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RESEARCH ARTICLE

The Effect of Routine Therapy Alone and Combined with Hyperbaric Oxygen Treatment on Prognostic Factors in Dogs with Acute Pancreatitis

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A B S T R A C T

The aim of this study was to evaluate the effect of supportive treatment combined with hyperbaric oxygen (HBO) therapy in dogs with acute pancreatitis by prognostic factors. Dogs entering the trial were randomly assigned to receive only regular supportive therapy (control group) or combined hyperbaric oxygen therapy with symptomatic and supportive therapy (HBOT group). The regular supportive measurements consisted of intravenous fluid, analgesia, antibiotics, antiemetics, gastric acid suppression, nutritional management, and so on. If the patient had diabetes mellitus, hyperglycemia was controlled by insulin. The dogs of the HBOT group were conducted in hyperbaric animal chamber (PAHI-A, Pan-America Hyperbarics Inc., R.O.C.) and HBO therapy involved 90 min of 100% oxygen treatment at a pressure of 2.5 ATA, once to twice daily for a total of 3 to 5 sessions. There were significant findings regarding to specific canine pancreatic lipase immunoreactivity (Spec cPL) and C-reactive protein (CRP) in the survivors, but no significant differences were found in the non-survivors. The down trend of sequential CRP concentration was noticed in HBOT group. The level of creatinine may be as an important criterion when the patients with AP were first visit clinic. The prognostic factors such as CRP, Spec cPL had a good response to routine combined with HBOT in survivors group. Likewise, the level of Spec cPL was decreased significantly after treatment no matter routine or routine combined with HBOT in survivors group. HBOT combined with symptomatic and routine treatment might improve systemic inflammation probably in canine acute pancreatitis. In survivors group the creatinine levels was significant lower than that in non-survivors group. Therefore, the levels of creatinine can be as prognostic factor in dogs with acute pancreatitis.

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INTRODUCTION

Acute pancreatitis (AP) is one of comparatively common disorders in dogs that can cause a wide range clinical signs, and sometimes induce multiple organ failure in severe cases (Vrolyk *et al.*, 2017). Dogs with pancreatitis remain high mortality rate, ranging from 27 to 58% (Watson, 2015). The key feature of severe disease is pancreatic tissue necrosis, leading to both local and systemic inflammatory responses. The pro-inflammatory response in pancreatitis in humans and rodents is characterized by generalized activation of pro-inflammatory cytokines. Tumor necrosis factor, interleukins 1, 6, and 8, chemokines, and platelet activation factors are the primary inflammatory mediators in acute pancreatitis. Circulating neutrophils and monocytes become activated and express adhesion molecules and release their proteolytic enzymes and oxygen radicals which damage vascular endothelial cells and organ parenchymal cells. Vascular endothelium is activated in the whole body and the expression of cellular adhesion molecules is upregulated which causes neutrophil extravasation and activation (Repo and Harlan, 1999). Endothelial permeability is enhanced leading to edema where vasoconstriction, inadequate perfusion, and increased blood viscosity are found. These microvascular

interference leads to lack of oxygen and results in dysfunction and injury of important organs (Mansfield, 2012a). In fact, microcirculatory disorders present not only in the pancreas but also in the colon, liver, kidneys, and lungs in an AP experiment (Foitzik *et al.*, 2002). Thus, lungs and kidneys are commonly injured organs in AP as they have an extensive capillary bed.

C-reactive protein (CRP) is one of acute phase proteins and being a marker for several diseases (Christensen *et al.*, 2015; Hillström *et al.*, 2016; Bremer *et al.*, 2017; Severo *et al*., 2018). When the inflammatory cells are activated by different inflammatory stimuli, the acute phase response is triggered and different cytokines are released from the inflammatory cell (Hillström *et al.*, 2015; Gommeren *et al*., 2018). After an acute inflammatory stimulation, CRP rises within a few hours and in the blood peak within 2-3 days. If the inflammation is eliminated, the CRP levels well quickly decrease. In humans, the half-life of radiolabeled CRP was reported to be 19 hours both in healthy subjects and in patients with systemic inflammatory disease (Vingushin, 1993). The CRP concentration has been found to be significantly higher in dogs with spontaneously occurring acute pancreatitis compared with healthy dogs (Holm *et al*., 2004).

