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The full details of the published version of the article are as follows:

TITLE: Plasma lactate concentrations in septic peritonitis: A retrospective study of 83 dogs (2007-2012)

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JOURNAL TITLE: JOURNAL OF VETERINARY EMERGENCY AND CRITICAL CARE

PUBLISHER: Wiley

PUBLICATION DATE: May/June 2015

DOI: [10.1111/vec.12234](https://doi.org/10.1111/vec.12234)

1 **Plasma lactate concentrations in septic peritonitis: a retrospective study of 83 dogs**
2 **(2007-2012)**

3

4 **Abstract**

5 Objective: To determine if absolute lactate or lactate clearance in patients with septic
6 peritonitis is associated with morbidity and mortality.

7

8 Design: Retrospective cohort study from 2007-2012.

9

10 Setting: University teaching hospital accepting referrals and primary emergencies.

11

12 Animals: Eighty-three dogs diagnosed with septic peritonitis were included. All the patients
13 had at least one lactate measurement taken during the course of the hospitalization.

14

15 Results: Sixty-four percent of the patients survived to discharge, 22% were euthanized and
16 14% died during hospitalization. Hyperlactatemia on admission (29% of the patients) was
17 associated with mortality ($p=0.001$). Median admission lactate was significantly different
18 between non-survivors (2.5 mmol/l, range 0.5-8.4) and survivors (1.4 mmol/l, range 0.5-9.7)
19 ($p=0.007$). Admission lactate higher than 4 mmol/l yielded a sensitivity of 36% and a
20 specificity of 92% for non-survival. The inability to clear lactate within 6 hours yielded a
21 sensitivity of 76% and specificity of 100% for non-survival. Post-operative hyperlactatemia
22 had a sensitivity of 46% and specificity of 88% for non-survival. Persistent post-operative
23 hyperlactatemia had a sensitivity of 93% and a specificity of 100% for non-survival. Area

1 under the curve (AUC) for lactate clearance at 6 hours was 0.85 and the best cut-off was 62%
2 (sensitivity 66% and specificity 80% for non-survival). AUC for lactate clearance at 12 hours
3 was 0.92, with the best cut-off value defined as 57% (sensitivity of 86% and a specificity of
4 100% for non-survival).

5 Conclusions: In this study absolute lactate and lactate clearance were good prognostic
6 indicators in septic peritonitis. Further studies are needed to assess its role as a resuscitative
7 end-goal parameter.

8

9

1 **Introduction**

2 Septic peritonitis is defined as the presence of bacteria in the peritoneal cavity¹. It carries
3 a high mortality with a reported survival to discharge rate in dogs ranging from 29% to 71%
4 ¹⁻³.

5 Septic peritonitis can be either primary or secondary to intra-abdominal organ leakage^{2,3}
6 and can lead, even with early surgical treatment, to septic shock. The pathophysiology of the
7 disease is intimately related to the complexity of sepsis⁴, including systemic inflammation
8 and its repercussions on major organ systems, cardiovascular instability and the underlying
9 disease process responsible for the peritonitis. It is therefore difficult to identify a unique and
10 reliable prognostic factor. In human medicine⁵ there has been growing interest towards
11 identification of biomarkers able to act not only as prognostic indicators but also as clinical
12 indicators to guide therapy. This interest has extended also to veterinary medicine⁶.

13 Many studies, both in human and veterinary medicine, have examined absolute lactate
14 level in the clinical context both for its diagnostic^{7,8} and prognostic value. Lactate is an end-
15 product of anaerobic metabolism and its increase can indicate tissue hypoxia^{9,10}. Therefore
16 its role is not only relevant in assessing the degree of overt or occult hypoperfusion but also
17 in assessing tissue oxygenation ^{11,12}.

18 Several studies have examined lactate in different critically ill populations and these
19 suggest that serial lactate measurements and the change in response to therapy are a more
20 significant prognostic indicator than the single lactate level at admission¹²⁻¹⁴. Lactate
21 clearance, expressed as the percentage change over time of lactate level, seems to be the most

1 sensitive prognostic indicator^{12,15} but interest has also been shown towards lactime, defined
2 as time from admission taken to normalize lactate levels¹⁴.

