

# Association between pancreatitis and chronic kidney disease in cats: a retrospective review of 154 cats presented to a specialty hospital between October 1, 2017, and October 1, 2022

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## OBJECTIVE

To investigate an association between pancreatitis and chronic kidney disease (CKD) in cats.

## ANIMALS

154 client-owned cats: 77 cats with pancreatitis and 77 control cats with no evidence of pancreatitis.

## METHODS

Retrospective record review from October 1, 2017, to October 1, 2022, including cats with gastrointestinal clinical signs, pancreatic lipase immunoreactivity (PLI)  $\geq 8.8$   $\mu\text{g/L}$  or PLI 4.5 to 8.7  $\mu\text{g/L}$  with sonographic evidence of pancreatitis. Control cats had a PLI  $\leq 4.4$   $\mu\text{g/L}$  with no sonographic evidence of pancreatitis.

## RESULTS

Cats with pancreatitis had significantly higher International Renal Interest Society CKD stages than controls ( $P < .001$ ; OR, 13 [95% CI, 6.3 to 31]), and mean creatinine was on average 0.79 mg/dL (95% CI, 0.56 to 1.0) higher than controls ( $P < .001$ ; age covariate ANCOVA,  $P = .003$ ). Odds of CKD in cats with pancreatitis compared to controls increased significantly with age ( $P = .002$ ). Cats aged 10 to  $< 15$  years and 15 to 20 years with pancreatitis had significantly higher prevalence of CKD stage 2 to 4 compared to controls ( $P < .001$ ; OR, 10.9 [95% CI, 3.4 to 44]; and  $P = .001$ ; OR, 66 [95% CI, 4.6 to  $> 1,000$ ], respectively). Cats with pancreatitis had significantly more sonographic renal infarcts ( $P = .004$ ; OR, 6.9 [95% CI, 1.8 to 46]) and concurrent diabetes mellitus ( $P = .002$ ; OR, 6 [95% CI, 1.9 to 27]). Cats with pancreatitis were fed more exclusively dry-food diets compared to controls ( $P = .014$ ).

## CLINICAL RELEVANCE

Pancreatitis is associated with CKD in cats. Investigating and treating these diseases concurrently early in the disease process may reduce morbidity and mortality due to progressive disease and expensive hospitalizations. Renal infarcts may be associated with pancreatitis in cats without overt cardiac disease.

**Keywords:** pancreatitis, kidney, infarct, cat, renal

Feline acute and acute on chronic pancreatitis are common conditions resulting in reduced quality of life with the potential for the development of distant organ damage. In 2007, histopathologic evaluation of 115 cats presented for necropsy demonstrated an overall prevalence of pancreatitis in 67%, chronic pancreatitis in 50.4%, acute pancreatitis alone in 6.1%, and acute on chronic pancreatitis in 9.6%. Of these cats, 45% were noted to have been clinically healthy without associated clinical signs.<sup>1</sup> Additionally, it has been reported that chronic or acute on chronic pancreatitis

accounts for 65% to 89% of all cases of feline pancreatitis.<sup>2</sup> An important relationship that has not yet been elucidated in veterinary literature is the potential association between pancreatitis and an increased prevalence of chronic kidney disease (CKD). Chronic kidney disease in cats is defined and staged via serum creatinine levels using the International Renal Interest Society (IRIS) staging guidelines, with substaging based on the presence of hypertension and/or proteinuria.<sup>3</sup> Current literature suggests that the overall prevalence of CKD in cats is 2% to 4%<sup>4</sup> or 1.6% to 20%,<sup>5</sup> increasing up to 30% to 40% in cats  $> 10$  years of age.<sup>4</sup>

A retrospective analysis of cats hospitalized for pancreatitis indicated that domestic shorthairs with a mean age of 9.5 years are predisposed. Clinical signs on presentation included dehydration, lethargy, anorexia, vomiting, weight loss, hypothermia,

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tachypnea, icterus, abdominal pain, diarrhea, and fever.<sup>6</sup> Definitive diagnosis of feline pancreatitis remains challenging due to nonspecific clinical signs, reported abdominal ultrasound sensitivity of 24% to 67%,<sup>7</sup> lack of consistent findings on CBC and serum biochemistry, and interference regarding pancreatic-specific lipase concentrations in cats with renal insufficiency.<sup>8</sup> However, pancreatic lipase immunoreactivity (PLI) testing has proven to be reliably specific for feline pancreatitis<sup>9</sup> while being unaffected by the patient's renal status,<sup>10</sup> including in-house qualitative feline PLI testing, which is reportedly 100% specific if the corresponding PLI is  $\geq 7.9 \mu\text{g/L}$ .<sup>11</sup> Quantitative feline PLI is currently the most consistently performed and reliable antemortem pancreatitis test, and a prospective study<sup>12</sup> using histological assessment for diagnosis of feline pancreatitis noted that PLI assays carry a 100% sensitivity in cats with moderate to severe pancreatitis and a specificity of 100% in cats without pancreatitis. Another study<sup>13</sup> indicated a quantitative feline PLI sensitivity and specificity of 79% and 82%, respectively.

Acute kidney injury (AKI) in humans is reported to occur secondary to severe acute pancreatitis (SAP) due to septic shock, abdominal compartment syndrome, and/or prerenal azotemia secondary to peripancreatic fluid sequestration and extracellular fluid volume reduction, among other causes. In 1 study,<sup>14</sup> 32% (32/100) of human patients with SAP developed AKI, and SAP with subsequent AKI development resulted in a ten-fold increase in mortality.<sup>15</sup> Severe acute pancreatitis in humans has also been associated with significant deleterious systemic effects and target organ damage.<sup>16</sup> Research into pancreatitis in humans using murine and canine models has demonstrated a complex network of inflammatory cascades.<sup>16</sup> The consequences of these cascades include systemic inflammation and target organ damage secondary to the cytokine storm, hypovolemia, coagulation anomalies, and/or other associated factors.<sup>16</sup> Systemic complications are not as well defined in cats, and acute severe pancreatitis may result in systemic inflammatory response syndrome and target organ damage.<sup>16-18</sup> Although the zymogen-inflammatory pathogenesis applies to acute pancreatitis, it is plausible that this event could incite the onset of chronic pancreatitis in cats,<sup>19</sup> as chronic pancreatitis in humans is considered a consequence of repeated inflammatory insults.<sup>20</sup> Chronic pancreatitis in cats is characterized by pancreatic mononuclear infiltration and fibrosis, as opposed to neutrophilic inflammation, and the course of disease is prolonged and can be subclinical.<sup>7</sup> Additionally, a correlation has been suggested between CKD and pancreatitis in humans, although the direction of causation is unclear.<sup>21</sup> In humans, renal infarcts are a recognized consequence of cardioembolic disease, atrial fibrillation, renal artery injury, fibromuscular dysplasia, hypercoagulable states potentially attributable to chronic inflammation, and other conditions.<sup>22</sup>

In this study, we primarily hypothesized that pancreatitis would be associated with an increased prevalence of IRIS stage 2 to 4 CKD and increased serum

creatinine in cats. We secondarily hypothesized that pancreatitis would be associated with the development of renal infarction in cats, that cats with pancreatitis consume more exclusively dry-food diets, and that cats with pancreatitis have an increased prevalence of diabetes mellitus (DM). Our study briefly reviewed the existing epidemiological data, clinical signs at presentation, and ultrasound data as they pertain to feline pancreatitis.

