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Research article

Clinical factors associated with death during hospitalization in parvovirus infection dogs

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Abstract

Canine parvovirus (CPV) is a highly contagious virus that causes significant mortality and morbidity especially in young dogs. The outcome of treatment may different depending on several factors. The aim of this study was to evaluate the association of clinical factors and the death in naturally acquired parvovirus infection dogs during hospitalization at the small animal teaching hospital. Forty-six dogs, with fecal polymerase chain reaction confirmed CPV, were studied during June 2016 to May 2017. All dogs received the standard treatment; intravenous fluids, broad spectrum antibiotics, antiemetic therapy, and deworming. The total clinical scores, routine blood test and hemoculture were examined at day 0, 3, 5 and 7 of hospitalization. Three factors associated with mortality were: predisposing breed (OR = 0.190, 95% CI = 0.095–0.383, P < 0.001), small breed (OR = 0.168, 95% CI = 0.076–0.374, p < 0.001) and low body weight (OR = 1.093, 95% CI = 1.005–1.189, P < 0.05). The overall mortality rate was 32.60% (15/46). The median time of hospitalization in survivors (n = 31) was 5 days. The incidence of mortality rate was highest on Day 3 (n = 12). Although treated with broad spectrum antibiotic, bacteremia can be found in 13 from 83 hemoculture samples (15.66%). In conclusion, the CPV dog with predisposing breed, small breed or low body weight had a significantly increasing risk with death. The first three day of hospitalization is a critical period and need more attention. The impact of sepsis and opportunistic bacteremia requires further studies.

Keywords: Blood profiles, Canine parvovirus, Clinical score, Mortality, Predisposing breed

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INTRODUCTION

Canine parvovirus (CPV) is a highly contagious virus and an important cause of infectious gastrointestinal disease in dogs (Arslan et al., 2012; Greene and Decaro, 2012). CPV first emerged in the early to mid-1970s and spread worldwide by 1978 (Parrish, 1999). The risk factors of CPV infection in puppies include lack of protective immunity, intestinal parasite, unsanitary, overcrowded and improper environment. The predisposing breeds are Doberman Pinscher, American Pit Bull terrier, Labrador retriever, German Shepherd, and Rottweiler (Glickman et al., 1985; Houston et al., 1996). CPV transmit from infected dog to susceptible dog by direct and/or indirect contact with feces (Nandi and Kumar, 2010). Following viremia, virus replicates in rapidly dividing cells including the gastrointestinal epithelium, lymphoid tissue and bone marrow, causing an acute small bowel enteritis, which may be hemorrhagic and led to dehydration, and leukopenia. Dogs succumb to canine parvoviral infection due to hypovolemic shock and sepsis (Goddard and Leisewitz, 2010).

Mortality rates differ among studies but vary between 4 and 48% with proper treatment (Glickman et al., 1985; Otto et al., 1997; Otto et al., 2001; Prittie, 2004), but high mortality up to 91% associated without treatment (Njenga et al., 1990). Infection with CPV carries a high risk of morbidity and mortality, especially in puppies between six months of age (Prittie, 2004) and predisposing breeds. Inherited immunodeficiency and von Willebrand's disease result increased susceptibility to disease and caused more severity (Brunner and Swango, 1985; Glickman et al., 1985). CPV infect lymphoid tissue, intestinal epithelium, and bone marrow in puppy greater than 2 week of age (Prittie, 2004). The collapse of intestinal epithelium was leading to loss of absorptive capacity and development to hemorrhagic diarrhea (Smith-Carr et al., 1997; Pollock and Coyne, 1993). Large fluid and protein losses in gastrointestinal tract could let to serious dehydration and and hypovolemic shock (Prittie, 2004).

The objective of this study was to evaluate the association of clinical factors and the death in naturally acquired parvovirus infection dogs during hospitalization at the small animal teaching hospital.

