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Prognostic values of physical and hematological parameters of dogs naturally infected with parvovirus PVC-2: retrospective study of 103 cases

[*Valores prognósticos de parâmetros físicos e hematológicos de cães naturalmente infectados pelo parvovírus PVC-2: estudo retrospectivo de 103 casos*]

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ABSTRACT

Canine parvovirosis is a high mortality disease with acute clinical picture. However, there are few available resources to help stablish prognosis accurately. This study aimed to determine the prognostic threshold values for vital and hematological parameters of dogs naturally infected by the *Carnivore protoparvovirus* 1 (CPV). A retrospective study of 103 canine parvovirosis cases was carried out. Twenty seven percent of these (28/103) died, 96% (27/28) of which within the first four days of hospitalization. Deceased animals had significantly higher median values for heart (HR) and respiratory (f) rates, as well as significantly lower systolic blood pressure (SBP) than survivors. Severely leukopenic animals (<1,000 cells/µL), had a significantly higher mortality rate (68%, n=13) compared to that of other patients (P<0.0007). Animals with at least two of the following findings: severe hypotension (SBP< 90mmHg), tachycardia (HR > 150 bpm) and leukopenia, represented 34% (34/101) of the cases and had a survival rate of 29% (10/34), while animals with at most one of these parameters represented 66% (67/101) and had a survival rate of 94% (63/67). The presence of two or three abnormal parameters was significantly related to the higher death risk among dogs with parvovirosis (P<0.0001).

Keywords: hypotension, leukopenia, mortality, parvovirosis, tachycardia

RESUMO

A parvovirose canina é uma doença de alta mortalidade e de quadro clínico agudo. No entanto, existem poucos recursos para se estabelecer prognóstico de maneira precisa. Este estudo objetivou analisar os valores prognósticos de parâmetros físicos e hematológicos de cães naturalmente infectados pelo Carnivore protoparvovirus 1 (CPV). *Um estudo retrospectivo de 103 casos de parvovirose canina foi realizado. Desses, 27% dos animais (28/103) foram a óbito, sendo 96% (27/28) com ocorrência nos primeiros quatro dias de internamento. Os cães que foram a óbito apresentaram medianas das frequências cardíaca (FC) e respiratória (f) significativamente maiores e pressão arterial sistólica (PAS) consideravelmente menor que a dos sobreviventes. Entre os animais mais intensamente leucopênicos (<1.000 células/µL), a taxa de mortalidade (68%, n=13) foi expressivamente maior que a dos demais pacientes (P<0,0007). Os animais com hipotensão grave (PAS<90mmHg), taquicardia (FC>150bpm) e leucopenia intensa (leucometria<1.000 células/µL), ou duas dessas alterações clínicas, representaram 34% (34/101) dos casos e tiveram taxa de sobrevida de 29% (10/34), enquanto os animais com, no máximo, um desses parâmetros alterados representaram 66% (67/101) dos animais, com taxa de sobrevida de 94% (63/67). A presença de dois ou três parâmetros alterados esteve significativamente relacionada ao maior risco de óbito de cães com parvovirose (P<0,0001).*

Palavras-chave: hipotensão, leucopenia, mortalidade, parvovirose, taquicardia

INTRODUCTION

Canine parvovirosis was first reported in 1973 and still represents a disease with high mortality rate in young dogs (Goddard and Leisewitz, 2010). Clinical signs can be acute and severe, forcing intensive care professionals to take immediate decisions regarding diagnosis and implementation of supportive therapy. Canine parvovirus (CPV) is a member of the Protoparvovirus genus (family Parvoviridae, subfamily Parvovirinae) responsible for canine parvovirosis. (Cotmore *et al.*, 2019). One to three days after exposure to contaminated feces, viral replication begins in the lymphoid tissue of the oropharynx, mesenteric lymph nodes and thymus, which may result in lymphoid cell depletion.

