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Long-term outcome of dogs recovering from acute kidney injury: 132 cases

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Abstract

Background: Information regarding long-term outcome of dogs recovering from acute kidney injury (AKI) is limited.

Objectives: Determine the long-term outcome of dogs recovering from AKI and identify predictors for serum creatinine concentration (sCr) normalization and long-term outcome.

Animals: One hundred thirty-two dogs with AKI that survived ≥30 days postdischarge.

Methods: Retrospective study. Search of medical records of dogs diagnosed with AKI that survived to discharge. Follow-up data were retrieved from medical records and by telephone interviews with the owners or primary care veterinarians or both.

Results: Estimated median survival time (MST) was 1322 days (95% confidence interval [CI], 1147-1626), and 76% of the dogs were alive at last contact. Normalization of sCr was documented in 55% of the dogs at discharge and in additional 20% during the follow-up period. The proportion of dogs with sCr normalization decreased with increase in AKI grade ($P = .02$). Long-term survival was not associated with sCr normalization ($P = .63$). Etiology was associated with the long-term outcome ($P = .004$).

Conclusion and Clinical Importance: Long-term survival of dogs with AKI is longer than previously described. Normalization of sCr in 99 dogs (75%) occurred, either at discharge or within the follow-up period. Normalization of sCr was not associated with long-term survival. Estimated MST of dogs with sCr normalization was not different compared with dogs that developed azotemic chronic kidney disease (CKD), presumably because of slow CKD progression rate. Etiology is an important factor determining sCr normalization and long-term survival, emphasizing the importance of the reversibility of renal injury rather than its severity.

KEYWORDS
azotemia, CKD, creatinine, outcome, renal failure, survival

Abbreviations: ACKD, acute on chronic kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; AKD, acute kidney disease; CI, confidence interval; DGGR, 1,2-o-dilauryl-rac-glycero glutaric acid-(6′-methylresorufin) ester; IRIS, International Renal Interest Society; MAT, microscopic agglutination test; MST, median survival time; sCr, serum creatinine concentration; UPC, urine protein-to-creatinine ratio.

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1 | INTRODUCTION

Acute kidney injury (AKI) is characterized by sudden onset of renal parenchymal injury, and often is associated with decreased renal function, retention of uremic waste products, as well as fluid, electrolyte, and acid-base imbalances.[1] Disruption of homeostasis and accumulation of uremic toxins are associated with damage to various body organs. Consequently, morbidity and mortality rates remain high despite intensive treatment.[2,3] Short-term prognosis of AKI is affected by multiple factors including the etiology (which influences the reversibility of the injury), comorbidities, complications, and treatment options.[3,4] In 2 large scale studies of AKI in dogs managed medically or by hemodialysis, short-term mortality rates were 56% (56/99 dogs) and 47% (86/182 dogs), respectively.[2,3] In the former study, 19/43 dogs (44%) that were discharged from the hospital had serum creatinine concentration (sCr) within the reference range during the follow-up period, whereas in the remaining 56% sCr remained above the reference range, and subsequently these dogs were diagnosed with chronic kidney disease (CKD). The long-term outcome however was not evaluated in this study.

Other veterinary studies have been focused mainly on a single etiology, and only short-term outcome has been reported. In a study evaluating the long-term outcome of dogs managed by intermittent hemodialysis, 49/93 dogs (53%) were discharged, and the overall 1-year survival was 33% (31/93 dogs).[5] Furthermore, this study found that the median overall and renal-related survival times were significantly longer for dogs with underlying infectious etiology compared to other etiologies.

Information regarding the long-term prognosis of AKI is important for both clinicians and owners. Such data would aid clinicians in decision making and guiding owners' expectations, because AKI is associated with high treatment costs and euthanasia might be considered. Moreover, these data will assist clinicians in tailoring long-term monitoring regimens and possible therapeutic interventions for dogs recovering from AKI. Our objectives were to determine the long-term outcome of dogs recovering from AKI, assess the proportion of dogs with normalization of sCr at discharge and during the follow-up period, and identify prognostic factors for both normalization of sCr and long-term outcome.

2 | MATERIALS AND METHODS

2.1 | Case selection

Medical records of dogs presented to the Koret School of Veterinary Medicine, The Robert H. Smith Faculty of Agriculture, Food and Environment, Hebrew University of Jerusalem, diagnosed with AKI and that survived to discharge, between the years 2015-2021, were reviewed retrospectively. Acute kidney injury was diagnosed based on the International Renal Interest Society (IRIS) guidelines, and included presence of acute onset of clinical signs consistent with AKI (eg, anuria, oliguria, polyuria, vomiting, inappetence) and acute onset of azotemia after exclusion of postrenal causes.[1,6] The maximal documented sCr during hospitalization was used to classify dogs according to IRIS AKI grades. Dogs with a previous diagnosis of CKD or ultrasonographic evidence consistent with CKD (eg, small irregular kidneys, decreased cortico-medullary distinction[7]) were excluded, as were dogs with postrenal azotemia.

