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Continuous Renal Replacement Therapy: Application of Kidney Disease Improving Global Outcomes Guidelines for Treatment Prescription in Dogs With Acute Kidney Injury and Outcome Prediction

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ABSTRACT

Background: Continuous renal replacement therapy (CRRT) is routinely used in human patients with acute kidney injury (AKI) but studies in dogs are scarce.

Objective: To describe CRRT in dogs and assess the utility of a previously validated scoring system for dogs with AKI undergoing hemodialysis, and the Acute Patient Physiological and Laboratory Evaluation ($APPLE_{Full}$/$APPLE_{Fast}$) scores, for outcome prediction.

Animals: Thirty, client-owned dogs.

Methods: Cases were retrospectively reviewed. Prognostic scores were calculated upon admission and before CRRT initiation. The CRRT effluent dose followed the KDIGO guidelines. Receiver operating characteristic curves (ROCC) were constructed to evaluate the prognostic utility of these scores.

Results: Median (IQR) serum creatinine (mg/dL) at CRRT initiation, at discharge, and 3 months after discharge were 9.4 (7.4), 3.4 (1), and 1.3 (0.3) respectively. Median (IQR) treatment duration and total number of treatments were 24 (18.5) h and 2 (2) treatments, respectively. The prescribed median (IQR) CRRT effluent dose was 29 (18.5) mL/kg/h. Median (IQR) overall time-average concentration for urea and creatinine were 92 (60) mg/dL and 3.7 (1.7) mg/dL, respectively. The normalized weekly median (IQR) standardized Kt/V was 2.41 (2.29). Eleven dogs (37%) survived to discharge/3-months after treatment. Areas under the ROCC for the $APPLE_{Full}$/$APPLE_{Fast}$ scores before CRRT initiation were 0.99 (95% CI, 0.99–1.00) and 0.91 (95% CI, 0.81–1.00), respectively. Optimal cutoff points were <35 for the $APPLE_{Full}$ and <23 for the $APPLE_{Fast}$, yielding sensitivities/specificities of 100% (95% CI, 74.12%–100.0%)/94.7% (95% CI, 75.36%–99.73%) and 90.9% (95% CI, 62.26%–99.53%)/78.95% (95% CI, 56.67%–91.49%), respectively.

Conclusion: The APPLE scores, unlike clinicopathological findings or the Segev score, proved to be a highly discriminatory prognostic tool. Additionally, the human-derived, KDIGO guideline-based CRRT protocol proved safe and efficacious in dogs undergoing CRRT.

Abbreviations: 95% CI, 95% confidence interval; AKI, acute kidney injury; APPLE, Acute Patient Physiologic and Laboratory Evaluation score; AUROCC, area under the receiver operating characteristic curve; CRRT, Continuous Renal Replacement Therapy; IHD, intermittent hemodialysis; IQR, interquartile range; KDIGO, Kidney Disease Improving Global Outcomes; ROCC, receiver operating characteristic curve; RRT, renal replacement therapy; SIRS, systemic inflammatory response syndrome; spKt/V, single-pool Kt/V; stdKt/V, standardized Kt/V; TAC, Time-averaged concentration.

1 | Introduction

Acute kidney injury (AKI) is associated with high morbidity and case fatality rate [1–3]. It often engenders severe metabolic derangements, might lead to multi-organ dysfunction, and requires urgent intervention. When standard treatments fail, renal replacement therapy (RRT) provides critical support for managing AKI in dogs [4–7]. Intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT) are the two main RRT modalities in human patients with severe AKI. The former often involves short-duration treatments performed over several days a week and is associated with rapid solute and fluid removal, thereby potentially increasing hemodynamic instability. The latter, conversely, entails slower, continuous treatment, which often exceeds 24 h, and mitigates the risks of dialysis disequilibrium or the deleterious consequences of rapid fluid and solute removal [5–8]. According to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, CRRT is suggested over IHD for hemodynamically unstable patients and for those with acute brain injury, increased intracranial pressure, or generalized brain edema. However, studies in humans report similar survival rates with either modality, even for hemodynamically unstable patients with AKI [9, 10].

Due to financial and staffing constraints, IHD and prolonged intermittent RRT are preferred in some veterinary facilities. However, because prolonged intermittent RRT and CRRT are technically easier to operate and do not require the specialized water purification systems needed for IHD, they have gained popularity in veterinary intensive care units in recent years. However, standardized protocols and further research are needed to optimize their use in dogs [6, 7].

Illness severity scores, such as the Acute Patient Physiologic and Laboratory Evaluation (APPLE) score, aid in standardizing disease severity among dogs and can be used for prognostication purposes. Two such scoring systems, the $APPLE_{Fast}$ for rapid bedside assessment and the $APPLE_{Full}$ for comprehensive evaluation, can guide treatment decisions and predict survival in critically ill dogs [11]. Their prognostic utility in dogs with AKI undergoing CRRT has yet to be determined.

The objectives of this study were to evaluate the clinical utility of the $APPLE_{Fast}$ and $APPLE_{Full}$ scores for outcome prediction in dogs undergoing CRRT and compare their performance to a previously validated scoring system for dogs with AKI undergoing RRT, established by Segev et al. (model B score) [3, 12, 13]. Additionally, we sought to investigate associations between clinical and laboratory measures and survival and to describe the management of dogs with AKI undergoing CRRT, adopting protocols derived from guidelines for CRRT in humans.

2 | Materials & Methods

2.1 | Study Design and Data Collection

Dogs diagnosed with AKI or acute-on-chronic kidney disease and treated with CRRT between 2021 and 2023 were retrieved retrospectively. Additional inclusion criteria required complete documentation of physical examination findings, ultrasound evaluation, and CRRT prescription details. Survival to discharge, in addition to 1-month and 3-month, post-discharge survival were used as outcome measures.

Grading of AKI was conducted according to International Renal Interest Society guidelines [14]. The $APPLE_{Fast}$, $APPLE_{Full}$ [11], and model B [3] scores were calculated, as previously described, upon admission and with $APPLE_{Fast}$ and $APPLE_{Full}$ also before CRRT initiation.

