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Evaluation of Acute Phase Proteins in Dogs Suffering from Various Diseases

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ABSTRACT

The proteins of acute phase response are sensitive markers of ongoing inflammatory processes also in dogs with increased production in many infections and organ diseases. However, the magnitude and intensity of increase in their concentrations may differ according to the type of injury or the causative agent of the disease which is not completely understood. Therefore, this study was conducted to determine major acute phase proteins (APP) concentrations in dogs with selected diseases and to compare the values among the various groups of dogs. The study was conducted on serum samples from 89 client-owned dogs with the following diseases: dogs with parvoviral enteritis (n=14), pyometra (n=21), acute pancreatitis (n=14), and babesiosis (n=39). Clinically healthy dogs (n=23) without any abnormal clinical conditions were also included in the study. The concentrations of serum amyloid A (SAA), haptoglobin (Hp), and C-reactive protein (CRP) were analysed in blood serum. The concentrations of all the evaluated APPs differed significantly between the groups of dogs (P<0.001). Although the average concentrations of all parameters were higher in diseased dogs compared to healthy animals, the magnitude of increase differed among the disease groups. Canine parvoviral enteritis and pyometra induced the most marked inflammatory response with the highest mean concentrations of SAA, Hp, and CRP. On the other hand, canine babesiosis was associated with less marked alterations among the evaluated diseases of dogs. The obtained data indicated that the investigated canine disorders were associated with different inflammatory responses, characterized by marked and significant differences in the assessed acute phase reactants.

Key words: Dogs, C-reactive Protein, Haptoglobin, Serum amyloid A, Pyometra, Enteritis.

INTRODUCTION

The acute phase protein response is a complex of nonspecific defence reactions of the host shortly after any tissue injury, damage, trauma, infections, or other causes that disrupt the controlled internal environment. It involves several physiological, immunological, and biochemical alterations that are aimed to restore homeostasis in the body through the isolation and destruction of infectious agents, removal of pathogens and dangerous materials, and the activation of repair processes. One of the most important biochemical changes during the inflammatory processes is the elevated synthesis of selected proteins that are called acute phase reactants (Ceron et al. 2005). Although a measurable increase of acute phase proteins does not indicate a specific disease, they may be of great importance in other parts of the diagnostic process. The highest concentrations of main inflammatory reactants are usually reached 24 – 48 hours after the initiation of the response. As the infection subsides, the inflammatory reactions also subside and in the absence of any further stimulus, the production of inflammatory proteins starts to decrease (Yogeshpriya and Selvaraj 2020). Therefore, the evaluation of alterations in the production of inflammatory reactants during the therapeutic process may be helpful in treatment monitoring and determination of the prognosis of diseases (Eckersall and Bell 2010; Schmidt and Eckersall 2015).

All animal species have a great number of acute phase proteins, but the type of diagnostically useful proteins that may be considered as major differs by species (Cray et al. 2009).

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In dogs, C-reactive protein has been found as the diagnostically most important inflammatory marker, but other reactants such as haptoglobin and serum amyloid A have also become useful as markers of inflammation and in the monitoring of disorders (Eckersall and Bell 2010; Jasensky et al. 2018). Their very low concentrations under physiological conditions and fast changes after the beginning of inflammatory processes make them highly sensitive inflammatory markers (Ceron et al. 2005; Solter et al. 1991). Numerous studies have shown that the serum concentrations of inflammatory markers markedly increase under many infectious conditions and organ disorders (Gebhardt et al. 2009; Mitchell et al. 2009; Viitanen et al. 2017; Gul et al. 2022). Nevertheless, the kinetics of inflammatory responses and the magnitude of increase of several inflammatory reactants may vary according to the extent of alterations, destruction of tissues, and disease condition that induced the inflammatory process. More progress is needed to clarify the possible implementation of different inflammatory markers in clinical practice of canine infectious or organ diseases. Therefore, the aim of the present study was to determine the differences in the concentrations of major inflammatory markers among dogs suffering from selected diseases, including parvoviral enteritis, acute pancreatitis, pyometra and babesiosis, and to compare the magnitude of their increase in dogs with these diseases.

MATERIALS AND METHODS

Statement of Ethics

As only blood was collected from the animals, and all diagnostic procedures were conducted for routine diagnostic and monitoring purposes, the study did not require ethical committee approval. All procedures complied with requirements for animal protection used for experimental purposes and were carried out in accordance with relevant ethical guidelines and institutional regulations of the Code of Ethics for Scientists on protection of animals used for scientific purposes (Directive 74/2019/UVLF) approved by the institutional Ethical Committee.