The cornerstone of AP management in the dog is a fluid therapy to ensure that any fluid, acid-base and electrolyte imbalances are corrected and targeted to prevent and treat systemic complications (Kylänpää *et al*., 2012; Mansfield, 2012b) and recently focusing on feeding management (Jensen and Chan, 2014; Harris *et al.*, 2017) and analgesics application (Mansfield, 2015). In spite of advances in the supportive management of AP, the mortality rate of severe AP still approaches 30% in human (Nikfarjam *et al*., 2007). Plenty of evidence proves that microcirculatory alterations play an important role in the pathogenesis of acute pancreatitis. In a rat AP model, hyperbaric oxygen therapy (HBOT) diminishes overall severity (Inal *et al.*, 2015) which includes macroscopic and microscopic severity score, reduces the extent of necrosis and improves survival in severe acute pancreatitis (Nikfarjam *et al*., 2007). However, there was limited information concerning the effect of HBOT combined with supportive therapy in dogs with AP. Therefore, the aim of this study is to evaluate the effect of routine therapy alone and combined with HBOT on the levels of prognostic factors, spec cPL and CRP in dogs with AP.

MATERIALS AND METHODS

Animals: Clinical signs, history, physical examination, complete blood count (CBC), serum biochemistry, SNAP cPL test kit (IDEXX Laboratories, Westbrook, USA), canine CRP (VET CHROMA, ANIVET Diagnostics Inc., Korea) and abdominal ultrasound examination were required for each patient to be enrolled in the study. Each patient had additional blood collected at the time of presentation for submitted to commercial laboratory for determination of specific canine pancreatic lipase immunoreactivity (Spec cPL) (IDEXX Reference Laboratories Inc., Korea). It was conducted between Dec 2016 and April 2018 at the veterinary medical teaching hospital at National Chung Hsing University, Taiwan (R.O.C.).

Experimental design: This was a prospective and randomized clinical trial. We collected the client-owned dogs which had acute pancreatitis (acute or acute-on-chronic) and they were classified to control group and HBOT group randomly.

Inclusion criteria: Pancreatitis was diagnosed when the following criteria were fulfilled: (1) at least 2 of the following compatible clinical signs: anorexia, lethargy, diarrhea, vomiting, abdominal pain and (2) an increase in Spec cPL concentration (Spec cPL greater than 400μg/L) (3) results of abdominal ultrasonography supportive of acute pancreatitis, such as hyperechoic peripancreatic fat, hypoechoic pancreatic parenchyma, hypoechoic pancreatic nodules within parenchyma, or unclear pancreatic lesions (Xario SSA-660A, Toshiba Medical Systems Corporation, Japan)(Fig. 3-1).

Exclusion criteria: Dogs were excluded if they had any malignant neoplasm. The comorbidity was chosen because of the complicated inflammatory response in the individual who had cancer. Patients that had a history of recent trauma and surgery were also excluded.

Treatment: Dogs entering the trial were randomly assigned to receive only routine supportive therapy (control group) or combined hyperbaric oxygen therapy with symptomatic and supportive therapy (HBOT group). The routine supportive measurements consisted of intravenous fluid, analgesia, antibiotics, antiemetics, gastric acid suppression, nutritional management, and so on. If the patient had diabetes mellitus, hyperglycemia was controlled by insulin. The dogs of the HBOT group were conducted in hyperbaric animal chamber (PAHI-A, Pan-America Hyperbarics Inc., R.O.C.). HBO therapy was involved 90 min of 100% oxygen treatment at a pressure of 2.5 ATA, once to twice daily for a total of 3 to 5 sessions. If they finished the 5 sessions still stay in hospital, they had received regular supportive therapy continuously.

