Research Article

Prognostic Value of Serum C-Reactive Protein (CRP), Procalcitonin, Fibrinogen, and D-Dimer Levels in Dogs with Parvoviral Gastroenteritis

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Abstract

This study investigated the prognostic value of various biomarkers in 20 puppies with parvoviral gastroenteritis. After treatment, 13 dogs recovered, and 7 died during the treatment process.

Clinically, general condition disorders such as loss of consciousness and fainting have been associated with increased mortality. Hematologically, marked leukopenia and lymphopenia were observed in deceased dogs, indicating the suppressive effect of parvovirus on the immune system.

Among the biomarkers examined, fibrinogen and D-dimer levels were the most reliable indicators with high accuracy (AUC = 1.00) in mortality prediction. CRP and procalcitonin levels did not differ significantly between the surviving and deceased groups.

A significant decrease in treated and recovered dogs, especially in D-dimer and aPTT levels, was detected, indicating an improvement in the coagulation system.

Fibrinogen and D-dimer are reliable biomarkers to predict disease severity and mortality risk in dogs with parvoviral enteritis. In contrast, CRP and procalcitonin are not suitable for this purpose. Early monitoring of coagulation parameters can improve clinical management.

Key words: Canine Parvovirus (CPV), Prognostic Biomarkers, D-dimer Leukopenia, Hemorrhagic Gastroenteritis

Introduction

Parvoviral enteritis in dogs continues to be a major disease worldwide, with a morbidity rate of up to 100% and a mortality rate of 10% (Goddard and Leisewitz, 2010; Brady et al., 2012). It is a life-threatening disease that usually occurs in young dogs between 6 and 20 weeks of age and rarely affects adults. It generally presents as acute, fibrinous, necrotic, and hemorrhagic enteritis, and sometimes with myocarditis (Goddard and Leisewitz, 2010; Baştan, 2012).

Rottweiler, Doberman pinscher, Berger Allemand, American pit bull, Staffordshire terrier, Labrador retriever, Springer spaniel, Dachshund, and Yorkshire terrier breeds are more susceptible to parvovirus enteritis (Glickman et al., 1985). Although the causes of racial sensitivity are not fully known, genetic characteristics are thought to play a role (Aktaş et al., 2011; Baştan, 2012). Parvoviral enteritis is twice as common in male dogs over six months of age as in females. The disease is more common in the summer than in the winter months (Houston et al., 1996). In addition to dogs, wolves, hyenas, and foxes from the canid family can also get the disease (Öcal and Ünsüren, 2009).

Deaths from parvoviral enteritis are due to bacteremia and endotoxemia.

Otto et al. in 2000 reported that 82% of dogs with CPV enteritis had a measurable endotoxin in the

circulation. Endotoxin initiates a procoagulant response on endothelial cells through cytokines (e.g., tumor necrosis factor). The first response to endotoxin is the activation of coagulation. But tests that measure clotting time in vitro depend mainly on clotting factor deficiency or factor inhibition, so this response cannot be well characterized. Systemic hypercoagulability may evolve to hypocoagulability as the inflammatory response progresses, and disseminated intravascular coagulation (DIC), known as DIC, may produce signs of fulminant bleeding (Otto et al., 2000). Within a few hours following infection, concentrations of acute-phase proteins (APP) such as haptoglobulin, serum amyloid A (SAA), and C-reactive protein (CRP) increase.

Prothrombin time, activated partial thromboplastin time, D-dimer, fibrinogen levels, anti-thrombin III activity, and platelet count are all factors to be considered for DIC evaluation. It is noted that bone marrow depression and gastrointestinal hemorrhage may occur in CPV infections. However, it is thought that the cause of hemorrhagic enteritis in CPV may be due to endotoxemia of coliform bacteria and an increase in cytokine levels (Er & Ok, 2015).

The D-dimer, which can be measured in whole blood and plasma, is a biomarker for fibrin production and breakdown. D-dimer levels are very low in healthy animals, but can rise rapidly in the case of thrombosis. Currently, the estimation of D-dimer levels is mainly used for the diagnosis of venous thromboembolism (VTE). In addition, they are frequently used to determine the ideal duration of anticoagulation and to monitor disseminated intravascular coagulation (DIC) in patients undergoing venous thrombosis (VTE) (Başer et al., 2022).CRP and Procalcitonin are biomarkers used in infectious and non-infectious inflammatory diseases. High levels of CRP in dogs with CPV infection have been associated with mortality.

