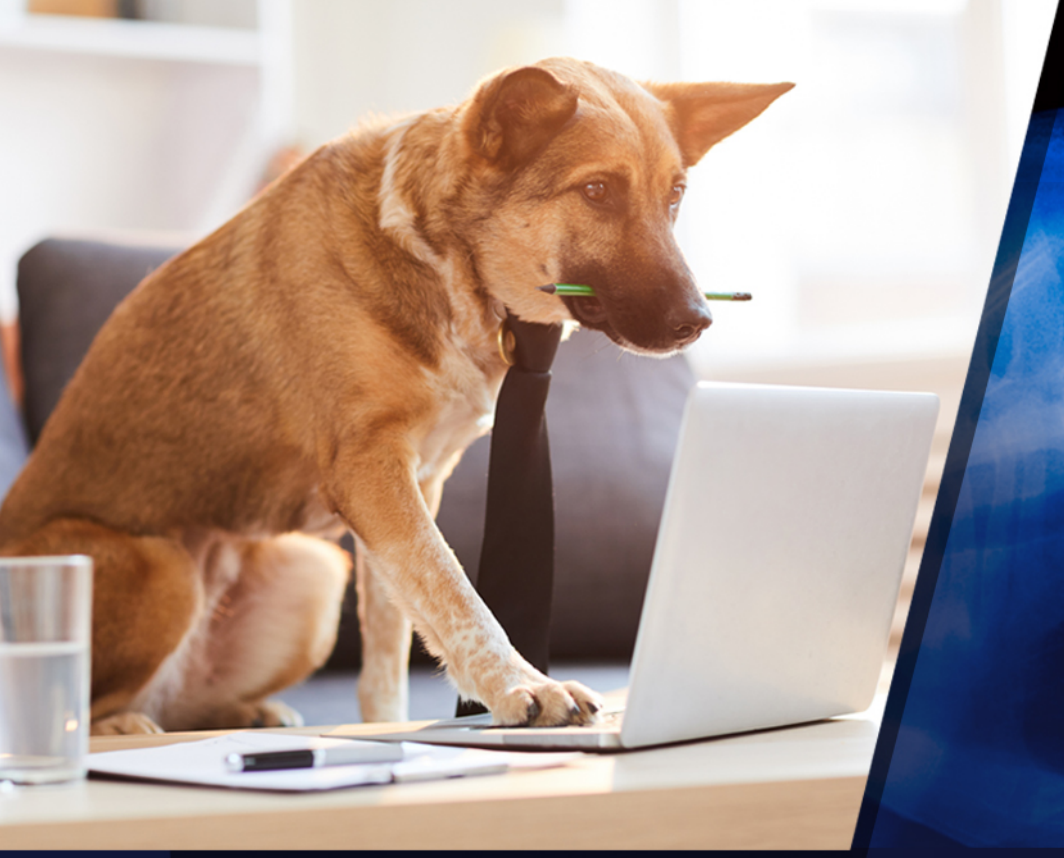

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Received: 15 January 2017 | Revised: 16 May 2017 | Accepted: 25 May 2017

DOI: 10.1111/vec.12868

ORIGINAL STUDY

Journal of Veterinary Emergency and Critical Care | WILEY

Utility of admission lactate concentration, lactate variables, and shock index in outcome assessment in dogs diagnosed with shock

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Presented in part as an abstract at the International Veterinary Emergency and Critical Care Symposium Grapevine, TX, September 2016.

Abstract

Objective: To determine whether admission venous plasma lactate concentration, calculated lactate variables, or shock index (SI) could discriminate hospital survivors from nonsurvivors in dogs admitted with shock.

Design: Prospective investigation performed over a 19-month period.

Setting: Large urban private teaching hospital.

Animals: Twenty-three dogs consecutively admitted to the ICU from January 2008 to July 2009 with initial peripheral venous plasma lactate concentration >2 mmol/L (18.0 mg/dL) and clinical and hemodynamic parameters consistent with shock.

Interventions: None.

Measurements and Main Results: Heart rate, systolic blood pressure, and venous plasma lactate concentrations were serially recorded at predefined time points and used to calculate SI (SI = heart rate/systolic blood pressure) and lactate variables, including lactime (time lactate > 2.0 mmol/L), lactate clearance ($[lactate_{initial} - lactate_{delayed}]/lactate_{initial} \times 100$), and LAC_{AREA} (area under the lactate concentration versus time curve). Primary outcome was survival to discharge. Overall survival rate was 61%. Admission venous plasma lactate concentration did not differ between groups ($P = 0.2$). Lactime was shorter in survivors versus nonsurvivors ($P = 0.02$). Lactate clearance at 1, 10, 16, 24, and 36 hours, and final lactate clearance were greater in survivors versus nonsurvivors ($P < 0.05$). LAC_{AREA} at time intervals 0–1, 1–4, 4–10, 10–16, 16–24, 24–30, and 30–36 hours was larger in nonsurvivors versus survivors ($P < 0.05$). Total LAC_{AREA} did not differ between groups ($P = 0.09$). Admission SI and time to normalize SI (SI < 0.9) were not different between survivors and nonsurvivors ($P > 0.05$).

Conclusions: While admission venous plasma lactate concentration could not discriminate between hospital survivors and nonsurvivors, lactate variables showed clinical utility to predict outcome in dogs with shock. Further studies are needed to determine SI reference ranges and optimal SI cut-off values to improve its prognostic ability in sick dogs.

KEYWORDS

canine, hypoperfusion, perfusion parameters, resuscitation

Abbreviations: ED, emergency department; HR, heart rate; SI, shock index; SBP, systolic blood pressure.

1 | INTRODUCTION

Shock characterized by inadequate cellular energy production occurs when oxygen delivery is insufficient to meet tissue metabolic needs.[1,2] Prolonged tissue hypoxia in hospitalized shock patients is an important contributor to patient morbidity and mortality.[3–7] Therefore, early recognition and correction of tissue hypoperfusion are paramount to improving outcomes in shock patients.

Various noninvasive and invasive methods intended to identify tissue hypoxia and guide resuscitation efforts have been reported.[1,2,8,9] Traditional endpoints of resuscitation, including heart rate (HR) and systolic blood pressure (SBP), are easily obtained at the bedside. However, these parameters may normalize despite ongoing shock and tissue hypoxia (ie, compensated shock) as evidenced by a persistently increased plasma lactate concentration or shock index (SI).[10–12] This suggests the need for assessment of more sensitive parameters that may improve the ability to diagnose occult shock.

