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Retrospective Study

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Evaluation of a prognostic scoring system for dogs managed with hemodialysis

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Abstract

Objective – To investigate prognostic models in a cohort of dogs with acute kidney injury (AKI) and acute on chronic kidney disease (AKI/CKD) managed by hemodialysis.
Design – Retrospective study from July 2011 to November 2014.
Setting – University Veterinary Teaching Hospital.
Animals – Forty dogs with historical, clinical, imaging, and laboratory findings consistent with AKI or AKI/CKD managed with intermittent hemodialysis were included.
Interventions – Scoring system models previously established by Segev et al for outcome prediction in dogs with AKI were applied to all dogs.
Results – Models A, B, and C correctly classified outcomes in 68%, 83%, and 85% of cases, respectively. In our cohort Model A showed sensitivity of 58% and specificity of 86%, Model B showed sensitivity of 79% and specificity of 87%, Model C showed sensitivity of 86% and specificity of 84%. The presence of anuria ($P < 0.0002$), respiratory complications ($P < 0.0001$), disseminated intravascular coagulation (DIC) ($P = 0.0004$), grade of AKI ($P = 0.0023$), pancreatitis ($P = 0.0001$), and systemic inflammatory response syndrome (SIRS) ($P = 0.0001$) was significantly higher in nonsurvivors compared with survivors.
Conclusions – In our cohort of patients, Segev's model C showed the best sensitivity and specificity for predicting prognosis, while model A had lower sensitivity. In our cohort of dialysis patients, the presence of respiratory complications, DIC, SIRS, and pancreatitis at hospitalization, were correlated with a poor prognosis.

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Keywords: AKI, dogs, hemodialysis, IRIS grading, prognosis

Abbreviations

AKI	acute kidney injury
AKI/CKD	acute on chronic kidney disease
aPPT	activated partial thromboplastin time
CKD	chronic kidney disease
CI	confidence interval
CC	correctly classified
DIC	disseminated intravascular coagulation
IC	incorrectly classified
IHD	intermittent hemodialysis
IRIS	International Renal Interest Society
NPV	negative predictive value
PPV	positive predictive value
PT	prothrombin time
RRT	renal replacement therapies
Spec	specificity
Sens	sensitivity
SIRS	systemic inflammatory response syndrome

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Introduction

The availability of extracorporeal renal replacement therapies (RRT) in veterinary medicine is growing.[1–3] Hemodialysis can facilitate the removal of uremic toxins, correct fluid, and electrolyte imbalances and is the treatment of choice for uremic patients when medical management fails.[4] Dialysis is indicated for patients with oliguria/anuria, life-threatening fluid overload, hyperkalemia, and electrolyte or acid-base disturbances, acute poisoning/drug overdose with substances that can be

removed by dialysis independent of urine output. In dogs, acute kidney injury (AKI) is the most common indication for hemodialysis.[5] However, hemodialysis can also be used to manage patients with acute impairment of chronic kidney disease (AKI/CKD).

Overall survival of dogs affected by AKI treated with hemodialysis has been reported between 47% and 50%,[6,7] but it is highly variable, mostly affected by the etiology.[8]

Multiple factors determine the outcome and long-term prognosis of dogs with AKI, including etiology, reversibility of renal injury, comorbid disorders, concurrent complications, and the availability of diagnostic and therapeutic services.[8] Etiology was shown to be a major determinant of the prognosis in dogs with AKI but it is often unknown at presentation.[6] Few studies have investigated the association of specific AKI etiologies with their outcome.[2,6,8]

Recently, 3 scoring systems were developed to predict outcome of dogs with AKI managed with intermittent hemodialysis.[6,7] The 3 scoring systems are based on clinical and laboratory parameters measured on the first day of presentation; 2 of these models are independent of etiology. Patients are assigned a predictive score, which is used to assess the probability of 30-day survival.[6,7]

The aim of this study is to evaluate the prognostic accuracy of models A, B, and C[6,7] in predicting outcome in a cohort of dogs with AKI and AKI/CKD managed by hemodialysis at University of Pisa. We also evaluated other clinical variables (presence of pancreatitis and systemic inflammatory response syndrome [SIRS]) as potential prognostic indicators.

