JOURNAL OF
Veterinary Emergency
AND Critical Care

Retrospective Study

Journal of Veterinary Emergency and Critical Care **28**(1) 2018, pp 54–61
doi: 10.1111/vec.12676

Retrospective evaluation of the prognostic utility of plasma lactate concentration, base deficit, pH, and anion gap in canine and feline emergency patients

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Abstract

Objective – To determine the association of plasma lactate concentration, pH, base deficit (BD), and anion gap (AG) in dogs and cats on presentation to an emergency room with outcome, and to compare the prognostic significance of hyperlactatemia with a concurrent metabolic acidosis with that of hyperlactatemia and a normal metabolic acid–base balance.
Design – Retrospective study.
Setting – University teaching hospital.
Animals – Five hundred sixty-six dogs and 185 cats that had venous blood gas analysis performed.
Interventions – None.
Measurements and Main Results – Medical records were reviewed for plasma lactate concentrations, electrolyte concentrations, and acid–base parameters obtained on emergency room admission, clinical diagnosis, and in-hospital mortality. The primary outcome measure was all-cause mortality for the hospitalized visit. Median plasma lactate concentration and AG were higher, BD was more negative, and pH was lower, in non-survivor dogs and cats. The prevalence of hyperlactatemia was 53% in dogs and 30% in cats. Lactic acidosis was present in 42% and 80% of hyperlactatemic dogs and cats, respectively. Multivariate regression analyses revealed that plasma lactate concentration, BD, and pH, but not AG, were independent predictors of mortality in dogs, and that only plasma lactate concentration was an independent predictor of mortality in cats. Mortality was highest for animals with lactic acidosis, at 59.8% in dogs and 49% in cats. Mortality in dogs with lactic acidosis was significantly higher than dogs with hyperlactatemia and a normal acid–base status ($P < 0.0001$).
Conclusions – The presence and magnitude of hyperlactatemia on presentation to the emergency room may help identify dogs and cats with high likelihood of in-hospital mortality, and the presence of lactic acidosis specifically may help identify dogs with yet higher risk of in-hospital mortality.

(J Vet Emerg Crit Care 2018; 28(1): 54–61) doi: 10.1111/vec.12676

Keywords: acidemia, base excess, hyperlactatemia, lactic acidosis, outcome

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Dr. Epstein is an Assistant Editor for the Journal but only participated in the peer review process as an author. The authors declare no other conflict of interest.

Presented in abstract form at the International Veterinary Emergency and Critical Care Symposium, Washington, DC, 2015 and the University of California, Davis, Veterinary Medical Teaching Hospital House Officer Seminar Day, 2015.

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Submitted November 01, 2015; Accepted April 27, 2016.

Abbreviations

AG	anion gap
BD	base deficit

Introduction

Plasma lactate concentration has been shown to have prognostic significance in human and veterinary patients. Hyperlactatemia has been associated with increased mortality in people in many clinical scenarios including trauma, infection, sepsis, and cardiac arrest.[1–7] Hyperlactatemia has been associated with poor outcome

in dogs with sepsis, gastric dilatation-volvulus, systemic hypotension, and immune-mediated hemolytic anemia.[8–11] In 2 recent studies, hyperlactatemia was associated with the need for blood transfusions in both dogs that sustained trauma and dogs that underwent splenectomy for splenic masses.[12,13] Additionally, lactate has been incorporated into 2 illness severity scores developed for canine and feline veterinary patients.[14,15] There are fewer studies evaluating the prognostic utility of lactate in cats. In contrast to many studies in people and dogs, a recent study reported that emergency room admission lactate concentration was not significantly different between cats that did or did not survive to hospital discharge.[16]

Acid–base parameters including blood pH, base deficit (BD), and anion gap (AG) have also been associated with outcome in human ICU and emergency room patients.[1,3,6,17] The association of acid–base parameters and outcome has not been well evaluated in small animal medicine. A study of dogs with blunt trauma found a low BD predicted transfusion requirements but not mortality.[18] Base deficit was also an independent predictor of mortality in dogs with sepsis and septic shock.[8] The prognostic utility of acid–base parameters has not previously been evaluated in a general emergency room population of dogs and cats.

