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RETROSPECTIVE STUDY

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Prognostic indicators at presentation for canine parvoviral enteritis: 322 cases (2001-2018)

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Abstract

Objective: To evaluate clinicopathological prognostic indicators associated with survival based on hematology and serum biochemistry profile findings at presentation of dogs with canine parvoviral enteritis (CPE). Secondary objectives were to describe the signalment, history, physical examination findings, and progression of disease while in hospital and correlate them to survival.

Design: Retrospective study from medical records of dogs diagnosed with CPE between 2001 and 2018.

Setting: University teaching hospital.

Animals: Three hundred twenty-two dogs diagnosed with CPE that received in-hospital treatment.

Interventions: None.

Measurements and main results: Of 322 hospitalized dogs, 294 dogs (91%) survived infection with a median hospitalization time of 79 hours. Multivariable analysis showed that glucose ($P = 0.04$), total magnesium ($P = 0.011$), and the dichotomized variable of a low HCT ($P = 0.033$) on presentation were significantly associated with survival. For every 1 mmol/L (18 mg/dL) decrease in glucose concentration, cases had 1.85 lower odds of survival. For every 0.1 mmol/L (0.2 mEq/L) increase in total magnesium concentration, cases had 2.50 lower odds of survival. Cases with a low HCT had 10.69 lower odds of survival. On univariable analyses, non-survivors had a lower median body weight ($P = 0.006$) and presented more commonly for diarrhea ($P = 0.015$). At least 1 episode of diarrhea ($P = 0.003$) and hematochezia or melena ($P < 0.001$) in hospital were negatively associated with outcome, in addition to the persistence of diarrhea ($P = 0.026$) and hyporexia ($P = 0.018$) in hospital for 5 to 6 days.

Conclusions: Survival rates of 91% were achieved with in-hospital treatment in this cohort of dogs. Negative biochemical prognostic indicators affecting survival include a low HCT, decreased blood glucose concentrations, and increased total serum magnesium concentrations at presentation.

KEYWORDS
dogs, illness severity, parvovirus, survival

Abbreviations: CPE, canine parvoviral enteritis; CPV, canine parvovirus; WCVM-VMC, Western College of Veterinary Medicine Veterinary Medical Centre

1 | INTRODUCTION

Canine parvovirus (CPV) is a major cause of morbidity and mortality in dogs worldwide, particularly those between 6 weeks to 6 months of age.[1] Since the initial appearance of CPV-2 in 1978,[2] the virus has undergone various mutations, resulting in a high prevalence of CPV-2a, CPV-2b, and, more recently, CPV-2c.[3–5] Historically, survival rates for CPV infection have been reported to be as low as 9.1% without treatment and 64% with treatment.[6] More recent studies have reported improved survival rates approximating 90% with appropriate therapy.[7–9]

The identification of prognostic indicators in canine parvovirus enteritis (CPE) has improved in-hospital treatment and monitoring.[5,10,11] Multiple potential prognostic indicators have been found to be associated with decreased survival, including leukopenia,[12–14] systemic inflammatory response syndrome,[15] and hypocholesterolemia.[16] It should be noted that the significance of these findings is not always replicated in subsequent studies. Additional prognostic indicators have been studied, such as tumor necrosis factor activity,[17] serum C-reactive protein,[18] serum cortisol,[19] and thyroxine[19,20] concentrations on presentation. The majority of historical prognostic factors associated with CPE have been identified with univariable analyses. A literature review by Schoeman et al[10] highlights the paucity of studies utilizing multivariable analysis to appropriately identify and quantify specific risk factors.

The primary objective of the current study was to evaluate clinicopathological data associated with the survival of dogs with CPE in a multivariable logistic regression model. Secondary objectives were to describe the signalment, history, physical examination findings, and progression of disease while in hospital and relate them to survival.

2 | MATERIALS AND METHODS

2.1 | Case selection

Medical records of all dogs admitted to the Western College of Veterinary Medicine Veterinary Medical Centre (WCVM-VMC) were searched via the hospital records database from 2001 to 2018 with a keyword diagnosis of either parvo or parvovirus. Inclusion criteria for consisted of either a positive SNAP Canine Parvovirus Antigen Test* or CPV isolation from a fecal swab† in addition to compatible clinical signs at presentation or in hospital, owners opted to pursue medical treatment, and that the dog was subsequently hospitalized at the WCVM-VMC. Further inclusion criteria were defined for the development of the multivariable logistic regression model, which consisted of having both hematology and serum biochemistry diagnostics performed at presentation. Cases that were transferred to another veterinary clinic for continued supportive therapy following stabilization and hospitalization at the university teaching hospital and cases that required re-hospitalization or euthanasia for the unresolved parvoviral-related disease at the university teaching hospital following discharge from initial treatment were included in the study in order to increase the data available for analysis at initial presentation. Cases were not included in the study if clients opted for humane euthanasia following a positive test result for CPV, death occurred prior to commencing hospitalization, or if the medical records were unavailable.

2.2 | Procedures

Data were recorded from the medical records pertaining to signalment, history, diagnostic methods, physical examination, hematology, serum biochemistry, the progression of clinical signs throughout hospitalization, and outcome.

Vaccination history was recorded as either unknown, unvaccinated, or having received 1, 2, or 3 sets of vaccinations against CPV prior to the onset of clinical signs associated with the disease. On physical examination records, a prolonged capillary refill time was defined as greater than 2 seconds. Cases were excluded from the analysis of hospitalization time if they were transferred to another veterinary clinic for continued supportive therapy, or required re-hospitalization or euthanasia the following discharge at the WCVM-VMC due to unresolved parvoviral-related disease. Survivors were defined as all dogs that survived to discharge the following hospitalization, excluding those that returned to the hospital within 72 hours for euthanasia pertaining to parvoviral-related disease. Non-survivors were defined as dogs that were admitted and treated and then either died or were euthanized during hospitalization, in addition to those that returned to the WCVM-VMC within 72 hours following discharge for euthanasia due to unresolved parvoviral-related disease. Necropsies were performed in only a fraction of all cases following euthanasia or death and were therefore excluded from the cost of treatment in all cases. The follow-up period of the study was 72 hours following discharge and included information recorded in the medical record from both telephone calls and re-check appointments.

