ORIGINAL ARTICLE

Veterinary Research Forum. 2024; 15 (3): 119 - 123
doi: 10.30466/vrf.2023.1990137.3795
Journal Homepage: vrf.iranjournals.ir

Veterinary Research Forum

Predictive role of lactate in dogs with acute pancreatitis advanced to systemic inflammatory response syndrome

Sei-Myoung Han*

Department of Animal Health and Welfare, College of Health and Biotechnology, Semyung University, Jecheon, South Korea.

Article Info

Article history:

Received: 22 February 2023
Accepted: 02 December 2023
Available online: 15 March 2024

Keywords:

Acute pancreatitis
Dog
Lactate
Specific canine pancreatic lipase
Systemic inflammatory response syndrome

Abstract

Acute pancreatitis (AP) can develop into life-threatening conditions such as systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction syndrome. Thirty-nine of 54 client-owned dogs admitted to the Referral Animal Medical Center and diagnosed with AP within 24 hr of onset were retrospectively reviewed to assess early predictors of progression from AP to SIRS. The patients were divided into SIRS (SIRS occurring after AP) and non-SIRS (AP occurring but no SIRS) groups. The population and mean values of laboratory variables within 24 hr of admission were assessed and compared between both groups. There were significantly more dogs with abnormal lactate levels in the SIRS group (80.00%) than non-SIRS group (11.10%). Other parameters did not differ significantly. Mean lactate level values were significantly higher at 3.64 ± 1.75 mmol in the SIRS group compared to 1.68 ± 0.52 mmol in the non-SIRS group. The increased energy required by activated immune cells may lead to metabolic changes characterized by anaerobic glycolysis and increased lactate production. This study's results suggest blood lactate monitoring in the early stages of progression from AP to SIRS in small animal clinical practice. Measuring lactate levels at the early stages of pancreatitis could lead to rapid therapeutic intervention for SIRS and ultimately reduce mortality.

Introduction

Pancreatitis, one of the most common diseases in dogs, is characterized by inflammation of the exocrine pancreas. Pancreatitis occurs primarily because of inappropriate zymogen activation within pancreatic tissue, resulting in auto-digestion, pancreatic inflammation, and necrosis of the pancreatic tissue.[1]

Pancreatitis can occur acutely or chronically; in acute pancreatitis (AP), clinical signs such as vomiting, diarrhea, lethargy, anorexia, or abdominal pain are observed early. These symptoms may be reversible under mild conditions; however, AP can cause multi-systemic complications, such as systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction syndrome, which can be life-threatening in severe conditions. It may also develop into other severe states, such as acute renal failure due to severe dehydration, ischemia, intra-vascular coagulopathy, and direct inflammation.[2]

The known AP mortality rate is 27.00% to 58.00% in severely progressed cases. Early prediction of AP severity is important to reduce mortality. The clinical symptoms and prognosis may vary depending on AP severity. Early and appropriate treatment interventions including intra-venous fluid administration, anti-emetics, antacids and nutritional management are important for rapid recovery and reduced mortality.[3,4]

Many patients with severe AP develop systemic inflammatory conditions induced by pro-inflammatory cytokines.[5] Morbidity and mortality can be predicted based on elevated cytokine levels during systemic inflammatory conditions such as sepsis or SIRS. Thus, inflammatory cytokines such as interleukin-8 are important in pancreatitis progression and severity.[6,7] According to Choi *et al*., interleukin-8 levels are significantly elevated in dogs with suspected AP;[8] interleukin-8 is an initiating cytokine that drives early neutrophil migration in several inflammatory diseases, including AP. The expression of interleukin-8 is consistent

***Correspondence:**

Sei-Myoung Han. DVM, PhD
Department of Animal Health and Welfare, College of Health and Biotechnology, Semyung University, Jecheon, South Korea
E-mail: smhan@semyung.ac.kr

with ongoing inflammation; however, its ability to differentiate between types of inflammation is limited.[9] Moreover, it is difficult to predict SIRS progression and progression to SIRS or sepsis increases patient mortality. Therefore, early diagnosis and prognostic assessment are important for optimal therapeutic intervention.

It is necessary to describe the limitations of various diagnostic methods of AP; hence, the aim of the study was to assess early predictors of progression from AP to SIRS.

