Received: 9 December 2022 | Accepted: 17 March 2023

DOI: 10.1111/jvim.16693

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Hyperlipasemia in dogs with acute kidney injury treated with and without hemodialysis

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Abstract

Background: Hyperlipasemia has been reported in dogs with acute kidney injury (AKI) but associations with AKI severity, hemodialysis (HD) treatment, and outcome have not been extensively evaluated.

Objectives: Investigate the prevalence and clinical relevance of hyperlipasemia in dogs with AKI, treated with and without HD.

Animals: Client-owned dogs ($n = 125$) with AKI.

Methods: Retrospective data extraction from medical records, including signalment, cause of AKI, duration of hospitalization, survival, plasma creatinine concentration, and 1,2-*o*-dilauryl-rac-glycero-3-glutaric acid-(6′-methyresorufin) ester (DGGR) lipase activity at admission and throughout hospitalization.

Results: A DGGR-lipase activity >3× the upper reference limit (URL) was found in 28.8% and 55.4% of dogs at admission and during hospitalization, respectively, but only 8.8% and 14.9% of dogs, respectively, were diagnosed with acute pancreatitis. Hyperlipasemia >10 × URL was observed in 32.7% of dogs during hospitalization. The DGGR-lipase activity was higher in dogs with International Renal Interest Society (IRIS) Grades 4–5 than Grades 1–3, but correlation between DGGR-lipase activity and creatinine concentration was poor ($r_s = .22$; 95% confidence intervals [CI], 0.04–0.38). Treatment with HD was not associated with DGGR-lipase activity independent of IRIS grade. Survival to discharge and 30 days after admission was 65.6% and 59.6%, respectively. High IRIS grades ($P = .03$) and high DGGR-lipase activity at admission ($P = .02$) and during hospitalization ($P = .003$) were associated with nonsurvival.

Conclusions and Clinical Importance: Hyperlipasemia is frequent and often marked in dogs with AKI despite only a minority being diagnosed with pancreatitis. Hyperlipasemia is associated with AKI severity but not independently with HD treatment. High IRIS grade and hyperlipasemia were associated with nonsurvival.

Abbreviations: AKI, acute kidney injury; AKI/CKD, acute on chronic kidney disease; AP, acute pancreatitis; CI, confidence intervals; CKD, chronic kidney disease; cPL, canine pancreas-specific lipase (Spec cPL, IDEXX laboratories); DGGR-lipase, 1,2-*o*-dilauryl-rac-glycero-3-glutaric acid-(6′-methyresorufin) ester lipase; HD, hemodialysis; IQR, interquartile range; IRIS, International Renal Interest Society; URL, upper reference limit.

KEYWORDS
acute pancreatitis, canine, lipase, pancreatic enzymes, renal replacement therapy

1 | INTRODUCTION

Acute kidney injury (AKI) and acute pancreatitis (AP) are common diseases in dogs, which may occur independently or as comorbidities. Indeed, concurrent AP was reported in 14%–34% of dogs with AKI or acute on chronic kidney injury (AKI/CKD),[1-4] and concurrent AKI was found in 26% of dogs with AP.[5] A clinical diagnosis of concurrent AP in dogs with AKI is challenging because of nonspecific and overlapping clinical signs. The most common biomarkers for AP currently used in dogs are lipase activity using the 1,2-*o*-dilauryl-rac-glycero glutaric acid-(6′-methylresorufin) ester assay (DGGR-lipase) and concentrations of canine pancreas-specific lipase (cPL; Spec cPL, IDEXX laboratories),[6-8] both of which may be affected by extrapancreatic diseases.[9-12] In particular, increased cPL concentrations or lipase activity have been reported in dogs with kidney disease,[13-15] with cPL concentrations ≥400 μg/L in 21/30 dogs with severe AKI in 1 study.[14] However, most studies showed poor correlation between plasma creatinine concentrations and either lipase activity or cPL concentrations.[16-18]

Increased pancreatic enzyme activity is common in people with kidney failure, and although an increased risk of AP is associated with kidney disease,[19-21] hyperenzymemia without clinical evidence of AP is also frequently observed.[22,23] Thus, the extent to which hyperenzymemia is caused by decreased renal clearance of pancreatic enzymes or concomitant pancreatic injury remains unclear in many cases. However, several studies have shown a link between treatment with hemodialysis (HD) and hyperlipasemia or hyperamylasemia or both in people, which has been variably attributed to hemodynamic factors, subclinical pancreatitis, heparin treatment, and decreased kidney function.[24-28]

Little information is available about hyperlipasemia in dogs undergoing HD. One study showed cPL concentrations ≥400 μg/L in 33/53 dogs with AKI undergoing HD, but found no association with outcome.[15] However, cPL concentrations were measured within 7 days before or after admission, and thus an association between HD treatment and hyperlipasemia was unclear. In another study of dogs with AKI or AKI/CKD undergoing HD, 6/40 dogs had concurrent AP, which was associated with nonsurvival.[2]

We have anecdotally observed severe hyperlipasemia in several dogs undergoing HD at our institution, particularly in dogs with leptospirosis, but the clinical relevance of this finding is unclear. Our aims were thus to investigate the prevalence of increased DGGR-lipase activity in dogs with AKI treated with and without HD, and to evaluate the clinical relevance of hyperlipasemia and its association with severity of kidney disease, treatment modality, and outcome. We hypothesized that increased DGGR-lipase activity would be frequent in dogs with AKI, and that hyperlipasemia would be associated with HD, more severe kidney injury, and negative outcome.

2 | MATERIALS AND METHODS

The medical records and clinicopathologic database were retrospectively reviewed for dogs presented to the Small Animal Clinic, Vetsuisse Faculty, University of Bern, Switzerland, between August 2018 and February 2021. Dogs were included in the study if AKI was diagnosed at admission, and if both DGGR-lipase activity and plasma creatinine concentrations were measured from the same blood sample within the first 24 hours of admission. Dogs presented for CKD were not considered eligible. Dogs also were excluded if they had a prior history of pancreatitis, if they were considered to have primary AP at admission, or if medical records were incomplete. For dogs presented on more than one occasion for AKI, only data from the first admission were included. For dogs receiving plasma exchange treatment, only admission data were included, because plasma exchange may decrease plasma lipase activity.[29]

A diagnosis of AKI was made by a board-certified internist or a primary clinician working under their direct supervision, and generally was based on recent history, compatible clinical signs (e.g., lethargy, anorexia, vomiting, diarrhea, weakness, oliguria, or anuria), supportive ultrasonographic findings (e.g., renomegaly, hyperechoic renal cortices, renal pelvic dilatation, and perirenal effusion), and supporting clinicopathologic evidence (e.g., azotemia, hyperkalemia, hyperphosphatemia, isosthenuria or minimally concentrated urine, glucosuria, cylindruria).[30] Likewise, a clinical diagnosis of secondary AP at admission or AP developing during hospitalization was made by a board-certified internist or primary clinician under their direct supervision, and generally was based on a combination of clinical signs, cPL or DGGR-lipase results or both, and ultrasonographic findings. All ultrasonographic examinations were performed by a board-certified radiologist or imaging resident under their direct supervision. The decision to perform HD was made by a board-certified internist specialized in veterinary nephrology and HD, and generally depended on clinical status, disease severity, response to conservative treatment, and owner agreement. Intermittent HD was performed as previously described, using citrate or a mixture of heparin and citrate as anticoagulant.[31]

Data collected included signalment, cause of AKI, duration of hospitalization, outcome (all-cause mortality including euthanasia) to discharge and 30-day outcome from day of admission, plasma creatinine concentrations, and DGGR-lipase activities at admission and throughout the period of hospitalization, treatment modality (conservative or HD), diagnosis of concurrent AP at admission or developing during hospitalization, and results of necropsy examinations where available.