Statistical analysis: All statistical analyses were performed using commercially available software (SAS institute Inc., NC, USA). To investigate the correlation between values of the first blood examination and outcome, all samples were divided into survivors and non-survivors. Each laboratory test was compared between control and HBOT groups using Mann-Whitney U-test, as well as survivors and non-survivors groups. The relationship between two treatments and the outcome was tested with Fisher's exact test. The relationship between values measured at presentation and the outcome was tested with the multivariable logistic regression model. Pre and post-treatment findings were compared by using Wilcoxon signed-rank test. The survival analysis of the two treatment groups (control and HBOT group) were using Cox proportional hazard model. Values of $P<0.05$ were considered significantly.

RESULTS

Fifteen dogs were enrolled in the study at the first. The HBOT group (n=6) consisted of 4 females (1 sexually intact, 3 spayed) and 2 males (all neutered). The median

age of HBOT group was 10 years old (interquartile range, 9-10) and median body condition score was 6.5 (interquartile range, 4-9). Breeds in the HBOT group were Miniature Schnauzer (n=1), Chihuahua (n=1), Toy poodle (n=2), mixed breed (n=2). The control group consisted of 3 females (all spayed) and 2 males (1 sexually intact, 1 neutered). The median age of control group was 10 years old (interquartile range, 9-10) and median body condition score was 6 (interquartile range, 6-7). Breeds in the control group were Bernese Mountain dog (n=1), Labrador retriever (n=1), Miniature Schnauzer (n=1), mixed breed (n=2). In the HBOT group, underlying or concurrent diseases and complications included external otitis (n=1), pododermatitis (n=1), diabetes mellitus (n=3), diabetic ketoacidosis (n=2), acute kidney injury (n=1), cholangiohepatitis (n=1), Cholecystitis (n=4). In the control group included acute kidney injury (n=1), cholangitis (n=1), hyperadrenocorticism (n=1), and pneumonia (n=1).

Both Spec cPL (Fig. 2) and CRP (Fig. 3) concentration had significant findings in the survivors of HBOT group (P=0.02; P=0.04). However, there was no significant finding between before and after treatment in the CRP concentration of the survivors in control group (P=0.9). Regarding to the spec cPL concentration, significant difference between before and after treatment was found in the survivors of control group (P=0.014).

The short-term survival rate of control group was 40%; the survival rate of HBOT group was 66.67%. The mortality rate of control group was 60%, and the death rate of HBOT group was 33.33% (Table 1). The survivors group tab(n=6) consisted of 3 females (all spayed) and 3 males (1 sexually intact, 2 neutered). The median age of survivors group was 9.5 years old (interquartile range, 8-10) and median body condition score was 7.5 (interquartile range, 6-9). Breeds in the survivors group were Miniature Schnauzer (n=1), Chihuahua (n=1), Toy poodle (n=1), mixed breed (n=2), and Bernese Mountain dog (n=1). The non-survivors group consisted of 4 females (1 sexually intact, 3 spayed) and 1 male (neutered). The median age of control group was 10 years old (interquartile range, 10-12) and median body condition score was 6 (interquartile range, 4-6). Breeds in the control group were, Labrador retriever (n=1), Miniature Schnauzer (n=1), Toy poodle (n=1), and mixed breed (n=2).

A comparison of the values at the first medical examination between survivors and non-survivors groups by using Mann-Whitney U-test showed on Table 2. The median Spec cPL concentration in the both of survivors and non-survivors groups were 1809 µg/l (n=6, IQR 1359-2000) and 2000 µg/l (n=5, IQR 2000-2000), and there was no significant difference (P=0.6). The level of creatinine between two groups had significant difference (P=0.04) (Fig. 4).