Environmental causes of AKI, including heatstroke and snakebite, were diagnosed based on history and characteristic clinical and laboratory findings [15, 16]. Systemic inflammatory response syndrome (SIRS) was identified based on clinical signs and laboratory findings, including fever/hypothermia, tachycardia, tachypnea, leukocytosis, or leukopenia [17]. Infection and sepsis were confirmed by fine needle aspiration and culture of infected organs (orchitis/septic arthritis), and pyelonephritis by ultrasonographic evidence of pyelectasis, with urinary infection (urinalysis and culture) [18, 19]. Hemoabdomen was diagnosed by abdominocentesis and the presence of sanguineous, nonclotting peritoneal fluid and large numbers of erythrocytes cytologically, with a packed cell volume > 5% [20], while splenic torsion was diagnosed sonographically, with the diagnosis confirmed via direct visualization at the time of laparotomy [21]. Hematologic disorders (thrombocytopenia/pancytopenia) were identified by CBC and accompanying blood smear. Idiopathic non-immune-mediated hemolysis and exertional hemolysis were identified based on a history of recent physical activity and the presence of anemia, mild bilirubinemia, hemoglobinemia, and hemoglobinuria. Diagnosis was supported by the absence of spherocytes on peripheral blood smear and a negative saline agglutination test [22, 23]. Pancreatitis was diagnosed based on a positive SNAP cPLI test (IDEXX Laboratories, Westbrook, ME, USA) and/or supportive ultrasonographic findings. These findings included pancreatic enlargement, hypoechoic parenchyma (focal or diffuse), hyperechoic surrounding mesenteric fat, peripancreatic fluid accumulation, evidence of extrahepatic biliary duct obstruction, or a combination thereof [24].

2.2 | CRRT Delivery

Delivery of CRRT was performed using the Prismaflex CRRT System (Prismaflex CRRT System; Baxter Healthcare Corp., Deerfield, IL, USA) with polyarylethersulfone or AN69 hemofilters (Prismaflex HF20, ST60, ST100, ST150; Baxter Healthcare Corp., Deerfield, IL, USA). The blood access lines and dialyzers were primed immediately before use with 0.9% saline containing 5000 U of unfractionated heparin (TEVA LTD, Israel) per liter. For cases where the extracorporeal circuit volume exceeded 20% of the dog's blood volume or the hematocrit was < 20%, packed red blood cells were used to prime the circuit [25].

A bicarbonate-based solution was used as both the dialysate and replacement fluid for convection. Hemosol B0 solution (Gambro, Baxter International, Deerfield, IL, USA.) was used, with the following final composition: $Na^+ = 140$ mEq/L; $K^+ = 0$ mEq/L; $HCO_3^- = 32$ mEq/L; $Ca^{2+} = 1.75$ mEq/L; $Mg^{2+} = 0.5$ mEq/L; $Cl^- = 109.5$ mEq/L; and lactate 3 meq/L. Additives such as potassium or sodium were included as necessary based on the dog's electrolyte and acid–base status.

Blood flow rate was adjusted incrementally (1–50 mL/min based on the dog's weight) over 10–15 min, targeting the maximum tolerated level. Filtration fraction was maintained below 25% to minimize hemoconcentration and clotting risks [26].

2.3 | Vascular Access

Vascular access was achieved using the modified Seldinger technique. Double-lumen dialysis catheters (GAMCATH Short-Term Catheters, Deerfield, IL, USA) were placed percutaneously under general anesthesia into the jugular vein through a venotomy. The catheters were used exclusively for dialysis and handled aseptically by dialysis personnel. To prevent clotting, 100–5000 U/mL [27] unfractionated heparin was instilled into each catheter lumen between dialysis treatments.

2.4 | Dialysis Prescription

A CRRT session was defined as a treatment period lasting ≥ 24 h. The initiation of CRRT was prompted by the failure of medical therapy to manage life-threatening complications of uremia, guided by criteria such as severe fluid overload with low urine output, progressive azotemia, oliguria or anuria, and azotemia with uncontrolled electrolyte derangements and/or clinical signs [5, 7, 28, 29]. Although the protocol aimed to deliver continuous, uninterrupted therapy, technical issues (e.g., filter clotting) sometimes resulted in shorter sessions (minimum 2 h). Conversely, when runs proceeded without interruption, circuits were maintained for up to 124 h before elective disconnection. The decision to initiate subsequent sessions was based on clinical evaluation. In anuric or oliguric dogs with persistent azotemia (serum creatinine > 2 mg/dL), treatment was resumed within 12 h if the previous session had been prematurely interrupted. In contrast, in urine-producing dogs with normalized hydration and electrolyte concentrations, CRRT was typically resumed after 24–48 h with a median interdialytic period of 12 h across all sessions.

Adhering to KDIGO guidelines, CRRT dosing targeted an effluent flow rate of 20–25 mL/kg/h [28]. To accommodate therapy interruptions, a prescribed effluent dose of 30 mL/kg/h was implemented. In hypercatabolic conditions such as heatstroke and sepsis, higher doses were prescribed with close monitoring to avoid complications like dialysis disequilibrium [6, 28, 30].

The therapeutic objective was to restore urine output, correct overhydration, normalize blood gas and electrolyte derangements, and reduce serum creatinine to < 2 mg/dL. The expected standardized Kt/V (stdKt/V) per 24-h session was approximately 1.2 in dogs with uncomplicated AKI (equivalent to 30 mL/kg/h effluent dose), and stdKt/V of 2.0–2.8 (equivalent to 50–70 mL/kg/h effluent dose) in hypercatabolic states. In these cases, the dose was gradually increased every 8–12 h to allow for progressive solute clearance and to minimize the risk of dialysis disequilibrium [31–33].

The time-averaged concentration (TAC) for urea and creatinine was calculated using the trapezoidal rule, incorporating both the intradialytic period and the subsequent interdialytic interval for each session. Guidelines for dialysis dose assessment, including the examined variables and calculations thereof, can be found in Appendix A.