2.2 | Medical records

Data extracted from the medical records included signalment, history, physical examination findings, CBC, serum biochemistry, urinalysis, urine culture, blood gas analysis, blood pressure measurements, ultrasonographic findings, and hospitalization duration. Dogs were excluded from analysis if they did not survive to discharge or died within 30 days after discharge.

The etiology of AKI was classified as follows: (1) inflammatory/ischemic (ie, systemic underlying inflammatory process with suspected decreased tissue perfusion), (2) infectious, (3) nephrotoxic, (4) other, or (5) unknown. Pancreatitis was included in the inflammatory/ischemic category and was diagnosed based on compatible history, clinical signs, ultrasonographic findings, increased serum 1,2-o-dilauryl-rac-glycero glutaric acid-(60-methylresorufin) ester (DGGR)-lipase activity (reference interval, <108 U/L) or some combination these.[8,9] Nephrotoxicity was diagnosed based on a history of recent (<72 hours before presentation) exposure to a nephrotoxin. Infectious causes included pyelonephritis and leptospirosis. Pyelonephritis was diagnosed based on urine sediment findings (ie, pyuria and bacteriuria), positive urine culture and ultrasonographic findings.[10,11] Leptospirosis was diagnosed if the titer of a single microscopic agglutination test (MAT) was ≥1:800 without recent (<12 months) history of vaccination, or when seroconversion in paired MAT titers (ie, 4-fold increase between the first and second samples) was documented.[12] Other etiology included AKI secondary to hypercalcemia or glomerulopathies, diagnosed based on the presence of marked proteinuria (urine protein-to-creatinine ratio [UPC] >2) after exclusion of extrarenal causes. Hospital-acquired AKI was diagnosed based on an increase in sCr of ≥0.3 mg/dL within 48 hours during hospitalization while receiving fluids IV.[13] If ≥2 etiologies were present, the primary cause was designated as the etiology for statistical analysis.

2.3 | Laboratory evaluation

Blood samples were collected in potassium-EDTA tubes for CBC (Advia 120 or 2120, Siemens, Erlangen, Germany; Abacus Junior Vet, Diatron, Wien, Austria), and whole blood samples in plain tubes with gel separators for serum biochemistry (Cobas 6000, Roche, Mannheim, Germany). Samples obtained in-house were analyzed within 60 minutes after collection. The CBC and serum biochemistry results from referring clinics were considered if obtained ≤24 hours before admission or during the follow-up period. Cystocentesis was used to collect urine samples for dipstick chemistry (Urilux, Roche, Mannheim Germany), measurement of specific gravity by refractometry, sediment evaluation, which was done either by experienced

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laboratory personal or automatically (SediVue Dx, IDEXX Laboratories, Westbrook, ME), and bacterial culture. Pyuria and hematuria were defined as presence of >5 WBCs or RBCs, respectively, per high-power field (hpf). Proteinuria was defined as a urine dipstick result of ≥1+ (ie, ≥30 mg/dL). The UPC (Cobas Integra 400 Plus or Cobas 6000, Roche, Mannheim, Germany) only was measured in dogs with severe proteinuria (urine dipstick result +4), inactive sediment, and when glomerular disease was suspected as the inciting cause for AKI.

2.4 | Follow-up

Dogs discharged from the hospital but not surviving 30 days post-discharge were excluded from the study and the minimum follow-up time was 30 days. Follow-up data were obtained from the electronic medical records or by telephone interview with the owner or primary care veterinarian or both, and included follow-up date, status of the dog (ie, alive, dead, euthanized), sCr, and whether the dog had another episode of AKI during the follow-up period.

Long-term survival of dogs was calculated as the number of days from discharge until the last follow-up date, death, or euthanasia. Dogs were diagnosed and classified by CKD stage based on the IRIS CKD staging system only if sCr measurements were available >3 months after discharge and only if sCr was stable (<10% change between at least 2 measurements >1 month apart). Normalization of sCr was defined as sCr <1.4 mg/dL at discharge or during the follow-up period. Dogs eligible for CKD staging in which normalization of sCr was documented were classified as CKD Stage 1.

2.5 | Statistical analysis

Continuous variables (eg, age, blood pressure, kidney function variables) were assessed for normality using the Shapiro-Wilk test. Continuous variables are presented as median and range and categorical variables as proportions. Because many variables were not normally distributed, the Mann-Whitney *U* test was used to compare continuous variables between the 2 groups. Chi-squared or Fisher's exact tests were used to examine the association between 2 categorical variables. Kaplan-Meier analysis was performed to assess long-term outcome, and the log-rank test was used to determine the effect of categorical variables (eg, pancreatitis, etiology, acute on chronic kidney disease [ACKD], AKI grade) on outcome. Dogs alive at last follow-up were right censored. Cox regression was used to assess the association of continuous variables (eg, age, blood pressure, kidney function test results) at presentation and maximal documented sCr during hospitalization) with both sCr normalization and long-term outcome. Cox regression also was used to perform multivariable analysis and further assess the relationship between variables found to be associated ($P < .1$) with long-term outcome in the univariate analysis. All tests were 2-tailed, and in all, $P < .05$ was considered significant. Analyses were performed using a statistical software package (SPSS 22.0 for Windows, IBM Corp., Armonk, N.Y., USA).

