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Retrospective Study

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Characterization of acute kidney injury in hospitalized dogs and evaluation of a veterinary acute kidney injury staging system

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Abstract

Objective – To retrospectively apply standards characterizing acute kidney injury (AKI) used in human medicine to a population of critically ill hospitalized dogs in order to identify dogs with potential AKI based on subtle increases in plasma creatinine concentration.
Design – Retrospective study.
Setting – University Veterinary Medical Teaching Hospital.
Animals – One hundred and sixty-four client-owned dogs admitted to the intensive care unit.
Interventions – None.
Measurements and Main Results – Medical records of 164 dogs meeting the study inclusion criteria were reviewed to identify age, results of creatinine measurements, discharge status, length of stay, performance of general anesthesia, number of diagnoses, and calculated survival prediction index scores (SPI2). A veterinary AKI (VAKI) staging system was retrospectively applied to classify dogs based on increase in creatinine concentration from baseline as follows: stage 0 (S0; <150%), stage 1 (S1; 150–199% or ≥26.5 μmol/L [≥0.3 mg/dL]), stage 2 (S2; 200–299%), or stage 3 (S3; ≥300%). Of the dogs evaluated, 140/164 were VAKI stage S0, 19/164 were classified as S1, 3/164 as S2, and 2/164 were S3. Mortality rate was greater for S1–3 (13/24; 54.2%) compared to S0 dogs (22/140; 15.7%) ($P < 0.0001$). Length of stay, general anesthesia, and number of diagnoses were not associated with survival. In a logistic regression model, stage and age were jointly, significantly associated with mortality ($P = 0.0002$ and $P = 0.0330$, respectively). Mean SPI2 scores were not different between S0 (0.52) and S1 (0.59) dogs ($P = 0.23$). Only 4/19 (21%) of S1 dogs had a peak plasma creatinine concentration above the laboratory reference interval.
Conclusions – Dogs meeting VAKI stage 1–3 criteria were less likely to survive to discharge. Small increases in plasma creatinine concentration may be clinically relevant even when absolute values are within reference intervals.

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Introduction

Acute renal failure (ARF) causes increased morbidity and mortality in hospitalized human patients.[1–5] Over 35 definitions of ARF have been used in the human literature,[6] making consistent identification and classification of patients difficult. Recently, the term acute kidney injury (AKI) has been used to reflect the fact that kidney injury leading to loss of function is a dynamic process.[7] Kidney injury implies that damage is occurring to nephron units that may or may not lead to renal failure. In human medicine, AKI is most commonly defined as an abrupt reduction in kidney function generally recognized in hospitalized patients by increased serum creatinine concentration or reduced urine output (UO).[6,8] However, both the definition and magnitude of change needed to constitute AKI are far from standardized.[7] One study of hospitalized human patients demonstrated that a mildly increased creatinine concentration of 26.5 μmol/L (0.3 mg/dL) from baseline increased the risk of death by 70% even after adjustment for other factors.[3] The authors demonstrated that very small

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changes in creatinine concentrations were common in the hospital population studied and identified a subset of patients with clinically significant kidney injury that would not have been identified with traditional, less stringent, definitions.

Two AKI staging schemes are currently used to classify critically ill people. In 2004, the Acute Dialysis Quality Initiative Group developed the first consensus definition for AKI, known as the RIFLE criteria, in order to consistently identify and classify patients with AKI.[9] The RIFLE criteria stratify patients into risk (R), injury (I), failure (F), loss (L) and end-stage disease (E) categories based on increased serum creatinine concentrations, decreased glomerular filtration rate (GFR), or decreased UO (Table 1). Retrospective application of the RIFLE criteria has repeatedly demonstrated a direct relationship between severity of AKI and increased mortality.[4,10] In 2007, the Acute Kidney Injury Network (AKIN) published the AKIN criteria as a modification of the RIFLE criteria to represent an even broader spectrum of renal dysfunction.[7] The AKIN stages are also based on increased serum creatinine or decreased UO, but do not include GFR criteria. Additionally, the creatinine increase required to move from stage 0 to stage 1 of the AKIN scale is lower than that required for classification of stage "R" of the RIFLE criteria (Table 1).

