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Research Article

Association of Coagulation Factors with Pathogenesis of Canine Parvovirus; an Insight into Disease Pathogenesis & Its Diagnosis

Kissa Zahra[1], Raheela Akhtar[1], Muhammad Ali Raza[2], Usman Ahmad[3]
[1] *University of Veterinary and Animal Sciences, Lahore, Pakistan.*
[2] *National Agricultural Research Centre, Islamabad, Pakistan.*
[3] *Pir Mehr Ali Shah, Arid Agriculture University, Rawalpindi, Pakistan.*

ABSTRACT

Canine Parvovirus (CPV) is a virus of the genus *Protoparvovirus* (family Parvoviridae, subfamily Parvovirinae). CPV is a single-stranded, small, non-enveloped DNA virus. Canine parvovirus is a virus that can cause acute hemorrhagic enteritis and, infrequently, fatal myocarditis in dogs. Non-immunized puppies are particularly susceptible, and the virus causes severe enteritis along with anorexia, depression, increase temperature, vomiting, rapid dehydration, and bloody diarrhea. The present study was conducted to investigate that during the pathogenesis of parvovirus, three coagulation factors (Factor IIa, IXa, and Xa) were affected due to decrease in Antithrombin III activity. The blood samples of 50 dogs of different ages, infected with canine parvovirus were collected from different clinics and from Pet center UVAS, Lahore. Then by using automation method we had run these samples in the coagulation analyzer CS-1600, it worked on multiwavelength detection or photo optical clot detection principle. The CS-1600 has an optical cable that can supply light of various wavelengths and a sensor that can receive light of various wavelengths. A variation in optical density (OD) of a test sample is used to identify clot formation in the photo optical method. Results of coagulation factors were in the form of percentages and clotting time in seconds. all these three coagulation factors were elevated from their normal reference range. Hypercoagulation was further confirmed by the increased prothrombin time, activated partial thromboplastin time.

Keywords: Canine Parvovirus, Coagulation Factors, Hypercoagulation.

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Correspondence
Muhammad Ali Raza
ali.raza1472@yahoo.com

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INTRODUCTION

Canine Parvovirus (CPV) is a virus of the genus Protoparvovirus (family Parvoviridae, subfamily Parvovirinae). CPV is a single-stranded, small, non-enveloped DNA virus. Its genome is made up of about 5,000 nucleotides. Through alternative splicing of the same mRNAs, DNA molecule contains two open reading frames (ORFs), ORF1 and ORF2, encoding for two non-structural (NS1 and NS2) and two structural (VP1 and VP2) proteins.(Mira *et al.* 2018) All CPV strains emerged from a single ancestor, which was thought to be a modification in the host range due to changes in feline panleukopenia virus, according to phylogenetic studies.(Liu et al. 2021)

CPV1 and CPV2 are the two types of canine parvovirus. CPV-1 is known as the minute canine virus because it does not produce significant infection in dogs. CPV-2, which was initially discovered in 1978 and has since spread all over the world, produces the most severe type of disease in dogs and wild canids. The three varieties of CPV type 2 are known as CPV-2a, CPV-2b, and CPV-2c. When compared to variants 2a and 2b, which are almost identical to the real CPV 2, variant type 2c exhibits a distinct pattern

of pathogenicity (Sun *et al*. 2018). The most common cause of acute canine enteritis is canine parvovirus (CPV), which causes significant damage to the intestinal barrier. Parvoviruses have a strong predilection for the small intestine, bone marrow, and lymphatic tissues because they require cells with a high proliferation rate for reproduction. It's been suggested that dogs who survive CPV infection may acquire chronic illnesses (Kilian *et al*. 2018). Canine parvovirus is still the most leading cause of morbidity and mortality in puppies, and the virus capacity to "reinvent" itself and evolve into new resistant and virulent strains is one of the reasons for its persistence (Abdel-Rhman et al. 2019).