Concurrently to this, destruction of hematopoietic cell precursors in the bone marrow and induction of a cellular immune response may occur, leading to severe hematological abnormalities, manifested mainly in neutrophil and lymphocyte blood counts (Parrish, 1995; Schoeman *et al.*, 2013). Lymphoid tissue depletion and destruction of bone marrow precursors, aggravated by increased cellular demand, can trigger leukopenia, which is correlated with a higher risk of death (Rosenfeld and Young, 1991; Goddard *et al.*, 2008; Schoeman *et al.*, 2013).

The most found risk factor in this disease is the lack of protective immunity, either by unsuccessful transferring of passive immunity or by incomplete/absent vaccination schedule. Vaccine-induced immunity failure may also happen due to interference from maternal antibodies, which have a half-life of approximately 10 days (Smith-Carr *et al.*, 1997; Truyen and Horzinek, 2007; Siedek *et al.*, 2011; Day *et al.*, 2016). With so many different tissues getting injured, by such pathogenic variety, there are still few tools to help stablish or gauge data such as patient's survival time or chance of recovery. The objective of this study was to verify the prognostic value of clinical parameters and hematologic abnormalities at admission time and throughout the hospitalization of dogs naturally infected with canine parvovirosis.

MATERIALS AND METHODS

A retrospective study of canine parvovirosis cases consulted at the Veterinary Hospital of the Federal University of Minas Gerais (UFMG), Brazil, from January 2014 to July 2017, was carried out through access to medical records database. Patients with less than 12 months old, with diagnosis of parvovirosis confirmed by means of the chromatographic immunoassay technique (BioEasy® - AlereParvovirose, Ag Bionote Inc., Korea) from a fecal swab sample, were included, totalizing 103 cases. Medical records were examined for age, number of days till death, heart rate (HR), respiratory rate (f), systolic blood pressure (SBP) and rectal temperature (Tr) at admission.

The following reference intervals/cut-offs were used for clinical parameters of puppies: HR between 70 and 150 bpm, f of up to 40 breaths per minute, Tr between 37.5°C and 39.2°C, and finally, the minimal SBP of 120mmHg and maximum of 150mmHg. Patients with SBP $\leq$ 90mmHg were classified as severe hypotension (Brown *et al.*, 2007; Acierno *et al.*, 2018). From the 103 cases analyzed, three were from the age group of zero to two months of age, 37 had two to four months of age, 29 had five to six months of age and 34 had seven to 12 months of age.

From the 103 cases analyzed, 101 (98.1%) had available complete blood count (CBC) from the day of admission to the veterinary hospital (M1). In addition, 29 cases (28.2%) had three serial CBC`s, performed at M1, between the second or third day of hospitalization (M2-3) and between the fourth or fifth day of hospitalization (M4-5). Blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) and processed within a maximum of 12 hours. Packed cell volume (PCV) was obtained by centrifugation. Erythrocyte, total leukocytes and platelet counts (PLT), along with hemoglobin concentrations were obtained using an automated hematological counter device. Erythrocytic indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH] and mean corpuscular hemoglobin concentration [MCHC]) were obtained by means of calculation. Leukocyte differential count were performed on 100 cells and the morphological evaluations done in blood smears made within a maximum of one hour after blood collection.

A completely randomized design was used. Plots were formed by two groups, defined by prognosis (survival or death) and each animal represented an

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experimental unit or repetition. The Prism 6.02 software (GraphPad, San Diego, CA, USA) was used and the differences were considered significant with P< 0.05. Frequency of deaths among the 101 cases was compared by the chi-square test. Considered criteria included time (less than or greater than four days), total leukocyte count (TLC, < 1000, 1000-1499, 1500-1999, 2000-2999, 3000-5999 and > 6000) and number of abnormal parameters (physical and hematological). Spearmann's correlation was used to verify the relation between the prognosis and the other variables studied (age, vital parameters and CBC data) among the 101 cases.

