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Prevalence of Elevated Serum Creatinine Concentration in Dogs Presenting to a Veterinary Academic Medical Center (2010–2014)

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Background: The epidemiology of kidney disease is not extensively described in dogs.

Hypothesis/Objectives: To better understand the prevalence of elevated serum creatinine concentration in dogs.

Animals: Client-owned dogs.

Methods: A retrospective, observational cross-sectional study design was used. We made a dataset of 115,631 hospital visits of all dogs presenting from October 2010 to October 2014. We estimated the prevalence and risk of elevated serum creatinine, defined as >1.6 mg/dL, in evaluated dogs.

Results: Of 115,631 visits, 98,693 were outpatient visits and 16,938 were hospital admissions. Among outpatient visits, 9,983 (10.1%) had serum creatinine assessment (4,423 [44.3%] visits were first visits), whereas, among hospital admissions, 12,228 (60.0%) had at least 1 serum creatinine (7,731 [75.6%] admissions were first admissions). The prevalence of elevated serum creatinine concentration in all evaluated dogs was 11.5% (95% CI: 11.0%, 11.9%); 10.2% (95% CI: 9.6%, 10.8%) of inpatients and 12.9% (95% CI: 12.1%, 13.8%) of outpatients had elevated serum creatinine concentration. The relative risk (RR) of elevated serum creatinine concentration was significantly higher in geriatric dogs (outpatient RR 1.45 [95% CI: 1.23, 1.70], inpatient RR 1.43 [95% CI: 1.16, 1.76]) and lower in young dogs (outpatient RR 0.39 [95% CI: 0.26, 0.59], inpatient RR 0.44 [95% CI: 0.32, 0.62]) when compared to the measured population risk.

Conclusions and Clinical Importance: When selected for laboratory evaluation, the proportion of dogs presenting to an academic medical center with evidence of kidney injury is high compared to previous reports and might reflect a population of sicker dogs.

Key words: Acute kidney injury; Chronic kidney disease; Cross-sectional; Epidemiology.

The impact of acute kidney injury (AKI) and chronic kidney disease (CKD) in dogs is insufficiently studied.[1–5] Far more data are available in people, where both AKI and CKD are associated with poor outcomes and are bidirectionally linked.[6,7] In human studies, acute kidney injury is a risk factor for CKD, with 30% of adults carrying a diagnosis of CKD within 1 year after an AKI hospitalization.[8] Illustrating the bidirectional link, people with preexisting CKD are 4 times more likely to develop an AKI episode compared to those with no history of CKD.[8]

The pathophysiology of naturally occurring AKI is likely similar in people and dogs. By definition, AKI is a clinical syndrome of acutely decreased glomerular filtration rate (GFR); this often occurs secondary to ischemic damage or direct toxic insult.[8] While the GFR has the capacity to fully recover from sublethal insults, incomplete repair might be a mechanism that initiates CKD. One model positing that AKI might lead to CKD describes a pathway of tissue damage (initiation) resulting in fibrosis (extension) that can perpetuate a cycle of continued damage (maintenance) instead of tissue recovery (repair).[9] Because mechanisms underlying many causes of AKI hypothesize renal vasculopathy and perfusion limitations, individuals with preexisting CKD could be at increased risk of AKI due to chronic vascular changes that ultimately contribute to the pathophysiology of CKD.[9] These suppositions are supported through meta-analyses in people, where a decreased estimated GFR is so strongly associated with the risk of AKI that it attenuates the effects of age, sex, race, hypertension, and diabetes.[7,10]

Little data exist on CKD and even less exist on AKI in dogs. The epidemiology of CKD in heterogeneous populations of dogs has been reported in 2 large European studies.[11,12] In over 600,000 dogs in Sweden, researchers estimated the prevalence of CKD as 1.6%

Abbreviations:

AKI	acute kidney injury
CKD	chronic kidney disease
FHSA	Henry and Lois Foster's Hospital for Small Animals
GFR	glomerular filtration rate
IQR	interquartile range
IRIS	International Renal Interest Society
mg/dL	milligram per deciliter
OR	odds ratio
POC	point-of-care
RR	relative risk

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from insurance claims data.[11] In the United Kingdom, a medical records database of 107,214 dogs estimated the prevalence of CKD to be 0.37%.[12] However, these studies likely underestimate the true prevalence and incidence of CKD since the investigators only identified cases if a claim was made or the medical record indicated a diagnosis of CKD; it is not reported what proportion of dogs were evaluated for CKD. In contrast, studies of acute kidney injury in hospitalized dogs could overestimate the prevalence of kidney injury.[4] Accordingly, as a first step in understanding the potential bidirectional link between AKI and CKD, we estimated the prevalence of elevated serum creatinine concentration, which is a composite of community-acquired AKI and CKD (prevalent kidney injury), in evaluated dogs presenting to a referral center treated either as an outpatient or as inpatient.