The presence of hyperlactatemia is often assumed to indicate lactic acidosis, and thus it may be thought that acid–base evaluation is unneeded if plasma lactate concentration is known. However, hyperlactatemia can be present with a normal metabolic acid–base status, either due to the mechanism of lactate production, or due to a coexisting metabolic alkalosis.[19,20] For example, in a study of critically ill people with hyperlactatemia, 20% had normal acid–base parameters.[20] Although there is some suggestion in the human literature that lactic acidosis has a greater association with mortality than hyperlactatemia alone, there have been few studies evaluating this relationship.[21,22]

The aims of the current study were to evaluate association of plasma lactate concentration, pH, BD, and AG with survival to discharge of dogs and cats on presentation to an emergency room, and to compare the prognostic significance of hyperlactatemia occurring with a concurrent metabolic acidosis with that of hyperlactatemia and a normal metabolic acid–base balance.

Materials and Methods

An electronic database was used to retrieve the first venous blood acid–base, electrolyte concentration, and lactate concentration values analyzed on a point of care machine[a] for dogs and cats presenting to a university teaching hospital small animal emergency room between January 2010 and December 2011. Samples were excluded if they were obtained > 2 hours after presentation, as these were considered less likely to reflect patient status upon presentation to the emergency room.

Additional information obtained from the medical records of all identified cases included the clinical diagnosis and case outcome. Outcome was listed as alive or dead, including euthanasia, at that visit. The clinical diagnosis was categorized as ≥ 1 of the following based on review of the medical record: trauma or hemorrhage, sepsis, neoplasia, respiratory disease, cardiac disease, hepatic disease, gastrointestinal disease including pancreatitis, urinary tract disease including kidney disease, endocrine or reproductive disease, intracranial disease, hematologic disease, spinal cord disease, or toxicosis. If the final diagnosis did not fit into 1 of these categories, they were assigned a diagnosis of other.

The anion gap was calculated using the formula $AG = (Na + K) - (Cl + HCO_3)$.

Statistical analysis

Patients were categorized as having either hyperlactatemia, defined as a plasma lactate concentration of > 2.5 mmol/L, or a normal lactate concentration if ≤ 2.5 mmol/L. Patients were categorized as having lactic acidosis if they had hyperlactemia with a concurrent metabolic acidosis defined as a pH < 7.32 and BD < –4 mmol/L in dogs, and a pH < 7.34 and BD < –5 mmol/L in cats, based on previously established reference intervals from our institution. Dogs and cats that did not fulfill criteria for lactic acidosis or hyperlactatemia with normal acid–base parameters were not included for group comparisons.

Parameters were assessed for normality using the Shapiro–Wilk test. Data not normally distributed are presented as median and interquartile range. Two-group comparisons of binary outcomes were made using Fisher's exact test.[b] Distributions of nonnormally distributed data were compared between 2 groups using a Mann–Whitney U test.

Univariate logistic regression analyses were performed on plasma lactate concentration, pH, BD, and AG to assess their association with mortality.[c] *P*-values < 0.05 were considered statistically significant.

Variables that were significantly associated with mortality in univariate analysis were added to a multivariate model for logistic regression analysis. If 2 variables were highly correlated, as determined by a Pearson's correlation coefficient of > 0.6, only 1 of the variables was placed in the multivariate analysis to determine association with mortality.

