Evidence of cardiac injury and dysfunction in dogs with acute kidney injury

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SUMMARY

Objectives: Cardiac involvement in the course of acute kidney injury (AKI) is described in humans as cardiorenal syndrome type 3 but has received only limited attention in dogs. This study was designed to evaluate cardiac injury and dysfunction in canine AKI and their association with outcome.

Methods: This prospective cohort study enrolled 25 client-owned dogs with AKI. Cardiac manifestations were evaluated with thoracic radiographs, echocardiography, 24h Holter monitoring and cardiac troponin I concentrations (cTnI) at admission and 7-10 days later.

Results: Most dogs were diagnosed with leptospirosis (n=19, 76%) and presented with moderate to severe AKI, IRIS grades III–V. Dogs with ≥100 ventricular premature complexes (VPCs) per 24h in the first examination (n=9) had significantly higher initial cTnI concentrations (P=0.005) and a worse outcome (P=0.040) compared to dogs with fewer VPCs. In ROC curve analysis, the number of VPCs was more predictive of outcome (AUC 0.85, P<0.001) than cTnI concentrations (AUC 0.78, P=0.022).

Clinical significance: AKI seems to be associated with cardiac injury and dysfunction in dogs. The data did not indicate a cardiac cause of poor outcome in dogs with increased VPCs, but an association possibly reflecting the severity of the disease.

Keywords: Acute kidney injury, arrhythmias, Holter monitoring, cardiac troponin I, echocardiography

INTRODUCTION

The interplay between the cardiovascular and renal systems involves multiple shared mechanisms related to volume regulation and adaptive responses to loss of function. Most kidney diseases may thus be expected to have direct or indirect cardiovascular effects that may include systemic hypertension, left ventricular hypertrophy, fluid volume dysregulation, as well as manifestations of the underlying disease or iatrogenic complications (Bagshaw *et al.* 2013, Ronco *et al.* 2008). When the primary condition is acute kidney injury (AKI), these interactions are termed acute renocardiac syndrome or cardiorenal syndrome type 3 in people. Several studies suggest that this syndrome also affects dogs (Mastrorilli *et al.* 2007, Porciello *et al.* 2008, Sharkey *et al.* 2009).

Cardiac diseases may be of functional or structural nature. Cardiac arrhythmias reflect functional myocardial disorders and long-term Holter electrocardiographic monitoring is typically indicated for their reliable quantification (Lipski *et al.* 1976, Marino *et al.* 1994, Meurs *et al.* 2001, Miller *et al.* 1999, Wess *et al.* 2010). Serum cardiac troponin concentration is regarded as the most accurate blood test for the evaluation of myocardial damage, with cardiac troponin I (cTnI) being the most sensitive (Adams *et al.* 1993, Schober *et al.* 2002, Shaw *et al.* 2004). Veterinary studies indicate that a large number of noncardiac diseases, including renal failure (Porciello *et al.* 2008, Sharkey *et al.* 2009), leptospirosis (Mastrorilli *et al.* 2007), babesiosis (Lobetti *et al.* 2002), ehrlichiosis (Diniz *et al.* 2008), immune-mediated haemolytic anaemia (Gow *et al.* 2011), snake envenomation (Segev *et al.* 2008), pyometra (Pelander *et al.* 2008), systemic inflammation (Langhorn *et al.* 2013) and gastric dilatation volvulus (Burgener *et al.* 2006), may induce myocardial injury and increased cTnI concentrations. In addition, several human studies have suggested that cTnI concentrations may be affected by decreased renal clearance (Diris *et al.* 2004, Fahie-Wilson *et al.* 2006) and haemodialysis (Assa *et al.* 2013, Deleaval *et al.* 2006, Farkouh *et al.* 2003, Tun *et al.* 1998, Wayand *et al.* 2000), but these findings remain controversial.

To the authors' knowledge, only few studies have reported cardiac involvement in canine kidney disease, and these were limited to demonstrating elevated cTnI concentrations (Mastrorilli *et al.* 2007, Porciello *et al.* 2008, Sharkey *et al.* 2009). However, without further cardiologic evaluation, the clinical relevance of these findings remains unclear. The goal of the present study was to evaluate the presence of functional and structural cardiac injury in dogs with AKI using Holter recordings, cTnI measurements,

thoracic radiographs and echocardiography, and to assess possible associations between these findings and outcome. We hypothesized that AKI is associated with cardiac arrhythmias and elevated cTnI concentrations, and that cardiac injury may indicate severe disease and increased mortality.