## Methods

Gastrointestinal panels were obtained for cats presenting with gastrointestinal signs to BluePearl Specialty Pet Hospital internal medicine or emergency departments in 2 locations between October 1, 2017, and October 1, 2022. Pancreatic lipase immunoreactivity values at the time of initial presentation were analyzed, and cats were included and divided into a pancreatitis group if their PLI was  $8.8$  to  $> 50 \mu\text{g/L}$  or a control group if their PLI was  $\leq 4.4 \mu\text{g/L}$  according to the most current 2023 Texas A&M University Gastrointestinal Laboratory guidelines. Cats that were within the equivocal pancreatitis range (PLI,  $4.5$  to  $8.7 \mu\text{g/L}$ ) required sonographic evidence of pancreatitis and compatible clinical signs to be included in the pancreatitis group. Control cats could not have any evidence of pancreatitis on abdominal ultrasound in addition to a PLI  $\leq 4.4 \mu\text{g/L}$ . Cats with clinical neoplasia, with moderate to severe peritoneal effusion (defined as diffuse and readily amenable to abdominocentesis) that was suspected to be due to another medical issue, or without biochemical data were not included in either group. Initial inclusion consisted of 136 pancreatitis cats and 83 control cats. A complete review of the medical record from presentation and prior referral records was conducted for each cat.

Epidemiological data and clinical signs at presentation were recorded for both the pancreatitis and control cats. Particular attention was given to the presence or absence of vomiting, diarrhea, constipation, anorexia, weight loss, pain, and lethargy. History of "picky eating" and pica in the absence of concurrent anemia were also noted. Known or suspected comorbidities and medication history were noted for each cat. Dietary data were recorded including whether cats were fed an exclusively dry-food diet or whether canned food was also fed. Dietary data were determined from thorough consultation history, and cats received their reported diet for at least 50% of their lives, with most cats having been fed only this diet during their lifetime.

Complete blood count, serum chemistry, venous blood gas, and urinalysis data corresponding to the date the gastrointestinal panel or PLI was performed were recorded. A small number of cats did not have these data available due to owner constraints, and in these cases these data were required to be available from the referring clinic within 1 week prior to presentation and while experiencing the same clinical signs to be included. Particular attention was given to BUN in mg/dL, creatinine in mg/dL, albumin in g/dL,

phosphorus in mg/dL, absolute RBC count in million cells/ $\mu$ L, urine specific gravity (USG), and urine sediment. Pancreatitis and control cats were divided into 4 groups on the basis of IRIS CKD staging guidelines. Cats without CKD (creatinine < 1.6 mg/dL and sonographically normal kidneys) and cats with CKD stage 1 (creatinine < 1.6 mg/dL, with chronic kidney changes as described below) were combined into 1 group. The remaining cats were divided by IRIS stage 2 (creatinine, 1.6 to 2.8 mg/dL), stage 3 (creatinine, 2.9 to 5.0 mg/dL), and stage 4 (creatinine > 5.0 mg/dL). Feline immunodeficiency virus and feline leukemia virus status, urine cultures, and total T4 levels were noted where available. For the pancreatitis group, cats were excluded for an equivocal PLI result (4.5 to 8.7  $\mu$ g/L) with no abdominal ultrasound evidence of pancreatitis, presumptive AKI based on acute creatinine increase within 1 week of > 0.3 mg/dL or phosphorus > 10 mg/dL, pyelonephritis (active urine sediment, inflammatory leukogram, hematuria, pyuria, bacteriuria), urolithiasis, suspected or established urinary tract infection, hyperthyroidism, prednisolone or budesonide administration that may have confounded the USG, furosemide administration, hypertrophic cardiomyopathy, polycystic kidney disease, hyperadrenocorticism, immune-mediated hemolytic anemia, bladder mass, gastrointestinal mass, and chronic lymphocytic leukemia. Overt dehydration (> 5% on physical examination, albumin > 4.0 g/dL, total protein > 8.5 g/dL, and RBCs  $\geq$  11 million cells/ $\mu$ L) also resulted in exclusion. Cats were excluded from the control group if they could not demonstrate PLI  $\leq$  4.4  $\mu$ g/L, abdominal ultrasound demonstrated evidence of pancreatitis, they demonstrated a PLI > 4.4  $\mu$ g/L at any point in their referral records, prednisolone was administered and confounded USG, they had cholelithiasis, or they had confounded or conflicting ultrasound or record information. For the purposes of this study, cats with previously diagnosed DM were included due to the lack of current evidence for diabetic nephropathy as a confounding factor.<sup>23</sup> Urine specific gravity was not available for all cats, and for those with USG data, these data were used to ensure no unidentified confounding renal factors were overlooked. Symmetric dimethylarginine was not commonly performed on these cats.

Abdominal ultrasonographic data for each cat were reviewed where available. Ultrasounds were performed by either a registered diagnostic medical sonographer with image loops reviewed by a board-certified veterinary radiologist or a board-certified small animal internal medicine specialist. For each cat, evidence of acute and/or chronic pancreatitis was noted in the left limb, right limb, body of the pancreas, or diffusely. Acute pancreatitis was defined as pancreatic enlargement with diffusely or focally hypoechoic pancreas, hyperechoic peripancreatic fat, and mild peripancreatic peritoneal effusion of a volume considered unsafe for sampling. Acute on chronic pancreatitis was defined as pancreatic enlargement with heterogenous pancreatic echotexture, cystic pancreas, or nodular pancreas.<sup>24</sup> Cats with constipation or diarrhea with pancreatitis noted in the left limb of the pancreas were noted.

