Standard Article

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Assessment of Canine Pancreas-Specific Lipase and Outcomes in Dogs with Hemodialysis-Dependent Acute Kidney Injury

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Background: Renal replacement therapies can be life-saving for dogs with severe acute kidney injury (AKI), however, comorbidities including pancreatitis might affect outcome.

Hypothesis/Objectives: To investigate the prevalence of pancreas-specific lipase (Spec cPL) measurements consistent with pancreatitis (≥400 μg/L) in dogs undergoing intermittent hemodialysis (IHD) for treatment of AKI and to determine whether there were associations between 30-days outcomes and Spec cPL measurements.

Animals: Fifty-three client-owned dogs presented to teaching hospitals between November 2008 and September 2016 that underwent IHD.

Methods: Retrospective medical record review from dogs that received IHD for management of AKI and also had a Spec cPL measurement. Association between survival, dialysis-dependency, and Spec cPL measurements was assessed.

Results: Forty of 53 (76%) dogs were alive at 30-days and 33/53(62%) had a Spec cPL result ≥400 μg/L. Spec cPL was not significantly different either between surviving (635.5 μg/L, range 29–1,001) and nonsurviving dogs (860 μg/L, range 56–1,001; $P = 0.75$) or between dialysis-dependent (1,001 μg/L, range 177–1,001) and nondialysis-dependent dogs (520 μg/L, range 29–1,001; $P = 0.08$). Spec cPL ≥400 μg/L was not significantly associated either with survival ($P = 0.74$) or dialysis-dependency ($P = 0.33$).

Conclusions and Clinical Importance: Results revealed a high prevalence of Spec cPL ≥400 μg/L in dogs with AKI treated with IHD. No significant associations between Spec cPL and survival or dialysis-dependency in dogs with AKI at 30 days were identified in the current study, however, the latter could be due to lack of power in this study.

Key words: Canine specific pancreatic lipase; Kidney failure; Renal recovery; Renal replacement therapy.

Acute kidney injury (AKI) is a common condition in animals that can be associated with morbidity and death. AKI represents a spectrum of disease severity ranging from clinically nondetectable to life-threatening kidney disease.[1,2] Dogs with severe grades of AKI and fulminant kidney failure can require renal replacement therapy (RRT) for successful management.[3,4] The decision to initiate RRT requires a considerable emotional and financial commitment for pet owners, especially because often it is difficult to determine prognosis at the onset of therapy. This inability to prognosticate is in part due to the varied etiologies and co-morbidities associated with AKI that can have different outcomes, as well as the limited reports detailing objective outcome data for dogs with AKI undergoing RRT.[5–7] In human medicine, outcome studies evaluating AKI, including the association of AKI with various co-morbidities including acute pancreatitis (AP) are extensive[8,9] and similar studies in veterinary medicine are lacking.

Abbreviations:

AKI	acute kidney injury
AP	acute pancreatitis
Spec cPL	canine specific pancreatic lipase
IHD	intermittent hemodialysis
iSCre	initial serum creatinine
RRT	renal replacement therapy

Acute pancreatitis is a common co-morbidity associated with AKI in dogs.[10] It can be both a cause of AKI, as well as a secondary consequence of AKI.[11,12] Despite this association, the impact of AP on renal recovery from AKI is not known in veterinary medicine. However, it is well established that inflammatory cytokines associated with AP can compromise renal perfusion, promote apoptosis of the tubular epithelium, and likely delay renal recovery.[13–15] Currently, serum specific pancreatic lipase (Spec cPL Test) measured by ELISA is the most commonly used biomarker for diagnosis of pancreatitis in dogs.[16,17] Spec cPL has good overall clinical diagnostic performance in diagnosing AP with a high sensitivity and specificity for the diagnosis of AP in clinical settings in dogs. Reported sensitivities for moderate to severe pancreatitis using the cut-off value of 400 μg/L range from 70 to 77% and specificities range from 78 to 88%.[18–21]

We hypothesized that Spec cPL results consistent with a diagnosis of pancreatitis would be negatively associated with survival in dogs with dialysis-dependent AKI, and elevated Spec cPL values would be associated with prolonged dialysis-dependency. The aims of this study were to determine the prevalence of Spec cPL results ≥400 μg/L in dogs undergoing RRT for treatment of AKI and the association between Spec cPL and outcomes in these dogs.