Materials and Methods

Case selection. In this retrospective study, 54 client-owned dogs admitted to the Referral Animal Medical Center located in Gyeonggi-do, South Korea, from January 2019 to August 2022 and diagnosed with AP within 24 hr of onset were reviewed. Dogs were diagnosed with AP based on the following inclusion criteria: Abnormal SNAP canine pancreatic lipase result (color intensity of the sample spot more intense than the control spot) or specific canine pancreatic lipase (Spec-cPL) concentration > 400 g L^{-1} and acute onset with at least two compatible clinical signs (anorexia, diarrhea, vomiting, abdominal pain or lethargy) with or without ultrasonographic findings (thickened and hypoechoic pancreas with blurred margins, being surrounded by hyperechoic fat tissue). Dogs were excluded from the study if clinical signs were present for more than 7 days or if a previous episode of pancreatitis was reported. Dogs with the following features were excluded from the study: Pre-hospital interval > 24 hr, chronic pancreatitis, recurrent pancreatitis, pyometra, cancer, microorganism infection, and those not being treated due to financial reasons. A SIRS diagnosis was made if a patient was positive for ≥ two of four criteria including a body temperature below 38.10 ℃ or above 39.20 ℃, heart rate of 120 beats *per* min or more, respiratory rate of more than 20 breaths *per* min and white blood cell count < 6,000 cells L^{-1} or > 16,000 cells L^{-1}.[5]

Laboratory parameters. The patients were divided into SIRS (SIRS occurring after AP) and non-SIRS (AP occurring but no SIRS) groups. Nine laboratory variables were assessed within 24 hr of admission and compared between groups. The population of dogs progressed to highly elevated D-dimer (> 2,000 ng mL^{-1}), C-reactive protein (> 70.00 mg L^{-1}), abnormal lactate (> 2.50 mmol), metabolic acidosis (< pH: 7.31), hypocalcemia (< 1.47 mmol), hyperkalemia (> 5.30 mEq L^{-1}), liver damage (more than three times of the upper limit of alanine amino-transferase), creatinine elevation (> 1.40 mg dL^{-1}), and Spec-cPL > 1,000 ug L^{-1} were compared between groups. According to the electronic charts, blood was collected from the jugular or cephalic veins. The collected blood was immediately transferred into an ethylenediaminetetra-acetic acid-containing tube for a complete blood count (CBC) test; some samples were also transferred to heparinized tubes for serum separation and centrifuged at 5,000 rpm for 5 min. The D-dimer and serum chemistry analyses were performed using Fuji Dri-Chem (NX700; Fujifilm Corp., Tokyo, Japan), and Spec-cPL was analyzed using VET CHROMA (Anivet Diagnostics Inc., Seoul, Korea) or SNAP cPL (IDEXX Laboratories Inc., Westbrook, USA).

Statistical analysis. Frequency and descriptive analyses were performed to analyze the characteristics of the dogs with AP. Comparisons were performed using chi-square analysis for categorical variables and an unpaired *t*-test for laboratory parameters. Log transformations were conducted on laboratory parameters before analysis to achieve a normal distribution. The receiver operating characteristic (ROC) curves and respective area under curves (AUCs) were calculated as the best combination of sensitivity and specificity. Differences were considered statistically significant at $p < 0.05$. The Statistical Package for Social Sciences Software (version 22.0; IBM Corp., Armonk, USA) was used to perform the statistical analyses.

Results

Thirty-nine dogs were included in this study. The demographic data of the dogs with AP, including age, sex, species and clinical symptoms are presented in Table 1. The cohort of dogs had a mean age of 8.51 (range: 1 ~ 19). There were 20 males (19 castrated) and 19 females (14 spayed). The following dog breeds were included: Maltese (n = 10), Miniature Poodle (n = 9), Yorkshire Terrier (n = 7), Japanese Spitz (n = 3), Schnauzer (n = 2), Shih Tzu (n = 2), French Bulldog, Miniature Pinscher, Pekinese, Pomeranian, West Highland White Terrier and Mixed dogs. The clinical symptoms included vomiting, anorexia, diarrhea, lethargy, and abdominal pain. Among the 39 dogs, 36 were hospitalized for a mean period of 5.02 days (range: 1 ~ 10 days). Three of the 39 dogs died on days 3, 4 and 6 of hospitalization, respectively. None of the dogs were euthanized.

