Original Study

Journal of Veterinary Emergency and Critical Care **25**(2) 2015, pp 226–233
doi: 10.1111/vec.12257

Prospective evaluation of the acute patient physiologic and laboratory evaluation score and an extended clinicopathological profile in dogs with systemic inflammatory response syndrome

Massimo Giunti, DVM, PhD; Roberta Troia, DVM; Paolo Famigli Bergamini, DVM and Francesco Dondi, DVM, PhD

Abstract

Objective – To investigate the prognostic value of the acute patient physiologic and laborartory evaluation (APPLE) score and relevant clinicopathological markers in dogs with systemic inflammatory response syndrome (SIRS).
Design – Prospective observational cohort study.
Setting – Veterinary teaching hospital.
Animals – Thirty-three dogs with SIRS admitted to the intensive care unit (ICU) were compared to 35 healthy control dogs. Dogs with SIRS were divided into septic ($n = 20$) and nonseptic ($n = 13$) etiologies and as survivors (alive to discharge, $n = 22$) and nonsurvivors ($n = 11$: died, $n = 6$, or humanely euthanized, $n = 5$).
Measurements and Main Results – For all dogs, physiological and laboratory parameters were prospectively collected for the calculation of the $APPLE_{fast}$ score. No difference between septic and nonseptic SIRS dogs was detected for any parameter evaluated. Survivors had significantly higher total protein, albumin concentrations, antithrombin activity (ATA), and base excess (BE), as well as significantly lower lactate, urea, creatinine concentrations, urinary protein to creatinine ratio and $APPLE_{fast}$ score compared to nonsurvivors. Higher values of creatinine, lactate, anion gap, alanine transaminase (ALT), and $APPLE_{fast}$ score were significantly associated with an increased risk of death in SIRS dogs, while higher values of total protein, albumin, ATA, and BE were associated with a significantly reduced risk of mortality. When a multivariate binary logistic regression analysis was performed, the $APPLE_{fast}$ score was the only significant parameter retained.
Conclusions – The determination of the $APPLE_{fast}$ score in clinical setting, as well as the measurement of APP, ATA, lactate, BE, anion gap, ALT, urinary proteins, and electrolytes may be beneficial for a better assessment of dogs with SIRS. Identified parameters were significantly related with the presence of SIRS and their evaluation should be considered for the assessment of disease severity, and guidance of the decision-making process in critically ill dogs.

(J Vet Emerg Crit Care 2015; 25(2): 226–233) doi: 10.1111/vec.12257

Keywords: biomarkers, canine, illness severity, urine, sepsis

From the Department of Veterinary Medical Sciences, Alma Mater Studiorum – University of Bologna, Ozzano dell'Emilia, Bologna, Italy.

The authors declare no conflict of interest.

Presented in part at the 11th EVECCS Congress, June 15th–17th, 2012, Barcelona, Spain.

Address correspondence and offprint requests to
Dr. Massimo Giunti, Department of Veterinary Medical Sciences, Alma Mater Studiorum – University of Bologna, via Tolara di sopra n° 50, 40064 Ozzano dell'Emilia, Bologna, Italy.
Email: massimo.giunti@unibo.it
Submitted December 11, 2012; Accepted October 06, 2014.

Introduction

Systemic inflammatory response syndrome (SIRS) and sepsis are frequently observed conditions in critically ill human patients.[1] Despite the lack of data on the prevalence of SIRS in veterinary patients, this syndrome has gained increasing attention and interest in recent years.[2–12] SIRS is characterized by activation of the acute phase response, hemostatic derangements, impaired tissue perfusion and oxygenation, and can ultimately progress to multiple organ dysfunction syndrome and