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Materials and Methods

Medical records were reviewed retrospectively to identify dogs that were admitted to the University of California-Davis William R. Pritchard Veterinary Medical Teaching Hospital and the University of California Veterinary Medical Center-San Diego between November 2008 and September 2016. Inclusion criteria were dogs with AKI managed by intermittent hemodialysis (IHD), that also had at least one Spec cPL measurement performed within 7 days before or after the first admission to our institutions. Data collected included signalment, date of admission, dates of initiation and discontinuation of hemodialysis, serum creatinine values at presentation (iSCre; initial serum creatinine concentration),[a] Spec cPL values, date of Spec cPL measurement and information regarding survival and dialysis dependency at 30 days after admission. Diagnosis of AKI was done by the attending clinician, and in general, was based on history, acute onset of clinical signs, progressive renal azotemia, and consistent findings on urinalysis and abdominal ultrasound. Post-renal azotemia, acute nephrotoxin ingestion without azotemia, and dogs that had been diagnosed previously with chronic kidney disease were excluded. Initiation of RRT was made at the discretion of the attending clinician. IHD treatments were also discontinued at the discretion of the attending clinician(s) when dogs could be maintained without RRT (typically when serum creatinine values were less than 5.0 mg/dL without RRT) or when owners elected for discontinuation because of financial or quality-of-life factors.

If information was available regarding survival status of dogs at 30 days after admission, they were included in the analysis. Animals were classified as alive or dead at 30 days after admission. Dogs classified in the dead group included dogs that died during hospitalization for AKI or were euthanized. If dogs were alive at 30 days, they were further classified as dialysis-dependent or nondialysis-dependent. Dogs were classified as dialysis-dependent if they required IHD for ongoing management to maintain creatinine values of <5 mg/dL at 30 days. If IHD treatments were discontinued based on improved kidney function and residual kidney function resulted in a creatinine <5 mg/dL, the dog was categorized to be nondialysis-dependent from the day after the last dialysis treatment. If the owner elected to discontinue the dialysis before recommended by the attending clinician, the dog was categorized into the dialysis-dependent group, provided the creatinine remained ≥5 mg/dL at 7 days or more after discontinuation of IHD.

The Spec cPL assay was performed by a monoclonal antibody sandwich ELISA as previously described.[21] According to the manufacturer, the reference interval is 0–200 μg/L, 201–399 μg/L is considered in the equivocal or "grey" zone, and ≥400 μg/L is consistent with pancreatitis.[b] Values of Spec cPL less than the detection limit and reported as <30 μg/L were assigned values of 29 μg/L for statistical analysis. Values of Spec cPL greater than 1,000 μg/L were assigned a value of 1,001 μg/L for statistical analysis. For cases with more than one Spec cPL measurement during the course of AKI, the first measurement was used for analysis. In this study, the decisions to measure Spec cPL were made by each attending clinician in accordance with clinical signs suggestive for pancreatitis, however, all dogs at the University of California-Davis William R. Pritchard Veterinary Medical Teaching Hospital have Spec cPL measurements made when undergoing RRT, to aid in medical management decision making, given the difficulty to distinguish AKI dogs with or without AP based on the clinical signs. Spec cPL values ≥400 μg/L were categorized as positive or consistent with a diagnosis of pancreatitis based on the laboratory reference intervals developed by the manufacturer.

Statistical Methods

Descriptive data are presented as percentages, median, and range. The Mann-Whitney *U*-test was used for comparison of the distribution between groups for Spec cPL values. Categorical data were compared with groups either between alive and dead dogs or between dialysis-dependent and nondialysis-dependent dogs by a Fisher's exact test. A value of $P < 0.05$ was considered significant. All analyses were performed with statistical software.[c]

Results

One hundred fifty-four dogs were identified for possible inclusion based on undergoing IHD for treatment of AKI. Among those, 101 dogs were excluded due to lack of Spec cPL measurement ($n = 91$) or because Spec cPL measurement was not performed within 7 days of admission to our hospitals ($n = 9$). Fifty-three dogs were enrolled for the analysis in this study.

