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Diagnostic Value of Echocardiography in Cats With and Without Ultrasonographic Evidence of Renal Infarction

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ABSTRACT

Background: Revisiting the association between heart disease and renal infarction (RI) in cats is relevant to determine whether those with RI should undergo echocardiographic screening.

Objective: Compare the relative frequency of echocardiographically detectable heart disease and other comorbidities in cats with and without ultrasonographic evidence of RI.

Animals: A total of 826 cats that underwent concurrent abdominal ultrasonography and transthoracic echocardiography and were assigned a cardiac diagnosis.

Methods: Two-center cross-sectional study with a study population recruitment period from January 1, 2011 to June 15, 2021. Demographic, clinical, clinicopathologic, and ultrasonographic data were recorded. Available echocardiographic images were reviewed to assign a standardized cardiac diagnosis. Occult heart disease was defined as structural heart disease without clinical signs of congestive heart failure. Risk factors for RI were evaluated by univariable or multivariable logistic regression.

Results: The relative frequency of structural heart disease in cats with and without RI was 63% (114/181) and 46% (297/645), respectively (adjusted odds ratio [OR] 95% confidence interval [CI], 1.6; 1.2–2.3). Older age ($p = 0.03$), higher maximum end-diastolic left ventricular wall thickness ($p = 0.02$), higher systolic blood pressure ($p = 0.02$), auscultable cardiac abnormalities other than murmur ($p = 0.04$), and diagnosis of acute kidney injury ($p = 0.002$), chronic kidney disease ($p = 0.005$), and occult heart disease (OR [95% CI], 2.4 [1.7–3.4]; $p \leq 0.001$) were associated with increased risk of RI. Strength and statistical significance of associations varied by site.

Conclusions and Clinical Importance: Occult heart disease is more frequent in cats with RI, and echocardiographic screening of these cats should be considered.

Renal infarction (RI) is the compromise of arterial blood supply to the kidney caused by occlusion of the renal artery or its segmental branches [1]. Ultrasonographically, RI can be identified as wedge-shaped cortical lesions perpendicular to the capsule [2]. Although these lesions might represent cortical scarring from other causes [3], renal lesions interpreted as chronic infarcts can be identified incidentally in cats during routine ultrasonographic evaluation for other conditions [4, 5].

Abbreviations: AKI, acute kidney injury; AUS, abdominal ultrasound; CKD, chronic kidney disease; HCM, hypertrophic cardiomyopathy; LA:Ao, left atrium: aortic root diameter ratio; LV, left ventricular; NoRI, no renal infarct group; RI, renal infarction.

Renal artery lesions, in situ thrombosis, thromboembolism, and idiopathic infarction are leading causes of RI in people [1, 6–8]. Although few studies have investigated the causes of RI in cats, diseases associated with a hypercoagulable state and arterial thromboembolism in this species include hyperthyroidism, pancreatitis, neoplasia, and cardiomyopathies [9, 10]. It is therefore plausible that these conditions could increase the risk for RI in cats.

Idiopathic (primary) hypertrophic cardiomyopathy (HCM), the most common heart disease in cats, has a reported prevalence of 16% in the general feline population [11]. Affected cats can be presented with or without clinical signs of congestive heart failure (CHF) or arterial thromboembolism [12–14]. Although thromboemboli affecting the aortic trifurcation are most commonly recognized, the kidneys and other organs also can be affected [15]. In one study, cats with RI ($n = 309$) were 4.5 times more likely to have HCM than those without RI ($n = 291$) [16], and the authors recommended echocardiographic screening for occult cardiomyopathies in cats with RI. However, in that study, occult cardiomyopathy was not defined. Based on our clinical experience, we did not suspect such a strong association between heart disease and RI in the cats seen at our institutions and hypothesized that the strength of the association might vary among different populations. Revisiting this association in different samples of cats is relevant to determine if echocardiographic screening in the absence of other indicators of heart disease is indicated for cats with RI.

Our main objectives were (1) to describe the relative frequency of ultrasonographically diagnosed RI in cats evaluated at two veterinary teaching hospitals and the relative frequency of echocardiographic examination in cats with and without ultrasonographic evidence of RI; and (2) to compare the relative frequency of echocardiographically detectable heart disease in cats with and without ultrasonographic evidence of RI. We hypothesized that (1) the relative frequency of echocardiographic examination would be similar in cats with and without RI, and (2) based on prior literature [16], that cats with RI would have a higher relative frequency of structural heart disease. A secondary, exploratory objective was to compare other comorbidities associated with RI in this same sample of cats. We hypothesized that cats with RI would have a higher relative frequency of comorbidities previously associated with hypercoagulable states, including neoplasia, hyperthyroidism, and pancreatitis.

1 | Materials and Methods

1.1 | Study Design

Ours was a two-center cross-sectional study (i.e., exposure and outcome were determined at the same time point), with a study population recruitment period from January 1, 2011, to June 15, 2021. Electronic medical records from the University of Georgia (Site A) and North Carolina State University (Site B) Veterinary Teaching Hospitals were retrospectively reviewed to identify cats that underwent abdominal ultrasonography (AUS). These records were used to determine the proportion of ultrasonographic examinations with evidence of RI. Cats then were divided into those with reported ultrasonographic evidence of RI (RI group) and those without (no renal infarct [NoRI] group). The proportion of cats that underwent echocardiography during the same hospital visit was determined for each group, and the reason for performing echocardiography was recorded. If a cat underwent AUS and echocardiography during more than one visit, data were included from only the first visit during which both examinations were performed.

1.2 | Medical Record Review

Medical records of individual cats for which AUS and echocardiography were performed during the same hospital visit were retrospectively reviewed in depth, and demographic and clinical information was collected. Demographic information included age, breed, sex, and reproductive status at the time of examination. Historical and physical examination data included prior history of echocardiographically diagnosed heart disease; diagnosis of comorbidities previously implicated in thromboembolic disease, including acute kidney injury (AKI), chronic kidney disease (CKD), hyperthyroidism, neoplasia, clinical diagnosis of pancreatitis [17, 18], and systemic arterial hypertension (defined as indirect systolic blood pressure ≥ 160 mmHg) [19]; medications administered before the hospital visit and ongoing medications listed in the discharge summary (limited to corticosteroids, antiplatelet and anticoagulant medications, erythropoiesis-stimulating agents, antihypertensive medications, and methimazole); body weight, presence or absence of a heart murmur or cardiac auscultation abnormality other than a heart murmur (e.g., arrhythmia, gallop sound), and presence or absence of clinical signs or diagnostic imaging findings consistent with a diagnosis of CHF (e.g., dyspnea, tachypnea, orthopnea, collapse, restrictive breathing pattern caused by pleural effusion, cardiogenic pulmonary edema, respiratory signs responsive to furosemide). Current or historical clinical signs suggestive of arterial thromboembolism to an extremity (i.e., weak or absent peripheral arterial pulses, pain on palpation, cold temperature, pallor, cyanosis, limb weakness, or a combination of these), and affected extremities were recorded. Recorded clinicopathologic data included hematocrit, platelet count, presence of platelet clumping, clotting times (prothrombin and activated partial thromboplastin times), serum creatinine concentration, and symmetric dimethylarginine concentration, urine specific gravity (USG), and urinary protein-to-creatinine ratio.

Abdominal ultrasonographic findings were extracted from imaging reports and included the presence or absence of RI (and chronicity of RI), degenerative renal changes (i.e., small kidneys [renal length < 3.2 cm] [2], irregularly shaped kidneys, decreased corticomedullary distinction, renal cysts, focal or diffuse cortical or medullary hyperechogenicity or both, medullary band sign [20], renal parenchymal mineralization, or a combination of these); RI in an otherwise structurally normal kidney was not interpreted as a degenerative renal change; changes that could be consistent with AKI (i.e., pyelectasia, hyperechoic renal cortices, ureteral distension, ureteral obstruction, renomegaly, peri-nephric effusion, hydronephrosis, renal mass effect, or a combination of these), pancreatic abnormalities, or evidence of suspected extra-renal thrombi or infarction.