MATERIALS and METHODS

Study population

This study was a prospective, approved by the Animal Care and Use Committee (FVM-ACUC Ref. no. S34/2559) prior the study initiation. Forty-six dogs of any breed, age and sex with clinical signs indicative of CPV infection and with infection confirmed a positive canine parvovirus polymerase chain reaction (PCR) test during June 2016 to May 2017 at Small Animal Teaching Hospital, Chiang Mai University were enrolled in the study. Upon enrollment, patients were admitted to the Institutional Small Animal Teaching Hospital with the owner's signed consent.

Treatment

All dogs were treated according to the standard of care; intravenous fluids, broad spectrum antibiotics, antiemetic therapy, deworming (Parax, B.M. Pharmacy Limited Partnership) and nutrition were provided as indicated. Supplementation with potassium chloride (Atlantic Laboratories Corporation Ltd.), glucose or dextrose (glucose 50%, A.N.B. Laboratories Co., Ltd.) was based on patients' laboratory results.

Complete blood count, serum chemistry and blood culture

Blood samples were collected from hospitalized dogs at days 0, 3, 5 and 7 by aseptic protocol and complete blood counts (CBC) (BC-5300Vet, Mindray), serum chemistry profiles, (BX-3010, Sysmex), electrolyte profiles (GASTAT-602i, Techno Medica), and blood cultures (LANNA LAB.COMP.) were performed. Not all dogs were sampled at all time-points; dogs that were discharged from the hospital or died were no longer sampled and thus not included in further analysis.

Clinical parameters and recovery

Clinical scores were assigned daily by the same veterinarian. The components of the clinical score scale included attitude, appetite, vomiting, fecal composition, frequency of defecation and hydration status. Each component was given score from level 0 to 3, such that total scores could range from 0 (normal) to 18 (most severe) (Proksch et al., 2014). Dogs were considered recovered and discharged when clinical signs resolved, the total white blood cell counts were within or above the reference range (higher than 5 X 10^3/L), and the fecal consistency score was lower than 5 of Purina Fecal Scoring System (Greco, 2011)

Statistical methods

Statistical analysis was performed in part by using a graphing and statistics software program (Graphpad Prism 6, La Jolla, CA, USA). A one-way ANOVA test was applied to assess differences in clinical score, total white blood cell count, hematocrit, total platelet count, albumin, potassium and blood urea nitrogen between groups on day 0 and day 3, and Tukey's post-hoc test for multiple comparisons was used for ANOVA tests in which a significant difference was detected among groups. P values less than 0.05 were considered significant.

Joint modeling of longitudinal and death data was performed using Package JM in R statistical software (Rizopoulos et al., 2010). Regarding death data, 12 factors including treatment, age, sex, predisposed breed, toy versus large breed, weight, total clinical score, severity score, appetite score, attitude, bacteremia, and white blood cell count at Day 0,3,5,7 of hospitalization were screened for their potential association to death of dogs in the univariate cox regression analysis. All variables with a significance of $P < 0.05$ at the univariable analysis were selected for an initial multivariable cox regression model analysis. All variables with a significance of $P < 0.05$ at the initial multivariable analysis were selected for a final multivariable cox regression model analysis.

For the final model, $P < 0.05$ was considered significant. Odds ratios (OR) and 95% confidence intervals (CI) were estimated to interpret the relationship between factors significantly associated with survival of CPV infection ($P < 0.05$).

RESULTS

A total of 46 dogs were enrolled in the study. This study planned to monitor the dogs until 7 days of hospitalization but on the day 5, from 46 dogs, 15 dogs were died, and 20 dogs were cured and discharged.

The signalment of dogs at the first day (Day 0) was described in Table 1; including sex, predisposing breed, breed, age (month), and bodyweight (kg). The predisposing breeds in this study were Rottweiler and Labrador retriever. Small breeds were Chihuahua (n = 1), French bull dog (n = 2), Miniature pincher (n = 2), Pomeranian (n = 4), Poodle (n = 1) and Shi Zhu (n = 3). Large breeds were Beagle (n = 2), Golden retriever (n = 2), Labrador retriever (n = 1), Mixed (n = 26), Rottweiler (n = 4) and Siberian husky (n = 2).