Methods

Study Design

A retrospective, observational cross-sectional study design was employed to estimate the prevalence of elevated serum creatinine concentration in dogs during evaluation at the Henry & Lois Foster Hospital for Small Animals (FHSA) at the Cummings Veterinary Center at Tufts University. Elevated serum creatinine concentration at presentation could represent either community-acquired AKI or CKD (or even both concurrently). This study design, while unable to identify incident kidney injury, was the most efficient design for reporting the prevalence of elevated serum creatinine concentration in this population. Dogs were identified by generating an investigator initiated custom computer database query to both an administrative hospital invoicing database and a laboratory record database.

Setting

FHSA is an academic veterinary medical center located 40 miles west of Boston. The facility sees more than 26,000 patient visits per year, the majority of which are dogs. A majority of animals present for specialist or emergency consultation.

Study Population

Dogs presenting to the FHSA during the study period of October 1, 2010, to September 30, 2014, a 4-year period, were eligible for inclusion. The catchment population includes dogs of any breed, age, or sex presenting for elective surgery, specialist consultation, or emergency services. Although included dogs can be owned, stray, or service animals, most dogs receiving care at the FHSA are privately owned. Owners are of any age, sex, race, ethnic group, socioeconomic status, education level, or locale typically found in the New England area. Although no study has been published, the apparent diversity of dogs and owners seen at the FHSA likely is representative of the population of dogs and owners residing in the New England region and probably comparable to other academic centers in the Northeast and mid-Atlantic regions.

Data Acquisition

A database was generated from all hospital invoices and abstracted electronic medical records. Databases were merged by linking hospital identification number and by calendar date. Age, sex, date of visit, hospital admission, number of inpatient days if hospitalized, and the number of laboratory tests ordered were included in each record as digitally recorded. Concurrently, a second database of clinicopathologic data was generated by collecting all laboratory orders, date reported, and measured creatinine values during the study period. When modeling was performed, only complete cases were included. The resulting database of all admissions and outpatients with clinicopathologic data was used for the analysis of prevalent kidney injury. All data abstraction and entry were performed by the investigator (JMB) or under direct supervision of the investigator.

Clinical Outcome Definitions

Elevated serum creatinine concentration, a composite of prevalent CKD and community-acquired AKI, was defined using the first measured serum creatinine concentration during any hospital visit. Creatinine concentration was measured using standard laboratory techniques either in a reference laboratory setting or at the bedside using a point-of-care analyzer networked to the laboratory database. The results obtained by these 2 classes of instruments were considered equivalent. Patients were categorized into kidney function groups based on likelihood of kidney injury. It is important to note that, because of the cross-sectional nature of the study design and the inability to determine whether preexisting kidney disease was present, it was impossible to differentiate the natural history of kidney injury present at evaluation. Because of this, the outcome of elevated serum creatinine concentration potentially includes prevalent CKD, community-acquired AKI occurring concurrently with CKD, and new community-acquired AKI in previously unaffected dogs occurring before hospitalization. Classification of elevated serum creatinine concentration concentrations into categories was based on a modification of the recently adopted International Renal Interest Society's (IRIS) AKI grading recommendations.[13] The modified classification system incorporated a category of creatinine elevation above what is considered normal; critically, it is difficult to determine whether the value is pathologic without additional diagnostics. Therefore, dogs were graded based on the following categories of kidney injury: no evidence (creatinine <1.0 mg/dL), mild (creatinine 1–1.6 mg/dL), moderate (creatinine >1.6–2.5 mg/dL), and severe (creatinine >2.5 mg/dL). Elevated serum creatinine concentration was defined by both the moderate and severe categories, comprising all dogs with serum creatinine >1.6 mg/dL.

Covariates

Age, sex, and breed of dogs were collected at initial evaluation, typically at the time of presentation to the FHSA. All 3 of these covariates are owner reported. Age was calculated as the difference between the discharge date and the owner reported date of birth or in many cases the estimated date of birth. Although age was available as a continuous variable, many dogs have owner estimated ages so dogs were categorized as juvenile (<6 months), young (6 months to 2 years), middle aged (>2 years to 7 years), older (>7 years to 11 years), and geriatric (>11 years) to assist in interpretation. Because there are no known recommendations for categorizing age groups, these age categories were defined before any analyses. These categories were selected based on reasonable definitions of life stage that most veterinarians would subscribe to. Similar to age, breed is owner reported. This includes pure bred dogs (e.g., American Kennel Club recognized breeds), designer mixes (e.g., Labradoodle), or some other combination of breeds (e.g., mixed breed dog). The number of

categories in this variable was found to be in excess of 500 and often reported as an ambiguous abbreviation. Due to this significant risk of information bias, this variable was excluded from further analysis. The sex of dogs in the study was also reported by the owner and confirmed by the veterinarian during routine physical examination as entire male, entire female, castrated male, or spayed female, reflecting both their sex and neuter status. Admission status (inpatient versus outpatient) was determined by the presence of a hospitalization charge on a dog's final invoice and recorded as an indicator variable. Whether or not creatinine was measured using a point-of-care (POC) instrument versus standard laboratory equipment was extracted from the laboratory database.

