

**STANDARD ARTICLE**

Acute on chronic kidney disease in cats: Etiology, clinical and clinicopathologic findings, prognostic markers, and outcome

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Abstract

Background: Chronic kidney disease (CKD) and acute decompensation of CKD (ACKD) are common in cats.

Objectives: To characterize the etiology, clinical and clinicopathologic findings, and the short- and long-term prognosis of feline ACKD.

Animals: One hundred cats with ACKD.

Methods: Retrospective study, search of medical records for cats with ACKD.

Results: Common clinical signs included anorexia (85%), lethargy (60%), weight loss (39%), and vomiting (27%). Suspected etiologies included ureteral obstruction (11%), renal ischemia (9%), pyelonephritis (8%), others (6%), or unknown (66%). Hospitalization duration was longer in survivors versus nonsurvivors (median = 7 days, range = 2-26 versus median = 3 days, range = 2-20, respectively, $P < .001$). The survival rate to discharge was 58%. Age, serum creatinine, urea, and phosphorous concentrations were higher and venous blood pH was lower in nonsurvivors. However, only serum phosphorus remained associated with the short-term outcome in the multivariable model ($P = .02$; 95% confidence interval = 1.03-1.39). Survivors had a median survival time of 66 days after discharge. Serum creatinine concentrations at presentation as well as at discharge were associated with long-term survival ($P < .002$ for both).

Conclusions: The short-term prognosis of ACKD is comparable to acute kidney injury, while the long-term prognosis is guarded.

KEYWORDS

acute kidney injury, azotemia, renal failure, survival, uremia

Abbreviations: ACKD, acute on chronic kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; DGGR, 1,2-o-dilauryl-Rac-glycero glutaric acid-(6'-methylresorufin) ester; GFR, glomerular filtration rate; IRIS, International Renal Interest Society; MST, mean survival time; sCr, serum creatinine; UO, ureteral obstruction.

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1 | INTRODUCTION

Chronic kidney disease (CKD) is common in cats, with an estimated prevalence of 1.6% to 20%.¹⁻³ Although CKD occurs in all ages, its prevalence increases with age,^{4,5} affecting up to 80% of cats above the age of 15 years, and is thus considered a leading death cause in geriatric cats.⁶⁻⁸ Several factors, including age, breed, vaccinations, hypertension, proteinuria, and acute kidney injury (AKI), are implicated in the pathogenesis of CKD.⁹⁻¹¹ With lack of early sensitive markers of decreased kidney function, CKD in cats is often diagnosed late in its course, when functional impairment exceeds the compensatory mechanisms and substantial irreversible damage to the renal parenchyma has already occurred.¹²

CKD is progressive in nature and is characterized by ongoing decrease in kidney function.^{1,4} Several risk factors, such as presence of proteinuria and hyperphosphatemia, are associated with its progression¹³; however, the pathogenesis of CKD is not fully characterized, and is probably multifactorial.¹⁰ CKD progression might be relatively constant, with ongoing intrinsic kidney damage, or alternatively, progression might be a consequence of sequential episodic bouts of AKI of variable magnitudes.¹⁰ The latter might remain undiagnosed, especially in the early stages of the disease because of compensatory adaptations, or be associated with clinical signs, especially in the late stages, when compensatory mechanisms have already been exhausted.¹⁰ Thus, the clinical manifestation of the disease depends of the stage of the CKD and the severity of the acute insult.

Acute kidney injury is characterized by abrupt renal parenchymal damage, often, but not always, accompanied by decreased renal function.¹⁴ Acute kidney injury is potentially reversible, with survival rates of approximately 50% in both small animals and humans.¹⁵⁻¹⁷ Recovery is facilitated by regeneration and repair processes within the kidneys once the inciting cause is no longer present, and the perpetuating events subside.¹⁴ The prognosis of AKI is variable and influenced by multiple factors, including the etiology (ie, reversible versus irreversible injury), severity of injury, involvement of other body organs, availability of therapeutic options (eg, hemodialysis), and owner's compliance.^{15,18,19}

Animals with stable CKD often experience acute decrease in kidney function (termed "acute on CKD" [ACKD]). The pathogenesis, clinical presentation, and laboratory findings resemble AKI,¹⁰ occasionally making differentiation of ACKD from AKI challenging. Although ACKD is suspected to occur commonly in cats, its etiology, disease course, and the short- and long-term prognosis have not previously been described, in contrast with feline CKD and AKI, which are well characterized.^{7,13,20} Due to overall guarded to poor long-term prognosis of cats with CKD, owners often inquire regarding the short- and long-term prognosis of ACKD, before pursuing treatment. Therefore, the aforementioned information is required to guide both proper therapeutic decision-making and prognostication.

The aim of this retrospective study was to characterize the etiology, clinical, and laboratory findings and the short- and long-term prognosis of cats with ACKD.

2 | MATERIALS AND METHODS

2.1 | Cats and definitions

Medical records of cats presented to the Koret School of Veterinary Medicine, The Robert H. Smith Faculty of Agriculture, Food and Environment, Hebrew University of Jerusalem and diagnosed with ACKD between the years 2017 and 2019 were retrospectively retrieved. Cats were eligible for inclusion if presented with an acute onset of clinical signs compatible with AKI (eg, anorexia, lethargy, vomiting),¹⁹ azotemia (serum creatinine [sCr] > 1.6 mg/dL) and at least one of the following criteria: (1) a previous diagnosis of CKD (in accordance with International Renal Interest Society [IRIS]) with a concurrent increase in sCr of >20% above the last sCr measurement; (2) a previous diagnosis of CKD with concurrent presence of urinary markers consistent with acute injury (eg, glucosuria in face of normoglycemia, cylindruria)²¹; and (3) unequivocal abdominal ultrasonographic findings characteristic of CKD, based on presence of ≥ 2 of the following: increased renal cortical echogenicity, markedly reduced renal corticomedullary differentiation, decreased kidney size (<2.8 cm), presence of renal cysts, or irregular renal contour.²²