Table 1: Comparison of Acute Kidney Injury Network versus RIFLE criteria[7,9]

	Serum creatinine criteria	Urine output criteria
AKIN		
Stage 1	≥26.5 μmol/L (0.3 mg/dL) or ≥150–200% increase from baseline serum creatinine	<0.5 mL/kg/h for ≥6 h
Stage 2	>200–299% increase from baseline serum creatinine	<0.5 mL/kg/h for ≥12 h
Stage 3	≥300% increase from baseline serum creatinine or absolute serum creatinine ≥354 μmol/L (4.0 mg/dL) with an acute rise of ≥44 μmol/L (0.5 mg/dL)	<0.3 mL/kg/h for ≥24 h or anuria ≥12 h
RIFLE		
Risk (R)	≥1.5-fold increase from baseline serum creatinine or decrease in GFR ≥25%	<0.5 mL/kg/h for ≥6 h
Injury (I)	≥2.0-fold increase from baseline serum creatinine or decrease in GFR ≥50%	<0.5 mL/kg/h for ≥12 h
Failure (F)	≥3.0-fold increase from baseline serum creatinine or decrease in GFR ≥75% or an absolute serum creatinine ≥354 μmol/L (4.0 mg/dL) with an acute rise ≥44 μmol/L (0.5 mg/dL)	<0.3 mL/kg/h for ≥24 h or anuria ≥12 h

AKIN, acute kidney injury network; GFR, glomerular filtration rate.

No definition or staging scheme has been universally adopted for AKI in veterinary patients. The primary goal of this study was to retrospectively apply standards characterizing AKI in human medicine to a population of critically ill, hospitalized dogs in order to identify dogs with potential AKI. Specifically, we defined a veterinary AKI (VAKI) staging scheme based on the AKIN creatinine criteria, and hypothesized that a creatinine increase of >150%, or 26.5 μmol/L (0.3 mg/dL), from baseline is associated with decreased survival.

Materials and Methods

Medical records of all dogs admitted to the intensive care unit (ICU) at the University of Missouri, Veterinary Medical Teaching Hospital between January 1, 2008 and December 31, 2009 were accessed for potential inclusion in the study. Only the first hospitalization episode was included for dogs admitted to the ICU multiple times during the study period. Dogs were included for further analysis if they were hospitalized in the ICU for >3 days and had a minimum of 2 in-house biochemistry profiles performed. All plasma creatinine measurements were performed on the same chemistry analyzer.[a] Dogs were categorized as azotemic or nonazotemic based on the first creatinine value obtained for that patient, using our laboratory reference interval for plasma creatinine concentration in dogs. Any dog with an initial plasma creatinine of >141.4 μmol/L (1.6 mg/dL) was classified as azotemic and excluded from further study. Dogs with an initial plasma creatinine of ≤141.4 μmol/L (1.6 mg/dL) were classified as nonazotemic and included for further analysis. For each dog meeting all inclusion criteria, age, results of all plasma creatinine measurements, discharge status (alive or dead), number of anesthetic episodes, and length of stay were also recorded. The number of diagnoses for each patient as determined by the attending clinician was also recorded. Additional information required to retrospectively calculate a survival prediction index score (SPI2) for each patient was collected if it was available and included respiratory rate, hematocrit, albumin, managing service, and mean arterial blood pressure (MAP).[11]

Staging system

The study used an AKI staging system novel to veterinary medicine. The system has 4 stages based on changes in creatinine from baseline and was modeled after the AKIN staging system for human patients.[7] Table 2 summarizes the proposed VAKI stages. Dogs were considered to have potential AKI if they met criteria for VAKI stages 1–3.

Table 2: Proposed Veterinary Acute Kidney Injury (VAKI) staging system for dogs

VAKI stage	Criteria
Stage 0	Creatinine increase <150% from baseline
Stage 1	Creatinine increase of 150–199% from baseline OR Creatinine increase of 26.5 μmol/L (0.3 mg/dL) from baseline
Stage 2	Creatinine increase of 200–299% from baseline
Stage 3	Creatinine increase of ≥300% from baseline OR An absolute creatinine value >354 μmol/L (4.0 mg/dL)

Application of staging system

The first in-house plasma creatinine value was used as baseline for each patient. The maximum increase in creatinine from baseline was then determined. For patients with >2 creatinine measurements during the hospitalization period, the creatinine value with the greatest increase from baseline was used to calculate the change in creatinine, regardless of the number of creatinine measurements available for that patient. For patients whose creatinine only decreased during their hospital stay, the maximum decrease was used and recorded as a negative value.