3 | RESULTS

3.1 | Animals and etiology

Medical records search yielded 249 dogs with AKI during the study period, of which 85 dogs did not survive to discharge or 30 days post-discharge, and 32 dogs were lost to follow-up. Thus, 132 dogs met the inclusion criteria and were included, of which 63 were males (36 castrated, 57%) and 69 were females (54 spayed, 78%). The most common breeds were mixed (61 dogs; 46%), German shepherd (9 dogs, 7%), Cavalier King Charles spaniel and Yorkshire terrier (5 dogs each, 4%), Siberian Husky, Labrador retriever, and Maltese (4 dogs each, 3%). Median age was 72 months (range, 1-216 months), and median weight at presentation was 19.3 kg (range, 1.2-75.8 kg).

Etiologies were ischemic/inflammatory (70 dogs, 53%) including pancreatitis (21 dogs, 16%), postanesthesia (14 dogs, 11%), severe gastroenteritis (8 dogs, 6%), peritonitis (6 dogs, 4%), heat stroke and severe bleeding (5 dogs, 4% each), diuretic treatment for heart failure (3 dogs, 2%), snake envenomation and myositis (2 dogs, 2% each), pyometra, cycad poisoning, road trauma and cardiac tamponade (1 dog each, 1% each); infectious (15 dogs, 12%), including leptospirosis (14 dogs, 11%) and pyelonephritis (1 dog, 1%); nephrotoxicosis (7 dogs, 5%), including nonsteroidal anti-inflammatory drug (NSAID) overdose (6 dogs, 5%), and grape or raisin ingestion (1 dog, 1%). Other etiologies (4 dogs, 3%) included hypercalcemia (3 dogs, 2%) and glomerulopathies (1 dog, 1%). The etiology of AKI was unknown for the remaining dogs (36 dogs, 27%). Hospital-acquired AKI was diagnosed in 13 (10%) dogs.

3.2 | Normalization of sCr and laboratory findings during hospitalization

Median sCr at presentation was 3.8 mg/dL (range, 1.1-37.9 mg/dL), increasing to 4.1 mg/dL (range, 1.1-43.2 mg/dL) during hospitalization. Maximal measured sCr during hospitalization was used to classify dogs by IRIS grades as follows: Grade I, 5 dogs (4%); Grade II, 25 dogs (19%); Grade III, 47 dogs (36%); Grade IV, 35 dogs (26%); and Grade V, 20 dogs (15%). Twenty-seven dogs were managed using hemodialysis. Median sCr at discharge was 1.3 mg/dL (range, 0.4-6.7 mg/dL). The sCr had normalized in 72 dogs (55%) by the time of discharge. Sixty dogs (45%) were discharged with sCr >1.4 mg/dL, of which 27 dogs (45%) had normalization of sCr during the follow-up period, documented between 2 and 1072 days after discharge. Overall, sCr normalized in 99 dogs (75%), either at discharge or during the follow-up period, of which 76 dogs (76/99, 77%) were alive at the time of last contact.

The sCr at presentation was significantly ($P < .001$) lower in dogs that experienced sCr normalization at any time point during the follow-up period (median, 3.3 mg/dL; range, 1.1-15.9 mg/dL) compared to dogs without normalization of sCr (median, 7.2 mg/dL; range, 1.5-37.9 mg/dL). Similarly, maximal sCr during hospitalization was lower in the former group (median, 3.7 mg/dL; range, 1.1-18.3 mg/dL) compared with the latter (median, 7.2 mg/dL; range, 2.1-43.2 mg/dL; $P < .001$; Figure 1).

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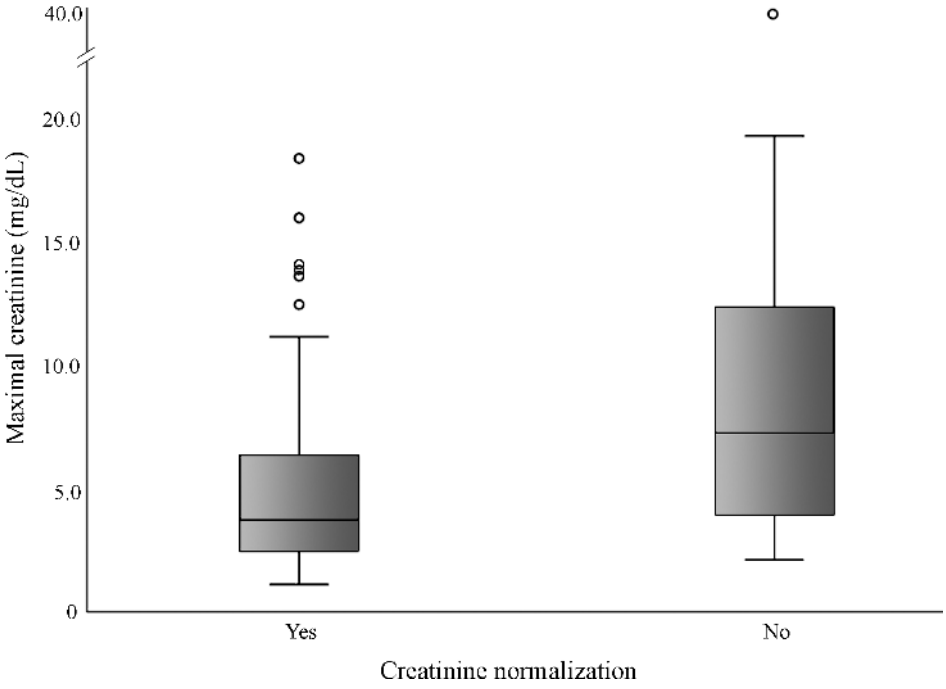