2.2 | Etiology and concurrent disease

The etiology of the ACKD was classified as ureteral obstruction (UO), pyelonephritis, renal ischemia, other renal related etiology ("other renal"), or unknown. Ureteral obstruction was diagnosed based on compatible clinical signs (eg, big, firm kidney), sonographic evidence of hydroureter, or pyelectasia of >7 mm, or both,²³ and was confirmed by nephropyelogram in equivocal cases. Cats with UO were only included if there was a clear sonographic evidence of CKD in the obstructed or contralateral kidney, concurrent with the obstruction. Pyelonephritis was suspected based on positive urine culture and pyuria on urinalysis with consistent ultrasonographic findings (including >2 mm pelvic dilatation). Renal ischemia was considered the etiology of ACKD in cats treated with furosemide or nonsteroidal anti-inflammatory drugs, in those where the acute exacerbation had occurred after general anesthesia and in cases that had experienced traumatic injury (eg, high-rise syndrome or being hit by car) just before presentation with ACKD. Additional etiologies (represented by ≤ 3 cats), including protein-losing nephropathy, cardiorenal syndrome (diagnosed in cats presenting with heart failure and not treated with diuretics before the current ACKD episode²⁴), and infected renal cortical cyst, were allocated into "other renal."

Pancreatitis was diagnosed in cats with compelling ultrasonographic findings,^{25,26} serum 1,2-o-dilauryl-Rac-glycero glutaric acid-(6'-methylresorufin) ester (DGGR)-lipase activity above the hospital's laboratory upper reference limit (26 U/L), or both.

Survivors were defined as being alive at discharge from the hospital, whereas nonsurvivors either died or were euthanized because lack of improvement during hospitalization. Cats were excluded if euthanized during the first 48 hours of hospitalization.

2.3 | Follow-up

The long-term outcome of the survivors was calculated as the number of days after discharge from the hospital to time of death or euthanasia. Time of death was obtained from the medical records or by telephone interviews with the owners. Cats lost to follow-up were censored.

2.4 | Collection of samples and laboratory methods

Blood samples for CBC (Advia 120 or 2120, Siemens, Erlangen, Germany; Abacus Junior Vet, Diatron, Wien, Austria) and serum chemistry (Cobas 6000, Roche, Mannheim, Germany) were collected in potassium-EDTA and plain tubes with gel separators, respectively, and analyzed within 60 minutes from collection. Urinalysis, including dipstick analysis, measurement of specific gravity by refractometry, sediment cytology (automated [SediVue Dx, IDEXX Laboratories, Westbrook, ME] or by manual microscopy), and bacterial culture and sensitivity, was done on urine samples obtained by cystocentesis. Hematuria and pyuria were defined as the presence of >5 erythrocytes or leukocytes (respectively) in a high power field. Bacteriuria was considered positive if bacteria were evident upon sediment cytology. Proteinuria was defined as a urine dipstick result of $\geq 1+$ (ie, >30 mg/dL).

2.5 | Statistical analysis

The distribution pattern of continuous variables was assessed using the Shapiro-Wilk test. Because most data were not normally distributed, the Mann-Whitney *U* test was used to compare 2 groups. The χ^2 or the Fisher's exact tests were used to examine the association between 2 categorical variables. Assessment of sCr concentration change during hospitalization (presentation versus discharge/death) was performed using the Wilcoxon rank test. Variables associated ($P < .1$) with death were included in a forward multivariable logistic regression analysis to further examine their association with the outcome. The Hosmer and Lemeshow test was used to assess the goodness of fit. Variables that remained statistically significant following the multivariable analysis were assessed using the receiver operating curve analysis to determine sensitivities and specificities for outcome prediction. The optimal cutoff point was selected as the value associated with the least number of misclassification. Kaplan-Meier survival curve, with the log-rank test, was used to compare median survival times (MSTs) of cats with IRIS AKI grades II-III versus IRIS grades IV-V at presentation, and of cat groups categorized based on their sCr concentration at discharge. Cox regression was used to compare the survival of cats with different ACKD etiologies and the association of sCr concentration at discharge with the long-term survival. Assumption that hazards are proportional was assessed by generating a time dependent covariate and assessing

for interactions. To test the association between sCr concentration at discharge and long-term outcome, cats were categorized into 4 groups, according to sCr concentration ranges, based on the IRIS CKD staging system. These categories were not referred to as CKD stages, since at discharge, the disease was not considered in steady state and therefore staging the disease at this point would not have been appropriate.

All tests were 2-tailed and $P < .05$ was considered significant. Analyses were performed using a statistical software package (SPSS 22.0, IBM, Chicago, Illinois).

3 | RESULTS

Acute on chronic kidney disease was diagnosed in 159 cats during the time period of the study. Thirty of these were excluded because of short hospitalization time (<48 hours) which was deemed insufficient to allow effective treatment. Additionally, 29 cats were excluded because of incomplete data in their medical records, precluding a reliable diagnosis of ACKD. In 7 out of those 29 cats, the evidence of CKD was not compelling, in 12 cats, acute decompensation could not be ascertained, in 7 cats presented with bilateral UO, a conclusive diagnosis of CKD before decompensation could not have been made, and in 3 cats laboratory test results or ultrasound examination were not available from our institution. Therefore, 100 cats with ACKD met the inclusion criteria and were included in the statistical analyses.

Fifty-eight (58%) cats were discharged (ie, survivors) and 42 (42%) either died (13 cats; 31%) or were euthanized (29 cats; 69%) during hospitalization (ie, nonsurvivors).

3.1 | Signalment

The cohort included the following breeds: domestic shorthair (72 cats), Persian (18), British shorthair (4), Siamese (3) and Burmese, Scottish fold and Himalayan (1 each). Nonsurvivors were significantly ($P = .01$) older compared with survivors (median = 138 months, range = 36-240 versus median = 120 months, range = 24-221, respectively). There were 58 males (castrated, 56; 97%) and 42 females (spayed, 33; 79%). There was no difference in body weight of survivors (median = 3.40 kg; range = 1.95-7.00) and nonsurvivors (3.26 kg; range = 1.47-7.50).

