Retrospective evaluation of risk factors for development of kidney injury after parenteral furosemide treatment of left-sided congestive heart failure in dogs

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Abstract
Background: Kidney injury (KI) has been documented in dogs treated with furosemide for left-sided congestive heart failure (CHF).
Hypothesis/Objectives: Determine risk factors for development of KI in furosemide-treated dogs and determine the effect of KI on survival.
Animals: Seventy-nine client-owned dogs receiving parenteral furosemide for CHF.
Methods: Serum creatinine (sCr) and electrolyte concentrations were determined during hospitalization and at first outpatient reevaluation to detect and stage KI (increase in sCr ≥ 0.3 mg/dL). Furosemide dosage administered between timepoints was calculated. Multivariable modeling was performed to identify predictors of KI and percent change in serum biochemistry results over time.
Results: Kidney injury was identified in 38/79 (48%) dogs and mostly occurred during hospitalization. Kidney injury was Grade I in 25 dogs, Grade II in 9 dogs, and Grade III in 4 dogs. Higher blood pressure was associated with acute KI during hospitalization (odds ratio, 1.03; 95% confidence interval [95% CI] 1.01-1.07; P = .03) whereas PO furosemide dosage was associated with KI after hospital discharge (odds ratio, 7.77; 95% CI, 2.05-68.6; P = .02). Baseline sCr and use of a furosemide continuous rate infusion were not associated with increased risk of KI. Kidney injury was not associated with long-term outcome. Of 13 dogs with Grade II-III KI, azotemia was reversible in 9 dogs, and 6 dogs survived >1 year after KI.
Conclusions and Clinical Importance: In this cohort of dogs receiving parenteral furosemide for CHF, KI was common, mostly nonazotemic (Grade I), and did not impact survival.
Furosemide can be administered parenterally and the chosen dosage often is guided by per-

However, it remains unknown how common KI is among dogs treated for CHF. We hypothesized that higher furose-
mide dosage, higher baseline serum creatinine concentration (sCr), or use of a furosemide CRI would be associated with higher risk of KI, and that occurrence of KI would negatively affect long-term prognosis. Secondary objectives included identifying variables associated with percent changes in renal function tests and serum electrolyte concentrations in furosemide-treated dogs.

The purpose of our study was to identify the incidence of, risk factors for, and survival impact of KI in dogs receiving parenteral furosemide as treatment for CHF. We hypothesized that higher furosemide dosage, higher baseline serum creatinine concentration (sCr), or use of a furosemide CRI would be associated with higher risk of KI, and that occurrence of KI would negatively affect long-term prognosis. Secondary objectives included identifying variables associated with percent changes in renal function tests and serum electrolyte concentrations in furosemide-treated dogs.

2 | MATERIALS AND METHODS

A retrospective medical record search was performed to identify dogs that had received at least 1 dose of furosemide parenterally for treatment of CHF at the Iowa State University Lloyd Veterinary Medical Center between 1 July 2015 and 1 July 2020. Diagnosis of CHF was based on the following criteria: clinical signs consistent with CHF (increased respiratory rate and effort, cough, exercise intolerance); echocardiography performed by a board-certified veterinary cardiologist or cardiology resident showing severe left heart disease; radiographic evidence of pulmonary edema including interstitial and alveolar lung patterns; and, positive clinical response to diuretic treatment. To be included in the study, dogs must have had sCr determined within 6 hours of presentation for CHF as well as on at least 1 subsequent timepoint (TP), either during hospitalization or at an outpatient reevaluation within 1 month. Dogs were excluded from the study if they received furosemide for reasons other than CHF or received IV fluid therapy during hospitalization. Dogs with a previous diagnosis of CHF that were already receiving loop diuretics PO at the time of hospital presentation were included, but only the first CHF presentation meeting all inclusion criteria (furosemide administered parenterally during hospitalization; sCr determined within 6 hours of presentation and at a subsequent TP within 1 month) for any individual dog was analyzed.

Data obtained from medical records at the time of first parenteral furosemide administration included date and time of hospital presentation; signalment; physical examination findings; systemic arterial blood pressure (BP) determined by Doppler; cardiac disease diagnosis; and, history and dosages of cardiac medications being administered before presentation. Data recorded for parenteral furosemide administration during hospitalization included date, time, route of administration, dose of furosemide, and whether the dose was administered as a bolus or CRI. Data recorded for each serum biochemistry panel performed during hospitalization included date and time of analysis and results for sCr, BUN, sodium, potassium, and chloride concentrations. Further information was gathered about the hospital stay including total duration of hospitalization, use of supplemental oxygen or mechanical ventilation, date and time that respiratory rate decreased below 40 breaths per minute, and cardiac medications administered during hospitalization and prescribed at discharge. Data collected from the first outpatient reevaluation after hospitalization included physical examination findings, BP, type and dosages of cardiac medications being administered, and serum biochemistry results as described above.