Anticoagulation strategies were tailored based on the dog's coagulation profile, as previously described: [28, 29, 34, 35] (1) nonheparin in cases of significant coagulopathies (prothrombin time/partial thromboplastin time > 25% above reference range or a platelet count < 30 000/μL); (2) minimal unfractionated heparin (5–10 U/kg/h) for mild coagulopathies (prothrombin time/partial thromboplastin time < 25% above reference range or a platelet count < 100 000/μL), with activated clotting time maintained below 180 seconds; (3) standard unfractionated heparin for cases without coagulopathies, administered first as a bolus (10–50 U/kg), followed by a constant rate infusion (20–50 U/kg/h) targeting an activated clotting time of 180–250 s. Heparin was immediately discontinued when bleeding occurred.

2.5 | Monitoring

Vital signs, including heart rate, respiratory rate, rectal temperature, and blood pressure, were recorded every 2–4 h. Blood gas analyses (including venous pH, HCO_3^-, lactate, and ionized calcium concentration) were performed at similar intervals. Serum creatinine was measured every 12 h, while CBC and chemistry analyses were performed before and after each session for most cases, either immediately after unplanned terminations or within 5 min of planned cessation. Pulse oximetry and ECG monitoring were documented as clinically indicated.

2.6 | Statistical Analyses

Continuous variables were described as medians and interquartile ranges (IQR), and the non-parametric Mann–Whitney U-test was used to compare continuous variables between 2 outcome groups. The Fisher's exact test was applied for testing associations between categorical variables. Receiver operating characteristic curves (ROCC) were constructed to evaluate the $APPLE_{Full}$/$APPLE_{Fast}$ and model B scores as predictors of survival. The maximal point of Youden's index (Sen-[1-Spec]) was used as the optimal cutoff value for ROCC analyses. All tests were 2-tailed, and $p < 0.0016$ was considered significant after Bonferroni correction for multiple comparisons. Statistical analyses were performed using a statistical software package (GraphPad Prism [version 10.2.3 for Windows, San Diego, California]).

3 | Results

3.1 | Study Group Demographics and Clinical Signs

Thirty dogs (63% females [53% neutered] and 37% males [17% neutered]) with a median (IQR) age of 66 (71.5) months were included in the study. Mixed-breed dogs accounted for 37% of the cases, followed by Golden retrievers (10%) and 16 additional breeds comprising 1 dog each.

Of the cases included, 27 were diagnosed with AKI, and 3 with acute-on-chronic kidney disease. Presumptive etiologies were identified in 67% of the dogs, including heatstroke (5/30), snakebite, trauma, pyelonephritis and hemolysis (2/30 for each etiology), and orchitis, septic arthritis, hemoabdomen (post-spaying), splenic torsion, pancytopenia, pancreatitis and idiopathic hepatic injury comprising 1 dog each.

Median (IQR) time from onset of clinical signs to presentation was 3 (3.75) days. Clinical signs at presentation included decreased appetite (60%), vomiting (57%), diarrhea (43%), and melena/hematochezia (30%). Before commencement of CRRT, anuria or oliguria was present in 70% of the dogs but did not correlate with survival ($p = 0.37$). Additionally, before initiation of CRRT, 13 dogs (43%) were overhydrated, 10 dogs (33%) required vasopressors, 4 dogs (13%) were mechanically ventilated, and 1 dog received oxygen support with humidified oxygen therapy.

3.2 | AKI Grading

Pre-treatment AKI grades were distributed as follows: Grade 1 in 3% of the dogs, Grade 3 in 13%, Grade 4 in 33%, and Grade 5 in 50%, with a median (IQR) pre-treatment creatinine concentration of 9.4 (7.4) mg/dL. Eight dogs (26.7%) developed AKI during hospitalization secondary to underlying conditions. One dog with IRIS AKI grade 1 underwent CRRT due to 20% fluid overload, anuria, and a rise in serum creatinine from 0.6 to 1.4 mg/dL after trauma and subsequent surgery for bilateral hip luxation. Despite initiating treatment, the dog died approximately 12 h into the first CRRT session. No ultrafiltration was possible due to persistent hypotension.

3.3 | Continuous RRT Prescription

A total of 74 CRRT sessions were administered to 30 dogs, with each dog undergoing between 1 and 7 sessions. Median (IQR) CRRT session duration and total number of sessions per dog were 24 (18.5) h and 2 (2), respectively. Ultrafiltration rate was guided by the degree of overhydration and tailored to remove fluid as rapidly as the dog could tolerate hemodynamically, without exceeding 10 mL/kg/h [36]. Hypovolemia was monitored using central venous oxygen saturation (> 70% via blood gas), rising PCV/TS and heart rate, and decreasing arterial blood pressure. Median (IQR) overall TAC urea and creatinine were 92.4 (60.46) mg/dL and 3.70 (1.66) mg/dL, respectively. The normalized weekly median (IQR) stdKt/V was 2.41 (2.29) [33]. Detailed treatment metrics, including effluent dose, total effluent volume, single-pool Kt/V (spKt/V) per session, normalized daily stdKt/V, TAC_{crea}, TAC_{urea}, overall URR and CrRR, hourly URR and CrRR, blood flow rate, pre-filter replacement rate, post-filter replacement rate, and ultrafiltration rate, are summarized in Table 1. All corresponding equations and calculation methods are provided in Appendix A.

In six cases where the extracorporeal circuit volume exceeded 20% of the dog's blood volume or the hematocrit was < 20% (17 cases), packed red blood cells were used to prime the circuit. Blood transfusions were required in 23 out of 30 dogs, while fresh frozen plasma transfusions were administered in 17 out of 30 dogs. These transfusions were provided before, during, or after CRRT as needed to manage bleeding diathesis or hypoalbuminemia.

Ten dogs were initiated on CRRT within the first 24 h of admission, while the remaining 20 dogs started CRRT later during hospitalization. Median (IQR) time from hospital admission to CRRT initiation was 39 (48) h. Median (IQR) difference (the median increase) between serum creatinine immediately before CRRT initiation and upon admission was 2.9 (3.39) mg/dL. Further information regarding pertinent chemistry and blood gas variables recorded before and after each CRRT session is summarized in Table 2.