Gastrointestinal changes were noted including thickening of the duodenal or jejunal submucosa (> 0.36 mm) and/or muscularis (0.35 mm) or generalized wall thickening (> 2.2 mm duodenum, jejunum, and ileum),<sup>25</sup> disruption of normal wall layering, and mucosal stippling while fasted. Renal architecture was assessed for changes including hyperechoic kidneys, perirenal effusion, pyelectasia (> 2 mm), and chronic changes including loss of corticomedullary distinction, chronic renal cortical infarction, renal cortical cysts, and irregular contours.<sup>26</sup> Hydronephrosis, hydroureter, nephrolithiasis, ureterolithiasis, polycystic kidney disease, and cystolithiasis were also noted, and cats were excluded for these signs as previously noted. When possible, acute on chronic pancreatitis was differentiated from acute pancreatitis on the basis of ultrasonographic appearance of the pancreas, prior records of PLI  $\geq$  8.8  $\mu$ g/L, and history of gastrointestinal clinical signs.

Overall, initial inclusion criteria for the pancreatitis cats included PLI  $\geq$  8.8  $\mu$ g/L or PLI 4.5 to 8.7  $\mu$ g/L with sonographic evidence of pancreatitis and CBC and serum chemistry data available at the time of presentation or within 1 week of presentation while experiencing the same gastrointestinal clinical signs. Initial inclusion criteria for control cats included a PLI  $\leq$  4.4  $\mu$ g/L with no sonographic evidence of pancreatitis, no referral history of a PLI  $\geq$  8.8  $\mu$ g/L at any available time point, available CBC and serum chemistry data, and no evidence of the disease processes noted above. For renal infarcts, suggestive cardiac disease could not be present based on cardiac auscultation, previous history of cardiac disease, N-terminal pro brain natriuretic peptide, and/or cardiac enlargement on thoracic radiographs.

Cats with pancreatitis were compared to controls without evidence of pancreatitis for prevalence of CKD stage 2 to 4, renal infarcts, DM, and diet composition. To better compare cats within specific age groups, pancreatitis and control cats were then subdivided by age: < 5 years, 5 to < 10 years, 10 to < 15 years, and 15 to 20 years. Each group was similarly compared for prevalence of CKD stage 2 to 4. Renal infarcts were then compared between all cats in the no CKD/CKD stage 1 group and all cats in the CKD stage 2 to 4 group to determine whether CKD stage 2 to 4 significantly affected the prevalence of renal infarcts in our population. Left-limb pancreatitis and prevalence of diarrhea and constipation were evaluated. Finally, epidemiological and presenting clinical sign data were noted for the pancreatitis cats.

## Statistical analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc). A significance threshold of .05 was used. Histograms, Q-Q plots, and skewness were used to confirm normality of age and creatinine by group. The single raw diet was excluded from the analysis of diet. Wilson 95% CIs were calculated on binomial proportions. Age and creatinine concentrations were compared between pancreatitis and control cats by Welch *t* tests. An ANCOVA was used to compare creatinine concentrations between

pancreatitis and control cats including age as a covariate. Creatinine concentrations were log-transformed prior to analysis with the ANCOVA due to nonhomogeneous variance. ANCOVA assumptions (normality and homoscedasticity of model residuals) were evaluated via inspection of Q-Q plots, histograms, and residual plots. Chronic kidney disease IRIS stages were compared between pancreatitis and control cats by a Mann-Whitney *t* test. Association of pancreatitis with CKD, renal infarcts, DM, diet, and CKD separately by age categories and associations of left-limb involvement with diarrhea and constipation were tested with likelihood ratio  $\chi^2$  tests. Association of CKD with renal infarcts was also tested with likelihood ratio  $\chi^2$  tests. Multiple logistic regressions with CKD, renal infarcts, or DM as the outcome variable and pancreatitis and age covariate as predictors were used to test whether the associations with pancreatitis changed on the basis of age. Log-likelihood *P* values and ORs with profile-likelihood CIs were reported. When quasi-separation (eg, 0% in 1 group) was present, Firth bias-reduced penalized log-likelihood ratio test *P* values and CIs were reported.

## Results

Of the initially included pancreatitis cats (*n* = 136), cats were excluded for equivocal PLI with no ultrasonographic evidence of pancreatitis (17), AKI (12), dehydration > 5% on physical examination (5), hyperthyroidism (5), confounded USG due to prednisolone or budesonide (3), hypertrophic cardiomyopathy (3), suspected urinary tract infection or pyelonephritis (4), urolithiasis (2), recent furosemide administration (2), polycystic kidney disease (1), feline hypercortisolism (1), immune-mediated hemolytic anemia (1), and suspected or confirmed neoplasia including bladder mass, chronic lymphocytic leukemia, and gastrointestinal mass (3). Of the initial control cats (*n* = 83), cats were excluded for conflicting referral records including prior elevated PLI or evidence of pancreatitis (4), prednisolone administration (1), and cholelithiasis (1). For the pancreatitis group, 111 of the initial cats received abdominal ultrasounds.

In the control group, 83 of the initial cats received abdominal ultrasounds.

In total, 77 cats were included in the pancreatitis group and 77 cats were included in the control group. Among the pancreatitis group, breeds consisted of domestic shorthair (*n* = 62 [80%]), Siamese (4), Maine Coon (2), Ragdoll (2), Sphynx (1), Tonkinese (1), Scottish Fold (1), Russian Blue (1), Bombay (1), Singapura (1), and Oriental Shorthair (1). Castrated males accounted for 57% (*n* = 44); spayed females, 40% (31); intact males, 3% (2); and no intact females were present. No cats were subjectively overweight, with all cats receiving a body condition score of 5/9 or lower. The presenting clinical signs included weight loss in 64 of 77 (83%), anorexia in 52 of 77 (68%), vomiting in 52 of 77 (68%), gastroesophageal reflux in 49 of 77 (64%), lethargy in 46 of 77 (60%), discriminate appetite/picky eating in 36 of 77 (47%), constipation in 22 of 77 (29%), diarrhea in 16 of 77 (21%), pain in 15 of 77 (19%), and pica in 12 of 77 (16%). All cats demonstrated at least one of these clinical signs. Control cats demonstrated similar clinical signs, and this comparison was not assessed for significance as these cats presented for gastrointestinal signs not secondary to pancreatitis.