Significant correlations were considered strong when they occurred in more than 49% of the studied population (r_S> 0.7), moderate, when they occurred in 9 to 49% ($0.3 < r_S$ <0.7), and weak when they occurred in less than 9% of the population (r_S <0.3). The parametric clinical (age, vital parameters) and hematological variables were tested for normality by the Kolmogorov-Smirnov test. Comparison of means (for parametric distribution) and medians (for nonparametric distribution) in the 101 cases among surviving and deceased patients were performed by the Mann-Whitney test (HR, f, Tr, SBP, TLC and PLT) and t-student (PCV). When considering the degree of leukopenia, patients were divided into six groups (<1000, 1000-1499, 1500-1999, 2000-2999, 3000-5999 and > 6000), and the comparison was performed by the Kruskal-wallis ad-hoc Dunns (age, platelets, neutrophils and lymphocytes counts) and ANOVA ad-hoc Tukey (PCV).

Considering the three moments of hematological evaluation (M1- admission, M2- second or third day of hospitalization, M3- fourth or fifth day of hospitalization), the Kruskal-wallis ad-hoc Dunns (TLC) and ANOVA ad-hocTukey (PCV and PLT) tests were used.

RESULTS AND DISCUSSION

In the present study, a mortality rate of 27.2% (28/103) was observed, attributed to complications from canine parvovirosis. This rate is similar to that reported in previous studies (Prittie, 2004; Gombač *et al.*, 2008; Ntafis *et al.*, 2010; Pintos *et al.*, 2011; Brady *et al.*, 2012; Castro *et al.*, 2013). Deaths were mainly

concentrated in the first four days of hospitalization. Twenty five percent (7/28) on the first day; 35.7% (10/28) on the second; 28.6% (8/28) on the third and 7.1% (2/28) on the fourth day of hospitalization. The first four days represented, therefore, the hospitalization time frame for 96.4% (27/28) of deceased animals. Eighty nine percent (25/28) of deaths occurred in the first three days. Only one case occurred outside the four-day period, more precisely on the eleventh day of hospitalization. Mortality rate was therefore 24.8% (27/103) on the first four days and 1.3% (1/76) on subsequent days. This difference was highly significant (P<0.0001) by the chi-square test.

The mean age of animals diagnosed with canine parvovirosis was 5.7±0.7 months, with 2/3 of cases (66.7%) concentrating within three to six months. This result agrees with Prittie (2004), who reports greater parvovirosis morbidity in dogs up to six months of age. Oliveira *et al.* (2019) and Filipov *et al.* (2011) also reported similar ranges for affected dogs. This age group accounted for 42.8% (12/28) of deaths in this study and, according to the Spearmann correlation analysis and the Mann-Whitney test, there was no association with death occurrence.

Most animals affected by canine parvovirosis had not been vaccinated (46.6%, n=48) or had an incomplete vaccination schedule (30.0%, n=31). Among the other dogs, 4.9% (n=5) had complete vaccination and in 18.4% (n=19) there was no information about vaccination status. Among the 31 dogs with incomplete vaccination schedule, 12 dogs belonged to the age group of 2 to 4 months, ten to the age group of 5 to 6 months and nine to the age group of 7 to 12 months. These data are similar to those reported by Ling *et al.* (2012) for Australian dogs with parvovirosis. As for death occurrence, there was no correlation between vaccination status and prognosis (P=0.4) and no difference in mortality compared to vaccination status, using the chi-square test (P=0.4). The main factors that may be associated with the percentage of vaccinated dogs that became ill (4.9% of cases) include interference from maternal antibodies, variant strains and excessive viral loads (Gese *et al.*, 1991; Schunck and Truyen, 1995; Van Heerden *et al.*, 2002; Decaro *et al.*, 2005; Lamm and Rezabek, 2008; Jin *et al.*, 2012).