3.2 | Clinical presentation

The most common clinical signs in the entire cohort were anorexia, lethargy, weight loss, and vomiting (Table 1). There were no significant differences in proportions of clinical signs between surviving and nonsurviving cats. The rectal temperature at presentation was lower ($P = .01$) in nonsurvivors (median = 36.6°C; range = 33.0-38.4) compared with survivors (median = 37.5°C; range = 34.8-40.4). The heart rate and respiratory rate did not differ significantly between groups.

TABLE 1 Clinical findings at presentation of 100 cats with ACKD

| Clinical sign | All cats (n = 100) n (%) | Survivors (n = 58) n (%) | Nonsurvivors (n = 42) n (%) | P value |
|----------------------|-----------------------------|-----------------------------|--------------------------------|---------|
| Anorexia | 85 (85) | 48 (82.8) | 37 (88.1) | .58 |
| Lethargy | 60 (60) | 31 (53.4) | 29 (69.0) | .15 |
| Weight loss | 39 (39) | 26 (44.8) | 13 (31.0) | .21 |
| Vomiting | 27 (27) | 18 (31.0) | 9 (21.4) | .37 |
| Dysuria | 8 (8) | 4 (6.9) | 4 (9.5) | .72 |
| Dyspnea | 5 (5) | 2 (3.4) | 3 (7.1) | .65 |
| Ataxia | 5 (5) | 2 (3.4) | 3 (7.1) | .65 |
| Oral discharge | 3 (3) | 2 (3.4) | 1 (2.4) | 1.00 |
| Dysphagia | 3 (3) | 2 (3.4) | 1 (2.4) | 1.00 |
| Hypersalivation | 3 (3) | 2 (3.4) | 1 (2.4) | 1.00 |
| Diarrhea | 2 (2) | 2 (3.4) | 0 (0.0) | .51 |
| Constipation | 2 (2) | 2 (3.4) | 0 (0.0) | .51 |
| Paraparesis | 2 (2) | 1 (1.7) | 1 (2.4) | 1.00 |
| Altered mentation | 2 (2) | 1 (1.7) | 1 (2.4) | 1.00 |
| Icterus | 1 (1) | 1 (1.7) | 0 (0.0) | 1.00 |
| Lameness | 1 (1) | 0 (0.0) | 1 (2.4) | .42 |
| Urinary incontinence | 1 (1) | 1 (1.7) | 0 (0.0) | 1.00 |

Abbreviation: ACKD, acute on chronic kidney disease.

TABLE 2 Putative etiologies of ACKD in 100 cats

| Etiology | All cats (n = 100) n (%) | Survivors (n = 58) n (%) | Nonsurvivors (n = 42) n (%) |
|----------------------|--------------------------------|--------------------------------|-----------------------------------|
| Unknown | 66 (66) | 34 (51.5) | 32 (48.5) |
| Ureteral obstruction | 11 (11) | 9 (81.8) | 2 (18.2) |
| Ischemia | 9 (9) | 8 (88.9) | 1 (11.1) |
| Pyelonephritis | 8 (8) | 4 (50.0) | 4 (50.0) |
| Other ^a | 6 (6) | 3 (50.0) | 3 (50.0) |

Abbreviation: ACKD, acute on chronic kidney disease.

^aIncluding cardiorenal syndrome (3 cats), protein-losing nephropathy (2 cats), and polycystic kidney disease with an infected renal cystic (1 cat).

3.3 | Etiology and concurrent diseases

Overall the proportions of the ACKD etiologies did not differ between the outcome groups ($P = .11$) (Table 2).

The overall median hospitalization period was 5 days (range = 2–26). Nonsurvivors had a shorter ($P < .001$) median hospitalization period compared with survivors (3 days, range = 2–20 versus 7 days, range = 2–26, respectively). There was no significant difference in hospitalization period among the etiology groups (Figure 1).

Pancreatitis was diagnosed in 48/89 (54%) cats (with available abdominal ultrasound or DGGR lipase). There was no difference in the proportion of cats diagnosed with pancreatitis between survivors and nonsurvivors ($P = .51$). Other concurrent diseases diagnosed in ≥ 5 cats

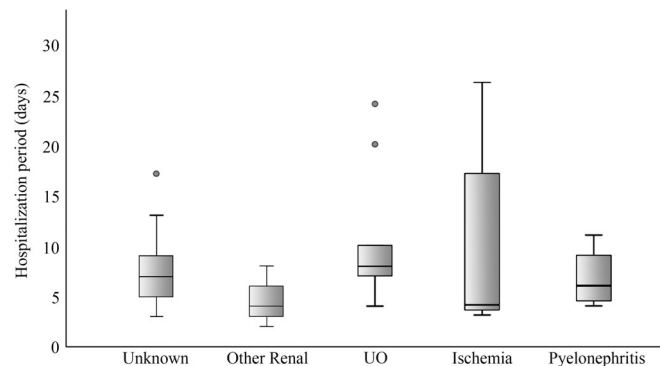


FIGURE 1 Hospitalization period based on the etiology of ACKD. Data are presented as box and whiskers. The box represents the second and third quartiles. The horizontal line within the box represents the median. The whiskers represent the range, and the circles indicate outlying values. The “other renal” category included cats with the following etiologies: cardiorenal syndrome, protein-losing nephropathy, and infected renal cortical cyst in a cat with polycystic kidney disease (3, 2, and 1 cats, respectively). ACKD, acute on chronic kidney disease; UO, ureteral obstruction

included heart disease (n = 12), gingivitis (n = 5), and polycystic kidney disease (n = 5).