Long-term follow-up information included frequency and time to recurrence of CHF, date and cause of death for dogs that died, and date of last follow-up for dogs still alive. When possible, cause of death was recorded and classified as cardiac or renal (or both); cardiac death was defined as death or euthanasia secondary to clinical signs consistent with CHF or sudden death at home when not attributable to another noncardiac cause, whereas renal death was defined as euthanasia related to AKI or progressive azotemia preventing further diuretic dosage escalation.

Three study TPs were defined for purposes of data analysis. Timepoint 1 (TP1) was defined as the time of first sCr measurement in hospital (within 6 hours of presentation). Timepoint 2 (TP2) was defined as the time of highest sCr documented during hospitalization, or second sCr documented in hospital for dogs with sCr that did not
increase. Timepoint 3 (TP3) was defined as time of sCr measurement at first outpatient reevaluation. Inclusion criteria required all dogs to have TP1 data as well as data for either TP2 or TP3, or both. Variables calculated for each time interval (TP1-2, TP2-3, and TP1-3) included total time elapsed, total dosage of furosemide administered (cumulative parenteral dosage for TP1-2, chronic PO dosage for TP2-3, and combination of cumulative parenteral dosage and chronic PO dosage for TP1-3), and percent change in renal function test results and serum electrolyte concentrations. Cumulative furosemide dosage also was calculated for the first 24 hours of hospitalization and total duration of hospitalization for each dog. When considering cumulative total furosemide dosage over time intervals, dosage was corrected for route of administration by assuming 100% bioavailability for furosemide administered IV or IM and 77% bioavailability for furosemide administered PO.13 Oral torsemide was accounted for by multiplying torsemide dosage by 10, assuming a potency of torsemide 10 times higher than that of furosemide.14-16

Acute kidney injury was defined as an increase in sCr of ≥0.3 mg/dL within a 48-hour interval, and was graded as Grade I (non-azotemic; sCr remained ≤1.6 mg/dL); Grade II (mild; sCr increased to 1.7-2.5 mg/dL); or Grade III (moderate to severe; sCr increased to 2.6-5.0 mg/dL), based on International Renal Interest Society (IRIS) guidelines (http://www.iris-kidney.com/pdf/4_ldc-revised-grading-of-acute-kidney-injury.pdf). Kidney injury was defined and staged identically to AKI, but occurring over a time period >48 hours.

Statistical analyses were performed using commercially available software (R version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria). Categorical data are reported as frequencies and proportions. Quantitative data are reported as median ± interquartile range (IQR) for all data because most variables were not normally distributed. Variables were compared among TPs using multiple comparisons t tests (for normally-distributed data) or Wilcoxon rank sum tests (for nonnormally-distributed data) with Benjamini-Hochberg adjustment. Proportion of missing data for individual TP was calculated; ≤5% frequency of missing data was considered acceptable without requiring data imputation. Dogs with TP2 data available were compared to those without TP2 data using Wilcoxon rank sum or chi square tests to determine whether absence of TP2 data in some dogs could bias the models.

Univariable and multivariable linear regression analysis was used to evaluate variables for their utility in predicting percent change over time in renal function test results and serum electrolyte concentrations, with each time interval (TP1-2, TP2-3, and TP1-3) assessed as an independent statistical model. Normality of residuals was confirmed by visual inspection of residual plots. Variables that were significant (P < .1) in univariable regression analyses were entered into multivariable backward stepwise regression analysis, with final model selection performed using the Akaike information criterion. Coefficients (parameter estimates) were provided for linear regression, with the sign of coefficients (positive or negative) indicating the relationship between predictive variable and outcome.

Similar logistic regression methods were used to assess variables for their utility in predicting KI among TPs. Goodness-of-fit was assessed using McFadden’s R-squared method. Discrimination of the models was assessed by visual inspection of receiver operating characteristic curves and calculation of area under the curve. Long-term outcome and survival were evaluated using Cox proportional hazard models, with assumptions of proportionality and model fit confirmed using Schoenfeld residuals. Survival times for different groups were compared using log-rank testing. Odds ratios (for logistic regression) and hazard ratios (for Cox proportional hazard models) were provided, with ratios >1 indicating increased risk of outcome and ratios <1 indicating decreased risk. Risk of confounding and collinearity was assessed using variance inflation factor, with values <5 considered acceptable.