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Table 1. Clinical (physical parameters) and main hematological parameters obtained at the time of admission at Veterinary Teaching Hospital in survivors (n=75) and non survivors (n=28) dogs with canine parvovirus infections

	Physical parameters				Hematological		
	HR (bpm)	f (Bpm)	Tr (°C)	SBP (mmHg)	PVC (%)	TLC (cells/µL)	PTL (x10³//µL)
Survivors (n=75) Mean ± SD [Median]	148±25.5a	28±15.6 a	38.5±0.9a	96±8.5a	38.4±7.6a	4.133±5.385 [2.470 a]	286.8±164.7 [265.0 a]
Non survivors (n=28) Mean ± SD [Median]	172±15.6 b	45±5.7 b	38.8±0.1 a	85±1.4 b	38.2±9.2 a	1.934±2.136 [1.030 b]	231.6±161.4 [211.7 a]
Statistics	Mann-Whitney (P=0.005)	Mann-Whitney (P=0.0006)	Mann-Whitney (P=0.8)	Mann-Whitney (P<0.0001)	t-student (P=0.9)	Mann-Whitney (P=<0.0001)	Mann-Whitney (pP=0.1)

HR: Heart rate; f: Respiratory rate; Tr: Rectal temperature; SBP: Systolic blood pressure; bpm: Beats per minute; Bpm: Breaths per minute; PVC: packed cell volume; TLC: total leukocyte count; PTL: platelets; SD Standard deviation. Different lowercase letters refer to distinct medians by statistical test.

Deceased animals had significantly higher median values for HR and f and significantly lower median value for SBP compared to those who survived. There was no significant difference in Tr between the two groups. The Spearmann test revealed a positive correlation between death and the variables HR (weak, P=0.005, r_S = 0.277) and f (moderate, P=0.0005, r_S = 0.366), and a negative correlation between death and SBP (moderate, P<0.0001, r_S = -0.442). These associations between clinical variables and prognosis were not observed by Kalli *et al.* (2010). The authors were able to observe that animals that met the criteria of systemic inflammatory response syndrome (SIRS) had greater severity, though.

Tachycardia was observed in 85.7% (24/28) of cases of death (moderate correlation, P=0.0005) and 44.0% (33/75) of survival cases. Tachypnea, present in 53.6% (15/28) of deceased dogs and in 25.3% (19/75) of those who survived, had a weak correlation with death (P=0.03). In relation to SBP, 89.2% (25/28) of deceased dogs had values consistent with severe hypotension (moderate correlation, P<0.0001). The same condition was observed in 28.0% (21/75) of survivors. In relation to Tr, there was no correlation (P=0.09) between the parameter and survival or death outcomes. Individuals from both groups presented predominantly in normothermia.

Tachycardia and hypotension may be attributed to decreased tissue perfusion generated by dehydration, secondary to gastrointestinal loss of fluid and proteins (Prittie, 2004; Schoeman *et al.*, 2013; Rolim *et al.*, 2014). Tachypnea may be a consequence of the response to abdominal pain, frequent in dogs with parvovirosis, or a compensatory response to a possible metabolic acidosis (Prittie, 2004; Goddard and Leisewitz, 2010; Mylonakis *et al.*, 2016).

CBC results from all animals at M1 revealed mean PCV of 38.3% (RI: 37-55%), TLC of 3,523 cells/µL (RI: 6.000-17.000 cells/µL), PLT of 272,000 cells/µL (RI: 175,000-500,000 cells/µL). Although mean PCV was within RI, 48.5% of dogs in the study presented anemia at M1. Thrombocytopenia was present in 24.8% of CBC`s and leukopenia was observed in 85.1% of cases, mainly due to neutropenia and lymphopenia, which were observed in 97.5% and 88.9% of CBC's, respectively. Results of CBC`s at M1, according to life status (death or survival), are shown in Table 1.

According to Table 1, there was no statistically significant difference between PCV from survival and death groups with both means near the lower reference cutoff for the species. There was also no significant difference between groups for PLT. In relation to TLC, however, deceased dogs had significantly lower values (P<0.0001) than survivors. In this study, mean TLC (4,133 cells/µL) in survival group was lower than those observed by Castro *et al.* (2013) and Goddard *et al.*, (2008), while severe leukopenia, among deceased dogs, was a common finding in all three studies. Neutropenia is one of the most common hematologic abnormality in dogs diagnosed with parvovirosis (Macartney *et al.*, 1984).