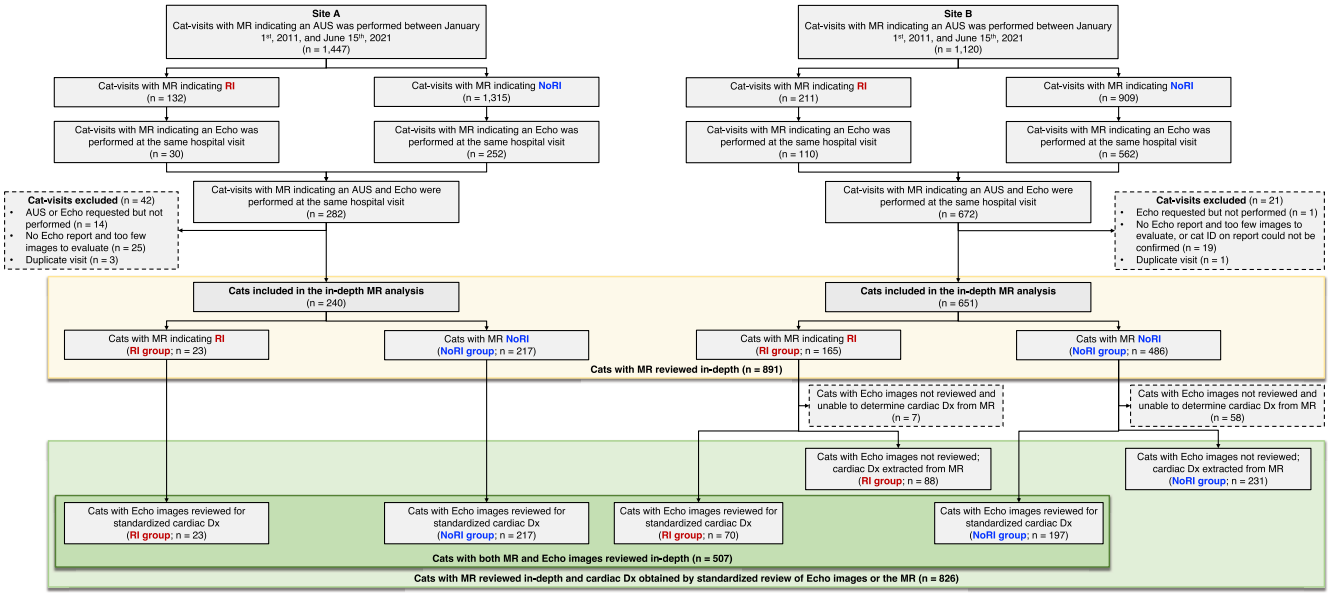

FIGURE 1 | Number of abdominal ultrasonographic and echocardiographic evaluations performed, frequency of renal infarction, and exclusion criteria for cats evaluated between January 1, 2011, and June 15, 2021, at two Veterinary Teaching Hospitals, site A (University of Georgia) and site B (North Carolina State University). AUS, abdominal ultrasound examination; Dx, diagnosis; Echo, echocardiogram; ID, identification; MR, medical record; NoRI, no ultrasonographic evidence of renal infarction; RI, ultrasonographic evidence of renal infarction.

Infarcts were classified as acute when appearing as mass-like hypoechoic or mixed echogenicity lesions or chronic when appearing as "wedge-shaped" hyperechoic regions within the renal cortex [21, 22].

1.3 | Cardiac Evaluation and Classification

Echocardiographic study images were retrospectively evaluated by a board-certified veterinary cardiologist (A.E.C., site A) or a cardiologist-in-training (C.M., site B), who assigned a standardized echocardiographic diagnosis (described below). For each case, the following echocardiographic variables were extracted from the echocardiographic report or, if not listed in the report, measured or calculated from available images: two-dimensional (2D) left atrial-to-aortic root diameter ratio (LA:Ao_{Sax}), calculated from measurements taken from a right parasternal short-axis view at the heart base; maximum average end-diastolic left ventricular (LV) wall thickness (mm) and end-diastolic LV internal diameter (cm); and LV fractional shortening (%). The presence or absence of each of the following was noted: systolic anterior motion of the mitral valve, spontaneous echogenic contrast, intracardiac thrombus, pleural effusion, and pericardial effusion. The presence or absence of atrial fibrillation or other cardiac arrhythmias also was recorded.

The presence or absence of LV concentric hypertrophy (i.e., end-diastolic wall thickness ≥ 6 mm affecting any LV segment) [23] or left atrial enlargement (i.e., LA:$Ao_{Sax} > 1.5$, or if LA:Ao_{Sax} was unavailable, subjective assessment) [23] also was recorded. For cases meeting the criterion for LV concentric hypertrophy, LV pseudohypertrophy was diagnosed when end-diastolic LV internal diameter was < 1.2 cm [24, 25] and the patient's history, physical examination, and biochemical findings suggested that intravascular volume contraction was likely.

Because of changes in reporting software and limited availability of echocardiographic images obtained before 2018, for cats evaluated at Site B, the review of echocardiographic studies and subsequent recording of cardiac variables was limited to cases evaluated between 2018 and 2021. For cases with images not reviewed, an echocardiographic diagnosis was extracted from the medical record if the diagnosis was deemed plausible by the study investigators (S.G., A.E.C., C.Z., T.H., A.A., and M.B.); (Figure 1).

Additional recorded echocardiographic variables included the stated reason for performing the echocardiogram and whether "renal infarction" was mentioned on the request. A final echocardiographic diagnosis was assigned and further classified into one of three main categories: normal (including cases without echocardiographic abnormalities and those with isolated, benign findings of dynamic right ventricular outflow tract obstruction or physiologic valvular insufficiency), physiologic abnormalities (including LV pseudohypertrophy and changes secondary to iatrogenic volume overload [e.g., transfusion-associated circulatory overload, corticosteroid-induced volume overload, and changes secondary to anemia]), and structural heart disease. Structural heart disease was further subcategorized into HCM phenotype (comprising idiopathic HCM, hypertensive cardiomyopathy, thyrotoxic cardiomyopathy, and other causes of HCM phenotype, including acromegaly, infiltrative neoplasia, and transient myocardial thickening, as well as cats with LV concentric hypertrophy of unknown cause), other cardiomyopathies (comprising dilated, restrictive, and arrhythmogenic right ventricular cardiomyopathies and cardiomyopathy of nonspecific phenotype), and other heart diseases (comprising congenital heart diseases, cardiac or pericardial masses, and acquired valvular heart disease). Classification of cardiomyopathies was in accordance with guidelines set forth by the American College of

Veterinary Internal Medicine [23]. An HCM phenotype was assigned in cats with generalized or regional LV concentric hypertrophy (i.e., end-diastolic wall thickness ≥ 6 mm) with a non-dilated left ventricle.

Finally, cats with structural heart disease were grouped according to whether their heart disease was occult or overt. For the purposes of our study, cats were considered to have occult heart disease when echocardiographic evidence of structural heart disease was present in the absence of overt clinical signs of CHF.

1.4 | Statistical Analysis

Statistical analyses were performed using commercially available software (SAS 9.4, Cary, NC; and GraphPad Prism for Mac, version 10.1.0, GraphPad Software Inc., La Jolla, CA). A significance threshold of 0.05 was used. The assumption of normality was evaluated by inspection of QQ- and PP-plots, histograms, and skewness. Continuous variables were summarized descriptively with mean ± SD, median (range), or mean (95% confidence interval [CI]), as appropriate. Normally distributed variables were compared between groups using a one-way analysis of variance (ANOVA), and non-normally distributed continuous variables were compared using the Kruskal–Wallis test. Proportions were compared between groups using the χ^2 test. Only selected comparisons were made to avoid increasing the likelihood of type 1 error. A χ^2 test was used to assess the significance of the association between RI and having echocardiography performed.

For analyses of association between RI and heart disease (main study objective), cats with a final echocardiographic diagnosis of normal or physiologic abnormality were combined, and only cats for which a standardized cardiac diagnosis could be assigned based on available data were included. A univariable logistic regression model was used to estimate the unconditional association between RI and heart disease, using the odds ratio. A multivariable logistic regression then was developed, adjusting for the effect of site. Site adjustment resulted in a decrease in the odds of heart disease in cats with RI compared with the odds of heart disease in cats without RI, leading us to conclude that site was a relatively strong confounder in the association between RI and heart disease. These analyses were repeated for the subset of cats for which a cardiac diagnosis was assigned after retrospective review of available echocardiographic images.

Evaluation of extra-cardiac risk factors for RI was conducted on a dataset including all cats that underwent AUS and echocardiography during the same hospital visit, for which the medical record was reviewed in depth. Univariable logistic regression models were developed to quantify the association between biologically plausible cardiac and extra-cardiac risk factors and the presence of RI. Because evaluation of these risk factors was exploratory (secondary study objective), unadjusted analyses were performed; data by study site and using both sites combined are presented. For these analyses, if one of the contingency table cells had a zero cell count (i.e., quasi-separation was present), Firth's bias-reduced penalized-logistic regression was used. Log-likelihood p values and ORs with profile-likelihood OR confidence limits were reported for all logistic regressions. Logistic regressions were performed for all cases and separately by site. Risk factor p values were adjusted for multiple comparisons using the linear step-up method of Benjamini and Hochberg (1995).

For the purposes of statistical analyses, activated partial thromboplastin times reported as >120 or >200 s were assigned a value of 120 and 200 s, respectively, and urine specific gravity values reported as >1.050 were assigned a value of 1.050.