MATERIALS AND METHODS

Animals

Dogs diagnosed with AKI between April and December 2013 were enrolled in this prospective cohort study. Small dogs weighing less than 7kg and dogs with dyspnoea were excluded due to the size of the Holter recorder and the potential breathing impairment caused by the recorder attachment system. Other exclusion criteria were chronic kidney disease and pre-existing heart disease, as well as splenic disease or pancreatitis, which have been associated with myocardial injury (Marino *et al.* 1994, Serra *et al.* 2010). The diagnosis of AKI required at least 2 of the following criteria: renal azotaemia persisting for ≥24h after correction of prerenal factors, an increase in serum creatinine concentration ≥100 µmol/L or ≥100% from baseline, persistent oligoanuria after volume repletion; and evidence of tubular injury based on urinalysis (Fraune *et al.* 2013). All procedures were conducted in accordance with the Animal Welfare Act (xx), and subject to informed owner consent.

Diagnostic examinations and grouping

Initial diagnostics included a complete blood count, biochemical and coagulation profiles, venous blood gas analysis, urinalysis, and abdominal ultrasound. Additional diagnostics, performed as indicated to identify the aetiology, included microscopic agglutination test (MAT) using a panel of ubiquitous and locally prevalent serovars (*L. interrogans* serovars Australis, Autumnalis, Bataviae, Bratislava, Canicola, Hardjo, Icterohaemorrhagiae, Pomona, Pyrogenes, Sejroe, and Tarassovi and *L. kirschneri* serovar Grippotyphosa) and a Leptospira IgM assay (Test-it lateral flow, LifeAssay Diagnostics, Cape Town, South Africa (Abdoel *et al.* 2011)). A diagnosis of leptospirosis was confirmed by either a 4-fold titre increase on paired serologies, a single MAT titre ≥1:800 for non-vaccine serovars, or a positive IgM assay (Schuller *et al.* 2015).

Cardiac evaluation, performed within 48h of presentation, included physical examination, thoracic radiographs evaluated by a board-certified radiologist, transthoracic echocardiography performed by a board-

certified cardiologist, 24h Holter monitoring and serum cTnI concentrations. Echocardiography was performed with an Aloka ProSound Alpha 5SV machine and a 5-MHz sector transducer in unsedated dogs. Serum samples were stored at -80°C and batched for measurements of cTnI concentrations (Centaur XP TnI-Ultra assay, Siemens Healthcare Diagnostics, Eschborn, Germany) (Beck *et al.* 1997). The measurement range was 0.006—50 ng/mL and the laboratory upper reference limit was 0.06 ng/mL (Serra *et al.* 2010). Holter monitoring was performed using a 2-channel CardioMem CM 3000 recorder and the CardioDay software (GETEMED, Teltow, Germany). All recordings were subsequently checked manually by the same examiner (XX). Holter recording and cTnI measurement was repeated 7-10 days after the initial examination.

The dogs were grouped based on the number of ventricular premature complexes (VPCs) during the first examination into Group 1 (<100 VPCs/24h) or Group 2 (≥100 VPCs/24h). This cut-off was chosen as it has been suggested as pertinent to detect relevant arrhythmias in previous studies (Hall *et al.* 1991, Meurs *et al.* 2001, Olsen *et al.* 1999, Ulloa *et al.* 1995, Wess *et al.* 2010).

Treatment and outcome

Therapy was adapted individually to the clinical needs of the dogs and consisted mainly of intravenous fluids, gastric protectants, antemetics, analgesics, antibiotics, and antihypertensives. In addition, dogs received renal replacement therapy as intermittent haemodiafiltration when this was indicated based on clinical condition, degree of azotaemia, potassium concentration and urine production. The outcome was defined as either fatal (death or euthanasia), full recovery (discharge without residual azotaemia) or partial recovery (discharge with persisting azotaemia).