Measurement of lipase activity was performed by the Clinical Diagnostic Laboratory, Vetsuisse Faculty, University of Bern, Switzerland using a commercial assay (LIPC, Ref. 03029590, Roche Diagnostics, Basel, Switzerland) based on the previously validated

DGGR method,[6] using a clinical chemistry analyzer (Cobas c501, Roche Diagnostics, Basel, Switzerland) according to the manufacturer's instructions, using lithium–heparin plasma samples. This is a catalytic colorimetric assay in which the DGGR substrate is cleaved by lipase in presence of colipase and bile salts. The substrate is preferentially hydrolyzed by pancreatic lipase, making it more specific for the detection of pancreatic lipase activity compared to 1,2-diglyceride-based assays.[6] During the study period, DGGR-lipase activity was measured in all plasma samples submitted for biochemical analyses to the diagnostic laboratory, but results were reported only if assays were specifically requested by clinicians. Plasma DGGR-lipase activity thus was measured regardless of clinicians' suspicion of pancreatic disease and only on plasma left over after all requested analyses were performed. The reference interval for DGGR-lipase activity (25–180 U/L) was previously established in-house using samples from 67 healthy adult dogs. Activities of DGGR-lipase were categorized into lipase Grade 1 (≤3× upper reference limit [URL]; ≤540 U/L), lipase Grade 2 (3–10 × URL; 541–1800 U/L), lipase Grade 3 (10–30 × URL; 1801–5400 U/L), and lipase Grade 4 (>30 × URL; >5400 U/L). For in-hospital DGGR-lipase activities, the maximum of DGGR-lipase measurements excluding the initial admission measurement was used for data analysis.

Plasma creatinine concentrations were measured on the same chemistry analyzer using a commercial enzymatic kit (CREP2, Ref. 03263991, Roche Diagnostics, Basel, Switzerland). All analyses were performed on heparinized plasma samples. Grading of AKI was performed at admission as well as during hospitalization for each dog according to guidelines of the International Renal Interest Society (IRIS; http://www.iris-kidney.com, last accessed July 2022), and dogs were grouped into mild to moderate AKI (IRIS Grades 1–3) or severe AKI (IRIS Grades 4–5). For data analysis, in-hospital IRIS grades corresponded to the maximum IRIS grade measured at any time point including the initial admission IRIS grade. Causes of AKI were grouped into infectious and noninfectious etiologies.

The study design was approved by the hospital board, and signed owner consent for the use of medical data and surplus samples for research was obtained for all dogs.

2.1 | Statistical analysis

Data analysis was performed using commercial software (MedCalc Statistical Software version 20.011, MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022) and, for Fisher's exact tests, online statistical software (http://vassarstats.net/ and https://astatsa.com/FisherTest/ last accessed October 2022). Data were analyzed for normality using Shapiro-Wilk tests and by examining normality plots. Because most data were not normally distributed, nonparametric analyses were performed. Continuous variables were reported as median, range and interquartile range (IQR), and differences between groups were analyzed using Mann-Whitney tests. Categorical variables were reported as numbers and percentages, and the differences between groups were analyzed using chi-squared or Fisher's exact tests, where appropriate. Wilcoxon's signed rank tests were used for comparisons between DGGR-lipase activity at admission and during hospitalization. Spearman's rank was used to assess the correlation between DGGR-lipase activity and plasma creatinine concentrations. Odds ratios for 30-day survival were calculated for dogs in different IRIS groups and for dogs with different lipase grades during hospitalization. Statistical significance was set at $P < .05$.

3 | RESULTS

3.1 | Animals

An initial 136 dogs met the inclusion criteria. Dogs were excluded for a prior history of pancreatitis ($n = 3$), a primary diagnosis of AP at admission ($n = 5$), and insufficient data in the medical records ($n = 3$). The final dataset therefore consisted of 125 dogs (Figure 1). Dogs considered to have primary AP at admission all were presented with severe clinical signs and imaging findings consistent with AP but only mild to moderate AKI, except for 1 dog with diabetic ketoacidosis, AP and severe AKI. Dogs represented 58 breeds, the most common being mixed breed (22/125; 17.6%), Labrador Retriever (17/125; 13.6%), and Malinois (5/125; 4%), with <5 each of other breeds. The median age was 5.8 years (range, 0.2–18.6; IQR, 2.9–9.6). There were 62 females (40 spayed) and 63 males (26 neutered).

The cause of AKI was unknown (29/125; 23.2%), leptospirosis (23/125; 18.4%), intoxication (14/125; 11.2%), pyelonephritis (13/125; 10.4%), sepsis (8/125; 6.4%), postoperative AKI (6/125; 4.8%), and ≤ 5 cases of other etiologies (including glomerulonephritis, neoplasia, heat stroke, immune-mediated disease, cardiovascular disorders, borreliosis, babesiosis, snake bite, liver failure, leishmaniosis, and AKI secondary to ureteral obstruction). There were 74/125 dogs (59.2%) in the noninfectious and 51/125 dogs (40.8%) in the infectious etiology group. Eleven dogs (8.8%) had a diagnosis of secondary or concurrent AP at the time of admission.

3.2 | Admission DGGR-lipase activities and plasma creatinine concentrations

At admission, DGGR-lipase activity ranged from 13 to 13 788 U/L (Table 1). The DGGR-lipase activity was ≤3 × URL (lipase Grade 1) in 89/125 (71.2%) dogs. Hyperlipasemia >3 × URL was present in 36/125 (28.8%) dogs; consisting of 25/125 (20.0%) dogs with lipase Grade 2 (3–10 × URL), 10/125 (8.0%) dogs with lipase Grade 3 (10–30 × URL), and 1 dog with lipase Grade 4 (>30 × URL).