Abbreviations

APP	acute phase proteins
APPLE	acute patient physiologic and laboratory evaluation
ATA	antithrombin activity
AUC	area under the curve
BE	base excess
CRP	C-reactive protein
FECa	fractional excretion of calcium
FENa	fractional excretion of sodium
FEP	fractional excretion of phosphorus
iCa	ionized calcium
iHCa	ionized hypocalcemia
ROC	receiver operating characteristic
SIRS	systemic inflammatory response syndrome
TIBC	total iron-binding capacity
TP	total protein
UAC	urinary albumin to creatinine ratio
UPC	urinary protein to creatinine ratio
uUA:C	urinary uric acid to creatinine ratio
OR	odds ratio
CI	confidence interval

death.[2–10] Despite advances in supportive care, SIRS and sepsis remain leading causes of mortality in the ICU setting, with overall mortality rates ranging from 27% to 64% in dogs.[2–4,6–12] Thus, the prompt diagnosis and assessment of disease severity still remain primary goals to improve the therapeutic decision making and the outcome in septic patients. Furthermore, the development of appropriate methods to precisely stratify critical patients according to disease severity, would better assist clinical researchers in the design of clinical trials.

A user-friendly scoring system, acute patient physiologic and laboratory evaluation (APPLE) score, has been recently validated to stratify mortality risk in hospitalized dogs, independent of the underlying disease, by illness severity.[13] The scoring system includes a 10-variable and a 5-variable model ($APPLE_{fast}$) that enable a rapid cage-side calculation based on simple and objective clinical data. Receiver operating characteristic (ROC) curve analysis showed that the area under the curve (AUC) of the APPLE score had a robust value to predict death in ICU patients in both models (AUC 0.91 and 0.85, respectively) and supported their use as prognostic indicators for research purposes in dogs with SIRS.[13]

The number of studies aimed to identify predictive biomarkers for SIRS/sepsis in dogs has grown dramatically in the last decade and several clinicopathological parameters have been evaluated,[2,14,15] including acute phase proteins (APP), antithrombin activity (ATA), ionized calcium (iCa), and urine protein.[3–8,11,16–24]

The aim of this study was to examine the prognostic value of the $APPLE_{fast}$ score (5-variable model) and to evaluate the predictive power of an extended panel of routinely measured clinicopathological markers in dogs with SIRS. In addition, all parameters evaluated were compared between dogs with SIRS and a population of healthy control dogs.

Materials and Methods

A prospective observational study was carried out at the University of Bologna's Veterinary Teaching Hospital between December 2010 and December 2011.

Dogs admitted to the intensive care unit (ICU) were included in the study as nonseptic SIRS if they exhibited 2 or more of the following criteria at admission to the hospital: body temperature <38.1°C or >39.2°C; heart rate >120/min; respiratory rate >20/min; WBC count $< 6.0 \times 10^9$/L [6,000/μL] or $>16.0 \times 10^9$/L [16,000/μL], percentage of bands >3% of the total WBC count.[25] Septic SIRS dogs were identified as patients meeting the above criteria (nonseptic SIRS) in addition to identification of a concurrent septic focus documented by means of cytology or positive culture. Dogs with SIRS were also classified as survivors (alive to discharge) or nonsurvivors (died despite medical treatment or humanely euthanized by the clinical investigators because of moribund conditions or end-stage disease). Dogs that were euthanized for financial reasons were excluded from the study. For all dogs, the length of hospitalization in ICU was also recorded.

Dogs that were younger than 1 year of age, that were diagnosed with chronic kidney disease or parathyroid gland disease, based on history, clinical and clinicopatholgical findings, and imaging results, or that received drugs (eg, steroids, diuretics, vitamin D, phosphate enemas) known to alter calcium metabolism before the admission to the ICU were excluded from the study.

Thirty-five control dogs (client owned and hospital staff-owned dogs) were considered healthy based on history, physical examination, and clinicopathological data, including concentrations of creatinine, glucose, urea, total protein (TP), total bilirubin, cholesterol, phosphorus, total calcium, ionized calcium (iCa), total iron, albumin, Na, K, Cl, Mg, total iron-binding capacity (TIBC), C-reactive protein (CRP), fibrinogen as well as activities of alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase, and γ-glutamyltransferase. Urinalyses including quantitative protein and albumin concentration on urine samples collected by cystocentesis ($n = 35$) were also performed.