Lactate, an intermediate metabolite formed from pyruvate during glycolysis, is produced in low concentrations during normal aerobic metabolism in health.[8,13–18] Tissue hypoperfusion and subsequent conversion to anaerobic metabolism is associated with a rise in plasma lactate concentration, as its production by hypoxic tissue overwhelms its hepatorenal elimination.[8,13–18] Therefore, increasing plasma lactate concentration serves as an indirect, downstream marker of global hypoperfusion and suggests accumulating oxygen debt.[8,13–15] Despite its usefulness in perfusion assessment, causes of an increased lactate concentration not related to tissue perfusion, such as muscle hyperactivity, accelerated aerobic glycolysis, systemic disease (eg, significant liver disease, diabetes mellitus, and renal disease), neoplasia, and pyruvate dehydrogenase inhibition, must be recognized.[2,8,13–18]

The superiority of plasma lactate concentration over traditional perfusion parameters and oxygen-derived variables in outcome prediction has been well established in heterogeneous populations of critically ill people.[19–21] Here, not only are single lactate concentration measurements related to morbidity and outcome,[22–29] but similarly are the duration of hyperlactatemia (ie, lactime),[5,6,23,24,29–32] the ability to clear lactate in response to resuscitative interventions (ie, lactate clearance),[20,25,33–38] and the area under the lactate concentration versus time curve.[23,24] Notably, lactate concentration relates to prognosis independent of shock or organ failure.[22]

SI, a ratio that relates HR to SBP as HR/SBP, has been proposed as a simple method to assess shock severity and response to therapy in critically ill people. In a healthy adult, the SI ranges from 0.5 to 0.7,[39] and a SI greater than 0.9 is considered high.[40–44] Early work demonstrated that SI was inversely related to left ventricular stroke work in acute circulatory failure.[39] Clinically, SI has been proposed as a measure of hemodynamic stability as well as a marker of early hypovolemia.[39,45] The value of SI in the prehospital and hospital settings in predicting both need for hospital admission and patient outcome has also been well established.[40–44,46]

Literature evaluating the use of plasma lactate indices and SI in outcome prediction in critically ill dogs and cats is relatively limited. The prognostic utility of both single and serial lactate concentration measurements in small animals has been described in injured and systemically ill dogs[47,48] and hospitalized cats,[49] as well as in a number of specific disease syndromes in dogs.[50–57] A recent study involving critically ill neonate foals reported that a novel parameter that incorporates both the severity and duration of hyperlactatemia, the area under the lactate concentration versus time curve (LAC_{AREA}), was significantly larger in nonsurvivors.[58] Two separate groups of investigators evaluating the clinical utility of SI in dogs demonstrated its potential usefulness in identifying shock in dogs[59] and also in suggesting ongoing hemorrhage.[60]

The purpose of the present study was to evaluate the clinical utility of admission venous plasma lactate concentration, calculated lactate variables (eg, lactime, lactate clearance, and LAC_{AREA}), admission SI, and time to normalize SI to help discriminate hospital survivors compared to nonsurvivors in a heterogeneous group of dogs admitted with shock.

2 | MATERIALS AND METHODS

Dogs that were consecutively presented to the emergency departments (ED) of a large urban private teaching hospital between January 2008 and July 2009 were eligible for study inclusion. Entry criteria required an admission peripheral venous plasma lactate concentration >2 mmol/L (18.0 mg/dL) and physical examination findings and hemodynamic parameters consistent with shock. The study protocol was approved by the Institutional Animal Care and Use Committee and informed client consent was obtained prior to study enrollment. Shock was defined as alterations in 3 or more of the following perfusion parameters: (1) capillary refill time > 2 seconds; (2) HR ≥ 150/min in dogs <15 kg or ≥ 120 /min in dogs ≥15 kg; (3) rectal temperature ≤ 37.7°C (≤ 99.8°F); and (4) mean arterial pressure (MAP) ≤ 60 mm Hg or SBP ≤ 90 mm Hg. Indirect systolic or systolic and mean arterial blood pressure measurements were obtained using either a Doppler* or oscillometric monitor,† respectively, on a peripheral limb utilizing a cuff size that was approximately 40% of the limb diameter. Cardiogenic shock patients were excluded on the basis of radiographic and echocardiographic findings consistent with cardiogenic pulmonary edema or systolic dysfunction in the presence of adequate intravascular volume.

Data recorded for each study participant at time of ED presentation included HR, respiratory rate, rectal temperature, capillary refill time, pulse quality, subjective assessment of distal extremity perfusion, and indirect blood pressure measurement as described above. Concurrently, 0.2–0.4 mL of venous blood was collected anaerobically into a heparinized syringe at time of initial peripheral catheter placement and analyzed immediately via a cage-side venous blood analyzer‡ to obtain the admission (0 hour) peripheral venous plasma lactate concentration. Following catheter placement, patients were resuscitated to traditional endpoints (ie, normalization of physical examination perfusion parameters and attainment of MAP > 60 mm Hg or SBP > 90 mm Hg) with the use of crystalloids, nonprotein colloids,

vasopressors, inotropes, or blood products chosen at the discretion of the attending criticalist or critical care resident.

Following initiation of resuscitation and ICU admission, a central sampling catheter was placed in the jugular, medial saphenous, or lateral saphenous vein; all subsequent blood samples obtained after 0 hour were collected via the central venous sampling catheter. Venous plasma lactate concentration as well as the aforementioned traditional perfusion parameters were obtained as described above and recorded at 0, 1, 4, 10, 16, 24, 30, 36, and 48 hours, and every 12 hours thereafter until death or hospital discharge. A missing value at any given time point was noted; however, patients with missing data were not excluded from the study unless 2 missing values were documented.

Serial venous plasma samples were analyzed to determine lactime, defined as the time in hours venous plasma lactate concentration was >2.0 mmol/L (18.0 mg/dL). If a patient died before normalization of lactate concentration was achieved, time of last increased venous plasma lactate concentration was used to determine lactime. Venous plasma lactate concentration measured at the predetermined time points was used to calculate lactate clearance using the formula: $[lactate_{initial} - lactate_{delayed}]/lactate_{initial} \times 100$, where $lactate_{delayed}$ equaled the central venous plasma lactate concentration measured at 1, 4, 10, 16, 24, 36, and 48 hours. Venous plasma lactate concentration measured immediately prior to discharge or death was used to calculate final lactate clearance using the formula: $[lactate_{initial} - lactate_{final}]/lactate_{initial} \times 100$. Sequential venous plasma lactate concentrations were finally used to calculate the area under the L-lactate concentration versus time curve (ie, LAC_{AREA}) for each time interval as well as for the total duration of hospitalization (ie, total LAC_{AREA}) by the trapezoidal method for numerical integration as previously described in equine neonates.[58]

SI, defined as HR/SBP, was determined for each study participant at the previously mentioned time points. A SI > 0.9 was considered abnormal. Serial SI measurements were assessed to determine the time to normalize SI, defined as the time in hours SI was > 0.9. If a patient died before normalization of SI was achieved, time of last increased SI was used.