2.3 | Clinicopathological data

Hematology and serum biochemistry profiles obtained at presentation were recorded when available. All clinicopathological data were obtained prior to therapeutic intervention. All manual blood smear diagnostics were performed on arrival at the WCVM-VMC; all hematology and serum biochemistry profile diagnostics were performed at Prairie Diagnostic Services, Inc.† Manual blood smears were interpreted as being consistent with leukopenia if a manual WBC count was $< 4.9 \times 10^9$ /L ($\times 10^3$/μL), visual inspection revealed < 2 WBCs or neutrophils per high power field (40x objective),[21] or if the blood smear was described in the medical record as leukopenic or neutropenic. Manual blood smears were interpreted as being consistent with a normal WBC count if a manual WBC count was $\geq 4.9 \times 10^9$/L ($\times 10^3$/μL),

and ≤15.4 × 10^9/L (×10^3/μL), visual inspection revealed ≥2 and < 20 WBCs or neutrophils per high power field (40x objection),[21] or if the blood smear was described as normal. Manual blood smears were interpreted as being consistent with leukocytosis if a manual WBC count was > 15.4 × 10^9/L (×10^3/μL), visual inspection revealed ≥20 WBCs or neutrophils per high power field (40× objection),[21] or if the blood smear was described as displaying a leukocytosis or neutrophilia. For analysis, CBC results that reported a WBC count of < 1 × 10^9/L (×10^3/μL) were inputted as 0.9 × 10^9/L (×10^3/μL); serum biochemistry results that reported a creatinine concentration of < 15 μmol/L (< 0.17 mg/dL) and a total plasma protein concentration of < 2 g/L (< 0.2 g/dL) were inputted as 14 μmol/L (0.16 mg/dL) and 1.9 g/L (0.19 g/dL), respectively.

2.4 | Statistical methods

The Shapiro–Wilk test was used to assess the normality of continuous variables. Mean, minimum, and maximum were used to describe parametric data while median, minimum, and maximum were used to describe nonparametric data. The median was reported for all clinicopathological data as the majority of variables were not normally distributed. Proportions were described using the count and percentage. The Wilson estimator was used to calculate 95% CIs for percentages equal to 0% and 100%; the binomial exact method was used to calculate 95% CIs for all other proportions. Dichotomous outcome variables were compared using the chi-squared test when cell counts in the 2-x-2 contingency table were greater than 5; Fisher's exact test was used when cell counts in the 2-x-2 contingency table were less than or equal to 5. Continuous outcome variables were compared using a 2-sample independent *t*-test for parametric data and a Wilcoxon rank-sum test for nonparametric data. All statistical calculations were conducted using a commercial software package.[‡] For all comparisons, $P < 0.05$ was considered statistically significant.

Clinicopathological variables potentially significant in univariable analyses ($P < 0.2$) were considered for further investigation with a multivariable logistic regression model to look for an independent association with the final survivor outcome variable. Age was assessed for inclusion in the model to account for clinicopathological variations typical of young dogs. Variables were evaluated for multicollinearity using Spearman's rank correlation coefficient with a critical *P* value of < 0.7. The assumption of linearity in the logit form was assessed by examining the significance of the addition of second-degree polynomials for the variable of interest in the logistic regression model. Backwards stepwise logistic regression was performed with level for important confounding set at ≥20% change in any remaining covariate, and significance evaluated at the 0.05 alpha level for the null hypothesis that the effect (slope) of the covariate was 0. The covariates remaining as significant independent determinants of outcome or significant confounders resulted in the intermediate model. Covariates with *P* values > 0.2 from the univariable logistic regression were sequentially added into the intermediate model to determine significance ($P < 0.05$), resulting in the main-effects model.

Covariates in the main-effects model were sequentially reassessed for linearity and the presence of significant 2-way interactions within the model at the 5% significance level. The main-effects model was then assessed with regression diagnostics. The link test for model specification, Pearson's chi-squared, and Hosmer–Lemeshow chi-squared were used to evaluate the goodness-of-fit of the model at the 0.05 alpha level. The final model was graphically assessed with a receiver operating characteristic (ROC) curve and standard residuals.

3 | RESULTS

A computerized search yielded 598 cases, 276 of which were excluded from the study upon review; consequently, 322 dogs were included in the study. The number of survivors, non-survivors, and total dogs with data available for each variable of interest is summarized in Table 1.

3.1 | Signalment

The median age of dogs at the time of diagnosis was 17 weeks (range, 2 weekk-9 years). One hundred sixty-five dogs (51%) were intact males, 139 dogs (43%) were intact females, 12 dogs (4%) were neutered males, and 6 dogs (2%) were neutered females.

One hundred and forty-six dogs (45%) were classified as mixed breeds, and 176 dogs (55%) were classified as purebreds. Notable breeds and crosses consisted of 27 (8%) German Shepherd crosses, 25 (8%) Labrador Retriever crosses, 16 (5%) Siberian Husky crosses, 14 (4%) Rottweiler crosses, 14 (4%) Rottweilers, 11 (3%) Labrador Retrievers, 10 (3%) Border Collie crosses, 10 (3%) Chihuahuas, 10 (3%) Shih Tzu crosses, and 9 (3%) German Shepherd Dogs.

3.2 | History

The median duration of presenting complaints was 2 days (range, 0.25-10.5 days). Two hundred ninety-six dogs (93%) presented with a history of vomiting, 224 dogs (70%) presented with lethargy, 211 dogs (66%) presented with diarrhea, 196 dogs (61%) presented with inappetence, and 68 dogs (21%) presented with either hematochezia or melena.

Eight dogs (3%) did not have information pertaining to their vaccination history available within the medical record. Fifty-one dogs (16%) had an unknown vaccination history. Of those with a known vaccination history, 106 dogs (40%) were unvaccinated at presentation, and 157 dogs (60%) had received at least 1 vaccination prior to the onset of clinical signs associated with the disease. One hundred and eleven dogs (42%) had a history of having received 1 vaccination, 32 dogs (12%) had received 2 vaccinations, and 14 dogs (5%) had received 3 or more vaccinations.