3 The objective of this study was to assess if elevated lactate levels at admission or lactate
4 clearance were able to predict survival in dogs with septic peritonitis. Additional study aims
5 were to evaluate the association between lactate levels and increased morbidity, defined as
6 longer ICU stay, transfusion administration, pressor or colloid requirements.

7

1 **Materials and Methods**

2 The electronic medical records databases at a university teaching hospital were searched
3 for cases of septic peritonitis in dogs. Inclusion criteria were a diagnosis of septic peritonitis,
4 either on presentation or at any point during hospitalization. The criteria for diagnosis were
5 defined as the finding of intracellular bacteria on cytological evaluation, isolation of a
6 bacterial or fungal agent on abdominal fluid culture or intra-operative evidence of
7 macroscopic leakage of the gastro-intestinal tract or intra-abdominal rupture of an abscess
8 or pyometra. At least one lactate measurement during the course of the hospitalization was
9 necessary to be included in the study.

10 Missing or incomplete records or uncertain diagnosis or euthanasia without attempted
11 surgical treatment were exclusion criteria.

12 Medical records for enrolled cases were reviewed by a single author. Data including
13 signalment, relevant history, cardio-respiratory parameters, available blood work,
14 intraoperative findings, post-operative requirements for pressors, transfusions and colloids,
15 and outcome were recorded. Hypotension was defined as a Doppler pressure less than 90
16 mmHg or a mean arterial pressure less than 60 mmHg when oscillometric or invasive
17 measurement was used. Multiple organ dysfunction syndrome (MODS) was identified based
18 on the criteria defined by Kenney et al¹⁶.

19 APPLE scores, in full and fast form ¹⁷, were also retrospectively calculated where suitable
20 data were available.

1 Blood lactate was measured with a bench-top blood gas analyzer^a using heparinized
2 venous or arterial blood samples. Hyperlactatemia was defined as a blood lactate
3 concentration $>2.5\text{mmol/L}$ ¹⁸.

4 Where available, serial blood lactate and base excess concentrations were recorded,
5 together with their time relative to presentation and surgery.

6 Lactate clearance, defined as the percentage change in lactate, was calculated for each case
7 that was initially hyperlactatemic at 3, 6, 12 and 24 hours from presentation as $[(\text{Lactate}_{\text{pres-}}$
8 $\text{lactate}_{\text{hour x}})/\text{lactate}_{\text{pres}}] \times 100$. The lactate levels at each of these time intervals, other than the
9 3 hour time point, was extracted from the medical records with a tolerance of ± 2 hours.

10

1 **Statistical analysis**

2 The retrospective data were recorded in a spreadsheet using Microsoft Excel^b and were
3 analyzed with SPSS^c.

4 Each data set was analyzed for distribution using the Shapiro-Wilk test and expressed as
5 mean (+/- SD) or median (range) depending on the presence or absence of a normal
6 distribution.

7 Continuous variables were compared with the Student's t-test for parametric data and
8 Mann Whitney-U test for non-parametric data. Discrete variables were analyzed for
9 difference using ANOVA for parametric data and Kruskal-Wallis test for non-parametric data.

10 Categorical variables were analyzed using Chi-squared or Fisher's exact test if the
11 contingency table contained an expected value <4.

12 For lactate clearance and absolute lactate levels, a ROC curve was elaborated and an
13 optimal cut-off visually defined for each time point.

14

1 **Results**

2 The initial medical record database search identified 363 cases. After application of the
3 inclusion and exclusion criteria, 83 dogs with septic peritonitis were included in the study.

4 The median age was 60 months (range 4-142) and the median weight was 25.7 kg (range
5 1.7-46.1). There were a variety of breeds represented in this study with the most represented
6 being Labradors (13), springer spaniels (8) and cross breeds (5). Males were 53/83 (64%)
7 (36/83 (43%) neutered and 17/83 (20%) entire) and females were 30/83 (36%) of the
8 population (spayed 20/83 (24%) and entire 10/83 (12%)).