2 | Results

2.1 | Frequency of RI and Echocardiographic Evaluation

Throughout the recruitment period, a total of 1447 and 1120 AUS examinations were performed in cats at study Sites A and B, respectively (Figure 1). The overall prevalence of ultrasonographically diagnosed RI was 15% (95% confidence interval [CI], 14%–17%); 9% (95% CI, 8%–11%) of cat visits at Site A versus 19% (95% CI, 17%–21%) of cat visits at Site B ($p < 0.001$).

The proportion of cat visits with an AUS and concurrent echocardiogram was significantly lower at Site A (20% [282/1447]) than Site B (60% [672/1120]; $p < 0.001$). The proportion of cat visits in the entire study sample (i.e., both Site A and Site B) during which both AUS and echocardiography were performed was similar between the RI (41% [140/343]) and NoRI (37% [814/2224]) groups ($p = 0.13$). The proportion of cat visits that received both imaging studies was not different between the RI (23% [30/132]) and NoRI (19% [252/1315]) groups at Site A ($p = 0.32$); however, RI cat visits at Site B were significantly less likely to have received both an AUS and echocardiogram than NoRI cat visits (52% [110/211] vs. 62% [562/909]; $p = 0.01$).

Fifteen percent (42/282) of Site A cat visits and 3% (21/672) of Site B cat visits were excluded from the in-depth analysis because of lack of information related to their imaging studies or having more than one visit per cat, leaving a total of 891 individual cats for which in-depth review of the medical record was performed. Overall, RI was diagnosed by ultrasonography in 21% (188/891) of cats evaluated with both an AUS and echocardiogram (95% CI, 19%–24%). The relative frequency of RI was higher at Site B (165/651; 25% [95% CI, 12%–29%]) compared with Site A (23/240; 10% [95% CI, 6%–14%]; $p < 0.001$).

2.2 | Demographic, Clinical, and Clinicopathologic Data

Tables 1 and S1 summarize the demographic, clinical, and clinicopathologic characteristics of cats evaluated at Site A and Site B, with or without evidence of RI, that had both AUS and echocardiography performed during the same hospital visit and underwent in-depth medical record review. Overall, the majority of cats included in our study were mature adult or senior [26] and of no defined breed. Male cats were overrepresented in a 1.3:1 male-to-female ratio (505 males and 386 females). Most included cats did not have a prior history of echocardiographically diagnosed heart disease. A heart murmur and auscultable

TABLE 1 | Demographic and clinical information for cats that had abdominal ultrasonography and echocardiography performed at the same visit to one of two Veterinary Teaching Hospitals (Site A [University of Georgia] and Site B [North Carolina State University]). Cats are grouped according to the presence or absence of ultrasonographic evidence of renal infarction (RI). The number (%) of cats in the group with available information is shown if it differs from the total number of cats in that group. Categorical data are shown as number and percentage of cats in the group with available information. Continuous data are shown as median (range).

	Site A			Site B			Both sites		
Variable	**Group No RI (*n* = 217)**	**Group RI (*n* = 23)**	**All Site A cats (*n* = 240)**	**Group No RI (*n* = 486)**	**Group RI (*n* = 165)**	**All Site B Cats (*n* = 651)**	**Group No RI (*n* = 703)**	**Group RI (*n* = 188)**	**All cats (*n* = 891)**
Age (years)									
N with information	217	23	240	486	165	651	703	188	891
Median (range)	11.00 (0.3–21.1)	9.7 (2.0–16.5)	10.7 (0.3–21.1)	11.0 (0.1–23.2)	12 (0.5–19.7)	11.29 (0.1–23.2)	11 (0.1–23.2)	12 (0.5–19.7)	11.0 (0.1–23.2)
Body weight (kg)									
N with information	217	22	239	486	165	651	703	187	890
Median (range)	4.50 (2.1–10.9)	4.7 (2.4–6.9)	4.5 (2.1–10.9)	4.51 (1.7–12.9)	4.4 (2.0–9.4)	4.5 (1.7–12.9)	4.5 (1.7–12.9)	4.5 (2.2–9.4)	4.5 (3.6–12.9)
Sex (*N* [% of column])									
Male, neutered	129 (59%)	11 (48%)	140 (58%)	275 (57%)	84 (51%)	359 (55%)	404 (57%)	95 (51%)	499 (56%)
Male, intact	4 (2%)	0 (0%)	4 (2%)	2 (0.4%)	0 (0%)	2 (0.3%)	6 (1%)	0 (0%)	6 (1%)
Female, spayed	83 (38%)	11 (48%)	94 (39%)	206 (42%)	79 (48%)	285 (44%)	289 (41%)	90 (48%)	379 (43%)
Female, intact	1 (1%)	1 (4%)	2 (1%)	3 (1%)	2 (1%)	5 (1%)	4 (1%)	3 (2%)	7 (1%)
Breed* (*N* [% of column])									
Mixed	170 (78%)	18 (78%)	188 (78%)	372 (77%)	145 (88%)	517 (79%)	542 (77%)	163 (87%)	705 (79%)
Maine Coon	12 (6%)	0 (0%)	12 (5%)	32 (7%)	3 (2%)	35 (5%)	44 (6%)	3 (2%)	47 (5%)
Other	35 (16%)	5 (22%)	40 (17%)	82 (17%)	17 (10%)	99 (15%)	117 (17%)	22 (12%)	139 (16%)

(Continues)

TABLE 1 | (Continued)

Variable	Site A			Site B			Both sites		
	Group No RI ($n=217$)	Group RI ($n=23$)	All Site A cats ($n=240$)	Group No RI ($n=486$)	Group RI ($n=165$)	All Site B Cats ($n=651$)	Group No RI ($n=703$)	Group RI ($n=188$)	All cats ($n=891$)
Prior history of heart disease diagnosed via echocardiogram									
N (% of group) with information	216 (99%)	22 (96%)	238 (99%)	486 (100%)	165 (100%)	651 (100%)	702 (99%)	187 (99%)	889 (99%)
No	207 (96%)	21 (96%)	228 (96%)	421 (87%)	134 (81%)	555 (85%)	628 (90%)	155 (83%)	783 (88%)
Yes	9 (4%)	1 (5%)	10 (4%)	65 (13%)	31 (19%)	96 (15%)	74 (11%)	32 (17%)	106 (12%)
Auscultable cardiac abnormalities									
N (% of group) with information	216 (99%)	22 (96%)	238 (99%)	486 (100%)	165 (100%)	651 (100%)	702 (99%)	187 (99%)	889 (99%)
No	209 (97%)	22 (100%)	231 (97%)	452 (93%)	143 (87%)	595 (91%)	661 (94%)	165 (88%)	826 (93%)
Yes	7 (3%)	0 (0%)	7 (3%)	34 (7%)	22 (13%)	56 (9%)	41 (6%)	22 (12%)	63 (7%)
Heart murmur									
N (% of group) with information	216 (99%)	22 (96%)	238 (99%)	486 (100%)	165 (100%)	651 (100%)	702 (99%)	187 (99%)	889 (99%)
No	181 (84%)	18 (82%)	199 (84%)	324 (67%)	107 (65%)	431 (66%)	505 (72%)	125 (67%)	630 (71%)
Yes	35 (16%)	4 (18%)	39 (16%)	162 (33%)	58 (35%)	220 (34%)	197 (28%)	62 (33%)	259 (29%)
Clinical signs of aortic thromboembolism									
N with information (% of group)	217 (100%)	21 (91%)	238 (99%)	486 (100%)	165 (100%)	651 (100%)	703 (100%)	186 (99%)	889 (99%)
No	207 (95%)	18 (86%)	225 (95%)	470 (97%)	157 (95%)	627 (96%)	677 (96%)	175 (94%)	852 (96%)
Yes	10 (5%)	3 (14%)	13 (6%)	16 (3%)	8 (5%)	24 (4%)	26 (4%)	11 (6%)	37 (4%)

(Continues)

TABLE 1 | (Continued)