Plasma creatinine concentrations at admission ranged from 0.49 to 19.75 mg/dL (43–1746 µmol/L; median, 5.38 mg/dL [476 µmol/L]; IQR, 3.25–8.46 mg/dL [287–748 µmol/L]), with 13/125 dogs (10%) classified as IRIS Grade 1, 15/125 (12%) as Grade 2, 26/125 (21%) as Grade 3, 50/125 (40%) as Grade 4, and 21/125 (17%) as Grade 5. A significant difference was found ($P = .03$) in admission DGGR-lipase activity between dogs in admission IRIS 1–3 and those in admission IRIS 4–5

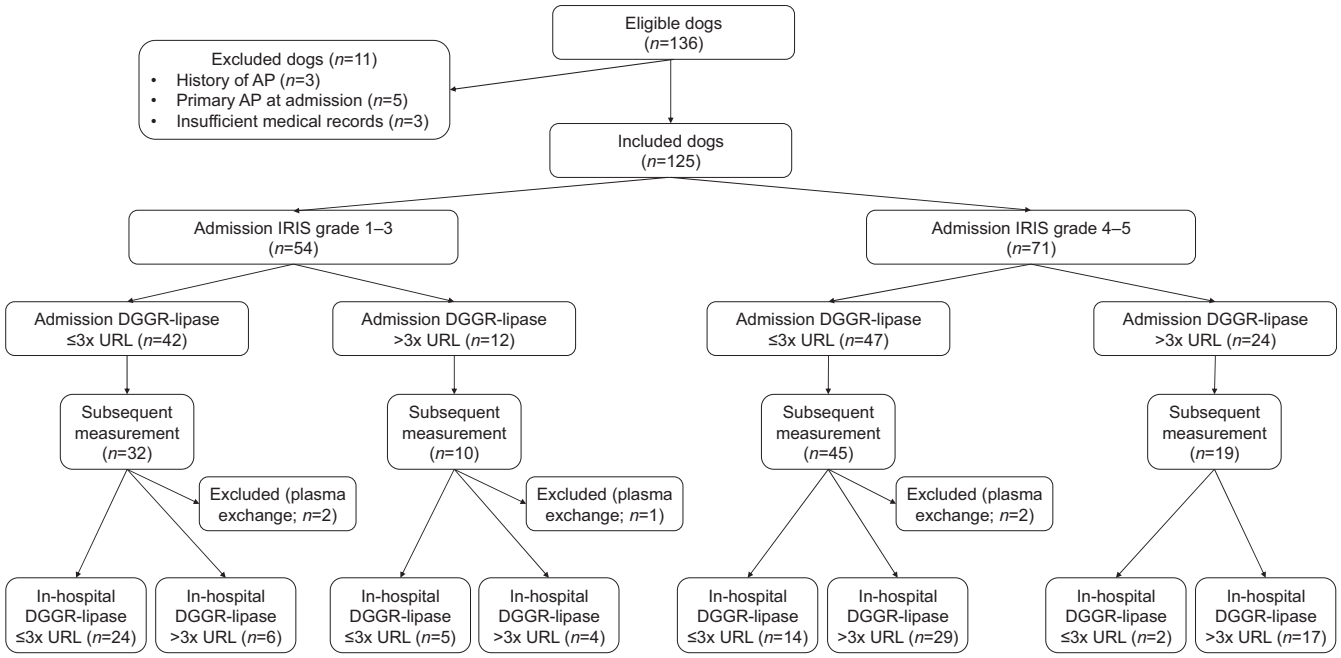

FIGURE 1 Flow diagram of dogs with acute kidney injury stratified by IRIS grades at admission, with admission and in-hospital DGGR-lipase activities. AP, acute pancreatitis; DGGR, 1,2-*o*-dilauryl-rac-glycero-3-glutaric acid-(6′-methyresorufin) ester; IQR, interquartile range; IRIS, International Renal Interest Society; URL, upper reference limit.

TABLE 1 DGGR-lipase activities at admission in 125 dogs with acute kidney injury.

Dog groups	*n* (%)	DGGR-lipase activity (U/L), median (Min; IQR; Max)
All dogs	125 (100%)	177 (13; 82–674; 13 788)
Admission IRIS Grades 1–3	54 (43.2%)	146 (13; 64–424; 5116)*
Admission IRIS Grades 4–5	71 (56.8%)	240 (17; 93–801; 13 788)*
Noninfectious causes of AKI	74 (59.2%)	149 (29; 78–507; 13 788)
Infectious causes of AKI	51 (40.8%)	249 (13; 86–789; 5116)
Survival to discharge	82 (65.6%)	144 (13; 79–484; 5116)†
Nonsurvival to discharge	43 (34.4%)	268 (17; 114–880; 13 788)†

Note: The same superscript symbols denote data that differed significantly.
Abbreviations: DGGR, 1,2-*o*-dilauryl-rac-glycero-3-glutaric acid-(6′-methyresorufin) ester; IQR, interquartile range; IRIS, International Renal Interest Society.

groups (Table 1). However, the correlation between admission DGGR-lipase activity and admission plasma creatinine concentration was poor ($r_s = .22$; 95% confidence intervals [CI], .04–.38). No significant difference ($P = .22$) was found in admission DGGR-lipase activities between dogs with infectious and those with noninfectious causes of AKI (Table 1).

3.3 | Duration of hospitalization and follow-up to discharge

The duration of hospitalization ranged from 1 to 26 days (median, 6 days; IQR, 3–10 days). Dogs survived to discharge in 82/125 cases (65.6%). These were 64/89 (71.9%) dogs with DGGR-lipase Grade 1, 14/25 (56%) dogs with Grade 2, and 4/10 (40%) with Grade 3. The only dog admitted with lipase Grade 4 died within 24 hours of admission. Median admission DGGR-lipase activity was significantly higher ($P = .02$) in nonsurvivors than in survivors (Table 1).

3.4 | Subsequent DGGR-lipase measurements

One-hundred six dogs had at least 1 DGGR-lipase activity measurement during hospitalization after the initial admission measurement. Of these, data for 5 dogs receiving plasma exchange were excluded (Figure 1). The remaining 19/125 dogs either died or were discharged without subsequent measurements of DGGR-lipase activity. For the 101 dogs included with in-hospital measurements, the median number of measurements after admission DGGR-lipase activity was 3 (IQR, 2–6.5 measurements). A total of 56/101 dogs (55.4%) had hyperlipasemia >3 × URL on at least 1 subsequent measurement, including 33/101 (32.7%) dogs with DGGR-lipase activity >10 × URL, and 17/101 (16.8%) dogs with DGGR-lipase activity >30 × URL. Admission DGGR-lipase activity was significantly ($P < .001$) lower than in-hospital activity (Table 2). The maximum of all DGGR-lipase activities measured occurred at admission in 20/101 (19.8%) dogs, of which 3 dogs were in the HD group, and subsequently in 80/101 (79.2%) dogs; in 1 dog, admission and in-hospital DGGR-lipase activities were the same. Likewise, the in-hospital lipase grades were significantly higher than admission grades ($P = .005$), whereby lipase increased by at least 1 grade from admission in 49/101 (48.5%) dogs but decreased in only 7/101 (6.9%) dogs (Figure 2). Median time for DGGR-lipase

TABLE 2 DGGR-lipase activity at admission and during hospitalization in 101 dogs with acute kidney injury, for which repeated lipase measurements were performed.