Statistical analyses

Statistical analyses were performed using commercial software (MedCalc 13.0.6.0, Ostend, Belgium; NCSS 9.0.15, Kaysville, Utah, USA). A sample size calculation was performed to estimate the number of dogs needed to show an increased number of VPCs (from 10 ± 5 to a mean ≥100 VPCs/24h) and an elevated concentration of cTnI (from 0.092 ± 0.066 to a mean ≥0.2 ng/ml), using previously published populations of normal dogs as references (Maier *et al.* 2010, Meurs *et al.* 2001). Samples of 6 (VPCs) and 11 dogs (cTnI)

were identified as necessary to show these differences with a 90% power, and the study was therefore designed to include the first 25 eligible dogs.

Comparison of categorical data was performed using Fisher's exact test. Continuous data were assessed for normality with normal probability plots and D'Agostino-Pearson test. Comparison between groups for continuous data was performed using independent samples t-tests when normally distributed and Mann-Whitney tests otherwise. Comparison between the first and second cTnI concentrations was performed using a Wilcoxon signed-rank test. Correlation between cTnI concentrations and creatinine was evaluated using Spearman's rank correlation. Prediction of outcome based on cTnI concentrations or VPCs was evaluated using ROC curve analysis and the optimal cut-off based on the Youden index. Significance was set at $P<0.05$ throughout.

RESULTS

Dogs and general diagnostic evaluation

During the 9 months of the study, 70 dogs were diagnosed with AKI at the authors' institution. Twenty-five dogs met the inclusion criteria and were enrolled (Table 1). These were 7 mixed breed dogs and 18 dogs from 12 different breeds. Nineteen of the 25 dogs (76%) were diagnosed with leptospirosis based on paired MAT seroconversion (n=11, 58%), positive MAT titre at presentation (n=13, 68%), or a positive IgM assay at presentation (n=13, 68%). Positive serovars in the first MAT serology (n=19) included Australis (68%), Bratislava (58%), Pomona (16%), and Autumnalis (11%). Other causes of AKI included anaesthesia-related ischaemia (n=1), renal thrombosis (n=1), grape toxicity (n=1), unidentified toxic nephrosis (n=1), and unknown aetiology (n=2).

The level of azotaemia at presentation ranged from mild to severe with serum creatinine and urea concentrations ranging between 294—1359 µmol/L and 20—106 mmol/L, respectively (Table 2). Six dogs (24%) were classified as IRIS AKI grade III, 8 dogs (32%) grade IV, and 11 dogs (44%) grade V.

Abnormalities found on routine bloodwork included anaemia (n=13; 52%), leukocytosis (n=17; 71%), left shift (n=10; 42%), hyperbilirubinaemia (n=10; 40%), hyperkalaemia (n=7; 28%), hypokalaemia (n=9; 36%), total hypercalcaemia (n=8; 32%), ionized hypocalcaemia (n=9; 38%), hyperphosphataemia (n=25; 100%), acidaemia (n=9; 38%), metabolic acidosis (n=10; 42%), and increased anion gap (n=18; 75%) (Table

2). No differences between the groups were found for any of the parameters analysed (Table 2). Urinalysis was available for 22 dogs and revealed proteinuria (n=17; 77%) and renal glucosuria (n=17; 77%).

Abdominal ultrasonography supported the diagnosis of AKI with normal renal architecture, renomegaly, and perirenal effusion. No evidence of chronic kidney disease, pancreatitis or splenic disease was observed.

Cardiac evaluation

At initial physical examination all dogs were considered normovolaemic and a grade II-III left-sided systolic heart murmur was identified in 3 dogs. Thoracic radiographs did not show any abnormal cardiac-related findings. However, 9/19 (47%) dogs with leptospirosis demonstrated evidence of pulmonary haemorrhage with peribronchial cuffing and moderate interstitial to alveolar lung patterns.

Initial echocardiographic examination was performed on all but one dog, considered too unstable to be evaluated. One dog was considered hypovolaemic, based on reduced filling of the left heart, and all others were considered normovolaemic. Valvular insufficiency was observed in 15 dogs (63%), including both atrioventricular valves in 6 dogs (25%), mitral valve alone in 5 dogs (21%), tricuspid and pulmonic valves in 3 dogs (13%), and pulmonic valve alone in 1 dog (4%). All other echocardiographic parameters were within normal limits in all dogs.