Median age of all dogs was 7.1 years (range: 0.7–14.5 years). Nineteen dogs were neutered male, 21 were spayed female, 9 were intact male, and 4 were intact female. Median iSCre value at presentation was 9.4 mg/dL (range: 3.4–16.6 mg/dL). Overall, 33/53 (62%) of dogs had Spec cPL values ≥400 μg/L, consistent with pancreatitis, and 10/53 (19%) of dogs were considered to be in "grey-zone" with Spec cPL values between 200 and 399 μg/L. All included dogs had clinical signs, such as vomiting, nausea, and abdominal pain, which could have been consistent with AKI, acute pancreatitis, or both diseases concurrently.

At 30 days from admission, 40/53 (76%) dogs were still alive. Of the 40 surviving dogs, 14 (35%) dogs were further classified as dialysis-dependent and 26/40 (65%) were classified as nondialysis-dependent. Twenty-six of 40 surviving dogs had IHD discontinued due to improvement as described above. One of 40 surviving dogs had IHD discontinued based on the attending clinician's decision, however, the creatinine value progressed to 6.3 mg/dL with discontinuation of IHD. Due to the progressive azotemia, this dog was classified in the dialysis-dependent group based on the study criteria above. All other dogs in which IHD was discontinued had sufficient residual kidney function to maintain creatinine <5 mg/dL and were therefore classified in the nondialysis-dependent group.

The median Spec cPL value for the dialysis-dependent group was 1,001 μg/L (range: 177–1,001 μg/L) and for the nondialysis-dependent group was 520 μg/L (range: 29–1,001 μg/L) (Fig 1). There was no significant difference in Spec cPL between dialysis-dependent and nondialysis-dependent groups ($P = 0.08$).

At 30 days from admission, 13/53 (25%) dogs died or were euthanized. Four of 13 dogs in the nonsurvival group died; one dog died from shock after development of disseminated intravascular coagulation, one dog developed cardiopulmonary arrest during an IHD treatment, one dog developed cardiopulmonary arrest in the ICU, and the final dog developed cardiopulmonary arrest during a procedure unrelated to dialysis. Nine of 13 dogs were euthanized at the owner's request. Reasons for euthanasia included poor quality-of-life or poor prognosis due to progressive concurrent disease ($n = 5$), lack of renal recovery despite dialytic management of uremia ($n = 2$), and owner financial limitations ($n = 2$). The 4 latter cases were stable at the time of euthanasia and were euthanized a median of 15 days (range: 6–24 days) from initial admission.

Median Spec cPL values for the survival and nonsurvival groups were 636? μg/L (range: 29–1,001 μg/L) and 860 μg/

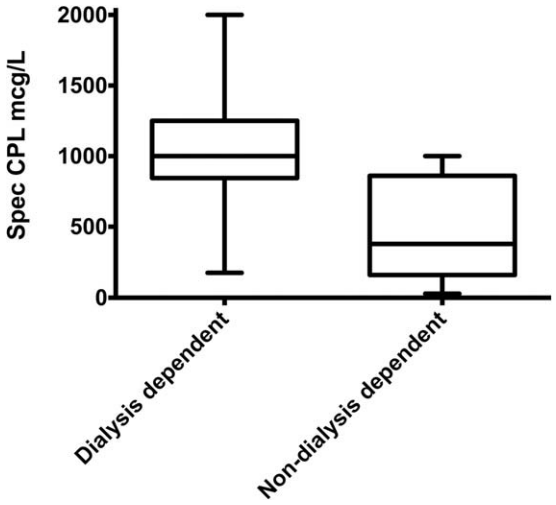

Fig 1. Whisker box plot comparing canine specific pancreatic lipase values between dialysis-dependent ($n = 14$) and nondialysis-dependent ($n = 26$) dogs. The vertical boundaries of the box represent the first and third quartiles of that data series, and the horizontal line in the box represent the median values. No statistically significant difference was detected. ($P = 0.08$).