Table 1 Description of pet characteristics

Parameters	Number of CPV dogs (n = 46)
Sex	Male (n = 22) : Female (n = 24)
Predisposing breed	Yes (n = 6) : No (n = 40)
Breed	Toy breed (n = 9) : Large breed (n = 37)
Age (month)	7.17 ± 7.25 (mean ± sd) 1.00 – 36.00 (min - max)
Bodyweight (kg)	5.34 ± 4.11(mean ± sd) 0.21 - 19.8 (min - max)

The total white blood cell counts at Day 0, 3, 5, 7 and the presence of bacteria in blood had not significantly relationship ($P = 0.83$); mean and standard error of total white blood cell count in dogs with positive bacteremia was 12.28±5.61 X 10^3/L and dogs with negative bacteremia was 11.04 ± 1.22 X 10^3/L.

The overall mortality rate was 32.60% (15/46). The mortality rate was highest on Day 3 (n = 12). As shown in Tables 2-4, the final best-fitting multivariate cox regression model included three variables: predisposed breed (Labrador retriever or Rottweiler) versus other, small versus large breed, and body weight. The non-predisposed breeds and large breeds were less likely to die from CPV infection ($P < 0.001$). The dog with low body weights were more likely to die from CPV infection ($P = 0.038$). The mixed model analysis of the total white blood cell indicated that an increasing total clinical severity score

was related to a lowering of white blood cell count (P = 0.005). Additionally, a longer duration of hospitalization was associated with an increasing white blood cell count (P = 0.012) (Table 5). The survival probability between predisposing breed and non-predisposing breed was presenting in Figure 1 (P = 0.0011).

Table 2 Univariable analysis (Cox regression) of factors associated with death in canine parvovirus infection.

Variables	Categories	Coefficient	OR	95% CI	P value
Age					
	< 3 months	Ref.			
	3–12 months	7.51e-01	2.12e+00	1.248-3.601	**0.005****
	>12 months	-1.79e+01	1.63e-08	0-Inf	0.995
Sex					
	Male	Ref.			
	Female	0.474	1.607	0.968-2.667	0.067
Predisposing Breed	Yes	Ref.			
	No	-1.324	0.266	0.150-0.470	**5.3e-06*****
Breed					
	Small	Ref.			
	Large	-0.683	0.505	0.297-0.860	**0.012***
Body weight (kg)		-0.079	0.924	0.858-0.996	**0.040***
Total clinical severity score	0-9	Ref.			
	10-18	0.318	1.374	0.509-3.711	0.530
Total clinical score					
	Normal (0)	Ref.			
	Mild (1-6)	1.87e+01	1.314e+08	0-Inf	1
	Moderate (7-12)	2.03e+01	6.745e+08	0-Inf	1
	Severe (13-18)	-8.55e-03	9.915e-01	0-Inf	1
Appetite score					
	Normal (0)	Ref.	11.145	1.009-	**0.049***
	Voluntary eats small amount (1)	2.41	16.040	123.151	**0.006****
	No interest in food (2)	2.78		2.149-119.718	
Attitude					
	Normal (0)	Ref.	9.991e-01	0-Inf	1
	Mild to moderate depression (1)	-9.42e-04	4.525e+07	0-Inf	1
	Severe depression (2)	1.76e+01	5.325e+08	0-Inf	1
	Collapsed or moribund (3)	2.01e+01			
Bacteremia					
	No	Ref.			
	Yes	0.349	1.417	0.518-3.879	0.500
Log of white blood cell count (/μL)		-0.422	0.656	0.434-0.990	**0.045***

*** P < 0.001, ** P < 0.01, * P < 0.05

OR = Odds ratio, CI = confidence interval, LRTS = likelihood ratio test statistic, Ref = reference category

Table 3 Initial multivariate Cox regression model of factors associated with death in canine parvovirus infection