Variable	Site A			Site B			Both sites		
	Group No RI ($n=217$)	Group RI ($n=23$)	All Site A cats ($n=240$)	Group No RI ($n=486$)	Group RI ($n=165$)	All Site B Cats ($n=651$)	Group No RI ($n=703$)	Group RI ($n=188$)	All cats ($n=891$)
Clinical signs of thoracic limb thromboembolism									
N with information (% of group)	217 (100%)	21 (91%)	238 (99%)	486 (100%)	165 (100%)	651 (100%)	703 (100%)	186 (99%)	889 (99%)
No	214 (98%)	20 (95%)	234 (98%)	485 (99%)	163 (99%)	648 (99%)	699 (99%)	183 (98%)	882 (99%)
Yes	3 (1%)	1 (5%)	4 (2%)	1 (0.2%)	2 (1%)	3 (1%)	4 (1%)	3 (2%)	7 (1%)
Evidence of congestive heart failure									
N (% of group) with information	217 (100%)	23 (100%)	240 (100%)	486 (100%)	165 (100%)	651 (100%)	703 (100%)	188 (100%)	891 (100%)
No	195 (90%)	23 (100%)	218 (91%)	412 (85%)	144 (87%)	556 (85%)	607 (86%)	167 (89%)	774 (87%)
Yes	22 (10%)	0 (0%)	22 (9%)	74 (15%)	21 (13%)	95 (15%)	96 (14%)	21 (11%)	117 (13%)
Systolic blood pressure (mm Hg)									
N (% of group) with information	103 (48%)	10 (44%)	113 (47%)	226 (47%)	75 (46%)	301 (46%)	329 (47%)	85 (45%)	414 (47%)
Median (range)	130 (34–224)	120 (105–150)	128 (34.00–224.00)	140 (40–280)	160 (70–300)	140.00 (40.00–300.00)	132 (34–280)	150 (70–300)	138 (34–300)
Symmetric dimethyl arginine (μg/dL)									
N (% of group) with information	1 (1%)	0 (0%)	1 (0.4%)	19 (4%)	7 (4%)	26 (4%)	20 (3%)	7 (4%)	27 (3%)
Median (range)	10	N/A	10	16 (9–78)	20 (11–23)	17.50 (9.00–78.00)	16 (9–78)	20 (11–23)	17 (9–78)
Urinary protein-to-creatinine ratio									
N (% of group) with information	12 (6%)	0 (0%)	12 (5%)	33 (7%)	31 (19%)	64 (10%)	45 (6%)	31 (17%)	76 (9%)
Median (range)	0.62 (0.13–3.4)	N/A	0.62 (0.13–3.40)	0.34 (0.08–12.81)	0.48 (0.12–13.6)	0.44 (0.08–13.60)	0.39 (0.08–12.81)	0.48 (0.12–13.60)	0.47 (0.08–13.60)

*Complete information on breed distribution is provided in Table S1. "Mixed" breed refers to domestic shorthair, medium-haired, and long-haired cats.

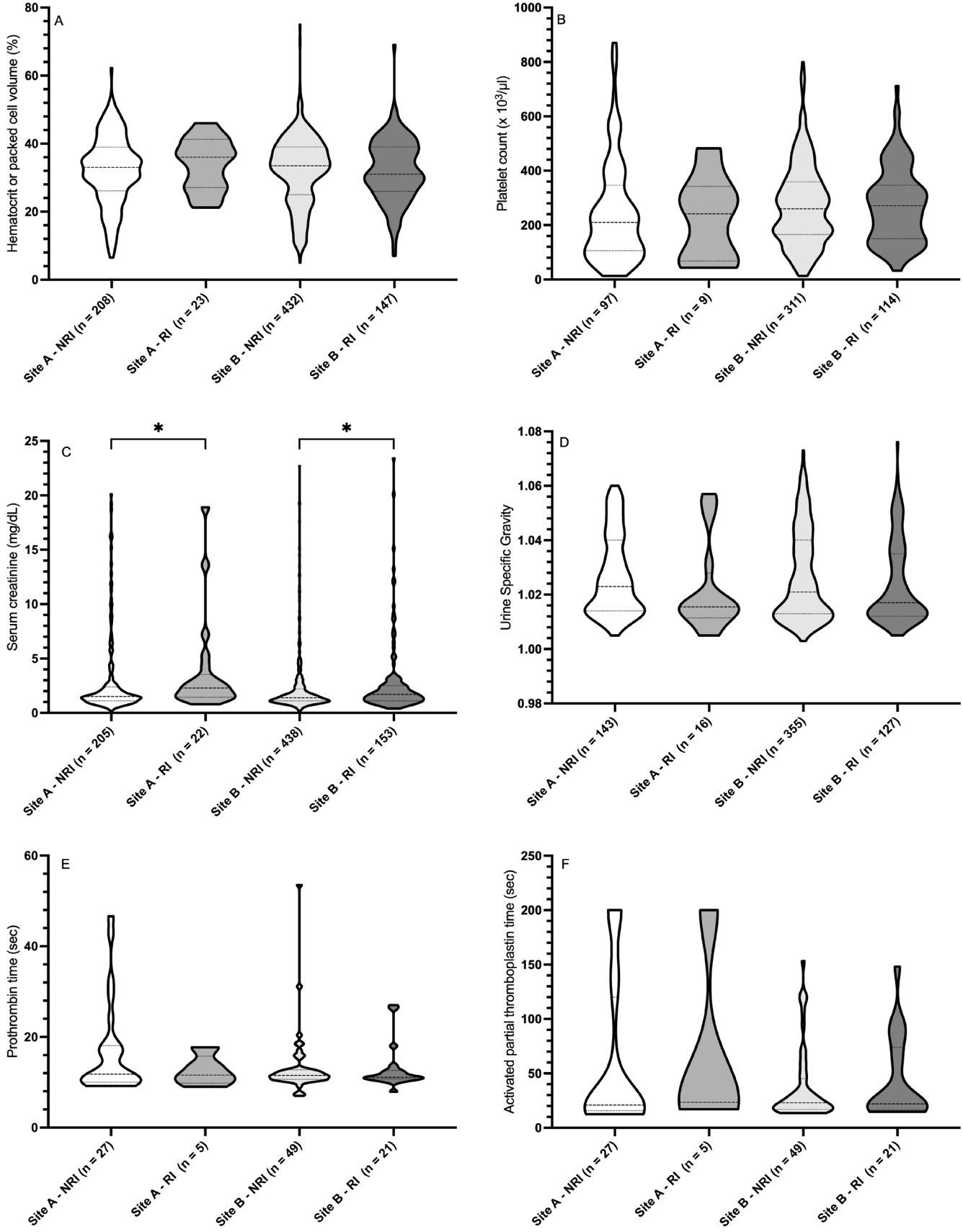

FIGURE 2 | Legend on next page.

FIGURE 2 | Violin plots of hematocrit or packed cell volume (panel A), platelet count (panel B), serum creatinine concentration (panel C), urine specific gravity (panel D), prothrombin time (panel E), and activated partial thromboplastin time (panel F) in a sample of 891 cats that underwent abdominal ultrasonographic and echocardiographic evaluation at the same visit to one of two Veterinary Teaching Hospitals (Site A [University of Georgia] and Site B [North Carolina State University]) and were diagnosed with renal infarcts (RI) or no renal infarcts (NRI). Within each violin, the dashed line represents the median, and the upper and lower dotted lines represent the 75th and 25th percentiles, respectively. The number of cats for which information is known is noted for each group. *$p < 0.05$.

cardiac abnormalities other than a murmur (e.g., arrhythmia, gallop sound) were noted in approximately 29% and 7% of cats, respectively. Only 5% of cats had clinical signs of distal aortic or thoracic limb thromboembolism, and CHF was present in a minority (approximately 13%) of cases.

Figure 2 shows selected clinicopathologic variables extracted from the medical record of each cat. At both sites, cats with RI had significantly higher serum creatinine concentrations than those with no RI (Site A, $p = 0.04$; Site B, $p = 0.03$). Serum symmetric dimethylarginine concentrations and urinary protein-to-creatinine ratios were measured in a minority of cases (Table 1).

Overall, cats were diagnosed with a range of 1–4 selected comorbidities, neoplasia being the most common.

2.3 | Infarct Chronicity and AUS Data

Information regarding RI chronicity was available for 186/188 RI cats. Infarcts were chronic in 176 (23, Site A; 153, Site B), acute in 6 (all Site B), and both acute and chronic in 4 (all Site B) cases.

Additional AUS data are summarized in Table 2. Degenerative renal changes were common, particularly in cats with RI. Acute renal changes were seen in a smaller subset of cats. Ultrasonographic evidence of pancreatic pathology was seen in approximately one-fourth of cats, and extrarenal thrombi were rare.

2.4 | Echocardiographic Data and Cardiac Diagnoses

The number of cat visits for which review of echocardiographic reports and images was possible was 240/240 (100%) at Site A and 264/651 (41%) at Site B. Echocardiographic data are presented in Table 3 and Figure 3. Information regarding the reason for performing the echocardiogram was available in 871 cats undergoing in-depth medical record review; no cat had RI listed as the reason for requesting the examination, and only three echocardiogram requests (all Site B) mentioned RI. Left atrial enlargement was common in this sample of cats. Spontaneous echogenic contrast and intracardiac thrombi were rare ($\leq 2\%$ of cases) in both groups. At Site A, but not Site B, RI cats had significantly higher maximum end-diastolic LV wall thickness than NoRI cats.

Echocardiographic diagnoses assigned to cats included in our study are listed in Tables 4 and S2. An echocardiographic diagnosis could not be assigned in 7% (65/891) of cases because of insufficient study images or medical record information. In the remaining sample, 50% (411/826) of cats were classified as having structural heart disease; 30% (73/240) at Site A and 58% (338/586) at Site B ($p < 0.001$). Most cats (342/411) with structural heart disease were diagnosed with HCM phenotype; 50% (170/342) were diagnosed with idiopathic HCM.

