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Prognostic factors for survival of dogs infected with canine parvovirus

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Abstract : To determine the prognostic factors for survival of dogs infected with canine parvovirus, clinical and laboratory data of 35 dogs with clinical signs compatible with canine parvoviral enteritis admitted to the Veterinary Medical Teaching Hospital, Seoul National University during the period 1997-1998 were collected. Dogs were grouped by some major covariates, which can be considered as guides to the relative prognosis of dogs in the different subgroups. The Kaplan-Meier survival analysis and Weibull proportional hazard model were used to estimate overall survival, evaluate the comparability between groups, and identify potential prognostic factors. The overall survival rate for all dogs was 45.7% over the study period, and the Kaplan-Meier estimate of one week survival was 0.4989. Gender was the most favorable prognosis ; male dog (median, 6 days) had significantly higher risk of dying than female dog (median, 17 days ; $p = 0.0023$). In addition to gender, age was significantly associated with survival, with juvenile dogs less than 6-month-old having higher risk ($p = 0.0359$). Dogs that vaccinated with complete protocol ($p = 0.0374$) and those of having higher value of mean corpuscular volume ($p = 0.0346$) were found to be of prognostic importance. The 7 dogs in which white blood cell count of less than 2000 had shorter median survival time (3 days) than the remaining 28 dogs (8 days), but no statistical significance was found between leukopenic and survival. The distribution of packed cell volume and hemoglobin measurement was such that the overall risk of dying in the two groups was comparable. Further studies are needed to more accurately assess these results.

Key words : canine parvovirus infection, risk factor, survival.

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Introduction

Viral gastroenteritis has become of great importance with the emergence of canine parvovirus (CPV) along with canine coronavirus and rotavirus as a new virus infecting dogs in the late 1970s after which it showed continuous antigenic changes[1]. Parvoviral enteritis is characterized by an acute hemorrhagic diarrhea often associated with fever and leukopenia in dogs, and primarily affects puppies less than six months of age[2]. Puppies are protected against infection for the first few weeks of life by maternal antibody. As their maternal antibody titers decline, however, they become susceptible to infection, and nearly all adult dogs are immune, either as a result of vaccination or natural exposure[3]. There is marked variation in the clinical response of dogs to infection with pathogenic CPV type-2, ranging from inapparent infections to acute fatal disease. It has reported that the morbidity and mortality are less than 20% and 5%, respectively, while the fatality varies from 10 to 90%[2]. According to results of serologic surveys[4], subclinical infection was much more common than clinical disease, especially in dogs greater than 6 months of age.

Several studies have considered risk factors for development of parvoviral enteritis in dogs. In these studies that examined risk factors investigators identified a significant association between CPV development and the following factors: gender, breed, vaccination, hematology, stress, and concurrent infections with intestinal parasites or bacteria[2,5-11]. However, to our knowledge, studies of prognostic indicators that predispose to survival are very limited. In view of the complete lack of information available, the purpose of this study was to evaluate predisposing factors associated with survival of the dogs with CPV and, thus provide clinicians insight into prognosis related to the disease. Additionally, meaningful information can be relayed to the patient's owner.

Materials and Methods

Data collection : Medical records of dogs with CPV admitted to the Veterinary Medical Teaching Hospital, Seoul National University (VMTH-SNU) from January 1, 1997, to December 31, 1998, were reviewed. Dogs were considered to be infected with canine parvovirus if clinical signs and physical examination findings were consistent with canine parvovirus infection, and canine parvovirus antigen test kit (IDEXX Laboratories, USA) or polymerase chain reaction on blood samples showed positive reaction. The following data were determined at the time of admission: age in month, gender, breed, weight, vaccination, complete blood count, serum chemistry, rectal temperature, respiratory rate (breaths per minute), or heart rate (beats per minute). Follow-up was obtained either by recheck at the VMTH-SNU or by telephone interview with referring veterinarians for a maximum period of 43 days.