This study aimed to investigate the prognostic value of Serum C-Reactive Protein (CRP), procalcitonin, antithrombin, fibrinogen, and D-dimer levels in dogs with Parvoviral Gastroenteritis, to determine the value of these markers in the prognosis of the disease and to guide the treatment.

Materials and Methods

This study was approved by Kırıkkale University Animal Experiments Local Ethics Committee (Approval No:39, date: 15.11.2023).

The animal material of the study consisted of 20 and 10 healthy puppies of different breeds and genders, ranging in age from 4 to 12 weeks, who were brought in with complaints of weakness, loss of appetite, vomiting, and diarrhea. A group of 20 dogs diagnosed with CPV infection using rectal swab samples and the Canivet® CPV Ag Test (Vet Diagnostik) commercial rapid test kit and a control group of 10 puppies aged 4-12 weeks who had no disease complaints, had a negative Parvo rapid test kit and were found to be healthy at examination. CPV-infected dogs are divided into two groups: dogs that recover and those that die based on their response to treatment. Physical and clinical examinations of all dogs were performed and recorded.

To determine the hematological and biochemical parameters, 4 ml blood samples were taken from the vena cephalica of puppies to EDTA tubes for hematological analysis, 4 ml to citrate tubes for aPTT, PT, D-dimer, and fibrinogen measurements, and 4 ml to non-anticoagulant tubes for serum. Hematologic analyses were performed using the Hasvet Mindray BC-5000 Vet device, aPTT, PT, D-dimer, and fibrinogen measurements were measured using the BCS XP Siemens device, Procalcitonin ELISA method (BIO-TEK EL X 800 and BIO-TEK EL X 50 devices), and CRP immunoturbidimetric method using the MINDRAY-BS400 device.

All puppies diagnosed with CPV infection were treated according to a standard treatment protocol. Cefazolin sodium, Metronidazole, Vitamins K and B, Metochlopromide, pantoprazole, isotonic sodium chloride, dextrose, and Ringer's lactate were used to maintain fluid and electrolyte balance.

For statistical analysis, the subjects were categorized into three groups: control (healthy), recovered patients, and deceased patients. Gender, race, general condition, rapid test result, and treatment outcome values in patients admitted to the clinic are given in the form of a frequency table. The normality of the data obtained in the study was evaluated by examining the Shapiro-Wilk and Kruskal-Wallis tests and the Skewness and Kurtosis coefficients, and the control of the homogeneity of the data was provided by the Levene test. The effect of general condition on response to treatment at the time of admission to the clinic was tested by Fisher's precision analysis. The Welch ANOVA test was used to examine the blood parameters examined during admission to the

clinic (Fox and Weisberg, 2023). Games-Howell multiple comparison test was applied to determine the difference between the groups. In recovered patients, pre-treatment and intra-treatment blood parameters were examined with a matched t-test. To examine the effect levels of biomarkers, the Receiver Operating Characteristic (ROC) curve analysis was performed. In this analysis, the "Deceased" group was defined as a positive class, and the area under the curve (AUC) was calculated for each biomarker. ROC analysis was used to evaluate the power of each parameter to distinguish cases resulting in death at the level of sensitivity and specificity. All analyses were completed using Jamovi and R programs, and the margin of error was evaluated as α=0.05 (Jamovi, 2024; R Core Team, 2024).

Results

Considering the gender distribution of the patients, there are 9 female and 11 male patients. 3 (33%) of females and 4 (36%) males died. No significant difference in survival by gender was observed (p = 1.00), indicating that gender was not a determining factor in survival. In terms of breed, 6 different breeds were identified, and the largest group was crossbred dogs (35%). Although the patients who died were mostly Cane Corso and crossbreeds, there was no significant difference between the breeds included in the study in terms of mortality-recovery rates (p = 0.403).

In terms of the general clinical situation, most of the patients (75%) presented with depression. The survival rate is higher in this group (10/15). On the other hand, all of the patients presenting with coma died (2/2). This difference was found to be very close to the limit of significance (p = 0.069), and this suggests that the general situation at the time of clinical admission may affect survival. It is observed that the prognosis of patients presenting with the depressive picture is better. Finally, according to the rapid test results, 13 of the 18 patients who were positive recovered, while two of the 2 patients who were negative died. Although a positive test result showed a higher rate of survival, this difference was not statistically significant (p = 0.111). However, this result is of limited significance as there were only two cases in the negative test group. The distribution of demographic and clinical variables according to the survival status of the individuals who make up the groups evaluated in the study is given in Table 1.