Atrial fibrillation was noted in only two NoRI cats (one from each site); both had structural heart disease (idiopathic HCM [$n = 1$] and unclassified cardiomyopathy [$n = 1$]).

2.5 | Renal Infarction and Heart Disease

In cats for which assignment of a cardiac diagnosis was possible ($n = 826$), the overall frequency of echocardiographically detectable heart disease was 63% (114/181) in those with ultrasonographic RI versus 46% (297/645) in those without RI. The adjusted odds of echocardiographically detectable heart disease in cats with ultrasonographic RI were 1.6 (95% CI, 1.2–2.3) times those of cats without ultrasonographic RI.

A significant difference in the frequency of heart disease between the RI and NoRI groups also was observed at each site (Site A: RI, 52% [12/23] vs. NoRI, 28% [61/217]; OR (95% CI), 2.8 (1.2–6.8); $p = 0.022$; Site B: RI, 65% [102/158] vs. NoRI, 55% [236/428]; OR (95% CI), 1.5 (1.0–2.2); $p = 0.04$). This association also was true when analyzing only cases that had echocardiographic images reviewed, for which the frequency of echocardiographically detectable heart disease was higher in cats of the RI group (65% [60/93]) compared with those in the NoRI group (42% [175/414]; adjusted OR [95% CI], 1.9 [1.2–3.1]).

Occult heart disease was diagnosed in 54% (98/181) of all cats with RI (52% [12/23] at Site A and 54% [86/158] at Site B) compared with 34% (216/645) cats without RI (19% [42/217] at Site A and 41% [174/428] at Site B; Table 5). Cats with occult heart disease had an increased risk of RI compared with cats with no structural heart disease (OR [95% CI], 2.4 [1.69–3.43]; $p < 0.001$). This increased risk remained significant when data were analyzed by site for cats at Site B (OR [95% CI], 1.71 [1.15–2.55]; $p = 0.04$) but did not reach significance when adjusted for multiple comparisons for cats at Site A (OR [95% CI], 4.08 [1.70–9.87]; $p = 0.06$; Table 6). Overall, overt heart disease was noted relatively infrequently.

For Site A cats, a significantly higher maximum average diastolic LV wall thickness was noted in the RI group (median [range], 6 mm [3.7–7.9]) compared with the NoRI group (median [range], 4.9 mm [3.1–9]; $p = 0.05$). The same was not true for cats evaluated at Site B (5.8 mm [3.7–9.9] versus 5.6 mm [4.9–10.4] for RI and NoRI groups, respectively; $p = 0.50$; Figure 3). Increasing maximum average diastolic LV wall thickness was associated with a significantly increased risk

TABLE 2 | Abdominal ultrasonographic findings for cats that had abdominal ultrasonography and echocardiography performed at the same visit to one of two Veterinary Teaching Hospitals (Site A [University of Georgia] and Site B [North Carolina State University]). Cats are grouped according to the presence or absence of ultrasonographic evidence of renal infarction (RI). For each variable, data are shown as *N* (% of cats in the group for which data is known).

	Site A			Site B			Both sites		
Variable	**Group No RI (*n* = 217)**	**Group RI (*n* = 23)**	**All Site A cats (*n* = 240)**	**All Site A cats (*n* = 240)**	**Group RI (*n* = 165)**	**All Site B cats (*n* = 651)**	**Group No RI (*n* = 703)**	**Group RI (*n* = 188)**	**All cats (*n* = 891)**
Degenerative renal changes									
N (% of group) with information	217 (100%)	23 (100%)	240 (100%)	486 (100%)	165 (100%)	651 (100%)	703 (100%)	188 (100%)	891 (100%)
No	116 (54%)	2 (9%)	118 (49%)	263 (54%)	36 (22%)	299 (46%)	379 (54%)	38 (20%)	417 (47%)
Yes	101 (47%)	21 (91%)	122 (51%)	223 (46%)	129 (78%)	352 (54%)	324 (46%)	150 (80%)	474 (53%)
Acute renal changes									
N (% of group) with information	217 (100%)	23 (100%)	240 (100%)	486 (100%)	165 (100%)	651 (100%)	703 (100%)	188 (100%)	891 (100%)
No	152 (70%)	15 (65%)	167 (70%)	426 (88%)	128 (78%)	554 (85%)	578 (82%)	143 (76%)	721 (81%)
Yes	65 (30%)	8 (35%)	73 (30%)	60 (12%)	37 (22%)	97 (15%)	125 (18%)	45 (24%)	170 (19%)
Pancreatopathy									
N (% of group) with information	217 (100%)	23 (100%)	240 (100%)	486 (100%)	163 (99%)	649 (99%)	703 (100%)	186 (99%)	889 (99%)
No	172 (79%)	19 (83%)	191 (80%)	340 (70%)	110 (68%)	450 (69%)	512 (73%)	129 (69%)	641 (72%)
Yes	45 (21%)	4 (17%)	49 (20%)	146 (30%)	53 (33%)	199 (31%)	191 (27%)	57 (31%)	248 (28%)
Extrarenal thrombi									
N (% of group) with information	217 (100%)	23 (100%)	240 (100%)	486 (100%)	165 (100%)	651 (100%)	703 (100%)	188 (100%)	891 (100%)
No	214 (99%)	23 (100%)	237 (99%)	477 (98%)	161 (98%)	638 (98%)	691 (98%)	184 (98%)	875 (98%)
Yes	3 (1%)	0 (0%)	3 (1%)	9 (2%)	4 (2%)	13 (2%)	12 (2%)	4 (2%)	16 (2%)

TABLE 3 | Echocardiographic findings for cats that had abdominal ultrasonography and echocardiography performed at the same visit to one of two Veterinary Teaching Hospitals (Site A [University of Georgia] and Site B [North Carolina State University]). Cats are grouped according to the presence or absence of ultrasonographic evidence of renal infarction (RI). For each variable, data are shown as *N* (% of cats in the group for which data is known).

	Site A			Site B			Both sites		
Variable	**Group No RI (*n* = 217)**	**Group RI (*n* = 23)**	**All Site A cats (*n* = 240)**	**Group No RI (*n* = 486)**	**Group RI (*n* = 165)**	**All Site B cats (*n* = 651)**	**Group No RI (*n* = 703**	**Group RI (*n* = 188)**	**All cats (*n* = 891)**
Renal infarct mentioned in echocardiogram request									
N (% of group) with information	199 (92%)	21 (91%)	220 (92%)	486 (100%)	165 (100%)	651 (100%)	685 (97%)	186 (99%)	871 (98%)
No	199 (100%)	21 (100%)	220 (100%)	486 (100%)	162 (98%)	648 (99%)	685 (100%)	183 (98%)	868 (99%)
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (2%)	3 (1%)	0 (0%)	3 (2%)	3 (0.3%)
Left atrial enlargement[a]									
N (% of group) with information	213 (98%)	23 (100%)	236 (98%)	194 (40%)	69 (42%)	263 (40%)	407 (58%)	92 (49%)	499 (56%)
No	176 (83%)	19 (83%)	195 (83%)	137 (71%)	47 (68%)	184 (70%)	313 (77%)	66 (72%)	379 (76%)
Yes	37 (17%)	4 (17%)	41 (17%)	57 (29%)	22 (32%)	79 (30%)	94 (23%)	26 (28%)	120 (24%)
Spontaneous echogenic contrast									
N (% of group) with information	211 (97%)	21 (91%)	232 (97%)	194 (40%)	70 (42%)	264 (41%)	405 (58%)	91 (48%)	496 (56%)
No	208 (99%)	21 (100%)	229 (99%)	189 (97%)	69 (99%)	258 (98%)	397 (98%)	90 (99%)	487 (98%)
Yes	3 (1%)	0 (0%)	3 (1%)	5 (3%)	1 (1%)	6 (2%)	8 (2%)	1 (1%)	9 (2%)
Intracardiac thrombus present									
N (% of group) with information	212 (98%)	21 (91%)	233 (97%)	194 (40%)	70 (42%)	264 (41%)	406 (58%)	91 (48%)	497 (56%)
No	210 (99%)	21 (100%)	231 (99%)	194 (100%)	70 (100%)	264 (100%)	404 (99%)	91 (100%)	495 (99%)
Yes	2 (1%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	2 (0.4%)

(Continues)

TABLE 3 | (Continued)

Variable	Site A			Site B			Both sites		
	Group No RI ($n=217$)	Group RI ($n=23$)	All Site A cats ($n=240$)	Group No RI ($n=486$)	Group RI ($n=165$)	All Site B cats ($n=651$)	Group No RI ($n=703$)	Group RI ($n=188$)	All cats ($n=891$)
Systolic anterior motion of the mitral valve									
N (% of group) with information	213 (98%)	22 (96%)	235 (98%)	194 (40%)	70 (42%)	264 (41%)	407 (58%)	92 (49%)	499 (56%)
No	194 (91%)	17 (77%)	211 (90%)	166 (86%)	59 (84%)	225 (85%)	360 (89%)	76 (83%)	436 (87%)
Yes	19 (9%)	5 (23%)	24 (10%)	28 (14%)	11 (16%)	39 (15%)	47 (12%)	16 (17%)	63 (13%)

[a]Left atrium: aortic root diameter ratio > 1.5, measured from a two-dimensional right parasternal short-axis view taken at the heart base.

of RI (OR [95% CI], 1.3 [1.09–1.55]; $p=0.02$) in the entire study sample, but not when sites were analyzed separately (Table 6). Similarly, in the complete sample, cats with RI were more likely to have a history of auscultable cardiac abnormalities other than a heart murmur (OR [95% CI], 2.15 (1.23–3.67); $p=0.04$), but this association was not significant when each site was analyzed separately.