Statistical Analysis

Summary statistics were calculated using proportions for binary and categorical covariates, mean and standard deviation for normally distributed covariates, and median and interquartile range (IQR as 25th and 75th percentile boundaries) for skewed distributions.

The prevalence of elevated creatinine in dogs was estimated from each hospital visit (i.e., encounter) to FHSA where creatinine was evaluated during the study period by calculating the proportion of dogs classified with moderate or severe elevated creatinine. Characteristics of dogs that were admitted to the hospital and outpatient appointments were compared using univariable associations between baseline characteristics and admission status to evaluate if these subgroups could be pooled or should be treated as separate populations. Binary and categorical covariates were tested using the chi-square test. Continuous covariates were tested using Student's *t*-test and Wilcoxon rank-sum test, as appropriate. The absolute risk of elevated creatinine was calculated using the number of encounters (i.e., hospital visits) meeting criteria for elevated creatinine (i.e., moderate or severe kidney injury) divided by the total number of dogs evaluated.

Because the clinical relevance of mild increases in creatinine is unknown in dogs and the relative importance in specific subgroups is also unknown, we performed a hypothesis generating subgroup analysis in both inpatients and outpatients to better understand any potential effects of age group and sex/neuter status on the relative risk of the pooled outcome of elevated creatinine as well as moderate/severe elevated creatinine subgroups. Stratification of the outcome was chosen instead of ordinal regression because of the exploratory nature of the analysis, ease of interpretation, and the low numbers expected in some subgroups.

Because not all dogs were evaluated for creatinine elevation, several one-way sensitivity analyses were conducted to assess the effect of various plausible values of elevated creatinine in the unevaluated dogs on the population estimate. We made a conservative assumption that the risk would be lower in unevaluated dogs and that this would be consistent in inpatient and outpatient populations. An additional sensitivity analysis was performed to investigate the effect of removing visit encounters of dogs that presented to the FHSA more than once on the prevalence of elevated creatinine. The effects of age and sex on the outcome of elevated creatinine were investigated using separate multivariable logistic regression models for elevated creatinine and severely elevated creatinine in inpatient and outpatient populations. We were also interested in whether elevated creatinine would be associated with being admitted to the hospital after adjustment for baseline characteristics; a multivariable logistic regression analysis was chosen to model the relationship among baseline characteristics, creatinine category, and admission status. Model diagnostics performed for each model included analysis of the c-statistic and Hosmer-Lemeshow test.

Model Building

For all models, due to its known clinical importance, age (categorized into age groups), was a priori included in analyses. All available variables then were added to the models in a stepwise fashion (sex followed by first creatinine elevation category, days hospitalized, and clinic evaluation [i.e., point-of-care creatinine measurement methodology]). Unadjusted and adjusted odds ratios with 95% confidence intervals were calculated from the effect estimates produced by fitting the model. For categorical covariates, castrated male, <6 months old, and with no evidence of elevated creatinine were selected as the reference groups. With no previous specific clinical insight or known interactions, as an exploratory analysis, interactions between age groups and sex were evaluated. No interactions were statistically significant, and therefore, all were excluded from final models.

An open source statistical software program was used for data analysis and manipulation.[a] A *P*-value of 0.05 was considered significant for all statistical tests.

Results

During the study period there were 115,631 hospital visits; 14.6% (N = 16,938) of those visits resulted in admission to the hospital whereas the remaining (N = 98,693) were outpatient visits. Among admissions, 60% (N = 10,228) had at least 1 creatinine measurement whereas 10.1% (N = 9,983) of outpatient visits had creatinine measured (Fig 1).

Baseline Characteristics

Dogs that were admitted to the hospital were slightly younger than dogs treated as outpatients (7.0 years versus 7.6 years, *P* value <0.001), and female dogs (both spayed female and female) were over represented in the inpatient and outpatient population compared to male and castrated male dogs (55.5% and 53.7%, *P* values <0.001 for both). A higher proportion of outpatient dogs had elevated creatinine relative to inpatient dogs. Point-of-care analyzers were used more frequently for inpatient measurement of creatinine compared to outpatients (69.3% versus 25.8%, *P* value <0.001) (Table 1).