Primary outcome was defined as survival to hospital discharge. Nonsurvivors were further described as being euthanized or having died during hospitalization. Lactate variables that were compared between survivors and nonsurvivors included admission (0 hour) venous plasma lactate concentration and lactime, along with lactate clearance measured immediately prior to discharge or death and at 1, 4, 10, 16, 24, 36, and 48 hours. Total LAC_{AREA}, as well as LAC_{AREA} measured at time intervals 0–1, 1–4, 4–10, 10–16, 16–24, 24–30, 30–36, and 36–48 hours, was compared between study groups. SI at admission (0 hour), as well as time needed to normalize SI to < 0.9, was compared between survivors and nonsurvivors.

3 | STATISTICAL METHODS

Baseline descriptive statistics are presented as mean and standard deviation (SD) for normally distributed variables, while nonnormally distributed variables are presented as median and range. Categorical variables were analyzed by a chi-square analysis. Between groups analyses were performed using ANOVA or the Wilcoxon as appropriate for the data distribution. The normality of the error residuals was analyzed by Kolmogorov–Smirnoff tests. All analyses were deemed significant at $P < 0.05$ as unadjusted probabilities and carried out using commercially available statistical software.[§]

4 | RESULTS

Twenty-three dogs were enrolled between January 2008 and July 2009. No dogs were excluded from the study due to missing data. The proportions of each sex (10 neutered females, 7 neutered males, 2 intact females, and 4 intact males) did not differ between survivors and nonsurvivors ($P = 0.55$). Mean (±SD) age of study survivors (6.1 ± 3.4 years) was not different compared to nonsurvivors (7.8 ± 3.3 years; $P = 0.25$). Mean body weight for survivors (25.0 ± 14.4 kg) did not differ from nonsurvivors (33.9 ± 23.9 kg; $P = 0.27$). The following breeds were represented in the study population: Rottweiler (2), Akita (2), English Bulldog (1), Doberman Pinscher (1), Cocker Spaniel (1), Bichon Frise (1), French Poodle (1), Weimaraner (1), Golden Retriever (1), German Shepherd (1), Labrador Retriever (1), Shih Tzu (1), Maltese (1), Bernese Mountain Dog (1), Japanese Chin (1), Portuguese Water Dog (1), Mastiff (1), Labrador Retriever-Standard Poodle (1), and mixed breed (3).

All dogs were diagnosed as having hypovolemic, hemorrhagic, distributive, or septic shock on the basis of physical examination, clinical pathologic, and diagnostic imaging findings. The predominant illnesses recorded at study entry were gastric dilatation-volvulus (GDV) (6), blunt trauma (5), heat stroke (2), and 1 each of the following: pancreatitis, Addisonian crisis, septic arthritis, myasthenia gravis with aspiration pneumonia, parvovirus, hemorrhagic gastroenteritis, and acute renal failure. A definitive diagnosis was not able to be made in 3 dogs but each exhibited hemodynamic parameters and increased venous plasma lactate concentrations that supported a diagnosis of shock.

Fourteen (61%) dogs survived to hospital discharge. Of the 9 that did not survive to discharge, 5 (56%) died while in the ICU and 4 (44%) were euthanized. Mean length of hospitalization for all dogs was 1.2 days (±1.1 days). Mean length of hospitalization was not different between survivors (1.2 ± 0.9 days) and nonsurvivors (1.1 ± 1.5 days; $P = 0.78$).

By study definition, all dogs were hyperlactatemic at time of hospital admission (0 hour). Mean admission venous plasma lactate concentration for all study participants was 7.0 mmol/L (±3.1 mmol/L) (63.1 ± 27.9 mg/dL). Mean admission venous plasma lactate concentration did not differ between survivors (6.3 ± 2.4 mmol/L; 56.8 ± 21.6 mg/dL) and nonsurvivors (8.1 ± 3.9 mmol/L; 73.0 ± 35.1 mg/dL; $P = 0.2$). Mean lactime for all dogs was 10.3 hours (±9.8 hours). Mean lactime was shorter in survivors (6.6 ± 4.4 hours) compared to nonsurvivors (16 ± 13.1 hours; $P = 0.02$) (Figure 1).

A greater mean lactate clearance was recorded in survivors compared to nonsurvivors at 1 hour (44.3 ± 27.4% vs 10.3 ± 46.3%;

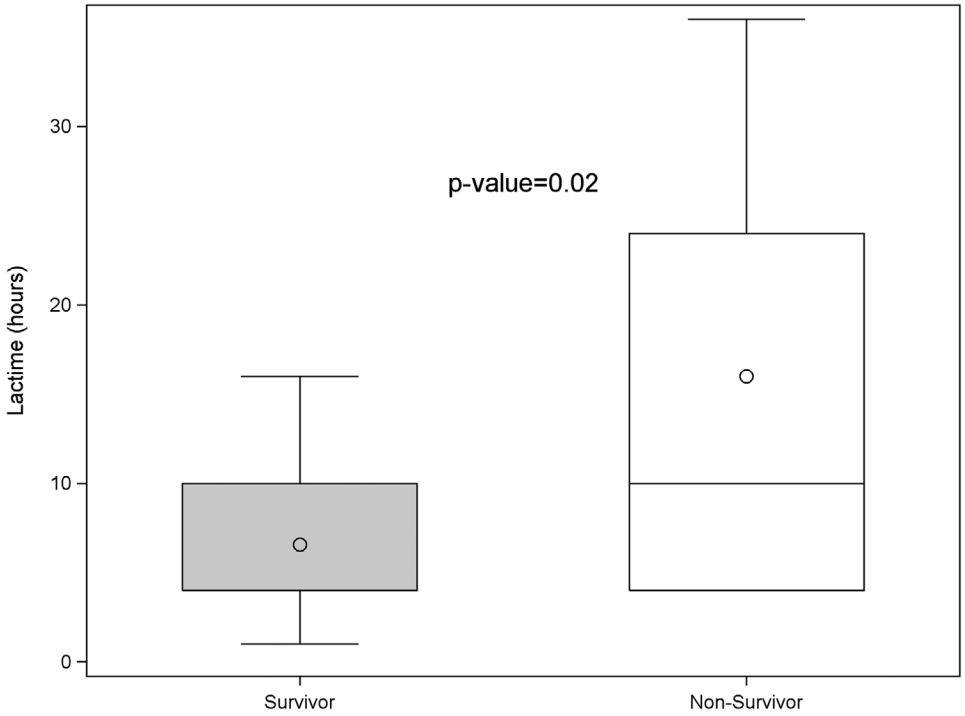

FIGURE 1 Comparison of lactime (hours) between surviving and nonsurviving dogs in shock. In each boxplot, the box represents the interquartile range, and the lines extending vertically represent the range of values. The line and open circle within each box represent the median and mean lactime, respectively. For survivors, the lower boundary of the box represents both the median and lower quartile for lactime as these values were identical. Significance was set at a *P*-value < 0.05

P = 0.04), 10 hours (72.5 ± 12.8% vs 45.3 ± 34.1%; *P* = 0.01), 16 hours (77.6 ± 16.2% vs 50.3 ± 22.2%; *P* = 0.006), 24 hours (83.8 ± 7.9% vs 56.0 ± 29.2%; *P* = 0.004), and 36 hours (86.3 ± 4.8% vs 65.0 ± 25.7%; *P* = 0.02) (Figure 2). Median and mean lactate clearances were not different between survivors and nonsurvivors at 4 hours (66.4%, range 25.4–84.6% vs 56.4%, range −228.9 to 80.4%; *P* = 0.15) and 48 hours (83.2 ± 5.1% vs 82.3 ± 9.3%; *P* = 0.82), respectively (Figure 2). Final mean lactate clearance was greater in survivors (83.7 ± 6.7%) compared to nonsurvivors (52.5 ± 26.2%; *P* < 0.001) (Figure 2).