TABLE 1 Number of survivors (n = 294), non-survivors (n = 28), and total dogs (n = 322) with data available for each variable of interest at presentation

Variable	No. Survivor Dogs	No. Non-Survivor Dogs	No. Total Dogs
Breed	294	28	322
Age, sex	293	28	321
Weight	293	27	320
Presenting complaints	294	25	319
Body temperature	287	26	313
Heart rate	289	27	316
Respiratory rate	245	20	265
Lung auscultation	292	27	319
Mucous membranes	286	27	313
Capillary refill time	168	23	191
% Dehydration	181	23	204
Abdominal palpation	289	25	314
Fluid therapy	291	27	318
Resolution of clinical disease in hospital	294	28	322
CBC	224	18	242
Manual blood smear	22	5	27
Serum biochemistry	136	9	145

3.3 | Diagnostic methods

Out of 322 dogs, a SNAP Canine Parvovirus Antigen Test* was performed in 320 dogs (99%). Three hundred and sixteen dogs (99%) had positive results on their first test. SNAP tests were repeated in 17 dogs (5%) and yielded positive and negative results in 12 (80%) and 3 (20%) dogs, respectively. Canine parvovirus isolation from a fecal swab[b] was performed in 3 dogs (1%) and yielded positive results.

3.4 | Physical examination findings

The median weight of dogs at presentation was 7.75 kg (range, 0.5-51.4 kg). Dogs had a median body temperature of 38.7°C (range, 33.8-41.3°C), heart rate of 140/min (range, 60–250/min), and respiratory rate of 32/min (range, 12–100/min). Pyrexia (> 39.2°C) was detected in 81 dogs (26%) at presentation. Three hundred and seven dogs (96%) had normal bronchovesicular sounds on auscultation, whereas 12 dogs (4%) had abnormal lung auscultations characterized by crackles, wheezing, increased respiratory effort, or a non-specified abnormality. Mucous membranes were described as pink in 190 dogs (61%), pale in 104 dogs (33%), tacky in 111 dogs (35%), and injected in 4 dogs (1%). One hundred and fifteen dogs (40%) had a prolonged capillary refill time. Dehydration was noted in 283 dogs (89%). Of the dehydrated dogs for which a percent dehydration score was recorded (n = 204), 59 dogs (29%) were 5 to 6% dehydrated, 84 dogs (41%) were 7 to 8% dehydrated, 53 dogs (26%) were 9 to 10% dehydrated, 6 dogs (3%) were 11 to 12% dehydrated, and 2 dogs (1%) were 13 to 14% dehydrated. On abdominal palpation, pain was elicited in 91 dogs (29%).

3.5 | Clinicopathological findings

A CBC was performed in 242 dogs (75%) at presentation (Table 2). Of 236 dogs with reports available on toxic change, 82 dogs (35%) had 0 toxic change, 48 dogs (20%) had slight toxic change, 52 dogs (22%) had 1^+ toxic change, 44 dogs (19%) had 2^+ toxic change, and 10 dogs (4%) had 3^+ toxic change associated with their WBCs at presentation. Manual blood smears were performed in 27 dogs (8%). Twelve dogs (44%) had a blood smear consistent with a normal WBC count, and 15 dogs (56%) had a blood smear consistent with leukopenia. No dogs met the criteria of leukocytosis on blood smear evaluation at presentation. Manual platelet counts were performed in 239 dogs (74%) in conjunction with a CBC. Seven dogs (3%) had an increased platelet count, 231 dogs (97%) had a normal platelet count, and 1 dog (0%) had a decreased platelet count. A serum biochemistry was performed in 145 dogs (45%) at presentation (Table 3).

3.6 | Resolution of clinical disease

The resolution of regurgitation, vomiting, diarrhea, and hyporexia throughout the duration of hospitalization is summarized in Figure 1. Most commonly, vomiting and diarrhea were present for less than 1 day in hospital; regurgitation and hyporexia persisted for 1 to 2 days

TABLE 2 CBC findings at presentation of dogs with canine parvoviral enteritis

Variable	No. Tested	Median	Range	Above RR	Normal Value	Below RR	Reference Range (RR)
WBC x 10^9/L (x 10^3/μL)	242	7.8	0.1 - 26.3	23 (10%)	157 (65%)	62 (26%)	4.9-15.4
Segs absolute 10^9/L (x 10^3/μL)	229	5.2	0 - 23.5	40 (17%)	118 (52%)	71 (31%)	3.0-10.0
Bands absolute x 10^9/L (x 10^3/μL)	229	0.3	0 - 3.3	154 (67%)	75 (33%)	NA*	0-0.1
Lymphs absolute x 10^9/L (x 10^3/μL)	229	0.9	0 - 5.1	1 (0%)	77 (34%)	151 (66%)	1.2-5.0
Eos absolute x 10^9/L (x 10^3/μL)	229	0.1	0 - 1.3	1 (0%)	228 (100%)	NA*	0-1.1
Baso absolute x 10^9/L (x 10^3/μL)	229	0	0 - 0.2	11 (5%)	218 (95%)	NA*	0-0.1
Monos absolute x 10^9/L (x 10^3/μL)	229	0.58	0.01 - 4.02	54 (24%)	162 (71%)	13 (6%)	0.08-1.0
Platelet count x 10^9/L (x 10^3/μL)	193	258	12 - 1,137	1 (1%)	141 (73%)	51 (26%)	200-900
HCT L/L (%)	238	0.42 (42%)	0.20 - 0.67 (20 - 67%)	25 (11%)	130 (55%)	83 (35%)	0.39-0.56 (39 - 56%)
MCV fL (μm^3)	237	68	46 - 76	15 (6%)	183 (77%)	39 (16%)	62-72
MCH fmol (pg)	237	1.42 (22.9)	0.96 - 1.58 (15 - 25)	8 (3%)	212 (89%)	17 (7%)	1.30 - 1.55 (21-25)
MCHC g/L (g/dL)	238	337 (34)	305 - 371 (31 - 37)	2 (1%)	184 (77%)	52 (22%)	330-360 (33 - 36)
RDW (%)	237	15	11 - 32	187 (79%)	50 (21%)	0 (0%)	11-14

MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin.
concentration; RW, red cell distribution width.
NA, not applicable.
Reference range established at Prairie Diagnostic Services, Inc.

in the majority of dogs. No dogs experienced an intestinal intussusception while in hospital.