There was a significant finding of Spec cPL in the survivors group between before and after treatment (P=0.002) (Fig. 5). However, no significant difference of Spec cPL was found between before and after treatment in the non-survivors group (P=0.6). The difference of CRP concentration between before and after treatment was no significant findings between before and after treatment in the both of survivors group (P=0.08) and non-survivors group (P=0.5). However, the timing was prolonged from the day of discharge to the first time revisit, significant difference was found in the survival group (P=0.008) (Fig. 6).

Table 1: The short-term survival rate and mortality rate of control group and HBOT group. There was no significant finding between two groups and outcome (P=0.56) by using Fisher's exact test

	Control group	HBOT group	Total
Survivors	n=2	n=4	n=6
	40%	66.67%	
Non-suvivors	n=3	n=2	n=5
	60%	33.33%	

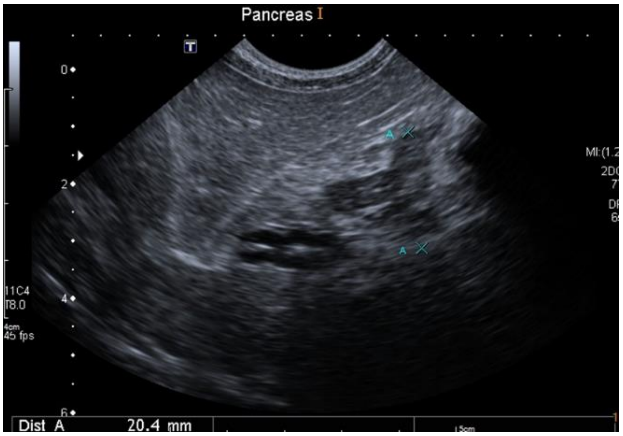

Fig. 1: The feature of pancrea which is displaying a typical hypoechoic pancreatic parenchyma with hyperechoic peripancreatic fat and from one case of this study.

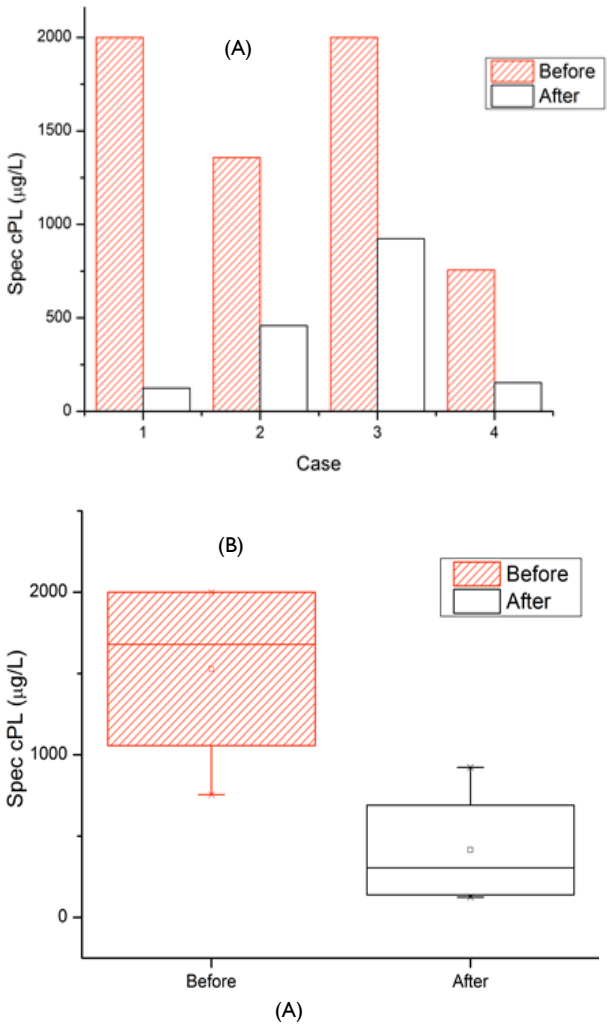

Fig. 2: Spec cPL concentration of before and after treatment in survival cases of HBOT group (A) and significant difference was exist between before and after treatment in survivors of HBOT group (B) (P=0.02).