		DGGR-lipase activity (U/L), median (Min; IQR; Max)	
Dog groups	***n* (%)**	**Admission**	**In hospital**
All dogs	101 (100%)	151 (13; 82–632; 5186)*	854 (25; 195–2511; 19 857)*
In-hospital IRIS Grades 1–3	36 (35.6%)	136 (13; 66–510; 3911)	239 (46; 126–543; 18 441)†
In-hospital IRIS Grades 4–5	65 (64.4%)	224 (17; 87–412; 5186)	1474 (25; 452–4382; 19 857)†
No hemodialysis	68 (67.3%)	183 (13; 82–712; 5186)	351 (25; 157–2052; 18 441)‡
Hemodialysis	33 (32.7%)	133 (40; 82–394; 4218)	1415 (49; 700–4789; 19 857)‡
Survival (30 days)	56 (59.6%)	132 (13; 79–419; 4183)†	768 (25; 163–1743; 8323)§
Nonsurvival (30 days)	38 (40.4%)	347 (17; 111–882; 5186)†	1709 (53; 395–8295; 19 857)§

Note: Survival data were available for 94 dogs. The same superscript symbols denote values with a significant difference.
Abbreviations: DGGR, 1,2-*o*-dilauryl-rac-glycero-3-glutaric acid-(6′-methyresorufin) ester; IQR, interquartile range; IRIS, International Renal Interest Society.

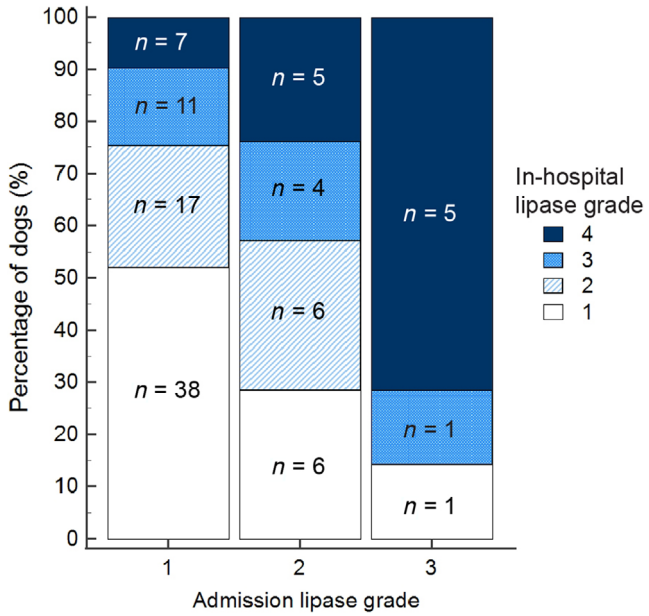

FIGURE 2 DGGR-lipase grades at admission compared to grades during hospitalization in 101 dogs with acute kidney injury. Grade 1, DGGR-lipase activity ≤3 × URL (upper reference limit); Grade 2, 3–10 × URL; Grade 3, 10–30 × URL; Grade 4, >30 × URL. DGGR, 1,2-*o*-dilauryl-rac-glycero-3-glutaric acid-(6′-methyresorufin) ester.

activity to peak was 2.7 days after admission (IQR, 0.6–4.7 days). In total, 33/101 (32.7%) dogs received HD and 68/101 (65.3%) did not. The highest in-hospital DGGR-lipase activity was measured after initiation of HD in 31/33 (94%) dogs undergoing HD.

A significant difference was found in in-hospital DGGR-lipase activity between dogs with in-hospital IRIS Grades 1–3 and those with IRIS Grades 4–5 ($P < .001$). However, no difference was found in admission DGGR-lipase activity between dogs with in-hospital IRIS Grades 1–3 compared to those with IRIS Grades 4–5 ($P = .16$; Table 2).

Between dogs treated with and without HD, no difference was found in admission DGGR-lipase activity ($P = .44$) or lipase grades ($P = .36$), but a significant difference was found in in-hospital DGGR-lipase activity ($P = .01$; Table 2) and grades ($P = .01$; Table 3). No difference was found in in-hospital DGGR-lipase grade (Table 3) or activity ($P = .21$ for IRIS Grades 1–3 and $P = .41$ for IRIS Grades 4–5) between dogs treated with or without HD within each of the 2 in-hospital IRIS groups evaluated separately.

A clinical diagnosis of concurrent AP at admission was made in 7/101 (6.9%) dogs, including 3/21 and 4/7 dogs with admission lipase Grades of 2 and 3, respectively. During hospitalization, AP developed in an additional 15/101 (14.9%) dogs, which were 1/45, 3/23, 3/16 and 8/17 dogs with in-hospital lipase Grades 1, 2, 3, and 4, respectively.

No difference was found between either admission ($P = .42$) or in-hospital ($P = .2$) lipase grades in dogs with an infectious and those with a noninfectious etiology of AKI.

3.5 | Outcome

The 30-day outcome for dogs with at least 1 in-hospital DGGR-lipase measurement was available in 94 dogs, of which 38 (40.4%) died within 30 days of admission (Table 2). The DGGR-lipase activity both at admission ($P = .02$) and during hospitalization ($P = .003$) was significantly associated with 30-day outcome (Table 2). Lipase grades also differed significantly during hospitalization ($P = .002$) but not at admission ($P = .08$) between survivors and nonsurvivors at 30 days (Figure 3), whereby 53/77 (68.8%) dogs with in-hospital lipase grades of 1, 2, or 3 survived compared to only 3/17 (17.6%) dogs with an in-hospital lipase Grade 4.

In addition, significantly longer 30-day survival ($P = .03$) was found in dogs with in-hospital IRIS Grades 1–3 compared to IRIS Grades 4–5, whereby 25/33 (75.8%) and 31/61 (50.8%) survived, respectively (Figure 4). The odds ratio for death within 30 days was 3.0 (95% CI, 1.2–7.8) for dogs with in-hospital IRIS Grades 4–5 compared to those with in-hospital IRIS Grades 1–3 ($P = .02$). The odds ratio for death within 30 days was 10.3 (95% CI, 2.7–39.2) for dogs

TABLE 3 Grades of DGGR-lipase activity during hospitalization in 101 dogs treated with and without hemodialysis for acute kidney injury, stratified by in-hospital IRIS Grades 1–3 versus IRIS Grades 4–5.