FIGURE 1 Maximal sCr during hospitalization in dogs with and without normalization of sCr. The box represents the second and third quartiles. The horizontal line within the box represents the median. The whiskers represent the range, and the circles indicate outliers. sCr, serum creatinine concentration

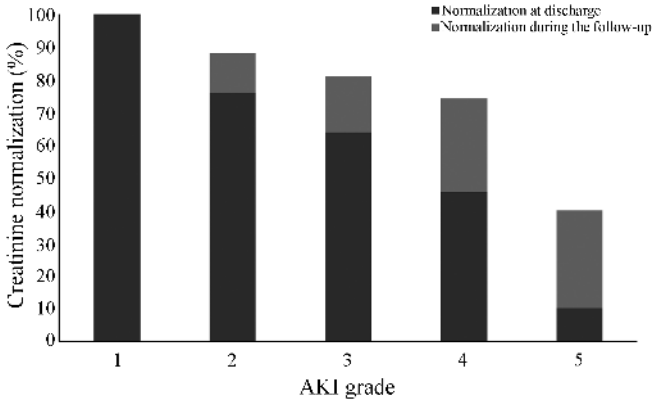


FIGURE 2 Association between International Renal Interest Society AKI Grade and sCr normalization at both discharge and during the follow-up period. AKI, acute kidney injury. sCr, serum creatinine concentration

The proportion of dogs with sCr normalization (either at discharge or during the follow-up period) decreased significantly with increase in IRIS AKI Grade ($P = .001$; Figure 2). The proportion of dogs with sCr normalization was lower in dogs managed by hemodialysis (27 dogs) compared with dogs managed medically (59% vs 84%, respectively; $P = .05$). Serum creatinine concentration normalized in 47%, 100%, 81%, 50%, and 72% of dogs with infectious, nephrotoxic, ischemic/inflammatory, other, and unknown etiology, respectively, with significant differences in the proportion of sCr normalization among AKI etiologies ($P = .02$).

3.3 | Long-term outcome

One hundred dogs (76%) were alive at last follow-up with an estimated median survival time (MST) of 1322 days (95% confidence interval [CI], 1147-1626 days; Figure 3). The proportion of dogs lost to follow-up after discharge was 10% (13/132) at 3 months, 11% (14/132) at 6 months, 12% (16/132) at 12 months, 32% (42/132) at 2 years, and 35% (47/132) >24 months after discharge. Thirty-two (24%) dogs died during the follow-up period, of which 16 dogs (50%) died naturally, whereas 15 dogs (47%) were euthanized (in 1 dog data regarding the cause of death were missing). Of the 32 dogs that died during the follow-up period, 12 died because of nonurinary related causes (hemoabdomen, cardiac tamponade, neoplasia, and post seizure), 10 dogs died due to further progression of their kidney disease, and in 10 dogs the cause of death could not be verified. After discharge, the proportion of surviving dogs was 95% (125/132 dogs) at 3 months, 90% (118/132 dogs) at 6 months, 87% (115/132 dogs) at 12 months, and 81% (107/132) at 24 months. The remaining 5% (7/132 dogs) died >24 months after discharge. A significant association was found between age and long-term outcome ($P < .001$; hazard ratio, 1.015; 95% CI, 1.008-1.022).

Clinical signs at presentation, hypertension, and pancreatitis were not associated with sCr normalization or long-term survival. No significant association was found between long-term survival and IRIS AKI grade ($P = .06$). No difference was found in long-term survival between dogs managed medically or using hemodialysis ($P = .15$). No association was identified between long-term survival and normalization of sCr at any time ($P = .63$), but significant differences in long-term survival were found among the AKI etiologies ($P = .004$; Figure 4); none of the dogs with infectious etiology died during the follow-up period.