3.4 | Adverse Effects

Adverse events that occurred during CRRT or shortly thereafter, and were potentially attributable to therapy, were observed in all 30 dogs. Common adverse events included anemia (73%), hypothermia (70%), hypotension (60%), hyponatremia (37%), thrombocytopenia (37%), alkalosis (30%), and fever/hyperthermia (30%). Less common adverse effects included hypercapnia (27%), melena (27%), shivering (23%), vomiting (20%), carboxyhemoglobinemia (20%), leukocytosis (20%) and hypertension (17%). Rare adverse events included catheter bleeding (13%), severe bleeding (rapid loss of a large volume of blood that necessitated the urgent administration of blood transfusion to stabilize the patient; 13%), catheter infection (7%), and itching at catheter insertion site (7%). Alarm-related complications during CRRT (per dog) were commonly observed, including low arterial pressure (access line; 80%), filter clotting (67%), inability to detect return flow (37%), high venous pressure (return line; 30%), fluid balance error (13%), air in the circuit (10%), and no communication errors (7%). There was no statistically significant difference in the prevalence of any of these complications between survivors and non-survivors.

3.5 | Outcome Prediction and Associations With Laboratory Analytes

Several potential associations between survival and clinical signs, laboratory test results, and the APPLE scores and model B were explored. Statistically significant differences between survivors and non-survivors were found with the $APPLE_{Fast}$ and $APPLE_{Full}$ scores at admission and before CRRT, total calcium and phosphate concentrations upon admission, and bilirubin, phosphate, and albumin concentrations before CRRT. However, barring the $APPLE_{Fast}$/$APPLE_{Full}$ scores, statistical significance was lost after adjusting for multiple comparisons (Table 3). All dogs with APPLE mentation scores of 3 or 4 died.

The AUROCC for the $APPLE_{Fast}$/$APPLE_{Full}$ scores as outcome predictors at admission were 0.88 (95% CI, 0.76–1.00) and 0.89 (95% CI, 0.78–1.00). The AUROCC for the $APPLE_{Fast}$/$APPLE_{Full}$ scores as outcome predictors before CRRT initiation were 0.91 (95% CI, 0.81–1.00) and 0.99 (95% CI, 0.99–1.00; Figure 1).

TABLE 1 | Detailed continuous renal replacement therapy (CRRT) metrics across 7 sessions of treatment in dogs with acute kidney injury.

CRRT session[a]	1st	2nd	3rd	4th	5th	6th	7th[b]
spKt/V	1.23 (2.24)	1.72 (3.11)	1.30 (1.38)	2.23 (0.77)	1.60 (2.12)	3.26 (2.69)	0.33 (0)
stdKt/V	1.23 (0.29)	1.25 (0.41)	1.13 (0.11)	1.61 (0.15)	1.61 (1.31)	2.01 (0.89)	4 (0)
TAC_{urea} (mg/dL)	165.85 (116.63)	62.77 (65.65)	70.27 (25.27)	70.97 (27.82)	47.97 (13.73)	55.90 (36.64)	132.68 (0)
TAC_{crea} (mg/dL)	5.75 (3.45)	2.95 (1.70)	2.70 (1.80)	2.45 (0.21)	2.83 (1.42)	3.85 (1.42)	3.85 (0)
URR[c] (%)	67.47 (25.53)	60 (20.24)	61.21 (32.03)	46.66 (28.12)	67.70 (0.78)	60.96 (23.65)	69.47 (0)
Hourly URR (%)	2.06 (1.72)	1.9 (2.80)	2.03 (2.3)	2.14 (0.50)	2.8 (0.03)	2.43 (0.67)	34.73 (0)
CrRR (%)	77.5 (23.90)	60 (39.65)	50 (33.25)	60.52 (17.72)	76.06 (9.4)	58.83 (24.72)	87.53 (0)
Hourly CrRR (%)	2.33 (2.28)	2.46 (2.83)	1.63 (1.62)	2.23 (0.63)	3.16 (0.39)	2.29 (0.55)	40.76 (0)
Total effluent volume (mL)	20886 (36463)	23616 (46776)	21555 (21267)	22320 (15216)	18506.40 (6591)	18619.2 (7819)	5820 (0)
Q_E (mL/kg/h)	31 (3)	32 (12)	30 (5)	32 (19)	38 (39)	56 (26)	97 (0)
Td (h)	24 (24)	24 (22)	24 (22)	28 (19)	24 (24)	30 (18)	2 (0)
Ti (hr)	0 (8)	12 (4)	12 (12)	8 (2)	36 (12)	24 (0)	—
Q_B (mL/min)	110 (65)	120 (75)	100 (70)	115 (60)	100 (20)	90 (0)	150 (0)
Q_D (mL/kg/h)	12.5 (1.5)	14.58 (1.5)	20.8 (4.5)	19.6 (2.5)	25 (2.5)	16.7 (1.5)	1500 (0)
Q_R^{pre} (mL/kg/h)	12.5 (4)	12.5 (2.5)	4.17 (1.5)	7.14 (1.5)	10.42 (1.5)	5.5 (1.5)	0 (0)
Q_R^{post} (mL/kg/h)	7.3 (1.5)	4.3(0.8)	8.3 (2.5)	2.7 (0.8)	0 (0)	1.3 (0.5)	0 (0)
Q_{UF} (mL/kg/h)	0 (1.96)	0.41 (1.38)	0 (1.26)	0 (0.5)	0 (1.83)	0 (0)	0 (0)

Abbreviations: Q_B, Blood flow rate; Q_D, Dialysate flow rate; Q_E, Effluent dose; Q_R^{post}, post-filter replacement rate; Q_R^{pre}, pre-filter replacement Rate; Q_{UF}, ultrafiltration rate; spKt/V, single-pool Kt/V; stdKt/V, daily standardized Kt/V; TAC_{crea}, time-averaged concentration creatinine -calculated per session and includes both the intradialytic treatment period and the following interdialytic interval.; TAC_{urea}, time-averaged concentration urea; Td, Td: duration of the dialysis session (intradialytic period)Ti, duration of the interval between dialysis sessions (interdialytic period); URR, Urea reduction ratio.

[a]Values are presented as medians (interquartile ranges).

[b]Session 7 was performed in a large dog with AKI and pre-existing CKD and intended as a short, high-efficiency prolonged intermittent renal replacement therapy session. This session yielded a substantially higher hourly URR of 34.7% but was unintentionally interrupted due to filter clotting. The dog remained dialysis-free for 3 months post-treatment but was ultimately euthanized due to progressive azotemia.