CPV infection is frequently seen in young puppies between the ages of two and six months, however clinical cases in older dogs are becoming increasingly common. The major route of infection is oronasal, which is caused by contact with infected dogs' faeces or contaminated fomites, which is made easier by the remarkable resilience of virus in the environment. Depression, inappetance, vomiting, and hemorrhagic diarrhea are the most common clinical symptoms (Decaro and Buonavoglia 2017). Ingestion of canine parvovirus excreted through the vomit or feces of an infected animal can cause exposure through nasal openings and cause infection in unvaccinated dogs. Infected animals will develop viremia in the oropharyngeal and mesenteric lymph nodes within 1-5 days after the virus replicates. In addition to lung, spleen, liver, and kidney, CPV also targets intestinal epithelial crypt cells, bone marrow, tongue epithelium, oral cavity, and rapidly dividing cardiomyocytes. Disruption of stomach and intestinal linings was led to clinical manifestations of vomiting, hemorrhagic diarrhea, as well as malabsorption of nutrients and intestinal bacterial translocation. If not treated in time, infected animals will face the risk of septic shock, systemic inflammatory response syndrome, multiple organ failure, death due to lack of immunity, as well as bacteremia due to bacterial intestinal translocation (Mazzaferro 2020).

Subclinical infection is also frequent, and some dogs can have the virus without showing any symptoms. Nonspecific symptoms including exhaustion, fever, dehydration, and inappetence will appear at first. Within 24-48 hours after the onset of clinical indications, these symptoms will usually progress to vomiting and diarrhea with a foul smelling or distinguishing smell. Intestinal cramping can also be caused by dilated and fluid-filled intestinal loops. Septic shock is accompanied by a decline in capillary refill time, tachycardia, and hypothermia in animals suffering from severe illnesses. Endotoxin and tumor necrosis factor (TNF) are found in detectable amounts in the blood of sick puppies, and there is a link between increased TNF activity and mortality. Endotoxin and proinflammatory cytokines are important mediators of the systemic inflammatory response and coagulation cascade activators (Ukwueze *et al*. 2021).

The examination of the hemogram, anamnesis is extremely important in case of parvovirus infection. Leukopenia has been linked to the degradation of hematopoietic stem cells in the bone marrow of leukocytes. Similarly, lymph proliferative organs are including the thymus, lymph nodes, and spleen's failure to respond to the digestive tracts inflammatory demand for neutrophils. According to study, dogs infected with CPV are more likely to develop clinical thrombosis or phlebitis, as well as testing evidence of hypercoagulability without diffuse intravascular coagulopathy (Franzo *et al.* 2019). Changes in blood parameters occur in all affected dogs during parvovirus infection; however these changes are more significant in some animals, leading to death by the fifth day of the illness. By the third day of the infection, thrombocytopenia has developed along with a rise in platelet function and the stability of the developed aggregates, and the amount of fibrinogen and SFMCs (soluble fibrin monomer complex) has increased together with a decrease in antithrombin activity. These animals do not improve by the fifth day of the infection. The morphological abnormalities in blood cell composition are intensified; platelet function is reduced; and the level of PT(prothrombin time), TT(thrombin time), APTT(activated partial thromboplastin time), rise considerably (Baruzdina and Soboleva 2019).

Histologic alterations revealed lymphocytopenia in the spleen, lymphocytopenia and reticulocytosis in the mesenteric lymph nodes, intestinal villus disintegration, and inflammatory cell infiltration of the intestinal lamina propria in dogs suffering from parvovirus who were terminated on fifth day.(Jia-Yu *et al.* 2018).In canine parvovirus infections, several parameters contribute to the development of sepsis. Biochemical abnormalities differ and depict organ dysfunctions that are occurring, either as a result of the infection or as a result of the inflammatory state (Alves *et al*. 2020). In the current research, blood samples were collected from parvo suspected dogs and are processed in laboratory for the evaluation of three coagulation factors (IIa, IXa, and Xa).

The main objectives of the study are to evaluate the three coagulation factors (IIa, IXa, and Xa) in the CPV infected dogs and to determine the correlation between three coagulation factors (IIa, IXa, and Xa) in the CPV infected dogs.