Mean LAC_{AREA} was larger in nonsurvivors compared to survivors for all time intervals (0–1, 1–4, 4–10, 10–16, 16–24, and 30–36 hours; *P* < 0.05) except for the time interval 36–48 hours (*P* = 0.08) (Table 1). Mean total LAC_{AREA} was not different between survivors (60.3 ± 25.3 mmol/L·h) and nonsurvivors (84.7 ± 40.5 mmol/L·h; *P* = 0.09) (Table 1).

An increased SI (>0.9) was recorded in all dogs at admission (0 hour); mean admission SI for all dogs was 2.2 (±1.3). There was no difference between surviving and nonsurviving dogs with respect to mean admission SI (2.5 ± 1.6 vs 1.8 ± 0.4, respectively; *P* = 0.2) or mean time to normalize SI (12.6 ± 16.4 hours vs 27.8 ± 19.5 hours, respectively; *P* = 0.06).

5 | DISCUSSION

Decompensated shock associated with abnormal macrovascular perfusion is generally recognizable. In contrast, states of compensatory shock are more difficult to detect given evidence suggesting that the use of traditional vital signs (eg, HR and SBP) alone may leave a large proportion of critically ill people in a state of persistent tissue hypoxia.[8–12] The contribution of uncorrected tissue hypoxia to patient morbidity and mortality has been well established.[3–7] In contrast, timely restoration of tissue perfusion through early and aggressive resuscitative interventions has been associated with a survival benefit in hospitalized shock patients.[61] Toward this end, the usefulness of plasma lactate concentration in shock recognition and risk stratification has been documented,[19–38] proving superior to traditional perfusion parameters and oxygen-derived variables in outcome prediction.[19–21] Moreover, given the lack of evidence suggesting the superiority of either arterial over venous or peripheral over central blood samples for obtaining accurate lactate concentrations,[62,63] measurement of both peripheral and central venous plasma lactate concentration serves as a noninvasive means of assessing global tissue perfusion.

Numerous studies in critically ill people evaluating serial plasma lactate concentration measurement have demonstrated that persistent hyperlactatemia, represented by either a prolonged time to normalize plasma lactate concentration or lower lactate clearance, predicts in-hospital mortality[5,6,20,23–25,29–38] and secondary outcomes.[23,36,64,65] A lactate clearance of 10% or more during initial resuscitation has been reported to predict survival from shock,[34,35,38] and a well-cited study in human trauma patients found that all patients in whom lactate concentration normalized by 24 hours survived, whereas the survival rate decreased to 75% and 14% for those patients clearing lactate between 24 and 48 hours and after 48 hours, respectively.[30]

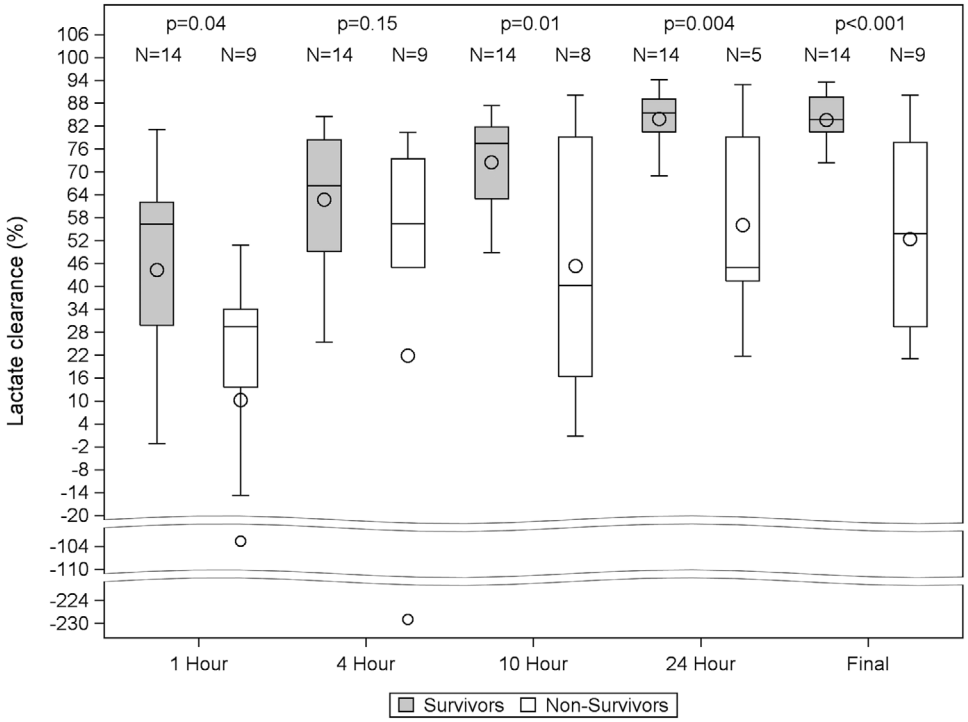

FIGURE 2 Comparison of lactate clearance (%) between surviving and nonsurviving dogs in shock during the first 24 hours of hospitalization and immediately prior to death or hospital discharge (final lactate clearance). In each boxplot, the box represents the interquartile range, and the lines extending vertically represent the range of values. The line and open circle within each box represent the median and mean lactate clearance, respectively. Significance was set at a *P*-value < 0.05

TABLE 1 Mean area under the lactate concentration versus time curve (LAC_{AREA}) in surviving and nonsurviving dogs in shock during the first 24 hours of hospitalization and throughout the entire hospitalization period

Time interval (hour)	Outcome	*N*	Mean ± SD (mmol/L·h)	*P*-value
0–1	Survivor	14	4.7 ± 1.5	0.02
	Nonsurvivor	9	7.2 ± 3.0	
1–4	Survivor	14	7.8 ± 2.8	<0.001
	Nonsurvivor	9	15.5 ± 5.4	
4–10	Survivor	14	10.9 ± 2.9	0.001
	Nonsurvivor	8	21.7 ± 10.1	
10–16	Survivor	14	8.4 ± 3.5	<0.001
	Nonsurvivor	7	22.1 ± 12.2	
16–24	Survivor	14	8.9 ± 4.6	<0.001
	Nonsurvivor	5	20.6 ± 8.1	
Total	Survivor	14	60.3 ± 25.3	0.09
	Nonsurvivor	9	84.7 ± 40.5	