Blood and urine from all dogs were collected and analyzed within one hour of ICU admission. Blood sampling was performed by venipuncture with vacutainer system[a] according to standard operating procedures. Urine was collected via cystocentesis or urinary catheterization. The following analyses were performed: venous blood gas with iCa, CBC, serum biochemistry (albumin, TP, glucose, ALT, aspartate transaminase, alkaline phosphatase, total bilirubin, γ-glutamyltransferase, cholesterol, total calcium, phosphorus, total iron) lactate, ATA, APP including CRP, fibrinogen, transferrin (as TIBC), and urinalysis including urinary protein to creatinine ratio (UPC), urinary albumin to creatinine ratio (UAC), urinary electrolytes, and urinary uric acid to creatinine ratio (uUA:C). A previously described standardized method[11] was used to collect venous blood samples to measure iCa and blood gas. Venous blood gas analysis also included pH, base excess (BE), HCO_3, monovalent electrolytes, $PvCO_2$, PvO_2, and anion gap measurements. All parameters were also measured in healthy control dogs.

Ionized hypocalcemia (iHCa) was defined as values lower than the lowest value of iCa measured in healthy control dogs (iCa < 1.21 mmol/L). The presence of an acute phase response was defined by an increased concentration above the reference interval of our lab for CRP (0 – 0.5 mg/dL) or fibrinogen (1.45 – 3.85 g/L). For each dog included in the study an $APPLE_{fast}$ score (5-variable model: glucose, albumin, mentation score, platelet count, and lactate) was calculated. In dogs with SIRS, the score was determined using data collected upon admission to ICU. The study protocol was approved by the local Scientific Ethical Committee for Animal Testing.

Laboratory methods

CBC was determined with an automated cell counter.[b] Lactate concentrations were measured using a portable lactate analyzer.[c] CRP[d] and urine albumin[e] were measured using immunoturbidimetric assays previously validated in our group for dog samples.[26,f] TIBC[g] and ATA[h] were measured using colorimetric methods. Ionized calcium and venous blood gas analysis were obtained using a blood gas analyzer.[i] UPC and UAC were calculated. Fractional excretion of calcium (FECa), sodium (FENa), and phosphorus (FEP) were calculated according to the following equation: fractional excretion = (UX/PX)/(UC/PC), where UX and PX were the concentrations of a specific analyte in urine and plasma, respectively, while UC and PC were creatinine concentrations in urine and plasma, respectively.[27] Urinary uric acid concentrations were measured using a colorimetric method[j] and normalized to urinary creatinine (uUA:C). All analyses were performed with an automated chemistry analyzer.[k]

Statistical Analysis

All data are described using standard descriptive statistics and reproted as median and range or mean ± standard deviation for nonnormal and normal distributions, respectively. Normality was assessed using D'Agostino–Pearson test. Mann–Whitney *U* test and Student's *t*-test were used to evaluate differences between groups. Results were considered statistically significant with P value < 0.05. In the population of dogs with SIRS, univariate logistic regression was used to assess the association between clinical and clinicopathological parameters and outcome. Parameters associated with outcome in the univariate analyses were entered into a multivariable model (backward selection, removing factors with P value > 0.1). Binary logistic regression results were presented as odds ratio (OR) and 95% confidence interval (CI). Overall model fit was assessed by the percentage of outcome correctly classified by the ROC curves analysis and by a significant Hosmer–Lemeshow test (P > 0.05). ROC curves were used to find optimal cut-off values for parameters predicting prognosis and to calculate the AUC. Correlations between parameters were assessed using Pearson or Spearman's rank correlation coefficients. All analyses were performed using an online available statistical software.[l]

Results

Sixty-two dogs (age >1 year) with signs of SIRS were admitted to ICU during the study period. Of these cases, 11 were excluded due to the presence of chronic kidney disease, and 10 were not enrolled due to investigators not being notified, causing incomplete blood and urine sampling upon admission. Eight dogs were euthanized for financial reasons and were ineligible for study inclusion.