MATERIALS AND METHODS

The 50 blood samples of dogs of different ages, infected with canine parvovirus were collected from Kennels and Private Clinics in Lahore and from Pet Center UVAS. Blood samples were collected in light blue top tubes containing

3.2 percent sodium citrate. Fifty (50) dogs were considered based on their clinical signs and history of these cases was also recorded. Blood samples were collected from those dogs which were having following history and clinical symptoms:

Diarrhea
Emaciation
Weight loss
Vomiting

All these samples within blue top vacutainers were properly labelled and transported to the laboratory in ice packs within few hours.

Blood collection

A syringe needle was placed into a cephalic vein, and a small volume of blood entered the syringe tip. Move the syringe's plunger backwards to collect 3ml of blood in the syringe. Remove the pressure from the cephalic vein and place the sterile cotton swab on the venipuncture site for 30 seconds after sample collection to ensure that blood stops completely. The blood should then be poured into the blue top tube as soon as possible to avoid clotting. Samples were transported to the laboratory by maintaining a cold chain.

Separation of plasma

Blood collected in blue top (anti-coagulant 3.2 percent sodium citrate) was processed for the separation of plasma.

A blood samples were then centrifuged at 2000 rpm for 15 minutes (at 4 ℃).

After that plasma was removed and placed in a polypropylene microcentrifuge tube or a 12X75 polypropylene tube after centrifugation.

Further than possible, avoid transferring the red cells with the plasma.

Coagulation analysis

Samples during this research were analyzed using Automated Blood Coagulation Analyzer CS-1600. The Sysmex CS-1600 system is a complete automated coagulation analyzer designed for mid-sized coagulation laboratories that require a cap-piercing analyzer. Sysmex has more than 20 years of emphasis on the development of safe and dependable cap-piercing equipment. This avoids risk of contamination and ensures that reliable results are delivered. The CS-1600 ensured that laboratories' testing findings were reliable in precision and validity. Different coagulation parameters can be measured using this analyzer including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, intrinsic and extrinsic coagulation factors. The processing capacity of this analyzer was 120 tests/hour.

It worked on multiwavelength detection or photo optical clot detection principle.

The CS-1600 has an optical cable that can supply light of various wavelengths and a sensor that can receive light of various wavelengths.

A variation in optical density (OD) of a test sample is used to identify clot formation in the photo optical method.

The amount of light landing on a photo-sensitive detector diminishes as the plasma sample clots and becomes more optically dense (i.e. transmitted light decreases).

The endpoint of coagulation is defined by the decline or change in light. The time it takes for coagulation to reach its endpoint is measured in seconds.

Inclusive criteria

The blood of infected dogs was collected from Kennels and Private Clinics in Lahore and from Pet Center University of Veterinary and Agriculture Science Lahore, Pakistan.

Exclusive criteria

The blood of infected dogs from other sites of the Punjab was not considered in the present study.

Statistical analysis

The data were subjected to statistical analysis using the analysis of variance (ANOVA) method to evaluate differences among treatment (n=50). Treatment means were compared using the Tukey Kramer Multiple Comparisons test at a 5% probability level, performed using the SPSS 21 statistical software.

RESULTS

In present study, the evaluations of three coagulation factors (IIa, IXa, and Xa) are determined in blood samples of infected dogs which are reported in table 1.

Table 1. Evaluation of Factor II, Factor IX, and Factor X levels in CPV infected dogs.