Persistent hyperlactatemia has likewise been shown to be associated with mortality in specific canine disease conditions, including septic peritonitis,[51] GDV,[52,54] immune mediated hemolytic anemia,[50] and babesiosis,[56] as well as in equine patients presenting for emergency evaluation.[66,67] One study assessing sick dogs requiring intravenous fluid therapy demonstrated that failure to improve lactate concentration by at least 50% at 6 hours of hospitalization was significantly associated with mortality, and that a lactate concentration above the reference interval at the 6-hour time-point was associated with a 16-fold increase in the likelihood of nonsurvival.[48] A single study assessing serial lactate concentrations in hospitalized cats with wide range of illness severities reported no relation between serial lactate concentrations and survival to hospital discharge.[49]

In agreement with data reported from these human and veterinary studies, the present study demonstrates that sustained hyperlactatemia in small animal shock patients is associated with in-hospital mortality. Animals that survived to hospital discharge had a significantly shorter mean lactime as well as a significantly higher degree of lactate clearance at almost all time points evaluated. Lactime remained significantly shorter in surviving dogs despite the confounding effect of early deaths leading to a shorter observation period for a subset of the nonsurviving dogs, likely reinforcing the robust prognostic utility of this parameter in dogs with shock. Lactate concentration normalization's prognostic value is likely related to its suggested association with the success of resuscitative interventions in restoring adequate tissue perfusion and, therefore, reversing the detrimental effects of tissue hypoxia.[36]

Utilization of admission lactate concentration to assess human shock patients is more controversial and possibly less reliable for predicting outcome than is serial evaluation of this parameter,[34,68,69] although a linear increase in mortality has been reported in

association with increasing initial lactate concentrations by some investigators.[22–29] Similarly, veterinary studies evaluating the usefulness of single time-point lactate concentrations in outcome assessment have been undertaken with conflicting results. While one group of investigators evaluating sick dogs concluded that admission blood lactate concentration was not significantly related to outcome,[48] others reported a higher median admission lactate concentration in nonsurviving versus surviving dogs in shock.[47] Increased admission lactate concentrations have also been associated with increased mortality in dogs with specific disease conditions,[50–57] as well in adult equine patients with colic and those undergoing abdominal surgery,[66,70] and hospitalized equine neonates.[71,72] While research examining the prognostic utility of lactate concentration measurement in cats is more limited, one study performed in hospitalized cats found no significant association between initial lactate concentration and outcome.[49]

Like several other investigators, the present study did not demonstrate a difference in admission venous blood lactate concentration between survivors and nonsurvivors, and substantial overlap between the 2 groups was observed. Both the relatively small sample size and the study individuals' heterogeneous disease conditions with associated differing lactate kinetics likely contributed to the lack of a detectable difference in admission venous plasma lactate concentrations between groups. An increased admission lactate concentration retains most prognostic significance when occurring in disease conditions with a high mortality rate or an associated shock state that is less readily reversible despite aggressive resuscitation (ie, as in sepsis).[18] In contrast, admission hyperlactatemia holds less prognostic usefulness when present in a patient with a disease condition or shock state that is more readily corrected (ie, GDV).[18] The large degree of overlap in admission venous plasma lactate concentrations between groups in this study emphasizes the dangers of predicting an individual patient's outcome based on a single admission lactate concentration.

The influence of primary disease process on not only the prognostic utility of admission lactate concentration, but also on a patient's ability to normalize lactate concentration, must be acknowledged. Marked differences in lactate half-life based on primary disease, independent of resuscitation effects, have been demonstrated in hospitalized people.[17] Evidence in critically ill people also suggests survival differences among different classes of shock despite similarly increased lactate concentrations.[14] However, increased plasma lactate concentration has been demonstrated to be related to mortality independent of the underlying disease process in human shock patients.[33]

A less well-described parameter, LAC_{AREA}, has also been used in outcome assessment in human shock patients as it incorporates both the duration and severity of hyperlactatemia during ICU hospitalization. Several groups have demonstrated a significant association between a higher LAC_{AREA} and increased mortality in critically ill human patients.[23,24] Recent work in critically ill equine neonates reported similar results, finding that LAC_{AREA} during the first 24 hours of hospitalization was significantly larger in nonsurviving foals.[58] LAC_{AREA} proved to be significantly different between survivors and nonsurvivors at most time intervals studied in the present investigation. While final LAC_{AREA} was not different between survivors and nonsurvivors, this result was likely confounded by nonsurviving dogs that died early in the study period. Patients experiencing early deaths would inherently have shorter observation periods and therefore a smaller LAC_{AREA} despite disease severity. This parameter might provide a novel means to help evaluate the association of hyperlactatemia with outcome in animals in shock, but the more advanced calculation required for its determination may limit its clinical application.

SI has been extensively evaluated in the human literature as a simple and rapid bedside parameter for the detection of occult shock in the ED. Early investigators demonstrated that SI was inversely related to left ventricular stroke work, cardiac index, and oxygen delivery, as well as directly related to degree of blood loss.[39] These findings were supported by a later study that reported a direct correlation between SI and acute blood loss in healthy human blood donors.[45] Clinically, a SI greater than 0.9 has been associated with increased mortality in sick people,[41–44] and an increased SI has been associated with secondary outcomes, including need for massive transfusion,[43,46,73] vasopressor therapy,[42,73,74] and ventilatory support,[42,43] as well as with the development of organ failure.[74] Furthermore, when compared to the traditional hemodynamic parameters from which it is comprised, SI has proven to be superior in shock detection and outcome prediction in patients with normal HR and SBP.[10,12,40,44,75,76] Early work found that up to 94% of human shock patients with stable hemodynamic parameters had a persistently increased lactate concentration or SI indicative of ongoing global hypoperfusion.[12]

Studies examining the usefulness of SI to predict outcome in small animals with shock are limited, and to the authors' knowledge, work evaluating the SI in feline patients has not been reported. One group of investigators assessing the SI in both healthy dogs and dogs presenting to the ED found that dogs deemed to be in shock had a significantly higher SI than both healthy dogs and sick dogs with no signs of shock, supporting the usefulness of SI in discriminating shock in dogs.[59] Based on their results, this group of investigators suggested a SI cut-off of 1.0 to differentiate canine shock from nonshock patients.[59] A second group of investigators found that dogs in hemorrhagic shock had a significantly higher SI than healthy control dogs, suggesting that an increased SI should prompt a search for ongoing hemorrhage.[60]

In the present study, admission SI was not found to be different between survivors and nonsurvivors, and a large degree of overlap in admission SI values between survivors and nonsurvivors was observed. Survivors had a higher mean SI than nonsurvivors at admission, and the highest admission SI was recorded in a discharged animal. Time to normalize SI also did not differ between survivors and nonsurvivors.