L (range: 56–1,001 μg/L), respectively (Fig 2). There was no statistically significant difference in Spec cPL values between these two groups ($P = 0.75$).

The distribution of dogs with or without Spec cPL results ≥400 μg/L was assessed according to their dialysis-dependency at 30 days. Among 14 dialysis-dependent dogs, 10/14 (71%) had Spec cPL results consistent with a diagnosis of pancreatitis, and 8/10 (80%) had a Spec cPL result of >1,000 μg/L. Among nondialysis-dependent dogs, 14/26 (54%) had Spec cPL results consistent with a diagnosis of pancreatitis, and 7/14 (50%) had a Spec cPL result of >1,000 μg/L. There was no statistical difference regarding a positive Spec cPL (≥400 μg/L) consistent with pancreatitis and dialysis-dependency ($P = 0.33$).

Overall, 33/53 (62%) dogs had Spec cPL values (≥400 μg/L), consistent with pancreatitis. Among the 40 dogs alive at 30 days after admission, 24/40 (60%) had Spec cPL results consistent with a diagnosis of pancreatitis, whereas, of 13 nonsurviving dogs, 9/13 (70%) had spec cPL results consistent with a diagnosis of pancreatitis. There was no statistically significant difference between dogs either with or without positive (≥400 μg/L) Spec cPL result regarding survival ($P = 0.74$).

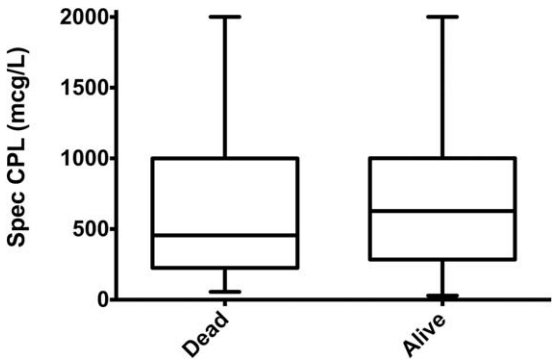

Fig 2. Whisker box plot comparing canine specific pancreatic lipase values between dead ($n = 13$) and alive ($n = 40$) dogs. The vertical boundaries of the box represent the first and third quartiles of that data series, and the horizontal line in the box represent the median values. No statistically significant difference was detected. ($P = 0.75$).

Discussion

Our study evaluates the association between Spec cPL and the outcome of dogs with dialysis-dependent AKI. Based on Spec cPL increases in conjunction with clinical assessment, a high prevalence of pancreatitis (62%) was documented in the dogs undergoing IHD for treatment of AKI in this study. In addition, Spec cPL results consistent with a diagnosis of pancreatitis based on the current cut-off recommendations were not significantly associated with survival or dialysis-dependency at 30 days in this cohort of dogs.

In a previous report, pancreatitis was the most common co-morbidity in dogs with AKI but that study did not include dogs managed with IHD and did not report outcomes after discharge from the hospital.[10] In the study referenced above, the Spec cPL assay was not available, and the criteria for the diagnosis of AP were not specified.[10] Given the high prevalence of AP in dogs with AKI, it is beneficial to understand the potential impact on dogs undergoing RRT for treatment of AKI so outcomes can be better understood.

In the current study, at 30 days after admission, 76% of dogs in this cohort were still alive. This survival rate is higher than previous reports of a 51–53% survival for AKI managed with RRT.[5–7] The possible explanations for this discrepancy could be case selection, definition of survival, and underlying etiologies for AKI. For example, in our study, cases lacking Spec cPL measurements were excluded, and this might have led to bias with case selection.

There were no statistically significant differences in Spec cPL values between the survival and nonsurvival groups, and based on these results, the presence or absence of AP should not be considered as a negative prognostic indicator for the dogs with AKI undergoing RRT. In human medicine, it is reported that AP followed by hospital-acquired AKI leads to decreased survival rates,[22–24] however, no dog in our study developed hospital acquired AKI secondary to AP. This discrepancy might be due to euthanasia of dogs with severe AP before development of AKI or due to other species-specific differences in pathophysiology. In addition, in dogs with elevated Spec cPL values, it is difficult to definitively determine if AP was truly present, and if present, if AP was a consequence of, or a cause of AKI.