A total of 33 dogs with SIRS were included in the study. Median age was 7.8 years (range: 1.3–15 y) and median body weight was 25.6 kg (range: 5.1–42 kg). Twenty-two dogs (67%) survived to hospital discharge (survivors), while 11 (33%) died (n = 6) or were humanely euthanized (n = 5) (nonsurvivors). Of the nonsurvivors, 6 septic SIRS dogs died despite treatments for refractory hypotension and multiple organ failure (4 dogs with septic peritonitis in the postoperative period, 2 dogs with severe urosepsis), 5 were euthanized due to the concomitant presence of multiple organ failure and a diagnosis of malignancy (Table 1). Rectal temperature <38.1°C or >39.2°C was identified in 2 and 26 dogs, respectively. Twenty-four dogs had tachycardia (HR>120/min) and 30 had tachypnea (RR > 20/min), as previously defined.[25] Twenty-six dogs had leukocytosis (WBC count > 16.0×10^9/L [16,000/μL]) and 3 had leukopenia (WBC count < 6.0×10^9/L [6,000/μL]).

Table 1: Diseases affecting 33 dogs with systemic inflammatory response syndrome (SIRS) stratified by outcome

Outcome	Septic SIRS group (20)	Nonseptic SIRS group (13)
Survivors ($n = 22$)	Septic pleuritis (4)	Osteomyelitis (2)
	Bite wound infection (4)	Eosinophilic pneumonia (2)
	Septic peritonitis (2)	Neoplasia (1)
	Pyometra (1)	diskospondylitis (1)
	Pyoderma (1)	Polyarthritis (1)
	Pyelonephritis/urosepsis (2)	Pneumonia (1)
Nonsurvivors ($n = 11$)	Septic peritonitis (4)	Neoplasia (5)
	Urinary tract infection/urosepsis (2)	

SIRS, systemic inflammatory response syndrome.
Number of affected patients in parentheses. To be classified as septic, diagnosis had to be confirmed cytologically or via positive bacterial culture result.

Thirteen dogs (39%) were classified as nonseptic, and 20 (61%) classified as septic. The most common cause of nonseptic SIRS was neoplasia ($n = 6$), while for septic SIRS was septic peritonitis ($n = 6$) (Table 1). For all the performed analyses, none of the tested parameters was significantly different between septic and nonseptic SIRS dogs.

Parameters that were significantly different between control and SIRS dogs, upon admission, are reported in Table 2. Positive (CRP and fibrinogen) and negative (TIBC, albumin, and antithrombin) APP values were all significantly different from control dogs (Table 2). The 22 survivors had significant higher values of albumin and ATA compared to the 11 nonsurvivors, while no differences were detected for the other APP (Table 3).

Urine specimens were collected in all patients; however, samples from 4 dogs were excluded from UPC and UAC analyses because a urinary tract infection with active sediment was observed. UPC and UAC were significantly higher in SIRS compared to the control dogs. UPC was significantly lower in survivors compared to nonsurvivors, while UAC did not vary (Table 3). FENa values were significantly correlated with both UAC and UPC (Table 4).

Survivors also had significantly higher values of serum TP and BE, as well as lower values of anion gap, $APPLE_{fast}$ score, lactate, urea, creatinine, and ALT concentrations compared to nonsurvivors (Table 2).

The $APPLE_{fast}$ score was significantly correlated with TP, urea, BE, total bilirubin, UPC, TIBC, and ATA (Table 4). Length of ICU stay was not significantly correlated to any of the investigated parameters.

Table 5 shows the parameters that were significantly associated with outcome using the univariate binary logistic regression analysis. There were positive associations between odds of mortality and values of creatinine, lactate and $APPLE_{fast}$ score, respectively. Higher values of albumin, TP, ATA, and BE were associated with a significant mortality risk reduction. When the multivariate binary logistic regression analysis was performed, the $APPLE_{fast}$ score was the only parameter retained by the model (Table 5).

Discussion

SIRS and sepsis are important syndromes in critically ill dog.[2–12] It is widely acknowledged that clinical criteria alone fail to identify and stratify these patients adequately. In our study, the potential prognostic significance of a wide panel of clinical and clinicopathological parameters that could be routinely measured in hospitalized dogs was investigated.