The present findings are intriguing and support the need to establish reliable normal SI reference ranges as well as optimal cut-off values to aid in outcome prediction in dogs. Given species differences in the normal physiologic parameters, particularly HR, from which SI is derived, species-specific reference ranges should be established. The higher HR of healthy dogs compared to people makes a higher normal range of canine SI values likely. Furthermore, the effect on SI of inherent HR variability due to both body weight[77] and age must

be considered. One group of investigators assessing human trauma patients found that the addition of an age multiplier increased the usefulness of the SI in outcome prediction in older patients,[76] and neonatal and pediatric animals are known to have an inherently higher HR than their adult counterparts.[78] In the present study, the highest canine SI was seen in a 4-month-old patient with parvovirus that survived to hospital discharge.

Notably, all dogs included in the study's shock cohort had a SI greater than 0.9, the accepted cut-off value for differentiating human shock from nonshock patients. While this SI cut-off extrapolated from the human literature correctly identified the present study's shock population, admission SI was not able to discriminate between surviving and nonsurviving dogs. Moreover, the group of survivors did not collectively achieve a mean SI less than 0.9 until 10 hours of hospitalization, diminishing its utility as a potential triage tool, an area where the SI has proved most useful in human medicine.

The current study has a number of limitations in addition to those discussed previously. While the data were collected prospectively, several years lapsed between data collection and analysis. This raises the potential for shifts in treatment paradigms that would diminish the applicability of the study findings to current shock patients. However, research in critically ill people undertaken over several decades has established the clinical utility of both lactate parameters and SI in outcome prediction regardless of changing resuscitation protocols.[19–38,40–44,46] Additionally, as resuscitation of shock patients in the present study was not standardized and was directed by multiple clinicians, the effect of variable treatment protocols on normalization of plasma lactate concentration and SI cannot be assessed. Until protocolized resuscitation becomes more widely adopted in veterinary medicine, lack of standardized treatment bundles will continue to influence future research findings.

An inherent limitation associated with the use of plasma lactate concentration measurement in critically ill patients is the fact that hyperlactatemia in these patients is not specific for diagnosis of tissue hypoperfusion.[2,8,13–18] Hyperlactatemia has classically been characterized as Type A or B, with the former consisting of increased lactate production due to tissue hypoxia and the latter representing all other causes of hyperlactatemia.[8,13,14,17,18] Although Type A hyperlactatemia is most common in shock patients, the complexity of disease affecting critically ill patients means that detectable hyperlactatemia can result from variable combinations of both Types A and B. It is important to acknowledge the contribution of Type B causes to a patient's hyperlactatemia as these may lead to a potential overestimation of a patient's true oxygen debt. In critically ill patients, conditions that can lead to lactate concentration increase irrespective of global tissue perfusion include, but are not limited to, muscle hyperactivity, accelerated aerobic glycolysis, significant liver disease, diabetes mellitus, renal disease, neoplasia, catecholamine infusion, and pyruvate dehydrogenase inhibition as can be seen in septic shock.[2,8,13–18]

Factors intrinsic to diagnostic techniques could have affected study results. Noninvasive BP measurements were obtained using both Doppler and oscillometric methods. These methods have been shown to be most inaccurate in the setting of significant hypotension,[79,80] which is present in the majority of patients early in the course of hospitalization. While blood sampling site was likely standardized for an individual patient through use of a single sampling catheter for serial blood collection, the vessel used for sampling catheter placement was not standardized between patients in the present study. Furthermore, the present study recorded both peripheral venous plasma lactate concentration at 0 hour, as well as central plasma lactate concentration at all subsequent time points. Evidence suggests, however, that small differences in plasma lactate concentration based on sampling site (ie, specific vessel or peripheral versus central venous sample) are not clinically significant.[62,63]

In the present study, no attempt was made to stratify patients based on illness severity, meaning the inherent effect of illness severity on mortality could not be evaluated. Additionally, the study's small sample size may lessen the applicability of the present results to a larger population of sick dogs. As is the case in most studies in veterinary medicine, the confounding effect of early death due to euthanasia on mortality must be considered. However, in the present study, the majority (56%) of patients that did not survive to hospital discharge died while in the ICU, meaning only 44% of patient deaths were due to euthanasia. All patients in the present study were enrolled following ICU admission, with owners being made aware of the likely financial commitment to patient care. This potentially lessened the confounding effect of euthanasia due to financial constraints on mortality.

In summary, the present study reinforces the usefulness of plasma lactate parameters in dogs in shock. In particular, the findings suggest the superiority of serial venous plasma lactate concentration evaluation over single time point admission venous plasma lactate concentration measurement in differentiating hospital survivors from nonsurvivors. Future research evaluating a larger population of critically ill dogs to allow for subgroup analysis is needed to determine if lactate parameters demonstrate enhanced prognostic ability in one particular shock class or disease process. The results of the current study additionally bring into question the applicability of extrapolating a normal SI cut-off value of 0.9 from the human literature for use in small animal shock patients. Further investigation to establish both normal canine SI reference ranges, as well as optimal cut-off values for shock discrimination and prognostication in small animals with shock, needs to be undertaken.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ENDNOTES

* Doppler ultrasonic flow detector, Parks Medical Electronics, Inc., Las Vegas, NV.

† Cardell 9401/9402 veterinary monitor, Midmark Corporation, Dayton, OH.

‡ Bayer Rapidlab 860, Bayer Healthcare LLC, Tarrytown, NY.

§ SAS 9.4, SAS Institute, Inc., Cary, NC.