2.6 | Renal Infarction and Other Risk Factors

In the entire study sample and at Site B, but not Site A, increasing age was associated with a slightly increased risk of RI (Table 7). In the entire study sample, additional significant extra-cardiac risk factors for RI included increased systolic blood pressure, degenerative renal changes on AUS, a diagnosis of AKI, and a diagnosis of CKD. Of these risk factors, only the presence of degenerative renal changes on AUS was a significant risk factor for RI at each site when the sites were analyzed separately.

A diagnosis of hyperthyroidism, neoplasia, pancreatitis, and administration of corticosteroids, antihypertensive medications, or methimazole were not significant risk factors for RI.

3 | Discussion

In our study, RI was diagnosed in 15% of cat visits in which an AUS was performed and in 21% of cats in which both an AUS and echocardiography were performed during the same visit. A significant difference was found in the relative frequency of RI between sites. Whether data from both sites were analyzed together or separately, the frequency of echocardiographically detectable heart disease was higher in cats with RI compared with cats without RI. Because performance of both AUS and echocardiography was required for the in-depth review performed in our study, the frequency of structural heart disease reported here likely differs from that of the general population of cats with RI. Importantly, clinicians at each site were not more likely to recommend an echocardiogram in cats with RI compared to those without RI, and renal infarction was mentioned in the echocardiogram request for only three cats at Site B. Several variables and comorbidities were associated with increased odds of RI when data from both sites were analyzed together, including a diagnosis of occult heart disease, older age, history of auscultable cardiac abnormalities other than a heart murmur, degenerative renal changes on AUS, clinical diagnoses of AKI or CKD, higher maximum average diastolic LV wall thickness, and higher systolic blood pressure. When data from each site were analyzed separately, however, there were important differences in conclusions drawn for several of these variables.

Our findings support an association between structural heart disease and RI in cats. In the entire study sample, cats with RI were 1.6 times more likely to have echocardiographic heart disease compared with cats without RI (2.8 times higher odds at Site A and a significant, 1.5 times higher odds at Site B). Furthermore, when cases with images retrospectively reviewed by a cardiologist or cardiologist-in-training were considered separately, this association persisted. In our study,

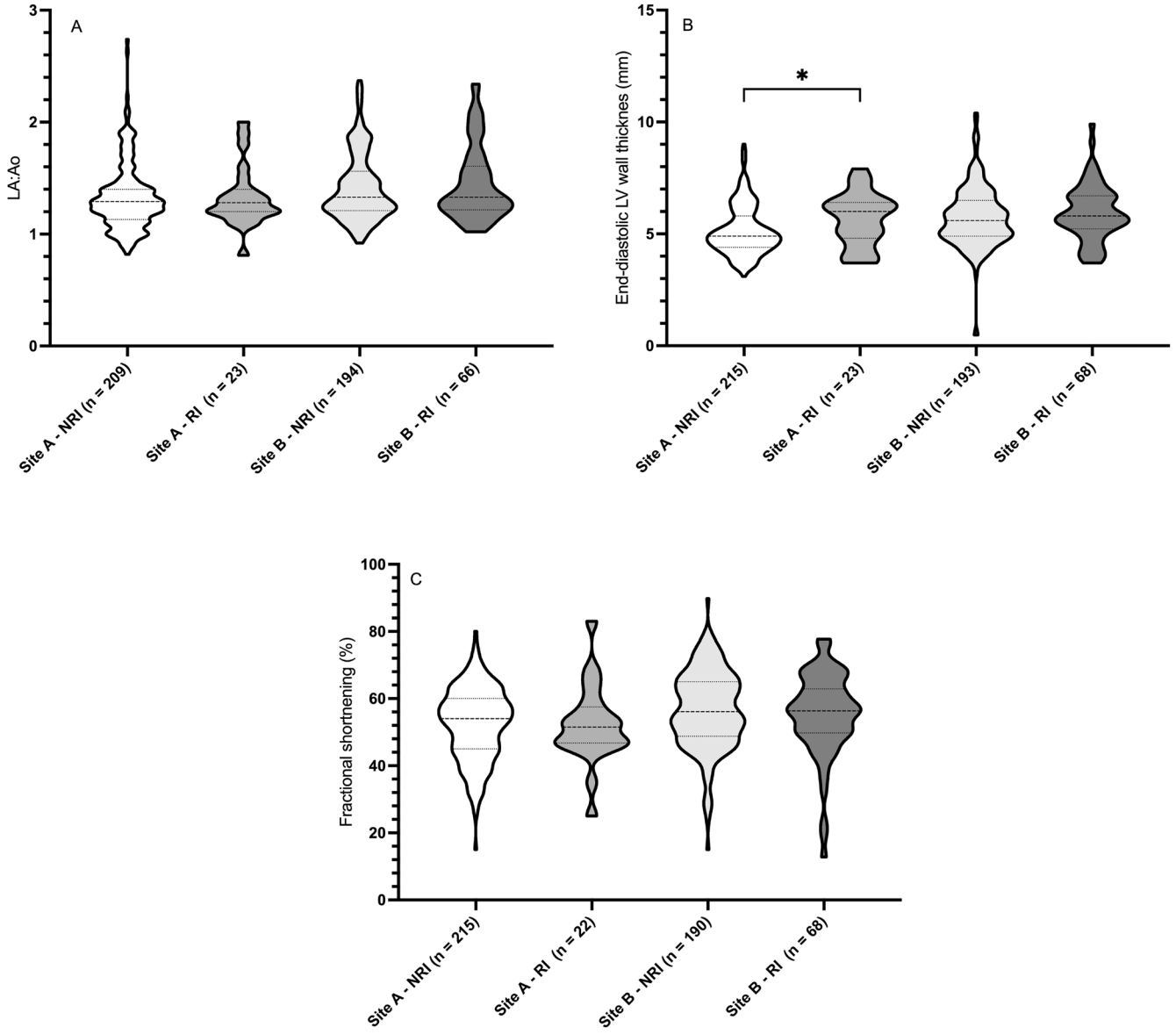

FIGURE 3 | Violin plots of two-dimensional, short-axis, left atrium: Aortic root diameter ratio (LA:Ao; panel A), maximum average end-diastolic left ventricular (LV) wall thickness (panel B), and left ventricular fractional shortening (panel C) in a sample of 891 cats that underwent abdominal ultrasonographic and echocardiographic evaluation at the same visit to one of two Veterinary Teaching Hospitals (Site A [University of Georgia] and Site B [North Carolina State University]) and were diagnosed with renal infarcts (RI) or no renal infarcts (NRI). Within each violin, the dashed line represents the median, and the upper and lower dotted lines represent the 75th and 25th percentiles, respectively. The number of cats for which information is known is noted for each group. *$p < 0.05$.

HCM phenotype was the most commonly diagnosed cardiomyopathy, consistent with previous studies [23]. Our results are consistent with a previous study, which found that cats with RI were 4.5 times more likely to have HCM than cats without RI [16], although the ORs in our study are lower. Hypertrophic cardiomyopathy is a well-documented cause of hypercoagulability in cats because of endothelial damage caused by turbulent blood flow [10] and activation of platelets [27]. This propensity for thromboembolic disease most commonly results in aortic thromboembolism, but the kidneys also can be affected [15]. In addition, cats with RI in our study were more likely to have CKD, AKI, an increased end-diastolic LV wall thickness, and systemic hypertension. It is plausible that renocardiac or cardiorenal syndrome could have contributed to the association between heart disease and RI in cats with primary kidney or heart disease, respectively [28].

In our study, a distinction was made between overt and occult heart disease [13, 14]. When data from both sites were analyzed together, cats with RI were more likely to have occult heart disease (54%) than those without RI (34%); this association persisted when cats at Site B were analyzed separately. The lack of statistical significance at Site A might have been a consequence of its smaller sample size, because the raw p value but not the adjusted p value was below the significance threshold.

