In particular, body weight correlated with IVSd and LVPWd values in pure-bred cats.25,26 Ventricular hypertrophy associated with body weight may increase the concentration of circulating cTnI. Further studies are needed to clarify the relationship between body weight and cTnI concentration.

Measurements of cTnI concentrations are used to diagnose heart disease in humans and dogs.27-30 In previous studies, serum cTnI concentrations were significantly increased in HCM cats compared with those in healthy cats.13-15 A study showed that plasma cTnI concentrations in cats with CHF (n = 6) were significantly higher than those in cats without CHF (n = 3).14 However, another study reported no difference (6 cats with CHF and 10 without CHF).13 These studies enrolled small numbers of animals, and the clinical implications of cTnI for assessing HCM severity remain controversial. We found that plasma cTnI concentrations were significantly increased in cats with HCM (including HOCM) compared with healthy controls, and concentrations in the HF group were significantly higher than in the ASYMP and LAD groups. These results suggest that plasma cTnI concentrations reflect HCM severity, especially HF, in cats.

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Other types of heart disease may affect cTnI concentrations.31,34 Increased cTnI concentrations have been reported in dogs with mitral valve disease, cardiomyopathy, and cardiac hemangiosarcoma.27,30,35 The cTnI concentration may support echocardiographic data but
cannot be used alone to diagnose any cardiac disease. Furthermore, many disease processes trigger myocardial injury, even in cats without primary cardiac disease. Increased cTnI concentrations have been reported in animals with systemic inflammatory disease, trauma, and hyperthyroidism. Such possible confounders should be considered when measuring cTnI concentrations in cats.

5 | LIMITATIONS

We included cats treated with cardiovascular medications; such animals often are encountered in clinical practice. Because the plasma cTnI concentrations in cats with historical CHF did not significantly differ from those in cats without clinical signs, we cannot rule out the possibility that the use of cardiovascular drugs affected our results. In particular, we included cats with chronic kidney disease in our diseased group, and cTnI concentrations often are increased in dogs and cats with azotemic renal failure, which indicates that these conditions often trigger myocardial injury.

6 | CONCLUSION

The plasma cTnI concentration reflects the severity of disease in cats with HCM, including HOCM. A plasma cTnI concentration <0.163 ng/mL likely excludes HCM, and a concentration ≥0.234 ng/mL may identify cats with severe HCM. Our results suggest that if other causes of cardiac injury have been ruled out, measuring cTnI provides additional information that is useful for assessing the severity of HCM.

CONFLICT OF INTEREST DECLARATION

The authors declare that they have no conflict of interest with the contents of this article.

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.

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