Materials and Methods

Patients and data collection

This study was performed retrospectively and included dogs with AKI or dogs with AKI/CKD managed with intermittent hemodialysis (IHD), presented between July 2011 and November 2014.

A diagnosis of AKI or AKI/CKD was based on history, clinical course, clinicopathologic findings, and ultrasonographic evidence of the disease. As in previous studies[6,7] the following criteria were chosen to enroll patients in AKI group: (1) acute onset of consistent clinical signs and history (eg, anuria, oliguria, vomiting, diarrhea, inappetence);[2] renal azotemia (serum creatinine concentration >265.2 μmol/L and urine-specific gravity <1.025); and[3] normal or enlarged kidney size (relative to the dog's body weight) as detected by ultrasound examination.

Dogs with a history of CKD were excluded. Dogs were assigned to the AKI/CKD group if they had evidence of AKI and ultrasound findings of decreased corticomedullary differentiation, in the absence of any clinical signs or clinicopathologic abnormalities consistent with CKD. Dogs with post renal AKI were also included.

All patients were also classified with IRIS AKI grading system on the basis of serum creatinine, urine output, and requirement of RRT.[9] They were subclassified on the basis of urine production during first 24 hours of hospitalization: anuric (no urine production), oliguric (<1 mL/kg/h), and nonoliguric (≥1 mL/kg/h).[9]

For all patients data were collected from the hospital's electronic medical database. Data collected included signalment, history, physical exam, CBC, serum biochemistry, ELISA canine pancreatic lipase immunoreactivity,[a] coagulation profile, blood gas analysis, urinalysis, abdominal ultrasound, thoracic radiographs, urine output, organs involved at presentation, and outcome (survival and nonsurvival). Patients were classified as survivors if they were discharged from the hospital, were alive, and not dialysis-dependent for at least 30 days after discharge. Patients were classified as nonsurvivors if they died or were euthanized for uncontrolled clinical signs during dialysis or hospitalization or within 30 days from discharge from the hospital. Patients who were dialyzed and euthanized for financial reasons within 2 weeks from initiation of dialysis were excluded from the study.

Laboratory findings

Complete blood cell count was performed using a hematology analyzer.[b] Serum creatinine, urea, phosphorus, albumin, and alanine aminotransferase were performed with a spectrophotometer.[c] Ionized calcium and anion gap were analyzed by a blood gas machine[d] and fibrinogen, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were measured with a coagulation analyzer.[e] Urine production was determined during the first 24 hours of hospitalization, through a closed urine collection system.

Organ dysfunction

Extrarenal organ dysfuction was classified retrospectively from the clinical records according to clinical signs, laboratory abnormalities, ultrasound, and radiographic findings. Respiratory dysfunction was defined as the presence of dyspnea and/or tachypnea, abnormal lung pattern on thoracic radiographs or hypoxia (SpO_2 <93% or PaO_2 <80 mm Hg). Neurological dysfunction was defined as involvement of the neurologic system at presentation (eg, ataxia), while disseminated intravascular coagulation (DIC) was diagnosed if concomitant prolongation of PT and aPTT, reduction in fibrinogen concentration and thrombocytopenia were present.

Systemic Inflammatory Response Syndrome was diagnosed based on recently published criteria.[10] Diagnosis of pancreatitis was based on the presence of clinical signs (abdominal pain, vomiting, diarrhea) and ultrasound abnormalities of the pancreas consistent

Table 1: Sensitivity and specificity with confidence interval of models in all patients

Model	Score	Sens (%)	CI (95%)	Spec (%)	CI (95%)	PPV (%)	CI (95%)	NPV (%)	CI (95%)	Surv (CC)	Surv (IC)	Died (CC)	Died (IC)
A	20.00	58	45-70	86	70-95	88	75-96	53	39-96	15	2	12	11
B	20.51	79	63-89	87	76-95	83	69-93	83	71-92	14	3	19	4
C	19.92	86	71-95	84	73-92	76	61-88	91	81-97	13	4	21	2