		DGGR-lipase activity grades (*n*)				
Dog groups	**Groups**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	***P***
All dogs	No hemodialysis	38	11	10	9	.01
	Hemodialysis	7	12	6	8	
In-hospital IRIS Grades 1–3	No hemodialysis	26	5	1	3	.99
	Hemodialysis	1	0	0	0	
In-hospital IRIS Grades 4–5	No hemodialysis	12	6	9	6	.18
	Hemodialysis	6	12	6	8	

Note: Grade 1, DGGR-lipase activity ≤3 × URL (upper reference limit); Grade 2, 3–10 × URL; Grade 3, 10–30 × URL; Grade 4, >30 × URL.
Abbreviations: DGGR, 1,2-*o*-dilauryl-rac-glycero-3-glutaric acid-(6′-methyresorufin) ester; IQR, interquartile range; IRIS, International Renal Interest Society.

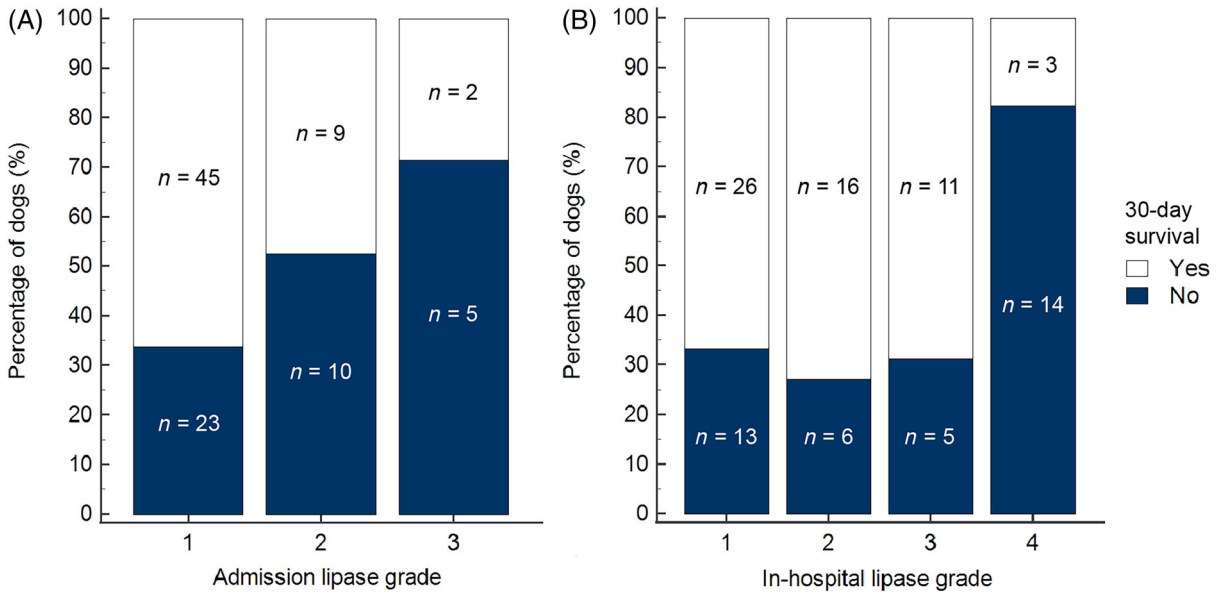

FIGURE 3 30-Days outcome in 94 dogs with acute kidney injury and different grades of DGGR-lipase activities, (A) at admission, and (B) during hospitalization. Lipase Grade 1, DGGR-lipase activity ≤3 × URL (upper reference limit); Grade 2, 3–10 × URL; Grade 3, 10–30 × URL; Grade 4, >30 × URL. DGGR, 1,2-*o*-dilauryl-rac-glycero-3-glutaric acid-(6′-methyresorufin) ester.

with in-hospital lipase Grade 4 compared to dogs with other grades ($P < .001$). When evaluating only dogs within the in-hospital IRIS 4–5 group, the odds ratio for death within 30 days was 9.7 (95% CI, 1.9–48.3; $P = .01$) for dogs with in-hospital lipase of Grade 4 compared to dogs with lipase Grades 1–3 (Figure 4).

For dogs undergoing HD, 18/33 (54.5%) survived to 30 days. Of these, only 1 dog had a plasma creatinine concentration >5 mg/dL (>442 µmol/L) and thus would have been considered dialysis-dependent at 30 days,[15] although dialysis was not continued at the owner's request.

Necropsies were performed in 9 dogs, with no signs of gross or microscopic pancreatic abnormalities in 6, of which 3 had an in-hospital DGGR-lipase Grade 1, 2 had Grade 2, and 1 had Grade 3; none of these were considered clinically to have AP. The 3 remaining dogs had a clinical diagnosis of AP during hospitalization, all with in-hospital lipases of Grade 4, including the dog with the highest measured DGGR-lipase activity of the study population. Histopathological examination of the pancreas determined that 1 of these dogs had extensive necrosis of peripancreatic fat and 1 dog had a grossly nodular pancreas, but no histopathological abnormalities of the pancreas itself were found in either. The last dog had histologic evidence of mild interstitial edema but no inflammation or parenchymal changes were observed.

4 | DISCUSSION

In our study, hyperlipasemia >3 × URL at admission and during hospitalization was found in 28.8% and 55.4%, respectively, of dogs presenting with AKI, and was associated with both high IRIS grade and a