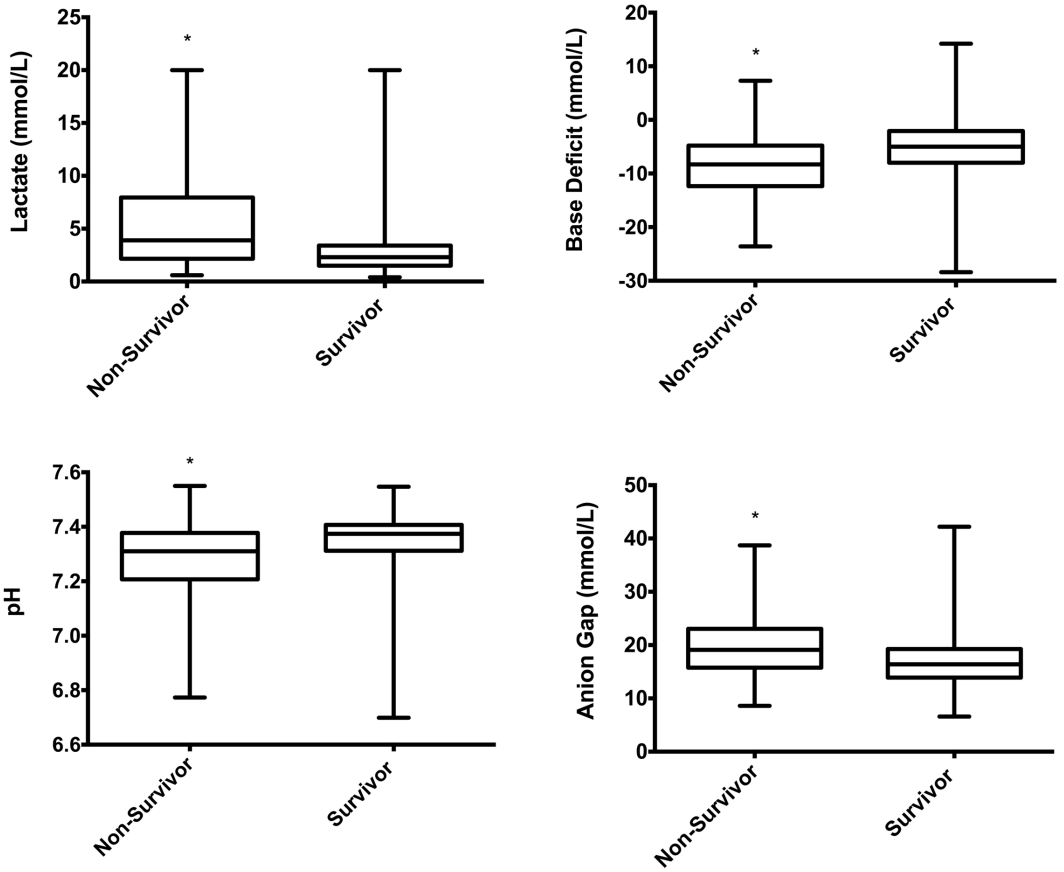

Figure 1: Box and whisker plots for plasma lactate concentration and acid–base values for 566 dogs that had venous blood gas analysis when presenting to an emergency room, grouped by mortality. For each box, the horizontal line represents the median value, and the upper and lower boundaries represent the 75th and 25th percentiles, respectively. Whiskers represent the minimum and maximum values.

*Compared to dog survivors $P < 0.0001$.

Results

In the 24 month study time period, 566 dogs and 185 cats had a venous blood gas analyzed within 2 hours of presentation. Of the animals included in this study, 302 dogs (53%) and 56 cats (30%) had a plasma lactate $>$ 2.5 mmol/L on presentation. Of the animals with hyperlactatemia, 127 (42%) dogs had a lactic acidosis while 50 (17%) dogs had hyperlactatemia in combination with normal acid–base status. Values for plasma lactate concentration, pH, BD, and AG for survivors and nonsurvivors are presented in Figures 1 and 2. Of the cats with hyperlactatemia, 45 (80%) had a lactic acidosis, while 5 (9%) cats had normal acid–base status. One hundred twenty-five dogs and 135 cats did not fulfill criteria for lactic acidosis or hyperlactatemia with normal acid–base parameters and were not included for group comparisons.