It is attributed to the destruction of hematopoietic precursors of granulocytic lineage in the bone marrow, as well as lymphoid precursors in other lymphoproliferative organs such as thymus, lymph nodes, and spleen (Boosinger *et al.*, 1982; Meunier *et al.*, 1985; Parrish, 1995; Breuer *et al.*, 1998; Dossin *et al.*, 2011).

Table 2. Number of animals, percentage of deaths, mean values and standard deviations (SD) for PCV and median values for platelets count (PLT) and age of 101 dogs naturally infected by CPV, according to total leukocyte count (TLC) interval, performed at admission moment

TLC (cells/µL)	Animals (n)	Deaths (n)	% of deaths in the group	% of deaths in total of deaths	Age (months)	PCV (%)	PLT (x10³ cells/µL)
					Median	Mean ± SD	Median
< 1,000	19	13a	68.4	46.4	5.0a	38.6±7.5a	240.0a
1,000-1,499	17	5b	29.4	17.9	4.0a	37.8±8.4a	319.0a
1,500-1,999	16	3b	18.8	10.7	5.0a	38.6±6.7a	279.5a
2,000-2,999	16	2b	12.5	7.1	5.5a	39.3±9.4a	282.5a
3,000-5,999	18	3b	16.7	10.7	6.0a	41.3±8.2a	210.0a
≥ 6,000	15	2b	13.3	7.1	6.0a	33.8±6.2a	268.0a
Statistics	-	I	-	-	II	III	IV

I: Chi-square (P< 0.0007); II: Kruskal-Wallis ad-hoc Dunns (P=0.4); III: ANOVA ad-hoc Tukey (P=0.08); IV: Kruskal-Wallis ad-hoc Dunns (P=0.1).

The non-leukopenic group (≥ 6,000 cells/µL) represented 14.9% (15/101) of total cases with CBC (Table 2). Mortality rate in this group was 13.3% (2/15). Groups containing cases with marked leukopenia (<2,000 cells/µL) represented 51.5% (52/101) of patients and had a 40.4% mortality rate (21/52). Mortality rate was significantly higher among patients with the lowest TLC (<1,000 cells/µL), according to the chi-square test (P<0.0007).

Abnormal TLC values were not accompanied by abnormalities in erythrogram and thrombogram. These findings can be associated with differences in half-life of each cell type. In dogs, neutrophils usually circulate for a few hours, platelets for 7-10 days and erythrocytes for approximately four months (Stockham and Scott, 2008; Weiser, 2012). Thus, in a situation of decreased/ insufficient bone marrow production secondary to multiple lineage hypoplasia, a low TLC may develop more prematurely(Stockham and Scott, 2008; Weiser, 2012). Table 3 shows the results of serial CBC`s performed at M1 and at the next four days, divided into two groups according to TLC from M1.

At M1, mean PCV from both groups was close to the lower range of normality and was below the minimum normal value in the next two moments, characterizing anemia. Mean PCVs from M2-3 and M4-5 were significantly different (P<0.0001) from M1 in the group TLC < 2,000 cells/µL. Mean PCV from M4-5 group was also significantly different from M1. These differences may be attributed to decreased production or represent a consequence of hemodilution effect caused by fluid therapy during hospitalization (Bastan *et al.*, 2012; Schoeman *et al.*, 2013).

As expected, mean TLC was significantly different (P<0.0001) at M1 between groups (Table 3). However, an increasing tendency in TLC in the group with less than 2,000 leukocytes/µL was noted in the next moment (M2-3) with concurrent decreasing tendency in the same variable for the group with more than 2,000 leukocytes/µL, which resulted in no significant difference between groups. The absence of statistical difference between groups was maintained in M4-5, with both groups showing an elevation in TLC (P< 0.0001).