The VAKI staging system was retrospectively applied to all dogs meeting inclusion criteria and survival differences among stages was determined. The associations between survival and VAKI stage, age, having an anesthetic episode, length of stay, and number of diagnoses were assessed. For all dogs meeting VAKI stages 1–3 criteria, the medical record was reviewed to record the primary disease process and secondary complications.

Statistical Analysis

Since none of the variables of interest were normally distributed, nonparametric methods were used. For purposes of statistical analysis, the dependent variable was survival outcome (survival or failure to survive to discharge). Independent variables were VAKI stage, age, occurrence of general anesthesia, length of stay, and number of diagnoses. Age, length of stay, and number of diagnoses were subdivided into categories for purposes of statistical analysis (Figure 1). Categorical data (VAKI stage 0 vs. stages 1–3, performance of general anesthesia) were analyzed with Chi-square testing, while ordinal data (age group, length of stay category, number of diagnoses category) were evaluated with the Mantel-Haenszel statistic. Logistic regression modeling was used to jointly evaluate individual predictors of

a *

Stage	S	NS	Total
S0	118	22	140
S1-3	11	13	24
Total	129	35	164
		p	<0.0001

b *

Age	S	NS	Total
0-3 y	30	4	34
3-6 y	38	5	43
6-8 y	11	7	18
8-10 y	21	5	26
10-12 y	20	7	27
12-16 y	9	7	16
Total	129	35	164
		p	0.0077

c

LOS	S	NS	Total
3-4 d	33	10	43
5-6 d	27	11	38
7-9 d	29	8	37
10-19 d	24	5	29
20-48 d	16	1	17
Total	129	35	164
		p	0.0695

d

Anesthesia	S	NS	Total
No	40	7	47
Yes	89	28	117
Total	129	35	164
		p	0.2015

e

# Diag.	S	NS	Total
1	92	23	115
2	26	9	35
3 to 6	10	3	13
Total	128	35	163
		p	0.5644

f *

Stage	S	NS	Total
S0	118	22	140
S1	8	11	19
Total	126	33	159
		p	<0.0001

Figure 1: Results of survival outcome for each independent variable (Veterinary Acute Kidney Injury [VAKI] stage, age group, length of hospitalization, general anesthesia, and number of diagnoses). (a) Survival outcome for VAKI stage 0 versus VAKI stage 1–3. (b) Survival outcome according to age group. (c) Survival outcome according to length of stay. (d) Survival outcome according to whether general anesthesia was performed. (e) Survival outcome according to the number of diagnoses. (f) Survival outcome for VAKI stage 0 versus VAKI stage 1. S, survivor; NS, nonsurvivor, LOS, length of stay. An asterisk (∗) denotes statistical significance.

Table 3: Survival results by VAKI stage

	Alive	Dead	Total
Stage 0	118	22	140
Stage 1	8	11	19
Stage 2	1	2	3
Stage 3	2	0	2
Total	129	35	164

outcome. The Wilcoxon rank-sum test was used to evaluate the difference between SPI2 scores for different stages of VAKI. A *P*-value of <0.05 was considered significant for all analyses. All data were analyzed by the Statistical Consulting Service at the University of Missouri, using commercially available computer software.[b]

Results

Two hundred and twenty-one dogs were initially identified, but 57 (25.8%) were azotemic (creatinine >141.4 μmol/L [1.6 mg/dL]) at admission and excluded from further analysis. The study population therefore consisted of 164 dogs that were nonazotemic (creatinine ≤141.4 μmol/L [1.6 mg/dL]) at admission.

The median age of all dogs was 7.0 years (range 0.16 to 16.0 y). A total of 117/164 dogs underwent general anesthesia. The median length of stay was 7 days (range 3 to 48 d). The median number of diagnoses was 1 (range 1 to 6), and 1 dog did not have a diagnosis recorded. The median baseline creatinine was 66.3 μmol/L (0.75 mg/dL) (range 8.8 μmol/L [0.1 mg/dL] to 141.4 μmol/L [1.6mg/dL]). The median creatinine value that was compared to baseline to determine the percent of change was 61.9 μmol/L (0.7 mg/dL) (range 8.8 μmol/L [0.1 mg/dL] to 389.0 μmol/L [4.4 mg/dL]). The median change in creatinine from the baseline value was –8.8 μmol/L (–0.1 mg/dL) (range 97.2 μmol/L [–1.1 mg/dL] to 344.8 μmol/L [3.9 mg/dL]).