Table 1. Distribution of demographic and clinical variables by survival status

Variable	**Result**		**Total**
Gender	**Died**	**Healed**	
Female	3	6	9
Male	4	7	11
P			**1.00**
Breed			
Cane Corso	2	0	2
Cross-bred	3	4	7
Kangal Shepherd Dog	1	4	5
Belgian Shepherd Dog	1	2	3
Standard Schnauzer	0	2	2
Doberman	0	1	1
P			**0.403**
Situation			
Coma	2	0	2
Faint	0	3	3
Depression	5	10	15
P			**0.069**
Rapid Test			
Negative	2	0	2
Positive	5	13	18
P			**0.111**

According to the results of the analysis, a significant difference was observed between the groups in terms of leukocyte (WBC), neutrophil (NEU), and lymphocyte (LYM) values. In particular, WBC levels were significantly lower in the deceased group (3.16 ± 1.07 $\times 10^9$/L), while it was highest in the control group (12.62 ± 0.59 $\times 10^9$/L) (P <0.001). Similarly, the NEU level was significantly lower in the deceased group (P <0.001). In terms of LYM level, there was a significant difference between the dying group (0.33 ± 0.01 $\times 10^9$/L) and the recovered group (0.98 ± 0.24 $\times 10^9$/L) (P = 0.013). Hemoglobin (HGB) and hematocrit (HCT) values were significantly higher in the deceased and recovered groups than in the control group (P = 0.003 and P = 0.007, respectively).

MCHC values also differed significantly between the groups, and significantly higher values were found in the recovered group (35.94 ± 0.37 g/dL) (P = 0.01). On the other hand, erythrocyte (RBC), mean erythrocyte volume (MCV), mean hemoglobin content (MCH), and platelet (PLT) levels did not show a statistically significant difference between the groups (P> 0.05). The values in terms of the blood parameters examined when they were brought to the clinic of the study evaluated groups are given in Table 2.

Table 2. Blood parameters of patients admitted to the clinic

Parameters	**Control**	**Deceased**	**Recovered**	**P**
WBC (10^9/L)	12.622±0.5925c	3.156±1.0676a	8.192±1.347b	**<0.001**
NEU (10^9/L)	8.694±0.5453b	2.509±1.0653a	6.392±1.2225a,b	**<0.001**
LYM (10^9/L)	5.012±2.0489a,b	0.33±0.0138a	0.978±0.2365b	**0.013**
RBC (10^9/L)	5.245±0.5238	6.139±0.1522	5.935±0.1631	**0.26**
HGB(g/dL)	10.19±0.5593 a	12.914±0.6874 b	13.069±0.3898 b	**0.003**
HCT(%)	29.08±1.6803a	36.543±1.6456b	36.423±1.1274b	**0.007**
MCV (fL)	61.26±0.6784	59.5±2.0012	61.446±1.2728	**0.703**
MCH (pg)	20.39±0.4466	21±0.7877	22.062±0.4399	**0.061**
MCHC (g/dL)	33.58±0.5312 a	35.3±0.5429 a,b	35.938±0.3732 b	**0.01**
PLT (10^9/L)	315±42.4992	365.714±109.993	365.538±39.9483	**0.692**

There is a statistical difference between groups bearing different labels in the same line (P<0.05)

According to the results of the analysis, a significant increase in lymphocyte (LYM) levels was observed during the treatment process (baseline: 0.978 ± 0.237; end: 2.342 ± 0.325; P <0.001). However, a statistically significant decrease was found in erythrocyte series parameters such as erythrocyte count (RBC) and hemoglobin level (HGB) (P= 0.038 and P = 0.038, respectively). Platelet count (PLT) tended to increase close to the limit of significance after treatment (baseline: 365.5 ± 39.9; end: 469.5 ± 55.8; P = 0.053). Other hematologic parameters, WBC, NEU, HCT, MCV, MCH, and MCHC values did not show a statistically significant difference between pre- and post-treatment (P> 0.05). The blood parameter values of the recovered patients, who were brought to the clinic and evaluated during the treatment, are given in Table 3.