Statistical analysis : Cases were divided into two groups based upon hematology and serum chemistry, with one for normal profile and one for abnormal profile. Dogs were also classified into two groups by age (juvenile, ≤ 6 months or other, > 6 months), or by weight in Kg as toy (≤ 5) and others (> 5). In the final analysis age of the dog was entered into the model with continuous variable. Data pertaining to white blood cell (WBC), hemoglobin (Hb), mean corpuscular volume (MCV), and packed cell volume (PCV) were logarithmically transformed to normalize data. Survival time was calculated as the difference in days between the date of diagnosis of CPV and the date of death. Dogs alive at the end of the study period or dying from or euthanized for causes unrelated to CPV were treated as censored outcomes. Dogs that were censored were included in the calculation of survival function until the time of censoring. Univariate analysis to assess for prognostic value of the different covariates was performed by the Kaplan-Meier product limit survival analysis[12], and differences in survival distribution between groups were tested using the log rank test. A Weibull survival analysis[12] was used to evaluate the multivariate interrelationships among variables after controlling other factors as well as interaction among these factors. A two-tailed Fisher's Exact or chi-square test of homogeneity was used to evaluate the hypothesis that breed distribution was homogeneous among dogs divided by some study factors. A P value of < 0.05 was considered significant for all

statistical tests. A positive coefficient indicated that as the value of the variables changed, the risk of the event at any time changed in the same direction; the opposite relationship existed for a negative coefficient. Analysis was performed using the statistical package SAS (release 6.12 for windows, SAS Institute, Cary, NC, U.S.A.)[13] and Medcalc (ver 4.30 for windows, Medcalc software, Belgium)[14].

Results

Of the 43 records originally retrieved, 8 were excluded because their demographic information was not available for analysis, and thus 35 dogs were eligible for entry into the study. The descriptive data for the dogs and median survival and its 95% confidence interval (CI) for the variables studied are presented in Table 1. Overall, 28 (80%) of the 35 dogs with definite CPV enteritis were less than 6 months of age (juvenile). The mean age at diagnosis of the cases was 6. 3 months, with a range of 1 to 36 months. Dogs of Yorkshire Terrier were the most numerous (7, or 20% in total), followed by 3 each Cocker Spaniel, Schnauzer, mongrel, and beagle and 16 others. The gender of the cases were evenly distributed (15 male and 20 female), and toy breed accounted for 82.9%. There were also no significant differences in the age or gender distributions of the two groups divided by WBC count of 2000.

The most common clinical signs were typical gastrointestinal symptoms such as vomiting, diarrhea, anorexia and lethargy in combination with a leukopenia under 4000 cells/㎕(10/27 dogs, or 37%). WBC counts from 14 cases (14/27 dogs, or 51.9%) were within normal limit of 6,000-17,000.

The cumulative hazard function of survival data demonstrated the appropriateness of the Weibull model of survival data (Fig 1), showing a linear trend of cumulative hazard over time. Four dogs were lost to follow-up after being discharged from the hospital, and thus an overall fatality of 54.3% (19/35 dogs) was obtained based on the number of dogs that survived over a maximum period of observation. The Kaplan-Meier estimate of survival after admission was 0.7714 on 2 days, 0.6571 on 3 days, 0.5880 on 4 days, 0.5488 on 6 days, and 0.4989 on 7 days after admission (Fig 2).

Table 1. Descriptive findings and median (50%) survival by covariates in 35 dogs with parvovirus infection

Covariate	n*	Percent	Survival	
			Median	95% CI¶
Age (month)				
≤6	28	80.0	7.0	3.0~17.0
〉6	7	20.0	-[c]	
Gender				
Male	15	42.9	6.0	2.0~16.0
Female	20	57.1	17.0	3.0~ .
Size[a]				
Toy	29	82.9	8.0	3.0~ .
Others	6	17.1	10.0	2.0~16.0
Vaccination				
Yes	8	25.0	-	
No	24	75.0	7.0	3.0~17.0
PCV[b]				
Normal	10	37.0	7.0	2.0~
Abnormal	17	63.0	16.0	3.0~ .
Hb[b]				
Normal	11	42.3	17.0	3.0~ .
Abnormal	15	57.7	6.0	2.0~ .
MCV[b]				
Normal	11	42.3	3.0	2.0~ .
Abnormal	15	57.7	16.0	4.0~ .
WBC1[b]				
Normal	13	48.1	3.0	2.0~ .
Abnormal	14	51.9	8.0	4.0~17.0
WBC2[b]				
〈=2000	7	20.0	3.0	2.0~ .
〉2000	28	80.0	8.0	4.0~17.0

¶ CI, confidence interval, * Total number of dogs for which data were avialable. [a] Size in Kg: toy, ≤5; others, 〉5. [b] Reference values for biochemical testing: PCV, packed cell volume, 37-55; Hb, hemoglobin, 12-18; MCV, mean corpuscular volume, 60-77; WBC, white blood cell, 6,000-17,000. [c] represents survival not dropped below 50%.