Variables	Categories	Coefficient	OR	95% CI	P value
Treatment					
	Control	Ref.			
	Treatment I	-8.328e-01	4.348e-01	0.101-1.868	0.263
	Treatment II	-5.398e-01	5.829e-01	0.084-4.060	0.586
Age					
	< 3 months	Ref.			
	3–12 months	-8.492e-01	4.278e-01	0.097-1.882	0.261
	>12 months	-2.085e+01	8.796e-10	0-Inf	0.997
Predisposing Breed	Yes	Ref.			
	No	-3.492e+00	3.043e-02	0.003-0.344	**0.005** *
Breed					
	Small	Ref.			
	Large	-2.807e+00	6.036e-02	0.011-0.343	**0.002** *
Body weight (kg)		2.938e-01	1.342e+00	1.084-1.661	**0.007** *
Total clinical score	Normal (0)	Ref.			
	Mild (1-6)	1.998e-01	1.221e+00	0.000-Inf	1.000
	Moderate (7-12)	1.893e-01	1.208e+00	0.000-Inf	1.000
	Severe (13-18)	-1.648e+01	6.935e-08	0.000-Inf	0.999
Appetite score					
	Normal (0)	Ref.			
	Voluntary eats small amount (1)	-1.414e+00	2.433e-01	0.011-5.260	0.367
	No interest in food (2)	4.931e-01	1.637e+00	0.174-15.385	0.666
Attitude					
	Normal (0)	Ref.			
	Mild to moderate depression (1)	5.433e-01	1.722e+00	0.000-Inf	1.000
	Severe depression (2)	2.048e+01	7.851e+08	0.000-Inf	0.999
	Collapsed or moribund (3)	2.483e+01	6.087e+10	0.000-Inf	0.999
Log of white blood cell count (/μL)		-1.930e-01	8.245e-01	0.463-1.469	0.512

* P <0.01
OR = Odds ratio, CI = confidence interval, Ref = reference category

Table 4 Final multivariate Cox regression model of factors associated with death in canine parvovirus infection

Variable	Category	Coef	S.E.	OR	95% CI	P-value
Predisposing						
Breed	Yes	Ref.				
	No	-1.660	0.357	0.190	0.095-0.383	3.29e-06 ***
Breed						
	Small	Ref.				
	Large	-1.784	0.408	0.168	0.076-0.374	1.21e-05 ***
Body weight (kg)		0.089	0.043	1.093	1.005-1.189	0.038 *

*** P < 0.001, ** P < 0.01, * P < 0.05
Coef = coefficient, S.E. = standard error, OR = odds ratio, CI = confidence interval, Ref = reference category

Table 5 Initial linear mixed model analysis of factor associated with white blood cell count in canine parvovirus infection.

Variable	Category	Coef	S.E.	95% CI	P-value
Day		0.174	0.065	0.041-0.307	0.012 *
Total clinical severity score	0-9	Ref.			
	10-18	-0.039	0.238	-1.228-(-0.251)	0.005**
Bacteraemia					
	No	Ref.			
	Yes	-0.528	0.272	-1.085-0.030	0.063