A comparison of the numerical tests performed within 24 hr of admission revealed a significant difference in the number of patients with abnormal lactate levels (Table 2). There were significantly more dogs with abnormal lactate levels in the SIRS group (80.00%) than non-SIRS group (11.10%). However, other parameters did not differ significantly.

The mean values of the laboratory variables were compared between the SIRS and non-SIRS groups (Table 3). The D-dimer level was higher at 1,632.59 ± 645.30 ng mL^{-1} in the non-SIRS group than 1,389.71 ± 567.89 ng mL^{-1} in the SIRS group, not being significantly different ($p = 0.526$). However, the lactate level was significantly higher at 3.64 ± 1.75 mmol in the SIRS group compared to 1.68 ± 0.52 mmol in the non-SIRS group ($p = 0.003$). Lipase and Spec-cPL levels were also higher in the SIRS group, with *p*-values of 0.011 and 0.063, respectively.

Table 1. Demographic data and clinical characteristics of the dogs with acute pancreatitis (n = 39).

Parameters	Values
Mean age (years)	8.51 (range: 1 ~ 19)
Sex	
Male	Intact: 1 (2.60%), Castrated: 19 (48.70%)
Female	Intact: 5 (12.80%), Spayed: 14 (35.90%)
Breed	
Maltese	10 (25.60%)
Miniature Poodle	9 (23.10%)
Yorkshire Terrier	7 (17.90%)
Japanese Spitz	3 (7.70%)
Schnauzer	2 (5.10%)
Shih Tzu	2 (5.10%)
French Bulldog	1 (2.60%)
Miniature Pinscher	1 (2.60%)
Pekinese	1 (2.60%)
Pomeranian	1 (2.60%)
West Highland White Terrier	1 (2.60%)
Mixed	1 (2.60%)
Symptom	
Vomiting	32 (82.10%)
Anorexia	18 (46.20%)
Diarrhea	14 (35.90%)
Lethargy	11 (28.20%)
Abdominal pain	4 (10.30%)

No significant results were obtained for lipase (AUC: 0.70; 95.00% confidence interval (CI): 0.280 ~ 1.000). The ROC curves are illustrated in Figure 1. The AUC of the ROC curve for serum lactate level was 0.92 (95.00% CI: 0.744 ~ 1.000; $p = 0.037$; Table 4).

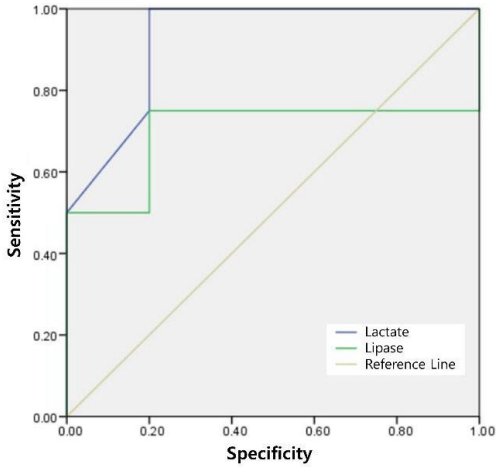

Fig. 1. Receiver operating characteristic curves for lactate and lipase in the prediction of systemic inflammatory response syndrome. The areas under the curves of lactate and lipase were 0.92 ($p = 0.037$) and 0.70 ($p = 0.327$), respectively.

Table 2. Univariable association between laboratory variables and systemic inflammatory response syndrome (SIRS).

Parameters	Total n/N_0	Non-SIRS n/N_1 (%)	SIRS n/N_2 (%)	*p*-value
D-dimer (> 2,000 ng mL^{-1})	8/28	5/18 (27.80%)	3/10 (30.00%)	0.615
CRP (> 70.00 mg L^{-1})	11/35	9/25 (36.00%)	2/10 (20.00%)	0.357
Lactate (> 2.50 mmol)	5/14	1/9 (11.10%)	4/5 (80.00%)	0.023
Venous blood pH (< 7.31)	8/16	5/10 (50.00%)	3/6 (50.00%)	0.70
Ionized calcium (< 1.47 mmol)	2/9	0/5 (0.00%)	2/4 (50.00%)	0.167
Potassium (> 5.30 mEq L^{-1})	1/29	0/19 (0.00%)	1/10 (10.00%)	0.345
ALT (> three times of upper limit)	5/32	2/23 (8.70%)	3/9 (33.30%)	0.121
Creatinine (> 1.40 mg dL^{-1})	5/34	3/24 (12.50%)	2/10 (20.00%)	0.465
Spec-cPL (> 1,000 g L^{-1})	16/22	10/16 (62.50%)	6/6 (100%)	0.107