Score, cut-off score for each model used in the study; Sens, sensitivity; Spec, specificity; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; Surv, survived; CC, number of dogs correctly classified; IC, number of dogs incorrectly classified.

with pancreatitis and a positive bedside ELISA canine pancreatic lipase immunoreactivity test result.[a]

Models

AKI classification and prognostic models (A, B, C) for outcome prediction in dogs with AKI were calculated for all dogs using previously described methods.[6,7]

Statistical analysis

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for models A, B, and C were calculated for all dogs included (Table 1). Chi-square test was used to compare categories of urine production as defined above and AKI grade (4 or 5) and extra-renal organ involvement between survivors versus nonsurvivors. All parameters considered by models (body weight, serum creatinine, serum phosphorus, red blood cells, lymphocytes, serum albumin, alanine aminotransferase, ionized calcium, and anion gap) were screened for normality by D'Agostino–Pearson omnibus normality tests. For parameters that did not follow a normal distribution nonparametric test (Mann–Whitney test) have been used. Normally distributed parameters were evaluated using a Student *t*-test.

Statistical analysis was performed commercial statistical software,[f] and $P < 0.05$ was considered statistically significant.

Results

This study included 40 dogs, of these 30 were males and 10 were females. The mean age was 5.4 ± 3.3 years. Mean body weight was 26.1 ± 12.4 kg.

Twenty-four dogs (24/40, 60%) were diagnosed with AKI, while 16 dogs (16/40, 40%) had AKI with ultrasonographic abnormalities suggestive of presence of underlying CKD (eg, decreased CM differentiation).

Causes of AKI included: leptospirosis (5/24, 21%), ethylene glycol toxicity (4/24, 17%), other toxicosis (3/24, 13%), pyelonephritis (2/24, 8%), postrenal causes (2/24, 8%), heatstroke (1/24, 4%), and snake bite (*Vipera aspis francisciredi*) (1/24, 4%). In 6 dogs (6/24, 25%) the cause of AKI was unknown.

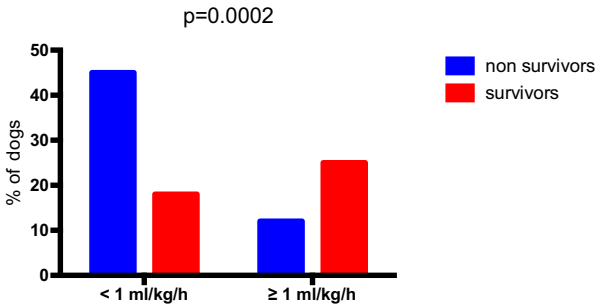

Figure 1: Chi-square test shows the difference in urinary output between survivors and nonsurvivors group at presentation ($P < 0.05$).

Of the dogs with AKI/CKD, 5 were diagnosed with *Leishmania infantum* (5/16, 31%). In 11 dogs the etiology was unknown (11/16, 69%).

Two dogs were graded IRIS AKI 3 (2/40, 5%), 19 dogs were graded IRIS AKI 4 (19/40, 47.5%), and 19 were graded IRIS AKI 5 (19/40, 47.5%). Nineteen dogs were anuric (19/40, 47.5%), 6 dogs were oliguric (6/40, 15%) and 16 dogs were nonoliguric (15/40, 37.5%); median urine production (within the first 24 hours) of all dogs was 0.15 mL/kg/h (range, 0–6 mL/kg/h). Survival rate in our cohort was 43%.

Serum biochemistry parameters of dogs included in this study are reported in Table 2. At presentation 16/40 dogs (40%) had respiratory dysfunction, 1/40 dog (2.5%) had neurologic dysfunction, 9/40 dogs (22.5%) had DIC, 6/40 dogs (15%) had pancreatitis and 6/40 dogs (15%) had SIRS.