Sr No	Reference value Factor II	Result (Factor II)	Reference value Factor IX	Result (Factor IX)	Reference value Factor X	Result (Factor X)	One Way ANOVA Test (P < 0.05)	Status
1	84-126	140 ± 3.16	67-163	168 ± 4.07	77-121	135 ± 3.71	0.000	Highly significant
2	84-126	145 ± 3.16	67-163	170 ± 4.07	77-121	137 ± 3.71	0.000	Highly significant
3	84-126	147 ± 3.16	67-163	168 ± 4.07	77-121	135 ± 3.71	0.000	Highly significant
4	84-126	150 ± 3.16	67-163	171 ± 4.07	77-121	132 ± 3.71	0.000	Highly significant
5	84-126	140 ± 3.16	67-163	174 ± 4.07	77-121	141 ± 3.71	0.000	Highly significant
6	84-126	143 ± 3.16	67-163	167 ± 4.07	77-121	139 ± 3.71	0.000	Highly significant
7	84-126	148 ± 3.16	67-163	172 ± 4.07	77-121	142 ± 3.71	0.000	Highly significant
8	84-126	138 ± 3.16	67-163	173 ± 4.07	77-121	137 ± 3.71	0.000	Highly significant
9	84-126	142 ± 3.16	67-163	169 ± 4.07	77-121	142 ± 3.71	0.000	Highly significant
10	84-126	140 ± 3.16	67-163	173 ± 4.07	77-121	140 ± 3.71	0.000	Highly significant
11	84-126	135 ± 3.16	67-163	178 ± 4.07	77-121	131 ± 3.71	0.000	Highly significant
12	84-126	141 ± 3.16	67-163	175 ± 4.07	77-121	142 ± 3.71	0.000	Highly significant
13	84-126	138 ± 3.16	67-163	168 ± 4.07	77-121	136 ± 3.71	0.000	Highly significant
14	84-126	146 ± 3.16	67-163	170 ± 4.07	77-121	132 ± 3.71	0.000	Highly significant
15	84-126	140 ± 3.16	67-163	179 ± 4.07	77-121	137 ± 3.71	0.000	Highly significant
16	84-126	148 ± 3.16	67-163	167 ± 4.07	77-121	135 ± 3.71	0.000	Highly significant
17	84-126	145 ± 3.16	67-163	169 ± 4.07	77-121	140 ± 3.71	0.000	Highly significant
18	84-126	139 ± 3.16	67-163	174 ± 4.07	77-121	138 ± 3.71	0.000	Highly significant
19	84-126	142 ± 3.16	67-163	177 ± 4.07	77-121	143 ± 3.71	0.000	Highly significant
20	84-126	140 ± 3.16	67-163	180 ± 4.07	77-121	141 ± 3.71	0.000	Highly significant
21	84-126	146 ± 3.16	67-163	176 ± 4.07	77-121	136 ± 3.71	0.000	Highly significant
22	84-126	144 ± 3.16	67-163	167 ± 4.07	77-121	139 ± 3.71	0.000	Highly significant
23	84-126	147 ± 3.16	67-163	179 ± 4.07	77-121	135 ± 3.71	0.000	Highly significant
24	84-126	139 ± 3.16	67-163	175 ± 4.07	77-121	137 ± 3.71	0.000	Highly significant
25	84-126	140 ± 3.16	67-163	180 ± 4.07	77-121	139 ± 3.71	0.000	Highly significant
26	84-126	143 ± 3.16	67-163	174 ± 4.07	77-121	137 ± 3.71	0.000	Highly significant
27	84-126	145 ± 3.16	67-163	164 ± 4.07	77-121	141 ± 3.71	0.000	Highly significant
28	84-126	146 ± 3.16	67-163	166 ± 4.07	77-121	139 ± 3.71	0.000	Highly significant
29	84-126	144 ± 3.16	67-163	172 ± 4.07	77-121	142 ± 3.71	0.000	Highly significant
30	84-126	142 ± 3.16	67-163	170 ± 4.07	77-121	143 ± 3.71	0.000	Highly significant
31	84-126	146 ± 3.16	67-163	178 ± 4.07	77-121	140 ± 3.71	0.000	Highly significant
32	84-126	143 ± 3.16	67-163	174 ± 4.07	77-121	138 ± 3.71	0.000	Highly significant
33	84-126	145 ± 3.16	67-163	169 ± 4.07	77-121	136 ± 3.71	0.000	Highly significant
34	84-126	140 ± 3.16	67-163	166 ± 4.07	77-121	139 ± 3.71	0.000	Highly significant
35	84-126	146 ± 3.16	67-163	170 ± 4.07	77-121	143 ± 3.71	0.000	Highly significant
36	84-126	143 ± 3.16	67-163	173 ± 4.07	77-121	145 ± 3.71	0.000	Highly significant
37	84-126	145 ± 3.16	67-163	171 ± 4.07	77-121	141 ± 3.71	0.000	Highly significant
38	84-126	141 ± 3.16	67-163	167 ± 4.07	77-121	142 ± 3.71	0.000	Highly significant
39	84-126	140 ± 3.16	67-163	170 ± 4.07	77-121	139 ± 3.71	0.000	Highly significant