[c]In cases where BUN values exceeded the laboratory detection threshold (> 130 mg/dL), a value of 130 mg/dL was used for consistency, unless an exact value was provided.

The optimal cutoff points of the $APPLE_{Fast}$/$APPLE_{Full}$ scores at admission, with their corresponding sensitivity/specificity, were < 23.5 (sensitivity: 100% [95% CI, 74.12% to 100.0%]; specificity: 63% [95% CI, 41.04% to 80.85%]) and < 33.5 (sensitivity: 100% [95% CI, 74.12% to 100.00]; specificity: 68.4% [95% CI, 46.01% to 84.64%]), respectively. The optimal cutoff points of the $APPLE_{Fast}$/$APPLE_{Full}$ scores before CRRT initiation, with their corresponding sensitivity/specificity, were < 23 (sensitivity: 90.9% [95% CI, 62.26% to 99.53%]; specificity: 78.9% [95% CI, 56.67% to 91.49%]) and < 35 (sensitivity: 100% [95% CI, 74.12% to 100.0%]; specificity: 94.7% [95% CI, 75.36% to 99.73%]), respectively.

Model B did not differentiate survivors from non-survivors ($p = 0.26$), with an AUROCC of 0.62 (95% CI, 0.40–0.84).

Eleven dogs (37%) survived to discharge and were alive at 1- and 3-months post-discharge. Overall, 4 dogs died while on CRRT, and 4 dogs were euthanized owing to lack of improvement, and after their owners had declined the transition to IHD. Among survivors, median (IQR) serum creatinine concentration (mg/dL) at discharge and at 1- and 3 months after discharge was 3.4 (1), 1.5 (1) and 1.3 (0.3), respectively.

4 | Discussion

In the present study, APPLE scores demonstrated excellent performance in distinguishing survivors from non-survivors among critically ill dogs with AKI, undergoing CRRT. Conversely, neither model B, hitherto considered a good discriminatory model in dogs with AKI [3, 12, 13], nor conventional laboratory tests proved useful for outcome prediction. Additionally, the results demonstrate the feasibility and efficacy of applying KDIGO guidelines for CRRT in dogs, with comparable results to previous studies.

The increased interest in RRT in veterinary medicine has shifted dialysis from being solely the domain of nephrologists to a growing interest among critical care specialists. This shift has been prompted by a concurrent shift from traditional intermittent extracorporeal methods toward continuous modalities, which are increasingly favored in critically ill humans and animals which might not tolerate the physiological and hemodynamic challenges associated with IHD [6–10]. Portable and user-friendly CRRT machines eliminate the need for costly and high maintenance water purification systems required for IHD. Their accessibility allows bedside treatment

TABLE 2 | Selected laboratory variables in dogs with acute kidney injury, before and after each continuous renal replacement therapy (CRRT) session.

CRRT session[a]	Number of dogs	sCr (mg/dL)		BUN (mg/dL)		pH		Na^+ (mmol/L)		K^+ (mmol/L)	
		Before	After	Before	After	Before	After	Before	After	Before	After
1	30	9.4 (7.5)	2.25 (1.6)	121 (45)	64 (55)	7.31 (0.15)	7.38 (0.11)	135 (10)	133 (4)	4.1 (0.9)	4.2 (0.6)
2	19	4.6 (2.5)	2.4 (1.5)	59 (19)	31	7.42 (0.08)	7.45 (0.07)	133 (6)	136 (7)	4.3 (0.9)	4.1 (0.4)
3	13	4.5 (4.9)	2.5 (1)	83 (43)	47 (20)	7.39 (0.04)	7.44 (0.14)	136 (5)	136 (4)	4.5 (1.3)	4.1 (0.9)
4	6	7.6 (2.6)	2.4 (0.7)	108 (12)	30 (36)	7.4 (0.17)	7.46 (0.01)	133 (11)	138 (4)	4.4 (0.6)	4.7 (0.9)
5	3	11.9 (0.2)	2.9 (1.2)	73 (30)	23 (10)	7.39 (0.02)	7.42 (0.04)	137 (8)	137 (3)	5.7 (0.9)	4.6 (0.7)
6	2	7.9 (0.6)	3.4 (2.2)	67 (20)	32 (11)	7.42 (0.02)	7.45 (0.05)	138 (4)	143 (2)	6.1 (1)	4.3 (0.2)
7	1	13 (0)	2.4 (0)	95 (0)	29 (0)	7.4 (0)	7.42 (0)	142 (0)	140 (0)	4.4 (0)	4 (0)

Abbreviations: BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; sCr, serum creatinine.
[a]Values are presented as medians (interquartile ranges).

in intensive care units without requiring dedicated space. By utilizing convection-based clearance mechanisms, these modalities may be particularly valuable for managing critically ill dogs with AKI and inflammatory or infectious diseases (e.g., SIRS and sepsis) [6–8, 29].

The present study represented one of the first applications of KDIGO guidelines for CRRT in dogs, providing a framework for standardized therapy. By prescribing effluent doses of 20–25 mL/kg/h and adjusting to 30 mL/kg/h to account for therapy interruptions, this protocol ensured effective solute clearance while minimizing complications [28]. This approach supports the feasibility and benefits of aligning veterinary practices with established human protocols, paving the way for advanced care and consistency in managing AKI in dogs.