PT sec. showed significant differences between the groups (P = 0.033). While the duration of PT was higher in the control group (9.35 ± 0.67 sec), it was shorter in the dying and recovered groups. A statistically significant difference was observed between the groups in terms of aPTT (P = 0.003). The duration of aPTT was significantly shorter (13.79 ± 0.41 sec) in the deceased group, while the recovered group remained intermediate in this respect. Fibrinogen levels differed significantly (P <0.001) and were significantly higher in the dying (4.81 ± 0.28 g/L) and recovered (4.41 ± 0.32 g/L) groups than in the control group (2.41 ± 0.17 g/L). D-dimer levels also differed significantly between the groups (P = 0.002). The highest value was found in the deceased group (5167.38 ± 1751.42 ng/mL) and the lowest value was found in the control group (439.15 ± 38.57 ng/mL). On the other hand,

C-reactive protein (CRP) and procalcitonin levels did not show a statistically significant difference between the groups (P> 0.05). In addition to the changes in the treatment process, the biomarker levels observed in different groups (control, recovered, and death) in terms of clinical outcome were also analyzed comparatively and summarized in Table 4. Fibrinogen (AUC = 1,000) and D-dimer (AUC = 1,000) showed excellent discriminating performance, providing complete differentiation between both groups. The threshold values of these markers were determined as 3.744 g/L and 1595.62 ng/mL, respectively, and both showed 100% sensitivity and 100% specificity. CRP (AUC = 0.529) has low classification power, with only 57% sensitivity and 70% specificity. This suggests that CRP plays a limited role in predicting mortality in this patient group. PT (AUC = 0.193) and aPTT.

When biomarker levels were examined before and after treatment in recovered patients, PT. There was a difference between the two measurements in terms of INRTS, aPTT AFS (sec), and D-dimèr (ng/mL) levels. (P<0.001 and P=0.038, respectively). Other markers did not show a statistically significant variability during the treatment process (P>0.05). Biomarker levels of patients who recovered during treatment were analyzed comparatively during and after admission to the clinic and summarized in Table 5.

Table 3. Examination of blood parameter values of recovered patients (±SX̄E)

Parameters	**Initial Measurement**	**Final Measurement**	**P**
WBC (10^9/L)	8.192±1.347	10.97±1.437	**0.22**
NEU (10^9/L)	6.392±1.222	7.134±1.22	**0.719**
LYM (10^9/L)	0.978±0.237	2.342±0.325	**<0.001**
RBC (10^9/L)	5.935±0.163	5.543±0.199	**0.038**
HGB(g/dL)	13.069±0.39	12.169±0.426	**0.038**
HCT(%)	36.423±1.127	34.431±1.1	**0.102**
MCV (fL)	61.446±1.273	62.177±1.003	**0.335**
MCH (pg)	22.062±0.44	21.962±0.354	**0.737**
MCHC (g/dL)	35.938±0.373	35.346±0.271	**0.146**
PLT (10^9/L)	365.538±39.948	469.462±55.823	**0.053**

Table 4. Biomarker values according to clinical outcome values (±SX̄E)

Biomarkers	**Control**	**Deceased**	**Recovered**	**P**
PT sec. TS(sec)	9.35±0.670b	7.9±0.476a,b	7.323±0.044a	**0.033**
PT. INRTS	0.62±0.01	0.643±0.042	0.6±0	-
aPTT AFS (sec)	20.3±1.56b	13.786±0.413a	17.885±2.373a,b	**0.003**
Fibrinogen (g/L)	2.411±0.165a	4.808±0.277b	4.407±0.324b	**<0.001**
D-dimer (ng/mL)	439.148±38.569a	5167.381±1751.421a,b	1549.261±266.295b	**0.002**
C-Reactive Protein (mg/L)	0.806±0.064	0.792±0.131	0.638±0.075	**0.269**
Procalcitonin(ng/mL)	815.317±87.675	988.149±103.842	891.55±67.788	**0.479**

Table 5. Biomarker values in the convalescent group (±SX̄E)