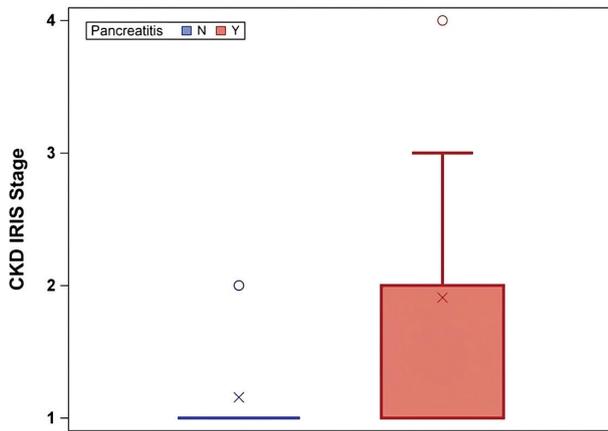
Results are summarized in **Table 1**. Cats with pancreatitis were on average 5.1 (95% CI, 3.9 to 6.4) years older than control cats (*P* < .001). Cats with pancreatitis had serum creatinine levels that were on average 0.79 mg/dL (95% CI, 0.56 to 1.0) higher than control cats (univariable *P* < .001; ANCOVA *P* = .003, with age added as a covariate). The mean (SD) serum creatinine level in pancreatitis cats was 2.1 mg/dL (1.0 mg/dL) and in the control cats was 1.3 mg/dL (0.4 mg/dL). In the pancreatitis group, 22 of 77 cats demonstrated a creatinine < 1.6 mg/dL, while 64 of 77 control cats demonstrated a creatinine < 1.6 mg/dL. Cats with pancreatitis had significantly higher CKD IRIS stages, with 22 stage 1 or no CKD, 41 stage 2, 13 stage 3, and 1 stage 4 than control cats, with 65 stage 1 or no CKD, 12 stage 2, and no stage 3 or 4 (*P* < .001; **Figure 1**). The prevalence of CKD stage 2 to 4 (univariable OR, 13.5 [95% CI, 6.3 to 31]; *P* < .001), DM (univariable OR, 6.0 [95% CI, 1.9 to 27]; *P* = .002), and renal infarcts (univariable OR, 6.9 [95% CI, 1.8 to 46]; *P* = .004) was significantly higher in pancre-

**Table 1**—Odds ratios and 95% CIs for odds of chronic kidney disease (CKD) stage 2 to 4 overall and among 4 matched age groups, renal infarcts, and diabetes mellitus in 77 cats with pancreatitis compared to 77 control cats presenting to a specialty hospital between October 2017 and October 2022. Odds ratios are reported as univariable analysis as well as multivariable analysis to account for the age difference between groups.

Outcome	Proportion in pancreatitis group (95% CI)	Proportion in control group (95% CI)	OR (95% CI)	<i>P</i> value <sup>a</sup>	OR (95% CI; multi)	<i>P</i> value (multi)
CKD stage 2-4	71% (61%-80%)	16% (9%-25%)	13.5 (6.3-31)	< .001	6.7 (2.8-16.3)	< .001
CKD stage 2-4 (age 0-5 y)	0% (0%-49%)	5% (1%-23%)	1.5 (0.01-34)	.813 <sup>b</sup>		
CKD stage 2-4 (age 5-10 y)	63% (31%-86%)	25% (13%-43%)	5.0 (0.98-30)	.053		
CKD stage 2-4 (age 10-15 y)	68% (52%-80%)	16% (6%-35%)	10.9 (3.4-44)	< .001		
CKD stage 2-4 (age 15-20 y)	92% (75%-98%)	0% (0%-66%)	66 (4.6-> 1,000)	.001 <sup>b</sup>		
Renal infarcts	19% (11%-30%)	3% (1%-11%)	6.9 (1.8-46)	.004	5.0 (1.0-37)	.043
Diabetes mellitus	19% (12%-30%)	4% (1%-11%)	6.0 (1.9-27)	.002	12.4 (3.1-68)	< .001

NC = Noncalculable.

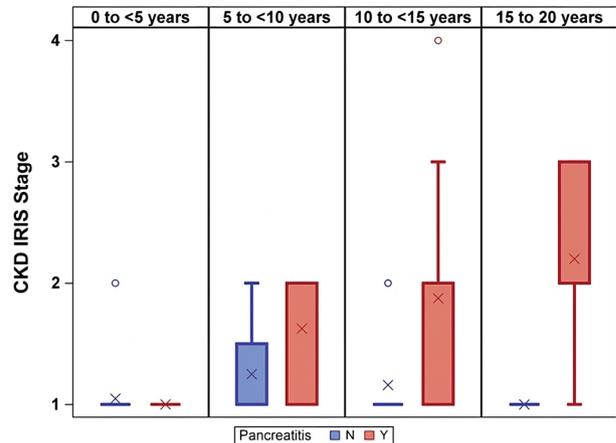
<sup>a</sup>Likelihood ratio test, unless otherwise noted. <sup>b</sup>Firth penalized likelihood ratio test.



**Figure 1**—Seventy-seven cats with pancreatitis compared to 77 control cats presenting to a specialty hospital between October 2017 and October 2022 assessed by International Renal Interest Society (IRIS) chronic kidney disease (CKD) stage. Stage 1 represents both stage 1 and no evidence of CKD. Each box is drawn from the 25th percentile to the 75th percentile (IQR). The mean IRIS stage is represented by an “X.” The whisker extends from the upper edge of the box to the largest-observed value  $\leq 1.5 \times$  IQR above the 75th percentile. Observations outside the whiskers are identified with an “O.”

atitis cats compared to controls. When including age as a covariate, the prevalence of CKD stage 2 to 4 (multiple OR, 6.7 [95% CI, 2.8 to 16.3];  $P < .001$ ), DM (multiple OR, 12.4 [95% CI, 3.1 to 68];  $P < .001$ ), and renal infarcts (multiple OR, 5.0 [95% CI, 1.0 to 37];  $P = .043$ ) was still significantly higher in pancreatitis cats compared to controls. When analyzed inversely, cats with CKD stage 2 to 4 had increased odds of having pancreatitis, which was identical to the odds of cats with pancreatitis developing CKD stage 2 to 4 (univariable OR, 13.5 [95% CI, 6.3 to 31];  $P < .001$ ; and multivariable OR, 6.7 [95% CI, 2.9 to 16.3];  $P < .001$ ). When analyzing cats with no CKD or CKD stage 1 with renal infarcts (5/68 [7.4%]) and without renal infarcts (63/68 [92.6%]) compared to CKD stage 2 to 4 cats with renal infarcts (9/56 [16.1%]) and without renal infarcts (47/56 [83.9%]), the comparison between CKD stage and renal infarcts was not significant ( $P = .127$ ). No cats with renal infarctions had evidence of cardiac disease. The prevalence of CKD stage 2 to 4 in pancreatitis cats compared to controls significantly increased with increasing age (**Figure 2**). Cats aged 10 to < 15 years ( $P < .001$ ) and 15 to 20 years ( $P = .001$ ) were significantly more likely to develop CKD, DM, and renal infarction in the pancreatitis group compared to age-matched controls. Within the 5- to < 10-year age group, more cats with pancreatitis demonstrated CKD stage 2 to 4 (5/8 [63%]) than control cats (8/28 [29%]); however, this result did not rise to significance ( $P = .053$ ). The distribution of diet was significantly different between pancreatitis cats (52% [36/69] canned or mixed, and 48% [33/69] dry) and control cats (72% [52/72] canned or mixed, and 28% [20/72] dry;  $P = 0.014$ ) (**Table 2**).