3.7 | Outcome

Two hundred and ninety-four dogs (91%) were classified as survivors, whereas 28 dogs (9%) were classified as non-survivors. Four dogs (1%) were euthanized within 6 hours of hospitalization, and 15 dogs (5%) were euthanized past 6 hours of hospitalization. The majority of dogs were euthanized due to a combination of lack of response to treatment and clinical deterioration. Excluding dogs that either died or were humanely euthanized at presentation prior to hospitalization, no dogs died within 6 hours of hospitalization, although 7 dogs (2%) died past 6 hours of hospitalization. The median duration of hospitalization was 75 hours (range, 4-1,243 h). Survivors had a median duration of hospitalization of 79 hours (range, 15-1,232 h), whereas non-survivors had a median duration of hospitalization of 52.5 hours (range, 4–138 h). Seven survivors (2%) were transferred to another veterinary hospital for continued supportive care at the time of discharge. All dogs were stable and clinically improving at the time of transfer. Of 296 dogs that were initially discharged, 11 dogs (4%) were re-hospitalized due to the persistence of parvoviral-related disease. The median time to re-hospitalization was 40 hours (range, 5–157 h), and the median re-hospitalization time of survivors was 48 hours (range, 6–212 h). One of the 11 dogs (9%) returned to the hospital 28 hours following discharge and was euthanized 15 hours into its second hospitalization period. One additional dog returned to the hospital 30 hours following discharge and was immediately euthanized upon arrival.

Non-survivors had a significantly lower median body weight (5.43 kg; range, 0.71–32 kg) at presentation compared to survivors (8.6 kg; range, 0.5-51.4 kg) ($P = 0.006$). However, there was no significant difference between the median age of survivors (18 weeks; range, 2–432 weeks) and non-survivors (11.5 weeks; range, 7–288 weeks) ($P = 0.054$).

The presenting complaint of diarrhea was the only historical finding with a significant negative association with survival on univariable analyses ($P = 0.015$). No significant association was found between the survival outcome and the presenting complaints of vomiting ($P = 1.000$), hematochezia or melena ($P = 0.395$), hyporexia ($P = 0.150$), or lethargy ($P = 0.479$), nor was the outcome associated with the duration of complaints prior to presentation ($P = 0.906$). Dogs that were unvaccinated were not significantly associated with a negative survival outcome compared to dogs with at least 1 vaccination prior to

TABLE 3 Serum biochemistry findings at presentation of dogs with canine parvoviral enteritis

Variable	No. Tested	Median	Range	Above RR	Normal Value	Below RR	Reference Range (RR)
Sodium mmol/L (mEq/L)	145	143	129 - 159	2 (1%)	122 (84%)	21 (14%)	140 - 153
Potassium mmol/L (mEq/L)	145	4.4	2.7 - 6.1	7 (5%)	122 (84%)	16 (11%)	3.8 - 5.6
Na/K ratio	145	32	0 - 53	16 (11%)	109 (75%)	20 (14%)	28 - 38
Chloride mmol/L (mEq/L)	145	104	86 - 121	1 (1%)	67 (46%)	77 (53%)	105 - 120
Bicarbonate mmol/L (mEq/L)	144	18	11 - 28	1 (1%)	136 (94%)	7 (5%)	15 - 25
Anion gap mmol/L (mEq/L)	144	25	13 - 37	53 (37%)	91 (63%)	0 (0%)	12 - 26
Total calcium mmol/L (mg/dL)	144	2.56 (4.65)	1.75 - 3.36 (7.00 - 13.44)	2 (1%)	139 (97%)	3 (2%)	1.91 - 3.03 (7.64 - 12.12)
Phosphorus mmol/L (mg/dL)	144	2.33 (7.22)	1.16 - 4.54 (3.59 - 14.06)	64 (44%)	80 (56%)	0 (0%)	0.63 - 2.41 (1.95 - 7.46)
Total magnesium mmol/L (mEq/L)	135	0.82 (1.64)	0.54 - 1.31 (1.08 - 2.62)	3 (2%)	123 (91%)	9 (7%)	0.70 - 1.16 (1.4 - 2.32)
Urea mmol/L (mg/dL)	145	5.2 (14.6)	2.3 - 22.1 (6.4 - 61.9)	6 (4%)	123 (85%)	16 (11%)	3.5 - 11.4 (9.8 - 31.9)
Creatinine μmol/L (mg/dL)	145	37 (0.42)	5 - 361 (0.06 - 4.08)	1 (1%)	62 (43%)	82 (57%)	41 - 121 (0.46 - 1.37)
Amylase U/L (unit/L)	52	9.89 (582)	2.81 - 34.80 (165 – 2,047)	4 (8%)	39 (75%)	9 (17%)	5.83 - 23.38 (343 – 1,375)
Lipase U/L (unit/L)	52	0.88 (51.5)	0.19 - 12.53 (11 - 737)	3 (6%)	38 (73%)	11 (21%)	0.43 - 6.00 (25 - 353)
Glucose mmol/L (mg/dL)	144	6.1 (109.9)	1.1 - 10.0 (19.8 - 180.2)	59 (41%)	80 (56%)	5 (3%)	3.1 - 6.3 (55.8 - 113.5)
Cholesterol mmol/L (mg/dL)	142	6.33 (244.6)	1 - 11.44 (38.7)	86 (61%)	54 (38%)	2 (1%)	2.70 - 5.94 (104.4 - 229.7)
Total bilirubin μmol/L (mg/dL)	140	2 (0.12)	0 - 13 (0 - 0.76)	11 (8%)	101 (72%)	28 (20%)	1 - 4 (0.06 - 0.23)
Direct bilirubin μmol/L (mg/dL)	49	0.2 (0.01)	0 - 3.8 (0 - 0.22)	3 (6%)	46 (94%)	NA*	0 - 2 (0 - 0.12)
Indirect bilirubin μmol/L (mg/dL)	49	0.8 (0.05)	0 - 5.2 (0 - 0.30)	4 (8%)	45 (92%)	NA*	0-2.5 (0 - 0.15)
ALP U/L (unit/L)	144	2.49 (150)	0.75 - 40.88 (45 - 2,453)	131 (91%)	13 (9%)	0 (0%)	0.15 - 1.5 (9 - 90)
GGT U/L (unit/L)	144	0.02 (1)	0 - 6.08 (0 - 365)	7 (5%)	137 (95%)	NA*	0 - 0.13 (0 - 8)
ALT U/L (unit/L)	144	0.87 (52)	0.05 - 14.97 (3 - 898)	58 (40%)	76 (53%)	10 (7%)	0.32 - 0.98 (19 - 59)
GLDH U/L (unit/L)	136	0.47 (28)	0.07 - 4.6 (4 - 276)	127 (93%)	9 (7%)	NA*	0 - 0.12 (0 - 7)
Creatine kinase U/L (unit/L)	144	7.36 (442)	0.43 - 31.07 (26 - 1,864)	76 (53%)	66 (46%)	2 (1%)	0.85 - 6.97 (51 - 418)
Total protein g/L (g/dL)	145	53 (5.3)	22 - 81 (2.2 - 8.1)	2 (1%)	61 (42%)	82 (57%)	55 - 71 (5.5 - 7.1)
Albumin g/L (g/dL)	144	28 (2.8)	11 - 37 (1.1 - 3.7)	0 (0%)	34 (24%)	110 (76%)	32 - 42 (3.2 - 4.2)
Globulin g/L (g/dL)	138	24 (2.4)	11 - 50 (1.1 - 5.0)	7 (5%)	103 (75%)	28 (20%)	20 - 34 (2.0 - 3.4)
Albulin/globulin ratio	144	1.15	0.62 - 2.12	5 (3%)	81 (56%)	58 (40%)	1.06 - 1.82

ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; ALT, alanine aminotransferase; GLDH, glutamate. dehydrogenase;.

*NA, not applicable.

Reference range established at Prairie Diagnostic Services, Inc.

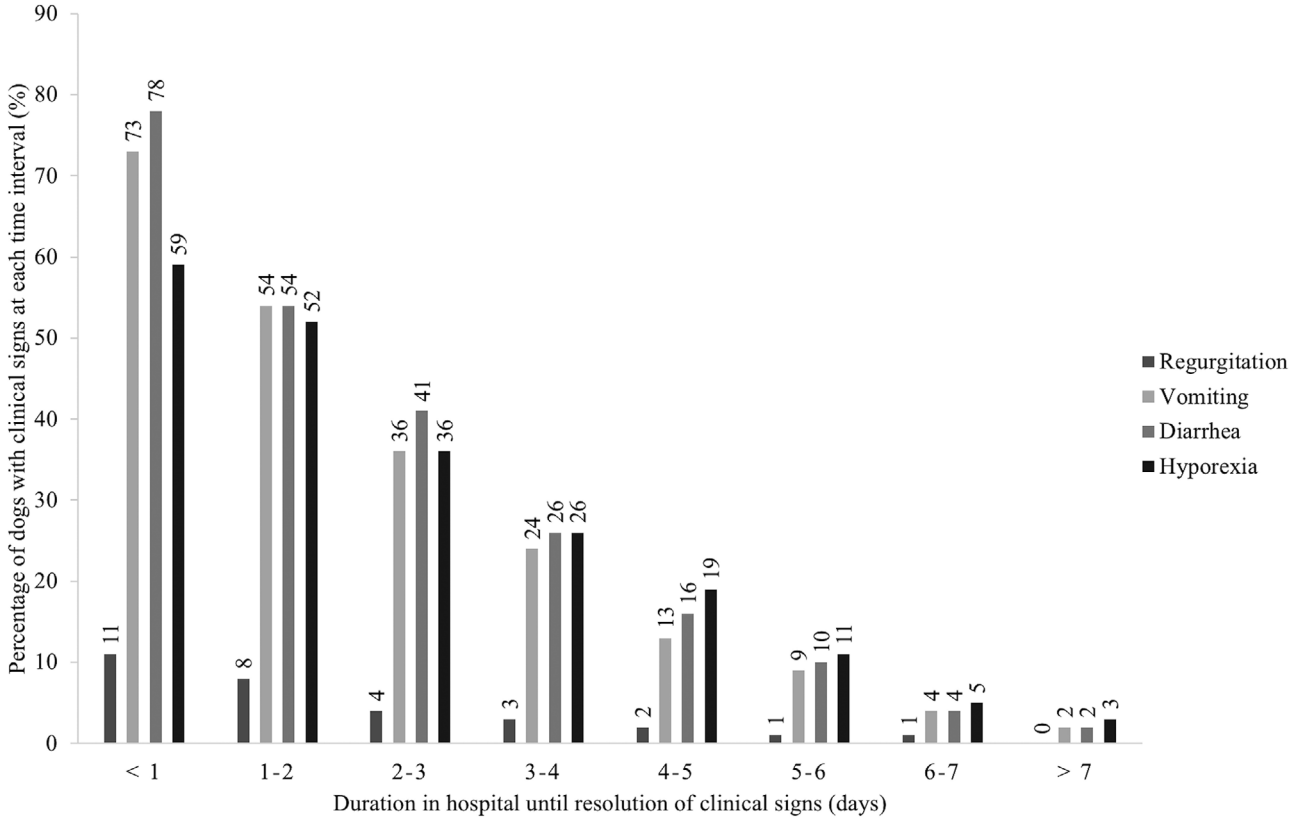

FIGURE 1 Resolution of regurgitation, vomiting, diarrhea, and hyporexia throughout the hospitalization of dogs with canine parvoviral enteritis

Time categories represent the percentage of total dogs that still displayed particular clinical signs as days progressed throughout hospitalization. Time range groups are not displayed as exclusive categories (ie, dogs that had a 2-day duration of diarrhea contribute to the percentage of dogs with diarrhea in both the < 1-day and 1- to 2-day category)

presentation in the current study ($P = 0.253$; dogs with unknown status excluded). Body temperature, heart rate, and respiratory rate in addition to the presence of dehydration were not significantly associated with the survival outcome.

A low HCT was present in 11 non-survivors (65%, 95% CI, 38–86%) and 72 survivors (33%, 95% CI, 26–39%) ($P = 0.007$). Lymphopenia was present in 6 non-survivors (50%, 95% CI. 21–79%) and 145 survivors (67%, CI 60–73%) ($P = 0.231$). Non-survivors had a significantly greater proportion of dogs presenting with an abnormal Na/K ratio ($P = 0.042$), BUN ($P = 0.03$), direct bilirubin ($P = 0.015$), and serum globulin concentration ($P = 0.001$). Azotemia was significantly more prevalent among the non-survivors (33%, 95% CI, 3–64%) compared to the survivors (2%, 95% CI, 0–5%) ($P = 0.003$). Hypermagnesemia was present in 1 non-survivor (11%, 95% CI, 0–48%) and 2 survivors (2%, 95% CI, 0–6%); hyperphosphatemia was present in 6 non-survivors (67%, 95% CI, 30–93%) and 58 survivors (43%, 95% CI, 35–52%). Hypermagnesemia ($P = 0.188$) and hyperphosphatemia ($P = 0.166$) were not significantly associated with outcome, nor were any of the leukogram or remaining serum biochemistry parameters.