3.4 | Hematology and serum chemistry

Anemia (hematocrit <27.7%) was common in both survivors and nonsurvivors (39.7% and 54.8%, respectively), with no significant

difference in median hematocrit between the outcome groups (Table 3). Hyperbilirubinemia was also common in survivors (41.4%) and nonsurvivors (57.1%), and serum total bilirubin did not differ between groups. Median sCr, urea, and phosphorous concentrations were significantly higher, and the venous blood pH was significantly lower in nonsurvivors compared with survivors (Table 4). Median sCr concentration at presentation (6.08 mg/dL; range = 1.73-29.1) significantly decreased

compared to discharge in survivors (3.79 mg/dL; range = 1.25-13.1) ($P < .02$). There was no significant parallel change in sCr among nonsurvivors between presentation and death or euthanasia (median = 8.40 mg/dL; range = 3.18-18.3 and median = 7.56 mg/dL; range = 2.27-17.6, respectively; $P = .22$). Moreover, median sCr concentration of the survivors at discharge was lower compared with nonsurvivors at death or euthanasia ($P < .02$).

TABLE 3 Hematological results of 100 cats with ACKD at presentation

| Analyte | RI | All cats (n = 100) Median (range) | Survivors (n = 58) Median (range) | Nonsurvivors (n = 42) Median (range) | P value |
|---|-----------|--------------------------------------|--------------------------------------|---|---------|
| WBC ($\times 10^3/\text{mm}^3$) | 6.3-19.6 | 14.0 (3.31-45) | 14.3 (7.8-45.0) | 12.6 (3.3-42.6) | .31 |
| RBC ($\times 10^6/\text{mm}^3$) | 6.0-10.1 | 6.4 (1.7-10.6) | 6.5 (2.9-10.6) | 5.9 (1.7-10.0) | .054 |
| Hematocrit (%) | 27.7-46.8 | 26.4 (6.5-43.5) | 27.6 (12.5-42.6) | 25.9 (6.5-43.5) | .09 |
| MCV (fL) | 41.3-52.6 | 43.5 (33.6-71.0) | 43.8 (34.0-71.0) | 42.1 (33.6-53.5) | .31 |
| MCHC (g/dL) | 27.0-32.8 | 34.4 (27.3-43.4) | 34.3 (27.3-43.4) | 34.8 (27.9-38.9) | .59 |
| RDW (%) | 14.4-19.4 | 17.9 (14.4-38.3) | 17.9 (14.5-38.3) | 18 (14.4-26.3) | .53 |
| Platelets ($\times 10^3/\text{mm}^3$) | 156-626 | 276 (10-756) | 298 (32-756) | 251.5 (10-717) | .47 |

Abbreviations: ACKD, acute on chronic kidney disease; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell count; RDW, red blood cell distribution width; RI, reference interval; WBC, white blood cell count.

TABLE 4 Serum chemistry results of 100 cats with ACKD at presentation

| Analyte | RI | All cats (n = 100) Median (range) | Survivors (n = 58) Median (range) | Nonsurvivors (n = 42) Median (range) | P value |
|-----------------------|-----------|--------------------------------------|--------------------------------------|---|---------|
| Albumin (g/dL) | 2.2-4.6 | 3.5 (1.4-5.5) | 3.5 (1.4-5.3) | 3.5 (2.5-5.5) | .87 |
| ALP (U/L) | 14-71 | 15 (1-39) | 16 (1-39) | 15 (5-33) | .38 |
| ALT (U/L) | 27-101 | 45 (10-507) | 53 (10-286) | 40 (10-507) | .53 |
| Amylase (U/L) | 500-1800 | 1801 (575-4634) | 1818 (575-4634) | 1667 (775-3679) | .81 |
| AST (U/L) | 17-58 | 41 (0-367) | 37 (0-193) | 53 (23-367) | .16 |
| Bicarbonate (mM/L) | 20.0-24.0 | 12.5 (5.4-22.4) | 13.2 (5.4-22.4) | 11.8 (6.1-19.8) | .065 |
| Bilirubin (mg/dL) | 0.0-0.2 | 0.2 (0.1-6.3) | 0.21 (0.1-6.3) | 0.2 (0.1-1.2) | .27 |
| Calcium (mg/dL) | 9.0-10.9 | 9.7 (6.5-12.0) | 9.8 (7.8-12.0) | 9.6 (6.5-11.3) | .18 |
| Chloride (mM/L) | 117-126 | 107 (78.3-137) | 108 (78.4-137) | 106 (78.3-130) | .97 |
| Cholesterol (mg/dL) | 89-258 | 203 (106-436) | 198 (106-436) | 234 (119-323) | .46 |
| CK (U/L) | 73-260 | 393 (64-14 022) | 360 (64-10 011) | 399 (83-14 022) | .67 |
| Creatinine (mg/dL) | 0.5-1.3 | 7.9 (1.7-29.1) | 6.1 (1.7-29.1) | 8.4 (3.2-18.3) | .011 |
| DGGR lipase (U/L) | 0-26 | 40.6 (14.5-367) | 21.8 (18.8-61.9) | 60.8 (14.5-367) | .42 |
| GGT (U/L) | 0-4 | 2 (0-16) | 2 (0-16) | 2 (0-10) | .48 |
| Glucose (mg/dL) | 63-118 | 135 (61-689) | 134 (61-604) | 135 (81-689) | .72 |
| Phosphorus (mg/dL) | 3.20-6.30 | 13.1 (4.10-24.9) | 9.84 (4.10-23.7) | 16.6 (5.90-24.9) | .006 |
| Potassium (mM/L) | 3.6-4.9 | 4.3 (1.9-9.0) | 4.3 (2.0-9.0) | 4.3 (1.9-6.8) | .67 |
| Sodium (mM/L) | 151-158 | 150 (124-175) | 149 (124-175) | 150 (128-172) | .60 |
| Total protein (g/dL) | 6.6-8.4 | 8.3 (5.5-10.9) | 8.3 (5.5-10.9) | 8.2 (6.1-9.8) | .58 |
| Triglycerides (mg/dL) | 8-80 | 72 (16-540) | 72 (24-369) | 70 (16-540) | .86 |
| Urea (mg/dL) | 38.5-70.6 | 307 (79.6-670) | 261 (79.6-670) | 351 (124-654) | .007 |
| Venous blood pH | 7.35-7.45 | 7.18 (6.90-7.40) | 7.21 (6.95-7.37) | 7.15 (6.90-7.40) | .026 |

Note: $P < .05$ is considered significant.