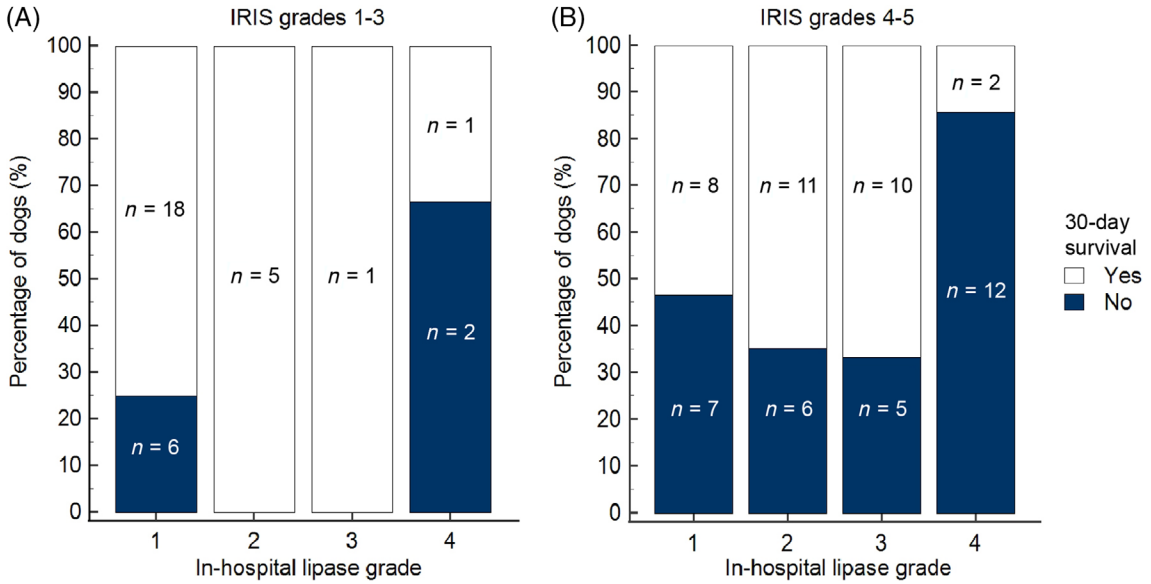

FIGURE 4 30-Days outcome in dogs with (A) IRIS Grades 1–3 ($n = 33$) and (B) IRIS Grades 4–5 ($n = 61$) and different grades of in-hospital DGGR-lipase activity. Lipase Grade 1, DGGR-lipase activity ≤3 × URL (upper reference limit); Grade 2, 3–10 × URL; Grade 3, 10–30 × URL; Grade 4, >30 × URL. DGGR, 1,2-*o*-dilauryl-rac-glycero-3-glutaric acid-(6′-methyresorufin) ester; IRIS, International Renal Interest Society.

negative outcome. To our knowledge, ours is the first study to examine the prevalence and development of hyperlipasemia, measured by the DGGR-lipase assay, in dogs with AKI both with and without HD treatment.

We found prevalences of hyperlipasemia in dogs with AKI similar to those reported in a previous study, which described cPL concentrations ≥400 μg/L in 62% of 53 dogs with AKI undergoing intermittent HD.[15] However, cPL concentrations in that previous study were measured at any time within 7 days before or after admission, and an association with either HD treatment or admission IRIS grades therefore cannot be inferred. Moreover, cPL concentrations were measured at the request of clinicians in the latter study, presumably because AP was suspected, but DGGR-lipase was measured in our study regardless of clinicians' suspected diagnoses. Similarly, another study found cPL concentrations ≥400 μg/L either at admission or within the first 8 days of hospitalization in 71% of 28 dogs with AKI of IRIS Grades 3–5 not undergoing HD.[14] Lipase activity also was measured in that study and reported to be significantly higher in dogs with AKI compared to healthy control dogs, but neither the assay method nor the prevalence of increased lipase activity were disclosed. Authors of both studies apparently interpreted increased cPL concentrations as evidence for pancreatitis,[14,15] without describing what other clinical data were used to support the diagnosis, despite cPL being reported to be increased in many extrapancreatic diseases, including gastrointestinal,[32-34] infectious,[11,12] and endocrine disease,[35] among others. In our study, a clinical diagnosis of AP was only made in 8.8% and 14.9% of dogs at admission and during hospitalization, respectively, which is similar to previous studies in dogs that reported concurrent pancreatitis in 15%[2] and 14%[4] of dogs presenting with AKI treated with and without HD, respectively, but somewhat lower than 2 studies describing AP in 22%[3] and 34%[1] of dogs with AKI and AKI/CKD, respectively. However, a diagnosis of AP in the face of AKI is challenging because clinical signs overlap and may be concealed by the administration of antiemetics and analgesics. Additionally, the suboptimal sensitivity of abdominal ultrasound examination limits its use as a diagnostic tool and, at our institution, ultrasound examination is rarely repeated in these patients during hospitalization after an initial examination unless clinical signs change substantially during hospitalization. The true prevalence of AP therefore may have been underestimated in our study, particularly because ultrasonographic changes in AP may occur after the onset of clinical signs.[36] Moreover, because results of DGGR-lipase activity were not reported unless the measurement was specifically requested, clinicians often were blinded to results, which may otherwise have increased the prevalence of a clinical diagnosis of AP. Because histopathological examination of the pancreas only rarely was performed postmortem, the extent to which increased DGGR-lipase activity was a consequence of AP in our study is not known. In people undergoing HD for CKD or end-stage kidney disease, increased pancreatic enzyme activities are reported in up to 80% of cases, but only occasionally exceed 3–5 × URL and rarely surpass 10 × URL.[22,28,37,38] Many of these studies found hyperlipasemia in the absence of clinical evidence of AP,[22,28,38] supporting our findings.

We observed a significant increase in DGGR-lipase activity during hospitalization compared to admission, which was >3 × URL in 55% of dogs. Moreover, DGGR-lipase activity was markedly increased (>10 × URL) in 33% of dogs during hospitalization but in only 8% of dogs at admission. This prevalence of in-hospital increases in DGGR-lipase activity was higher than the 23% previously reported in dogs presenting with critical illness of any cause, which included dogs presenting with primary AP.[16] Kidney disease was the most frequent diagnosis in dogs with in-hospital DGGR-lipase increases in that study,

and of dogs with kidney disease, approximately one-third had hyperlipasemia >3 × URL at admission and half had significant increases during hospitalization, paralleling our findings.

We found that high DGGR-lipase activity at admission and particularly during hospitalization was associated with high IRIS grades, although correlation of DGGR-lipase activity and plasma creatinine concentrations at admission was poor. One previous study in dogs, in which cPL concentrations ≥400 μg/L were measured within 1–8 days of admission in 71% of 28 dogs with IRIS Grades 3–5, found a positive correlation between cPL and plasma creatinine concentrations, which was interpreted as evidence of predisposition to AP in dogs with severe AKI.[14] However, dogs with AKI were compared to healthy controls and the extent to which the severity of AKI was associated with increased cPL concentrations was not evaluated. Moreover, most other studies showed poor correlation between plasma creatinine concentrations and either DGGR-lipase activity or cPL concentrations in dogs.[17,18]

We measured higher DGGR-lipase activity during hospitalization in dogs receiving HD treatment compared to those treated conservatively. However, no difference was found in DGGR-lipase activity between the treatment groups when evaluated separately in dogs with IRIS Grade 1–3 or IRIS Grade 4–5, respectively. This finding suggests that only the severity of AKI but not treatment modality itself was associated with high DGGR-lipase activity. However, only 1 dog in the IRIS 1–3 group underwent HD, and thus statistical analysis within this IRIS group was likely underpowered, potentially leading to type II statistical error. The only previous study evaluating lipase in dogs undergoing intermittent HD found no association between cPL ≥400 μg/L and dialysis-dependency at 30 days, but it is not clear from the study design how many measurements were performed before or after HD, and thus the relationship between cPL and HD itself cannot be evaluated.[15] Only 1 dog in our study would have been considered dialysis-dependent at 30 days, and thus evaluation of any association between hyperlipasemia and 30-day dialysis dependency was not possible. Similarly, in a study of uremic people, 80% were found to have hyperlipasemia with higher enzyme activity in patients with more severe kidney impairment, but no difference was found between predialysis and postdialysis activities.[28]

In some studies in human medicine, however, an increase in postdialysis lipase activity was found when heparin was used as an anticoagulant for HD,[26] likely because of heparin-induced release of lipoprotein lipase or hepatic lipase or both. In cats and dogs, the use of heparin also leads to increases of DGGR-lipase activity, but these were short-lived (<20 minutes) and of minimal magnitude with a median increase from 49.8 to 54.1 U/L in dogs.[39] Because we use citrate or a mixture of citrate and heparin as anticoagulant at our institution and previously reported heparin-induced increases in lipase were minimal compared to the increases we observed during hospitalization, heparin-induced release of nonpancreatic lipases was unlikely to be a clinically relevant factor affecting lipase activity in our study.