Prevalence of and Risk Factors for Elevated Creatinine

Among evaluated dogs, 2,322 (11.5%, 95% CI 11.0%, 11.9%) had elevated creatinine at first measure; any elevation in first creatinine was present in 1,283 outpatients (12.9%, 95% CI 12.1%, 13.6%) and in 1,039 inpatients (10.2%, 95% CI 9.6%, 10.8%) (Tables 2 and 3). In the outpatient population, young (RR 0.39 [0.26, 0.59]) and older dogs (RR 0.81 [0.68, 0.96]) were at lower risk for elevated first creatinine, whereas geriatric dogs were at increased risk (RR 1.22 [1.03, 1.43]) when compared to the risk of all dogs treated as outpatients. Spayed female dogs treated as outpatients were at higher risk of elevated first creatinine (RR 1.22 [1.03, 1.43]) as compared to the risk of all dogs treated as outpatients.

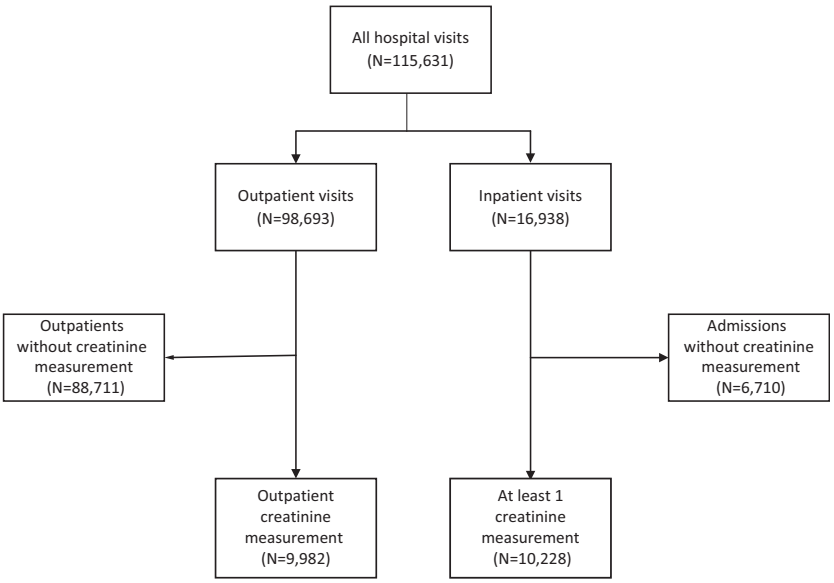

Fig 1. Flow schematic of dogs presenting to the FHSA between October 1, 2010, and September 20, 2014.

Table 1. Baseline characteristics of dogs by visit type. Clinic evaluation is the proportion of creatinine measurements evaluated using point-of-care instrumentation.

Characteristic	Outpatient (N = 98,693)	Inpatient (N = 16,938)	All Visits (N = 115,631)	*P* Value
Age				
Mean ± SD	7.6 ± 4.2	7.0 ± 4.2	7.47 ± 4.18	<0.0001
<6 month—% (No.)	2.4% (2,377)	3.6% (614)	2.6% (2,991)	<0.0001
6 month to 2 years—% (No.)	9.3% (9,155)	12.2% (2,071)	9.7% (11,226)	
>2–7 years—% (No.)	32.2% (31,789)	32.4% (5,485)	32.2% (37,274)	
>7–11 years—% (No.)	32.5% (32,046)	31.4% (5,323)	32.3% (37,369)	
>11 years—% (No.)	23.6% (23,326)	20.3% (3,445)	23.2% (26,771)	
Sex				
Castrated male—% (No.)	34.6% (30,243)	32.0% (4,593)	34.2% (34,836)	<0.0001
Male—% (No.)	11.8% (10,300)	12.6% (1,805)	11.9% (12,105)	
Spayed female—% (No.)	45.5% (39,814)	46.7% (6,707)	45.7% (46,521)	
Female—% (No.)	8.1% (7,129)	8.8% (1,270)	8.2% (8,399)	
Creatinine				
Median [IQR]	0.9 [0.7, 1.2]	0.8 [0.7, 1.0]	0.9 [0.7, 1.1]	<0.0001
<1.0 mg/dL—% (No.)	54.2% (5,415)	67.2% (6,871)	60.8% (12,286)	<0.0001
1.0–1.6 mg/dL—% (No.)	32.9% (3,285)	22.7% (2,318)	27.7% (5,603)	
>1.6–2.5 mg/dL—% (No.)	6.8% (682)	4.5% (462)	5.7% (1,144)	
>2.5 mg/dL—% (No.)	6.0% (601)	5.6% (577)	5.8% (1,178)	
Creatinine evaluated—% (No.)	10.1% (9,982)	60.4% (10,228)	17.5% (20,210)	<0.0001
POC evaluation—% (No.)	25.8% (2,571)	69.3% (7,088)	47.8% (9,659)	<0.0001

Among dogs treated as inpatients, those <2 years old had a lower risk of elevated first creatinine, whereas geriatric dogs were found to have a higher risk (RR 1.43 [1.16, 1.76]) compared to all dogs. When evaluating the stratified RR of sex on elevated first creatinine, there are no RR that are statistically significant (e.g., all 95% CI include RR = 1).