To evaluate CRRT adequacy and enable comparison across dialysis modalities, we calculated overall and hourly URR, CrRR, stdKt/V, spKt/V, TAC_{urea}, and TAC_{crea}. In the present study, the median (IQR) overall (all sessions included) TAC_{urea} was 92.40 (60.46) mg/dL, aligning with veterinary IHD studies that support a TAC_{urea} below 128 mg/dL to optimize clinical outcomes [37]. Similarly, human studies link time-averaged urea $\leq$96.3 mg/dL in CRRT with improved survival [38]. These findings support the adequacy of solute control achieved with the studied CRRT protocol herein. While URR is commonly used in IHD, it is less reliable in CRRT due to first-order kinetics, where solute removal declines as concentrations fall. Effluent-based dosing remains the cornerstone of CRRT prescription in humans, but actual solute clearance can vary under clinical conditions. The assumption of a 1:1 ratio between effluent volume and urea clearance might not hold true, especially with impaired filter performance, therapy interruptions, or significant pre-dilution [33]. In the current study, pre-filter replacement fluid represented approximately one-quarter of the total effluent dose and was accounted for in stdKt/V and spKt/V calculations using a pre-dilution correction factor, helping to minimize overestimation of urea clearance. Moreover, because not all sessions lasted $\geq$24 h, stKt/V values were normalized to a 24-h equivalent to allow consistent comparisons across treatments. In intermittent dialysis, individual Kt/V values cannot be summed. However, owing to the continuous nature of CRRT, simple summation of daily stdKt/V values can produce a representative weekly stdKt/V [33], thereby allowing cross-modality comparisons. In this study, the normalized weekly median (IQR) stdKt/V was 2.41 (2.29), exceeding the KDOQI minimum target of 2.1 for IHD [39] and lower than the typical native kidney function (stdKt/V = 16) [40]. Notably, some sessions extended beyond 24 h, during which circuit downtime and declining filter performance might have reduced solute clearance (due to clogging and clotting) [41]. This underscores the need for further research into solute clearance and filter efficiency during CRRT, particularly in evaluating discrepancies between prescribed and delivered dialysis doses.

A higher median ultrafiltration rate was observed during the second session. This can be attributed to improved hemodynamic stability in many dogs compared to the initial session. Although CRRT is considered the safer modality for hemodynamically unstable dogs, 60% of the dogs in the present study developed hypotension during treatment. However, given that one-third of the cohort required vasopressor support before

TABLE 3 | Selected CBC, chemistry, and blood gas analytes in dogs with acute kidney injury undergoing continuous renal replacement therapy (CRRT). Values are presented as median (interquartile range), both at admission and before initiation of CRRT.

	Survivors		Non-survivors		*p* value		
Analyte[a]	**Admission**	**Before CRRT**	**Admission**	**Before CRRT**	**Admission**	**Before CRRT**	**Reference interval**
Leukocytes (x10^3/μL)	16.8 (7.1)	17.2 (6.4)	10.83 (11.08)	14.24 (16.82)	0.13	0.54	5.05–16.76
Hematocrit (%)	39.5 (13.5)	28.6 (8.8)	38 (20)	26.8 (16)	0.71	0.38	37.3–61.7
Platelets (10^3/μL)	174 (149)	102 (139)	164 (154)	89 (138)	0.34	0.67	148–484
Albumin (g/dL)	3.2 (0.8)	2.7 (0.5)	2.9 (0.9)	2.2 (0.6)	0.10	0.02[b]	2.2–3.9
Bilirubin (mg/dL)	0.7 (2)	0.5 (0.9)	0.8 (0.6)	1.6 (0.8)	0.88	0.04[b]	0.0–0.9
ALT (U/L)	79 (178)	79.5 (66)	137 (295)	157 (254)	0.58	0.45	10–125
Creatinine (mg/dL)	7.6 (8.5)	10.5 (4.9)	4.2 (6.5)	8.6 (5.1)	0.22	0.06	0.5–1.8
BUN (mg/dL)	99 (5)	122 (45)	44 (61)	88 (45)	0.062	0.10	7–27
Phosphate (mg/dL)	8.9 (9.7)	9.9 (4.5)	5.3 (4.2)	8.7 (6.8)	0.025[b]	0.04[b]	2.5—6.8
K^+ (mEq/L)	4.4 (0.9)	4.1 (0.5)	4.6 (1.3)	4.1 (1.4)	0.76	0.99	3.5–5.8
NA^+(mEq/L)	140 (9)	139 (9.5)	138 (8)	134 (7)	0.74	0.37	144–160
Cl^- (mEq/L)	111 (12)	94.5 (21.7)	109 (8)	100 (9)	0.40	0.56	109–122
iCa^{+2} (mmol/L)	1.2 (0.1)	1.2 (0.1)	1 (0.1)	1.1 (0.3)	0.92	0.42	0.85–1.35
Lactate (mmol/L)	1.5 (1.1)	1.1 (0.8)	2.3 (2.2)	1 (0.8)	0.20	0.91	< 2.5
Venous blood pH	7.33 (0.16)	7.36 (0.10)	7.34 (0.16)	7.26 (0.15)	0.74	0.08	7.31–7.42
HCO_3 (mmol/L)	17.1 (10)	19.2 (4.9)	17.6 (3.6)	18.4 (4.5)	0.96	0.63	17–24
$APPLE_{FULL}$	26 (7)	29 (5)	37 (7.5)	41 (8)	0.00044	< 0.00001	N/A
$APPLE_{FAST}$	18 (4.5)	20 (4)	26 (9.5)	26 (7)	0.00068	0.00026	N/A
Age (months)	48 (56.5)		84 (72)		0.54		N/A
Weight (kg)	26.5 (6)		30 (23.8)		0.77		N/A
CRRT-D (h)	56 (44.5)		48 (56.5)		0.45		N/A

Abbreviations: ALT, alanine transaminase; $APPLE_{Fast/Full}$, Acute Patient Physiologic and Laboratory Evaluation—Fast/Full versions; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; CRRT-D, CRRT duration; N/A, none applicable.

[a]Results are presented as median (interquartile range); the Mann–Whitney U-test was used to compare the two groups (survivors versus non-survivors) at admission or before CRRT.

[b]Significance was lost after applying the Bonferroni correction for multiple comparisons.