Dogs in which sCr did not normalize during follow-up period had median sCr concentration of 1.9 mg/dL (range, 1.4-6.5 mg/dL) at last follow-up. In 32 dogs, sCr was not stable during the follow-up period, hence these dogs were not classified by CKD Stage, and 14 of these dogs experienced a continuous decrease in sCr up to 3 months after discharge. Sixty-four dogs had stable sCr ≥3 months after discharge

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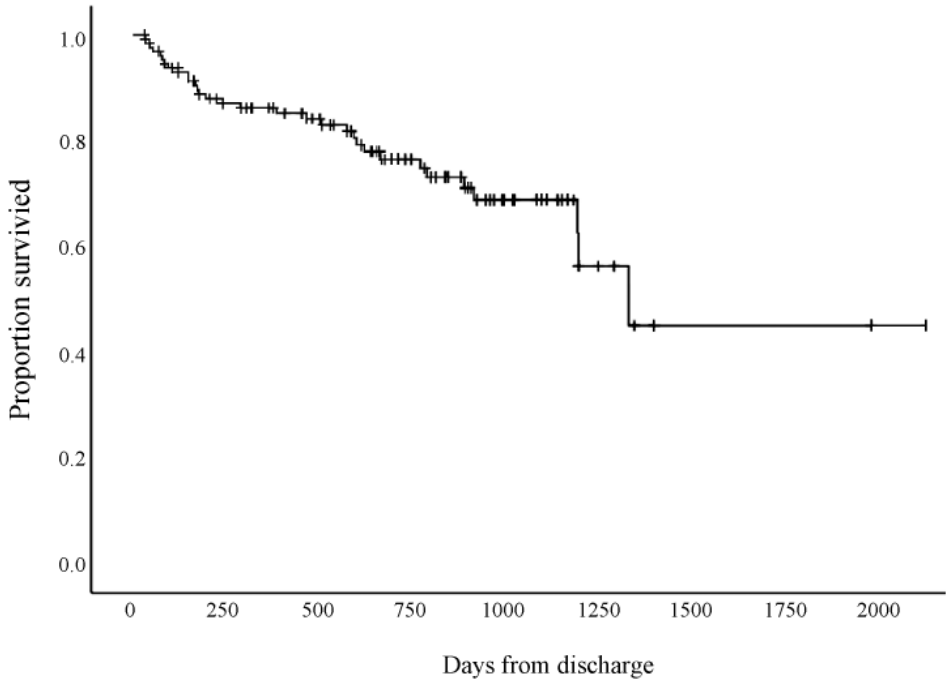


FIGURE 3 Long term follow-up in dogs surviving acute kidney injury

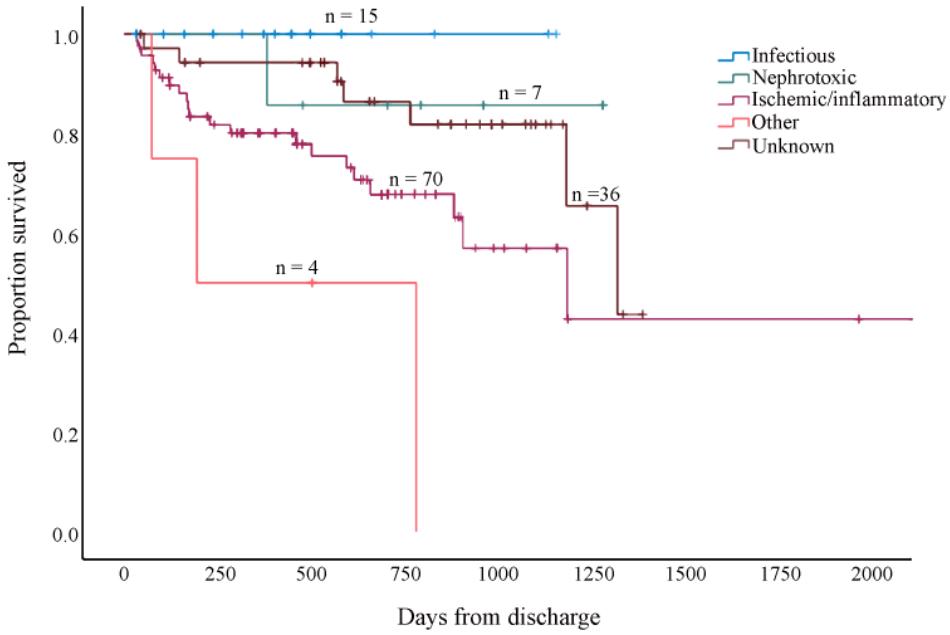


FIGURE 4 Association between etiology of acute kidney injury and long-term survival. AKI, acute kidney injury

and were classified by IRIS CKD stages as follows: 49/64 dogs (77%) were classified as IRIS CKD stage 1 and 15/64 dogs (23%) were classified as IRIS CKD stage 2.

Sixty-five dogs with sCr normalization at any time had sufficient follow-up data (ie, ≥ 1 sCr after sCr normalization) to assess whether azotemia recurred, and azotemia was documented in 9 of these dogs (14%), 219-1077 days after discharge.

3.4 | AKI during the follow-up period

Fourteen dogs (11%) developed another episode of AKI (ie, ACKD) during the follow-up period, within a median time of 222 days (range, 4-1309 days). These dogs were significantly ($P = .01$) older (124 months; range, 10-174 months) compared to dogs that did not develop ACKD (median, 72 months; range, 1-216 months). The etiologies of ACKD were ischemic/inflammatory (9 dogs, 64%) including pancreatitis (4 dogs, 29%) and diuretic treatment for heart disease (2 dogs, 14%), acute hepatitis (1 dog, 7%), severe gastroenteritis (1 dog, 7%), and immune-mediated hemolytic anemia (1 dog, 7%). The etiology for ACKD was unknown in 5 (36%) dogs. No difference was found in the proportion of dogs that developed ACKD between dogs with or without normalization of sCr at any time (10% vs 12%; $P = .75$). Long-term survival of these dogs was significantly shorter ($P < .001$; hazard ratio, 3.7; 95% CI, 1.8-7.8) compared to dogs that did not develop ACKD (median, 677 days; 95% CI, 397-957 days vs median, 1549 days; 95% CI, 1322-1778 days, respectively).