Previous studies have reported increased lipase activity or cPL concentrations in dogs with a variety of infectious disorders, including ehrlichiosis, babesiosis, and parvovirosis.[11,12,32] Infectious disease therefore may have contributed to hyperlipasemia in some dogs in our study, but we found no difference in DGGR-lipase activity between dogs with and without an infectious cause of AKI. However, not all dogs were tested for all possible infectious agents, and therefore some underlying infectious etiologies may have been missed.

Overall survival (66% to discharge and 60% to 30 days) was similar to or higher than that previously reported for dogs with AKI both with and without HD, which ranges from 27% to 76%.[2,3,14,15,40,41] However, survival was defined differently among studies, and some studies only included dogs undergoing HD whereas others only evaluated dogs not treated by HD. In addition, some studies enrolled only dogs with IRIS Grades of ≥3. Thus, direct comparison among studies is difficult. Additionally, we found that hyperlipasemia was associated with lower survival to discharge and at 30 days after admission. Moreover, only 18% of dogs with severe in-hospital hyperlipasemia (>30 × URL) survived to 30 days, representing an >10× higher odds of negative outcome compared to lower lipase grades. Although negative outcome at 30 days also was associated with IRIS grades, as previously described,[1] extremely high in-hospital DGGR-lipase activity was associated with poor outcome for dogs within IRIS groups 4–5. This observation suggests that severe hyperlipasemia may be an independent predictor of survival in dogs with severe AKI, rather than merely mirroring IRIS grades. Similarly, DGGR-lipase activity was significantly higher in nonsurvivors in a study of 100 dogs with AKI/CKD.[1]

Our study had some limitations. The timing and frequency of measurements of DGGR-lipase was not standardized and assays were performed only if clinicians submitted samples for biochemical analyses, presumably to monitor patient progress. Dogs with higher IRIS grades and those receiving HD thus were more likely to have frequent samples analyzed than those in lower IRIS grades or those not receiving HD. Because only the maximum measured DGGR-lipase after admission was used for data analysis of in-hospital lipase activity, this design feature may have favored increased DGGR-lipase activity in these dogs, because peak lipase activity would more easily be found. Likewise, the maximum of in-hospital measurements was compared to a single analysis at admission, favoring higher measurements during hospitalization compared to admission. Additionally, the decision to perform HD was not only based on medical indication but also on owner financial constraints and ethical perceptions. Therefore, not all dogs for which HD was considered medically indicated subsequently were treated with HD. Furthermore, the review of medical records to determine whether dogs were considered to have concurrent AP or AP developing during hospitalization may have been biased by a lack of standardized criteria for a diagnosis of AP. Lastly, only few nonsurvivors underwent necropsy examination. For these reasons, the degree to which hyperlipasemia reflected AP in our study remains unclear.

In conclusion, hyperlipasemia, including severe hyperlipasemia, was frequent in dogs with AKI at admission and during hospitalization, despite only a minority being considered clinically to have AP. Hyperlipasemia was associated with the severity of AKI but was not independently associated with HD treatment. Extreme hyperlipasemia (>30 × URL) was

associated with increased odds of all-cause mortality at 30 days. Additional studies are needed to evaluate the underlying causes for marked hyperlipasemia in dogs with AKI and to assess the extent to which clinically relevant AP is a contributing factor.

ACKNOWLEDGMENT

No funding was received for this study.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUCU) OR OTHER APPROVAL DECLARATION

Approved by the Small Animal Clinic, Department of Clinical Veterinary Medicine, University of Bern hospital board. Signed owner consent for the use of medical data and left-over samples for research was obtained for all dogs.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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REFERENCES