40	84-126	143 ± 3.16	67-163	176 ± 4.07	77-121	145 ± 3.71	0.000	Highly significant
41	84-126	146 ± 3.16	67-163	174 ± 4.07	77-121	140 ± 3.71	0.000	Highly significant
42	84-126	145 ± 3.16	67-163	177 ± 4.07	77-121	142 ± 3.71	0.000	Highly significant
43	84-126	142 ± 3.16	67-163	168 ± 4.07	77-121	146 ± 3.71	0.000	Highly significant
44	84-126	144 ± 3.16	67-163	170 ± 4.07	77-121	141 ± 3.71	0.000	Highly significant
45	84-126	148 ± 3.16	67-163	177 ± 4.07	77-121	143 ± 3.71	0.000	Highly significant
46	84-126	143 ± 3.16	67-163	174 ± 4.07	77-121	140 ± 3.71	0.000	Highly significant
47	84-126	142 ± 3.16	67-163	172 ± 4.07	77-121	145 ± 3.71	0.000	Highly significant
48	84-126	141 ± 3.16	67-163	169 ± 4.07	77-121	147 ± 3.71	0.000	Highly significant
49	84-126	145 ± 3.16	67-163	172 ± 4.07	77-121	144 ± 3.71	0.000	Highly significant
50	84-126	147 ± 3.16	67-163	174 ± 4.07	77-121	145 ± 3.71	0.000	Highly significant

(n= 50) ± S.D One Way ANOVA test (α significance at 0.05)

Reference value of Coagulation Factor II fall between 84-126% and the average of all these 50 samples were 143.16%. Similarly, the average value of Coagulation Factor IX was 172.12% and Coagulation Factor X was 139.68% in relation to their reference range 67-163% and 77-121% respectively. This shows that the values of coagulation factors are significantly different i.e increasing from their normal range in case of Canine parvo virus and their mean values in CPV of infected dogs are shown in figure 1.