In a one-way sensitivity analysis, we assumed a range of plausible prevalence values of elevated first creatinine (from 1% to the observed prevalence of 12.9% in evaluated dogs) for unevaluated outpatient dogs. This resulted in a minimum prevalence of 2.2% and a maximum equal to the observed prevalence of 12.9% in evaluated dogs. A similar analysis of inpatient dogs resulted in a prevalence of elevated first creatinine from 6.5% to the observed prevalence of 10.2% in evaluated inpatient dogs.

In evaluated dogs, we identified 4,423 (44.3%) unique (i.e., first visit during the study period) outpatient visits and 7,731 (75.6%) unique (i.e., first admission during the study period) hospital admissions. When analyzing the first visit only, the prevalence of any elevated creatinine was 8.9% (95% CI 8.1%, 9.6%) in outpatients and 9.6% (95% CI 9.0, 10.3%) in first hospital admissions.

Table 2. Number of dogs treated as outpatients and relative risks (RR) of moderate and severe elevated first creatinine stratified by age group and sex. Total elevated is a pooled category of moderate and severe elevated first creatinine. The number of dogs with no elevation in creatinine is included for comparison.

	No Elevation (≤1.6 mg/dL)	Moderate Elevation (>1.6–2.5 mg/dL)		Severe Elevation (>2.5 mg/dL)		Total Elevated (≥1.6 mg/dL)		Total Evaluated
Variable	N = 8,700	N = 601	RR [95% CI]	N = 601	[95% CI]	N = 1,283	[95% CI]	N = 9,983
Age								
<6 month	90	3	0.46 [0.15, 1.44]	3	0.52 [0.16, 1.65]	6	0.49 [0.22, 1.07]	96
6 month to 2 years	468	18	0.53 [0.31, 0.91]	7	0.24 [0.11, 0.53]	25	0.39 [0.26, 0.59]	493
>2–7	2,352	139	0.76 [0.55, 1.05]	169	1.06 [0.75, 1.49]	308	0.90 [0.75, 1.08]	2,660
>7–11 years	3,395	212	0.82 [0.60, 1.11]	183	0.80 [0.57, 1.13]	395	0.81 [0.68, 0.96]	3,790
>11 years	2,395	310	1.54 [1.15, 2.07]	239	1.35 [0.96, 1.89]	549	1.45 [1.23, 1.70]	2,994
Sex								
Castrated male	2,906	190	0.85 [0.63, 1.16]	165	0.84 [0.59, 1.19]	355	0.85 [0.71, 1.01]	3,261
Male	1,559	131	1.08 [0.78, 1.49]	86	0.80 [0.55, 1.17]	217	0.95 [0.79, 1.15]	1,776
Spayed female	2,756	261	1.17 [0.87, 1.58]	250	1.27 [0.91, 1.78]	511	1.22 [1.03, 1.43]	3,267
Female	1,440	95	0.85 [0.61, 1.20]	94	0.96 [0.66, 1.39]	189	0.90 [0.74, 1.10]	1,629

Table 3. Number of dogs treated as inpatients and relative risks (RR) of moderate and severe elevated first creatinine stratified by age group and sex. Total elevated is a pooled category of moderate and severe elevated first creatinine. The number of dogs with no elevation in creatinine is included for comparison.

	No Elevation (≤1.6 mg/dL)	Moderate Elevation (>1.6–2.5 mg/dL)		Severe Elevation (>2.5 mg/dL)		Total Elevated (≥1.6 mg/dL)		Total Evaluated
Variable	N = 9,189	N = 462	RR [95% CI]	N = 577	[95% CI]	N = 1,039	[95% CI]	N = 10,228
Age								
<6 month	312	2	0.14 [0.03, 0.59]	6	0.33 [0.14, 0.79]	8	0.25 [0.12, 0.50]	320
6 month to 2 years	974	22	0.48 [0.27, 0.86]	24	0.42 [0.25, 0.70]	46	0.44 [0.32, 0.62]	1,020
>2–7	3,012	139	0.93 [0.59, 1.45]	166	0.89 [0.62, 1.28]	305	0.91 [0.73, 1.12]	3,317
>7–11 years	2,972	153	1.02 [0.65, 1.59]	201	1.07 [0.75, 1.53]	354	1.05 [0.85, 1.29]	3,326
>11 years	1,919	146	1.44 [0.92, 2.25]	180	1.42 [0.99, 2.04]	326	1.43 [1.16, 1.76]	2,944
Sex								
Castrated male	3,002	135	0.91 [0.58, 1.43]	154	0.83 [0.57, 1.20]	289	0.86 [0.70, 1.07]	3,291
Male	879	36	0.82 [0.48, 1.39]	59	1.07 [0.71, 1.63]	95	0.96 [0.74, 1.25]	974
Spayed female	2,625	127	0.95 [0.60, 1.49]	213	1.27 [0.89, 1.82]	340	1.13 [0.92, 1.39]	2,965
Female	660	45	1.35 [0.82, 2.24]	31	0.75 [0.46, 1.21]	76	1.02 [0.77, 1.34]	736