Holter monitoring was performed in all 25 dogs at initial evaluation and in 21 dogs surviving for the second evaluation. One recording at the second evaluation contained only 6h of readable data and was excluded. During the first evaluation, VPCs were detected in 20 dogs (80%); 16 dogs (64%) had <100 VPCs/24h (Group 1) and 9 dogs (36%) ≥100 VPCs/24h (Group 2) (Table 3). No other arrhythmias were identified and antiarrhythmic therapy was not considered indicated in any dog. No difference was found between the groups for any of the signalment, disease, clinical or laboratory parameters evaluated (Tables 1 and 2). However, initial cTnI concentration was increased in 23 dogs (92%) and was significantly higher in Group 2 than in Group 1 (Table 3, Figure 1). No correlation was observed between the initial cTnI and creatinine concentrations (r_s=0.229; *P*=0.270).

During the second evaluation, VPCs were detected in 11/20 dogs (55%); 17 dogs (85%) had <100 VPCs/24h and 3 dogs (15%) ≥100 VPCs/24h. The cTnI concentrations were significantly lower compared to the first evaluation (*P*=0.008). No difference was found between groups for both parameters (Table 3).

Treatment and Outcome

Seventeen dogs (68%) required renal replacement therapy, a treatment not associated with a difference in the number of VPCs (*P*=0.192), initial cTnI concentrations (*P*=0.336) or outcome (*P*=0.621).

Twenty dogs (80%) recovered from their disease and were discharged from hospital, 8 dogs with complete and 12 dogs with partial recovery. Of dogs not surviving, 3 were euthanized and 2 died. Main causes of fatal outcome included severe pulmonary haemorrhages (n=2), persistent seizures (n=2), and lack of renal recovery (n=2). Necropsy was performed in 2 dogs and revealed interstitial nephritis and thrombi in multiple organs in one dog and acute tubular necrosis and interstitial nephritis in the other. Both hearts were macroscopically and histologically unremarkable.

Mortality was significantly higher in Group 2 than in Group 1 (*P*=0.04, Figure 2). Although initial cTnI concentrations were higher in dogs that died (median 1.75 ng/ml; range 0.28—47.15) than in survivors (median 0.39 ng/ml; range 0.04—3.07), this difference was not statistically significant (*P*=0.057). Based on ROC curve analysis (Figure 3), the number of VPCs/24h at presentation was predictive of outcome with an AUC of 0.85 (95% CI, 0.65—0.96, *P*<0.001) and a calculated optimal cut-off of 18 VPCs/24h (sensitivity 100%, specificity 70%). Initial cTnI concentrations were also predictive of outcome with an AUC of 0.78 (95% CI, 0.57-0.92, *P*=0.023) and a calculated optimal cut-off of 0.65 ng/ml (sensitivity 80%, specificity 70%).

DISCUSSION

Data from the present study indicate that functional and structural myocardial injuries commonly occur in canine AKI. Although none of the fatalities seemed to be directly cardiac related, increased numbers of VPCs were associated with higher mortality, suggesting an indirect association or a common cause. Disease severity was not obviously different between the groups but the study was not designed and powered to examine this aspect.