Abbreviations: ACKD, acute on chronic kidney disease; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; DGGR lipase, 1,2-o-dilauryl-Rac-glycero glutaric acid-(6'-methylresorufin) ester-lipase; GGT, gamma-glutamyltranspeptidase; RI, reference interval.

In a multivariable forward regression model including age, rectal temperature, sCr, phosphorus, urea concentrations, and venous blood pH, only phosphorous concentration remained significantly associated with the outcome ($P = .02$; 95% confidence interval [95% CI] = 1.03-1.39), while the difference in age did not reach significance ($P = .06$; 95% CI = 0.999-1.026). The overall correct classification was 68% (Hosmer and Lemeshow goodness of fit = 0.303). The area under the curve for phosphorus as an outcome predictor was 0.68 (95% CI = 0.56-0.78). A cutoff value of 16.7 mg/dL corresponded to sensitivity and specificity of 53% and 77%, respectively.

3.5 | Urinalysis

The median urine specific gravity of the entire cohort was 1.015 (range = 1.006-1.040). The urine specific gravity did not differ between

TABLE 5 Urinalysis abnormalities in 87 cats with ACKD and available urinalysis results (in 3 cats only sediment evaluation was available) and 56 cats with available urine culture results

| Analyte | Positive result n (%) |
|------------------|-----------------------|
| Bacteriuria | 30/87 (35) |
| Urine culture | 16/56 (29) |
| Hematuria | 25/87 (29) |
| Pyuria | 17/87 (20) |
| Glucosuria | 15/84 (18) |
| Proteinuria | 74/84 (88) |
| Ketonuria | 4/84 (5) |
| Bilirubinuria | 3/84 (4) |
| Cylinduria | 3/87 (3) |
| Crystalluria | 2/87 (2) |
| Urobilinogenuria | 1/84 (1) |

Abbreviation: ACKD, acute on chronic kidney disease.

the outcome groups ($P = .15$). The most frequent urinalysis abnormalities were bacteriuria, hematuria, proteinuria, and pyuria (Table 5). Urine culture was positive in 16/56 cats (29%) (Table 5). The isolated bacteria included *Escherichia coli* (9 cats; 56%), *Pseudomonas aeruginosa* (2 cats; 12.5%), and *Streptococcus canis*, *Proteus mirabilis* and *Enterococcus faecium* (1 cat each; 6%). Two isolates were not specified (12.5%).

Proteinuria (urine dipstick protein ≥ 30 mg/dL) was present in 74/84 (88.1%) cats.

3.6 | Follow-up and long-term survival

Follow-up data after discharge were available in 53/58 cases. The MST of all discharged cats was 66 days (95% CI = 19-113) (Figure. 2),

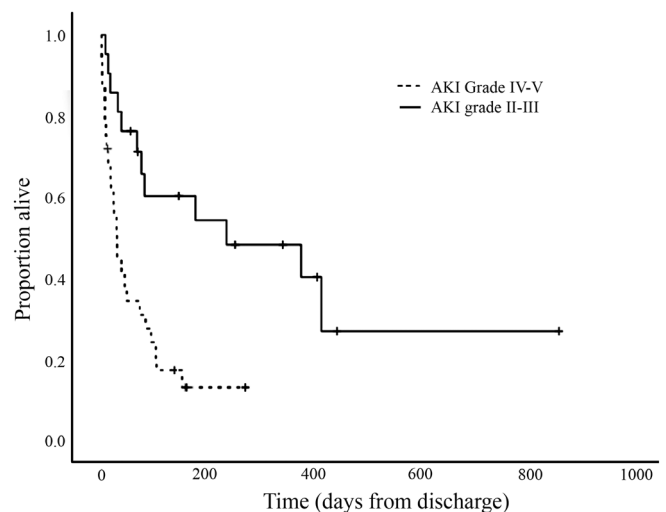


FIGURE 3 Kaplan-Meier survival curve of 53 cats with ACKD with International Renal Interest Society AKI grades II or III ($n = 21$) and AKI grades IV or V ($n = 32$) at presentation to the hospital. ACKD, acute on chronic kidney disease; AKI, acute kidney injury

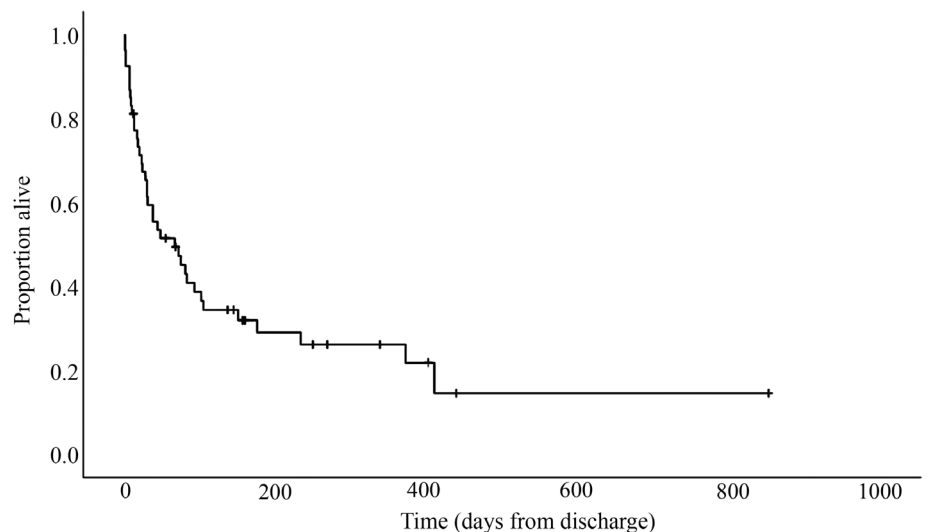


FIGURE 2 Kaplan-Meier survival curve of 53 cats with ACKD. ACKD, acute on chronic kidney disease