Regarding abdominal ultrasound data for the pancreatitis cats, in-house ultrasound successfully



**Figure 2**—International Renal Interest Society CKD stage of pancreatitis and control cats described in Figure 1, evaluated by age groups (0 to < 5 years, 5 to < 10 years, 10 to < 15 years, and 15 to 20 years). Stage 1 represents both stage 1 and no evidence of CKD. Each box is drawn from the 25th percentile to the 75th percentile (IQR). The mean is represented by an “X,” and the median is represented by the solid line within the box. Whiskers extend from the upper edge of the box to the largest-observed value  $\leq 1.5 \times$  IQR above the 75th percentile, and from the lower edge of the box to the smallest-observed value  $\geq 1.5 \times$  IQR below the 25th percentile. Observations outside the whiskers are identified with an “O.”

**Table 2**—Number of pancreatitis cats eating exclusively dry-food diets versus diets with canned food added compared to control cats described in Table 1.

Diet	Pancreatitis		Total
	N	Y	
Canned or mixed	52	36	<b>88</b>
Dry	20	33	<b>53</b>
<b>Total</b>	<b>72</b>	<b>69</b>	<b>141</b>

Frequency missing = 13.

$P = .014$ , likelihood ratio  $\chi^2$ . The single raw diet case was not included in the analysis.

identified acute or acute on chronic pancreatitis in agreement with PLI in 91%. Subsequent radiology review via telemedicine successfully identified pancreatitis in 70% of the cats. The overall accuracy between in-house and radiologist review was 80%. For cats with chronicity data available, 24% (8/33) of cats demonstrated purely acute pancreatitis on the basis of lack of prior episodes of PLI  $\geq 8.8$  and presence of only acute pancreatic changes on ultrasound. Seventy-six percent (25/33) of cats demonstrated acute on chronic pancreatitis on the basis of prior PLI  $\geq 8.8$   $\mu\text{g/L}$  in their records and chronic changes noted on ultrasound. There was no significant difference between those that demonstrated left-limb pancreatitis on abdominal ultrasound and development of diarrhea ( $P = .269$ ) or constipation ( $P = .655$ ). However, among the cats that demonstrated these clinical signs, 9 of 11 (82%) cats with

diarrhea had pancreatitis involving the left limb and 14 of 15 (93%) cats with constipation had pancreatitis involving the left limb.

## Discussion

In this study, we hypothesized that pancreatitis would be associated with an increased prevalence of IRIS stage 2 to 4 CKD and increased median serum creatinine in cats. On the basis of our results, cats with a higher CKD stage and higher serum creatinine have a higher prevalence of pancreatitis, proving our hypothesis after statistical analyses to evaluate for disparate ages between groups. This was most evident in the age groups of 10 to < 15 years and 15 to 20 years, and while more cats with pancreatitis aged 5 to < 10 years had stage 2 to 4 CKD, this result did not achieve significance. When evaluated together with 76% of the cats with chronicity data available demonstrating evidence of acute on chronic pancreatitis, these findings strongly support an association between pancreatitis, particularly acute on chronic pancreatitis, and CKD in cats. The pathophysiologic interaction between pancreatitis and CKD in cats has not been established; however, this relationship is likely bidirectional. Although not specifically evaluated in this study, 25 of 33 (76%) cats with pancreatitis with chronicity data available demonstrated previous PLI  $\geq 8.8$   $\mu\text{g/L}$  prior to development of CKD. A prospective study is warranted to further evaluate for potential directionality between feline pancreatitis and CKD.

We secondarily hypothesized that pancreatitis would be associated with the development of renal infarction in cats, that cats with pancreatitis consume more exclusively dry-food diets, and that cats with pancreatitis have an increased prevalence of DM. Our results supported these hypotheses after statistical evaluation correcting for age disparity between groups, and significantly more renal infarcts were noted in cats with pancreatitis. When compared for significance between CKD stage and prevalence of renal infarcts, significance was not achieved, though this may be due to type 2 error. This finding also supports a relationship between pancreatitis and CKD, although, again, causality cannot be determined in this study. Cats with pancreatitis had a higher prevalence of DM as previously reported. Cats with pancreatitis were fed more exclusively dry-food diets for  $\geq 50\%$  of their lives, with most cats having been fed the same diet lifelong.

A statistically significant number of our cats demonstrated evidence of acute or acute on chronic pancreatitis, which, given the relationship to CKD, demonstrates that these processes should be evaluated together. Without recognizing this association, cats can undergo multiple lengthy and financially cumbersome hospitalizations due to progressive CKD and AKIs with only isolated renal supportive treatments having been pursued. This can lead to poor outcomes that we hope can be avoided with greater awareness at the primary care level. Pancreatitis, specifically acute on chronic pancreatitis,

should be considered concurrently or as a differential diagnosis for any cat demonstrating IRIS stage 2 to 4 CKD and/or renal infarction. This is particularly true if the patient is young, an AKI occurs in a young to middle-aged cat for no clinically obvious reason, or a patient's CKD is rapidly progressive. We recommend performing a PLI on cats with CKD as part of a wellness screen or if gastrointestinal signs are present, and these cats may benefit from sonographic evaluation of both the pancreas and kidneys. Conversely, any cat with a known history of pancreatitis should be carefully monitored for the development of CKD. A prospective study is warranted to further validate these findings and recommendations.

