Asian Clin. Vet. Med., 2020, 1(1): 6-10
ISSN: 2433-2313 (Online)

Case-control study

Submit : 22/5/2020 Accept : 30/9/2020 Published : 6/10/2020

Elevated Kidney Biomarker Levels and Thrombocytopenia During Treatment as Prognostic Factors for Canine Acute Pancreatitis

Kohtaro HAYASHI[1]*, DVM, PhD; Hiromi TOIZUME[1], DVM; Kaori MATSUMOTO[1], DVM; Masaru OKAMURA[1], DVM; Katsuaki SHIRAI[1], DVM, PhD; Takurou KARIYA[1], DVM

Abstract

Canine acute pancreatitis prognostic indicators are uncertain, and methods for determining the condition's severity are not backed by sufficient evidence. Therefore, we aimed to identify prognostic blood test-related factors associated with this disorder during treatment. We performed a retrospective cohort study of dogs hospitalized and treated for acute pancreatitis. Diagnoses were based on clinical signs, abnormal canine pancreas-specific lipase results (>400 μg/L), and abnormal pancreas ultrasonography findings. Signalment and biomarkers before and during treatment were statistically examined to assess mortality risk. A month after the start of treatment, 147 dogs were alive; 62 had died. The death risk was higher in dogs over age 10 (P=0.007, odds ratio [OR]: 3.56). At the first visit, the death risk was higher in dogs with elevated levels of blood urea nitrogen (P<0.0001, OR: 5.71), creatinine (P<0.0001, OR: 5.05), and phosphate (P<0.0001, OR: 5.53) and thrombocytopenia (P=0.038, OR: 2.47). Mortality risk was higher in dogs with elevated blood urea nitrogen levels during the first examination and after 3 to 5 days of treatment (P<0.0001, OR: 7.2) and in those with thrombocytopenia during treatment (P=0.018, OR: 4.1). For canine acute pancreatitis treatment, we recommend hospitalization with intensive, regular kidney biomarker and platelet count monitoring.

Keywords: blood urea nitrogen; dog; pancreatic disease; prognostic factor; risk factor

Introduction

Pancreatitis is the most prevalent exocrine pancreatic disease among dogs; when severe, it causes a wide variety of clinical symptoms and multiple organ failure with a concomitantly high mortality rate of 27–58%.[1,2] Some dogs recover within a few days with supportive care, but more serious presentations can be fatal if not immediately recognized and treated.[3] Previously, canine acute pancreatitis (AP) was not easily diagnosed, particularly antemortem, but it is now easier to diagnose AP using the canine pancreas-specific lipase (Spec cPL™) test.[4] This test, however, has been reported to have a false positive rate of 40%.[5] Thus, the diagnosis of pancreatitis requires comprehensive judgment of history, physical examination findings, complete blood count results, biochemical analysis results, and abdominal ultrasonography findings.

Prognostic indicators of acute pancreatitis in canines are uncertain, and methods for determining the condition's severity are not backed by sufficient evidence. Before the introduction of the Spec cPL™ test, hypothermia and metabolic acidosis were identified as prognostic factors.[1,3] The recent development of a clinical severity index based on the presence of systemic inflammatory response syndrome, coagulation disorders, increased creatinine (CRE) levels, and ionized hypocalcemia[6] has improved diagnostic sensitivity. Prognostic information for AP was previously based on hyponatremia, elevated blood urea nitrogen (BUN) levels, elevated CRE levels, decreased platelet counts, markedly elevated Spec cPLTM concentrations (≥1,000 μg/L), and oligoanuria.[7-9]

There are few analyses of prognostic factors for canine pan-

*Corresponding author: Kohtaro Hayashi, DVM., [1]Kariya Animal Hospital Group, 3-12-7 Kitasuna, Koto-ku, Tokyo 136-0073, Japan
E-mail: kohtaro.hayashi5956@gmail.com

creatitis during treatment. A study assessing C-reactive protein (CRP) concentrations on the third and fourth days of treatment revealed a significant difference between survivors and non-survivors.[9] Severe pancreatic necrosis and multiple organ dysfunction are associated with a poor prognosis.[3] In humans, BUN values at the time of initial hospitalization and 24 hours later can predict mortality due to AP.[10] Although several blood test-related prognostic factors for AP have been identified, their sensitivity during treatment has not been assessed.

To address this shortcoming in the clinical literature, we aimed to identify the prognostic factors for AP before and during treatment.