The APPLE score has been recently validated to stratify illness severity by mortality risk in hospitalized dogs.[13] In order to obtain a simple and practical calculation of the score, we applied the 5-variable $APPLE_{fast}$ model to a population of critically ill dogs. This score was able to discriminate between survivors and nonsurvivors upon admission with the highest predictive power. Thus, our results support the application of the $APPLE_{fast}$ score in the clinical setting to identify and properly manage high-risk ICU patients. However, its use as an exclusive tool to guide therapeutic decisions needs to be addressed in further clinical trials.

The quantification of APP, particularly C-reactive protein (CRP), allows an early identification of inflammatory processes, and represents an objective monitoring tool to evaluate the response of the patient to selected therapies.[5,16,28] However, the prognostic value of APP still remains controversial.[3–5,20,24] A panel of APP was investigated in the present study, including positive (CRP and fibrinogen) and negative (albumin and transferrin-TIBC) acute phase proteins. The activation of an acute phase response,[29] defined by a concentration above the reference interval of the measured positive APP (CRP, fibrinogen), was noted in all the dogs with SIRS. However, the prognostic role of positive APP is questionable, as their concentrations were not related with outcome, disease severity, or duration of hospital stay. In contrast, dogs with higher albumin concentrations

Table 2: Clinical and clinicopathological parameters in cohort of critically ill dogs with systemic inflammatory response syndrome (SIRS) and healthy controls on admission

Parameter	Units	Reference interval	Control dogs	*n*	SIRS dogs	*n*	*P* value
iCa	mmol/L	1.21–1.35	1.30 ± 0.03	35	1.22 ± 0.08	33	< 0.0001
Total calcium	mmol/L	2.25–2.95	2.6 [2.4–2.8]	35	2.3 [1.8–3.2]	33	<0.0001
Total calcium	mg/dL	9.0–11.8	10.2 [9.7–11.2]	35	9.3 [7.2–12.9]	33	< 0.0001
Anion gap	mmol/L	9–22	20 ± 3	35	23 [20–31]	33	0.008
BE	mmol/L	−2.0 to 2.0	0 [–1 to 3]	35	–2 [–10 to 5]	33	0.0001
Phosphorus	mmol/L	0.84–1.6	1.3 [0.65–1.6]	35	1.8 ± 0.8	33	0.001
Phosphous	mg/dL	2.6–4.9	4.1 [2.0–4.9]	35	5.5 ± 2.5	33	0.001
Creatinine	μmol/L	57.5–119.3	98.1 ± 14.1	35	77.8[38.8–556.0]	33	0.005
Creatinine	mg/dL	0.65–1.35	1.11 ± 0.16	35	0.88 [0.45–6.29]	33	0.005
UPC		0–0.4	0.09 [0.05–0.20]	35	0.80 [0.10–5.80]	29	< 0.0001
UAC		0–0.024	0 [0–0.020]	35	0.100 [0–3.100]	29	< 0.0001
FECa	%	0–0.5	0.09 [0.03–0.68]	35	0.23 [0.06–1.86]	33	0.0007
FEP	%	3–45	11.1 [0.9–48.1]	35	7.3 [0–61]	33	0.009
uUA:C			0.05 [0.03–0.15]	35	0.19 [0.01–0.62]	33	< 0.0001
$Apple_{fast}$ score			13 [7–15]	35	24 [14–39]	33	< 0.0001
CRP	mg/dL	0–0.5	0.28 [0.01–0.6]	35	7.9 [0.20–31.1]	33	< 0.0001
Fibrinogen	g/L	1.45–3.85	2.70 ± 0.70	35	3.25 [1.64–9.60]	33	< 0.0001
ATA	%	105–166	130 ± 14	35	86 ± 18	33	< 0.0001
Albumin	g/L	28.0–37.0	32.9 ± 3.1	35	24.6 ± 7.0	33	<0.0001
Albumin	g/dL	2.80–3.70	3.29 ± 0.31	35	2.46 ± 0.70	33	< 0.0001
TIBC	μmol/L	50.1–84.1	66.6 [51.9–86.6]	35	46.0 ± 15.4	33	<0.0001
TIBC	μg/dL	280–470	372 [290–484]	35	257 ± 86	33	< 0.0001
Total iron	μmol/L	13.4–50.1	28.5 ± 7.5	35	12.5 [5.2–37.9]	33	< 0.0001
Total iron	μg/dL	75–280	159 ± 42	35	70 [29–212]	33	< 0.0001