For all models, a subset of clinicopathologic variables was chosen for entry into the initial univariable model based on assessment of likely clinical relevance, with the goal of limiting the total number of predictors offered to the model to decrease the risk of overfitting. A complete list of variables offered to each model can be found in the respective table legends. For all statistical tests, a value of P < .05 was considered significant.

3 | RESULTS

3.1 | Demographics, physical examination, and cardiovascular assessment

Electronic medical records were searched using the following variables: records of dogs only; date range 1 July 2015 to 1 July 2020; discharge summary terms “furosemide” OR “lasix” OR “salix” OR “stage c”; and billing codes for either IV furosemide OR the combination of an echocardiogram AND IV catheter placement. This search initially identified 203 dogs, 124 of which were excluded for the following reasons: 3 dogs did not receive furosemide; 64 dogs received furosemide PO only; 26 dogs did not have L-CHF; 2 dogs did not have baseline renal function tests performed; 27 dogs did not have renal function tests reevaluated after receiving parenteral furosemide; and 2 dogs received IV fluids during hospitalization.

Seventy-nine dogs met final inclusion criteria. Of included dogs, 36 (46%) were female and 43 (54%) were male; 10 dogs were sexually intact (3 female, 7 male). Median age was 10.3 years (range, 0.4-15.6 years) and median weight was 8.8 kg (range, 2-59 kg). Breeds of dogs included mixed breed (n = 22), Chihuahua (n = 9), Cavalier King Charles spaniel (n = 8), dachshund (n = 6), Doberman pinscher (n = 6), Labrador retriever (n = 3), miniature schnauzer (n = 3), boxer (n = 3), Maltese (n = 2), and 1 each of 17 other breeds. Underlying heart diseases included myxomatous mitral valve disease (58 dogs, 73%), dilated cardiomyopathy (17 dogs, 22%), mitral valve dysplasia (2 dogs, 2.5%), subaortic stenosis with severe aortic insufficiency (1 dog, 1.3%), and third-degree atrioventricular block (1 dog, 1.3%). Presumed concurrent right-sided CHF (peritoneal or pleural effusion) was identified in 12/79 (15%) dogs. Arrhythmias were identified in 17/79 (22%) dogs and included atrial fibrillation (n = 7), ventricular ectopy (n = 5), and supraventricular ectopy (n = 5). Dogs had various...
TABLE 1  Clinical data and clinicopathologic results at hospital presentation (TP1), point of highest measured serum creatinine concentration (TP2), and first reevaluation (TP3) in 79 dogs treated parenterally with furosemide for left-sided congestive heart failure

| Result | TP1 (n = 79) | TP2 (n = 46) | TP3 (n = 70) | P-value |
|--------|--------------|--------------|--------------|---------|
| Heart rate (bpm) | 160 (142-176) | - | 132 (113-155) | - - <.0001* |
| Respiratory rate (rpm) | 60 (50-80) (n = 71) | - | 36 (29-46) (n = 59) | - - <.0001* |
| Rectal temperature (F) | 101.2 (100.4-101.8) (n = 78) | - | 101.4 (100.8-102.0) (n = 59) | - - .28 |
| Systolic blood pressure (mm Hg) | 120 (103-134) (n = 66) | - | 130 (114-159) (n = 66) | - - .002* |
| Blood urea nitrogen (mg/dL) | 20.0 (16.0-25.5) | 29.0 (18.0-39.0) | 25.0 (20.0-35.5) | .005* .98 .001* |
| Creatinine (mg/dL) | 0.9 (0.8-1.15) | 1.1 (0.8-1.3) | 1.1 (0.8-1.4) | .012* .98 .005* |
| Sodium (mEq/L) | 145 (143-149) (n = 45) | 144 (140-148) (n = 45) | 144 (141-147) (n = 45) | .012* .98 .007* |
| Potassium (mEq/L) | 4.4 (4.1-5.0) (n = 77) | 4.0 (3.7-4.2) (n = 45) | 4.4 (4.0-4.7) (n = 45) | <.0001* .002* .20 |
| Chloride (mEq/L) | 113 (107-116) (n = 53) | 104 (100-109) (n = 43) | 109 (105-112) (n = 43) | <.0001* .002* .007* |

Note: Data are expressed as median (IQR). Numbers of patients with data available are shown for variables and timepoints with incomplete datasets. Significant differences (P < .05) between timepoints are denoted with an asterisk (*).

noncardiac comorbidities (most commonly allergic dermatitis [n = 8], intervertebral disc disease [n = 6], otitis externa [n = 5], and osteoarthritis [n = 5]), but none were considered relevant to kidney function.