Clinical diagnoses of animals with hyperlactatemia are shown in Table 1 with the most common categories in dogs being traumatic injuries and hemorrhage (21%), neoplasia (19%), and gastrointestinal disease (19%). In cats the most common categories were urinary tract disease (25%), traumatic injuries and hemorrhage (21%), and gastrointestinal disease (13%).

Mortality for all animals included in the study was 34.8% for dogs and 28.6% for cats. Mortality and median plasma lactate concentration associated with acid–base diagnoses in dogs and cats are presented in Tables 2 and 3. Dogs with lactic acidosis had the highest mortality at 59.8%, while the lowest mortality was in dogs with a normal plasma lactate concentration (22.7%). The mortality of dogs with hyperlactatemia in conjunction with normal acid–base parameters (26%) was not significantly different than the mortality of dogs with a normal lactate concentration.

Cats with a normal blood lactate concentration had the lowest mortality at 22.6%, which was significantly different than the mortality in cats with hyperlactatemia

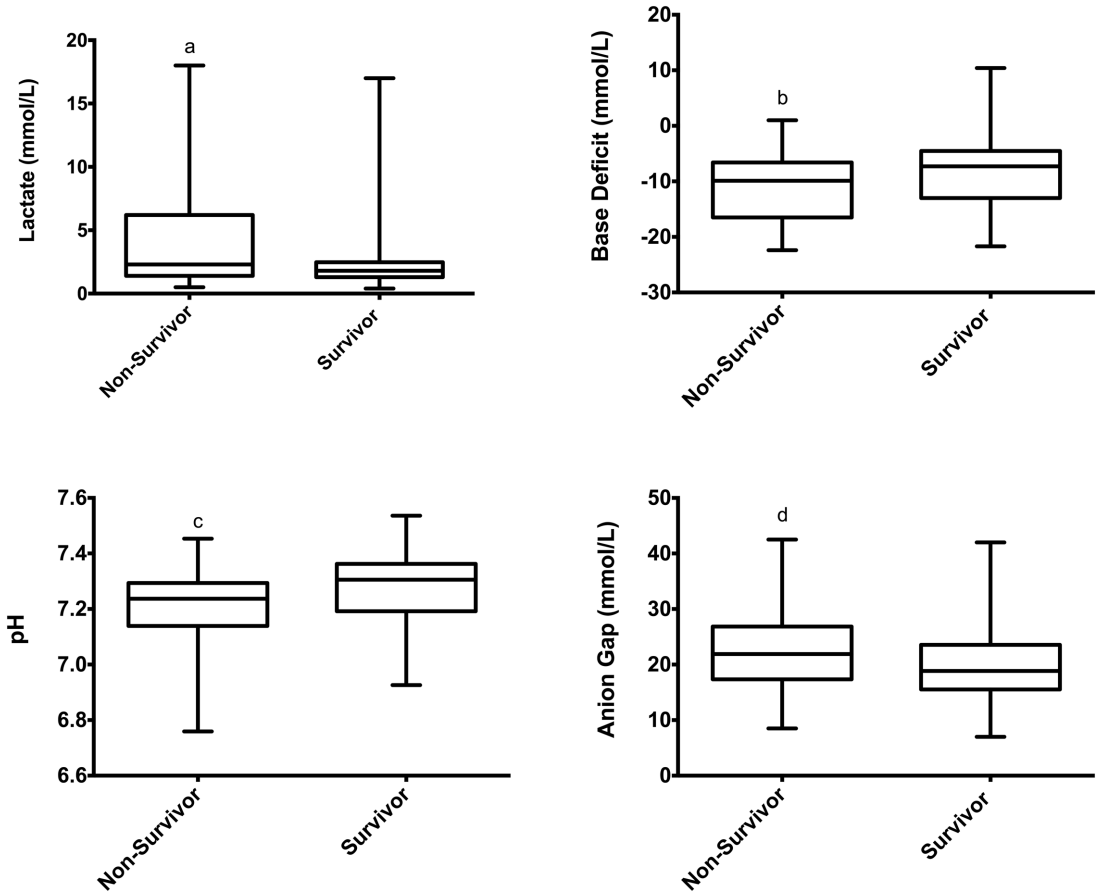

Figure 2: Box and whisker plots for plasma lactate concentration and acid–base values for 185 cats that had venous blood gas analysis when presenting to an emergency room, grouped by mortality. For each box, the horizontal line represents the median value, and the upper and lower boundaries represent the 75th and 25th percentiles, respectively. Whiskers represent the minimum and maximum values. a, $P = 0.015$; b, $P = 0.026$; c, $P = 0.001$; d, $P = 0.011$ when compared to survivor group of cats.

Table 1: Clinical diagnosis categories for dogs and cats that had hyperlactatemia on venous blood gas analysis when presenting to an emergency room

	Dogs			**Cats**		