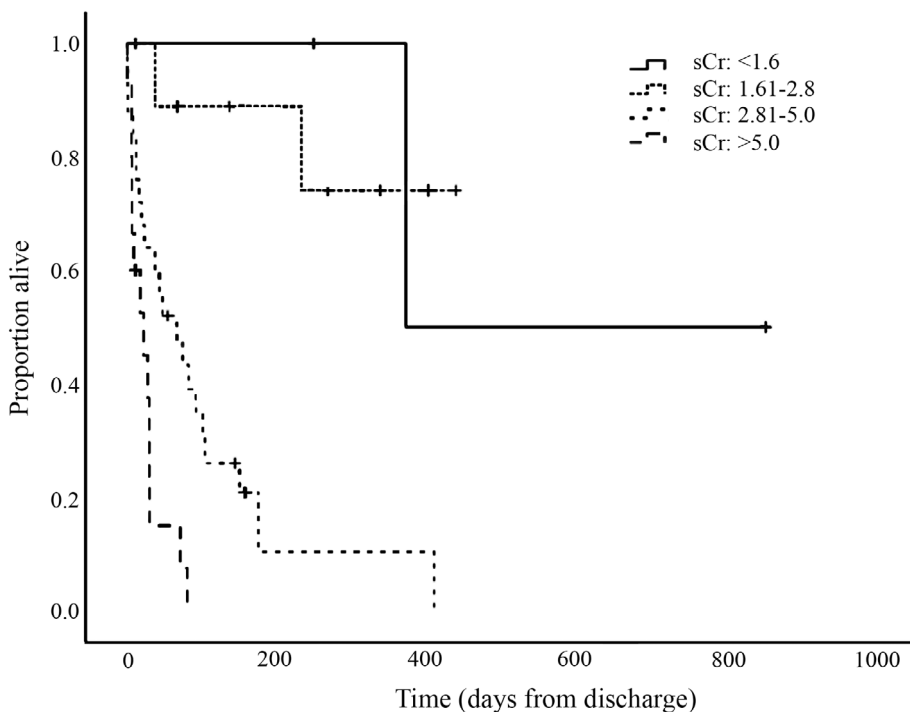


FIGURE 4 Kaplan-Meier survival curve of 53 cats with ACKD, grouped based on serum creatinine concentration at discharge from the hospital. Each category represents serum creatinine range comparable to IRIS CKD stage (stage 1: n = 3, stage 2: n = 10, stage 3: n = 25, stage 4: n = 15). ACKD, acute on chronic kidney disease; CKD, chronic kidney disease; IRIS, International Renal Interest Society

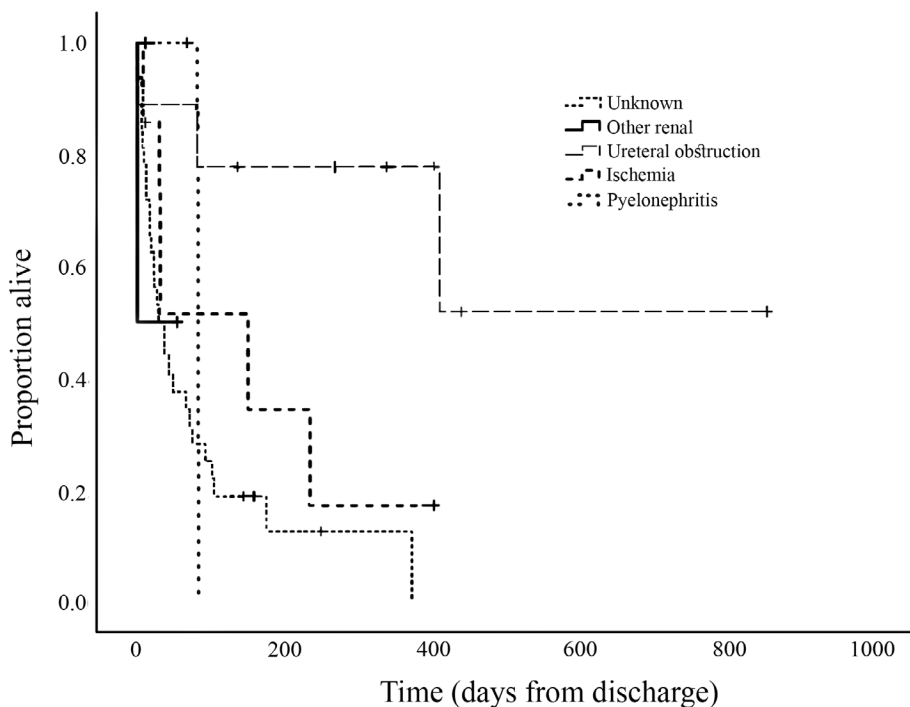


FIGURE 5 Kaplan-Meier survival curve of 53 cats with ACKD grouped based on the etiology, including unknown, ureteral obstruction, renal ischemia, pyelonephritis, and other renal causes. ACKD, acute on chronic kidney disease

with 43 (81%) and 4 cats (8%) surviving up to 6 months and 12 months, respectively. Six cats (11%) were still alive 24 months after the ACKD episode. In a Cox regression model, only sCr concentration at discharge was significantly ($P < .02$) associated with long-term survival. For every 1.0 mg/dL increase in sCr concentration at discharge, there was a 1.43-fold (95% CI = 1.243- to 1.639-fold) increase in the risk for death at any time point.