When the VAKI staging system was applied, 140/164 (85.3%) dogs were stage 0 (S0), 19/164 (11.5%) were stage 1 (S1), 3/164 (1.8%) were stage 2 (S2), and 2/164 (1.2%) were stage 3 (S3) (Table 3). Within the study population, 24/164 (14.6%) of the dogs developed increases in creatinine concentration consistent with AKI according to the VAKI scale. Dogs in VAKI stages 1–3 were grouped into 1 category for purposes of statistical analyses since the numbers of dogs in the S2 and S3 stages were small.

Overall mortality in the study population was 35/164 (21.3%). For S0 dogs, 22/140 (15.7%) died, while 13/24 (54.2%) of S1–S3 dogs died (Figure 1). This difference was significant ($P < 0.0001$). Even considering S1 dogs alone, 11/19 (57.9%) dogs died, which maintains statistical significance when compared to S0 dogs ($P < 0.0001$) (Figure 1).

Nonsurvivors were significantly more likely to be in older age-group categories than survivors ($P = 0.0077$; Figure 1). The median age of survivors was 6 years (range 2 mo to 16 y) and for nonsurvivors was 5 years (range 1 y to 15 y). Length of stay, performance of general anesthesia, and number of diagnoses were not significantly different between survivors and nonsurvivors (Figure 1).

Since there were only 35 dogs in the nonsurvivor category, only the predictors of stage and age were considered in the logistic analysis. When considered jointly using logistic regression modeling, both stage and age were significantly associated with outcome ($P = 0.0002$ and $P = 0.0330$, respectively).

For S1 patients, 16/19 cases underwent anesthesia. Of the 11 S1 dogs that died, 10/11 (90.9%) had undergone anesthesia. For S2 patients, 2/3 cases underwent anesthesia. Of the 2 S2 dogs that died, both had undergone anesthesia. For S3 patients, 2/2 cases underwent anesthesia and both of these cases survived. Table 4 summarizes the major clinical features of the dogs in VAKI S1–S3.

Data to calculate SPI2 scores were available for 82/164 dogs. The mean SPI2 score for S0 dogs was 0.52 (±0.18) and for S1 dogs was 0.59 (±0.17), which was not significantly different ($P = 0.23$). There were insufficient data to calculate SPI2 scores for any S2 or S3 dog.

Only 4/19 (21%) of S1 dogs had a peak plasma creatinine above the laboratory reference interval (ie, >141.4 μmol/L [1.6 mg/dL]). Plasma creatinine peaked above the reference interval in all S2 and S3 dogs. Table 4 lists peak creatinine values for all VAKI S1–S3 dogs.

Discussion

Depending on the criteria used, the incidence of AKI is as high as 67% in critically ill hospitalized human patients.[4] AKI not only increases mortality rates of critically ill people, but has also been shown to drastically increase the cost of care for these same patients.[3] The information reported herein is the first time that the AKIN criteria used to identify AKI in people have been applied to a veterinary population. The presence of AKI has not previously been documented in dogs in this way. Using these guidelines, 14.6% of hospitalized dogs were categorized into a stage consistent with AKI, and these dogs had a mortality rate of 54.2%. This highlights an important but previously unrecognized phenomenon in critically ill dogs. We believe the dogs in our study reflect a truly critically ill population that would be expected to have a high mortality rate. While the classification of AKI and the high mortality rate in those dogs may be a surrogate for critical illness, it has been consistently demonstrated in the human literature that patients with AKI have an increased risk of mortality independent of