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REFERENCES

1. de Laforcade A, Silverstein DC. Shock. In: Silverstein DC, Hopper K, eds. *Small Animal Critical Care Medicine*. 2nd ed. St. Louis, MO: Saunders Elsevier; 2015:26–30.
2. Pieracci FM, Biffl WL, Moore EE. Current concepts in resuscitation. *J Intensive Care Med*. 2011;*27*:79-96.
3. Blow O, Magliore L, Claridge JA, et al. The golden hour and the silver day: detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. *J Trauma*. 1999;*47*:964-969.
4. Crowl AC, Young JS, Kahler DM, et al. Occult hypoperfusion is associated with increased morbidity in patients undergoing early femur fracture fixation. *J Trauma*. 2000;*48*:260-267.
5. Claridge JA, Crabtree TD, Pelletier SJ, et al. Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. *J Trauma*. 2000;*48*:8-14.
6. Meregalli A, Oliveira RP, Friedman G. Occult hypoperfusion is associated with increased mortality in hemodynamically stable, high-risk, surgical patients. *Crit Care*. 2004;*8*:R60-R65.
7. Howell MD, Donnino M, Clardy P, et al. Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Med*. 2007;*33*:1892-1899.
8. Prittie J. Optimal endpoints of resuscitation and early goal-directed therapy. *J Vet Emerg Crit Care*. 2006;*16*:329-339.
9. Napolitano LM. Resuscitation endpoints in trauma. *Transfus Altern Transfus Med*. 2005;*6*:6-14.
10. Rady MY. The role of central venous oximetry, lactic acid concentration and shock index in the evaluation of clinical shock: a review. *Resuscitation*. 1992;*24*:55-60.
11. Rady MY, Rivers EP, Nowak RM. Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. *Am J Emerg Med*. 1996;*14*:218-225.
12. Rady MY, Rivers EP, Martin GB, et al. Continuous central venous oximetry and shock index in the emergency department: use in the evaluation of clinical shock. *Am J Emerg Med*. 1992; *10*:538-541.
13. Allen SE, Holm JL. Lactate: physiology and clinical utility. *J Vet Emerg Crit Care*. 2008;*18*:123-132.
14. Lagutchik MS, Ogilvie GK, Wingfield WE, Hackett TB. Lactate kinetics in veterinary critical care: a review. *J Vet Emerg Crit Care*. 1996;*6*:81-95.
15. Bakker J, Nijsten MW, Jansen TC. Clinical use of lactate monitoring in critically ill patients. *Ann Intensive Care*. 2013;*3*:12.
16. De Backer D. Lactic acidosis. *Intensive Care Med*. 2003;*29*:699-702.
17. Pang DS, Boysen S. Lactate in veterinary critical care: pathophysiology and management. *J Am Anim Hosp Assoc*. 2007;*43*:270-279.
18. Rosenstein PG, Hughes D. Hyperlactatemia. In: Silverstein DC, Hopper K, eds. *Small Animal Critical Care Medicine*. 2nd ed. St. Louis, MO: Saunders Elsevier; 2015:300–305.
19. Jansen TC, van Bommel J, Mulder PG, et al. The prognostic value of blood lactate levels relative to that of vital signs in the pre-hospital setting: a pilot study. *Crit Care*. 2008;*12*:R160.
20. Bakker J, Coffernils M, Leon M, et al. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. *Chest*. 1991;*99*:956-962.
21. Musikatavorn K, Thepnimitra S, Komindr A, et al. Venous lactate in predicting the need for intensive care unit and mortality among nonelderly sepsis patients with stable hemodynamic. *Am J Emerg Med*. 2015;*33*:925-930.
22. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*. 2009;*37*:1670-1677.
23. Bakker J, Gris P, Coffernils M, et al. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg*. 1996;*171*:221-226.
24. van Beest PA, Brander L, Jansen SP, et al. Cumulative lactate and hospital mortality in ICU patients. *Ann Intensive Care*. 2013;*3*:6.
25. Nichol A, Bailey M, Egi M, et al. Dynamic lactate indices as predictors of outcome in critically ill patients. *Crit Care*. 2011;*15*:R242.
26. Houwink AP, Rijkenberg S, Bosman RJ, van der Voort PH. The association between lactate, mean arterial pressure, central venous oxygen saturation and peripheral temperature and mortality in severe sepsis: a retrospective cohort analysis. *Crit Care*. 2016;*20*:56.
27. Khosravani H, Shahpori R, Stelfox HT, et al. Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. *Crit Care*. 2009;*13*:R90.
28. Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in patients with infection. *Intensive Care Med*. 2007;*33*:970-977.
29. Manikis P, Jankowski S, Zhang H, et al. Correlation of serial blood lactate levels to organ failure and mortality after trauma. *Am J Emerg Med*. 1995;*3*:619-622.
30. Abramson D, Scalea TM, Hitchcock R, et al. Lactate clearance and survival following injury. *J Trauma*. 1993;*35*:584-589.
31. McNelis J, Marini CP, Jurkiewicz A, et al. Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit. *Am J Surg*. 2001;*182*:481-485.
32. Husain FA, Martin MJ, Mullenix PS, et al. Serum lactate and base deficit as predictors of mortality and morbidity. *Am J Surg*. 2003;*185*:485-491.
33. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med*. 2010;*182*:752-761.
34. Vincent JL, Dufaye P, Berre J, et al. Serial lactate determinations during circulatory shock. *Crit Care Med*. 1983;*11*:449-451.
35. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med*. 2004;*32*:1637-1642.
36. Nguyen HB, Loomba M, Yang JJ, et al. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. *Journal of Inflamm*. 2010;*7*:6.
37. Marty P, Roquilly A, Vallee F, et al. Lactate clearance for death prediction in severe sepsis or septic shock patients during the first 24 hours in intensive care unit: an observational study. *Ann of Intensive Care*. 2013;*3*:3.
38. Arnold RC, Shapiro NI, Jones AE, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock*. 2009;*32*:35-39.
39. Rady MY, Nightingale P, Little RA, Edwards JD. Shock index: a re-evaluation in acute circulatory failure. *Resuscitation*. 1992;*23*:227-234.
40. Rady MY, Smithline HA, Blake H, et al. A comparison of the shock index and conventional vital signs to identify acute, critical illness in the emergency department. *Ann Emerg Med*. 1994;*24*:685-690.
41. Montoya KF, Charry JD, Calle-Toro JS, et al. Shock index as a mortality predictor in patients with acute polytrauma. *J Acute Dis*. 2015;*4*:202-204.
42. Cevik AA, Dolgun H, Oner S, et al. Elevated lactate level and shock index in nontraumatic hypotensive patients presenting to the emergency department. *Eur J Emerg Med*. 2015;*22*:23-28.
43. McNab A, Burns B, Bhullar I, et al. A prehospital shock index for trauma correlates with measures of hospital resource use and mortality. *Surgery*. 2012;*152*:473-476.