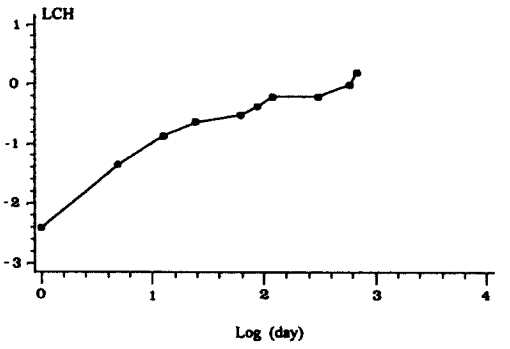


Fig 1. Logarithmic cumulative hazard (LCH) function (LLS graph) of survival data. X-axis, log (day); Y-axis, log(-log S(day)).

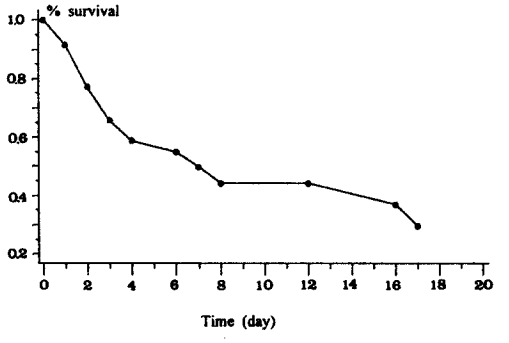


Fig 2. Weibull survival curve for 35 dogs with parvoviral enteritis. The survival time in days after diagnosis is presented on the horizontal axis. The survival of the dogs is presented on the vertical axis where '1' represents 100% of the dogs alive and '0.5' represents 50% of the dogs still alive.

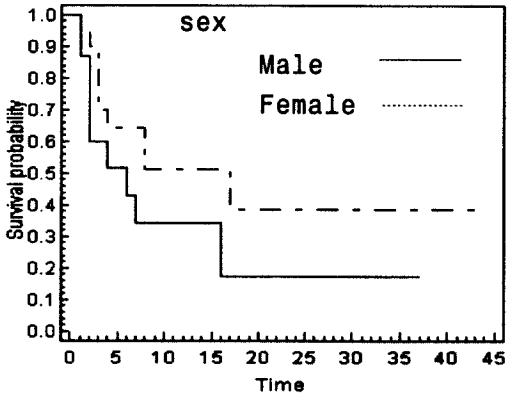
Among the 7 dogs that had less than 2000 WBC counts only 2 (28.6%) remained alive at the end of the study period. Adult dogs were more likely to survive, with a survival of 50% or more over the study period than juvenile dogs. Kaplan-Meier survival curves of dog with CPV by some selected covariates were shown in Fig 3. Median survival of male and female dogs was 6 and 17 days, respectively. Other breed had longer median survival than toy breed (10 versus 8 days). Neither PCV nor Hb measurement contributed significantly in survival. When juvenile dogs were grouped according to vaccination status, 59.1% of the unvaccinated dogs died, compared to only 25% of vaccinated dogs (Table 2). An inverse correlation between vaccination and survival was noted.

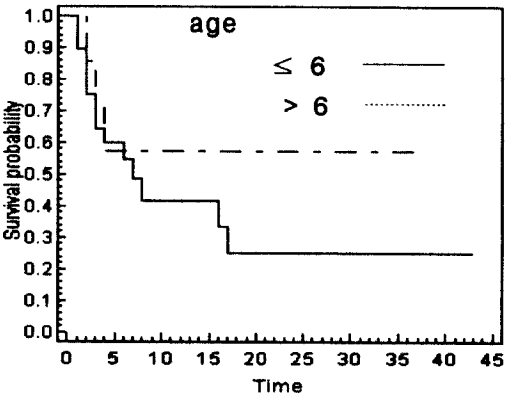
Table 2. Results of death profile in two age group by vaccination status

	Juvenile (26)[a]		Adult (6)[b]	
	No.	Death	No.	Death
Vaccination	4	1 (25%)	4	2 (50%)
Unvaccination	22	13 (59.1%)	2	0 (0)

[ab] Information on vaccination was not available; 2 in juvenile and 1 in adult group.

In Weibull proportional hazard survival analysis, a male, a non-vaccinated, and a decreasing value of MCV were significantly associated with an increased risk of dying (Table 3). An increase in age was associated with decreased risk of dying. Among non-significant variables dogs that had lower PCV value tended to be at higher risk of dying.