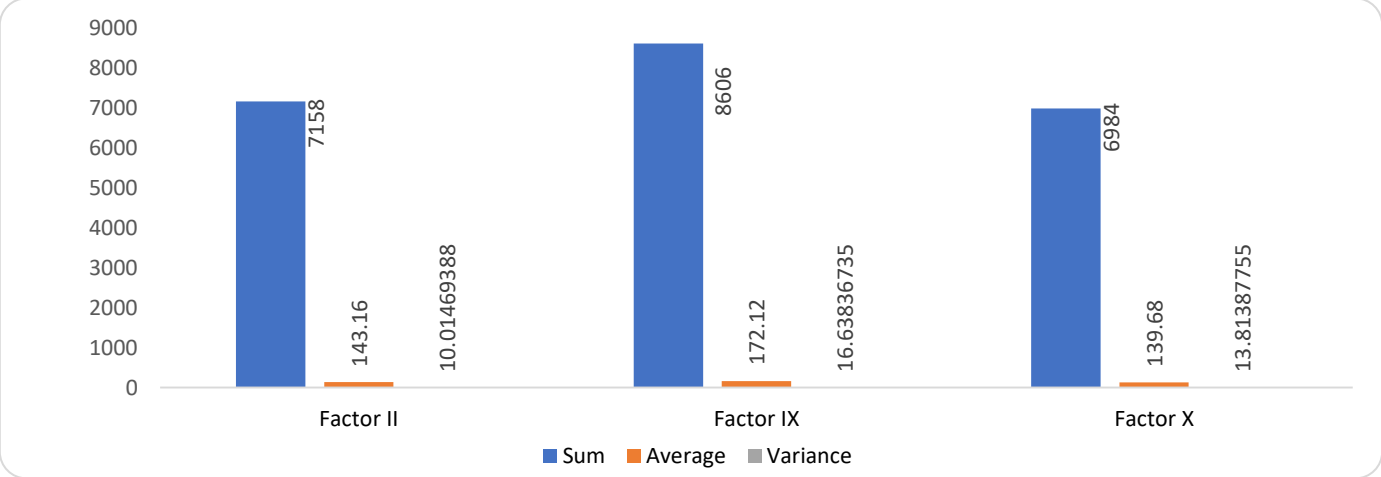

Figure 1, Mean values of Factor II, Factor IX, and Factor X levels in CPV infected dogs.

The correlation ship between the three coagulation factors (IIa, IXa, and Xa) are determined in CPV of infected dogs are shown positive correlation with each other as reported in table 2.

Table 2. Correlation between different factors in CPV infected Dogs.

Pearson Correlation Matrix (P < 0.05)			
	FACTOR II	FACTOR IX	FACTOR X
FACTOR II	1		
FACTOR IX	0.969278263	1	
FACTOR X	0.970235332	0.967511479	1

The significance is determined by One Way ANOVA Test at α 0.05 between three coagulation factors (IIa, IXa, and Xa) in CPV infected dog. For the sake of accuracy data were recorded as Standard Deviation ± S.D, the statically significant value of sample is less than 0.05 (P < 0.05) while the P value of sample is greater than (P < 0.05) than there is not significant relation present between three coagulation factors (IIa, IXa, and Xa) in CPV infected dog reported in table 3.

After one way anova test for further analysis, The Tukey Kramer Multiple Comparisons Test between different parameters of CVP infected dogs was performed to determine the association within the samples and it indicated that Factor IX and Factor X have strong relationship between them as reported in table 4.

Table 3. Correlation between different factors in CPV infected dogs.

Parameters	Correlation	One Way ANOVA Test	Status (P<0.05)
Factor II vs Factor IX	0.96	0.000	significant
Factor II vs Factor X	0.97	0.000	significant
Factor IX vs Factor X	0.96	0.000	significant

One Way ANOVA test (α significance at 0.05)

Table 4: Association between different factors in CPV infected dogs.

Tukey Kramer Multiple Comparisons Test (STATISTICS)					
Comparisons between different parameters (In Columns)	Absolute Difference	Critical Value	Result	One Way ANOVA Test (P-value) P < 0.05	Remarks
FACTOR II VS FACTOR IX	-28.96	7	Not Significantly difference	0.000	Week Association
FACTOR II VS FACTOR X	3	7	Not mean Significantly difference	0.000	Week Association
FACTOR IX VS FACTOR X	32.44	7	Mean Significantly difference	0.000	Strong Association

DISCUSSION

Canine parvovirus infection is a viral disease caused by the canine parvovirus, a member of the parvoviridae virus family. It's the smallest DNA virus, non-enveloped and single-stranded. It's a virus that can withstand heat, solvents, disinfectants, and pH changes. In young dogs, this virus causes gastroenteritis. The most common symptoms of this illness are vomiting and bloody diarrhea. Diarrhea is the most common ailment in dogs. It's linked to low weight gain and a higher death rate in puppies owing to dehydration and intestinal damage. Intestinal diseases, environmental disturbances, and incompetent management approaches can all cause diarrhea in dogs.(Mila et al. 2018). Canine parvovirus infection is the most common cause of diarrhea in puppies. This condition is fatal for puppies aged six weeks to six months since it has a high mortality rate of up to 90% if not treated. Despite routine immunization, CPV is an infectious disease that accounts for up to 26% of mortality among all viral diseases in dogs (Verma et al. 2016). In the majority of instances, this virus causes vomiting and bloody diarrhea. Diarrhea is a typical symptom of parvovirus infection in dogs. Canine parvovirus infection has no particular treatment due to its viral nature.