Fifty-seven dogs (72%) were diagnosed with first-onset CHF at TP1, whereas this hospitalization represented a relapse of CHF in the remaining 22 dogs (28%). Of the 22 dogs with recurrent CHF, all were receiving loop diuretics before TP1, 28/79 (35%) dogs were receiving an angiotensin converting enzyme inhibitor (ACEI), 24/79 (30%) dogs were receiving pimobendan, an adenocarcinoma was receiving piroxicam; no other dogs received non-cardiac medications with potential adverse effects on kidney function.

All 79 dogs had TP1 data, 46 dogs had TP2 data, and 70 dogs had TP3 data. No significant differences were found in clinical or treatment variables between the 46 dogs that had TP2 data compared to the 33 dogs that did not. Vital signs including heart rate, respiratory rate, rectal temperature and BP were measured at TP1 and TP3 and are shown in Table 1; these data were not recorded at TP2. Both heart rate and respiratory rate decreased significantly between TP1 and TP3, whereas BP increased (Table 1). Frequency of missing data (single clinical or clinicopathologic variables not recorded at a specific TP for an individual dog) was 5%.

3.2 Hospitalization and furosemide treatment

Dogs were hospitalized for a median of 26 hours (IQR, 21-40) and received a median cumulative parenteral furosemide dosage of 7.7 mg/kg (IQR, 4.4-12.7) during hospitalization. Of 74 dogs with information recorded, 58 (78%) received supplemental oxygen therapy, with the majority (49/58, 84%) being placed in an oxygen kennel and the remaining 9/58 (16%) receiving oxygen through a nasal cannula. Three dogs (4%) were mechanically ventilated. In 13 dogs (16%), clinical signs were deemed mild enough that supplemental oxygen was not required. Other information about hospitalization, including time elapsed and cumulative furosemide dosage administered before achieving clinical response goals, is shown in Table 2. Furosemide CRI was utilized in 35/79 (44%) dogs, whereas the other 44 dogs (56%) were treated exclusively by intermittent furosemide bolus administration. Furosemide dosages administered between study TPs are shown in Table 3. In addition to furosemide, all 79 dogs received pimobendan.
in hospital; 10/79 (13%) dogs also received an ACEI during hospitalization, 6 of which had been receiving an ACEI before TP1. The dog with third-degree atrioventricular block underwent transvenous pacemaker implantation. At the time of hospital discharge, all dogs were prescribed furosemide (except the single dog that was continued on torsemide), all dogs were prescribed pimobendan, 64/79 (81%) were prescribed an ACEI, 8/79 (10%) were prescribed spironolactone, 3/79 (4%) were prescribed amlodipine, and 12/79 (15%) were prescribed various antiarrhythmic medications (sotalol, mexiletine, diltiazem, or digoxin). At the first reevaluation (TP3), ACEI were prescribed in an additional 3 dogs, spironolactone was added in 35 dogs, amlodipine was prescribed in 1 dog, and sotalol was added in 3 dogs.

3.3 | Clinical pathology results and kidney injury

Clinicopathologic data and statistical comparisons among TPs are shown in Table 1. Both BUN and sCr increased between TP1-2 and TP1-3, and statistically significant changes in serum electrolyte concentrations occurred between various study TPs. Percent change in clinicopathologic variables among TPs is displayed graphically in Figure 1. Variables associated with percent change in creatinine, BUN, sodium, potassium, and chloride among TPs in multivariable analysis are shown in Table 4. For all analytes except BUN, the baseline result of the analyte was negatively associated with percent change across TPs. Use of a furosemide CRI was associated with higher percent change in BUN, sodium, and chloride during hospitalization (TP1-2). Higher daily PO furosemide dosage (mg/kg) administered after hospital discharge was associated with higher percent change in many analytes for TP1-3 and TP2-3. History of loop diuretic use before TP1 and prescription of spironolactone at time of discharge were associated with lower percent change in several analytes after hospital discharge (TP2-3 or TP1-3). Higher cumulative dose of furosemide administered in the hospital was associated with lower percent change in sCr between TP2-3 and TP1-3, and with higher percent change in serum sodium and potassium concentrations between TP2-3.