Subgroup Analyses: Risk Factors for Elevated Creatinine in Evaluated Dogs

Dogs categorized as adult (elevated creatinine inpatient OR 4.41 [2.09, 11.4], all visits OR 3.18 [1.85, 6.04]; severely elevated creatinine inpatient OR 2.99 [1.23, 9.89], all visits OR 2.68 [1.35, 6.35]), older (elevated creatinine inpatient OR 4.99 [2.37, 11.4], all visits OR 3.13 [1.82, 5.94]; severely elevated creatinine inpatient OR 3.86 [1.59, 12.8], all visits OR 2.56 [1.29, 6.05]), and geriatric (elevated creatinine inpatient OR 7.09 [3.36, 18.3], all visits OR 5.47 [3.18, 10.4]; severely elevated creatinine inpatient OR 5.06 [2.07, 16.6], all visits OR 3.90 [1.96, 9.22]) were associated with increased odds of elevated creatinine or severely elevated creatinine in both the inpatient and all visits groups compared to juvenile dogs (Table 4). Geriatric dogs being treated as outpatients also had increased odds of elevated creatinine (OR 3.42 [1.6, 8.85]) compared to juvenile dogs. Spayed female dogs had increased odds of elevated creatinine and severe elevation of creatinine in inpatient, outpatient, and all visit groups (elevated creatinine inpatient OR 1.34 [1.14, 1.59], outpatient OR 1.48 [1.28, 1.71], all visits OR 1.42 [1.28, 1.59]; severely elevated creatinine inpatient OR 1.58 [1.27, 1.95], outpatient OR 1.53 [1.25, 1.88], all visits OR 1.55 [1.34, 1.80]) compared to castrated male dogs. Female and male dogs have increased odds of elevated creatinine in the inpatient and all visit groups compared to castrated male dogs (female inpatient OR 1.51 [1.15, 2.00], all visits OR 1.28 [1.10, 1.49]; male inpatient OR 1.33 [1.03, 1.69], all visits OR 1.27 [1.10, 1.47]). Additionally, male dogs treated as inpatients had increased odds of severe elevation of creatinine compared to castrated male dogs (OR 1.54 [1.12, 2.10]).

Table 4. Results of multivariable logistic regression analyses of clinical characteristics and elevated creatinine or severely elevated creatinine in inpatients, outpatients, and all visits.