9 Seventy-seven (93%) were referred from another veterinary practice whereas 6/83 (7%)
10 were seen as primary emergency cases. Sixty-one (74%) of the patients received intravenous
11 fluids at another clinic prior to presentation, while 22/83 (26%) did not receive any fluids
12 beforehand. Forty-four (53%) had had another surgery within the 10 days prior presentation.

13 Regarding the focus of the septic peritonitis, in 73 dogs (89%) the gastro-intestinal system
14 was involved, in 5 dogs (6%) there was a urogenital focus, 3 dogs (4%) had hepatobiliary
15 disease and 1 (1%) had a primary peritonitis. In terms of underlying disease, 38 dogs (46%)
16 had a gastro-intestinal foreign body, 11 (13%) had gastro-intestinal ulceration, leading to
17 perforation, 6 (7%) were diagnosed with neoplasia, 7 (8%) had intestinal biopsies, 4 (6%)
18 had a gastric-dilation volvulus. Three (4%) had an intussusception, 2 (2.4%) each had hepatic
19 disease, pyometra, abscessation, mesenteric volvulus, trauma and 1 (1%) each had a
20 caesarean section, a mesenteric thrombus, a gossypiboma, a primary peritonitis.

21 Fifty-three (64%) of the patients survived to discharge, 18/83 (22%) were euthanized and
22 12/83 (14%) died during hospitalization.

1 Median hospitalization time was 7 days (range 0-21) and the median time spent in the ICU
2 was 3 days (range 0-17). MODS was identified in 15/83 (18%) of the patients. Median APPLE
3 full score was 0.06 (range 0.00-0.95) and median APPLE fast score was 0.21 (range 0.01-
4 0.99). APPLE full and fast score was available in 46/83 patients (Table 1).

5 The mean heart rate was 126 bpm (± 34), the median respiratory rate was 32 bpm (range
6 14-100) and the median temperature was 38.6°C (range 36-40.4). The mean Doppler blood
7 pressure recorded on admission was available for 37/83 cases and was 140 mmHg (± 35),
8 with 4/83 (5%) of these dogs being hypotensive. Oscillometric blood pressure was recorded
9 in 6/83 dogs on admission and the mean of the mean blood pressure was 85 (± 13). Median
10 blood glucose was 5.8 mmol/l (range 1.8-10.4).

11 Lactate on admission was available for 81/83 cases with a median of 1.7 mmol/l (range
12 0.5-9.7) and median base excess for 78/83 dogs was -4.9 mmol/l (range -17.1 - +5.3).

13 Synthetic colloids were used in 46/83 (55%) of the patients, human albumin in 9/83
14 (11%), blood products (packed red blood cells or plasma) in 30/83 (36%) and vasopressors
15 in 16/83 (19%) of the patients.

16 Lactate level on admission was not associated with administration of colloids (p 0.14) or
17 albumin (p 0.53). A significant difference was found in lactate levels in the use of blood
18 products (p<0.01) and vasopressors (p < 0.01). Dogs with hyperlactatemia on admission had
19 a significantly shorter ICU stay (median 2 days, range 0-11) compared to patients presenting
20 with normolactatemia (median 4, range 0-17) (p 0.003).

1 Twenty-four (29%) patients had hyperlactatemia on admission and 14 of these dogs did
2 not survive. Hyperlactatemia on admission was associated with mortality ($p=0.01$) (Figure
3 1).

4 Lactate on admission higher than 4 mmol/l was significantly associated with mortality
5 (odds ratio 7.1, 95% C.I 2-25, $p=0.002$). 15/83 patients had lactate higher than 4 mmol/l. Of
6 these (11/15) 73% of the patients died, versus (19/68) 28% of the patients with a lactate <
7 4 mmol/l. Lactate higher than 4 mmol/l yielded a sensitivity of 36% and a specificity of 92%
8 for non-survival.

9 Lactime could be calculated for 24 dogs of which 13 patients died and 11 survived. Of the
10 24 dogs, 10 failed to resolve hyperlactatemia (ranging from 1 hour to 24 hours) over the
11 documented measurements and all of these patients did not survive. Of the remaining 14
12 patients that did have resolution of hyperlactatemia, 11 survived and 3 did not survive.