Thirty-eight of 79 dogs (48%) had documented KI at ≥ 1 time interval. Kidney injury was Grade I (nonazotemic) in 25 dogs (66% of
| Variable                          | Percent change from TP1-2 (N = 46) | Percent change from TP2-3 (N = 37) | Percent change from TP1-3 (N = 70) |
|----------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Creatinine @TP1                  | -106                               | -60.1                              | -5.67                              |
| History of loop diuretic prior to TP1 | -33.1                              | -66.1                              | 0                                  |
| Total furosemide dosage in hospital | -4.5                                | -6.9                               | -21                                |
| Daily PO furosemide dosage in mg/kg (TP2-3) | 30.8                                | 18.6                               | 43.0                               |
| ACE inhibitor                    | -96.3                              | 16                                 | .06                                |
| Spironolactone                   | -256                               | -427                               | -86                                |
| Blood urea nitrogen Furosemide CRI | 68.3                                | 20.8                               | 115.8                              |
| History of loop diuretic prior to TP1 | -103                                | -167                               | -39.0                              |
| Furosemide CRI                   | -55.0                              | -107                               | -26                                |
| Daily PO furosemide dosage in mg/kg (TP2-3) | 50.1                                | 30.8                               | 69.3                               |
| Spironolactone                   | -461                               | -729                               | -194                               |
| AKI during TP1-2                 | -53.2                              | -103                               | -37                                |
| Sodium @TP1                      | -0.4                               | 0.2                                | -0.2                               |
| Furosemide CRI                   | -4.4                               | -8.0                               | -0.8                               |
| Sodium @TP2                      | -0.5                               | -0.6                               | -0.3                               |
| Furosemide CRI                   | -3.2                               | -5.6                               | -0.8                               |
| History of loop diuretic prior to TP1 | 2.1                                | -0.1                               | 4.3                                |

(Continues)
Table 4 (Continued)

| Variable                  | Coefficient | 95% CI lower | 95% CI upper | P-value |
|---------------------------|-------------|--------------|--------------|---------|
| Total furosemide dosage in hospital | 0.3         | 0.05         | 0.5          | 0.02    |
| Daily PO furosemide dosage in mg/kg (TP2-3) | -0.6        | -1.1         | -0.1         | 0.01    |

| Variable                  | Coefficient | 95% CI lower | 95% CI upper | P-value |
|---------------------------|-------------|--------------|--------------|---------|
| Total furosemide dosage during first 24 h in hospital | 1.7         | 0.7          | 27           | 0.002   |
| Daily PO furosemide dosage in mg/kg (TP2-3) | -4.6        | -8.1         | -10          | 0.01    |
| Spironolactone            | 68.4        | 16.6         | 120          | 0.01    |
| AKI during TP1-2          | -9.6        | -18.9        | -0.2         | 0.05    |

| Variable                  | Coefficient | 95% CI lower | 95% CI upper | P-value |
|---------------------------|-------------|--------------|--------------|---------|
| Furosemide CRI            | -1.9        | -3.6         | -0.1         | 0.04    |
| Daily PO furosemide dosage in mg/kg (TP1-3) | -0.8        | -1.5         | -0.2         | 0.02    |
| Spironolactone            | 10.3        | 1.3          | 19.4         | 0.03    |

Note: Variables considered in all models included the absolute value of the clinicopathologic variable at the first TP in the comparison; history of loop diuretic prior to TP1; diagnosis of dilated cardiomyopathy; use of a furosemide CRI in hospital; total dosage of parenteral furosemide administered during the first 24 h of hospitalization or the entire hospitalization period. For TP2-3 and TP1-3 models, additional variables considered were daily PO furosemide dosage (in mg/kg) administered during the indicated time interval; administration of an angiotensin-converting enzyme (ACE) inhibitor or spironolactone during the indicated time interval; and occurrence of acute kidney injury (AKI) during TP1-2 (during hospitalization). Positive coefficients indicate a positive relationship between the explanatory variable and percent increase in the outcome variable (higher value of the explanatory variable is associated with a percent increase in the outcome variable). Negative coefficients indicate a negative relationship between the explanatory variable and the outcome variable (higher value of the explanatory variable is associated with a percent decrease in the outcome variable). Note that P-values for some variables exceed .05, because the final model was selected using the Akaike information criterion which utilizes a combination of P-value and number of variables to select the best fit model. Abbreviations: ACE, angiotensin-converting enzyme; CRI, continuous rate infusion.
dogs with KI and 32% of all dogs). In Grade I dogs, initial sCr ranged from 0.5 to 1.1 mg/dL, and final sCr ranged from 1.0 to 1.6 mg/dL. Nine dogs (24% of dogs with KI and 11% of all dogs) had Grade II (mild) KI during at least 1 time interval; in Grade II dogs, initial sCr ranged from 0.5 to 1.7 mg/dL, and final sCr ranged from 1.7 to 2.5 mg/dL. Four dogs (11% of dogs with KI and 5% of all dogs) had Grade III (moderate to severe) KI during at least 1 time interval. In Grade III dogs, initial sCr ranged from 0.9 to 1.6 mg/dL, and final sCr ranged from 2.6 to 3.4 mg/dL. All dogs not having KI had sCr values ≤1.6 mg/dL at all TPs, except for 1 dog with a sCr of 2.8 mg/dL at TP1 that decreased to 1.3 mg/dL at both TP2 and TP3. Frequency and severity of KI at each interval is reported in Table 3, and sCr values at each TP for dogs exhibiting KI are shown in Figure 2.