Table 4: Summary of clinical features of dogs meeting VAKI stage 1–3 criteria

	Signalment	Primary	Complications	Anesthesia	Outcome	Baseline creatinine μmol/L (mg/dL)	Peak creatinine μmol/L (mg/dL)	VAKI stage
1	11 yo MC mixed breed	Splenic mass	Sepsis, MODS	Yes	Died	1.5	2.0	1
2	3 yo FS Golden Retriever	Total hip replacement	Aspiration pneumonia requiring mechanical ventilation	Yes	Died	1.0	1.4	1
3	4 yo MC Doberman Pinscher	Wobbler's disease	Seizure post myelogram; aspiration pneumonia	Yes	Died	0.9	1.3	1
4	1 yo FS Miniature Poodle	Hydronephrosis and immune mediated thrombocytopenia	Presumptive sepsis	Yes	Died	0.6	1.1	1
5	10 yo FS Bichon Frise	Penetrating thoracic wound from dog bite	Respiratory failure requiring mechanical ventilation	Yes	Died	0.8	1.5	1
6	13 yo FS Yorkshire Terrier	Gallbladder rupture and sterile bile peritonitis	Septic peritonitis 4 days postoperatively	Yes	Euthanized	0.5	0.8	1
7	7 yo FS Chihuahua	Hit by car with multiple fractures and diaphragmatic hernia	Seizure and respiratory arrest	Yes	Euthanized	0.6	1.0	1
8	13 yo FS German Shepherd	Biliary mucocele	Aspiration pneumonia	Yes	Euthanized	0.5	0.9	1
9	13 yo MC Standard Poodle	Acetabular fracture from vehicular trauma	Pneumonia, sepsis	Yes	Euthanized	0.7	1.3	1
10	10 yo FS Golden Retriever	Thoracic wall mast cell tumor invading the chest	Presumed sepsis	Yes	Euthanized	0.9	1.8	1
11	9 yo FS Pug	Multiple pelvic fractures and body wall hernia from vehicular trauma		No	Euthanized	0.7	1.9	1
12	8 yo MC Labrador Retriever	Unilateral nephroblastoma with caval invasion		Yes	Alive	1.1	1.5	1
13	13 yo FS Golden Retriever	Hit by car with multiple fractures	Orthopedic implant infection	Yes	Alive	0.7	1.0	1
14	9 yo MC Tibetan Terrier	Hypoadrenocorticism		No	Alive	1.1	1.7	1
15	9mo MI Bulldog	Bronchopneumonia, brachycephalic airway syndrome	Progressive pneumonia requiring mechanical ventilation	Yes	Alive	0.3	0.6	1
16	12 yo MI West Highland White Terrier	Pericardial effusion treated with intrathoracic chemotherapy		Yes	Alive	0.5	0.9	1
17	4 yo FS Dachshund	Intervertebral disc disease (T3-L3)	UTI	Yes	Alive	0.5	1.0	1
18	6 yo FS Chihuahua	Traumatic brain injury from dog fight		No	Alive	0.4	0.9	1

Continued.

Table 4: (Continued)

	Signalment	Primary	Complications	Anesthesia	Outcome	Baseline creatinine μmol/L (mg/dL)	Peak creatinine μmol/L (mg/dL)	VAKI stage
19	3 yo MC Jack Russell Terrier	Flail chest and open chest wound from dog fight	Cardiac arrest	Yes	Alive	0.6	1.5	1
20	11 yo MC Mixed breed	Metastatic adrenal carcinoma	Sepsis	Yes	Died	0.9	2.7	2
21	13 yo MC Mixed breed	Metastatic oral melanoma	Aspiration pneumonia	No	Euthanized	0.9	2.8	2
22	6 you FS Boxer	Fibrocartilagenous embolus (T3-L3)	UTI, bladder rupture and urosepsis	Yes (to correct bladder rupture)	Alive	1.0	3.2	2
23	12 yo FS English Shepherd	Intervertebral disc disease (T3-L3)	Bladder rupture	Yes (for IVDD and bladder rupture)	Alive	0.5	2.4	3
24	4 yo F Labrador Retriever	Necrotizing mastitis and septic peritonitis		Yes	Alive	0.5	4.4	3

FS, female spayed; IVDD, intervertebral disc disease; MC, male castrated; MI, male intact; MODS, multiple organ dysfunction syndrome; UTI, urinary tract infection; VAKI, veterinary acute kidney injury; yo, year old.

comorbid conditions and illness severity.[4,5,12] Prospective evaluation of a large population of critically ill dogs using the VAKI system would be needed to validate the VAKI system and determine if VAKI stage was independently associated with mortality.