iCa, ionized calcium; BE, base excess; UPC, urinary protein to creatinine ratio; UAC, urinary albumin to creatinine ratio; FECa, fractional excretion of calcium; FEP, fractional excretion of phosphorus; uUA:C, urinary uric acid to creatinine ratio; CRP, C-reactive protein; ATA, antithrombin activity; TIBC, total iron-binding capacity.

Results are expressed as median and [range] or mean ± standard deviation based on data distribution.

and higher ATA at admission were less likely to die, confirming their prognostic significance in dogs with SIRS and critical illness, as previously reported.[6,7,12,17]

Ionized hypocalcemia has been associated with mortality and longer duration of hospital stay in critically ill dogs.[11,18,19] The pathophysiology of iHCa associated with critical illness remains unclear but could involve increased renal excretion of calcium.[30] No significant association between iCa and mortality, duration of ICU stay or severity of disease was identified in our population. A significant correlation between FECa and iCa in our population was not found, suggesting that calcium excretion should not have a major influence on blood iCa.

An increased loss of urinary proteins, particularly albumin, has been reported in dogs with SIRS and in a variety of ICU settings.[2,21] Presence of albuminuria may be a risk factor for death in critically ill veterinary patients.[20,22] Our findings support that proteinuria and albuminuria are common features during SIRS and SIRS-associated kidney injury.[21] UPC (but not UAC) was significantly different in survivors versus nonsurvivors in our population, suggesting that nonglomerular proteinuria could play a prognostic role in dogs during SIRS.[21] The possibility of a preexisting proteinuria could not be completely excluded and should be considered when interpreting these results.

Although the evaluation of FENa is influenced by numerous parameters, a value above 1% in human patients with acute kidney injury usually indicates intrinsic renal injury, while levels < 1% support prerenal azotemia.[31–33] FENa above 1% was reported in 5 of the 33 SIRS dogs, of whom 3 were azotemic. The significant correlation between FENa and both UAC and UPC might represent an additional relevant index of SIRS-associated kidney injury.

Urinary uric acid is a marker of oxidative stress in people and animals.[34] In normal dogs, 98–100% of glomerular filtrated uric acid is reabsorbed into the proximal tubule and metabolized by the liver.[35] The significant increase in uUA:C noted in dogs with SIRS (Table 2) might have resulted from tissue hypoperfusion or renal damage caused by the underlying condition, since none of the dogs included in our study had a known breed predisposition to hyperuricosuria. The relevance of this finding warrants further evaluation.

A number of limitations of the current study should be considered when interpreting the data presented.

Table 3: Comparison between survivors and nonsurvivors in respect to selected initial clinical and clinicopathological parameters in cohort of critically ill dogs with systemic inflammatory response syndrome (SIRS)