Of the 9 dogs with Grade II KI, 4 experienced AKI between TP1-2 that resolved (sCr normalized to baseline) by TP3, and none of these dogs experienced a recurrence of KI before death (n = 6) or during a follow-up period of at least 500 days (n = 3). Two dogs had Grade II KI between TP1-3 with no TP2 data available. In 1 of these dogs, sCr resolved to baseline at a subsequent reevaluation 2 months after TP3 and remained stable until death 134 days after TP1. In the other dog, sCr progressively increased and the dog was euthanized 136 days after TP1 forer combination of uncontrolled CHF and worsening azotemia. Three dogs with Grade II KI had sCr values that progressively increased from TP1-2 to TP2-3. In 1 of these dogs, azotemia continued to worsen and resulted in euthanasia 55 days after TP1. In another dog, azotemia worsened but then stabilized (maximum sCr of 2.4 mg/dL) and the dog was still alive 510 days after TP1. In the third dog, sCr normalized at a subsequent reevaluation 2 months after TP3 and remained stable until death 559 days after TP1.

Of the 4 dogs with Grade III KI, 2 had AKI documented during hospitalization (between TP1-2), 1 episode of which resolved by TP3 and 1 that was progressive (sCr increased from 3.0 mg/dL at TP2 to 3.3 mg/dL at TP3). The other 2 dogs had KI documented only between TP2-3 after having stable sCr measurements at TP1-2. Azotemia later resolved in 3 of the dogs (2 weeks, 6 months, and 6 months after TP3) and did not recur until death (22, 366, and 579 days after TP1, respectively). In the remaining dog, azotemia was progressive and led to euthanasia 14 days after TP1.

### 3.4 Outcome and survival

Twenty-two of 79 dogs (27%) experienced relapse of CHF within the study period, occurring a median of 125 (range, 3-562) days after...
Thirty-five of 79 dogs (44%) were alive at the end of the study period, with median follow-up time of 218 days from TP1. The remaining 44/79 (55%) dogs died during the study period, with median survival of 149 (range, 4-734) days from TP1, or median of 175 (range, 4-919) days from first documented episode of CHF. The majority (32/44, 73%) of deaths were cardiac. In 4/44 (9%) dogs, death was categorized as renal. These included 3 dogs that had Grade II-III KI during the study period as described above, as well as 1 dog with Grade I KI that resolved, but the dog was euthanized for severe AKI (sCr, 7.5 mg/dL) that occurred 278 days after TP1.

Median survival time did not differ between dogs with documented KI at any point during the study compared to those without KI (127 vs 160 days; \( P = .9 \)), nor did survival differ between dogs experiencing Grade II or III KI compared to all other dogs (median survival, 134 vs 155 days; \( P = .6 \)). Four dogs with Grade II KI and 2 dogs with Grade III KI lived >1 year from TP1 (1 dog died after 559 days; 5 were still alive after 366, 502, 510, 540, and 579 days).

Variables predictive of long-term outcomes in multivariable analysis, including survival from TP1 and incidence of KI between TPs, are shown in Table 5. The only variable found to be predictive of survival from TP1 was history of loop diuretic use before TP1. The only variable predictive of AKI between TP1-2 was higher BP at TP1. Of dogs with AKI during TP1-2, median BP was 130 mm Hg; 3 dogs had BP \( \geq 160 \) mm Hg (maximum, 190 mm Hg) and only 2 dogs had BP \( \leq 90 \) mm Hg (minimum, 80 mm Hg). In contrast, of dogs not having AKI during TP1-2, median BP was 104 mm Hg; maximum BP in this group was 140 mm Hg, and 6 of these dogs had BP \( \leq 90 \) mm Hg (lowest 50 mm Hg).