13 An ROC curve of the lactime yielded poor sensitivity and specificity for survival with an
14 area under the curve of 0.66.

15 Data regarding resolution of hyperlactatemia within 6 hours were available for 24 dogs.
16 All the patients that did not clear lactate within 6 hours died (10/10). Of the dogs which
17 cleared their hyperlactatemia within 6 hours (14/24), 11 (79%) survived and 3 (21%) died.
18 The inability to clear lactate within 6 hours yielded a sensitivity of 76% and specificity of
19 100% for non-survival.

20 Lactate post-surgery was recorded in 76 dogs. Post-operative hyperlactatemia was
21 present in 18 dogs, 12 of which died ($p=0.02$). Of the 58 dogs which were not hyperlactatemic

1 post-operatively, 14 died (24%) and 44 survived (76%). Post-operative hyperlactatemia had
2 a sensitivity of 46% and specificity of 88% for non-survival.

3 Persistent post-operative hyperlactatemia was significantly associated with mortality (p
4 < 0.001). Of 20 dogs which were hyperlactatemic postoperatively, 13 failed to clear lactate.
5 All of them (13/13, 100%) did not survive to discharge. Of the remaining 7 dogs with post-
6 operative hyperlactatemia that resolved, 6 survived and 1 did not survive despite clearing
7 lactate. Persistent hyperlactatemia post-operatively yielded a sensitivity of 93% and a
8 specificity of 100% for non-survival.

9 An ROC curve was generated for lactate concentration at 6 hours (55/83) following
10 admission which had an AUC of 0.87 with a cut-off 2.3 mmol/l yielding a sensitivity of 68%
11 and specificity of 92% for non-survival. Lactate clearance at 6 hours could be calculated for
12 20 patients and ROC curve analysis produced an AUC of 0.81 with a sensitivity 54% and
13 specificity 91% for non-survival at 21% clearance (Figure 2).

14 Absolute lactate concentration at 12 hours post admission produced an ROC curve with
15 an AUC of 0.86 ($n=54$) with a cut-off of 2.4 mmol/l resulting in a sensitivity of 54% and a
16 specificity of 100% for non-survival. Lactate clearance at 12 hours post-admission could be
17 calculated for 18 patients and ROC curve analysis produced a curve with an AUC of 0.90 and
18 an optimal cut-off of 42% resulted in a sensitivity of 82% and specificity of 100% for non-
19 survival (Figure 2).

20 Lactate clearance was not significantly different between survivors and non-survivors at
21 3 hours post admission ($n=9$, $p=0.25$).

22

1 **Discussion**

2 Septic peritonitis is a complex and severe process with fluid loss and systemic
3 inflammation caused by bacteria in the peritoneal cavity and the causative underlying
4 disease. Interactions between the inflammatory response, the coagulation and endothelial
5 systems may lead to abnormalities in the macro- and micro-circulation, multi-organ failure
6 and ultimately death. Hypoperfusion may occur through various pathophysiologic pathways,
7 including hypovolemia, cardiogenic shock, vasoplegia, and splanchnic microthrombi ¹⁹. It is
8 essential to ensure that adequate organ perfusion and oxygenation are maintained in septic
9 patients. Clinical parameters are often unreliable for detection of hypoperfusion in these
10 patients as they can be affected by several factors such as hypovolemia, pain, anemia or
11 exogenous catecholamines, thus resulting in misinterpretation.

12 Hyperlactatemia either represents an imbalance between tissue oxygen supply and
13 demand (type A) or altered cellular metabolism (type B). In septic patients hyperlactatemia
14 may occur due to hypoperfusion, mitochondrial dysfunction, increased leukocyte activity,
15 organ dysfunction, decreased lactate clearance, Na⁺-K⁺ ATPase activation, hypoglycemia or
16 dysregulation of pyruvate dehydrogenase^{20,21}. Recent veterinary studies have found
17 neoplasia to be a cause of increased lactate but typically this is not clinically significant and
18 was unlikely to be a significant confounder in our study as a neoplastic process was only
19 identified in 7% of the enrolled patients^{22,23}.