Biomarkers	**Initial Measurement**	**Final Measurement**	**P**
PT sec. TS(sec)	7.323±0.04408	7.515±0.05975	**0.760**
PT. INRTS	0.6±0	0.608±0.00769	**<0.001**
aPTT AFS (sec)	17.885±2.37306	14.2±0.5051	**<0.001**
Fibrinogen (g/L)	4.407±0.32439	1.946±0.17358	**1.000**
D-dimèr (ng/mL)	1549.261±266.29551	1363.903±271.36166	**0.038**
C-Reactive Protein(m-g/L)	0.638±0.0756	0.633±0.07959	**0.582**
Procalcitonin(ng/mL)	891.55±67.7883	844.752±40.53414	**0.771**

(AUC = 0.129) did not exhibit significant predictive power with very low AUC values. While the highest specificity was achieved for these markers, the sensitivity was 0%; In other words, the correct classification of death at these threshold values has failed. The predictive power of the biomarkers evaluated in the study was analyzed with ROC curves and AUC (Area Under the Curve); optimal cut-off, sensitivity, and specificity values were calculated (Figure 1).

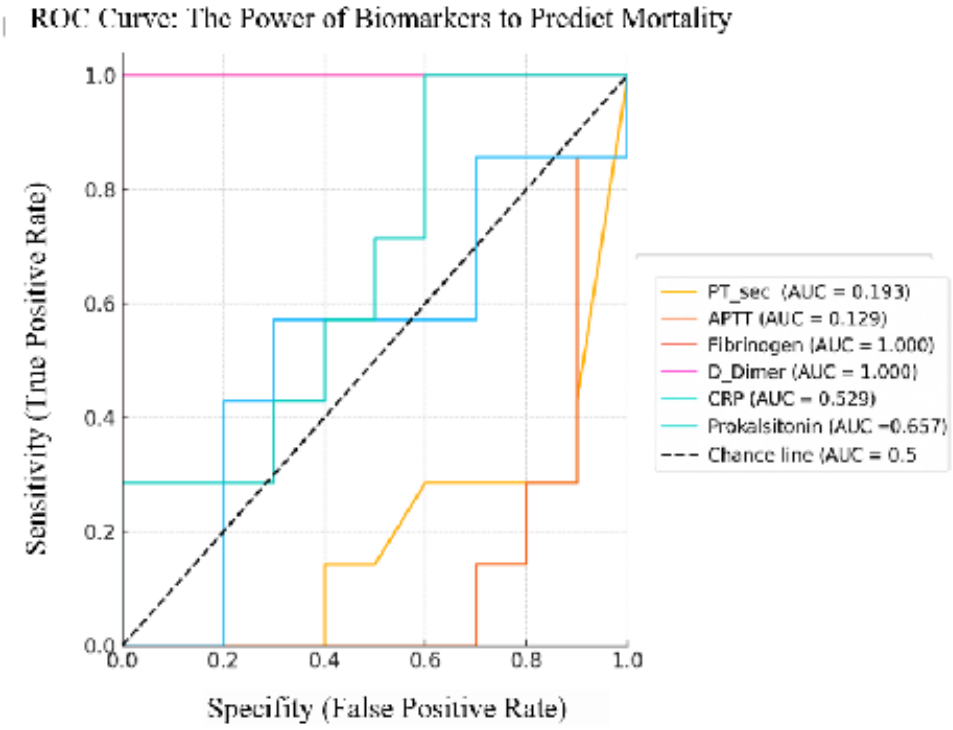

Figure 1. AUC, cut-off, sensitivity, and specificity values of biomarkers in mortality discrimination

Discussion

Clinical manifestations observed in dogs with parvoviral enteritis include loss of appetite, depression, vomiting, bloody and foul-smelling diarrhea, dehydration, and fever are consistent with the classic symptoms described in the literature (Bird et al., 2013; Martin et al., 2002; Ulaş, 2015; Ince, 2017; Akdag, 2014). These findings directly reflect the severity of the infection, and it is characteristic that in the early stages of the disease, it starts with mild fever and depression, and soon develops into intense gastrointestinal symptoms. This picture has been confirmed in our cases.