DISCUSSION

Kidney injury was common in our study, being documented in 48% of dogs treated with parenteral furosemide for CHF. Most KI was nonazotemic (Grade I), but grades II and III KI occurred in 11% and 5% of dogs, respectively. It is challenging to compare prevalence of KI in our study to previous veterinary literature because of variable definitions of renal insufficiency in published clinical trials. For example, in dogs receiving PO furosemide in the CARPODIEM trial, “nonserious” renal adverse events occurred in 17% of dogs and “acute renal failure” occurred in 0.6% of dogs. However, it is unclear what degree of increase in sCr defined these categories. Most prospective trials of dogs with CHF do not specifically report change in sCr over time. In a retrospective study of 76 dogs with CHF, mean sCr increased during hospitalization from 0.9 to 1.2 mg/dL in dogs receiving intermittent bolus furosemide treatment and from 1.1 to 1.5 mg/dL in dogs receiving furosemide CRI, suggesting that the average dog in this cohort experienced Grade I AKI. In another retrospective study of 90 dogs with CHF, 17% of dogs had increased sCr at the time of hospital admission and 32% developed increased sCr during hospitalization, but absolute or percent changes in sCr were not reported.

In our study, KI was documented most often at TP1-2, occurring in 41% of dogs with data available. These results suggest that the most clinically relevant increases in sCr occurred during hospitalization when parenteral furosemide was utilized. This observation is similar to the situation in humans with acute decompensated CHF, where worsening renal function (WRF; defined similar to veterinary AKI as increases in sCr \( \geq 0.3 \) mg/dL) is documented in approximately 25% to 33% of patients during hospitalization. Contrary to our hypothesis, AKI between TP1-2 was not associated with cumulative parenteral furosemide dosage during this time interval or use of a furosemide CRI. The only variable predictive of AKI at TP1-2 was higher BP. It is possible that in dogs with acute CHF and cardiovascular-renal axis dysregulation, higher BP could be particularly damaging to the glomerulus and increased afterload could worsen renal congestion. Interestingly, higher BP (>131 mm Hg) was also a negative prognostic indicator in the BESST study, suggesting that even relatively mild systemic hypertension may worsen outcome in dogs with CHF.

Occurrence of KI after hospital discharge (TP2-3 and TP1-3) was associated with higher daily dosage (mg/kg/day) of PO furosemide. Kidney injury after discharge was not associated with higher dosages of furosemide administered parenterally during hospitalization or use of a furosemide CRI, contrary to our hypothesis and some previous studies documenting higher sCr values in dogs after furosemide CRI. In fact, frequency of KI at TP2-3 was negatively associated with total furosemide dosage administered parenterally in hospital. This finding could suggest that more aggressive renal decongestion during hospitalization might have a renoprotective effect after hospital discharge, and that KI after hospital discharge is influenced primarily by chronic PO dosage of furosemide. These results are consistent with the very short duration of action (1-2 hours) for parenterally administered furosemide in dogs, and underscores the importance of judicious use of chronic PO furosemide in dogs with CHF.

We also hypothesized that higher baseline sCr values at TP1 would be a risk factor for KI in our study sample. This was not the case, and in fact, higher sCr at TP1 was associated with lower percent increase in sCr at all time intervals and was associated with lower risk of KI at TP1-3. A similar pattern also was true for all serum electrolyte concentrations that decreased with furosemide treatment (sodium, potassium, and chloride). This observation might represent the phenomenon of regression to the mean, wherein measured results of a clinical variable become progressively less extreme (closer to sample mean) with repeated assessment over time. Because absolute changes in renal function test results and serum electrolyte concentrations in our study were relatively small, a dog with a sCr (or serum sodium concentration) at TP1 that was relatively low would be more likely to experience an increase toward the sample mean, rather than a further decrease. Our results do not imply a true protective effect of a higher TP1 sCr, only that higher baseline sCr did not increase risk of KI in our study sample.

Administration of ACEI or spironolactone was not associated with the frequency of KI in our study and instead was associated with lower percent increases in sCr after hospital discharge. This finding likely reflects clinician bias in prescription practices rather than a beneficial effect in that ACEI and spironolactone would be prescribed...
A retrospective study showed that increased renal function test results prompting dosage decrease or discontinuation occurred in only 3% of dogs treated with an ACEI for cardiovascular disease, and other studies have shown no difference in renal adverse effects between ACEI and either placebo or pimobendan. Overall, results of our study are consistent with previous veterinary literature suggesting that risk of KI in dogs receiving ACEI or spironolactone for treatment of CHF is low.