Table 3. Mean and standard deviation (SD) values for PCV and platelet count (PLT) and median value for total leukocyte count (TLC) in blood from dogs naturally infected with CPV obtained at admission (M1), second or third day of hospitalization (M2 -3) and fourth or fifth day of hospitalization (M4-5), according to the TLC interval from M1

Parameter	TLC on M1 (céls/μL)	Cases (n)	Moment			Statistics
			M1	M2-3	M4-5	
PCV (%)	< 2,000	15	38.9 ± 8.2Aa	27.6 ± 5.7Ab	28.1 ± 7.2Ab	ANOVA ad-hoc
	> 2,000	14	38.3 ± 9.4 Aa	32.7 ± 5.5 Aa	28.5 ± 6.1 Ab	Tukey
	All	29	38.6 ± 4.2	30.1 ± 0	28.3 ± 2.8	(P< 0.0001)
TLC (cells/μL)	< 2,000	15	1.270 Aa	3.480 Aab	5.865 Ab	Kruskal-Wallis
	> 2,000	14	3.105 Bab	2.520 Aa	9.105 Ab	ad-hoc Dunns
	All	29	1.960	2.570	8.190	(P< 0.0001)
PLT (cells x 10³ /μL)	< 2,000	15	311.1 ± 155.5 Aa	161.0 ± 126.5 Ab	252.2 ± 173.4Aab	ANOVA ad-hoc
	> 2,000	14	215.5 ± 78.3 Aa	181.3 ± 119.1 Aa	195.5 ± 139.2 Aa	Tukey
	All	29	264.9 ± 883.8	170.8 ± 155.6	223.4 ± 247.5	(P< 0.03)

Different capital letters in the same column indicates significant differences between groups; different lowercase letters in the same row indicates significant differences between the evaluation moments.

Mortality by canine parvovirosis occurred mainly in the first three days of hospitalization (89.3% of cases) and in patients with severe leukopenia (75.0% of cases). Unlike the latter group, which showed a continuous and progressive increase in TLC, CBC of patients with more than 2,000 leukocytes/μL had a reduction in TLC during the first two days of hospitalization and an increase in the following two. This finding suggests that dogs of the second group may have been referred to the veterinary hospital at an earlier stage of the disease. Bone marrow changes of these patients would still be in progress and they would have a greater chance of survival due to early institution of supportive therapy.

Microscopic morphological assessment of leukocytes was performed in all CBC`s. Reactive lymphocytes were significantly represented in 32.5% of CBC`s from M1, 25.0% of M2-3 and 30.4% of M4-5. Neutrophilic toxic change was present in 13.3%, 22.2% and 34.8% of CBC`s from M1, M2-3 and M4-5, respectively. Because the mean neutrophil count and the number of CBC`s with reported toxic change increased concurrently in each different evaluated moment, it can be inferred that the increase in number of toxic neutrophils was absolute and not just relative. According to Stockham and Scott (2008), toxic neutrophils are found in circulating blood because of defects in cell maturation when there is acceleration of neutropoiesis.

This finding is mainly associated with severe inflammatory process and infectious or necrotic processes. Reactive lymphocytes, on the other hand, are observed in a wide variety of inflammatory diseases, being more common in chronic inflammatory conditions, or those associated with a strong antigenic stimulation (Stockham and Scott, 2008). The morphological abnormalities observed in this study are, therefore, most likely a consequence of viral antigenic stimulation and secondary bacterial infection. There was no significant difference at M1 for the variable PLT between groups with more and less than 2,000 leukocytes/μL. Both groups had mean PLT within the reference range (Table 3). The significant decrease (P<0.03) in PLT for the severely leukopenic group in M2-3 can be attributed to decreased bone marrow production and/or increased consumption/ destruction (Wilson and Hermann-Dekkers, 1982).

The number of abnormal parameters had influence on the survival rate of the animals, 66.3% (67/101) of all animals exhibited either only one or none abnormal parameters and had a survival rate of 94.0%. Patients with two or three abnormal parameters (33.7% or 34/101) had a survival rate of 29.4%. The presence of two or three abnormal parameters was significantly associated with a higher death risk of dogs with CPV (P<0.0001).

CONCLUSIONS

The association of physical and hematological findings is very useful as a prognostic factor for dogs with parvovirosis. Patients with severe hypotension, tachycardia and leukopenia, or at least two of these conditions, have significantly higher risk of death.

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