Chi-square test showed a statistically significant association between the outcome and urinary output (<1 mL/kg/h vs ≥1 mL/Kg/h) ($P = 0.0002$) (Fig. 1), severity of AKI (4 vs 5) ($P = 0.0023$) (Fig. 2), presence of respiratory complications ($P < 0.0001$) (Fig. 3), pancreatitis ($P = 0.0001$) (Fig. 4), SIRS ($P = 0.0001$) (Fig. 5), and DIC ($P = 0.0004$) (Fig. 6) at the time of presentation. Mann–Whitney test showed a significant difference in serum concentration of creatinine ($P = 0.0084$) and phosphorus ($P = 0.0163$) between survivors and nonsurvivors.

Models A, B, and C correctly classified outcomes in 68%, 83%, and 85% of cases, respectively. Sensitivity and

Table 2: Mean value and standard deviation of parameters investigates in all dogs ($n = 40$) and in survivors/not survivors at presentation

Parameters	Units (SI) (CU)	All dogs ($n = 40$)	Survivors ($n = 17$)	Nonsurvivors ($n = 23$)	Reference range	*P*-value
Body weight	Kg	27.1 ± 12.4	26.7 ± 3.5	26.9 ± 2.3		0.9448
Red blood cells	x10^{12}/L	4.85 ± 1.35	4.97 ± 1.44	4.77 ± 1.32	5.6–8.8	0.7920
	x10^{6}cell/μL	4.85 ± 1.35	4.97 ± 1.44	4.77 ± 1.32	5.6–8.8	
Lymphocytes count	x10^{9}/L	2.03 ± 1.76	1.91 ± 1.10	2.12 ± 2.14	1.0–5.1	0.3893
	x10^{3}cell/μL	2027.67 ± 1763.1	1905 ± 1106	2118 ± 2145	1,0005,100	
Creatinine	μmol/L	931 ± 408	747 ± 67	1067 ± 92	53.0–132.6	**0.0084***
	mg/dL	10.5 ± 4.6	8.5 ± 0.8	12.1 ± 1.0	0.6–1.5	
Phosphorus	mmol/L	4.8 ± 1.9	4.0 ± 1.4	5.5 ± 0.4	0.8–1.6	**0.0163***
	mg/dL	15.2 ± 6.0	12.5 ± 4.3	17.1 ± 6.5	2.5–5.0	
Ionized calcium	mmol/L	1.1 ± 0.2	1.2 ± 0.3	1.0 ± 0.2	1.1–1.4	0.0643
	mEq/L	2.2 ± 0.4	2.4 ± 0.6	2.1 ± 0.4	2.2–2.8	
Anion gap	mmol/L	23.2 ± 6.1	21.5 ± 6.8	24.4 ± 5.3	12–20	0.1410
	mEq/L	23.2 ± 6.1	21.5 ± 6.8	24.4 ± 5.3	12–20	
Albumin	g/L	28 ± 7	28.1 ± 8.1	27.3 ± 6.9	26–41	0.6889
	g/dL	2.8 ± 0.7	2.8 ± 0.8	2.7 ± 0.7	2.6–4.1	
Alanine aminotransferase	U/L	123.5 ± 185.6	140.6 ± 264.3	111.0 ± 99.6	20–70	0.3119
	U/L	123.5 ± 185.6	140.6 ± 264.3	111.0 ± 99.6	20–70	

All parameters were also compared between survivors and not survivors group with unpaired *t*-test or Mann–Whitney test. In the table are reported mean values with standard deviation, reference range and *P*-value for each parameter. *Statistically significant value.
SI, systeme international unit; CU, common unit.