Clinicopathological parameters on hematologic and serum biochemistry profiles were assessed for a univariable association with the survival outcome; this is summarized in Table 4. Variables included for assessment in the multivariable logistic regression model consisted of the WBC count, absolute monocyte count, HCT, chloride, phosphorus, total magnesium, BUN, glucose, albumin, and age. The WBC count and HCT variables were not linearly related to survival. Therefore, the WBC count and HCT variables were dichotomized into low or not low. Total magnesium concentrations were multiplied by a factor of 10 for inclusion in the model to evaluate changes of 0.1 mmol/L for clinical relevance. Following multivariable analysis, glucose ($P = 0.04$), total magnesium ($P = 0.011$), and the dichotomized variable of a low HCT ($P = 0.033$) on presentation were the only selected variables significantly associated with the survival outcome. Phosphorus was retained in the final model as a significant confounder of total magnesium relation to survival. For every 1 mmol/L (18 mg/dL) decrease in glucose concentration, cases had 1.85 lower odds of survival (95% CI, 1.03-3.33). For every 0.1 mmol/L (0.2 mEq/L) increase in total magnesium concentration, cases had 2.50 lower odds of survival (95% CI, 1.24-5.06). Cases with a low HCT had 10.69 lower odds of survival (95% CI, 1.21-94.71). Information from 133 dogs (124 survivors and 9 non-survivors) was complete for these variables and included in the final model. Model diagnostics demonstrated reasonable fit (Pearson's chi-squared, $P = 0.816$; Hosmer–Lemeshow chi-squared, $P = 0.756$; area under receiver operating characteristic curve = 0.887) with a final

TABLE 4 Clinicopathological univariable survival outcome variables on presentation of dogs with canine parvoviral enteritis

Variable	Survivor median	Survivor range	Survivor No. Tested	Non-survivor median	Non-survivor range	Non-survivor No. Tested	*P*-value
WBC* x 10^9/L (x 10^3/μL)	7.9	0.1 - 26.3	224	5.05	0.3 - 26.1	18	**0.031**
Absolute segmented neutrophils x 10^9/L (x 10^3/μL)	5.2	0 - 20.8	217	4.7	0.0 - 23.5	12	0.608
Absolute band neutrophils x 10^9/L (x 10^3/μL)	0.3	0 - 3.3	217	0.2	0 - 1.6	12	0.979
Absolute lymphocytes x 10^9/L (x 10^3/μL)	0.9	0 - 5.1	217	1.2	0.2 - 2.9	12	0.911
Absolute eosinophils x 10^9/L (x 10^3/μL)	0.1	0 - 1.3	217	0.1	0 - 0.3	12	0.585
Absolute basophils x 10^9/L (x 10^3/μL)	0	0 - 0.2	217	0	0 - 0.1	12	0.715
Absolute monocytes* x 10^9/L (x 10^3/μL)	0.6	0 - 4	217	0.3	0 - 2.3	12	0.057
Hematocrit* L/L (%)	0.43 (43%)	0.20 - 0.67 (20 - 67%)	221	0.35 (35%)	0.26 - 0.63 (26 - 63%)	17	**0.017**
Chloride* mmol/L (mEq/L)	104	86 - 121	136	100	98 - 107	9	**0.043**
Anion gap mmol/L (mEq/L)	25	13 - 37	135	26	19 - 37	9	0.139
Phosphorus* mmol/L (mg/dL)	2.32 (7.19)	1.16 - 3.89 (3.60 - 12.06)	135	2.65 (8.22)	1.87 - 4.54 (5.80 - 14.07)	9	**0.037**
Magnesium* mmol/L (mEq/L)	0.82 (1.63)	0.54 - 1.31 (1.08 - 2.62)	126	0.94 (1.88)	0.73 - 1.22 (1.46 - 2.44)	9	**0.008**
Blood urea nitrogen* mmol/L (mg/dL)	5.1 (14.3)	2.3 - 19.9 (6.4 - 55.7)	136	6.3 (17.6)	3.1 - 22.1 (8.7 - 61.9)	9	0.057
Glucose* mmol/L (mg/dL)	6.1 (109.9)	2.1 - 10 (37.8 - 180.2)	135	4.8 (86.5)	1.1 - 8 (19.8 - 144.1)	9	**0.030**
Direct bilirubin μmol/L (mg/dL)	0.2 (11.7)	0 - 3.8 (0 - 222.2)	45	1.4 (81.9)	0 - 2.4 (0 - 140.3)	4	0.142
ALP U/L (unit/L)	2.48 (149)	0.75 - 40.88 (45 - 2,453)	135	2.9 (174)	1.45 - 5.63 (87 - 338)	9	0.566
GGT U/L (unit/L)	0.02 (1)	0 - 6.08 (0 - 365)	135	2.9 (174)	1.45 - 5.63 (87 - 338)	9	0.053
ALT U/L (unit/L)	0.87 (52)	0.05 - 14.97 (3 - 898)	135	0.97 (58)	0.3 - 1.3 (18 - 78)	9	0.626
GLDH U/L (unit/L)	0.47 (28)	0.07 - 4.6 (4 - 276)	127	0.55 (33)	0.3 - 2.8 (18 - 169)	9	0.428
Creatine kinase U/L (unit/L)	7.3 (438)	0.43 - 30.87 (26 - 1,852)	135	10.35 (621)	6.03 - 31.07 (362 – 1,864)	9	**0.026**
Total protein g/L (g/dL)	53 (5.3)	22 - 81 (2.2 - 8.1)	136	44 (4.4)	27 - 70 (2.7 - 7.0)	9	0.159
Albumin* g/L (g/dL)	28 (2.8)	11 - 37 (1.1 - 3.7)	135	25 (2.5)	12 - 33 (1.2 - 3.3)	9	0.053

*Variables were further investigated with a multiple logistic regression model.
Boldface indicates significance.

model pseudo-R^2 value of 0.388. It was not possible to include dehydration directly in the logistic regression model as all non-survivors were dehydrated. However, a subset analysis of only cases that were dehydrated ($n = 113$), did not change variables included in the model or their interpretation (data not shown).