Parameter	Units	Reference interval	Survivors	*n*	Nonsurvivors	*n*	*P* value
Albumin	g/L	28.0–37.0	26.8 ± 5.9	22	20.4 ± 7.3	11	0.011
Albumin	g/dL	2.80–3.70	2.68 ± 0.59	22	2.04 ± 0.73	11	0.011
TP	g/L	56.0–79.0	69.3 ± 12.3	22	54.9 ± 15.8	11	0.007
TP	g/dL	5.60–7.90	6.93 ± 1.23	22	5.49 ± 1.58	11	0.007
ATA	%	105–166	94 ± 15	22	72 ± 15	11	0.0004
BE	mmol/L	−2.0 to 2.0	−1 ± 2	22	−4 [−10 to 5]	11	0.004
Anion gap	mmol/L	9–22	22 [20–30]	22	25 ± 3	11	0.025
Lactate	mmol/L	0–2	1.8 [0.5–7.5]	22	3.8 [2.5–8.6]	11	0.005
Creatinine	μmol/L	57.5–119.34	66.3 [39.8–245.8]	22	88.4 [65.4–556.0]	11	0.009
Creatinine	mg/dL	0.65–1.35	0.75 [0.45–2.78]	22	1.00 [0.74–6.29]	11	0.009
Urea	mmol/L	6.4–19.6	8.2 [4.2–79.3]	22	17.5 [8.6–106.7]	11	0.0005
Urea	mg/dL	18–55	23 [12–222]	22	49 [24–299]	11	0.0005
ALT	U/L	20–55	29 [11–163]	22	195 ± 213	11	0.016
UPC		0–0.4	0.83 ± 0.63	20	1.60 [0.20–5.80]	9	0.04
$APPLE_{fast}$ score			22 ± 4	22	31 ± 4	11	<0.0001
iCa	mmol/L	1.21–1.35	1.20 ± 0.09	22	1.23 ± 0.07	11	0.80
CRP	mg/dL	0–0.5	8.2 [2.3–31.1]	22	7.3 [0.2–9.8]	11	0.44
Fibrinogen	g/L	1.45–3.85	3.02 [1.96–9.60]	22	4.65 ± 2.47	11	0.48
TIBC	μmol/L	50.1–84.1	48.3 ± 15.4	22	40.9 ± 15.0	11	0.22
TIBC	μg/dL	280–470	270 ± 86	22	229 ± 84	11	0.22

TP, total protein; ATA, antithrombin activity; BE, base excess; ALT, alanine transaminase; UPC, urinary protein to creatinine ratio; iCa, ionized calcium; CRP, C-reactive protein; TIBC, total iron-binding capacity.
Results are expressed as median and [range] or mean ± standard deviation based on data distribution.

Table 4: Correlations between the acute patient physiologic laboratory evaluation (APPLE) score, base excess, urinary: albumin:creatinine ratio, urinary protein:creatinine ratio and select laboratory parameters in a cohort of 33 dogs with systemic inflammatory response syndrome

APPLE score			Base excess			Urinary albumin: creatinine ratio			Urinary protein: creatinine ratio		
Parameter	***r***	***P* value**	**Parameter**	***r***	***P* value**	**Parameter**	***r***	***P* value**	**Parameter**	***r***	***P* value**
TP	−0.3	0.02	FECa	−0.4	0.03	FECa	0.42	0.02	FECa	0.57	0.001
Urea	0.4	0.004				FENa	0.48	0.008	FENa	0.5	0.004
BE	−0.4	0.02									
TBil.	0.4	0.01									
TIBC	−0.4	0.02									
ATA	−0.4	0.01									
UPC	0.3	0.03									

BE, base excess; UAC, urinary albumin to creatinine ratio; UPC, urinary protein to creatinine ratio; TP, total proteins; TBil, total bilirubin; TIBC, total iron-binding capacity; ATA, antithrombin activity; FECa, fractional excretion of calcium; FENa, fractional excretion of sodium.

The relatively small sample size may have resulted in insufficient statistical power for some of the investigated parameters (eg, iCa, UAC). Furthermore, the intrinsic limitations of the SIRS criteria may have resulted in the inclusion of a very heterogeneous population of patients in terms of disease processes and with varying severity. The low specificity of SIRS criteria[25] utilized may have allowed the inclusion of false-positive SIRS dogs in our population; however, measured APP were highly suggestive that dogs evaluated had systemic inflammatory processes. Four dogs with suspected infection (2 osteomyelitis, 1 dyskospondylitis, 1 pneumonia), but that did not have a focus of infection confirmed by cytology or bacterial culture results, were classified as nonseptic SIRS. The diagnostic challenges of identifying septic patients in the clinical setting could have biased the comparison between septic and nonseptic SIRS dogs in our study. Since we defined survival as an outcome, the inclusion among the nonsurvivors that died naturally and those that were humanely euthanized could have influenced the analysis of the data. However, the exclusion of dogs euthanized for financial constraints may have partly limited this bias.