	Hyperlactatemia *N* = 302 *n* (%)	**Lactic acidosis *N* = 127 *n* (%)**	**Hyperlactatemia with normal AB *N* = 50 *n* (%)**	**Hyperlactatemia *N* = 56 *n* (%)**	**Lactic acidosis *N* = 45 *n* (%)**	**Hyperlactatemia with *n*ormal AB *N* = 5 n (%)**
Trauma/hemorrhage	63 (21)	31 (24)	8 (16)	12 (21)	10 (22)	0
GI/pancreatitis	56 (19)	21 (17)	12 (24)	7 (13)	2 (4)	2 (40)
Neoplasia	57 (19)	25 (20)	5 (10)	4 (7)	3 (7)	1 (20)
Sepsis	26 (9)	14 (11)	0	5 (9)	4 (9)	1 (20)
Toxin	26 (9)	8 (6)	5 (10)	0	0	0
Intracranial disease	24 (8)	5 (4)	8 (16)	2 (4)	2 (4)	0
Respiratory disease	20 (7)	7 (6)	4 (8)	0	0	0
Cardiac disease	15 (5)	7 (6)	0	3 (5)	3 (7)	0
Endocrine/repro	16 (5)	10 (8)	2 (4)	1 (2)	1 (2)	0
Hematologic disease	14 (5)	5 (4)	2 (4)	5 (9)	5 (11)	0
Spinal disease	10 (3)	3 (2)	4 (8)	0	0	0
Hepatic disease	6 (2)	2 (2)	3 (6)	0	0	0
Renal/urinary disease	6 (2)	4 (3)	1 (2)	14 (25)	14 (31)	0
Other	12 (4)	5 (4)	3 (6)	4 (7)	2 (4)	2 (33)

AB, acid–base status; GI, gastrointestinal; *n*, number; repro, reproductive disease. Patients can be represented in > 1 category.

Table 2: Plasma lactate concentration and mortality outcome based on acid–base parameters in 566 dogs that had venous blood gas analysis when presenting to an emergency room [median and (interquartile range)]

	Median lactate mmol/L	Survivors	Nonsurvivors	Mortality (%)
All dogs ($n = 566$)	2.7 (1.6–4.6)	369	197	34.8
Normal plasma lactate concentration ($n = 264$)	1.6 (1.2–2.0)	204	60	22.7
Hyperlactatemia ($n = 302$)	4.3 (3.3–7.7)	165	137	45.4*
Lactic acidosis ($n = 127$)	7.1‡ (4.0–10.5)	51	76	59.8*,‡
Hyperlactatemia with normal acid–base ($n = 50$)	3.2 (2.7–3.8)	37	13	26†

*$P < 0.0001$.
†$P = 0.589$ when compared to normal lactate group.
‡$P < 0.0001$ when compared to hyperlactatemia with normal acid–base group.
n, number.