The pathophysiological mechanism driving the relationship between pancreatitis and CKD in cats is likely multifactorial. As chronic dehydration is considered a potential contributor to development of both chronic pancreatitis and subsequent or isolated CKD in cats,<sup>27</sup> the addition of canned food was assessed between groups. Dietary data were determined from thorough consultation history, and cats received their reported diet for at least 50% of their lives, with most cats having been fed only this diet during their lifetime. Cats with pancreatitis were fed significantly more exclusively dry-food diets, while control cats were fed significantly more diets that included canned food. Cats fed an exclusively dry-food diet may experience unresolved chronic whole-body water depletion. In 1 study,<sup>28</sup> cats fed a canned food diet obtained 91% of their moisture from the diet. When fed a dry-food diet, total water intake was only 49% of those eating the canned diet, indicating a lack of resolution via voluntary drinking. Therefore, an explanation for the increased prevalence of pancreatitis in cats fed an exclusively dry-food diet may be that they are chronically dehydrated, resulting in disrupted pancreatic microcirculation and chronic pancreatitis. Exclusively dry-food diets and chronic dehydration may also contribute to the development of CKD, and the effect between pancreatitis and CKD is likely bidirectional. As our study suggests, certain lifestyle changes such as the addition of canned food and ensuring adequate dietary moisture may help delay or prevent the onset of chronic pancreatitis as well as CKD in cats. Although our study suggests a potential link between dry-food diets and pancreatitis, prospective studies are warranted to further explore this conclusion.

A well-recognized mechanism of kidney injury in humans with acute pancreatitis involves the systemic inflammatory response and target organ damage secondary to the cytokine storm.<sup>17</sup> Chronic and acute on chronic pancreatitis are known to occur due to continuous activation of the pancreatic inflammatory pathways, in particular the NF- $\kappa\text{B}$  pathway and sustained proinflammatory cytokine production.<sup>29</sup> Rarely, autoimmune pancreatitis has been implicated as a cause for chronic pancreatitis in humans. On the basis of lymphoplasmacytic infiltrates noted with pancreatic histopathology in cats with chronic pancreatitis, the pathogenesis of feline chronic pancreatitis is likely similar to chronic pancreatitis in humans.<sup>19</sup> Regardless

of the inciting cause, a sustained proinflammatory cytokine cascade may negatively impact renal function in cats via target organ damage, as is well established in human medicine.

A third potential pathophysiological mechanism for the relationship between pancreatitis in CKD in cats involves the development of a hypercoagulable state and subsequent thromboembolic disease. It has been established that human patients with pancreatitis are twice as likely to develop a venous thromboembolism. A recent study<sup>30</sup> noted that acute pancreatitis results in a transient hypercoagulable state in mice as demonstrated by thromboelastography, an increased maximum amplitude, Lysis 30 of 0, and significantly increased coagulation index. In the mice, significantly elevated circulating tissue factor resulted in enhanced platelet aggregation and development of deep vein thrombosis with significantly increased clot weight and clot length. In dogs, general hypercoagulability and portal venous thrombosis have been associated with acute pancreatitis.<sup>31,32</sup> A case report<sup>33</sup> was identified in which 1 Jack Russell Terrier developed a cerebellar infarct secondary to acute pancreatitis, although an association between pancreatitis and renal infarction specifically is absent from the veterinary medical literature at large. Given the extent of pancreatic and renal microcirculation, sustained hypercoagulability secondary to chronic pancreatitis in cats may result in thromboembolic events leading to renal infarction, progressive CKD, and potentially further episodes of pancreatitis secondary to disrupted pancreatic microcirculation due to thrombi. Alternatively, studies have demonstrated the possibility of a mild hypercoagulable state in humans with CKD, suggesting that CKD may also cause impaired microcirculation and pancreatitis in cats.<sup>34</sup> Further studies investigating findings of thromboelastography, fibrinogen, and d-dimers in cats with pancreatitis and CKD are warranted.

Our study further supports an association between pancreatitis and development of DM in cats. It is well established that a link exists between these common comorbidities, either through direct inflammation and necrosis of pancreatic  $\beta$  cells and/or via amyloidosis secondary to pancreatitis and subsequent  $\beta$  cell destruction.<sup>35</sup> Feline DM results in significant morbidity, mortality, financial hardship, and owner compliance challenges. Prevention of DM through prevention and/or active management of pancreatitis can significantly improve longevity and quality of life in cats, as well as improving client satisfaction. Control of pancreatitis in cats with previously diagnosed DM may also markedly improve glycemic control by preventing insulin-resistant states. Therefore, prevention of feline DM should include prevention or management of pancreatitis.

Our study noted similar presenting clinical signs with feline pancreatitis as reported in previous literature,<sup>19</sup> with the most common signs being weight loss, anorexia, vomiting, and lethargy and fewer cats presenting with diarrhea, constipation, pica, pain on abdominal palpation, and picky or discriminate appetite. Interestingly, 64% of cats presented with evidence

of gastroesophageal reflux such as hard swallowing, enlarged tonsils without concurrent severe dental or respiratory disease, reluctance to eat in the morning, and/or hacking cough in the absence of respiratory pathology.<sup>36</sup> This is potentially due to intestinal dysmotility and delayed gastric emptying secondary to direct pancreatic inflammation and/or systemic inflammatory cytokine release and oxidative damage.<sup>37</sup> Pancreatitis should be a differential diagnosis in cats demonstrating signs of gastroesophageal reflux, though it should be noted that evaluation of gastroesophageal reflux is regarded as highly subjective. Because these signs can be indistinguishable from inflammatory bowel disease, small-cell gastrointestinal lymphoma, and other primary gastrointestinal pathology, a complete diagnostic analysis is warranted.

Additionally, although our study did not find significance between left-limb pancreatitis and cats that developed diarrhea or constipation, 82% of cats with diarrhea and 93% of cats with constipation had pancreatitis involving the left limb. Lack of significance may be due to type 2 error, given the small subset of cats for which these results could be determined ( $n = 11$  and  $15$ , respectively). These findings may have implications for chronically constipated cats that were previously diagnosed with idiopathic constipation and required repeated deobstipation procedures and hospitalizations and that later progressed to demonstrating megacolon. Constipation in cats is known to occur secondary to CKD,<sup>38</sup> which by extension may involve chronic pancreatitis on the basis of results of our study. A currently unknown mechanism may also contribute to left-limb pancreatitis and colonic disturbances. Further research with a larger sample size is required to demonstrate the statistical significance of left-limb pancreatitis and diarrhea or constipation in cats. While colonic disturbances can indicate pathology in any portion of the GI tract, it is important that any constipated cat be evaluated for pancreatitis, specifically in the left limb of the pancreas.