The hemogram, as well as the anamnesis, are extremely important in the case of parvoviral enteritis. Leukopenia has been linked to the degradation of hematopoietic stem cells in leukocytes' bone marrow, as well as lymphoproliferative organs including the thymus, lymph nodes, and spleen's incapacity to adapt to the digestive tract's inflammatory requirement for neutrophils. Dogs with CPV enteritis were shown to have a significant prevalence of clinical thrombosis or phlebitis, as well as laboratory evidence of hypercoagulability, but no diffused intravascular coagulopathy.(Elitok and Caliskan 2018)**.** Antithrombin is one of a variety of coagulation cascade regulation mechanisms that acts as a clot-prevention strategy. It inhibits thrombin generation by providing up to 80% of the inhibitory component, as well as factor IXa and factor Xa inhibition. Antithrombin deficiency has been linked to an increased risk of thrombosis, thromboembolism, and the problems that come with a hypercoagulable state.(Hsu and Moosavi 2019). The decrease in anti-thrombin activity is accompanied by worsening protease activity during parvovirus pathogenesis, resulting in rapid fibrin production and lysis, which leads to numerous organ dysfunction. This occurs when the body's injured or necrotizing tissue produces tissue factor into the bloodstream in significant quantities.

The present research study was conducted to investigate the relationship of three coagulation factors (Factor IIa, Factor IXa, Factor Xa) with the pathogenesis of canine parvo virus. Blood samples of 50 dogs were collected based on their clinical signs (vomiting, diarrhea, emaciation) and previous history. About 5 ml blood was taken (aseptically from the cephalic vein), in blue top vacutainer containing 3.2 percent sodium citrate as an anti-coagulant in it. Then after separating plasma the coagulation analysis was conducted using coagulation analyzer. The values of these three coagulation factors along with PT and APTT were used to classify hyper-coagulation. In addition to 50 blood samples 6 normal samples were also collected to compare their values also. Positive samples clearly showed hyper

coagulation with an increase of prothrombin time (PT), activated partial thromboplastin time(APTT), and decrease in AT III (antithrombin III) activity. ANOVA was performed in statistical analysis and according to this, Reference value of Coagulation Factor II fall between 84-126% and the average of all these 50 samples were 143.16%. Similarly, the average value of Coagulation Factor IX was 172.12% and Coagulation Factor X was 139.68% in relation to their reference range 67-163% and 77-121% respectively. All our concerned coagulation factors (Factor II, IX, and X) were also increased from their normal value.

Further in ANOVA table the P-value 0.000 which is less than the significant value 0.05 also suggests that our null hypothesis is rejected, and alternative is accepted. So, our results are highly significant. Our study explains that 50 samples of parvo positive dogs were examined for hypercoagulation due to in AT III insufficiency and all these dogs have increased level of our desired parameters i.e Coagulation Factor II, IX, and X. Hypercoagulation is further confirmed by increase in prothrombin time (PT) and activated partial thromboplastin time (APTT). Another study performed by Elitok shows a mild correlation with our study by demonstrating the evidence of hypercoagubility with the evidence of coagulation parameters.(Elitok and Caliskan 2018).

CONCLUSION

The coagulation factors II, IX, and X that we were looking for were all found to be greater in 50 samples of parvo-affected dogs that were examined for hypercoagulation caused by AT III insufficiency. Hypercoagulation is further confirmed by increases in activated partial thromboplastin time (APTT) and prothrombin time (PT). Additionally, the factor IX, and factor X showed strong association between them for hypercoagulation caused by AT III insufficiency.

AUTHOR CONTRIBUTIONS

Kissa Zahra: Writing-original draft, Conceptualization, conducted experiment. Raheela Akhtar: Conceived the Idea, overall management of the work. Usman Ahmad: Analysis and Interpretation of Results, Visualization. Muhammad Ali Raza: Analysis and Interpretation of Results and Review the literature. Kissa Zahra: Data Collection and field experiment layout preparation. Muhammad Ali Raza: Reviewed the original draft. All the authors reviewed the results and approved the final version of the manuscript.

COMPETING OF INTEREST

The authors declare no competing interests.

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