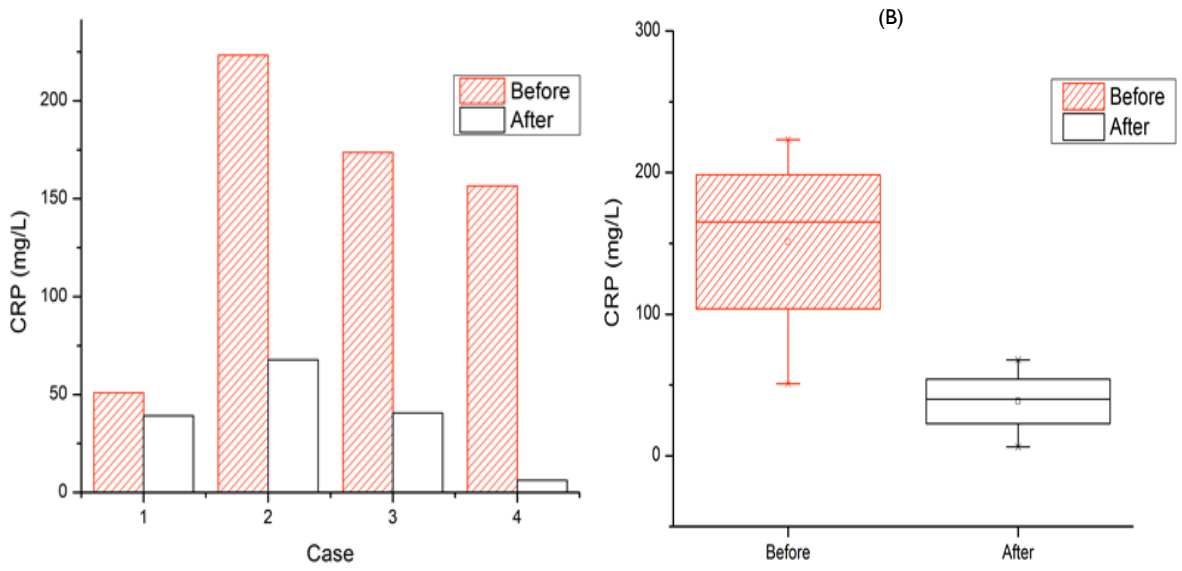

Fig. 3: C-Reactive protein (CRP) concentration of before and after treatment in survival cases of HBOT group (A) and significant difference was found between before and after treatment in survivors of HBOT group (B) (P=0.04).