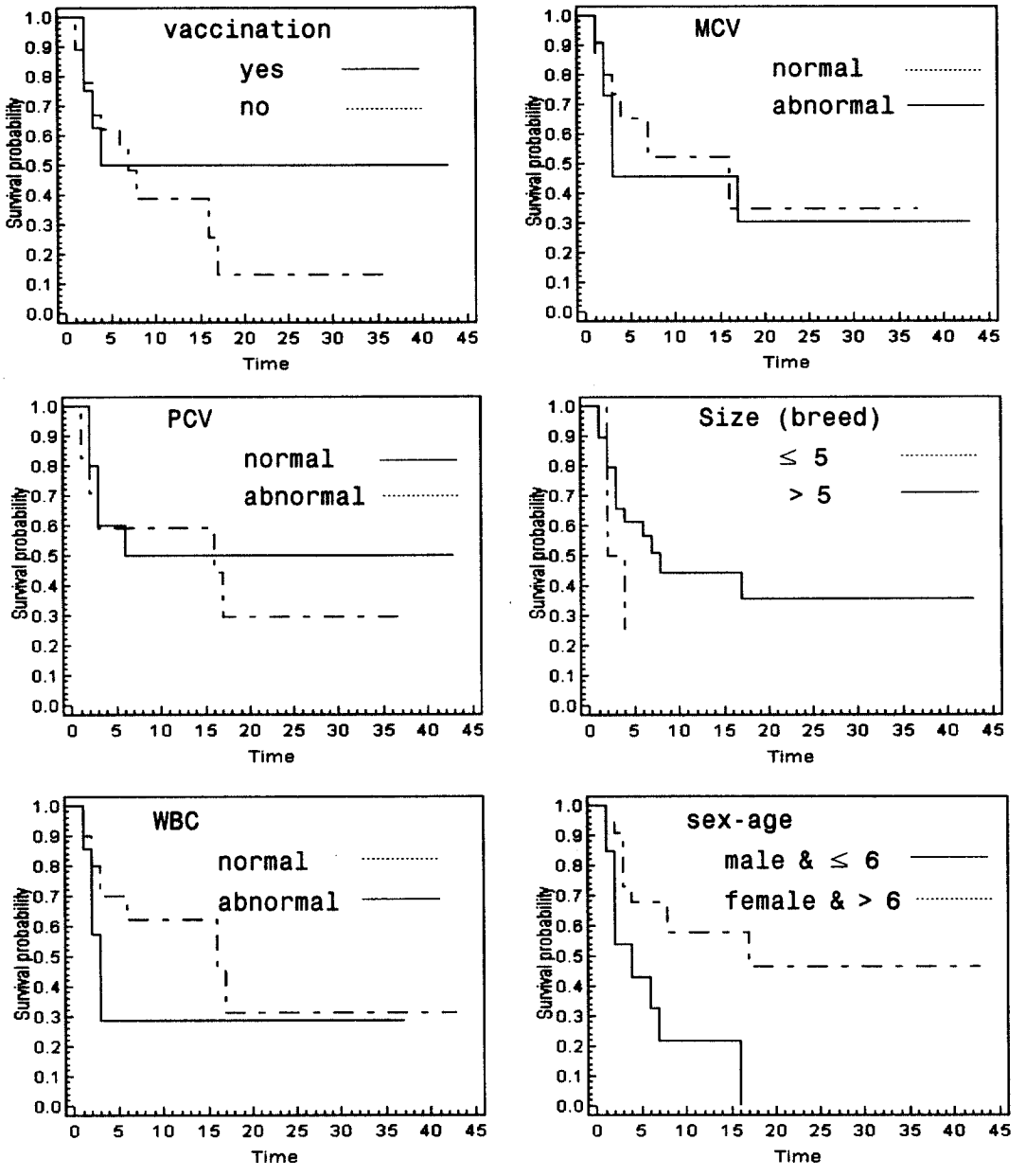


Fig 3. Kaplan-Meier survival curves for parvovirus-infected dogs by some selected covariates. Time on X-axis represents time in days after diagnosis.