20 In our study lactate at admission was significantly different between survivors and non-
21 survivors, although median lactate for non-survivors (2.5 mmol/L) was only the upper
22 reference limit of 2.5mmol/l outlined by a previous study¹⁸. This suggests that even moderate

1 increase in lactate should be concerning, warranting immediate attention to the patient. In
2 previous veterinary studies lactate on admission has achieved different significance. In a
3 study on a heterogenous population of systemically ill dogs it was not found to be
4 significantly associated with mortality¹²; in patients with IMHA survivors had a lower lactate
5 on admission (median 2.9 mmol/l) in comparison to non-survivors (4.8 mmol/l)¹⁴. In dogs
6 with Babesiosis the difference between survivors and non-survivors was more marked (2.6
7 mmol/l in survivors vs 8.5 mmol/l in non-survivors) and significant¹⁵.

8 Severe hyperlactatemia on admission was defined as lactate higher than 4 mmol/l and
9 was associated with a higher mortality. These results are in accordance with studies in
10 human patients in which hyperlactatemia was associated with a higher mortality,
11 independent of organ failure or shock²⁴ and that a lactate higher than 4 mmol/l at admission
12 was associated with a six-fold higher probability for death within 3 days²⁵. A retrospective
13 study on dogs with IMHA showed that a cut-off of 4.4 mmol/l on admission was a good
14 predictor of outcome¹⁴. In dogs with gastric dilation-volvulus an admission lactate of < 4.1
15 mmol/l was the best cut-off based on a ROC curve analysis for predicting survival²⁶.

16 Interestingly, and in contrast to another veterinary study⁶ base excess on admission was
17 not significantly associated with survival in this study ($p=0.17$), highlighting that base excess
18 can vary for reasons unrelated to lactate accumulation in septic patients.

19 Lactate on admission was associated with patient morbidity in this study, with a higher
20 median lactate reported for dogs that received transfusions or vasopressors. This finding is
21 to be expected as transfusions are likely to be given to anemic patients and vasopressors to
22 hypoperfused patients, with both of these conditions causing hyperlactatemia. Somewhat

1 surprisingly, hyperlactatemia was associated with a shorter ICU stay in this patient
2 population. This finding is likely explained by the early euthanasia or death of this population.

3 Lactate was recorded at 3 hours and at 6, 12 and 24 +/- 2 hours after admission when
4 available. The best area under ROC curves for absolute lactate levels were obtained at 6 and
5 12 hours post admission; lactate level higher than 2.3 mmol/l at 6 hours or higher than 2.4
6 mmol/l at 12 hours were good predictors of mortality (specificity 92% and 100%
7 respectively). These levels are only mildly elevated or within the reference range suggesting
8 that the reference range should be revised or that higher levels of lactate, but still within
9 normal limits, could indicate inadequate tissue oxygenation and the need for more medical
10 attention.

11 The percentage clearance of lactate at 6 and 12 hours after admission was also found to
12 be a good predictor of mortality in this study. This is in accordance with the findings of
13 Stevenson et al.¹² who examined systemically ill dogs with a variety of diseases and found
14 that lactate clearance <50% at 6 hours after admission was associated with mortality.
15 Similarly, Nel et al.¹⁵ found that a lactate clearance <50% at 8 and 16 hours after admission
16 was a poor prognostic indicator in canine babesiosis. Additionally, failure to normalise
17 lactate within 6 hours of admission has been found to be associated with mortality in dogs
18 with immune mediated hemolytic anemia¹⁴. Studies in people have found that in patients
19 with sepsis lactate clearance at 6 hours was found to be an independent predictor of death
20 and in certain cases to be prognostically superior to central venous saturation of oxygen
21 (ScvO₂)²⁷. Another study in surgical ICU human patients with septic shock showed that
22 lactate levels were significantly different between survivors and non-survivors not only at
23 admission and at 6 hours, but also at 12 and 24 hours. The clearance in 24 hours from

1 admission was the best predictor for 28-day mortality suggesting that interpretation of
2 lactate clearance seems to be useful well beyond the 6 hour time point that is traditionally
3 used for resuscitation strategies²⁸.