In-hospital observations were assessed with univariable analyses following presentation. A significantly greater proportion of non-survivors had at least 1 episode of diarrhea ($P = 0.003$) and hematochezia or melena ($P < 0.001$) in hospital. Dogs that had both diarrhea ($P = 0.026$) and hyporexia ($P = 0.018$) persisting for 5 to 6 days

in hospital were negatively associated with the survival outcome. All dogs either died or were euthanized within 5 to 6 days in hospital; consequently, non-survivors had a significantly shorter median duration of hospitalization (52.5 h; range, 4–138 h) compared to survivors (79 h; range, 15-1,232 h) ($P = 0.004$).

4 | DISCUSSION

The aim of this retrospective study was to evaluate clinicopathological data associated with survival of dogs with CPE in a multivariable logistic regression model. Secondary objectives were to describe the signalment, history, physical examination findings, and progression of disease while in hospital and investigate their univariable associations with survival.

Anemia has been reported as a less frequent finding associated with CPE,[15,22] although as the disease progresses it is not uncommon.[11] Although another study failed to demonstrate a relationship between the HCT on presentation and the survival outcome,[12] multivariable analysis in the current study found that a low HCT on presentation was associated with 10.69 lower odds of survival. Of further interest, age was not found to be a significant confounder of a low HCT, or other clinicopathological indicators. Although a low HCT at presentation has been attributed to the suppression of erythropoiesis secondary to viral infection of the bone marrow,[23,24] it has also been argued that this is unlikely the cause of the anemia in CPV infection due to the long half-life of circulating red blood cells relative to the period of viral infection of the bone marrow.[11,25] Hemorrhage through the gastrointestinal tract,[11,26,27] rehydration fluid therapy,[11,26,27] and anemia of inflammatory disease[28] likely play a significant role in the development of this clinicopathological abnormality.

Hypoglycemia is a severe complication of CPE,[5,15] and correction of the abnormality is an important aspect of disease management.[11] In the current study, only 3% of all dogs presented with hypoglycemia; however, blood glucose concentration on admission was associated with the survival outcome on both univariable and multivariable analyses. Cases had 1.85 lower odds of survival for every 1 mmol/L (18 mg/dL) decrease in glucose concentration. The predisposition for pediatric patients to develop hypoglycemia further emphasizes the importance of blood glucose concentrations in CPE.[29,30] Juvenile patients will have limited glycogen stores and hepatic gluconeogenic activity requiring oral intake to maintain blood glucose concentrations, which is compromised by malnutrition due to the presence of vomiting, diarrhea, and anorexia. Additional causes of hypoglycemia include hypermetabolism, sepsis, and liver dysfunction.[1,11] Malnutrition throughout hospitalization may also significantly contribute.[1]

Although hypomagnesemia of critical illness has been the primary focus of clinical research related to magnesium concentration,[31,32] hypermagnesemia has also been reported to be associated with a negative survival outcome.[33,34] In the current study, total magnesium was significantly associated with the survival outcome at both the univariable and multivariable level. Cases had 2.50 lower odds of survival for every 0.1 mmol/L (0.2 mEq/L) increase in total magnesium concentration on serum biochemistry at presentation. In human pediatrics, critically ill patients with hypermagnesemia have been reported to have a longer duration of hospitalization and a 6-fold increase in the chance of death.[33] Another study found that although only 13% of critically ill dogs were hypermagnesemic on presentation, patients with this abnormality on serum biochemistry were 2.6 times more likely to succumb to their illness compared to dogs with a normal magnesium concentration.[34] Although a previous study failed to find an association between total and ionized magnesium concentrations and outcome in CPE, it was found that total and ionized hypermagnesemia were more prevalent than hypomagnesemia among the dogs with magnesium abnormalities.[35] A lack of power was proposed as a limitation in the evaluation of the prognostic value of magnesium.[35]

The underlying mechanism of increases in magnesium concentration in critically ill patients has been reported to be associated with both acute kidney injury[36] and circulating endotoxins.[37] In the current study, azotemia was present in a significantly greater proportion of non-survivors than survivors on univariable analysis, although it was not independently associated with survival following the multivariable model development. With regards to circulating endotoxins, total and ionized magnesium concentrations have been shown to significantly increase in response to the administration of *Escherichia coli* lipopolysaccharide as a model of experimental sepsis in rats.[37] As a large proportion of total body magnesium is complexed to ATP, intracellular magnesium ions are released in response to sepsis-induced ATP hydrolysis and a rise in extracellular magnesium subsequently follows.[31,37–39] Dehydration and volume depletion resulting in decreased glomerular filtration rate may also be contributing to the increase of total magnesium in non-survivors. However, because magnesium had similar effects on survival even when only dehydrated cases were considered, it is likely an important independent predictor. Although serum magnesium concentration are not representative of total body magnesium,[31,32] the authors speculate that trends in total magnesium may reflect the renal function of patients with CPE and provide insight into the recognition of sepsis. Further research is needed to elucidate the role of magnesium in CPE.

Dogs with acute enteritis or gastroenteritis, particularly those with CPE, have been reported to have a predisposition for the development of an intestinal intussusception.[40] In a previous study of 220 dogs with acute gastroenteritis in which 85 cases (38.6%) were positive for CPV-2 antigen detection, intestinal intussusception was reported in 29 total dogs (13%); however, only 10 of these dogs (34.5%) were positive for CPV-2 antigen.[40] As multiple causes of enteritis were included in the previous study, conclusions cannot be drawn regarding rates of intussusception in CPE. None of the 322 dogs in the current study developed an intestinal intussusception.