188 Previous studies evaluating dogs with non-renal diseases found similar associations between short-
189 time electrocardiography, cTnI, and outcome (Diniz *et al.* 2008, Lobetti *et al.* 2002, Schober *et al.* 2002). To
190 avoid over-interpretation of small numbers of VPCs, a cut-off of 100/24h was used in the present study.
191 Although this is clearly higher than numbers expected in healthy dogs (10 ± 5 VPCs/24h), similar cut-offs
192 (100-150 VPCs/24h) have been used to detect clinically relevant disease in breeds prone to arrhythmias (Hall
193 *et al.* 1991, Olsen *et al.* 1999, Ulloa *et al.* 1995, Wess *et al.* 2010).
194 Valvular insufficiencies were observed in 63% of the dogs from the present study. However, these
195 were minimal and not associated with structural alterations of the heart chambers and were, therefore, not
196 expected to cause relevant myocardial injury (O'Brien *et al.* 2006, Spratt *et al.* 2005). Cardiac changes
197 associated with AKI, including left ventricular hypertrophy in rats (Burchill *et al.* 2008) or impaired systolic
198 function in humans (Bagshaw *et al.* 2013), were not observed in the present study.
199 Acute kidney injury may increase the risk for cardiac injury by inducing pro- and anti-inflammatory
200 cytokines and activating the sympathetic and renin-angiotensin-aldosterone systems (Bagshaw *et al.* 2013).
201 Furthermore, metabolic disturbances characteristic of AKI, including acidaemia, hyperkalaemia,
202 hypocalcaemia, hyperphosphataemia, azotaemia, and anaemia, may have profound effects on myocardial
203 electrical activity and function (Bagshaw *et al.* 2013, Serra *et al.* 2010, Zeidman *et al.* 2004). Although no
204 significant difference was found between groups for any of these parameters in the present study, this could, at
205 least in part, be due to small sample sizes and different pre-referral therapeutic interventions. As population
206 size was designed to address power with regards to the principal aims of the study, further investigations
207 should evaluate the role of these factors in AKI-related myocardial injury. Overzealous fluid therapy has been
208 described to predispose to VPCs and impaired myocardial performance (Bagshaw *et al.* 2013, Ip *et al.* 2011).
209 However, this was unlikely a factor in the present study, based on physical examination, thoracic radiographs
210 and echocardiography.
211 A great number of dogs required renal replacement therapy, and this intervention may increase the
212 risk of hypotension, hypovolaemia and rapid electrolyte and fluid shifts and therefore cause myocardial injury
213 (Selby *et al.* 2007). Haemodiafiltration may further affect cTnI concentrations by partial clearance of this 24-
214 kDa molecule (Tattersall 2007, Wayand *et al.* 2000). However, the short half-life of cTnI (approximately 2h)
215 (Katus *et al.* 1989), the timing of expected increase (4-12h after cardiac injury) (Goldmann *et al.* 2001), and

the timing of blood sampling (prior to the first treatment and ≥4d after the last treatment) make it unlikely that dialysis affected cTnI concentrations in the present study (Assa *et al.* 2013, Deleaval *et al.* 2006, Farkouh *et al.* 2003, Tun *et al.* 1998).

Decreased renal clearance has also been suggested to increase cTnI concentrations. However, the absence of correlation between azotaemia and cTnI in the present study suggests that this did not play a major role in cTnI elevations, paralleling results from other studies (Ellis *et al.* 2001, Mastrorilli *et al.* 2007, Porciello *et al.* 2008, Van Lente *et al.* 1999). Based on these considerations, data in the present study support the hypothesis of a real and severe myocardial injury associated with canine AKI (Gallegos *et al.* 2004, Ricchiuti *et al.* 1998).

Leptospirosis has been shown to affect the cardiovascular system and has been associated with arrhythmias, increased cTnI concentrations, and myo-, endo-, or pericarditis (Mastrorilli *et al.* 2007, Skerk *et al.* 2011). Given that 76% of the dogs in the present study were diagnosed with leptospirosis, the extent to which myocardial injury was due to AKI itself or due to leptospirosis remains unclear.

In conclusion, the results of the present study confirm our hypotheses that AKI is associated with cardiac arrhythmias and substantial but reversible myocardial injury. The worse outcome for affected animals is likely multifactorial and may result from higher disease severity, but this could not be substantiated in the present study. Further studies focusing on the inflammatory and the neuro-endocrine status of canine AKI are necessary to evaluate more precisely the possible pathophysiologic processes responsible for these cardiorenal effects.

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352 **Figure legends**

353

354 **Figure 1**. Bar chart showing the median (95% confidence intervals) for cTnI concentrations in the 2 groups of

355 dogs: group 1, 16 dogs with AKI and <100 VPCs/24h; group 2, 9 dogs with AKI and ≥100 VPCs/24h.

356

357 **Figure 2**. Frequency chart showing outcome in the 2 groups of dogs: group 1, 16 dogs with AKI and <100

358 VPCs/24h; group 2, 9 dogs with AKI and ≥100 VPCs/24h.

359

360 **Figure 3**. ROC curves representing the predictive value of the parameters VPCs (AUC 0.85) and cTnI (AUC

361 0.78) on outcome for dogs with AKI.