4 The observations that lactate at admission and subsequent time points is associated with
5 mortality has led to investigations into its use not only for prognosticating but also to aid
6 triage and to guide early goal-directed therapy. A study in human medicine has showed
7 reduced mortality when patients were triaged with the aid of lactate measurements²⁹. In
8 veterinary medicine, a recent prospective study⁶ in septic surgical patients with pyometra
9 analyzed the application of a resuscitative bundle, following the model outlined by River et
10 al³⁰. In this study population lactate, along with ScvO₂ and base excess was significantly
11 different between survivors and non-survivors, with survivors having lower lactate levels.
12 There was also a reduction of lactate over the course of the resuscitation, which was not
13 present for other parameters such as base excess and ScvO₂.

14 In a study performed by Jansen et al⁵ human patients with hyperlactatemia on admission
15 were randomized in two groups. The control group was resuscitated according to the early-
16 goal directed therapy guidelines outlined by the Rivers and colleagues³⁰, while in the study
17 group resuscitation was also implemented to achieve 20% of lactate clearance every 2 hours
18 for 8 hours. The study population was weaned faster from mechanical ventilation and
19 inotropic support, had a reduction in mortality and in ICU stay.

20 By contrast another clinical trial³¹, involving human patients with severe sepsis and septic
21 shock, showed no reduction in hospital mortality using a lactate clearance of >10% in
22 addition to central venous pressure, mean arterial pressure and ScvO₂ end-goals.

1 There are several limitations to this study, most of which are intrinsic to its retrospective
2 design. The majority of the patients (93%) included in the study were referred from another
3 veterinarian and may have received treatment and in some cases even had surgery prior
4 referral. As a result lactate measurements taken at the same time from admission may not
5 represent the same stage of the disease in different patients. The lactate values were
6 extracted from records rather than being prospectively timed and this likely led to more data
7 points being available in the sickest patients. It is assumed that stable patients with normal
8 lactate recorded continued to have normal lactate but in patients with hyperlactatemia on
9 admission samples were serially measured to look for normalization.

10 The number of patients for which lactate was available at our predetermined time-points
11 was low and therefore the power of the study when looking at lactate at time points other
12 than admission is reduced. The ability to euthanize patients is another limitation inherent to
13 many veterinary studies. Given that the majority of patients were referred from another
14 centre it is likely that financial constraints and owner motivation were less of a confounding
15 factor in this population. The difference in APPLE scoring between the survivors and non-
16 survivors supports the notion that mortality in this population was associated with disease
17 severity rather than socioeconomic factors.

18 In conclusion, this study showed that in dogs with septic peritonitis lactate was associated
19 with mortality and morbidity. In particular the results suggest that lactate clearance within
20 a 6 to 12 hour window is associated with mortality and that post-operative hyperlactatemia
21 should raise particular concerns. Further prospective studies are needed in order to assess
22 the potential role of lactate-guided therapy in sepsis.