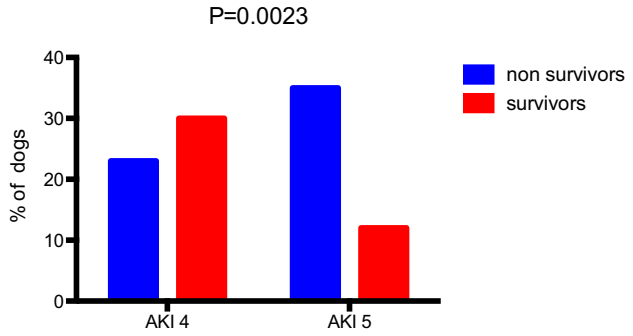

Figure 2: Chi-square test shows the severity of acute kidney injury (AKI) (4 vs 5) between survivors and nonsurvivors group at presentation ($P < 0.05$).

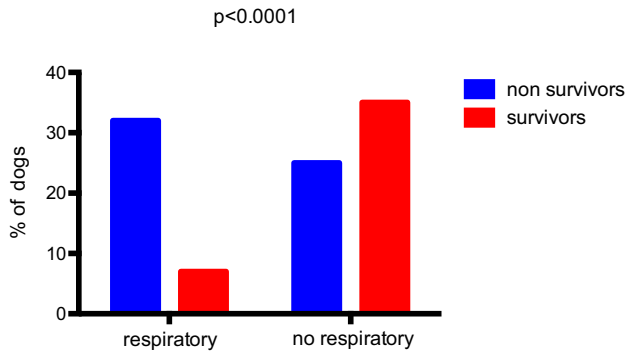

Figure 3: Chi-square test shows the presence of respiratory implications between survivors and nonsurvivors group at presentation ($P < 0.05$).

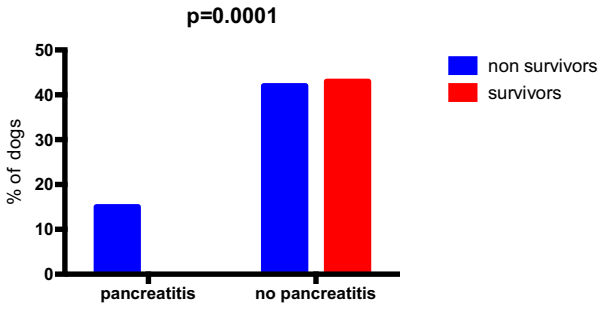

Figure 4: Chi-square test shows the presence of pancreatitis between survivors and nonsurvivors group at presentation ($P < 0.05$).

specificity of model A were 58% (CI 45–70) and 86% (CI 70–95). Model A was found to have positive predictive value of 88% (CI 75–96%) and negative predictive value of 53% (CI 39–96%). Model B showed a sensitivity of 79% (CI 63–89%) and specificity of 87% (CI 76–95%). Model B was found to have positive predictive value of 83% (CI 69–93%) and negative predictive value of 83% (CI 71–92%). Sensitivity and specificity of model C were 86% (CI 71–95%) and 84% (CI 73–92%). Model C showed a positive predictive value of 76% (CI 61–88%), negative predictive value of 91% (CI 81–97%) (Table 1).

Discussion

This study demonstrates comparable sensitivities and specificities to the original study, expect for lower

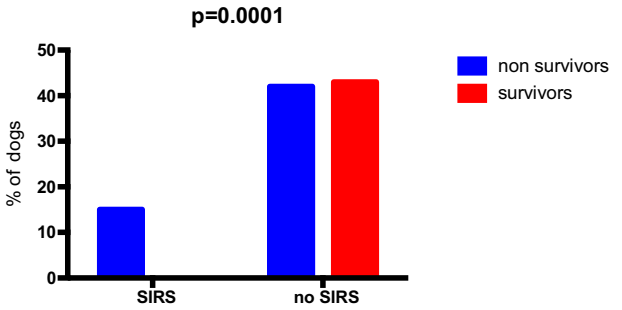

Figure 5: Chi-square test shows the presence of Systemic Inflammatory Response Syndrome (SIRS) between survivors and nonsurvivors group at presentation ($P < 0.05$).