The current literature regarding kidney injury in hospitalized veterinary patients is limited. One veterinary study evaluated 29 hospitalized dogs that were considered to have developed ARF while hospitalized.[13] In this study, hospital-acquired ARF (HARF) was diagnosed in dogs that had a serum creatinine within the reference interval in the 2 weeks preceding hospital admission, which then increased to >221 μmol/L (2.5 mg/dL) while hospitalized. Animals with pre- and postrenal causes of azotemia were excluded. Overall, mortality was 62% for dogs with HARF, and serum creatinine at admission did not differ between survivors and nonsurvivors.[13] Criteria to determine kidney injury were not as stringent as ours, reflecting an older definition of kidney failure rather than the more strict standards currently reported in the human literature to identify early kidney injury. This study cannot be directly compared to the results presented here due to different inclusion criteria, but the mortality rate is similar to our findings.

Another veterinary study evaluated the association between organ dysfunction and outcome in 114 dogs with septic peritonitis.[14] In this population, renal dysfunction was defined as an increase in creatinine of >44.2 μmol/L (0.5 mg/dL) from preoperative values. Of the 14/114 (12%) patients that met this criteria, only 2/14 (14%) dogs survived. Multivariate analysis indicated that dysfunction of the renal system increased the odds of death, independent of other factors. These study criteria are similar to ours in that small increases in creatinine are compared to baseline values. However, the mortality rate reported for dogs with AKI in this study (86%) is higher than in our population (54%). This may be related in part to difference in the patient population. A population consisting entirely of dogs with septic peritonitis is different from ours, which reflects a more general ICU population that included only a few dogs documented to be septic. It is well documented in the human literature that AKI secondary to sepsis carries a higher mortality rate as compared to most other precipitating conditions.[15–17]

Recently, a retrospective study presented the results of application of modified RIFLE criteria in 853 dogs presented to a veterinary teaching hospital from 2000 to 2006.[18] The authors reported increased 30-day mortality for dogs in each of 3 categories of "R, I, and F." Dogs were enrolled based upon an elevated creatinine value at the time of admission, and were reported to have normal kidney function 14 days prior. Additionally, the authors used a modified RIFLE criteria by utilizing the GFR ranking standards of the original RIFLE criteria in the following manner: a baseline "normal canine" GFR of 2.61 mL/min/kg was selected, a decrease of 25%, 50%, and 75% of baseline was calculated from this baseline GFR, and a historically published formula was utilized to equate these GFR numbers to creatinine values of 116–174 μmol/L (1.3–1.9 mg/dL) for "R," 175–347.9 μmol/L (2.0–3.9 mg/dL) for "I," and > 348 μmol/L

(> 4.0 mg/dL) creatinine for "F." This study did not use the original RIFLE criteria of an increase in absolute creatinine from baseline. Actual GFR measurements were not published from dogs included in the study, and percentage of increase from a baseline creatinine was not presented. This study differs from our study in that dogs in our study were categorized based upon documented increases from baseline as measured on our in-hospital clinical chemistry analyzer, and were not azotemic at the time of admission. We believe our methodology more accurately represents a subset of patients without underlying renal dysfunction at the time of hospital admission, and is more closely aligned with the RIFLE and AKIN criteria.

Inclusion criteria for our study limited enrollment to dogs hospitalized in the ICU for at least 3 days. In our hospital, stable postoperative patients are commonly admitted to the ICU for 1 night following surgery for fluid therapy, analgesia, and monitoring. A minimum duration of 3-day hospitalization in ICU was chosen to identify a population of dogs that was more likely to have serious illness, as well as serial biochemistry monitoring that was necessary to identify changes in creatinine. All plasma creatinine values were measured on the same in-hospital chemistry analyzer, which eliminates intermachine variability. Modern chemistry analyzers have a small coefficient of variation when measuring creatinine, making it unlikely that interassay variation will lead to increases in creatinine when using the same analyzer.[7]

Renal function prior to hospitalization was unknown for all patients, and hydration status at the time of admission and during hospitalization was impossible to accurately determine retrospectively. Therefore, dogs that developed increases in plasma creatinine concentrations during hospitalization may have had a prerenal, renal, or postrenal contribution to their azotemia. The AKIN recommendations state that the criteria should only be applied after optimal fluid resuscitation has been achieved.[7] However, other studies have evaluated patients without regard to fluid status.[10,19,20] Patients admitted to our ICU are generally treated with IV fluids. Any patient with prerenal azotemia secondary to dehydration would theoretically have declining creatinine concentration in the face of fluid therapy and would be classified as S0 according to our scheme. However, fluid balance can be difficult to assess in critically ill patients. Some patients in our study that became azotemic while hospitalized may have developed a prerenal azotemia secondary to dehydration due to unrecognized ongoing losses, without any underlying renal dysfunction. This remains an inherent limitation to our retrospective study. However, since dehydration can ultimately result in intrinsic renal damage, any patient with progressive azotemia in the face of fluid therapy could reasonably be classified as S1 or higher.