In our study, overt heart disease was not associated with RI at either site. The frequency of overt heart disease was numerically

TABLE 4 | Main echocardiographic diagnoses assigned to cats that had abdominal ultrasonography and echocardiography performed at the same visit to one of two Veterinary Teaching Hospitals (Site A [University of Georgia] and Site B [North Carolina State University]).

Main echocardiographic diagnosis	Site A			Site B			Both sites		
	Group No RI ($n=217$)	Group RI ($n=23$)	All Site A cats ($n=240$)	Group No RI ($n=486$)	Group RI ($n=165$)	All Site B cats ($n=651$)	Group No RI ($n=703$)	Group RI ($n=188$)	All cats ($n=891$)
Normal, DRVOTO, or physiologic valvular insufficiency									
N	134	8	142	155	50	205	289	58	347
% of column	62%	35%	59%	32%	30%	32%	41%	31%	39%
Physiologic abnormality									
N	22	3	25	37	6	43	59	9	68
% of column	10%	13%	10%	8%	4%	7%	8%	5%	8%
Structural heart disease									
N	61	12	73	236	102	338	297	114	411
% of column	28%	52%	30%	49%	62%	52%	42%	61%	46%
Unable to determine									
N	0	0	0	58	7	65	58	7	65
% of column	0%	0%	0%	12%	4%	10%	8%	4%	7%

Note: Specific echocardiographic diagnoses assigned to cats with physiologic or structural abnormalities are presented in Table S2.
Abbreviations: DRVOTO, dynamic right ventricular outflow tract obstruction; RI, renal infarction.

TABLE 5 | Frequency of occult and overt heart disease in cats that had abdominal ultrasonography and echocardiography performed at the same visit to one of two Veterinary Teaching Hospitals (Site A [University of Georgia] and Site B [North Carolina State University]), for which a specific echocardiographic diagnosis and presence or absence of congestive heart failure could be determined. Occult heart disease was defined as structural heart disease in the absence of clinical signs of congestive heart failure.

	Site A			Site B			Both sites		
Echocardiographic diagnosis	**Group No RI ($n=217$)**	**Group RI ($n=23$)**	**All Site A cats ($n=240$)**	**Group No RI ($n=428$)**	**Group RI ($n=158$)**	**All Site B cats($n=586$)**	**Group No RI ($n=645$)**	**Group RI ($n=181$)**	**All cats ($n=826$)**
No structural heart disease									
N	159	11	170	190	55	245	349	66	415
Column %	73%	48%	71%	44%	35%	42%	54%	37%	50%
Occult heart disease									
N	42	12	54	174	86	260	216	98	314
Column %	19%	52%	23%	41%	54%	44%	34%	54%	38%
Overt heart disease									
N	16	0	16	64	17	81	80	17	97
Column %	7%	0%	7%	15%	11%	14%	12%	9%	12%

Abbreviation: RI, renal infarction.

lower at both sites in cats with RI compared with those without, and this finding is seemingly contradictory to previous studies, which identified a higher risk of thromboembolic disease [9, 10, 12, 15] and RI in these cats [16]. Cautious interpretation is warranted, however, because we selected cats that underwent both AUS and echocardiography at the same hospital visit, and it is likely that clinicians would have been less apt to recommend AUS in cats with clinical signs of CHF.

Overall, 14% and 21% of cats in our study had a clinical diagnosis of AKI and CKD, respectively. The number of cats with CKD was likely higher because 53% of cats had degenerative renal changes on AUS (54% at Site B and 51% at Site A). Based on recommendations of the International Renal Interest Society, stage 1 CKD can be defined by degenerative changes in the kidneys without overt azotemia [29]. When analyzing data from both sites, cats with RI were 4.62 times more likely to have degenerative renal changes on AUS, 1.94 times more likely to be diagnosed with CKD, and 2.27 times more likely to have changes consistent with AKI, compared with cats without RI. When data were analyzed separately, AKI changes were associated with an increased risk of RI at Site B ($p=0.02$), but not Site A. The association between protein-losing nephropathies and hypercoagulability is well documented in dogs and cats [30]. Although this association frequently is attributed to loss of antithrombin, the pathogenesis is multifactorial [31]. A paucity of evidence exists for hypercoagulability in cats with non-proteinuric CKD and AKI, but non-proteinuric CKD in humans has been associated with the development of a hypercoagulable state via activation of the tissue factor pathway [32]. Additionally, 70% of dogs with CKD and one-third of dogs with AKI in one study were hypercoagulable [33]. More research is needed to examine the mechanisms of hypercoagulability in non-proteinuric CKD and AKI in cats.

In the entire study sample, increasing average maximum end-diastolic LV wall thickness was the only evaluated echocardiographic variable associated with an increased odds of RI (OR, 1.3; $p=0.02$); this was not true when data from each site were analyzed separately. A prior study found higher degrees of LV concentric hypertrophy to be a risk factor for death associated with distal aortic thromboembolism in cats with HCM [34]. Interestingly, other previously reported echocardiographic findings associated with arterial thromboembolism, including left atrial size and enlargement, intracardiac thrombus, and spontaneous echogenic contrast, were not found to be risk factors for RI in our study.

In the entire study sample, the odds of RI increased by 9% for every 10 mmHg increase in systolic blood pressure. When each site was analyzed separately, this association remained significant at Site B only. Conclusions from the overall and Site B datasets agree with previous studies identifying the kidneys as a target organ for hypertensive damage. Although acute RI was rare in our study, in people, it can present with concurrent hypertension [35]. Additionally, it is plausible that hypertension could contribute to vascular changes, subsequent in situ thrombus formation, and consequent RI in cats [36].

A relatively large proportion (27%) of cats in our study had concurrent neoplasia, a finding that was not surprising given the median age of approximately 11 years. Concurrent neoplasia or hyperthyroidism did not increase the risk of RI in our study,

TABLE 6 | Unconditional associations (i.e., unadjusted for study site) between cardiac risk factors and renal infarction for Site A (University of Georgia), Site B (North Carolina State University), and both sites combined.

		Site A					Site B					Both sites				
Cardiac risk factors	**Effect**	**OR**	**Lower 95% CL**	**Upper 95% CL**	***p***	***FDR p***	**OR**	**Lower 95% CL**	**Upper 95% CL**	***p***	***FDR p***	**OR**	**Lower 95% CL**	**Upper 95% CL**	***p***	***FDR p***
History of heart disease diagnosed via Echo	1 vs. 0	1.10	0.06	6.26	0.93	0.98	1.50	0.93	2.38	0.10	0.28	1.75	1.10	2.73	0.018	0.073
Heart murmur	1 vs. 0	1.15	0.32	3.31	0.81	0.98	1.08	0.75	1.57	0.67	0.78	1.27	0.90	1.79	0.18	0.34
Auscultable cardiac abnormality[a]	1 vs. 0	0.62	0.00	5.39	0.73	0.98	2.05	1.15	3.59	0.016	0.071	2.15	1.23	3.67	0.008	0.037
Clinical signs of ATE	1 vs. 0	3.45	0.73	12.50	0.11	0.65	1.50	0.60	3.47	0.37	0.63	1.64	0.76	3.29	0.20	0.34
Evidence of CHF	1 vs. 0	0.18	0.00	1.42	0.13	0.65	0.81	0.47	1.34	0.43	0.63	0.80	0.47	1.29	0.36	0.48
LA:Ao	Per 1	1.02	0.21	3.94	0.98	0.98	1.43	0.58	3.43	0.43	0.63	1.64	0.79	3.31	0.18	0.34
End-diastolic LV wall thickness (mm)	Per 1	1.43	1.00	2.04	0.049	0.56	1.12	0.91	1.38	0.29	0.55	1.30	1.09	1.55	0.003	0.021
SAM	1 vs. 0	3.00	0.91	8.61	0.069	0.54	1.11	0.50	2.31	0.80	0.87	1.61	0.85	2.94	0.14	0.31
Fractional shortening (%)	Per 10	0.97	0.65	1.47	0.89	0.98	0.91	0.72	1.15	0.43	0.63	1.01	0.83	1.23	0.95	0.95
Spontaneous echocardiographic contrast	1 vs. 0	1.38	0.01	15.00	0.84	0.98	0.55	0.03	3.48	0.56	0.70	0.55	0.03	3.06	0.55	0.68
Occult heart disease category	Occult vs. Normal	4.08	1.70	9.87	0.004	0.060	1.71	1.15	2.55	0.008	0.044	2.40	1.69	3.43	<0.001	<0.001
Occult heart disease category	Overt vs. Normal	0.42	0.00	3.50	0.004	0.060	0.92	0.49	1.67	0.78	0.87	1.12	0.61	1.98	0.70	0.82

Abbreviations: 95% CL, 95% confidence limits; ATE, aortic thromboembolism; CHF, congestive heart failure; Echo, echocardiogram; FDR, false discovery rate; LA:Ao, left atrium: aortic root diameter ratio; LV, left ventricular; OR, odds ratio; SAM, systolic anterior motion of the mitral valve.