	Inpatient				Outpatient				All Visits			
	Elevated Creatinine		Severe Elevation		Elevated Creatinine		Severe Elevation		Elevated Creatinine		Severe Elevation	
Variables	OR [95% CI]	*P* Value	OR [95% CI]	*P* Value	OR [95% CI]	*P* Value	OR [95% CI]	*P* Value	OR [95% CI]	*P* Value	OR [95% CI]	*P* Value
Age												
<6 month	Referent		Referent		Referent		Referent		Referent		Referent	
6 month to 2 years	1.82 [0.80, 4.87]	0.19	1.23 [0.45, 4.34]	0.71	0.79 [0.33, 2.18]	0.62	0.43 [0.12, 2.05]	0.23	1.27 [0.70, 2.51]	0.46	0.84 [0.38, 2.12]	0.68
>2–7	4.41 [2.09, 11.4]	0.0004	2.99 [1.23, 9.89]	0.035	1.99 [0.94, 5.16]	0.11	2.10 [0.77, 8.65]	0.21	3.18 [1.85, 6.04]	0.0001	2.68 [1.35, 6.35]	0.011
>7–11 years	4.99 [2.37, 12.9]	0.00015	3.86 [1.59, 12.8]	0.009	1.74 [0.82, 4.52]	0.19	1.55 [0.57, 6.38]	0.46	3.13 [1.82, 5.94]	0.0001	2.56 [1.29, 6.05]	0.016
>11 years	7.09 [3.36, 18.3]	<0.0001	5.06 [2.07, 16.6]	0.0018	3.42 [1.6, 8.85]	0.004	2.67 [0.99, 11.0]	0.098	5.47 [3.18, 10.4]	<0.0001	3.90 [1.96, 9.22]	0.00048
Sex												
Castrated male	Referent		Referent		Referent		Referent		Referent		Referent	
Female	1.51 [1.15, 2.0]	0.0029	1.12 [0.74, 1.65]	0.58	1.16 [0.96, 1.40]	0.13	1.24 [0.95, 1.60]	0.11	1.28 [1.10, 1.49]	0.0016	1.20 [0.97, 1.49]	0.089
Male	1.33 [1.03, 1.69]	0.026	1.54 [1.12, 2.11]	0.0067	1.21 [1.00, 1.45]	0.043	1.00 [0.77, 1.31]	0.97	1.27 [1.10, 1.47]	0.0013	1.17 [0.95, 1.43]	0.13
Spayed female	1.34 [1.14, 1.59]	0.00052	1.58 [1.27, 1.95]	<0.0001	1.48 [1.28, 1.71]	<0.0001	1.53 [1.25, 1.88]	<0.0001	1.42 [1.28, 1.59]	<0.0001	1.55 [1.34, 1.80]	<0.0001
POC evaluation	1.03 [0.88, 1.21]	0.74	0.90 [0.74, 1.10]	0.31	1.13 [0.98, 1.29]	0.08	1.15 [0.95, 1.39]	0.14	1.00 [0.91, 1.10]	0.97	1.04 [0.91, 1.18]	0.57
Events	800		457		1,272		595		2,072		1,052	
Observations	7,897		7,897		9,865		9,865		17,762		17,762	

Association of Clinical Characteristics of Dogs and Hospitalization

In both unadjusted and adjusted models, adult, older, or geriatric dog age groups had decreased odds of being admitted to the hospital compared with juvenile dogs (Table 5). Similarly, castrated males were most likely to be hospitalized. All categories of elevated creatinine were associated with a lower odds of being hospitalized when compared to dogs with normal creatinine. The methodology of creatinine measurement had a strong association with hospitalization, with dogs having their creatinine measured by a POC instrument being more likely to be hospitalized (OR 6.00 [5.61, 6.42]).

Discussion

In a large cohort of dogs evaluated at an academic veterinary hospital, the prevalence of moderately or severely elevated creatinine was 11.5%. Using a retrospective cross-sectional analysis of multiple years of hospital visits, we were able to show that the risk of elevated creatinine in outpatient dogs was 2.7% higher than that of dogs treated as inpatients. In both outpatient and inpatient populations, geriatric dogs had a higher risk of elevated creatinine and young dogs had a lower risk of elevated creatinine compared to all dogs. In adjusted models testing the association between baseline covariates and elevated creatinine, spayed females and older age groups of dogs were at higher risk.

These results represent one of the largest veterinary epidemiologic studies of companion animals with patient level data. In a recently published insurance claims study out of Sweden, the investigators found an estimated prevalence of 1.6% for kidney related claims.[11] These contrast with these results, which are more than 8-fold higher. This might represent a difference in the investigated populations and so-called referral bias or distortion of the true prevalence of a disease for dogs presenting to a referral hospital. An additional contrast between these results and ours is that, in the Swedish analysis, a claim was required to identify dogs with kidney injury, whereas we looked directly at creatinine as a marker of kidney function without considering the clinical diagnosis. This methodology is likely more sensitive than claims data. Similarly, a study in the UK found a CKD prevalence of 0.37% in a multicenter study of 89 practices and 107,214 dogs.[12] Prevalence was calculated by the presence of key words within the medical record rather than a diagnostic test. Additionally, there are no data on the total number of dogs evaluated for prevalent CKD. These results could represent a geographic or practice related difference from these recent claims and electronic medical record studies. This study highlights the importance of reporting the number of dogs evaluated for kidney disease and the number unevaluated. Evaluating every dog by measuring creatinine would provide an accurate assessment of the total burden of disease; however, due to cost and differences in care processes, this has not been done. We found that by knowing the total number of dogs evaluated in both inpatient and outpatient populations, we could

Table 5. Univariate and multivariable logistic regression analysis of clinical characteristics and hospital admission in all dogs.