Table 3: Plasma lactate concentration and mortality based on acid–base parameters in 185 cats that had venous blood gas analysis when presenting to an emergency room [median and (interquartile range)]

	Median plasma lactate concentration (mmol/L)	Survivors	Nonsurvivors	Mortality (%)
All cats ($n = 185$)	1.9 (1.3–3.3)	132	53	28.6
Normal lactate ($n = 129$)	1.5 (1.2–2.0)	101	28	21.7
Hyperlactatemia ($n = 56$)	4.7 (3.5–8.7)	31	25	44.6*
Lactic acidosis ($n = 45$)	5.3 (3.6–8.7)	23	22	49†
Hyperlactatemia with normal acid–base ($n = 5$)	4.2 (3.0–8.4)	3	2	40‡,§

*$P = 0.002$.
†$P = 0.001$.
‡$P = 0.31$ when compared to the normal lactate group.
§$P = 0.31$ when compared to lactic acidosis.
n, number.

(44.6%). Cats with lactic acidosis had the highest mortality at 49%, however there was no significant difference between any of the acid–base subgroups.

Univariate regression analysis in both dogs and cats showed that plasma lactate concentration, pH, BD, and AG were all associated with mortality. Base deficit was excluded from the multivariate regression analysis because of a high degree of correlation between pH and BD in both dogs ($r = 0.61$) and cats ($r = 0.81$). The multivariate models are shown in Table 4. In cats, only plasma lactate concentration was independently associated with mortality. Anion gap was not a significant independent predictor of mortality in neither dogs or cats when controlling for the other variables in the model.

Table 4: Multivariate logistic regression analysis of plasma lactate concentration and acid–base parameters as independent predictors of mortality in 566 dogs and 185 cats that had venous blood gas analysis when presenting to an emergency room

		Odds ratio	95% confidence interval	*P* value
Dogs	Lactate	1.19	1.10–1.27	< 0.001
	pH	0.10	0.01–0.75	0.026
	Anion gap	1.02	0.99–1.06	0.224
Cats	Lactate	1.17	1.05–1.31	0.006
	pH	0.08	0.002–2.89	0.166
	Anion gap	1.00	0.95–1.3	0.947

Discussion

Hyperlactatemia was a common finding in this population of dogs presenting to the emergency room when a blood gas analysis was performed. In comparison, hyperlactatemia was less common in the cats evaluated in this study. There are few previous studies to which these results can be compared. A recent study at another university teaching hospital emergency room reported hyperlactatemia in 55% of cats in which plasma lactate was measured.[16] The difference in prevalence of hyperlactatemia in cats between the previous study and the current study may reflect differences in disease severity or clinician preference in what values are measured. These studies can only reflect the occurrence of hyperlactatemia in cats in which a clinician elected to evaluate plasma lactate concentration, not all cats

presenting to the emergency room. As such, the population evaluated will depend on clinician decision making, as well as any financial constraints of the owners. To the authors' knowledge, there are no previous studies reporting the prevalence of hyperlactatemia in dogs presenting to an emergency room. The prevalence of hyperlactatemia in human emergency patients has been reported to range from 15.5 to 31.3%.[23–26] However, given the differences in financial constraints and patient characteristics between veterinary and human patients, comparison of prevalence of hyperlactatemia between these groups may not be appropriate.

The prevalence of hyperlactatemia in a patient population is likely to depend on the diseases present in the patients evaluated. In this study, the most common clinical diagnoses in dogs with hyperlactatemia were trauma or hemorrhage, gastrointestinal diseases, and neoplasia. In contrast, urinary tract disease was the most common clinical diagnosis in cats with hyperlactatemia, followed by trauma or hemorrhage. It is unknown if the population presenting to our emergency room is representative of populations presenting to other veterinary emergency rooms. When comparing the population of cats in the current study with the previously mentioned study of cats presenting to an emergency room, there was a similar proportion of cats with renal disease and gastrointestinal disease, although the proportion of cats with trauma was greater in the current study.[16] Future multicenter investigations would help fully characterize the epidemiology of hyperlactatemia in small animal emergency room patients.