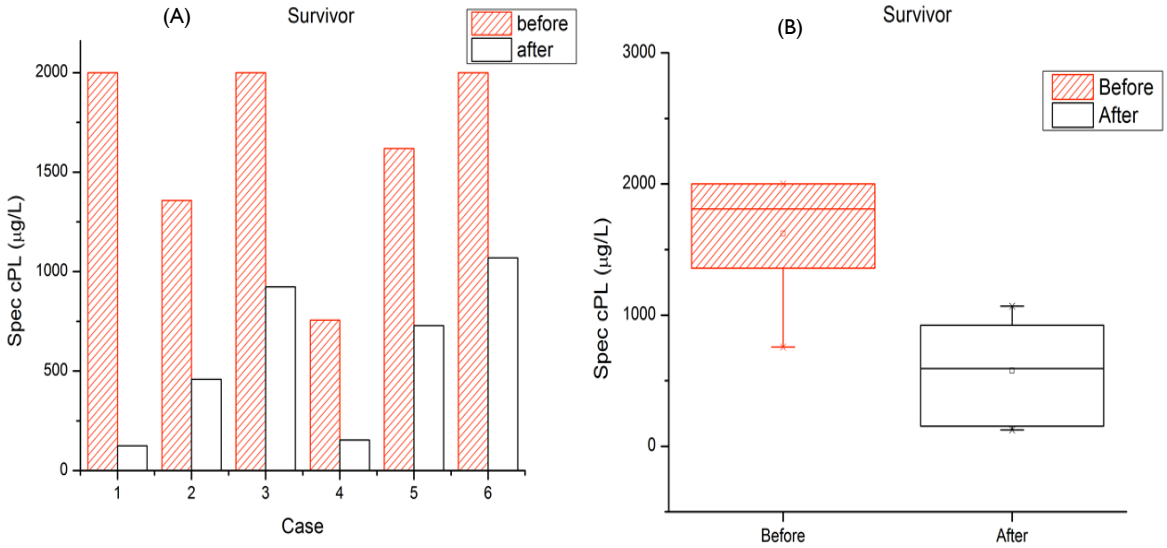

Fig. 5: Spec cPL concentration of before and after treatment in survival cases (A) and significant difference was found between before and after treatment in survivors group (B) (P=0.002).

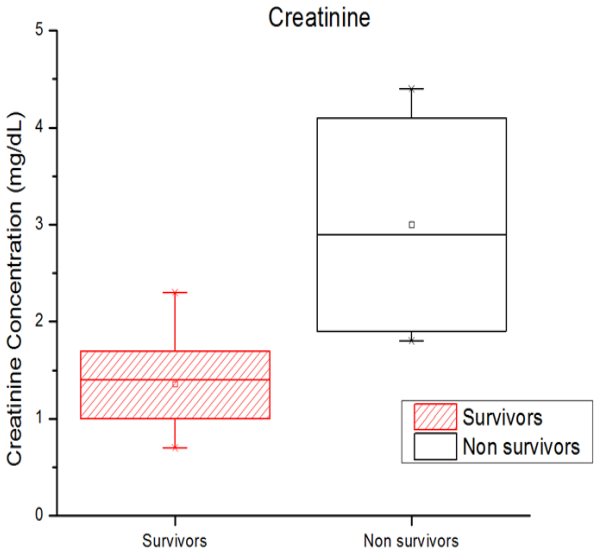

Fig. 4: The level of creatinine between survivors and non-survivors had significant difference by using Mann-Whitney U-test (P=0.04).

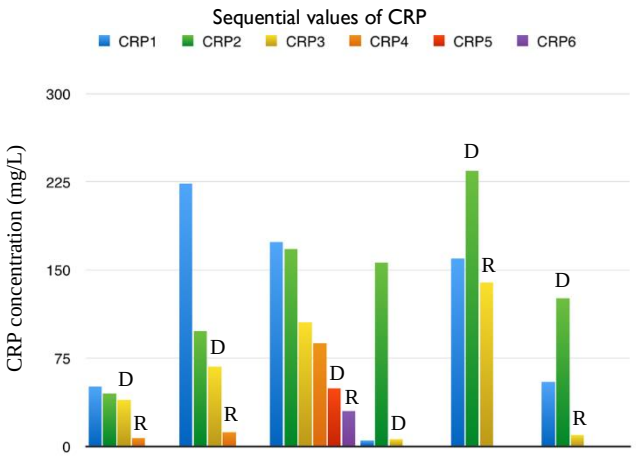

Fig. 6: Comparison of CRP concentration between before and after treatment in survivors. If the "after" timing was at discharge day, no statistical significance was found (P=0.08). If we postponed the "after" timing from the discharge to the day of revisit, there was a significant finding (P=0.008). Case 1, Case 2, Case 3, and Case 4 belonged to HBOT group; Case 5 and Case 6 were control group. D: The day of discharge. R: The day of revisit.