When the discharged cats were grouped based on to their IRIS AKI Grade at presentation (Figure 3), there was a difference ($P = .001$)

in long-term survival between cats categorized with IRIS AKI grades II or III (n = 21) compared with those with IRIS AKI grades IV or V (n = 32). The MST of the former was 233 days (95% CI = 0-566) compared with 29 days (95% CI = 20-38) of the latter.

The MST differed significantly ($P < .002$) between cats grouped based on sCr concentration at discharge (Figure 4). Three cats had discharge sCr concentration <1.6 mg/dL (ie, comparable to IRIS CKD stage 1), of which 1 died 372 days from discharge and the 2 others were still alive at the time of writing the manuscript (249 and 853 days from

discharge). Ten cats were discharged with sCr in the ranges of IRIS CKD stage 2, of which, 2 died 37 and 233 days from discharge, while 8 were still alive at the time of writing the manuscript (11-439 days after discharge). The MSTs of cats with sCr at discharge equivalent to IRIS CKD stages 3 and 4 were 66 days (95% CI = 17.8-114.2) and 22 days (95% CI = 0.0-44.4), respectively.

There was a significant difference ($P = .01$) in long-term survival among the etiology groups (Figure 5), with cats in the UO group having a longer survival time compared with all other etiologies combined ($P = .001$).

4 | DISCUSSION

This study describes the clinical and laboratory findings, the etiology, and the short- and long-term prognosis of a large cohort of cats with ACKD. Because cats with ACKD require intensive treatment, often with prolonged hospitalization and considerable financial costs, tools to assess the short- and long-term prognosis are important for clinical decision-making.

The clinical presentation of cats in this study resembles that of AKI, as in both conditions the most common manifestations include lethargy, anorexia, and vomiting.¹⁹ This similarity, with the concurrent azotemia, might make differentiation between ACKD and AKI challenging in some cases. However, weight loss, noted in 39% of this cohort, is more characteristic of CKD,⁷ and when present, could be helpful to distinguish ACKD from AKI.¹⁹

This cohort had a relatively high proportion of nonspayed females. Although in our country, some female cats are not spayed, the proportion of nonspayed cats in this cohort is considerably higher compared to their proportion in our hospital's population, and the reasons for this discrepancy are unclear. Yet, this relatively high, unexpected proportion of nonspayed females likely had neither a role in the acute exacerbation of the CKD, nor any influence on the findings of this study.

The median age of the cats in this cohort is younger compared to ages of cats diagnosed with CKD in previous reports.²⁷⁻²⁹ Possibly, routine health checks (including "geriatric laboratory profiles") have become more common and clinicians are presently more aware of the clinical significance of small increases in sCr, and apply the IRIS guidelines for sCr trending, all of which result in an earlier diagnosis of CKD. In addition, more sensitive markers (eg, symmetric dimethylarginine) have recently become available, further promoting earlier diagnosis of CKD. The etiology of CKD might also play a role regarding the age upon diagnosis. Ureteral obstruction occurs at relatively younger age^{30,31} compared with the ages reported for cats with CKD in absence of UO. Although UO often results in acute uremic crisis, in some cats, it may also take a more chronic course, when ureteroliths partially, temporarily, but repeatedly obstruct the ureters, leading to gradual decline of kidney function, which is proportional to the degree and chronicity of the obstructions.³²⁻³⁴

The etiologies of ACKD were identified in only approximately a third of the cats in this study and were in partial agreement with

reported etiologies of AKI.¹⁴ Because acute decrease in kidney function and exacerbation of CKD is suspected to occur commonly in cats, characterization of the etiologies might have a future role in the prevention of this devastating disorder. Some of the present etiologies should be regarded as putative, as cause and effect relationship is difficult to prove. For example, a definitive diagnosis of renal ischemia in natural circumstance is clinically impossible to make. Likewise, occurrence of AKI concurrently with positive bacterial urine culture and consistent ultrasonographic findings is not a definite proof for pyelonephritis. Therefore, etiologies in this study should be regarded as suspected only. In the present study, UO was the most common etiology of ACKD (11%), and was associated with better short-term outcome, in agreement with a previous study of AKI in cats.¹⁹ The high frequency of UO as a cause of both AKI and ACKD in cats is in accordance with the documented increase in the incidence of calcium oxalate urolithiasis and ureteral calculi in cats in the past decades.^{14,35-37} The favorable outcome of both UO-associated AKI and ACKD is probably related to its inciting cause, which can be surgically eliminated. Moreover, the presence of intrinsic kidney injury is associated with the degree and chronicity of the UO. Thus, timely diagnosis and intervention are expected to result in a prompt recovery of kidney function, opposed to other etiologies of ACKD that directly induce renal parenchymal injury. It therefore seems that despite the treatment costs of managing UO, its relatively favorable outcome should encourage owners to pursue treatment, in spite of concurrent CKD. The present results are in accordance with previous findings, reporting UO, pyelonephritis, and ischemia as common etiologies of AKI.^{15,19} Conversely, nephrotoxicity, a major cause of AKI in cats,^{15,19} was uncommon herein. The etiology of ACKD was not identified in 66% of cats in this study; however, unknown etiology of ACKD was not associated with worse short- or long-term outcomes, and therefore, should not be considered a negative prognostic factor.