There were several limitations associated with our study, the most significant of which being its retrospective nature. General bias may have been introduced due to presentation to a referral hospital and potentially greater magnitude of illness, stringent exclusion criteria for the pancreatitis cats, and the difference in ages between pancreatitis and control cats. Multivariable statistical analysis was used to attempt to minimize any bias due to age, and stratification into age groups was performed for direct comparisons. Two cats in our initial pancreatitis group were excluded for significant peritoneal effusion upon suspicion of unconfirmed underlying neoplasia, which may have introduced mild bias into the initial inclusion. We also combined cats without evidence of CKD with cats demonstrating CKD stage 1, which could have potentially distorted nuance between the groups but was deemed appropriate given standardization using IRIS CKD staging guidelines and our division of cats by CKD stage 2 and higher. Our study also did not control for CKD but rather pancreatitis in cats, and follow-up studies are warranted to control for CKD. A significant limitation of any retrospective study of pancreatitis is

the lack of a true gold-standard diagnostic method for antemortem diagnosis aside from histopathology. Because pancreatitis was suspected in many of the pancreatitis cats, pancreatic biopsy was not pursued due to the potential for worsening their quality of life. However, antemortem pancreatic biopsy is also considered to be significantly fallible due to the segmental nature of histopathologic pancreatic changes and low sensitivity.<sup>39</sup> No nonsurviving cats were submitted for necropsy to confirm histopathologic pancreatitis. We relied upon PLI values together with abdominal ultrasound and clinical signs, which may have resulted in a small number of false-positive cases. A future prospective study that includes histopathology of the pancreas and kidneys at necropsy can provide stronger evidence of association. Regarding renal infarcts, an echocardiogram was not performed with a cardiologist, and data regarding murmurs, N-terminal pro brain natriuretic peptide, and thoracic radiographs were used as a surrogate for cardiac evaluation. Of the original cohort of 136 cats, 12 cats presented with fulminant AKI and were excluded from analyses. However, it is worth noting that nearly 10% of the cats presenting with possible pancreatitis had concurrent AKI. Given our parameters of an increase in serum creatinine  $\geq 0.3$  mg/dL within 1 week or phosphorus  $> 10$  mg/dL at presentation, it is possible that additional cats with AKI were overlooked. However, stable presentation to internal medicine, cats that were not transferred from the emergency department and lack of subsequent hospitalization increased our confidence. Additionally, CKD cats were not hospitalized and it is not known whether their IRIS stages would have improved with hospitalization. Some cats had concurrent pancreatic changes and gastrointestinal changes on abdominal ultrasound, which may have caused distortions of the presenting clinical sign data. A prospective study would ideally include gastroduodenoscopy with GI biopsies or surgical GI biopsies. Additionally, ultrasounds performed by a boarded internal medicine specialist were not reviewed by a veterinary radiologist. Urine specific gravity and symmetric dimethylarginine data were not available for all cats due to owner constraints and clinician preferences, and existing USG data were used to determine whether confounding renal factors were present that should exclude subjects from analysis. A goal of a prospective study would be to ensure a urinalysis is performed for each patient. For the diet analysis, diets were fed for more than half the lifetime of each cat; however, potential individual variations in diet composition could not be accounted for. Assessing dry-food diet in cats in our study was confounded by the effect of dehydration on both pancreatitis and CKD and the bidirectional relationship between these conditions. Further studies are warranted to determine the effect of diet composition on development of pancreatitis and CKD.

In conclusion, feline pancreatitis, particularly acute on chronic pancreatitis as evidenced in 76% of our cats, is associated with an increased prevalence of CKD. This is most evident between the ages of 10 and 20 years, but younger cats were also affected at a rate of over 2:1.

Cats with pancreatitis have a significantly higher prevalence of renal infarction in the absence of overt cardiac disease, which may provide clues to the pathogenesis of this relationship; however, further studies are needed. The relationship between CKD stage and prevalence of renal infarction was not significant, though further studies are warranted. As previously noted, cats with pancreatitis are significantly more likely to have DM. Diets that included canned food were associated with reduced prevalence of pancreatitis. Cats demonstrating subjective signs of gastroesophageal reflux should be evaluated for the presence of acute or acute on chronic pancreatitis. Diarrhea or constipation in cats may be due in part to pancreatitis involving the left limb of the pancreas where this finding is noted. Pancreatitis is an important comorbidity and/or differential diagnosis that should be considered and promptly treated in any case of CKD, renal infarction, DM, gastroesophageal reflux, and potentially diarrhea or constipation in cats. Future prospective studies that are designed to reduce confounding factors are warranted to further evaluate these conclusions.

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## References

1. De Cock HE, Forman MA, Farver TB, Marks SL. Prevalence and histopathologic characteristics of pancreatitis in cats. *Vet Pathol.* 2007;44(1):39–49. doi:10.1354/vp.44-1-39
2. Xenoulis PG, Steiner JM. Current concepts in feline pancreatitis. *Top Companion Anim Med.* 2008;23(4):185–192. doi:10.1053/j.tcam.2008.08.005
3. International Renal Interest Society guidelines for chronic kidney disease. International Renal Interest Society. Accessed February 1, 2023. [www.iris-kidney.com/guidelines/](http://www.iris-kidney.com/guidelines/)
4. Kongtasai T, Paepe D, Meyer E, et al. Renal biomarkers in cats: a review of the current status in chronic kidney disease. *J Vet Intern Med.* 2022;36(2):379–396. doi:10.1111/jvim.16377
5. Polzin DJ. Chronic kidney disease. In: Ettinger S, Feldman E, Côte E, eds. *Textbook of Veterinary Internal Medicine.* Vol 2. 8th ed. Elsevier; 2017:1938–1939.
6. Nivy R, Kaplanov A, Kuzi S, et al. A retrospective study of 157 hospitalized cats with pancreatitis in a tertiary care center: clinical, imaging and laboratory findings, potential prognostic markers and outcome. *J Vet Intern Med.* 2018;32(6):1874–1885. doi:10.1111/jvim.15317
7. Armstrong PJ, Williams DA. Pancreatitis in cats. *Top Companion Anim Med.* 2012;27(3):140–147. doi:10.1053/j.tcam.2012.09.001
8. Jaensch SM. The effect of naturally occurring renal insufficiency on serum pancreatic-specific lipase in cats. *Comp Clin Pathol.* 2013;22:801–803.