Table 5: Univariate and multivariate binary logistic regression and receiver operator curve (ROC) analysis results of clinical and clinicopathological parameters measured at admission that were associated with the outcome (survivors/nonsurvivors) in 33 dogs with systemic inflammatory response syndrome (SIRS)

		Univariate binary logistic regression				ROC curve analysis		
Parameter	**Units**	**Regression coefficient**	**SE**	**Odds ratio [95% CI]**	***P* value**	**AUC [95% CI]**	**SE**	***P* value**
Albumin	g/dL	−1.799	0.809	0.166 [0.034–0.809]	0.026	0.785 [0.608–0.908]	0.104	0.006
TP	g/dL	−0.940	0.405	0.391 [0.177–0.864]	0.020	0.777 [0.599–0.903]	0.098	0.005
Creatinine	mg/dL	1.390	62.259	4.016 [1.185–13.607]	0.025	0.783 [0.606–0.907]	0.080	0.0006
Lactate	mmol/L	0.706	0.315	2.027 [1.092–3.761]	0.025	0.861 [0.693–0.957]	0.065	< 0.0001
BE	mmol/L	−0.424	0.199	0.655 [0.443–0.967]	0.033	0.826 [0.641–0.941]	0.103	0.002
Anion gap	mmol/L	0.325	0.164	1.384 [1.003–1.910]	0.048	0.795 [0.601–0.923]	0.085	0.0005
ATA	(%)	−0.114	0.043	0.893 [0.820–0.972]	0.009	0.855 [0.686–0.954]	0.066	< 0.0001
$APPLE_{fast}$ score		0.511	0.175	1.667 [1.183–2.346]	0.003	0.942 [0.798–0.994]	0.038	< 0.0001
		Multivariate binary logistic regression				**ROC curve analysis**		
$APPLE_{fast}$ score		0.560	0.213	1.751 [1.154–2.658]	0.008	**0.95* [0.793–0.998]**	**0.0468**	**< 0.0001**

SE, standard error; CI, confidence interval; TP, total protein; BE, base excess; ATA, antithrombin activity.
∗Sensitivity 80% and specificity 90.4% for $APPLE_{fast}$ score >27.
Only parameters with $P < 0.05$ are presented.

In conclusion, the present study underlines the usefulness of performing an extensive evaluation of traditional and newer blood and urinary biomarkers in a population of dogs with SIRS for prognostic purposes. The routine measurement of positive APP could improve the sensitivity and specificity of the criteria commonly used to detect SIRS in dogs.[25] Clinicopathological parameters, including lactate, BE, albumin, creatinine, UPC, and ATA were moderately accurate in predicting outcome in this study population. The $APPLE_{fast}$ score was highly accurate in predicting mortality in dogs with SIRS in the present study, hence its use in the clinical setting is recommended for the early assessment of critically ill dogs. Based on our data, screening of canine patients with SIRS for early renal injury is recommended. The potential role of using illness severity scores in guiding therapeutic decisions should also be further evaluated.

Footnotes

[a] S-Monovette, Sarstedt, Germany.
[b] Advia 2120 Hematology System, Siemens Healthcare Diagnostics, Tarrytown, NY.
[c] Lactate Scout Analyzer, Senslab, Leipzig, Germany.
[d] CRP OSR6147, Olympus/Beckman Coulter, Munich, Germany.
[e] Microalbumin OSR6167, Olympus/Beckman Coulter.
[f] Gentilini F, Mancini D, Dondi F, et al. Validation of a human immunoturbidimetric assay for measuring canine C-reactive protein. Vet Clin Path 2005; 34(suppl):318.
[g] UIBC OSR61205, Olympus/Beckman Coulter.
[h] Antithrombin III, Roche/Hitachi, Mannheim, Germany.
[i] IDEXX VetStat, IDEXX Laboratories, Westbrook, ME.
[j] Uric acid OSR6098 Olympus/Beckman Coulter.
[k] Olympus AU 400, Olympus/Beckman Coulter.
[l] MedCalc Statistical Software 9.5.2.0.

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