23

1 *Footnotes:*

2 a. *Critical Care Xpress and Phox Ultra, Nova Biomedical*

3 b. *Microsoft Excell, version 2008, Microsoft Inc.*

4 c. *SPSS, version 20, SPSS Inc, Chicago Ill*

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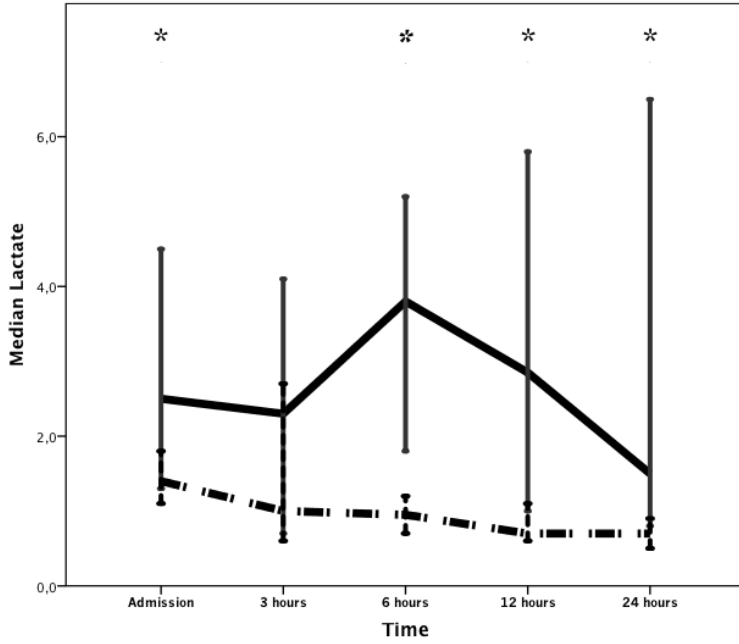
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	SURVIVORS	NON-SURVIVORS	P value
Heart rate (bpm)	117 (\pm 32)	141 (\pm 30)	0.001
Respiratory rate (brpm)	32 (14-100)	32 (20-100)	0.6
Temperature (C°)	38.6 (36.3-40.3)	38.4 (36-40.1)	0.52
Doppler pressure (mmHg)	145 (\pm 26)	121 (\pm 42)	0.04
Blood glucose (mmol/l)	5.7 (2.9-10.9)	6.3 (1.8-9.6)	0.16
Ionized Calcium (mmol/l)	1.16 (0.99-1.42)	1.1 (0.87-1.34)	0.013
Lactate adm. (mmol/l)	1.4 (0.5-9.7)	2.5 (0.5-8.4)	0.007
Base excess adm. (mmol/l)	-4.8 (-15- -0.2)	- 6.2 (-17.1-5.3)	0.17
ICU stay (days)	4 (1-17)	3 (0-11)	0.039
Hospital stay (days)	7 (4-21)	3 (0-12)	0.001
Time of administration of antibiotics from admission (hours)	3 (0-48)	3 (1-56)	0.72

Time from admission to surgery (hours)	3 (1-48)	3 (1-56)	0.83
APPLE full	0.03 (0-0.38)	0.2 (0.01-0.95)	0.001
APPLE fast	0.13(0.01-0.77)	0.55 (0.05-0.99)	0.001

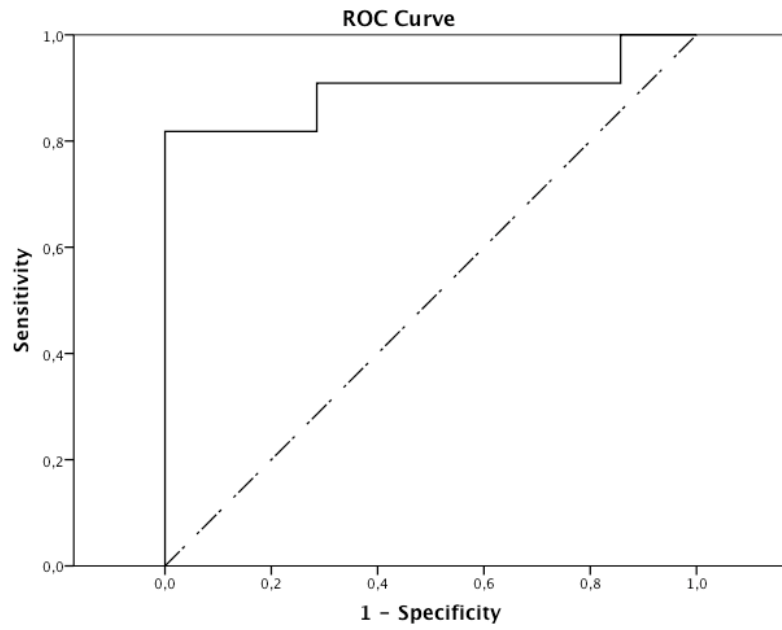
1 Table 1: Various parameters in dogs with septic peritonitis compared between survivors
2 and non-survivors. Data presented as mean (+/- SD) or median (range). A p value of <0.05
3 was considered statistically significant.

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Figure 1: Median lactate level at different time points in survivors and non-survivors. Survivors are defined by butted line and non survivors by a continuous line. Significant differences between survivors and non-survivors are represented by (*).



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2 **Figure 2: ROC analysis of lactate clearance at 12 hours following admission for prediction of non-survival in**
3 **hyperlactatemic dogs with septic peritonitis (AUC 0.90).**

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