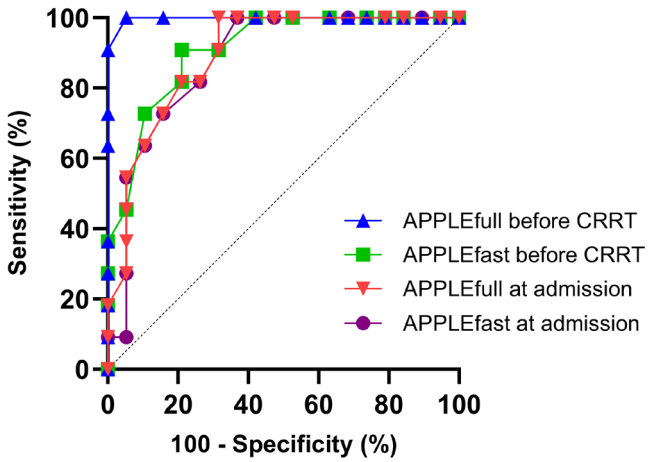

FIGURE 1 | Receiver operating characteristic curves (ROCC) of the Acute Patient Physiologic and Laboratory Evaluation (APPLE)full/APPLE fast scores as predictors of outcome in dogs with acute kidney injury undergoing continuous renal replacement therapy (CRRT). The curves were constructed for either score, both at admission or just before initiation of CRRT. Areas under the ROCC (AUROCC) before commencement of CRRT were 0.99 (95% CI, 0.99–1.00) for the APPLE full and 0.91 (95% CI, 0.81–1.00) for the APPLE fast. At admission, the AUROCC for the APPLE full and APPLE fast were 0.89 (95% CI, 0.78–1.00) and 0.88 (95% CI, 0.76–1.00), respectively.

CRRT initiation, it is difficult to determine whether hypotension developed because of treatment, secondary to the severity of the underlying illness, or both. Twelve dogs, including vasopressor-dependent or ventilated dogs, did not survive beyond the first session, representing the most critically ill subgroup. As a result, the remaining dogs receiving a second session were generally more stable and better tolerated fluid removal. In some cases, dogs that could not undergo ultrafiltration during the first session improved clinically and became suitable for fluid removal in subsequent treatments. Furthermore, after the second session, several dogs began producing urine spontaneously, reducing the need for ultrafiltration in later sessions. Collectively, these factors accounted for changes in ultrafiltration rates employed in the different sessions.

Treatment protocol stratification based on initial azotemia was not used herein, as the KDIGO-recommended effluent dose (20–25 mL/kg/h, adjusted to 30 mL/kg/h for interruptions) is relatively low and considered safe even for patients with severe azotemia. As a result, hourly URR values in sessions 1 through 6 remained low (range: 1.9%–2.8%), aligning with veterinary IHD guidelines that recommend limiting URR/h to < 5% in the most azotemic and neurologically vulnerable dogs to minimize the risk of dialysis disequilibrium syndrome. The survival rate in the present study was comparable to studies in humans, ranging from 31%–60% [42–44] but lower than those reported in previous veterinary studies utilizing RRT of different modalities [2–4, 45]. Reported survival rates for dogs and cats undergoing CRRT, IHD, or peritoneal dialysis treatments range from 50% to 53% at discharge [2], but some of these studies also include dogs that become IHD-dependent after hospitalization [2–4, 45] or after CRRT [6]. Accordingly, one-year survival rates drop significantly, from 53% at discharge to 33%–38% in dogs and cats, with 23% of the dogs requiring ongoing IHD treatments in one study [45]. In the present study, CRRT proved a feasible treatment modality after conventional medical treatment had failed; 70% of the dogs had developed diuretic-resistant oliguria/anuria and presented with high disease severity scores.

Carboxyhemoglobinemia was commonly documented in dogs herein and likely resulted from increased extracorporeal hemolysis [46]. Consequently, increased hemoglobin catabolism ensued, and endogenous carbon monoxide production was increased, thereby resulting in high carboxyhemoglobin concentrations [47]. Measurements, however, were inconsistently documented in dogs in general and across sessions, and therefore associations with treatment efficacy or complications thereof could not have been investigated.

A number of clinicopathological variables, clinical findings, and treatment complications were examined in this study for possible association with survival, whether at presentation, before CRRT initiation, or during treatment. Most of these analyses did not reveal find statistically significant associations with outcome, except the APPLE scores. All dogs in the present study which required advanced oxygen support (four on mechanical ventilation and one on humidified oxygen therapy) and exhibited respiratory complications, in addition to dogs with higher mentation scores, died, in agreement with previous reports in dogs and humans [3, 4, 12, 48–50]. Conversely, neither urine output (anuria/oliguria) nor the severity of azotemia was associated with survival in this study. Lack of association between urine output and survival aligns with previous reports in humans [9, 51, 52] but not with studies of IHD in dogs, where urine production is considered a significant predictor of death [2, 3, 12, 53]. Similarly, the prognostic value of creatinine remains unclear. While some studies in humans associate higher creatinine concentration before CRRT initiation with worse outcome [52, 54], others do not [48, 49]. In dogs with AKI and treated with IHD, the evidence is equally conflicting, with an apparent association between survival and a higher creatinine concentration reported in one study [12], but not in most others [53, 55, 56]. Additional prognostic markers previously reported in studies involving dogs and people undergoing RRT, including overhydration [50, 51, 57, 58], bilirubin [55, 59, 60]/albumin [61, 62]/lactate [63]/phosphate [12, 61, 63, 64], age [54, 63], vasopressor use [59, 63], white blood cell count [59, 63], platelet count [59, 63], and CRRT duration [50] failed to differentiate survivors from non-survivors herein. These discrepancies might stem from inherent differences between study groups, which vary, in part, in terms of species, underlying etiologies, and treatment modalities, but might also be the result of a relatively small sample size in most studies, including the present study. Contrary to the above, the robustness of the APPLE scores for outcome prediction was corroborated in the present study, in agreement with previous studies of dogs with septic shock [65], urosepsis [66], critical illness [67], critical illness-related corticosteroid insufficiency [68], SIRS [69], and myocardial injury [70]. Future studies are warranted to investigate whether the APPLE scores can also be used to stratify dogs with AKI by illness severity and guide CRRT strategies accordingly.

There are few studies that specifically evaluate scoring systems in dogs undergoing RRT with AKI. In one such study in dogs with AKI and managed with CRRT, the APACHE III scoring

system, adopted from human medicine, failed to predict survival [71]. Another study, in which several novel models were constructed to predict survival in dogs with AKI and managed by IHD, reported excellent performance of 2 scoring systems ("model B" and "model C", the latter also including etiological data), with AUROCC values of 0.88–0.91 [3]. These models were later validated prospectively in 2 different studies [12, 13], with comparable results. However, when model B was assessed in the present study, it performed poorly and failed to differentiate survivors from non-survivors. This discrepancy might be attributed to population-specific factors, most importantly those regarding etiology, and treatment modality (i.e., IHD versus CRRT). In our cohort of dogs, neither leptospirosis- a readily treatable disease, nor ethylene glycol intoxication- a potentially irreversible disease, were included [2, 3, 55, 56]. Exclusion of these two etiologies, unlike the original studies where model B was constructed and assessed, might have affected its discriminatory efficacy. This finding underscores the shortcomings of scoring systems and predictive models that are based on relatively small groups of dogs and highlights the strong influence of etiology on the outcome.