A secondary objective of our study was to investigate changes in serum electrolyte concentrations during furosemide treatment and identify risk factors for electrolyte derangements. Previous studies have documented electrolyte depletion in furosemide-treated healthy dogs as well as hyponatremia, hypochloremia, and hypokalemia in furosemide-treated dogs with CHF. Sodium, potassium, and chloride concentrations decreased across TPs in our study, with the most significant changes occurring between TP1-2. Use of a furosemide CRI was associated with higher percent decreases in sodium and chloride concentrations during hospitalization, consistent with previous studies.

Daily PO furosemide dosage (mg/kg/day) was associated with higher percent decreases in serum electrolyte concentrations at TP2-3 or TP1-3. Although spironolactone was associated with lower percent decrease in serum potassium concentration between TP1-2 (consistent with its mechanism of action as a potassium-sparing diuretic), overall, ACEI and spironolactone and ACEI alone had minimal impact on serum electrolyte concentrations across TPs, consistent with previous reports. Contrary to our hypothesis, KI was not associated with increased risk of death or recurrence of CHF in our study. In humans with CHF, WRF generally is associated with worse survival. However, recent studies have shown that patients for whom WRF is transient (resolves before hospital discharge) actually have a more favorable long-term prognosis than those who do not experience WRF. One explanation for this finding could be that WRF is a marker of adequate decongestion and less diuretic resistance. This hypothesis is supported by the finding that patients with transient WRF had more decrease in B-type natriuretic peptide concentrations and increased diuretic response compared to patients with persistent WRF. In our study, azotemia resolved at subsequent reevaluations in all but 5 dogs, potentially explaining the lack of association between KI and survival.

Our results are inherently limited by the retrospective nature of the study and relatively low sample size. Our study included dogs experiencing a relapse of CHF as well as those with new-onset CHF, which introduced variability in our study sample. Multiple cardiac diseases were included, severity of CHF was variable, and dogs did not receive standardized treatments or timing of clinicopathologic assessments. Dosage and administration of furosemide, as well as other treatments, was based on clinician preference. Only dogs receiving furosemide parenterally were included, and thus our study could not determine frequency of KI in dogs receiving PO furosemide exclusively. As a single-center study, the repertoire of prescribing practices was limited to a small number of cardiologists with similar practice styles. Dogs received cumulative in-hospital parenteral furosemide dosages of approximately 8 mg/kg and chronic PO dosages of approximately 4 mg/kg/day, dosages that are consistent with current consensus guidelines and are similar to or lower than dosages reported in other clinical trials of CHF in dogs. Our results might not be applicable to practices that use higher dosages of furosemide to treat CHF.

Study TPs were defined with the goal of documenting KI occurring between initial hospital presentation and first outpatient reevaluation and calculating the dosage of furosemide administered during the interval in which KI occurred for each particular dog. For this reason, time elapsed between TP1-2 and TP2-3 differed for each dog, and not all dogs included in the study had data available at all TPs (particularly TP2). Especially given evidence that sCr can continue to increase 24 hours after discontinuation of a furosemide CRI in healthy dogs, it is reasonable to assume that some dogs in our study experienced KI after hospital discharge that resolved before TP3, which would not be identified without earlier and more frequent monitoring of renal function. Finally, our definition and staging of KI were adapted from the IRIS classifications for AKI, which were intended for acute clinical scenarios (< 48 hours). Factors other than furosemide could have contributed to increases in sCr in these dogs with CHF, particularly during the longer time frames of TP2-3 and TP1-3.

In conclusion, KI was documented in nearly half of our cohort of dogs treated parenterally with furosemide for CHF, most commonly during hospitalization. Most KI was nonazotemic (Grade I), but Grade II or III KI occurred in 13 (16%) dogs. Higher BP was associated with higher risk of AKI at TP1-2, whereas PO furosemide dosage was predictive of KI after hospital discharge. Use of a furosemide CRI was associated with higher percent changes in serum electrolyte concentrations, but not with percent increase in sCr or incidence of KI. Azotemia was transient in most dogs, and occurrence of KI was not associated with worse survival.

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CONFLICT OF INTEREST DECLARATION

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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.
HUMAN ETHICS APPROVAL DECLARATION

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

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