1. Dunaevich A, Chen H, Musseri D, et al. Acute on chronic kidney disease in dogs: etiology, clinical and clinicopathologic findings, prognostic markers, and survival. *J Vet Intern Med*. 2020;34:2507-2515.
2. Perondi F, Lippi I, Ceccherini G, Marchetti V, Bernicchi L, Guidi G. Evaluation of a prognostic scoring system for dogs managed with hemodialysis. *J Vet Emerg Crit Care (San Antonio)*. 2018;28:340-345.
3. Rimer D, Chen H, Bar-Nathan M, Segev G. Acute kidney injury in dogs: etiology, clinical and clinicopathologic findings, prognostic markers, and outcome. *J Vet Intern Med*. 2022;36:609-618.
4. Vaden SL, Levine J, Breitschwerdt EB. A retrospective case-control of acute renal failure in 99 dogs. *J Vet Intern Med*. 1997;11:58-64.
5. Gori E, Lippi I, Guidi G, Perondi F, Pierini A, Marchetti V. Acute pancreatitis and acute kidney injury in dogs. *Vet J*. 2019;245:77-81.
6. Graca R, Messick J, McCullough S, Barger A, Hoffmann W. Validation and diagnostic efficacy of a lipase assay using the substrate 1,2-o-dilauryl-rac-glycero glutaric acid-(6′ methyl resorufin)-ester for the diagnosis of acute pancreatitis in dogs. *Vet Clin Pathol*. 2005;34:39-43.
7. Cridge H, Twedt DC, Marolf AJ, Sharkey LC, Steiner JM. Advances in the diagnosis of acute pancreatitis in dogs. *J Vet Intern Med*. 2021;35:2572-2587.
8. Steiner JM, Teague SR, Williams DA. Development and analytic validation of an enzyme-linked immunosorbent assay for the measurement of canine pancreatic lipase immunoreactivity in serum. *Can J Vet Res*. 2003;67:175-182.
9. Rallis TS, Koutinas AF, Kritsepi M, et al. Serum lipase activity in young dogs with acute enteritis or gastroenteritis. *Vet Clin Pathol*. 1996;25:65-68.
10. Han D, Choi R, Hyun C. Canine pancreatic-specific lipase concentrations in dogs with heart failure and chronic mitral valvular insufficiency. *J Vet Intern Med*. 2015;29:180-183.
11. Koster LS, Steiner JM, Suchodolski JS, et al. Serum canine pancreatic-specific lipase concentrations in dogs with naturally occurring Babesia rossi infection. *J S Afr Vet Assoc*. 2015;86:E1-E7.
12. Mylonakis ME, Xenoulis PG, Theodorou K, et al. Serum canine pancreatic lipase immunoreactivity in experimentally induced and naturally occurring canine monocytic ehrlichiosis (Ehrlichia canis). *Vet Microbiol*. 2014;169:198-202.
13. Jaensch S. Associations between serum amylase, lipase and pancreatic specific lipase in dogs. *Comp Clin Pathol*. 2010;21:157-160.
14. Rosa DBSK, Veado JCC, Ceregatti MG, et al. Predisposition to acute pancreatitis in dogs with severe acute renal failure. *Pesq Vet Bras*. 2021;41:41.
15. Takada K, Palm CA, Epstein SE, Cowgill LD. Assessment of canine pancreas-specific lipase and outcomes in dogs with hemodialysis-dependent acute kidney injury. *J Vet Intern Med*. 2018;32:722-726.
16. Prummer JK, Howard J, Grandt LM, et al. Hyperlipasemia in critically ill dogs with and without acute pancreatitis: prevalence, underlying diseases, predictors, and outcome. *J Vet Intern Med*. 2020;34:2319-2329.
17. Hulsebosch SE, Palm CA, Segev G, Cowgill LD, Kass PH, Marks SL. Evaluation of canine pancreas-specific lipase activity, lipase activity, and trypsin-like Immunoreactivity in an experimental model of acute kidney injury in dogs. *J Vet Intern Med*. 2016;30:192-199.
18. Steiner JM, Finco DR, Williams DA. Serum lipase activity and canine pancreatic lipase Immunoreactivity (cPLI) concentration in dogs with experimentally induced chronic renal failure. *Vet Res*. 2010;3:58-63.
19. Lankisch PG, Weber-Dany B, Maisonneuve P, Lowenfels AB. Frequency and severity of acute pancreatitis in chronic dialysis patients. *Nephrol Dial Transplant*. 2008;23:1401-1405.
20. Hou SW, Lee YK, Hsu CY, Lee CC, Su YC. Increased risk of acute pancreatitis in patients with chronic hemodialysis: a 4-year follow-up study. *PLoS One*. 2013;8:e71801.
21. Barbara M, Tsen A, Rosenkranz L. Acute pancreatitis in chronic dialysis patients. *Pancreas*. 2018;47:946-951.
22. Ventrucci M, Campieri C, Di Stefano M, et al. Alterations of exocrine pancreas in end-stage renal disease. Do they reflect a clinically relevant uremic pancreopathy? *Dig Dis Sci*. 1995;40:2576-2581.
23. Vaziri ND, Chang D, Malekpour A, Radaht S. Pancreatic enzymes in patients with end-stage renal disease maintained on hemodialysis. *Am J Gastroenterol*. 1988;83:410-412.
24. Chen YH, Yang WC, Wang FM, et al. Risk factors associated with elevated serum pancreatic amylase levels during hemodialysis. *Hemodial Int*. 2011;15:79-86.
25. Wang H, Rong J, Song C, et al. Hemodialysis and risk of acute pancreatitis: a systematic review and meta-analysis. *Pancreatology*. 2021;21:89-94.
26. Montalto G, Soresi M, Carroccio A, et al. Influence of haemodialysis on lipase activity. *Eur J Clin Chem Clin Biochem*. 1997;35:237-238.
27. Shibasaki T, Matsuda H, Ohno I, et al. Significance of serum lipase in patients undergoing hemodialysis. *Am J Nephrol*. 1996;16:309-314.
28. Lin XZ, Chen TW, Wang SS, et al. Pancreatic enzymes in uremic patients with or without dialysis. *Clin Biochem*. 1988;21:189-192.
29. Yamauchi H, Takeda K, Sunamura M, et al. Effect of plasma exchange on acute pancreatitis. *Tohoku J Exp Med*. 1985;145:103-104.
30. Cowgill LD, Langston C. Acute kidney injury. In: Bartges J, Polzin DJ, eds. *Nephrology and Urology of Small Animals*. 1st ed. Ames, IA: Wiley-Blackwell; 2011:472-523.
31. Francey T, Schweighauser A. Regional citrate anticoagulation for intermittent hemodialysis in dogs. *J Vet Intern Med*. 2018;32:147-156.
32. Kalli IV, Adamama-Moraitou KK, Patsika MN, et al. Prevalence of increased canine pancreas-specific lipase concentrations in young dogs with parvovirus enteritis. *Vet Clin Pathol*. 2017;46:111-119.

33. Israeli I, Steiner J, Segev G, et al. Serum pepsinogen-a, canine pancreatic lipase immunoreactivity, and C-reactive protein as prognostic markers in dogs with gastric dilatation-volvulus. *J Vet Intern Med*. 2012;26:920-928.
34. Haworth MD, Hosgood G, Swindells KL, Mansfield CS. Diagnostic accuracy of the SNAP and spec canine pancreatic lipase tests for pancreatitis in dogs presenting with clinical signs of acute abdominal disease. *J Vet Emerg Crit Care (San Antonio)*. 2014;24:135-143.
35. Mawby DI, Whittemore JC, Fecteau KA. Canine pancreatic-specific lipase concentrations in clinically healthy dogs and dogs with naturally occurring hyperadrenocorticism. *J Vet Intern Med*. 2014;28:1244-1250.
36. Leoni FP, Pelligra T, Citi S, et al. Ultrasonographic monitoring in 38 dogs with clinically suspected acute pancreatitis. *Vet Sci*. 2020;7(4):180.
37. Aatif T, Akka R. Pancreatic enzymes in end-stage renal disease patients on maintenance hemodialysis. *Indian J Med Biochem*. 2019;23:343-346.
38. Masoero G, Bruno M, Gallo L, Colaferro S, Cosseddu D, Vacha GM. Increased serum pancreatic enzymes in uremia: relation with treatment modality and pancreatic involvement. *Pancreas*. 1996;13:350-355.
39. Lim SY, Xenoulis PG, Stavroulaki EM, et al. The 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylresorufin) ester (DGGR) lipase assay in cats and dogs is not specific for pancreatic lipase. *Vet Clin Pathol*. 2020;49:607-613.
40. Segev G, Kass PH, Francey T, Cowgill LD. A novel clinical scoring system for outcome prediction in dogs with acute kidney injury managed by hemodialysis. *J Vet Intern Med*. 2008;22:301-308.
41. Eatroff AE, Langston CE, Chalhoub S, Poeppel K, Mitelberg E. Long-term outcome of cats and dogs with acute kidney injury treated with intermittent hemodialysis: 135 cases (1997-2010). *J Am Vet Med Assoc*. 2012;241:1471-1478.

How to cite this article: Bendeler KS, Howard J, Francey T, Schweighauser A, Peters LM. Hyperlipasemia in dogs with acute kidney injury treated with and without hemodialysis. *J Vet Intern Med*. 2023;1-10. doi:10.1111/jvim.16693