There are several limitations to this study. First, the study group was relatively small, and did not include common etiologies for AKI such as leptospirosis and ethylene glycol intoxication. Second, owing to the retrospective nature of the study, clinical and laboratory data could not always be found for all dogs at different time points during hospitalization. This precluded the assessment of model B before CRRT initiation and prevented the assessment of other analytes for outcome prediction during and after CRRT. Third, 4 dogs were euthanized owing to lack of response and after their owners had declined follow-up IHD therapy. Thus, our findings might not apply to dogs whose management includes IHD after initial stabilization with CRRT. Fourth, due to the upper reporting limit of 130 mg/dL for some BUN values, direct comparison of urea-based metrics across different modalities, especially with IHD, might be limited. This constraint could have led to underestimation of URR, hourly URR, and TAC_{urea} in some cases. Fifth, given the lack of standardized protocols for CRRT in dogs with AKI, we used the human-based, KDIGO guidelines for treatment prescription, regardless of etiology or illness severity except for hypercatabolic conditions.

In conclusion, only the $APPLE_{Fast}$/$APPLE_{Full}$ scores effectively differentiated survivors from non-survivors in critically ill dogs with AKI undergoing CRRT, supporting their potential use as ancillary tools for illness severity stratification and for prognostication. Their performance was improved when constructed immediately before CRRT initiation, rather than upon admission. In addition, given the findings of the present study, applying the KDIGO guidelines to dogs undergoing CRRT is a feasible, effective protocol for managing dogs with AKI, which can be used in the ICU setting, yielding comparable outcomes to previous studies. Whether APPLE scores can be used to refine treatment decisions and CRRT protocols remains to be determined.

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Disclosure

Authors declare no off-label use of antimicrobials.

Ethics Statement

Authors declare no institutional animal care and use committee or other approval was needed. Authors declare human ethics approval was not needed.

Conflicts of Interest

The authors declare no conflicts of interest.

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Appendix A

Dialysis Delivered Dose Assessment

Urea and Creatinine Reduction Ratios

Urea Reduction Ratio (URR)

$$URR\ (\%) = ([\text{pre-BUN} - \text{post-BUN}]/\text{pre-BUN}) \times 100$$

Creatinine Reduction Ratio (CrRR)

$$CrRR\ (\%) = ([\text{pre-creatinine} - \text{post-creatinine}]/\text{pre-creatinine}) \times 100$$

Single-Pool Kt/V (spKt/V)

$$Kt/V = (K \times T)/V$$

Where:

K = clearance (mL/min)

T = treatment duration (minutes)

V = urea distribution volume (mL), calculated as:

V = body weight (kg) × hydration factor

Adapted from:

Cowgill LD. Vet Clin North Am Small Anim Pract. 2011;41(1):193–225. doi:10.1016/j.cvsm.2010.12.002

Clearance (K) was calculated using an effluent-based formula:

$$K\ (mL/min) = [(Qr + Qd + Quf)/(1 + Qr/Qb)]$$

Where:

Qr = replacement fluid rate (mL/min)

Quf = ultrafiltration rate (mL/min)

Qb = blood flow rate (mL/min)

Qd = dialysate flow rate (mL/min)

Adapted and modified to account for pre-dilution effect on dialysate from: Chen H, Klainbart S, Kelmer E, et al. Continuous renal replacement therapy is a safe and effective modality for the initial management of dogs with acute kidney injury. J Am Vet Med Assoc. 2022; 261: 87–96.

Standardized Kt/V (stdKt/V)

Standardized to a 24-hour equivalent and calculated as:

StdKt/V = [(Qd + Qr + Quf) × (Qp/(Qp + Qr))] ×1440/(weight × hydration factor)

Where:

Qp = plasma flow rate (mL/min) = (1 – hematocrit) × Qb (mL/min)

1440 = 24 h × 60 min

All other parameters as above

Adapted from:

Diaz-Buxo JA, Pérez Loredo J. Adv Ren Replace Ther. 2003;10(3):205–212.

Clark WR, Leblanc M, Ricci Z, Gao D, Ronco C. Adequacy of continuous renal replacement therapy: prescription and delivery. In: Ronco C, Bellomo R, Kellum JA, eds. Critical Care Nephrology. 3rd ed. Philadelphia, PA: Elsevier; 2019:1029–1034.e2.

Time-Averaged Concentration (TAC)

TAC = AUC/(td + ti)

Where:

AUC = area under the BUN or creatinine-time curve (mg/dL × hours), calculated using the trapezoidal rule

td = intradialytic period (hours)

ti = interdialytic interval (hours)

Adapted from: Cowgill LD. Vet Clin North Am Small Anim Pract. 2011;41(1):193–225. doi:10.1016/j.cvsm.2010.12.002

Weekly Standardized Kt/V (StdKt/V)

Standardized to a 7-day equivalent and calculated as: weekly StdKt/V = Total StdKt/V

Adapted from: Clark WR, Leblanc M, Ricci Z, Gao D, Ronco C. Adequacy of continuous renal replacement therapy: prescription and delivery. In: Ronco C, Bellomo R, Kellum JA, eds. Critical Care Nephrology. 3rd ed. Philadelphia, PA: Elsevier; 2019:1029–1034.e2.

Each TAC value was calculated per session, incorporating both the treatment duration and the following interdialytic period. For each dog, overall TAC was calculated by summing all AUCs and dividing by the total duration of dialysis and intersession periods.

Due to laboratory limitations, BUN values reported as "> 130 mg/dL" were conservatively recorded as 130 mg/dL unless an exact value was provided. To mitigate this limitation and improve accuracy, CrRR and TAC for creatinine were included in the analysis. URR was not used to guide therapy but was calculated for comparison with previous studies.