In addition, findings such as impaired consciousness, hypothermia, and bradycardia progressing to coma in some cases were evaluated as signs of the development of sepsis and multiple organ failure. The survival rates we obtained are similar to the data reported in the literature. According to Melo et al. (2024), the development of systemic inflammatory response syndrome (SIRS) in CPV-2-infected dogs increases mortality by approximately 13 times. According to Paul et al. (2023), the mortality rate was significantly higher in dogs diagnosed with SIRS. This supports the relationship between mortality and severe clinical findings observed in our study. Loss of appetite, depression, vomiting, bloody and foul-smelling diarrhea, dehydration, and fever are consistent with the classic symptoms described in the literature (Bird et al., 2013; Martin et al., 2002; Ulaş, 2015; Ince, 2017; Akdag, 2014). These findings directly reflect the severity of the infection, and it is characteristic that in the early stages of the disease, it starts with mild fever and depression, and soon develops into intense gastrointestinal symptoms. This picture has been confirmed in our cases. In addition, findings such as impaired consciousness, hypothermia, and bradycardia progressing to coma in some cases were evaluated as signs of the development of sepsis and multiple organ failure.

Leukopenia, one of the most striking hematologic changes in dogs with parvoviral enteritis, is particularly in the form of neutropenia and lymphopenia, which is decisive for prognosis (Azetaka et al., 1981; Mylonakis et al., 2016). In our study, a significant decrease in WBC, neutrophil, and lymphocyte counts was found in the deceased group. These findings are in line with the data reported in a retrospective study of 401 cases by González-Domínguez et al. (2024). In this study, the mean lymphocyte count was 0.82×10^9/L in the deceased group and 1.27×10^9/L in the surviving group. Similarly, in our study, the WBC value in the deceased group was approximately 3.2×10^9/L and 12.6×10^9/L in healthy controls. These data confirm that severe leukopenia, and especially lymphopenia, is decisive for prognosis has been determined. These findings indicate the suppressive effect of viral infection on bone marrow and lymphoid tissues and the weakness of the immune system (Castro et al., 2013; Kruse et al., 2010; Sykes, 2014).

A significant increase in the number of lymphocytes in the surviving dogs after treatment indicated that the immune system had recovered, and recovery had begun. In erythrocyte parameters, hemoconcentration due to dehydration was detected in the infected group; this led to significant increases in HGB and HCT. However, in advanced cases, blood loss through diarrhea and vomiting may have masked anemia (Gülersoy et al., 2022; Terzungwe et al., 2018).

In our study, CRP and procalcitonin levels were reported in a study conducted by McClure et al. (2013), where CRP levels reached an average of 88 mg/L at admission in puppies with parvovirus infection, and this value was significantly higher in fatal cases. In addition, Paul et al. (2023) showed in their study that combined models including MPV and chloride levels, as well as CRP, predicted mortality more effectively. In light of these findings, it is understood that CRP may be associated with sepsis or poor prognosis when it is above certain threshold values, but it may not be sufficient on its own. Although it increased in the infected group, it was observed that there was no significant difference between the deceased and the survivors. This suggests that these biomarkers may not be strong prognostic markers on their own for CPV (McClure et al., 2013; Dossin, 2019). However, in the literature, it is reported that the CRP/Alb ratio is correlated with the severity of infection and may be prognostically beneficial (Bozkurt et al., 2021; Cagnasso et al., 2023).

On the other hand, fibrinogen and D-dimer levels were strongly correlated with the severity of CPV infection. It is noteworthy that fibrinogen and D-dimer levels were found to be high in the

deceased group, similar to the threshold values in the ROC analyses reported in the study of Corda et al. (2023). In our analysis, the optimal cut-off point for fibrinogen was determined as 3.74 g/L and for D-dimer as 1596 ng/mL, and the AUC value for both parameters was found to be 1.00. These values were determined similarly in the study of Corda et al., and ≥3.5 g/L for fibrinogen and ≥1500 ng/mL for D-dimer were associated with DIC and poor prognosis.

These results show that the data in our study are consistent with other findings in the literature and that the prognostic discrimination power of both markers is quite high. Significantly higher levels are associated with the development of coagulopathy and DIC (Whitehead et al., 2020; Corda et al., 2023). In the ROC analysis, the AUC value for these two markers was found to be 1.00. This shows that the prognostic discrimination power is very high. In addition, the decrease in antithrombin levels promotes the development of hypercoagulability and DIC. These findings suggest that coagulation system markers play an important role in the prognosis determination of CPV infection.

Conclusion

This study revealed that the combined evaluation of clinical, hematologic, and biochemical parameters in puppies with CPV made important contributions to the determination of the disease prognosis. In particular, monitoring parameters such as fibrinogen, D-dimer, and antithrombin may be effective in early detection of patients with poor prognosis and in determining aggressive treatment strategies.

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