ALT: Alanine aminotransferase; CRP: C-reactive protein; Spec-cPL: Specific canine pancreatic lipase; N: Number of dogs in which the abnormality was investigated (N_0: Total number of dogs; N_1: Number of dogs without SIRS; N_2: Number of dogs with SIRS); n: Number of dogs with abnormal laboratory parameters.

Table 3. Univariate analysis between systemic inflammatory response syndrome (SIRS) and non-SIRS groups.

Parameters	Normal values	Non-SIRS (n = 29)	SIRS (n = 10)	*p*-value
D-dimer (ng mL^{-1}) †	0.00 ~ 300	1,632.59 ± 645.30 (n = 18)	1,389.71 ± 567.89 (n = 10)	0.526
CRP (mg L^{-1}) †	0.00 ~ 9.00	50.32 ± 12.18 (n = 25)	52.97 ± 19.75 (n = 10)	0.731
Lactate (mmol) †	0.50 ~ 2.50	1.68 ± 0.52 (n = 9)	3.64 ± 1.75 (n = 5)	0.003
WBC (cells L^{-1}) †	6,000 ~ 17,000	27,963.50 ± 13,995.59 (n = 20)	19,738.75 ± 2,999.64 (n = 8)	0.522
Hematocrit (%)	37.00 ~ 55.00	48.57 ± 2.26 (n = 20)	54.06 ± 5.30 (n = 8)	0.269
Platelet (cells L^{-1})	150,000 ~ 500,000	475,420.00 ± 63,790.74 (n = 20)	340,393.75 ± 107,421.38 (n = 8)	0.277
pH	7.31 ~ 7.46	7.30 ± 0.03 (n = 10)	7.30 ± 0.08 (n = 6)	0.985
Ionized calcium (mmol)	1.16 ~ 1.47	1.31 ± 0.40 (n = 10)	1.22 ± 0.12 (n = 6)	0.407
Potassium (mEq L^{-1})	3.60 ~ 5.30	3.74 ± 0.15 (n = 19)	3.93 ± 0.31 (n = 10)	0.543
Albumin (g dL^{-1})	2.60 ~ 4.00	3.47 ± 0.09 (n = 22)	3.33 ± 0.19 (n = 10)	0.444
Amylase (U L^{-1})	200 ~ 1,400	1,359.22 ± 140.40 (n=18)	1,708.00 ± 162.81 (n = 9)	0.142
Lipase (IU L^{-1}) †	10.00 ~ 160	271.15 ± 56.59 (n = 13)	701.78 ± 191.90 (n = 9)	0.011
Creatinine (mg dL^{-1})	0.40 ~ 1.40	1.03 ± 0.23 (n = 24)	1.23 ± 0.30 (n = 10)	0.622
Spec-cPL †	< 400	1,367.68 ± 190.62 (n = 16)	1,733.33 ± 155.60 (n = 6)	0.063

CRP: C-reactive protein; Spec-cPL: Specific canine pancreatic lipase; WBC: White blood cell.
† analyzed after a logarithmic transformation.

Table 4. Comparison of lactate and lipase for systemic inflammatory response syndrome prediction.

Parameters	AUC	95.00% CI for AUC	*p*-value
Lactate	0.925	0.744 ~ 1.000	0.037
Lipase	0.700	0.280 ~ 1.000	0.327

AUC: Area under the curve; CI: Confidence interval.

Discussion

The condition, AP, is potentially fatal, and its severity ranges from mildly edematous to severely necrotizing. At the onset, the abnormal activation of pancreatic enzymes results in pancreatic inflammation and injury. Milder or chronic forms of the condition are not easily recognized, but can cause significant pain and reduce the quality of animal life. In severe cases, AP can induce thrombosis and further aggravate injury. It is associated with a systemic inflammatory response that, in severe cases, can result in multi-organ failure, diffuse intra-vascular coagulation, and eventually death.[10]

In this study, the prognostic values of various parameters were evaluated for the dogs with AP. To investigate the diagnostic and prognostic values at the initial admission, D-dimer, C-reactive protein, serum lactate, venous blood pH, ionized calcium, potassium, Spec-cPL, CBC, and other serum chemistry tests results were evaluated in dogs having AP with or without SIRS.