Table 1. Clinical data in dogs with acute kidney injury and <100 VPCs/24h (Group 1) or ≥100 VPCs/24h (Group 2).

Variable		All dogs (n=25)	Group 1 (n=16)	Group 2 (n=9)	*P-value*
Gender	Male [n (%)] Female [n (%)]	16 (64%) 9 (36%)	10 (63%) 6 (37%)	6 (67%) 3 (33%)	1.000
Body weight, kg [median (range)]		25.1 (7.2—57.0)	21.5 (7.2—57.0)	26.3 (11.8—47.6)	0.396
Age, years [median (range)]		6.7 (0.3—13.5)	5.6 (0.3—13.5)	8.5 (0.4—12.1)	0.536
Leptospirosis [n (%)]		19 (76%)	13 (81%)	6 (67%)	0.630
Pulmonary haemorrhage [n (%)]		9 (36%)	5 (31%)	4 (44%)	0.671
Renal replacement therapy [n (%)]		16 (64%)	9 (56%)	7 (78%)	0.401
Survival at 90 days [n (%)]		20 (80%)	15 (94%)	5 (56%)	**0.040**

VPCs ventricular premature complexes.

Table 2. Median (25^{th}-75^{th} percentile) of laboratory data in dogs with acute kidney injury and <100 VPCs/24h (Group 1) or ≥100 VPCs/24h (Group 2).

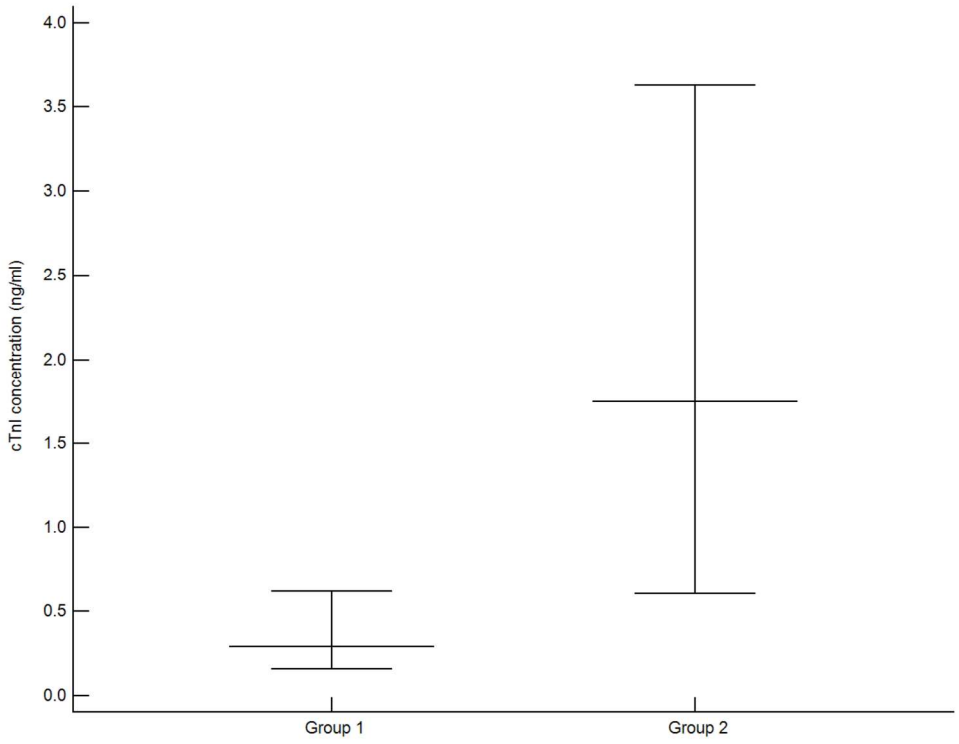
Parameter	**All dogs** (n=25)	**Group 1** (n=16)	**Group 2** (n=9)	***P*-value**
Hematocrit (L/L)	0.39 (0.33—0.44)	0.39 (0.34—0.43)	0.36 (0.32—0.47)	0.909
WBC ($x10^9$/L)	14.22 (11.57—21.59)	13.66 (11.55—20.67)	15.68 (12.85—21.18)	0.387
Creatinine (µmol/L)	748 (492—1082)	704 (463—1095)	892 (548—1069)	0.711
Urea (mmol/L)	57.69 (42.63—62.71)	47.00 (40.26—61.33)	59.54 (53.82—66.62)	0.428
Na (mmol/L)	145 (143—148)	144 (142—148)	147 (143—149)	0.410
K (mmol/L)	4.61 (3.96—5.6)	4.58 (4.03—5.49)	5.18 (3.93—5.60)	0.737
P (mmol/L)	4.27 (2.69—6.03)	4.32 (2.42—5.60)	4.09 (3.36—6.45)	0.692
Total Ca (mmol/L)	2.62 (2.31—2.89)	2.52 (2.20—2.87)	2.71 (2.56—3.03)	0.174
Ionized Ca (mmol/L)	1.14 (1.03—1.24)	1.16 (1.02—1.26)	1.09 (1.04—1.21)	0.788
pH	7.34 (7.29—7.37)	7.36 (7.31—7.37)	7.31 (7.29—7.34)	0.144
HCO_3^- (mmol/L)	19.0 (17.1—21.6)	19.6 (18.0—21.7)	17.5 (16.6—19.7)	0.449
PCO_2 (mmHg)	36.2 (34.9—40.0)	36.3 (35.2—39.1)	35.5 (33.5—40.8)	0.644