Table 2: The results of physical and blood & blood chemistry between survivors and non-survivors

Variable	RI	Survivors (no.,IQR)	Nonsurvivors (no., IQR)	P value
Age, median (years)		9.5 (n=6,8-10)	10 (n=5,10-12)	0.15
Sex				0.4
Male		3	1	
Female		3	4	
BCS, median (9-point system)		7.5 (n=6, 5-9)	6 (n=5, 4-6)	0.12
Heart rate(/min)		132 (n=6, 108-144)	120 (n=5, 36-100)	0.9
Respiratory rate (/min)		55 (n=6, 36-100)	54 (n=5, 36-100)	1
Body temperature (℃)		38.5 (n=6, 38.3-39)	38.8 (n=5,37.6-39.4)	1
CRP(mg/L)	<10	107.12 (n=6, 50.9-173.66)	100.6 (n=5,62.14-144.4)	0.9
Spec CPL (ug/L)	0-200	1809 (n=6, 1358-2000)	2000 (n=5, 2000-2000)	0.6
Platelet (1000/uL)	134-621	369.5 (n=6, 324-553)	127 (n=5, 14-507)	0.33
WBC (1000/uL)	5.0-17.0	14.46 (n=6, 11.92-20.61)	23.43 (n=5, 14.32-27.78)	0.53
BAND (1000/uL)	0-0.45	0.53 (n=6, 0-1.48)	0.68 (n=5, 0-1.43)	0.92
RBC (1000000/uL)	5.0-8.5	7.18 (n=6, 7.14-8.46)	6.91 (n=5, 5.8-8.65)	0.53
HCT(%)	35-58	43.7 (n=6, 42-52.3)	41.4 (n=5, 38.3-49.9)	0.43
AST (U/L)	5-55	65.5 (n=6, 39-75)	69 (n=5, 43-105)	0.83
ALT (U/L)	10-109	72 (n=6, 55-129)	82 (n=5, 61-400)	0.53
ALP (U/L)	1-150	453 (n=6, 223-724)	619 (n=5, 97-1908)	0.65
T. Bilirubin (mg/dL)	0-0.6	0.7 (n=6, 0.4-0.75)	0.5 (n=3, 0.3-0.5)	0.4
Glucose (mg/dL)	63-120	123 (n=6, 97-482)	87 (n=5, 83-137)	0.43
BUN (mg/dL)	7-30	17.5 (n=6, 14-34)	76 (n=5, 24-172)	0.17
Creatinine (mg/dL)	0.5-1.7	1.4 (n=6, 1-1.7)	3.3 (n=5, 2-3.8)	0.04*
T. Protein (g/dL)	5.2-7.5	6.6 (n=6, 5.4-6.7)	6.8 (n=5, 6.8-7.7)	0.26
Albumin (g/dL)	2.5-4.2	3 (n=6, 2.8-3.1)	3.3 (n=5, 3.0-3.3)	0.65
Globulin (g/dL)	1.9-4.4	3.4 (n=6, 3-3.6)	3.5 (n=5, 3.5-4.7)	0.53
Calcium (mg/dL)	9.0-11.7	9.8 (n=4, 9-10.4)	10.2 (n=3, 10.1-10.4)	0.4
Phosphorus (mg/dL)	2.7-6.1	6.6 (n=4, 5.05-9.95)	6.5 (n=5, 5.2-15)	0.9
Magnesium (mg/dL)	1.2-2.5	2 (n=4, 1.5-2.45)	2.2 (n=3, 1.6-2.3)	0.86
Sodium (mEq/L)	141-153	148 (n=6, 143-154)	146 (n=5, 143-147)	0.48
Potassium (mEq/L)	3.5-5.6	4.05 (n=6, 3.8-4.2)	3.8 (n=5, 3.6-4.4)	1
Chloride (mEq/L)	107-124	116.5 (n=6, 102-122)	102 (n=5, 94-111)	0.19
TCO2 (mEq/L)	12-29	13.3 (n=4, 11.15-19.45)	16.75 (n=4, 12.25-21.7)	0.67

RI, reference intervals; IQR, interquartile range; BCS, body condition score; CRP, C reactive protein; Spec cPL, specific canine pancreatic lipase. *P<0.05 was considered statistically significant.