In the univariable analyses, sCr, urea, phosphorous concentrations, and venous blood pH were associated with a worse short-term outcome, which is expected as they all reflect the severity of the injury. In the multivariable analysis, serum phosphorous concentration remained the only significant outcome predictor. Phosphorus is freely filtered by the glomeruli,³⁸ thus, its concentration is highly affected by the glomerular filtration rate (GFR), and acute decrease in GFR will result in a proportional increase in serum phosphorous concentration.¹³ In CKD, compensatory mechanisms as well as therapeutic interventions (eg, phosphate binders and restricted dietary phosphorus) attenuate hyperphosphatemia, despite the decreased GFR. Nevertheless, even mild, but sustained hyperphosphatemia might result in soft tissue mineralization (including the kidneys), and thereby potentially contributes to progression of CKD.^{39,40} Accordingly, hyperphosphatemia is associated with the progression rate of CKD, and every 1 mg/dL increase in serum plasma phosphorus, increases the risk of progression of CKD within 1 year by 43%.¹³ In our study, hyperphosphatemia might have been the consequence of CKD, the acute decrease in kidney function, or both. The degree of hyperphosphatemia might be an indicator for the severity of the acute injury, and thus was associated with the outcome; yet, hyperphosphatemia previously was not a negative prognostic

factor in cats with AKI.^{19,41} Alternatively, the component of the hyperphosphatemia contributed by the CKD might have had a greater influence on the outcome, as higher phosphorous concentration might have been suggestive of a more advanced CKD state, before the occurrence of the acute exacerbation of the CKD, thereby influencing the likelihood of survival. Measurement of parathyroid hormone and fibroblast growth factor 23 might aid answering these questions.

Pancreatitis was diagnosed in 54% of this cohort and was similarly frequent in the outcome groups. Acute pancreatitis is an inflammatory condition, and as such, might be an initiating cause for AKI (or ACKD).⁴²⁻⁴⁴ On the other hand, AKI and pancreatitis share common underlying pathogenesis (eg, decreased perfusion),⁴⁵ and therefore, might occur concurrently, and not necessarily indicate a cause and effect relationship. Acute pancreatitis is common in dogs with AKI, with a reported incidence of as high as 62%.^{17,46} Similar studies in cats with AKI are lacking; however, based on the present results, it appears that pancreatitis in cats with ACKD is common. Pancreatitis was not a negative prognostic factor in our study, in agreement with findings in dogs with AKI.⁴⁶

The hospitalization period was longer in cats surviving to discharge compared with nonsurvivors. Euthanasia and early death obviously affected the duration of hospitalization of nonsurvivors, and it is thus not surprising that it was shorter. Yet, all cats included in the study were treated for at least 48 hours. Euthanasia was performed only with lack of improvement or occurrence of clinical deterioration and concurrent complications (eg, congestive heart failure). The hospitalization period of the survivors (median, 7 days) is comparable to the hospitalization duration reported in cats with AKI.¹⁵ This finding can guide owners' expectations before hospitalization.

The present survival to discharge rate of cats with ACKD was 58%, which is similar to that of cats with AKI (53%).¹⁵ This was unexpected, as cats with CKD have fewer number of functioning nephrons before the acute insult compared with healthy cats that sustain AKI, and therefore, the proportion of nephrons that has to recover to gain acceptable kidney function is higher in the former. The similar survival rate of cats with ACKD compared to those with AKI might be associated with the etiology of the insult, and the reversibility of the injury. Ischemia, pyelonephritis, and UO, noted herein, are all considered reversible whereas nephrotoxicities (eg, lily and ethylene glycol intoxications) are more often irreversible, and were under represented in this cohort compared with previous studies of cats with AKI.¹⁵ In addition, owners of cats previously diagnosed with CKD might be more aware of subtle changes in their cat's behavior, seeking veterinary care earlier and thus facilitating prompt diagnostic and therapeutic measures. It therefore seems that the short-term prognosis for cats with ACKD is as favorable as of cats with AKI.

Despite the apparently fair short-term outcome, the long-term prognosis for cats in this study was guarded, with MST of 66 days. In a previous study evaluating the long-term prognosis of 211 cats with CKD, the MSTs of cats with IRIS stages 2 (modified), 3, and 4 were 1151 days, 778 days, and 103 days, respectively.⁷ In our study, sCr at discharge was also associated with long-term survival. However, the MSTs were considerably shorter (66 days and 22 days for sCr comparable to IRIS CKD stages 3 and 4, respectively), suggesting that the

acute exacerbation of CKD greatly and adversely affects the long-term prognosis of cats with CKD, increasing its progression rate and decreasing the survival time. Possibly, the kidney damage caused during the acute exacerbation episode to kidneys already impaired was not completely reversible and accounted for the shortened survival of cats with ACKD compared with those with CKD. This is supported by studies of AKI, demonstrating that approximately 50% of the animals do not regain complete function after an acute episode.¹⁵ Partial recovery in animals with CKD has greater clinical implications for the long-term compared with AKI. As sCr concentration just before the acute insult was not available in this cohort, we cannot assess whether kidney function had returned to its baseline at discharge. It is more likely that sCr concentration at discharge was higher than its baseline (before the insult) concentration, and resulted in advancement into a higher IRIS CKD stage. It is also likely that after an AKI, sustained active injury persists, leading to a faster deterioration of kidney function. The present data provide better understanding of the disease course, allowing improved communication with owners and case management.

This retrospective study has several limitations. First, some data were missing in the medical records, which could not be retrieved, weakening some statistical analyses, and possibly precluding identification of other risk factors for death and prognostic markers. Second, determining the etiology of the acute insult leading to ACKD was based on identifying conditions known to cause AKI, and should therefore be regarded as putative. Third, our institution admits first opinion cases but is also a secondary and a tertiary referral center, which is adding to the heterogeneity of the population. Fourth, the treatment administered both during hospitalization and after discharge was not standardized, which possibly affected the outcome. Nevertheless, the guidelines used in our hospital for treating ACKD and CKD are rather consistent. Fifth, election of euthanasia was influenced, in addition to the patients' clinical condition, by the attending veterinarians' assessment and the owners' financial and emotional constraints. Finally, the effect of pre-existing CKD stage has been shown to influence the outcome in people⁴⁷; however, CKD stage could not have been assessed herein because sCr just before the acute decompensation (while in steady state) was unavailable in many cats.

In conclusion, UO, presumptive pyelonephritis, and ischemic events are commonly identified etiologies for ACKD. The short-term outcome for ACKD in cats is comparable to AKI; however, long-term prognosis is guarded. Serum phosphorus is a prognostic factor for survival to discharge while sCr at discharge predicates long-term prognosis.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

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

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