Diarrhea as a presenting complaint as well as in-hospital diarrhea were associated with a negative outcome in the univariable analysis. In previous studies, 100% of dogs with CPE had diarrhea, precluding the analysis of this clinical sign as a prognostic factor. [12,16,19,20,22,41]

Leukopenia has been reported as a common finding on presentation in CPE,[5,11] particularly in dogs severely affected by the disease.[2] Furthermore, this finding has previously been associated with a poor

prognosis.[12,14,25,42,43] The positive predictive value for survival associated with a lack of leukopenia 24 hours into hospitalization has also been reported to be 100%.[43] Leukopenia was not significantly associated with the survival outcome at the multivariable level in the current study, similar to the lack of significance found in another report.[44]

The significance of leukogram abnormalities on admission varies among studies. Lymphopenia has commonly been reported to be the most consistent hematological finding in cases of CPE.[1,2,11] This trend is consistent with the findings of the current study as 66% of dogs presented with this abnormality. No statistically significant difference was found at the univariable level between the proportion of survivors and non-survivors with lymphopenia on presentation. However, 1 study found an increase in lymphocytes over time to be the most accurate predictor of survival in comparison to changes in other leukogram parameters.[43] The same study also found that segmented neutrophil counts on admission and their change over time did not differ between survivors and non-survivors,[43] despite a report from 1980 that neutrophils are the most important WBC to monitor throughout hospitalization.[42] No significant difference was found between survivors and non-survivors for segmented and band neutrophil counts on presentation in the current study. The lack of an association between neutrophil counts and survival suggests that its historical importance as a prognostic indicator in CPE may lack adequate scientific justification.

A medical history indicating that a dog was unvaccinated was not associated with a negative survival outcome in the current study. Although some studies have failed to demonstrate vaccination status as a significant risk factor for death,[30,45] other work suggests that a lack of protective immunity is the most reported risk factor for infection,[46] and having received at least 1 vaccination prior to presentation has been shown to decrease the odds of parvoviral-related disease.[15] Additional causes for the lack of an association between vaccine status and the outcome may include vaccine failure, interference from maternal antibody in puppies < 12 weeks of age,[47] inadequate history taking and medical record reporting, and client error in reporting a history of vaccination. The high proportion of dogs in the current study with a history of having received at least 1 vaccination supports the concept that regardless of reported vaccine status, CPE should remain a differential for a presentation otherwise consistent with the disease.[45] The high proportion of vaccinated dogs may have also limited our ability to assess the effect of non-vaccination. Despite the lack of an association with survival in this study, vaccination remains an important preventative in CPE, and the promotion of herd immunity within the canine population is essential to increased protection.[1,5,47]

Although the current study has contributed to the knowledge of prognostic indicators associated with CPE, it does have its limitations. For completeness, weight and diarrhea could have been included in the multivariable analysis to evaluate their potential significance both as independently associated variables and as confounders in the model; however, the primary objective of the current study was to identify clinicopathological values that correlated with survival status. The true significance of low body weight on survival in the current study is limited by numerous potential confounders such as age, breed, body condition score, and hydration status at presentation. Unfortunately, as 100% of non-survivors were classified as dehydrated on presentation, the potential role of hydration status as both an independent determinant and as a confounder in the logistic regression model was unable to be assessed due to its perfect association with non-survival. As a result, conclusions pertaining to hydration status were limited to its lack of association with survival at the univariable level.

Additionally, data and tests performed lacked standardization due to the retrospective nature of the study. As data were obtained in a non-standardized fashion, a misclassification bias may have been introduced. Furthermore, as not all animals diagnosed with CPE are hospitalized, nor do they always have similar diagnostic tests performed due to finances and or potential outcome, a selection bias may have been introduced. The lack of hematology and serum biochemistry data available from dogs in which owners opted against treatment and from dogs that were euthanized on presentation resulted in the exclusion of these cases from the current study. As these cases may have represented sicker dogs with risk factors for a poor outcome, the current study is limited by their exclusion. Data pertaining to clinical signs throughout hospitalization were also likely subject to an observer bias. As a relatively low proportion of cases had both hematology and serum biochemistry data available on presentation, the current study was also limited by decreased power. In order to increase the number of non-survivors, dogs that died naturally and those that were euthanized were compiled into a single group. The negative survival outcome was consequently confounded by owners' financial and personal decisions. Furthermore, the current study included 7 cases that were transferred to another veterinary hospital for continued supportive therapy following stabilization and hospitalization at the university teaching hospital. Despite being stable and clinically improving at the time of transfer, it is possible that these dogs were misclassified as survivors as the study lacked follow-up confirmation after the transfer; however, these cases only contributed 2% (7 of 294 dogs) to the overall survivor population.

Further limitations of the current study include the use of multiple analytical machines due to the timeframe of the study, thus creating increased variability associated with the clinicopathological results. Additionally, all cases with a positive SNAP Canine Parvovirus Antigen Test[a] were included in the current study, regardless of recent vaccination. It has been reported that recent vaccination with a modified-live CPV vaccine within 3 to 10 days can result in a false-positive ELISA test;[1,2] however, a recent study[48] found that there was no diagnostic interference with in-clinic (ELISA-based) tests for any CPV vaccine, even when discrete titers for the virus reached levels that should be detected. Furthermore, all dogs included in our study showed clinical signs consistent with active parvoviral infection such as vomiting, diarrhea, hyporexia, or lethargy either on the presentation or throughout hospitalization. In combination, it has been reported that a positive ELISA test and clinical illness should be interpreted as sufficient evidence for natural infection.[5]

As many owners may opt for outpatient care due to financial limitations, the selection of cases was likely also socioeconomically biased.

However, the assessment of clinical pathological measures included only those cases that paid for initial testing, so while it may affect generalizability, both survivors and non-survivors had similar chances of being included.

In conclusion, CPE remains an ongoing treatment concern for clinicians across the globe. Although specific treatment advances have been made over the years, supportive therapy remains the pillar of CPE management. The identification of scientifically based prognostic indicators is crucial to the justification of clinicians' management decisions and to the education provided to owners when making decisions regarding hospitalization approaches. This retrospective study of 322 dogs positive for CPV antigen detection has identified the prognostic usefulness of blood glucose and total magnesium concentrations at presentation, in addition to the presence of a low HCT. Lower blood glucose concentrations and higher total magnesium concentrations at presentation were associated with decreased survival. Dogs with a low HCT on presentation had decreased survival. Additional prospective and large-scale retrospective studies on CPE are required to further evaluate potential confounders to the prognostication of CPE

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Notes

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‡ StataCorp, 2017, Stata Statistical Software: Release 15, StataCorp LLC, College Station, TX.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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