[a]Other than murmur.

TABLE 7 | Unconditional associations (i.e., unadjusted for study site) between extra-cardiac risk factors and renal infarction for Site A (University of Georgia), Site B (North Carolina State University), and both sites combined.

		Site A					Site B					Both sites				
Extra-cardiac risk factors	**Effect**	**OR**	**Lower 95% CL**	**Upper 95% CL**	***p***	***FDR p*-value**	**OR**	**Lower 95% CL**	**Upper 95% CL**	***p***	***FDR p***	**OR**	**Lower 95% CL**	**Upper 95% CL**	***p***	***FDR p***
Age (years)	Per 1	0.97	0.88	1.08	0.61	0.93	1.06	1.02	1.11	0.003	0.023	1.06	1.02	1.10	0.005	0.029
Sex	F vs. M	1.73	0.73	4.15	0.22	0.79	1.28	0.90	1.82	0.18	0.44	1.37	0.99	1.89	0.056	0.16
Reproductive status	IF vs. SF	7.27	0.55	95.40	0.26	0.79	1.86	0.30	9.72	0.48	0.68	2.49	0.55	10.40	0.11	0.28
	IM vs. NM	1.25	0.01	12.90	0.26	0.79	0.65	0.00	8.12	0.48	0.68	0.33	0.00	2.80		
Body weight (kg)	Per 1	0.93	0.67	1.23	0.63	0.93	0.93	0.83	1.04	0.20	0.44	0.94	0.85	1.04	0.25	0.40
Systolic blood pressure	Per 10	0.92	0.75	1.10	0.36	0.83	1.10	1.03	1.17	0.002	0.023	1.09	1.03	1.16	0.002	0.015
Hct/PCV	Per 10	1.19	0.77	1.89	0.44	0.85	1.00	0.83	1.22	0.97	0.97	1.02	0.86	1.22	0.80	0.87
Platelet Count	Per 100	0.75	0.41	1.19	0.25	0.79	1.02	0.85	1.20	0.86	0.90	0.99	0.84	1.15	0.89	0.91
PT	Per 1	0.92	0.69	1.05	0.29	0.82	0.99	0.89	1.07	0.88	0.90	0.97	0.88	1.03	0.34	0.46
aPTT	Per 10	1.01	0.86	1.14	0.92	0.98	1.05	0.90	1.20	0.54	0.70	1.01	0.91	1.10	0.88	0.91
Creatinine	Per 1	1.05	0.94	1.15	0.36	0.83	1.05	0.99	1.11	0.12	0.32	1.03	0.98	1.08	0.20	0.34
USG	Per 0.1	0.07	0.00	3.04	0.18	0.79	0.33	0.09	1.19	0.09	0.28	0.27	0.08	0.93	0.037	0.14
UPCR	Per 1	Not evaluated—N too small					0.95	0.78	1.13	0.56	0.70	0.97	0.80	1.15	0.75	0.84
Degenerative renal changes on AUS	1 vs. 0	12.10	3.42	76.50	<0.001	<0.001	4.23	2.83	6.44	<0.001	<0.001	4.62	3.17	6.87	<0.001	<0.001
Acute renal changes on AUS	1 vs. 0	1.25	0.48	3.02	0.64	0.90	2.05	1.29	3.22	0.002	0.019	1.46	0.98	2.13	0.06	0.16
Extrarenal thrombi on AUS	1 vs. 0	1.30	0.01	14.10	0.87	0.98	1.32	0.35	4.10	0.657	0.782	1.25	0.35	3.64	0.71	0.82
Comorbidity AKI	1 vs. 0	1.88	0.41	6.28	0.37	0.83	2.08	1.32	3.24	0.002	0.023	2.27	1.49	3.43	<0.001	0.002
Comorbidity CKD	1 vs. 0	1.69	0.46	4.97	0.39	0.85	1.72	1.16	2.53	0.008	0.039	1.94	1.34	2.78	<0.001	0.005
Comorbidity hyperthyroidism	1 vs. 0	0.58	0.06	2.43	0.50	0.87	1.72	0.97	2.96	0.06	0.23	1.44	0.85	2.36	0.17	0.34

(Continues)

TABLE 7 | (Continued)

Extra-cardiac risk factors	Effect	Site A OR	Site A Lower 95% CL	Site A Upper 95% CL	Site A *p*	Site A *FDR p*-value	Site B OR	Site B Lower 95% CL	Site B Upper 95% CL	Site B *p*	Site B *FDR p*	Both sites OR	Both sites Lower 95% CL	Both sites Upper 95% CL	Both sites *p*	Both sites *FDR p*
Comorbidity neoplasia	1 vs. 0	0.97	0.34	2.46	0.95	0.98	0.80	0.53	1.20	0.28	0.57	0.83	0.56	1.19	0.31	0.46
Comorbidity pancreatitis	1 vs. 0	0.71	0.04	3.85	0.74	0.98	0.77	0.38	1.45	0.43	0.63	0.83	0.42	1.50	0.54	0.68
Comorbidity systemic hypertension	1 vs. 0	1.78	0.26	7.24	0.50	0.87	1.30	0.74	2.21	0.35	0.63	1.49	0.88	2.46	0.13	0.31
Corticosteroids	1 vs. 0	0.74	0.17	2.31	0.63	0.93	1.36	0.86	2.11	0.19	0.44	1.25	0.82	1.87	0.30	0.46
Antihypertensives	1 vs. 0	0.49	0.03	2.58	0.46	0.85	1.56	0.97	2.47	0.067	0.23	1.58	1.00	2.43	0.048	0.16
Methimazole	1 vs. 0	0.47	0.03	2.43	0.42	0.85	2.14	1.18	3.81	0.013	0.066	1.70	0.98	2.85	0.06	0.16

Abbreviations: 95% CL, 95% confidence limits; AKI, acute kidney injury; aPTT, activated partial thromboplastin time; AUS, abdominal ultrasound; CKD, chronic kidney disease; F, female; FDR, false discovery rate; Hct, hematocrit; IF, intact female; IM, intact male; M, male; NM, neutered male; OR, odds ratio; PCV, packed cell volume; PT, prothrombin time; SF, spayed female; UPCR, urinary protein-to-creatinine ratio; USG, urine specific gravity.

consistent with previous literature [16]. Although hyperthyroidism has been associated with hypercoagulability in humans [37], a recent study of hyperthyroid cats reported that these cats were not more likely to be hypercoagulable despite evidence of higher von Willebrand factor antigen concentration, antithrombin activity, and fibrinogen concentration [38]. Although certain types of neoplasia can result in hypercoagulability as a consequence of blood stasis and endothelial damage [39], the propensity for thromboembolic disease is likely dependent on the type of neoplasia. Many cats in our study did not have a histopathologic diagnosis; this information would be required to investigate the association of specific neoplasms with hypercoagulability and risk of RI.

Our study had some limitations, mainly because of its retrospective, cross-sectional design. First, the data obtained depended on the completeness of medical records, which was not standardized between the two sites. Although available echocardiographic images were systematically reviewed by two trained individuals, all AUS data were exported from reports generated by numerous individuals. Additionally, because of software changes and limited availability of echocardiographic images before 2018, retrospective review of echocardiographic images and reports was limited to 2018–2021 at Site B. Other cases ultimately were excluded because of inadequate medical records, which might have affected the results obtained. Moreover, Site B contributed a larger number of cases for the in-depth review dataset than Site A, which likely led to a higher statistical power to detect significant differences within the Site B sample. Cats with RI also were disproportionate between sites (25% at Site B and 10% at Site A). These data highlight possible differences between clinical practices and other unknown variables between the two sites, which challenges the interpretation of the aggregate data. Importantly, unlike in the prior investigation of this research question [16], RI was diagnosed solely by AUS in our study, with no histopathology performed. It is possible that a subset of cases included in the RI group had renal scarring for other reasons. Finally, no longitudinal assessment was performed.

In conclusion, our results suggest that cats with RI have a higher frequency of occult heart disease than cats without RI. Therefore, echocardiographic screening should be considered in cats with RI to facilitate early diagnosis and therapeutic intervention. Additionally, CKD and AKI were convincingly associated with RI in our study sample. On the other hand, the effect of other variables on the risk of RI, such as older age, higher maximum average diastolic LV wall thickness, and higher systolic blood pressure, differed between sites, resulting in different conclusions when data from each site were analyzed together versus separately. Therefore, results of single-site retrospective studies should be interpreted with caution because conclusions can be influenced by site-specific factors. Future prospective, longitudinal studies are needed to evaluate the effect of these other variables on the risk of RI and to determine factors that might lead to the eventual development of overt heart disease in cats with occult disease.

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Disclosure

Authors declare no off-label use of antimicrobials.

Ethics Statement

Authors declare no institutional animal care and use committee or other approval was needed. Authors declare human ethics approval was not needed.

Conflicts of Interest

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.