Among the surviving dogs, Spec cPL values did not show a significant difference between dialysis-dependent and nondialysis-dependent dogs at 30 days from initial admission. This finding suggests that an elevated Spec cPL might not be a negative prognostic indicator for dogs with AKI undergoing IHD. Given the large discrepancy in median Spec cPL values between the dialysis-dependent and nondialysis-dependent groups, however, it is possible that larger case numbers and the ability to more accurately

define absolute Spec cPL values between 1,000 and 2,000 μg/L might have resulted in a significant association between Spec cPL and dialysis dependency.

Despite the lack of significant differences in Spec cPL between groups, the highest proportion (8/10, 80%) of the extremely high Spec cPL values (>1,000 μg/L) was obtained in the dialysis-dependent group, whereas only 7/14 (50%) of dogs had the same degree of Spec cPL results in the nondialysis-dependent group. As depicted in Fig 1, while significant results were not identified, it is possible that lack of power might have prevented significance. This could suggest that the presence of more severe pancreatitis might cause slower renal recovery and might correlate with a longer course of disease. It is important to note the possibility that higher Spec cPL values could correlate with more severe decreases in endogenous urinary clearances, not representative of true pancreatic inflammation. However, a previous report showed no significant association between severity of AKI as defined by degree of creatinine elevation, and Spec cPL elevation. no significant association between severity of AKI and Spec cPL elevation.[25] Further studies and larger case numbers are warranted, but it is possible a specific Spec cPL cut-off predicting prolonged dialysis dependency due to AP might be able to be established.

The retrospective nature of this study imposes several limitations. First, the case numbers in each group were relatively small and might have led to the nonsignificant results of this study. For the extremely high Spec cPL results (>1,000 μg/L), the exact values were not possible to be obtained at the time when this study was conducted, and this also might have led to the nonsignificant results of this study. The time points for Spec cPL measurement were not uniform for all dogs. Some samples were submitted by the referring veterinarian before referral to our institution, and some samples were submitted after initiation of RRT. This lack of precise timing of Spec cPL measurement could influence the accuracy of establishing a definitive diagnosis of AP. In addition, Spec cPL was used to predict AP, and biopsy samples were not obtained for the confirmation in any case. The influence of IHD on Spec cPL values is also unknown, however, canine pancreatic lipase was reported to have a molecular weight of approximately 50.7 kDa, and unlikely to be influenced by the clearance of the hemodialysis due to its large size.[26,27] Dogs included in the study also had variable etiologies causing AKI, which might have affected outcomes beyond the effect of Spec cPL. Lastly, only initial Spec cPL results were included for the analysis, and it is possible that AP could have developed in hospital and might have not been diagnosed at the time of the initial measurement, or that depending on attending clinician's assessment, cases could have been pre-selected to measure Spec cPL at the time of admission to the hospital; the latter is less likely, as all cases undergoing IHD at the University of California-Davis William R. Pritchard Veterinary Medical Teaching Hospital have Spec cPL measurements performed to aid in medical management, primarily in dietary prescriptions. To address these limitations, a multicentric prospective study with sequential Spec cPL concentrations is warranted.

In conclusion, this report showed a high prevalence of elevated Spec cPL values in the dogs with AKI treated with RRT. A positive Spec cPL result consistent with a diagnosis of pancreatitis (≥400 μg/L) was not associated with outcomes prediction of survival or dialysis-dependency at 30 days of admission in this cohort of dogs. Severe AP as predicted by Spec cPL >1,000 μg/L might influence recovery of kidney function in dogs with AKI or influence the duration of dialysis-dependency.

Footnotes

[a] VMTH Clinical Diagnostic Laboratory Services, University of California-Davis, Davis, CA
[b] IDEXX Laboratories Inc, Sacramento, CA
[c] GraphPad Prism 6.0 for Mac, GraphPad Software Inc, La Jolla, CA

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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 (IACUC) or Other Approval Declaration: Authors declare no IACUC or other approval was needed.

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