9. Lee C, Kathrani A, Maddison J. Retrospective study of the diagnostic utility of Spec fPL in the assessment of 274 sick cats. *J Vet Intern Med.* 2020;34:1406–1412. doi:10.1111/jvim.15797
10. Xenoulis PG, Moraiti KTR, Finco D, Suchodolski JS, Steiner JM. Serum feline pancreatic lipase immunoreactivity and trypsin-like immunoreactivity concentrations in cats with experimentally induced chronic kidney disease. *J Vet Intern Med.* 2021;35(6):2821–2827. doi:10.1111/jvim.16296
11. Schnauß F, Hanisch F, Burgener IA. Diagnosis of feline pancreatitis with SNAP fPL and Spec fPL. *J Feline Med Surg.* 2019;21(8):700–707. doi:10.1177/1098612X18796624
12. Forman MA, Marks SL, De Cock HE, et al. Evaluation of serum feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med.* 2004;18(6):807–815. doi:10.1892/0891-6640(2004)18<807:eosfpl>2.0.co;2
13. Oishi M, Ohno K, Sato T, et al. Measurement of feline lipase activity using a dry-chemistry assay with a triolein substrate and comparison with pancreas-specific lipase (Spec fPL(TM)). *J Vet Med Sci.* 2015;77(11):1495–1497. doi:10.1292/jvms.15-0149
14. Manokaran S, Edwin F, Srinivasaprasad ND, Sujit S. A study of acute kidney injury in severe acute pancreatitis in a tertiary care hospital from South India. *IOSR J Dent Med Sci.* 2018;17(3):45–48. doi:10.9790/0853-1703114548
15. Petejova N, Martinek A. Acute kidney injury following acute pancreatitis: a review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2013;157(2):105–113. doi:10.5507/bp.2013.048
16. Mansfield C. Pathophysiology of acute pancreatitis: potential application from experimental models and human medicine to dogs. *J Vet Intern Med.* 2012;26(4):875–887. doi:10.1111/j.1939-1676.2012.00949.x
17. Kylänpää L, Rakonczay Z Jr, O'Reilly DA. The clinical course of acute pancreatitis and the inflammatory mediators that drive it. *Int J Inflam.* 2012;2012:360685. doi:10.1155/2012/360685
18. Liu D, Wen L, Wang X, et al. The mechanism of lung and intestinal injury in acute pancreatitis: a review. *Front Med (Lausanne).* 2022;9:904078. doi:10.3389/fmed.2022.904078
19. Forman MA, Steiner JM, Armstrong PJ, et al. ACVIM consensus statement on pancreatitis in cats. *J Vet Intern Med.* 2021;35(2):703–723. doi:10.1111/jvim.16053
20. Klöppel G, Detlefsen S, Feyerabend B. Fibrosis of the pancreas: the initial tissue damage and the resulting pattern. *Virchows Arch.* 2004;445(1):1–8. doi:10.1007/s00428-004-1021-5
21. Avram MM. High prevalence of pancreatic disease in chronic renal failure. *Nephron.* 1977;18(1):68–71. doi:10.1159/000180768
22. Radhakrishnan J. Renal infarction. UpToDate Inc. Accessed February 1, 2023. <https://www.uptodate.com/contents/renal-infarction>
23. Zini E, Benali S, Coppola L, et al. Renal morphology in cats with diabetes mellitus. *Vet Pathol.* 2014;51(6):1143–1150. doi:10.1177/0300985813516645
24. Hecht S, Henry G. Sonographic evaluation of the normal and abnormal pancreas. *Clin Tech Small Anim Pract.* 2007;22(3):115–121. doi:10.1053/j.ctsap.2007.05.005
25. Di Donato P, Penninck D, Pietra M, Cipone M, Diana A. Ultrasonographic measurement of the relative thickness of intestinal wall layers in clinically healthy cats. *J Feline Med Surg.* 2014;16(4):333–339. doi:10.1177/1098612X13509080
26. Debruyne K, Haers H, Combes A, et al. Ultrasonography of the feline kidney: technique, anatomy and changes associated with disease. *J Feline Med Surg.* 2012;14(11):794–803. doi:10.1177/1098612X12464461
27. Brown CA, Elliott J, Schmiedt CW, Brown SA. Chronic kidney disease in aged cats: clinical features, morphology, and proposed pathogenesis. *Vet Pathol.* 2016;53(2):309–326. doi:10.1177/0300985815622975
28. Anderson RS. Water balance in the dog and cat. *J Small Anim Pract.* 1982;23:588–598. doi:10.1111/j.1748-5827.1982.tb02519.x
29. Sah RP, Dawra RK, Saluja AK. New insights into the pathogenesis of pancreatitis. *Curr Opin Gastroenterol.* 2013;29(5):523–530. doi:10.1097/MOG.0b013e328363e399
30. Rao P, Niemann B, Szeligo B, et al. Acute pancreatitis induces a transient hypercoagulable state in murine models. *Pancreatology.* 2023;23(3):306–313. doi:10.1016/j.pan.2023.02.007
31. Nielsen L, Holm J, Rozanski E, et al. A multicenter investigation of hemostatic dysfunction in 15 dogs with acute pancreatitis. *J Vet Emerg Crit Care (San Antonio).* 2019;29:264–268. doi:10.1111/vec.12840
32. von Stade LE, Shropshire SB, Rao S, Twedt D, Marolf AJ. Prevalence of portal vein thrombosis detected by computed tomography angiography in dogs. *J Small Anim Pract.* 2021;62(7):562–569. doi:10.1111/jsap.13315
33. Hall H, Valls Sánchez F, Gardini A, Corbetta D, Florey J. Cerebellar ischaemic infarct: a rare complication of pancreatitis. *Vet Rec Case Rep.* 2019;7:e000685. doi:10.1136/vetreccr-2018-000685
34. Huang MJ, Wei RB, Wang Y, et al. Blood coagulation system in patients with chronic kidney disease: a prospective observational study. *BMJ Open.* 2017;7(5):e014294. doi:10.1136/bmjopen-2016-014294
35. Jotha-Mattos L, Vieira AB, Castelo MDSM, et al. Amyloidogenesis of feline amylin and plasma levels in cats with diabetes mellitus or pancreatitis. *Domest Anim Endocrinol.* 2021;74:106532. doi:10.1016/j.domaniend.2020.106532
36. Han E. Diagnosis and management of reflux esophagitis. *Clin Tech Small Anim Pract.* 2003;18(4):231–238. doi:10.1016/S1096-2867(03)00051-3
37. Yoshida N. Inflammation and oxidative stress in gastroesophageal reflux disease. *J Clin Biochem Nutr.* 2007;40(1):13–23. doi:10.3164/jcbn.40.13
38. Benjamin SE, Drobatz KJ. Retrospective evaluation of risk factors and treatment outcome predictors in cats presenting to the emergency room for constipation. *J Feline Med Surg.* 2020;22(2):153–160. doi:10.1177/1098612X19832663
39. Xenoulis PG. Diagnosis of pancreatitis in dogs and cats. *J Small Anim Pract.* 2015;56(1):13–26. doi:10.1111/jsap.12274