	Model 1[a]		Model 2[b]		Model 3[c]	
Variable	OR [95% CI]	*P* Value	OR [95% CI]	*P* Value	OR [95% CI]	*P* Value
Age						
<6 month	Referent		Referent		Referent	
6 month to 2 years	0.88 [0.79, 0.97]	0.01	0.47 [0.36, 0.61]	<0.0001	0.59 [0.44, 0.79]	0.0004
>2–7	0.67 [0.61, 0.73]	<0.0001	0.25 [0.19, 0.31]	<0.0001	0.39 [0.29, 0.51]	<0.0001
>7–11 years	0.64 [0.59, 0.70]	<0.0001	0.17 [0.13, 0.21]	<0.0001	0.30 [0.23, 0.39]	<0.0001
>11 years	0.57 [0.52, 0.63]	<0.0001	0.14 [0.11, 0.18]	<0.0001	0.27 [0.20, 0.35]	<0.0001
Sex						
Castrated male			Referent		Referent	
Female			0.36 [0.33, 0.40]	<0.0001	0.40 [0.35, 0.44]	<0.0001
Male			0.47 [0.43, 0.52]	<0.0001	0.51 [0.46, 0.57]	<0.0001
Spayed female			0.90 [0.84, 0.97]	0.0054	0.92 [0.85, 0.99]	0.027
Creatinine						
<1 mg/dL					Referent	
1–1.6 mg/dL					0.62 [0.58, 0.67]	<0.0001
>1.6–2.5 mg/dL					0.56 [0.48, 0.65]	<0.0001
>2.5 mg/dL					0.86 [0.74, 0.99]	0.035
POC evaluation					6.00 [5.61, 6.42]	<0.0001
Events	16,938		7,966		7,897	
Observations	115,631		17,899		17,762	

[a]Model 1 is the univariable model.
[b]Model 2 adjusts for sex/neuter status.
[c]Model 3 adjusts for sex/neuter status, first creatinine measurement, and clinic evaluation of creatinine.

estimate the magnitude of bias present. Because the observed burden of disease is high, dogs presenting to a tertiary care facility should be evaluated for underlying kidney disease.

It is likely that older dogs, similar to older people, have decreased GFR and therefore higher serum creatinine. These results show that nearly 1 in 5 assessed dogs older than 11 years old have elevated creatinine. Despite losses in muscle mass associated with aging and therefore less creatinine generation, geriatric dogs still are more likely to have elevated creatinine. This suggests that the gradual loss of functional nephrons with aging appears to be greater than relative loss of muscle mass, resulting in higher creatinine. Because of these opposite effects, an elevated creatinine in an older dog with cachexia can represent more severe disease than a younger dog with the same measured creatinine. In people, age is an important adjuster when estimating GFR from serum creatinine to account for lower creatinine generation due to lower muscle mass among older adults; these equations have not been developed for dogs. Nonetheless, clinicians should be less tolerant of even small increases in creatinine in geriatric dogs. The relationship between muscle mass and GFR is hypothesized to be important when interpreting the results of heavily muscled dogs; however, this relationship has not been formally investigated.[14]

It was surprising that older dogs with elevated creatinine were being discharged as outpatients. This might be because (1) healthy dogs presenting for elective inpatient procedures have more laboratory tests performed preoperatively skewing the inpatient population to lower creatinine, (2) a large outpatient CKD population being managed by the internal medicine service, or (3) it could reflect values of owners. Older dogs with a perceived poorer prognosis might not receive the same care or be hospitalized as frequently as younger otherwise "healthy" dogs because of a value trade-off between quality of life, duration of life, cost of care, and role within the family. It could also be that these dogs are being euthanized because of their older age, more severely elevated creatinine, or other factors not captured in this data.

This study has several important limitations. The retrospective and observational nature of this data suggests that there is the potential for confounding. Important variables that could contribute to an elevated creatinine, such as toxin exposures, certain medications, and comorbid conditions, are not captured in this cross-sectional analysis. Including these variables as adjustors would likely reduce our reported effect estimates. Additionally, the lack of medical history and longitudinal data could lead to misclassification of the outcome. In this analysis, we defined this outcome as elevated creatinine, which is a composite of community-acquired AKI, AKI with CKD, and prevalent CKD, to reflect that we did not know the contribution of different types of kidney injury. If community-acquired AKI is the predominate contributor to this composite, the proportion of dogs with elevated creatinine that truly have CKD might approach that of previous studies. All dogs were not evaluated for elevated creatinine, which is a source of selection bias. In order to address selection bias introduced by only being able to evaluate dogs with creatinine measurements, we performed sensitivity analyses. In one sensitivity analysis, we recalculated the elevated creatinine risk from conservative prevalence rates (assuming a 1% prevalence in

unevaluated dogs) up to and including the measured prevalence. This analysis suggested a minimum risk of 2.2% in outpatients or 6.5% in inpatients when a very low population prevalence of elevated creatinine was assumed among those dogs not assessed. These rates are still higher than recently published reports of CKD.[11,12]

This study is the largest study of the epidemiology of kidney injury where serum creatinine concentration was measured. The prevalence of kidney injury reported here is greater than previous reports which suggest that prospective surveillance programs could be warranted to better understand the full impact of these diseases.

Footnote

[a] RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/

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