In both dogs and cats, plasma lactate concentration was a significant and independent predictor of mortality in this study. The odds of mortality increased with an increasing magnitude of hyperlactatemia, meaning that patients with a higher plasma lactate concentration had a higher likelihood of death. These findings are similar to the results of numerous human investigations. In a recent human study it was shown that a single arterial lactate concentration measurement on presentation to the emergency department predicts 30-day mortality independent of other measures of illness severity.[25] A systematic review including 8 publications found that even an intermediate increase in lactate concentration, defined as a lactate concentration between 2.0 and 3.9 mmol/L, was associated with a moderate to high risk of mortality in patients with suspected infection.[27] Another systematic review evaluating acutely ill patients admitted to the hospital concluded that all patients with a lactate concentration of > 2.5 mmol/L should be closely monitored for signs of deterioration, and several of the included studies demonstrated a positive correlation between lactate and mortality.[28] Lactate concentration has also been shown to have prognostic significance in a variety of veterinary disease populations.[8,9,11,29] Given the results of previous studies, in addition to the current investigation, routine plasma lactate concentration monitoring may be valuable in evaluation of the emergency room patient.

The venous blood pH remained an independent predictor of mortality in multivariate analysis for dogs but not cats in this study. Acid–base parameters have previously been associated with mortality in both human and veterinary patient populations.[3,18,30–32] In a large, heterogeneous group of human patients who visited the emergency department, a low pH was correlated with higher mortality.[32] Several acid–base parameters including pH, BD, and AG were able to discriminate survivors from nonsurvivors of major vascular injury, and BD on hospital admission was found to be an important indicator of mortality in human trauma patients.[3,31] In veterinary medicine, studies evaluating the association of acid–base disturbances with mortality have shown conflicting results. In a study of dogs presenting with blunt trauma, BD on admission predicted the need for transfusions, but was not independently associated with mortality.[18] In dogs with gastric-dilatation-volvulus, BD was found to be a poor predictor of outcome.[30] In contrast, a prospective study of 30 dogs with sepsis or septic shock reported that BD was independently associated with mortality. Additionally, along with central venous oxygen saturation, BD was one of the best discriminators between survivors and nonsurvivors.[8] There appears to be a growing body of evidence to support the role of acid–base parameters as markers of disease severity in dogs. As acid–base analysis generally requires a small volume of blood and is readily accessible in many practice settings, it lends itself to emergency room patient evaluation.

Although AG was associated with mortality in dogs and cats in univariate analysis in this study, it did not add predictive value when included in multivariate analyses. This suggests that pH is more useful, especially when evaluated in conjunction with plasma lactate concentration. Studies in people have reported conflicting results with regard to AG performance as a prognostic indicator.[33–36] A major limitation of AG is the impact of hypoalbuminemia.[37] To interpret AG in patients with hypoalbuminemia a correction formula can be used to account for the change in albumin concentration.[38] It is possible that AG would have had a stronger relationship with mortality in the multivariate analysis if a corrected AG value were analyzed. However, as albumin concentration is not readily available on many point-of-care analyzers, corrected AG values would require a serum biochemistry profile in many emergency patients.

In cats, plasma lactate concentration was the only parameter that was significantly associated with mortality in the multivariate models. There is a paucity of studies

looking at the association between plasma lactate concentration and mortality in cats and there is variability in the reported lactate concentration reference intervals of healthy cats.[39,40] A recent study of cats presenting to an emergency room found no significant difference in lactate concentration values for survivors compared to nonsurvivors.[16] In the current study, there was only a small, although significant, difference in median plasma lactate concentration between the cats that survived and those that did not. Unlike in dogs, acid–base derangements did not correlate with mortality in cats. This may have been a result of small sample size or differences in underlying disease processes. It is apparent that more studies are needed to further define the association between blood lactate concentration and mortality in cats.