DISCUSSION

Our study has identified elevated creatinine level could be as the prognostic factor for canine pancreatitis at initial presentation when the patients were first visiting between survival and non-survival groups. The result of creatinine level in this study was similar as previous published study (Marchetti *et al*., 2017; Sato *et al.*, 2017). However, there were different findings of prognostic factors compared to previous study. According to previous results (Sato *et al.*, 2017), the prognostic factors for canine pancreatitis included decreased platelet count (<200000/µl) and remarkable elevation of Spec cPL concentration (>1000µg/l) at the first diagnosis. In our study, there was no significant difference in Spec cPL concentration between survivors and non-survivors groups at the first blood examination, but the values of Spec cPL concentration in most cases (82%) were greater than 1000µg/l. It may indicate that Spec cPL could not be prognostic factor probably between survivor and non-survivors but could be as prognostic factor of survivors between before and after treatment. Actually, the higher Spec cPL concentration indicated the severity of pancreatitis was higher because of severe damage caused by increased inflammation. In survivors, the Spec cPL concentration would be decreased significantly when the inflammation has been improved between before and after treatment in this study.

Our study results showed that the serial CRP concentrations (comparison of before and after treatment) measured during hospitalization were significantly different between the before and after treatment in the survivors. In contrast to the survivors group, there was no significant finding in the death group. The finding was no differences existed between the survivors and non-survivors regarding the CRP concentration at the initial examination is consistent with previous report (Sato *et al.*, 2017). Initial serum CRP concentrations were not predictive of outcome in dogs with AP. The dogs with AP had persistent elevations in serum CRP concentrations at presentation and at followed up were associated with poor prognosis.

The second CRP value in most cases in our study was measured at the third day of hospitalization. If the patient response to an anti-inflammatory treatment, the CRP decrease normally very rapid, decreases with about 50% within 2-3 days (Markanday, 2015). We observed that CRP levels were going up at the third day with their clinical signs improved and Spec cPL level decreased significantly in two cases of the survivors group and the CRP level were going down obviously at the fifth day. The CRP concentration was still in high level indicating the existence of systemic inflammation still there; meanwhile, the inflammation of pancreas was under controlled in those cases. In addition, there was a dog model study of cerulein-induced AP, and they found Spec cPL peaked and normalized faster than CRP without other concurrent diseases (Lim *et al.*, 2014). May be it was another reason why the concentration of Spec cPL decreased significantly and CRP level increased conversely. Therefore, clinical presentation, Spec cPL, and CRP levels have to be considered together for monitoring treatment and assessing prognosis.

In our study, we observed the CRP values were decreased progressively in the survivors of HBOT group; the CRP levels were going up at the third day and then

going down obviously at the fifth day in the survivors of control group. The patient response to an anti-inflammatory treatment, the CRP decreased normally very rapid. The only one different management between HBOT group and control group was hyperbaric oxygen therapy, which was done to assist to modify local and systemic inflammatory response and microcirculatory changes in AP. Serial concentrations of serum CRP are used to predict the development of necrosis, infection or both and assess treatment efficacy in humans with acute pancreatitis (Riché *et al.*, 2003). It has been concluded that the pancreatic and systemic microcirculation and acute inflammation are potentially improved by HBO therapy (Cuthbertson and Christophi, 2006). Although our study population was small, we could observe the difference of trends in serial CRP measurement between two groups. Therefore, we could evaluate the efficacy of treatment by measuring CRP was to detect and monitor systemic inflammatory activity and combining with sequential Spec cPL concentration to know the local inflammation of pancreas and clinical presentation of individual.

Conclusions: To have a good prognosis, the level of creatinine may be as an important criterion when the patients with AP were first visit clinic. In survivors group the creatinine levels was significant lower than that in non-survivors group. The prognostic factors such as CRP, Spec cPL had a good response to routine combined with HBOT in survivors. Likewise, the level of Spec cPL was decreased significantly after treatment no matter routine or routine combined with HBOT in survivors group.

Authors contribution: IJ and WM conceived and designed the study. TH, HC and KS executed the experiment and analyzed the sera and tissue samples. IJ analyzed the data.

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