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3.5 | Multivariable analysis

In a multivariable Cox regression model including age, ACKD, etiology and AKI Grade, only age ($P < .001$) and etiology ($P = .02$) remained statistically significant whereas ACKD did not ($P = .07$).

4 | DISCUSSION

Dogs that recovered from AKI and survived >30 days had a good long-term prognosis in our study. Normalization of sCr was documented in 75% of the dogs, either at discharge or during the follow-up period.

Acute kidney injury is a severe syndrome, often requiring prolonged and costly hospitalization, with overall mortality as high as 45% to 62%, even with advanced treatment.[2,3,14-16] Despite its acute nature and potential for reversibility, AKI also may affect long-term outcome, because not all surviving dogs regain completely normal kidney function. The latter sustain CKD and as such, are prone to progression, because CKD in dogs is progressive in nature, and thus is expected to influence long-term survival. This information likely influences decision making of both clinicians and owners once AKI has been diagnosed. Currently, large scale studies describing the long-term outcome of dogs recovering from AKI are lacking.

In our study, the estimated MST of dogs recovering from AKI was 1322 days (95% CI, 1147-1626 days), longer than previously described in veterinary studies.[2,5] This rather long survival time is probably an underestimation of the actual MST, because many of the dogs were still alive at last follow-up. In accordance with previous studies, sCr normalized in approximately half of the animals by the time of discharge.[2,17] However, our results further documented that sCr normalization occurs in many dogs after discharge. Indeed, sCr normalized during the follow-up period in 45% of the dogs discharged with sCr above the reference range, and subsequently sCr normalized in 75% of the dogs, which is a higher proportion than previously described (44%).[2]

As might be expected, the proportion of dogs with sCr normalization decreased significantly with increase in IRIS AKI grade (Figure 2). Yet, long-term survival was not associated with IRIS AKI Grade. The magnitude of azotemia during AKI represents the severity of kidney dysfunction, but not necessarily the potential for reversibility, which is highly influenced by the underlying cause.[18] The role of etiology in AKI recovery and short-term outcome has been well established in several studies,[3,5] and also is documented here by differences in the proporations of dogs with sCr normalization among different AKI etiologies. In our study, the effect of etiology on long-term outcome also is demonstrated. Etiology affects the nature of the injury and the availability of specific treatments to eliminate the underlying cause. It is likely that some etiologies exert their effect also after recovery from the acute insult (e.g., glomerulopathies) whereas others do not (e.g., infectious).

The time until sCr normalization during the follow-up period varied, and could not have been assessed very accurately because normalization occurred between 2 succeeding visits. Because of the nature of our study, the time interval between visits was not constant and was sometimes long. In some dogs, sCr normalized within a few days after discharge, whereas in others normalization was documented after several months. These results suggest that renal recovery and repair processes after AKI may last weeks to months before a new steady state is reached.

During AKI recovery, 2 separate processes may occur: renal repair and activation of compensatory mechanisms in the remaining nephrons (ie, compensatory hypertrophy). Renal repair processes include repopulation of the tubules by regenerating epithelial cells that also undergo maturation.[19,20] Under certain circumstances, these repair mechanisms may lead to maladaptive renal changes, resulting in persistent renal dysfunction and CKD.[19,21] Simultaneously, compensatory hypertrophy and hyperfiltration occur, as the surviving nephrons compensate for the loss in renal functional mass.[22,23] Compensation processes might result in a gradual decrease in sCr over months after the abrupt impairment in kidney function.[24] The term AKD (acute kidney disease) has been proposed to represent the time window after AKI during which renal pathophysiologic processes may be active and ongoing.[19,25-27] The prolonged recovery phase documented in our study is consistent with guidelines used in humans, indicating that CKD can only be diagnosed after AKI when azotemia persists and is stable for >3 months.[28] This guideline also should be considered in veterinary medicine, because the time for sCr normalization in our cohort was as long as 3 months. This new information regarding the extended recovery process should be taken into consideration before making final diagnoses and clinical decisions.

Despite the high proportion of dogs with resolved azotemia, it is plausible that irreversible parenchymal damage and decreased renal function are present in dogs with apparent clinical recovery and normalization of biochemical variables. These changes might not be reflected in traditional renal functional markers (eg, sCr and symmetric dimethylarginine), and thus a diagnosis of CKD stage 1 should be made in all dogs recovering from AKI. Dogs with CKD are at increased risk for developing uremic crises (ie, ACKD),[29] thus recognition of stage 1 CKD, including routine monitoring, is important. Indeed, the proportion of dogs developing another episode of AKI was not different between dogs that had normalization of sCr and dogs that did not. Increased owner awareness about mild clinical signs is important, because it also has been shown that ACKD carries a guarded long-term prognosis in both dogs and cats.[30,31] Early diagnosis of ACKD will facilitate therapeutic intervention and might improve outcome. The fact that 14% of the dogs with sCr normalization had recurrence of azotemia further supports the notion that despite apparent complete recovery from AKI, dogs with sCr normalization after an AKI episode should be considered as stage 1 CKD (or at least to have higher risk for CKD and ACKD), and thus should be monitored and treated appropriately. Dogs diagnosed with another episode of AKI during the follow-up period in our study were significantly older compared to dogs that did not, and therefore older dogs recovering from AKI may need closer monitoring.