In this study, the mortality of dogs with hyperlactatemia and a concurrent normal acid–base status was significantly lower than the mortality in dogs with lactic acidosis. This difference suggests that the presence of a lactic acidosis has prognostic significance while hyperlactatemia itself may not. Despite the large number of studies in human medicine evaluating the association of lactate concentration with outcome, few have compared the prognostic significance of hyperlactatemia with lactic acidosis. In people with hyperlactatemia due to sepsis and septic shock, arterial pH but not lactate concentration itself was an independent predictor of mortality.[22] In human ICU patients, a metabolic acidosis was associated with a higher mortality than normal acid–base parameters, with the highest mortality occurring in patients with lactic acidosis.[21] This suggests that measuring lactate concentration in combination with acid–base values may maximize the prognostic utility of these parameters.

There are several potential mechanisms by which hyperlactatemia can develop. The classic example of anaerobic metabolism is associated with hyperlactatemia and concurrent development of a metabolic acidosis. It is important to note that acid production during anaerobic metabolism occurs via a separate pathway than that of lactate anion generation. The concurrent accumulation of lactate and hydrogen ions leads to the commonly recognized "lactic acidosis." There are other mechanisms of hyperlactatemia that are not associated with concurrent metabolic acidosis. These include stimulation of cellular energetics by catecholamines or proinflammatory cytokines. This state of accelerated aerobic glycolysis occurs when carbohydrate metabolism exceeds the process of oxidative phosphorylation. Pyruvate is produced due to increased glycolysis, which leads to an accumulation of lactate.[41] Hyperlactatemia without acidosis can also occur with some neoplastic diseases or as an erroneous finding due to blood sample contamination by sodium lactate.[42–44] Given that the disease mechanisms leading to a lactic acidosis tend to differ from those that cause hyperlactatemia without an acidosis, it may explain why there is a difference in prognostic significance between these findings. This may further support the suggestion that the disease mechanisms responsible for lactic acidosis differ from those that cause hyperlactatemia without acidosis. This finding was not present in cats; however, only 5 cats had hyperlactatemia with normal acid–base status.

This study has several limitations inherent to a retrospective veterinary study. We included euthanasia in the mortality statistics and there was no standardization of the treatment the patients received. As a consequence the outcome in this study may not accurately reflect the severity of the primary disease process. As clinicians were not blinded in this study, blood lactate concentration may have influenced treatment recommendations and outcome. It is interesting to note that there were patients with a lactate of 20 mmol/L in both the survivor and nonsurvivor groups. Another possible limitation of our enrollment criteria is that therapy may have been provided prior to presentation, or between presentation and initial venous blood sampling. A future prospective study would be necessary to eliminate this concern. Additionally, serial analysis of lactate and acid–base values was not evaluated, which may have provided valuable information regarding response to therapy. This study could not determine an incidence of hyperlactatemia in emergency room patients as not all animals presenting to the emergency room have venous blood gas evaluation.

Recognition of animals that have a higher risk of mortality on presentation to the emergency room could help guide clinical management, as well as owner expectations. This study suggests that the presence and magnitude of hyperlactatemia might identify dogs and cats at high risk of in-hospital mortality, while acid–base parameters might further identify dogs with a higher risk of mortality. Evaluation of acid–base status in conjunction with blood lactate concentration analysis of dogs in the emergency room may have more value than plasma lactate concentration assessment alone. These findings should be supported with more studies on the performance of plasma lactate concentration and acid–base parameters as predictors of mortality in dogs and cats.

Footnote

[a] ABL 800, Radiometer Medical A/S, Copenhagen, Denmark.
[b] GraphPad Prism 6.0, Graph Pad Software, La Jolla, CA.
[c] Stata IC/12.1, StataCorp LP, College Station, TX.

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