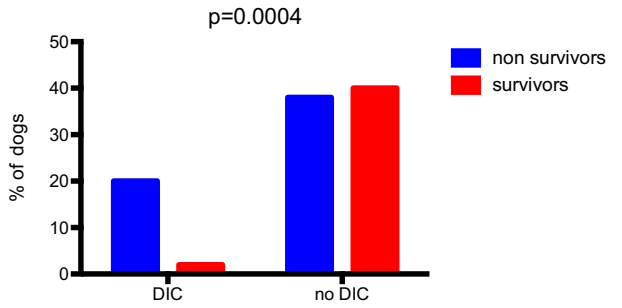

Figure 6: Chi-square test shows the presence of disseminated intravascular coagulation (DIC) between survivors and nonsurvivors group at presentation ($P < 0.05$).

sensitivity for model A.[6] In our cohort the highest sensitivity was found for model C and the highest specificity for model B (Table 1). The Segev models were recently validated in a multicenter cohort of dogs.[7] In that study, the 3 models showed similar sensitivity and specificity to the original study and were able to correctly classify 78–80% of the patients.[7]

In our study model C showed the best combination of sensitivity (86%) and specificity, (84%) using the previously established cutoff points. Model A showed a reduced sensitivity (58%) compared to the other models. This difference in sensitivity and specificity may be caused by the fact that Segev models were originally designed for evaluating patients with intrinsic AKI only. In our cohort 60% of dogs were diagnosed with AKI and 40% dogs diagnosed with AKI/CKD. Due to low number of dogs with AKI/CKD we were unable to accurately assess the performance of the models in this population.

The overall survival in our cohort was 43% at 30 days from discharge from the hospital, and is comparable to other studies.[6,7]

In this study, patients with oliguria at presentation had higher probability ($P < 0.0002$) of not surviving compared to nonoliguric patients (Fig. 1). This finding was in agreement with previous retrospective studies,[11,12] in which reduced urinary output was associated with poor prognosis not only in AKI dogs managed medically, but also in dogs managed with hemodialysis.[6]

In our study, patients with respiratory complications showed a poorer prognosis compared to patients with no respiratory signs (Fig. 3). The association between poor outcome and presence of respiratory complications has also been reported in human patients, where it has been mainly associated with fluid overload.[13]

In our study, a significant difference in the presence of DIC, SIRS, and pancreatitis was found between survivors and nonsurvivors (Figs. 4–6). This has not been previously identified in dogs with AKI undergoing hemodialysis.[6]

Nonsurvivors had significantly higher serum creatinine and phosphorous concentrations compared to survivors (Table 2). No significant difference was found in the other analyzed parameters between the 2 groups. The significant role of creatinine in predicting negative outcome seemed also to be confirmed by the difference in prevalence of more severe AKI grades (AKI grades 4 and 5) among survivors and nonsurvivors (Fig. 2).

In our cohort of patients, Segev model C was more accurate for predicting prognosis. Sensitivity was not satisfactory for models A and B. In our cohort of dialysis patients, the presence of respiratory complications, DIC, SIRS, and pancreatitis at hospitalization, were significantly associated with poor prognosis.

Limitations of the Study

The present study has a number of limitations. First of all, the relatively low number of patients involved in the study. We also had significant heterogeneity of our dialysis population. As the aim of our study was to evaluate the accuracy of Segev models in predicting outcome in dogs managed by hemodialysis, dogs with different etiologies of AKI and AKI/CKD were involved. We opted to include dogs with AKI/CKD or post renal AKI, as they were part of our dialysis population and felt that as these diagnoses may not be known on presentation to exclude them may result in significant bias.

Footnotes

[a] IDEXX SNAP® cPL™, IDEXX Laboratories, Italy.
[b] IDEXX ProCyte Dx™, IDEXX Laboratories, Italy.
[c] LIASYS© AMS Assel S.r.l., Aprilia, Italy.
[d] ABL 700 Series ™ Radiometer, Diamond Diagnostics, Holliston, MA.
[e] CLOT 2 S SEAC™ Radim group, Calenzano, Italy.
[f] Graphpad Prism 6 for Windows, GraphPad Software, La Jolla, CA, USA.

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