Conventional teaching in veterinary medicine is that kidney failure or injury is diagnosed when azotemia occurs concurrently with low urine-specific gravity. However, we did not assess urinalyses to determine urine-specific gravity in our study population due to the inability to determine retrospectively that a particular urine-specific gravity value was obtained at the same time as each creatinine value. Interestingly, human nephrologists do not emphasize urine-specific gravity when diagnosing AKI in hospitalized people and the diagnosis is made based on increasing creatinine or decreasing UO.[7–9] Likewise, given that treatments for critically ill animals such as IV fluid therapy will decrease urine-specific gravity independent of renal function, serial urine-specific gravity determinations are not generally useful in hospitalized dogs to determine renal function.

Two dogs, 1 each in the S2 and S3 stages, were diagnosed with uroabdomen secondary to bladder rupture that occurred while in the hospital. Both of these dogs had normal baseline creatinine values at admission that increased after being admitted to the ICU. This clearly constitutes a postrenal azotemia, and classification of these patients as having AKI may be questioned. However, one could argue that uroabdomen could lead to events causing AKI, such as decreased renal perfusion from systemic inflammatory response syndrome (SIRS), hypovolemia, and sepsis, such as the dog with a urinary tract infection prior to bladder rupture (see Table 4). When the S2 and S3 dogs were removed from the statistical analysis, S1 dogs alone were still significantly less likely than S0 dogs to survive to discharge. However, the appropriate classification of patients with a postrenal azotemia is unknown and requires prospective investigation.

The appropriate classification of dogs that are azotemic at ICU admission requires further study. These dogs were excluded from our study to minimize the effect of more profound azotemia and reduce the risk of Type 1 error. Additionally, we were interested in determining whether a population that would be classified by human standards as having "HARF" existed in our population. Since our study was retrospective, we were unable to accurately determine if dogs that were azotemic at admission had prerenal or renal azotemia. Furthermore, if the azotemia was classified as "renal" in these dogs, determining the chronicity of renal failure was not possible for this population. There are no clear guidelines to follow from the human literature when evaluating AKI in patients with pre-existing renal disease.[7] With loss of an undetermined percentage of renal function that cannot be quantified clinically, the incremental increases in creatinine used to diagnose AKI may be different

compared to nonazotemic patients. To further complicate the appropriate classification of patients that are azotemic, the presence of pre-existing renal disease is a risk factor for developing AKI in both humans and dogs.[13,21,22]

We attempted to assess the complexity and severity of disease in the study population by evaluating the number of diagnoses recorded for each patient, in addition to an SPI2 score. Our hospital's computerized medical records system requires at least one final diagnosis for each patient as determined by the attending clinician, but more can be added as needed to reflect the patient's condition. Considering that critically ill patients often have multiple concurrent disease processes, we attempted to determine if those patients with more diseases were less likely to survive. We did not find any difference considering the number of diagnoses between survivors and nonsurvivors. However, using this method to assess complexity of disease for each patient is limited by the subjective opinion of the attending clinician as to what should be coded in the medical record as the final diagnoses. Since only one diagnosis is required in the record, the clinician may fail to list all the diagnoses for dogs with multiple diseases.

Survival prediction index scores were also retrospectively determined for 82/164 dogs in this study. Calculation of an SPI2 score requires, among other parameters, an MAP measurement obtained within the first 24 hours of hospitalization.[11] Although blood pressure monitoring is a standard procedure in our hospital, MAP is generally only available when indirect oscillometric or direct blood pressure monitoring is performed. Therefore, patients evaluated using Doppler blood pressure monitoring were not included for SPI2 calculation. Even though S1 patients in our study were more likely to die as compared to S0 patients, the SPI2 score was not significantly different between the 2 stages. Illness severity scores have been validated in both human and veterinary medicine to objectively classify disease severity in order to predict outcome in a population.[23] A number of global illness scoring systems have been developed for critically ill people,[24–26] but these may not be applicable to particular subsets of patients,[27] and are believed to underestimate the effect of renal dysfunction on mortality.[4,19] Although the illness severity scoring systems developed for veterinary patients include creatinine as a factor in overall illness severity score,[11,28] their utility in specifically evaluating dogs with AKI has not been evaluated and these systems may possess the same inherent limitations demonstrated in human patients when assessing AKI.