VPCs ventricular premature complexes, WBC white blood cell count.

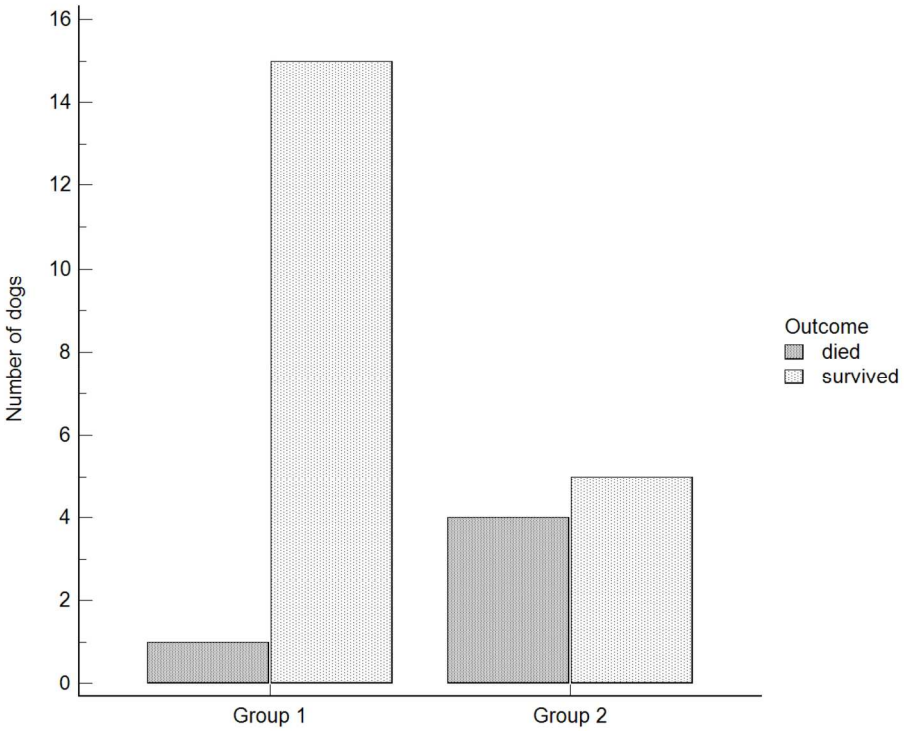
Table 3. Concentrations of cTnI and 24h-Holter monitoring in dogs with acute kidney injury and <100 VPCs/24h (Group 1) or ≥100 VPCs/24h (Group 2) at initial examination