44. Cannon CM, Braxton CC, Kling-Smith M, et al. Utility of the shock index in predicting mortality in traumatically injured patients. *J Trauma*. 2009;*67*:1426-1430.
45. Birkhahn RH, Gaeta TJ, Terry D, et al. Shock index in diagnosing early acute hypovolemia. *Am J Emerg Med*. 2005;*23*:323-326.
46. Pandit V, Rhee P, Hashmi A, et al. Shock index predicts mortality in geriatric trauma patients: an analysis of the National Trauma Data Bank. *J Trauma Acute Care Surg*. 2014;*76*:1111-1115.
47. Lagutchik MS, Ogilvie GK, Hackett TB, Wingfield WE. Increased lactate concentrations in ill and injured dogs. *J Vet Emerg Crit Care*. 1998;*8*:117-127.
48. Stevenson CK, Kidney BA, Duke T, et al. Serial blood lactate concentrations in systemically ill dogs. *Vet Clin Pathol*. 2007;*36*:234-239.
49. Redavid LA, Sharp CR, Mitchell MA, Beckel NF. Hyperlactatemia and serial lactate measurements in sick cats. *J Vet Emerg Crit Care*. 2016;*26*:495-501.
50. Holahan ML, Brown AJ, Drobatz KJ. The association of blood lactate concentration with outcome in dogs with idiopathic immune-mediated hemolytic anemia: 173 cases (2003-2006). *J Vet Emerg Crit Care*. 2010;*20*:413-420.
51. Cortellini S, Seth M, Kellett-Gregory LM. Plasma lactate concentrations in septic peritonitis: a retrospective study of 83 dogs (2007-2012). *J Vet Emerg Crit Care*. 2015;*25*:388-395.
52. Green TI, Tonozzi CC, Kirby R, Rudloff E. Evaluation of initial plasma lactate values as a predictor of gastric necrosis and initial and subsequent plasma lactate values as a predictor of survival in dogs with gastric dilatation-volvulus: 84 dogs (2003-2007). *J Vet Emerg Crit Care*. 2011;*21*:36-44.
53. Beer KA, Syring RS, Drobatz KJ. Evaluation of plasma lactate concentration and base excess at the time of hospital admission as predictors of gastric necrosis and outcome and correlation between those variables in dogs with gastric dilatation-volvulus: 78 cases (2004-2009). *J Am Vet Med Assoc*. 2013;*242*:54-58.
54. Zacher LA, Berg J, Shaw SP, Kudej RK. Association between outcome and changes in plasma lactate concentration during presurgical treatment in dogs with gastric dilatation-volvulus: 64 cases (2002-2008). *J Am Vet Med Assoc*. 2010;*236*:892-897.
55. Jacobson LS, Lobetti RG. Glucose, lactate, and pyruvate concentrations in dogs with babesiosis. *Am J Vet Res*. 2005;*66*:244-250.
56. Nel M, Lobetti RG, Keller N, Thompson PN. Prognostic value of blood lactate, blood glucose, and hematocrit in canine babesiosis. *J Vet Intern Med*. 2004;*18*:471-476.
57. Sharma D, Holowaychuk MK. Retrospective evaluation of prognostic indicators in dogs with head trauma: 72 cases (January-March 2011). *J Vet Emerg Crit Care*. 2015;*25*:631-639.
58. Wilkins PA, Sheahan BJ, Vander Werf KA, et al. Preliminary investigation of the area under the L-lactate concentration-time curve (LAC_{AREA}) in critically ill equine neonates. *J Vet Intern Med*. 2015;*29*:659-662.
59. Porter AE, Rozanski EA, Sharp CR, et al. Evaluation of the shock index in dogs presenting as emergencies. *J Vet Emerg Crit Care*. 2013;*23*:538-544.
60. Peterson KL, Hardy BT, Hall K. Assessment of shock index in healthy dogs and dogs in hemorrhagic shock. *J Vet Emerg Crit Care*. 2013;*23*:545-550.
61. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;*345*:1368-1377.
62. Hughes D, Rozanski ER, Shofer FS, et al. Effect of sampling site, repeated sampling, pH, and PCO_2 on plasma lactate concentration in healthy dogs. *Am J Vet Res*. 1999;*60*:521-524.
63. Gallagher EJ, Rodriguez K, Touger M. Agreement between peripheral venous and arterial lactate levels. *Ann Emerg Med*. 1997;*29*:479-483.
64. Jansen TC, van Bommel J, Woodward R, et al. Association between blood lactate levels, Sequential Organ Failure Assessment subscores, and 28-day mortality during early and late intensive care unit care stay: a retrospective observational study. *Crit Care Med*. 2009;*37*:2369-2374.
65. Chertoff J, Chisum M, Simmons L, et al. Prognostic utility of plasma lactate measured between 24 and 48 h after initiation of early goal-directed therapy in the management of sepsis, severe sepsis, and septic shock. *J Intensive Care*. 2016;*4*:13.
66. Tennent-Brown BS, Wilkins PA, Lindborg S, et al. Sequential plasma lactate concentrations as prognostic indicators in adult equine emergencies. *J Vet Intern Med*. 2010;*24*:198-205.
67. Hashimoto-Hill S, Magdesian KG, Kass PH. Serial measurement of lactate concentration in horses with acute colitis. *J Vet Intern Med*. 2011;*25*:1414-1419.
68. Pal JD, Victorino GP, Twomey P, et al. Admission serum lactate levels do not predict mortality in the acutely injured patient. *J Trauma*. 2006;*60*:583-587.
69. Bernardin G, Pradier C, Tiger F, et al. Blood pressure and arterial lactate level are early indicators of short-term survival in human septic shock. *Intensive Care Med*. 1996;*22*:17-25.
70. Radcliffe RM, Divers TJ, Fletcher DJ, et al. Evaluation of L-lactate and cardiac troponin I in horses undergoing emergency abdominal surgery. *J Vet Emerg Crit Care*. 2012;*22*:313-319.
71. Borchers A, Wilkins PA, Marsh PM, et al. Sequential L-lactate concentration in hospitalised equine neonates: a prospective multicentre study. *Equine Vet J*. 2013;*45*:2-7.
72. Wotman K, Wilkins PA, Palmer JE, Boston RC. Association of blood lactate concentration and outcome in foals. *J Vet Intern Med*. 2009;*23*:598-605.
73. Mutschler M, Nienaber U, Munzberg M, et al. The shock index revisited—a fast guide to transfusion requirement? A retrospective analysis on 21,853 patients derived from the TraumaRegister DGU. *Crit Care*. 2013;*17*:R172.
74. Wira CR, Francis MW, Bhat S, et al. The shock index as a predictor of vasopressor use in emergency department patients with severe sepsis. *West J Emerg Med*. 2014;*15*:60-66.
75. Zampieri FG, Colombari F. Use of shock index as a prognostic marker in patients with normal heart rate and blood pressure at ICU admission. *Intensive Care Med Exp*. 2015;*3*:A596.
76. Zarzaur BL, Croce MA, Fischer PE, et al. New vitals after injury: shock index for the young and age x shock index for the old. *J Surg Res*. 2008;*147*:229-236.
77. Hezzell MJ, Humm K, Dennis SG, et al. Relationship between heart rate and age, bodyweight and breed in 10,849 dogs. *J Small Anim Pract*. 2013;*54*:318-324.
78. Moon PF, Massat BJ, Pascoe PJ. Neonatal critical care. *Vet Clin North Am Small Anim Pract*. 2001;*31*:343-367.
79. Shih A, Robertson S, Vigani A, et al. Evaluation of an indirect oscillometric blood pressure monitor in normotensive and hypotensive anesthetized dogs. *J Vet Emerg Crit Care*. 2010;*20*:313-318.
80. Bosiack AP, Mann FA, Dodam JR, et al. Comparison of ultrasonic Doppler flow monitor, oscillometric, and direct arterial blood pressure measurements in ill dogs. *J Vet Emerg Crit Care*. 2010;*20*:207-215.

How to cite this article: Zollo AM, Ayoob AL, Prittie JE, Jepson RD, Lamb KE, Fox PR. Utility of admission lactate concentration, lactate variables, and shock index in outcome assessment in dogs diagnosed with shock. *J Vet Emerg Crit Care*. 2019;29:505–513. https://doi.org/10.1111/vec.12868