Our study did not investigate the cause of AKI in these dogs. Documented causes of kidney injury or failure in hospitalized veterinary patients include the use of nephrotoxic drugs, increased age, heart disease, preexisting renal disease, neoplasia, fever, ischemic events and recent anesthesia.[13,29–31] Multiple large-scale epidemiologic studies have identified risk factors for the development of AKI in humans and include radiographic contrast media, major surgery, pre-existing renal disease, sepsis, drugs such as aminoglycosides, and decreased renal perfusion from a variety of other causes such as hypovolemia.[1,2,15,21] However, the development of AKI is likely multifactorial in both veterinary and human patients. The VAKI S1–S3 dogs in our study had many of these known risk factors, but we did not evaluate each patient for all the known risk factors. Therefore, causation cannot be determined from this study.

Limitations of our study are a result of its retrospective nature. In our analysis, no differentiation was made between dogs that were euthanized versus those that died a natural death. We were unable to determine a reason for euthanasia retrospectively, so cost and the clinical judgment of the attending clinician may have factored into the euthanasia of some dogs. Even though UO is an important marker of renal function, UO criteria were not evaluated in our study or included in our classification scheme. Quantitative UO measurements are not recorded for all hospitalized patients in our institution since indwelling urinary collection systems are only used when medically indicated. We believe this likely reflects management practices at many other facilities since there are risks inherent in continuous urethral catheterization.[32] However, the addition of UO criteria is useful in human AKI staging systems and could be an important component of staging veterinary patients with AKI. In addition, creatinine was measured at variable time points for each patient, which is a potential limitation of our study. Although the AKIN criteria specify that the initial evidence of AKI should occur within 48 hours of hospitalization, we did not place any time constraints as to when the peak creatinine concentration must occur in our staging system. Prospective evaluation is necessary to determine the optimal time interval between creatinine measurements. In critically ill people with AKI, patients may progress from lower to higher AKIN stages during their hospitalization.[4,33] We only identified the peak VAKI stage in our patient population and did not evaluate for progression or resolution of AKI.

We undertook this study to determine the potential applicability of a VAKI staging system in critically ill dogs. Although we have identified an association between VAKI stage and survival to discharge, we cannot predict a direct causal relationship retrospectively. Given the possibility of AKI developing in critically ill dogs, clinicians should critically evaluate renal function and take measures to promote renal protection.

Only 21% of S1 dogs in this study had a plasma creatinine concentration peak above of the laboratory reference interval. This highlights the importance of monitoring trends in creatinine to assess kidney function, as opposed to waiting for an absolute creatinine concentration above of the reference interval to suspect kidney injury has occurred. Unfortunately, creatinine measurement as a surrogate of renal function possesses inherent limitations.[8] Incorporating newer biomarkers of renal function such as urine proteins (eg, neutrophil gelatinase-associated lipocalin [NGAL]) and N-acetyl-B-D-glucosaminidase [NAG]) may facilitate earlier diagnosis of AKI and should be investigated as well.[34,35]

In conclusion, we were able to document that subtle changes in creatinine concentrations consistent with AKI occur in hospitalized dogs. Dogs meeting AKI criteria were less likely to survive to discharge from a veterinary ICU. While causation and prognostic information cannot be inferred from this study, the importance of small increases in creatinine appears to be clinically relevant, even when all creatinine values remain within the reference range. This information highlights the importance of continued investigation of AKI in veterinary patients in order to identify risk factors, prognostic indicators, the incidence of renal recovery, and the effects of different management practices on outcome. Prospective application of the VAKI system in hospitalized dogs is needed to test its accuracy and usefulness in the diagnosis of AKI in dogs.

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Footnotes

[a] Olympus AU400e, Olympus America, Center Valley, PA.
[b] SAS v9, SAS Institute Inc., Cary, NC.

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