Time	Parameter	All dogs	Group 1	Group 2	*P-value*
T0	Number of dogs (n)	25	16	9	
	VPCs/24h [median, (IQR)]	17 (2—321)	5 (0—14)	711 (304—3183)	
	cTnI, ng/mL [(median (IQR)]	0.59 (0.19—1.81)	0.29 (0.16—0.63)	1.75 (0.68—3.23)	**0.005**
	cTnI >reference [n (%)]	23 (92%)	14 (88%)	9 (100%)	0.520
T1	Number of dogs (n)	21*	14	7*	
	VPCs/24h [median, (IQR)]	1 (0—50)	1 (0—17)	42 (0—854)	0.495
	<100 VPCs/24h [n (%)] ≥100 VPCs/24h [n (%)]	17 (85%) 3 (15%)	13 (93%) 1 (7%)	4 (67%) 2 (33%)	0.202
	cTnI, ng/mL [(median (IQR)]	0.22 (0.05—0.52)	0.12 (0.04—0.31)	0.23 (0.10—1.54)	0.168
	cTnI >reference [n (%)]	14 (67%)	8 (57%)	6 (86%)	0.337

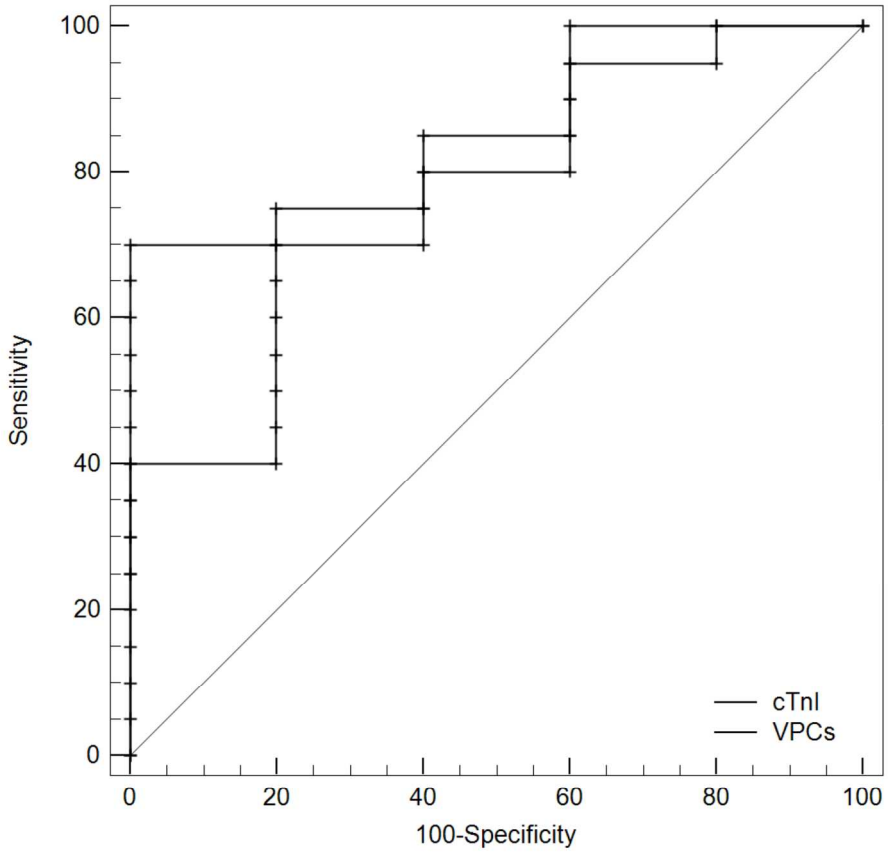
* Holter data missing due to incomplete recordings in 1 dog, cTnI cardiac troponin I, IQR interquartile range, T0 initial examination, T1 follow-up examination, VPCs ventricular premature complexes.



Bar chart showing the median (95% confidence intervals) for cTnI concentrations in the 2 groups of dogs: group 1, 16 dogs with AKI and <100 VPCs/24h; group 2, 9 dogs with AKI and ≥100 VPCs/24h.
221x177mm (300 x 300 DPI)



Frequency chart showing outcome in the 2 groups of dogs: group 1, 16 dogs with AKI and <100 VPCs/24h; group 2, 9 dogs with AKI and ≥100 VPCs/24h.
214x173mm (300 x 300 DPI)



ROC curves representing the predictive value of the parameters VPCs (AUC 0.85) and cTnI (AUC 0.78) on outcome for dogs with AKI.
196x180mm (300 x 300 DPI)