The proportion of dogs with abnormal lactate levels was significantly higher in the SIRS group. Of the 14 dogs whose lactate levels were measured, only one dog had abnormal lactate level (11.10%) in the non-SIRS group; whereas, four of the five dogs (80.00%) in the SIRS group had abnormal lactate levels. No significant differences were observed in the other values. Differences were observed in the average lactate and lipase levels. The average lactate level in the SIRS group was 3.64 ± 1.75 (n = 5), being significantly higher than that of the non-SIRS group (1.68 ± 0.52; n = 9).

Lactate is a normal by-product of energy use, and its concentration in the blood is a measure of anaerobic metabolism in the body. Elevated lactate levels (hyper-lacticemia) are caused mainly by systemic and local decreases in blood flow to the cells. Lactate is commonly used to indicate tissue hypoperfusion in heart failure and aortic or pulmonary thromboembolisms. Therefore, the blood lactate level is recognized as a prognostic indicator and therapeutic target in human and veterinary emergency patients.[11]

Rosenstein *et al.* divided patients into two broad hyper-lacticemia categories including insufficient oxygen supply and inadequate oxygen availability.[11] Exercise, seizures, hypoperfusion, severe hypoxemia and severe anemia are possible causes of insufficient oxygen supply. Causes of inadequate oxygen availability include other diseases such as hepatic failure, SIRS/sepsis and pheochromocytoma, drugs and toxic substances like glucocorticoids or xylitol. Therefore, blood lactate level measurement can indicate the degree to which oxygen is adequately transported around the body or other disease states. Thus, blood lactate offers ways to assess the severity of cardiovascular diseases and the body's response to treatment and predict health outcomes, and influences decisions regarding prognosis improvement.[12] As inflammatory immune cells are activated, anaerobic glycolysis occurs, and lactate levels increase. The increased energy required by activated immune cells leads to metabolic changes characterized by anaerobic glycolysis, increased lactate production and reduced use of tricarboxylic acid cycle.[13] Similarly, an increase in lactate levels can be observed when systemic inflammation progresses in AP.

To diagnose pancreatitis, a serum biochemical profile analysis is usually performed, although the findings are not specific to pancreatitis. Serum lipase activities are usually high in patients with pancreatitis.[1] Serum lipase has low to moderate accuracy and specificity (60.00%) for diagnosing pancreatitis in dogs;[14,15] whereas, Spec-cPL (called pancreas-specific) is synthesized and released only by pancreatic acinar cells.[16,17] The serum lipase concentrations in the SIRS group were significantly higher, possibly due to other systemic conditions (decreased renal function due to pancreatitis) rather than systemic inflammation.[18]

In humans, serum D-dimer level is a good predictor of AP[19,20] and could help stratify patients presenting to the emergency department with signs of sepsis.[21] Similar to Nielson *et al*. study,[22] this study confirmed that D-dimer levels were elevated in patients with AP. However, the range of change in the value was too wide to be used as a predictor of SIRS. No significant differences were observed between the SIRS and non-SIRS groups. Therefore, further research is required to investigate this relationship.

This study had some limitations. First, the number of dogs enrolled in this study was small. Pancreatitis is a common disease; however, the sample size was small because only dogs met the inclusion criteria were included. Second, coagulation tests could not be compared between the SIRS and non-SIRS groups because fewer than five patients underwent the tests.

Measuring lactate levels in the early stages of pancreatitis can lead to rapid therapeutic intervention for SIRS and ultimately reduce mortality. Lactate levels have not been proven to predict mortality; however, they may help reduce mortality if they can predict the progression to SIRS. This study's results suggest blood lactate monitoring in the early stages of progression from AP to SIRS in small animal clinical practice.

Acknowledgments

This study was supported by a research grant from Semyung University, Jecheon, South Korea, in 2022.

Conflict of interest

No conflicts of interest to declare.