Materials and Methods

Inclusion criteria

In this retrospective cohort study, we analyzed the records of dogs with AP who underwent hospitalization and treatment from October 2013 to April 2018 at a single animal hospital. AP was diagnosed on the basis of clinical signs (anorexia, lethargy, diarrhea, vomiting, abdominal pain, or a combination of these) and abnormal Spec cPL™ results (>400 μg/L). In addition, we targeted cases in which there were structural or echogenic abnormalities in the pancreas on abdominal ultrasonography. We excluded cases in which tumors or foreign bodies were identified on abdominal ultrasonography and/or cytology. All dogs were managed with fluid therapy, antiemetics, pain medications, and antacids. Additional treatment was provided with prednisolone, fuzapladib, dopamine, and fresh frozen plasma in some dogs. Our study design did not need Institutional Ethics Committee approval due to its retrospective nature.

Evaluation of prognostic factors

Medical history, signalment, hematology results, and biochemical analysis results were obtained from the dogs' medical records. For the assessment of mortality risk at the first visit, dogs were included in the study if data for the following parameters were available: white blood cell count (WBC), platelet count, albumin (ALB) level, BUN level, CRE level, phosphate level, alkaline phosphatase (ALP) level, alanine aminotransferase (ALT) level, total calcium level, sodium level, and CRP level. For the assessment of mortality risk in dogs with worsening values for each parameter during treatment, we included dogs if single or repeated data were available for the following parameters: platelet count, ALB level, BUN level, CRE level, potassium level, ALP level, ALT level, calcium level, and CRP level. Mortality risk during treatment was assessed based on the parameter progression after 3 to 5 days of treatment. Non-survivors of AP included dogs that died within 30 days of the initial visit. Complete blood counts (ProCyte Dx; Idexx Laboratories, Tokyo, Japan) and serum biochemistry profiles (Catalyst Dx; Idexx Laboratories) were obtained using automated clinical analyzers.

Statistical analysis

Signalment and biomarkers before and during treatment were statistically examined to assess mortality risk. We used Fisher's exact tests (GraphPad Prism 5 Software; San Diego, CA, USA). A P value <0.05 was considered statistically significant.

Results

Cases

The study included 209 dogs (111 males: 50 intact, 61 neutered; 98 females: 27 intact, 71 spayed) of several breeds. The median age was 13 years (range: 0 to 18 years). The most commonly affected breeds were miniature dachshunds (n=58), Chihuahuas (n=30), toy poodles (n=24), and Yorkshire terriers (n=11). Some dogs had a history of heart disease (n=52). The main clinical symptoms were anorexia (n=163, 78%), vomiting (n=132, 63%), lethargy (n=125, 60%), diarrhea (n=99, 47%), and abdominal pain (n=27, 13%).

Evaluation of prognostic factors at the first medical examination

One month after the start of treatment, 147 dogs were alive, while 69 had died. A comparison of signalment and laboratory values at the first medical examination between survivors and non-survivors showed that mortality risk was higher among dogs older than 10 years (P=0.007, odds ratio [OR]: 3.56; Table 1). At the first visit, mortality risk was higher in dogs with elevated BUN levels (P<0.0001, OR: 5.71, sensitivity: 87.6%, specificity: 44.6%), elevated CRE levels (P<0.0001, OR: 5.05, sensitivity: 79.4%, specificity: 56.6%), elevated phosphate levels (P<0.0001, OR: 5.53, sensitivity: 80.8%, specificity: 56.9%), and thrombocytopenia (P=0.038, OR: 2.47, sensitivity: 72.8%, specificity: 48.0%; **Table 1**).

Evaluation of prognostic factors during treatment

Comparison of laboratory values at a medical examination after 3 to 5 days of treatment between survivors and non-survivors showed that mortality risk was very high in dogs in whom elevated BUN levels were noted at the first examination and after 3 to 5 days of treatment (P<0.0001, OR: 7.2,

Table 1. Variables measured during the first medical examination, compared between survivors and non-survivors using univariate analysis

Variable	Criteria	No. Survivors	No. Non-Survivors	*P*-Value	Odds Ratio
White blood cell count [/μL]	>16760	66	36	0.0963	1.699
	≤16760	81	26		
Platelet count [×10^3/μL]	<148	13	12	0.0382*	2.474
	≥148	134	50		
Albumin [g/dL]	<2.3	3	1	1	0.7869
	≥2.3	144	61		
Blood urea nitrogen [mg/dL]	>27	62	50	< 0.0001 §	5.712
	≤27	85	12		
Creatinine [mg/dL]	>1.8	23	30	< 0.0001 §	5.054
	≤1.8	124	32		
Phosphate [mg/dL]	>6.8	25	33	< 0.0001 §	5.553
	≤6.8	122	29		
Alkaline phosphatase [U/L]	>212	66	36	0.0963	1.699
	≤212	81	26		
Alanine aminotransferase [U/L]	>125	41	24	0.1419	1.633
	≤125	106	38		
Canine pancreas-specific lipase [μg/L]	≥1000	77	32	1	0.9697
	<1000	70	30		
Total calcium [mg/dL]	<7.9	12	6	0.7884	1.205
	≥7.9	135	56		
Sodium [mmol/L]	<144	11	2	0.3526	0.4121
	≥144	136	60		
C-reactive protein [mg/dL]	≥10	74	31	1	0.99
	<10	73	31		
Age [years]	≥10	112	57	0.0072 †	3.563
	<10	35	5		
Heart disease	Present	33	19	0.2236	1.526
	Absent	114	43		

Fisher's exact test: *P<0.05, †P<0.01, ‡P<0.005, §P<0.001

sensitivity: 80.0%, specificity: 64.3%; Table 2). Additionally, mortality risk was higher in dogs with thrombocytopenia during treatment (*P*=0.018, OR: 4.1, sensitivity: 86.6%, specificity: 38.9%; **Table 2**).