Discussion

This study aimed to determine the potential prognostic factors affecting the survival of dogs diagnosed with CPV infection. The overall survival rate of 45.7% in the study was lower than 64.0% in other reports[7]. Of the variables studied, gender was found to be of most prognostic importance. Additionally, juvenile male dogs (n = 22) survived significantly short period of time (3.4 versus 6.1 days) when com-

Table 3. Effects of several factors on the survival function as determined by Weibull proportional hazard survival analysis

Covariates	Degree of freedom	Estimate	Standard error	x^2	P-value
INTERCPT	1	-0.837	5.016	0.028	0.8674
SIZE	1	-0.242	1.922	0.016	0.9000
SEX	1	-3.097	1.018	9.255	0.0023
AGE	1	0.147	0.070	4.402	0.0359
LOGWBC	1	0.655	0.491	1.778	0.1824
VAC	1	1.899	0.913	4.331	0.0374
PCV	1	-1.199	1.073	1.251	0.2633
MCV	1	-2.237	1.059	4.464	0.0346
SCALE	1	1.077	0.270		
L_0 : -48.02193433	L : -26.54558494		$x^2_{0.95}(7) = 14.067$		

L_0 : Log likehood of baseline hazard function; L ; Log likelihood of model hazard function.

pared with adult female dogs (n = 13). In a study on the risk factors for CPV infection[7] authors reported that there was no association between the risk of parvoviral enteritis and the gender of the affected dogs, but not in others[10].

Several studies reported on breed difference in the susceptibility to CPV enteritis[7-9]; young Rottweilers, Doberman pinschers, and pit bull terriers were either more susceptible to clinical CPV infection or that clinical disease readily appeared after infection than were most other breeds. No studies, however, have been reported on any breed differences related to the survival after CPV infection. Because the current study was limited by the small number of breeds, we investigated instead breed-related factor in toy and other breed divided by their individual weight, and no statistical difference in survival was found between these groups. To confirm whether the survival distribution is different by breeds further studies are needed.

Of great importance is that dogs received vaccination against CPV with complete protocol had significantly longer survival than unvaccinated dogs; median survival in vaccinated dogs did not drop under 50% over the study period, while that of unvaccinated dogs was 7 days. Of 8 vaccinated dogs 3 (37.5%) died, while 13 (54.2%) of 24 unvaccinated dogs died. By age group, among 26 dogs of juvenile dogs, 22 (84.6%) did not receive vaccination, of which 13 (59.1%) died. On the contrary 1 (25%) of 4 vaccinated dogs died. An inverse phenomenon was observed among adult dogs; 2 (50%) of 4 vaccinated dogs died and no death was occurred in 2 unvaccinated dogs. The observed high mortality among vaccinated adult dogs may be explained by vaccine failure; inadequate immunization such as incomplete or untimely vaccination interfered with maternal antibody. The observed increased risk of dying among unvaccinated juvenile dogs may indicate that timely vaccination of dogs in puppies against CPV could be the underlying factors leading to survival, as observed by other investigator[11]. In addition, our results along with the previous report[2] may indicate that age could be a contributing factor for not only acquiring of the CPV but also subsequent surviving of the dog after CPV infection. In the future, the relationship between survival and the variables of vaccination-related factor need to be studied further with sufficient survival data. Further, since less amount of maternal antibody is required to suppress response to a killed vaccine as compared to live vaccine[3,15], the relationship between vaccination and its effect on protective immunity, and between maternal antibody titer and puppy survival should also be a subject of study.

The viremia coincide roughly with the onset of leu-

kopenia that is considered as an indicator of a fatal prognosis. Although most studies reported decreased lymphocytic responsiveness to mitogens during the course of disease[16], immunosuppression associated with CPV is still controversial in the literature. In the present study 7 dogs that had less than 2000 counts of WBC had a median survival of 3 days, while that of the remaining 28 dogs was 8 days. Leukopenic dogs did not have a significantly increased mortality when compared with dogs without leukopenia ; 61.5% of leukopenic dogs died, compared with 38.5% of nonleukopenic dogs ($x^2 = 1.385$; $P = 0.239$). The author's data were similar to the report of Glickman *et al*[7], but not in others[11,17]. Consequently, these data may indicate that leukopenia should not be used as the critical criteria of prognosis related to the condition.

As with all retrospective studies, our study had limitations ; complete data were not always available from the medical records, follow-up contacts were not possible for each dog, and data in regard to previous medical treatment, in particular, were often incomplete. Despite these shortcomings, the results of the study suggested that all dogs be immunized with effective products. Clinicians need to educate dog owners about the necessity of vaccination, emphasizing that timely vaccination with complete schedule with annual booster is indispensable to avoid the disease, as was seen by McCaw *et al*[18]. Additionally, it is important to provide clients information that puppies should not be taken out of their home environment until the vaccination protocol is completed. Further well-designed prospective studies into the relationship between survival after CPV infection and host-related contributing factors such as breed are indicated.

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