References

1. Xenoulis PG. Diagnosis of pancreatitis in dogs and cats. J Small Anim Pract 2015; 56(1): 13-26.
2. Zhang XP, Wang L, Zhou YF. The pathogenic mechanism of severe acute pancreatitis complicated with renal injury: a review of current knowledge. Dig Dis Sci 2008; 53(2): 297-306.
3. AK, Breitschwerdt EB, Levine JF, et al. Risk factors associated with acute pancreatitis in dogs: 101 cases (1985-1990). J Am Vet Med Assoc 1993; 203(5): 673-679.
4. Schaer M. A clinicopathologic survey of acute pancreatitis in 30 dogs and 5 cats. J Am Anim Hosp Assoc 1979; 15(6): 681-687.
5. Hirota M, Sugita H, Maeda K, et al. Concept of SIRS and severe acute pancreatitis [Japanese]. Nihon Rinsho 2004; 62(11): 2128-2136.
6. Mansfield C. Pathophysiology of acute pancreatitis: potential application from experimental models and human medicine to dogs. J Vet Intern Med 2012; 26(4): 875-887.
7. Bhatia M, Brady M, Shokuhi S, et al. Inflammatory mediators in acute pancreatitis. J Pathol 2000; 190(2): 117-125.
8. Choi SW, Kim YH, Kang MS, et al. Serum concentration of inflammatory cytokines in dogs with suspected acute pancreatitis. Vet Sci 2021; 8(3): 51. doi: 10.3390/vetsci8030051.
9. Karlsson I, Hagman R, Johannisson A, et al. Cytokines as immunological markers for systemic inflammation in dogs with pyometra. Reprod Domest Anim 2012; 47(Suppl 6): 337-341.
10. Kakafika A, Papadopoulos V, Mimidis K, et al. Coagulation, platelets, and acute pancreatitis. Pancreas 2007; 34(1): 15-20.
11. Rosenstein PG, Tennent-Brown BS, Hughes D. Clinical use of plasma lactate concentration. Part 1: physiology, pathophysiology, and measurement. J Vet Emerg Crit Care (San Antonio) 2018; 28(2): 85-105.
12. Sharkey LC, Wellman ML. Use of lactate in small animal clinical practice. Clin Lab Med 2015; 35(3): 567-577.
13. Manosalva C, Quiroga J, Hidalgo AI, et al. Role of lactate in inflammatory processes: friend or foe. Front Immunol 2022; 12: 808799. doi: 10.3389/fimmu.2021.808799.
14. Dossin O. Laboratory tests for diagnosis of gastro-intestinal and pancreatic diseases. Top Companion Anim Med 2011; 26(2): 86-97.
15. Kathrani A, Steiner JM, Suchodolski J, et al. Elevated canine pancreatic lipase immunoreactivity concentration in dogs with inflammatory bowel disease is associated with a negative outcome. J Small Anim Pract 2009; 50(3): 126-132.
16. Simpson KW, Simpson JW, Lake S, et al. Effect of pancreatectomy on plasma activities of amylase, isoamylase, lipase, and trypsin-like immunoreactivity in dogs. Res Vet Sci 1991; 51(1): 78-82.
17. Xenoulis PG, Steiner JM. Canine and feline pancreatic lipase immunoreactivity. Vet Clin Pathol 2012; 41(3): 312-324.
18. Mansfield CS, Jones BR. Plasma and urinary trypsinogen activation peptide in healthy dogs, dogs with pancreatitis and dogs with other systemic diseases. Aust Vet J 2000; 78(6): 416-422.
19. Wan J, Yang X, He W, et al. Serum D-dimer levels at admission for prediction of outcomes in acute pancreatitis. BMC Gastroenterol 2019; 19(1): 67. doi: 10.1186/s12876-019-0989-x.
20. Zhang G-Q, Wang G, Li L, et al. Plasma D-dimer level is an early predictor of severity of acute pancreatitis based on 2012 Atlanta classification. Med Sci Monit 2019; 25: 9019-9027.
21. Goebel PJ, Williams JB, Gerhardt RT. A pilot study of the performance characteristics of the D-dimer in presumed sepsis. West J Emerg Med 2010; 11(2): 173-179.
22. Nielsen L, Holm J, Rozanski E, et al. Multicenter investigation of hemostatic dysfunction in 15 dogs with acute pancreatitis. J Vet Emerg Crit Care (San Antonio) 2019; 29(3): 264-268.