Discussion

In this study, the kidney biomarkers BUN, CRE, and phosphate were significantly elevated in the non-survivor group at the first visit. This result is consistent with previous reports that increased BUN and CRE levels are associated with increased mortality risk in canines with AP.[7,9] Elevated BUN, CRE, and phosphate levels at the first visit may be useful prognostic factors for canine AP. In human medicine, acute kidney injury (AKI) is a common complication of severe pancreatitis.[11-13] AKI is associated with hypoxemia, oxidative stress, decreased renal perfusion, and hypoglycemia caused by pancreatitis.[13] Therefore, it has been suggested that AKI occurs in dogs with severe AP and that mortality risk is higher in AP cases with AKI.

Our analysis showed that dogs with elevated BUN levels during treatment had a very poor prognosis. In human medicine, elevated BUN levels are very important to the scoring of AP severity.[14-16] The BUN values at the time of admission with AP and 24 hours after admission together predict persistent organ failure and pancreatic necrosis.[17] In addition,

Table 2. Variables measured during treatment, compared between survivors and non-survivors using univariate analysis

Variable	Criteria	No. Dogs	No. Survivors	No. Non-Survivors	P-Value	Odds Ratio
Platelet count [$\times 10^3/\mu L$]	≤148×103	100	11	7	0.0181*	4.107
	>148×103		71	11		
Albumin [g/dL]	Decrease by ≥0.3	98	7	6	0.079	3.19
	Other		67	18		
Blood urea nitrogen [mg/dL]	Increase by ≥10	98	10	18	<0.0001 §	7.2
	Other		56	14		
Creatinine [mg/dL]	Increase by ≥0.3	89	4	5	0.267	2.596
	Other		54	26		
Phosphate [mg/dL]	Increase by ≥0.3	65	6	4	0.461	1.778
	Other		40	15		
Alkaline phosphatase [U/L]	Increase by ≥10	89	16	8	0.7964	1.211
	Other		46	19		
Alanine aminotransferase [U/L]	Increase by ≥10	81	9	2	0.4887	0.4259
	Other		46	24		
Total calcium [mg/dL]	Increase by ≥0.3	58	5	2	1	1.057
	Other		37	14		
C-reactive protein [mg/dL]	Increase by ≥1	159	44	17	0.2447	1.606
	Other		79	19		

Fisher's exact test: *P<0.05, †P<0.01, ‡P<0.005, §P<0.001

elevated BUN levels within 48 hours of admission predict the development of primary infected pancreatic necrosis in patients with AP.[18] It has been suggested that repeated BUN measurements over time are effective evaluators of pancreatic necrosis and multiple organ failure in dogs.

In our study, mortality was higher in dogs older than 10 years. The risk of chronic disease increases with age; chronic kidney disease (CKD) is particularly prevalent among elderly dogs.[19] Because severe AP can cause AKI, dogs with CKD are expected to incur higher levels of kidney damage than those without CKD.[7] In this study, the proportion of CKD cases in the elderly group is unclear. However, the possibility of having a history of CKD was considered higher in old age group than in young age group. Therefore, we considered it possible that the risk of death among older dogs in our cohort.

Our data also showed that mortality risk was higher among dogs that were thrombocytopenic before and during treatment. In dogs, thrombocytopenia is reported to be a prognostic factor for AP,[1,20] and severe AP can cause disseminated intravascular coagulation (DIC). In a 4-year retrospective cohort study similar to ours, 11 of 80 dogs with AP developed thrombocytopenia, and 5 died; one of these 5 dogs was diagnosed with DIC.[3] Therefore, thrombocytopenia may be a prognostic marker of AP. In addition, dogs who developed thrombocytopenia during treatment had a higher mortality risk. Thus, we considered it necessary to monitor platelet counts daily.

Our study has some limitations. We used 3 criteria for the diagnosis of pancreatitis: clinical symptoms, Spec cPL™ concentrations, and exclusion of other diseases by abdominal ultrasonography.[21] For most dogs, histopathological examination was not performed. Because of the retrospective nature of our study, treatment protocols were not uniform for all dogs. However, all dogs were managed with fluid therapy, antiemetics, pain medications, and antacids, with additional treatment with prednisolone, fuzapladib, dopamine, and fresh frozen plasma in some dogs. We did not consider the effects of different drugs and dosages on mortality.