Dogs without normalization of sCr >3 months after the acute insult were considered to have azotemic CKD (stage 2 or higher). The

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MST of these dogs is apparently longer than is reported for dogs with CKD, and likely results from a slow CKD progression rate in dogs recovering from AKI.[32,33] The reason for this apparently slower progression might be related to the degree of compensatory hypertrophy and the processes governing progression in CKD. It is possible that, once substantial kidney function is regained (as occurred in our study), compensatory maladaptive processes that occur in further progression of CKD[23] do not occur to their full extent, or do not occur at all. Indeed, in our study, azotemic dogs eligible for CKD staging only were classified as IRIS CKD stage 1 or 2. Another potential explanation for the apparently slow progression may be related to CKD etiology. The etiology of CKD often is unknown at the time of diagnosis, but likely exerts its negative effect on kidney function throughout the disease course, contributing to further progression of the disease. These factors might not be present in dogs with CKD after AKI, and therefore would not promote progression, and thus, in the absence of compensatory hypertrophy and activation of maladaptive processes, kidney function may remain relatively stable. Another plausible explanation for the lack of difference in survival time between dogs with or without normalization of sCr relates to the fact that half of the dogs discharged with sCr above the reference range showed a decrease in sCr during the follow-up period. Thus, sCr normalization potentially also had occurred in these dogs, but was never documented. The notion of slow CKD progression after AKI also is supported by the fact that 12/22 dogs (55%) with a known cause of death during the follow-up period died of causes unrelated to their kidney disease, and only 10 dogs died or were euthanized because of CKD progression.

Our study had some limitations, mostly related to its retrospective design. Incomplete medical records might have weakened the power of some statistical analyses. Classification of some etiologies could not be proven and these therefore were presumed. It is possible the severity of azotemia at presentation was affected by dehydration in some of the dogs, but because evaluation of hydration status is very subjective and was assessed by multiple clinicians during the study period, we elected not to include this information. The follow-up period varied among dogs, because some were discharged only months before final analysis, resulting in a relatively short follow-up period, and other were still alive years after discharge, and censored, possibly underestimating MST. After discharge, monitoring and treatment of dogs were performed by different clinicians, at primary care clinics, using different machines (with potentially different reference ranges), which possibly affected our results. We did not use breed-specific reference ranges to define sCr normalization although a sCr <1.4 mg/dL could be considered high for some (especially miniature) breeds, thereby overestimating sCr normalization. Relevant kidney function variables (eg, blood urea nitrogen concentration, urine specific gravity) were not evaluated consistently during the follow-up period and thus could not be included in the overall assessment of kidney function. Differentiation between renal and nonrenal related death during the follow-up period was not always possible. Because most of the dogs had normalization of sCr and some of the other dogs were not eligible for CKD staging, the number of dogs that were included in the CKD staging was relatively low.

In conclusion, our findings suggest that dogs recovering from AKI have a relatively good long-term outcome. In most of the dogs, sCr normalized at discharge, and a substantial number of dogs experienced sCr normalization within the following weeks to months after discharge. Normalization of sCr was less likely to occur with increasing IRIS AKI grade, but normalization was not associated with long-term survival, suggesting slow progression rate of CKD after AKI. Significant differences in sCr normalization and long-term survival were observed among AKI etiologies, emphasizing the importance of reversibility of renal injury rather than the severity of renal dysfunction during AKI to the long-term outcome. These findings should facilitate clinical decision making and provide owner guidance during hospitalization as well as dictate long-term monitoring of dogs with AKI.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

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

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REFERENCES

1. Langston CE. Acute kidney injury. In: Ettinger SJ, Feldman EC, eds. *Textbook of Veterinary Internal Medicine*. 8th ed. Philadelphia, PA: Saunders WB; 2010:4650-4685.
2. Vaden SL, Levine J, Breitschwerdt EB. A retrospective case-control of acute renal failure in 99 dogs. *J Vet Intern Med*. 1997;11:58-64.
3. Segev G, Kass PH, Francey T, et al. A novel clinical scoring system for outome prediction in dogs with acute kidney injury managed by hemodialysis. *J Vet Intern Med*. 2008;22:301-308.
4. Rimer D, Chen H, Bar Nathan M, et al. Acute kidney injury in dogs: etiology, clinical and clinicopathologic findings, prognostic markers, and outcome. *J Vet Intern Med*. 2022;36(2):609-618.
5. Eatroff AE, Langston CE, Chalhoub S, et al. Long-term outcome of cats and dogs with acute kidney injury treated with intermittent hemodialysis: 135 cases (1997-2010). *J Am Vet Med Assoc*. 2012;241:1471-1478.
6. Cowgill L. *Grading of Acute Kidney Injury*. International Renal Interest Society; 2016. http://www.iris-kidney.com/pdf/4_ldc-revised-grading-of-acute-kidney-injury.pdf. Accessed April 2022.