** P <0.01, * P < 0.05
Coef = coefficient, S.E. = standard error, OR = odds ratio, Ref = reference category

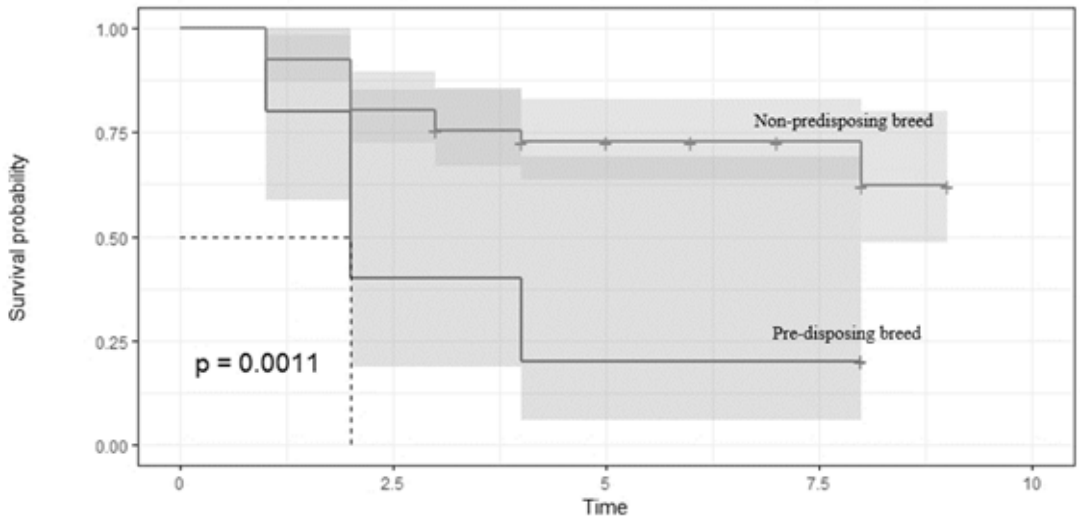

Figure 1 The survival probability between predisposing breed and non-predisposing breed.

DISCUSSION

In this study, predisposed breed (Labrador retriever or Rottweiler) had a high mortality rate of CPV infection. Similar to this study, Rottweiler is one of breeds associate with increased risk of CPV (Glickman et al., 1985; Houston et al., 1996) due to the presence of inherent gene in this breed. (Glickman et al., 1985). Rottweiler pups are more likely to have a von Willebrand's disease and an immunodeficiency disease (Brunner and Swango, 1985); serum IgG and IgA deficiency, making them more susceptible, to mucosal infection from parvovirus (Day, 1999). Moreover, predisposing breeds such as Doberman Pinscher, American Pit Bull terrier, Labrador retriever, German Shepherd, and Rottweiler are more likely to develop disease when infected, or more likely to develop severe clinical disease (Glickman et al., 1985).

In the previous studies, bodyweight was not associated with CPV infected dog (Miranda et al., 2015) or survival rate (Kalli et al., 2010). However, the final multivariable analysis in this study showed the significantly correlation between low body weight or small breed with the mortality rate. The small dogs or puppies had higher risk to death, as a result of their low body weight and not tolerant to massive loss fluids and energy.

In this study revealed a correlation of the CPV severity and the lowering of white blood cell count (leukopenia) which is corroborated with some previous studies (Goddard et al., 2008, Greene and Decaro, 2012). Leukopenia is a characteristic of canine parvovirus infection that mostly in consequence of the most severe neutropenia (2-6% of normal values) and lymphopenia. Lymphocyte values commonly decreases to approximately 50% of normal values (Potgieter et al., 1981). In non-survivors had more viral infection effect other than bloody diarrhea. Disease process in those patients was rapidly progressive and destroy a bone marrow response which resulted death. In addition, the virus-induced neutropenia and lymphopenia, could be possible for increasing of

the susceptibility to opportunistic bacteria (Greene and Decaro, 2012) which developing septicemia, a systemic inflammatory response and a higher risk of death (Prittie, 2004). Secondary bacterial infections from anaerobic microflora and gram-negative bacteria cause of complication concern with intestinal damage, bacteremia and endotoxemia, disseminated intravascular coagulation (Greene and Decaro, 2012). However, this study found the longer duration of hospitalization were associated with an increasing of total white blood cell count. This result can be explained as the survival dogs with active body defense mechanism were mostly admitted in the hospital for 5 days but the non-survival dogs; high severity, leukopenia commonly died at the day 3 after hospitalization. The dogs with CPV infection if they can survived the first 4 days, they will recover rapidly and have immunity for against parvovirus for life (Nandi and Kumar, 2010).

CONCLUSION

In conclusion, the CPV dog with predisposing breed, small breed or low weight had a significantly increasing risk with death. The first three day of hospitalization is a critical period and need more attention. The dogs had severe clinical sign tended to leukopenia and followed by bacteremia. The impact of sepsis and opportunistic bacteremia requires further studies.

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CONFLICT of INTEREST

None of the authors of this paper have a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper

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