In conclusion, the dogs that died in this study had elevated levels of the kidney impairment biomarkers BUN, CRE, and phosphate in addition to decreased platelet counts. Of these, elevated BUN levels and decreased platelet counts during treatment were associated with higher mortality risk.

Therefore, intensive treatment during hospitalization is required for cases in which renal disorder and/or thrombocytopenia are diagnosed at a primary visit, and frequent, regular BUN level and platelet count measurements are essential.

References

1. Mansfield C. Acute pancreatitis in dogs: advances in understanding, diagnostics, and treatment. Top Companion Anim Med. 2012;27:123-132.
2. Watson P. Pancreatitis in dogs and cats: definitions and pathophysiology. J Small Anim Prac. 2015;56:3-12.
3. Pápa K, Máthé A, Abonyi-Tóth Z, Sterczer A, Psáder R, Hetyey C, et al. Occurrence, clinical features and outcome of canine pancreatitis (80 cases). Acta Vet Hung. 2011;59:37-52.
4. Xenoulis PG, Steiner JM. Canine and feline pancreatic lipase immunoreactivity. Vet Clin Pathol. 2012;41:312-324.
5. Haworth MD, Hosgood G, Swindells KL, Mansfield CS. Diagnostic accuracy of the SNAP and Spec canine pancreatic lipase tests for pancreatitis in dogs presenting with clinical signs of acute abdominal disease. J Vet Emerg Crit Care (San Antonio). 2014;24:135-143.
6. Fabrès V, Dossin O, Reif C, Campos M, Freiche V, Maurey C, et al. Development and validation of a novel clinical scoring system for short-term prediction of death in dogs with acute pancreatitis. J Vet Intern Med. 2019;33:499-507.
7. Gori E, Lippi I, Guidi G, Perondi F, Pierini A, Marchetti V. Acute pancreatitis and acute kidney injury in dogs. Vet J. 2019;245:77-81.
8. Marchetti V, Gori E, Lippi I, Luchetti E, Manca ML, Pierini A. Elevated serum creatinine and hyponatraemia as prognostic factors in canine acute pancreatitis. Aust Vet J. 2017;95:444-447.
9. Sato T, Ohno K, Tamamoto T, Oishi M, Kanemoto H, Fukushima K, et al. Assessment of severity and changes in C-reactive protein concentration and various biomarkers in dogs with pancreatitis. J Vet Med Sci. 2017;79:35-40.
10. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008;57:1698-1703.
11. Halonen KI, Leppaniemi AK, Puolakkainen PA, Lundin JE, Kemppainen EA, Hietaranta AJ, Haapiainen RK. Severe acute pancreatitis: prognostic factors in 270 consecutive patients. Pancreas. 2000;21:266-271.
12. Kes P, Vucicević Z, Ratković-Gusić I, Fotivec A. Acute renal failure complicating severe acute pancreatitis. Ren Fail. 1996;18:621-628.
13. Petejova N, Martinek A. Acute kidney injury following acute pancreatitis: a review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2013;157:105-113.
14. Harrison DA, D'Amico G, Singer M. The Pancreatitis Outcome Prediction (POP) Score: a new prognostic index for patients with severe acute pancreatitis. Crit Care Med. 2007;35:1703-1708.
15. Imrie CW, Benjamin IS, Ferguson JC, McKay AJ, Mackenzie I, O'Neill J, Blumgart LH. A single-centre double-blind trial of Trasylol therapy in primary acute pancreatitis. Br J Surg. 1978;65:337-341.
16. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet. 1974;139:69-81.
17. Koutroumpakis E, Wu BU, Bakker OJ, Dudekula A, Singh VK, Besselink MG, et al. Admission hematocrit and rise in blood urea nitrogen at 24 h outperform other laboratory markers in predicting persistent organ failure and pancreatic necrosis in acute pancreatitis: a post hoc analysis of three large prospective databases. Am J Gastroenterol. 2015;110:1707-1716.
18. Talukdar R, Nechutova H, Clemens M, Swaroop Vege S. Could rising BUN predict the future development of infected pancreatic necrosis? Pancreatology. 2013;13:355-359.
19. Bartges JW. Chronic kidney disease in dogs and cats. Vet Clin North Am Small Anim Prac. 2012;42:669-692.
20. Feldman BF, Madewell BR, O'Neill S. Disseminated intravascular coagulation: antithrombin, plasminogen, and coagulation abnormalities in 41 dogs. J Am Vet Med Assoc. 1981;179:151-154.
21. Xenoulis PG. Diagnosis of pancreatitis in dogs and cats. J Small Anim Pract. 2015;56:13-26.