19391676, 2022, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jvim.16435 by NHMRC National Cochrane Australia, Wiley Online Library on [30/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

7. Bragato N, Borges NC, Fioravanti MCS. B-mode and Doppler ultrasound of chronic kidney disease in dogs and cats. *Vet Res Commun*. 2017;41:307-315.
8. Xenoulis PG. Diagnosis of pancreatitis in dogs and cats. *J Small Anim Pract*. 2015;56:13-26.
9. Mansfield C. Pathophysiology of acute pancreatitis: potential application from experimental models and human medicine to dogs. *J Vet Intern Med*. 2012;26:875-887.
10. Wettimuny S. Pyelonephritis in the dog. *J Comp Pathol*. 1967;77:193-197.
11. Widmer WR, Biller DS, Adams LG. Ultrasonography of the urinary tract in small animals. *J Am Vet Med Assoc*. 2004;225:46-54.
12. Sykes JE, Hartmann K, Lunn KF, et al. 2010 ACVIM small animal consensus statement on leptospirosis: diagnosis, epidemiology, treatment, and prevention. *J Vet Intern Med*. 2011;25(1):1-3.
13. Thoen ME, Kerl ME. Characterization of acute kidney injury in hospitalized dogs and evaluation of a veterinary acute kidney injury staging system. *J Vet Emerg Crit Care*. 2011;21:648-657.
14. Legatti SAM, El-dib R, Leggati E, et al. Acute kidney injury in cats and dogs: a proportional meta-analysis of case series studies. *PLoS One*. 2018;13:1-18.
15. Brown N, Segev G, Francey T, et al. Glomerular filtration rate, urine production, and fractional clearance of electrolytes in acute kidney injury in dogs and their association with survival. *J Vet Intern Med*. 2015;29:28-34.
16. Harison E, Langston C, Palma D, et al. Acute azotemia as a predictor of mortality in dogs and cats. *J Vet Intern Med*. 2012;26:1093-1098.
17. Worwag S, Langston CE. Acute intrinsic renal failure in cats: 32 cases (1997-2004). *J Am Vet Med*. 2008;5:728-732.
18. Segev G. Outcome prediction of acute kidney injury in dogs and cats. *Isr J Vet Med*. 2011;66:82-88.
19. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2005;67:2089-2100.
20. Venkatachalam MA, Weinberg JM, Kriz W, et al. Failed tubule recovery, AKI-CKD transition, and kidney disease progression. *J Am Soc Nephrol*. 2015;26:1765-1776.
21. Ferenbach DA, Bonventre JV. Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. *Nat Rev Nephrol*. 2015;11:264-276.
22. Schmiedt CW, Brainard BM, Hinson W, et al. Unilateral renal ischemia as a model of acute kidney injury and renal fibrosis in cats. *Vet Pathol*. 2016;53:87-101.
23. Brown CA, Rissi DR, Dickerson VM, et al. Chronic renal changes after a single ischemic event in an experimental model of feline chronic kidney disease. *Vet Pathol*. 2019;56:536-543.
24. Katz AI, Epstein FH. Relation of glomerular filtration rate and sodium reabsorption to kidney size in compensatory renal hypertrophy. *Yale J Biol Med*. 1967;40:222.
25. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol*. 2017;13:241-257.
26. Forni LG, Darmon M, Ostermann M, et al. Renal recovery after acute kidney injury. *Intensive Care Med*. 2017;43:855-866.
27. Kellum JA, Sileanu FE, Bihorac A, et al. Recovery after acute kidney injury. *Am J Respir Crit Care Med*. 2017;195:784-791.
28. Kellum JA, Lameire N, Aspelin P, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2:1-138.
29. Cowgill LD, Polzin DJ, Elliott J, et al. Is progressive chronic kidney disease a slow acute kidney injury? *Vet Clin North Am Small Anim Pract*. 2016;46:995-1013.
30. Dunaevich A, Chen H, Musseri D, et al. Acute on chronic kidney disease in dogs: etiology, clinical and clinicopathologic findings, prognostic markers, and survival. *J Vet Intern Med*. 2020;34:2507-2515.
31. Chen H, Dunaevich A, Apfelbaum N, et al. Acute on chronic kidney disease in cats: etiology, clinical and clinicopathologic findings, prognostic markers, and outcome. *J Vet Intern Med*. 2020;34:1496-1506.
32. O'Neill DG, Elliott J, Church DB, et al. Chronic kidney disease in dogs in UK veterinary practices: prevalence, risk factors, and survival. *J Vet Intern Med*. 2013;27:814-821.
33. Rudinsky AJ, Harjes LM, Byron J, et al. Factors associated with survival in dogs with chronic kidney disease. *J Vet Intern Med*. 2018;32:1977-1982.

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