Animals

Samples of blood from 89 dogs owned by clients, and clinical cases suffering from various health disorders were included into the study. The dogs were of both sexes (51 females and 38 males), of various breeds and at the age from 2 months to 14 years. They were treated in the Small Animal Clinic of the University of Veterinary Medicine and Pharmacy in Košice (Slovak Republic) during the years 2016 - 2020. According to the observed clinical signs and the diagnosed disease, the dogs were categorized into four groups: dogs with parvoviral enteritis (PVE, n=14), dogs with pyometra (PM, n=21), dogs with acute pancreatitis (AP, n=14), and dogs with babesiosis (B, n=39). All animals were regularly clinically examined to assess the general health status and identify the suspected health problem. If necessary, further specific examinations were performed according to the abnormal clinical condition. At hospital admission, samples of blood were taken before any treatment for routine hematologic, biochemical, or microscopic examinations. The clinical signs in dogs with parvoviral infection were the following: watery, bloody diarrhea, severe depression and increased body temperature, refusal to feed intake, frequent vomiting, and moderate or severe dehydration. The age of these dogs ranged from two to six months. All animals with parvoviral enteritis had positive test results for the commercially available fecal diagnostic rapid Canine Parvovirus Antigen assay (IDEXX Laboratories, Westbrook, Maine, USA). The dogs with pyometra showed anorexia, increased body temperature (11 out of 22 dogs), vaginal discharge, leukocytosis (16 out of 22 dogs), and enlarged lumen of the uterus filled with liquid content determined by ultrasound examination. All animals with findings underwent surgical intervention - ovariohysterectomy. In dogs with acute pancreatitis signs of anorexia, diarrhea, vomiting, and abdominal pain during the physical examination were observed. The clinical examination was completed with laboratory analyses and diagnostic imaging using abdominal ultrasound. The ultrasonographic findings were consistent with acute pancreatitis and included an enlarged pancreas with hypoechoic lesions and irregular shape. Furthermore, the following abnormalities were observed: localized free abdominal fluid, hyperechoic mesentery, inflammatory lesions in the adjacent intestines, thickened gastric and intestinal walls, and dilation of the common bile duct. These finding were considered as secondary and were described by Mansfield (2012) as typical to pancreatitis. The diagnosis was confirmed by the analysis of the activity of pancreatic amylase and lipase. The activities of these enzymes were determined by Roche cobas clinical chemistry analyzer with commercial diagnostic tests (Roche Diagnostics GmbH, Mannheim, Germany). Increased activities of pancreatic amylase and lipase were recorded in all dogs included in this group of animals. The dogs with babesiosis were apathic, showed increased body temperature, inappetence, pigmenturia, and the mucous membranes were pale. All the dogs included into the study produced positive test for *Babesia* in blood smears taken from capillaries of the earlobe. The *Babesia* parasites were stained using Diff-Quick (Medion Diagnostics AG, Düdingen, Switzerland). They were observable within the infected red blood cells and were identified as *B. canis* according to their typical large form. Further assessment of the subspecies of *B. canis* was not performed. The control group of animals (H) consisted of twenty-three clinically healthy dogs without any abnormal clinical conditions, hematologic and biochemical findings, and were in good general condition. They were taken to the University Veterinary Hospital for routine preventive clinical examination with vaccination. Informed written consent and permission to blood collection and sample analyses were obtained from all dog owners.

Blood Collection and Laboratory Analyses

Samples of blood for the determination of inflammatory markers were collected from *v. cephalica* into tubes with gel for the separation of serum and without any anticoagulants (Sarstedt, Germany). The blood serum was yielded after centrifuging 10min at 3,500g. The harvested blood serum was distributed into tubes and used for the analysis of serum amyloid A (SAA, μg/mL), haptoglobin (Hp, mg/mL), and C-reactive protein (CRP, μg/mL). SAA was determined by sandwich type of

enzyme-linked immunosorbent assay (ELISA) with TP-802 Multispecies SAA test (Tridelta Development, Kildare, Ireland). Canine CRP was analysed using TP-803 solid-phase CRP ELISA test (Tridelta Development, Kildare, Ireland). Haptoglobin was measured spectrophotometrically with TP-801 colorimetric tests (Tridelta Development, Kildare, Ireland) in microplates. The absorbance was read on Opsys MR automatic microplate reader (The Dynex Technologies, USA). The Revelation QuickLink version 4.25 computer software was used for the calculation of results (The Dynex Technologies, USA).

Statistical Analyses

Arithmetic means (x) and standard deviations (SD) were calculated for the investigated inflammatory markers in each group of animals. Kolmogorov-Smirnov normality test was used for the description of data distribution. The significance of differences in the concentrations among the evaluated groups of dogs was assessed using Kruskal-Wallis test with Dunn`s Multiple Comparisons post-hoc test. The GraphPad Prism V5.02 program (GraphPad Software Inc., California, USA) was used to analyse the obtained data.

RESULTS

The analysis of the inflammatory markers showed significant differences among the investigated groups of dogs for SAA, Hp, as well as CRP ($P<0.001$, Table 1). Significantly elevated Hp values in comparison to healthy animals were recorded in all groups of sick dogs. The mean Hp values found in dogs with parvoviral enteritis, acute pancreatitis, and pyometra were the highest among the evaluated groups of animals (approximately 5-fold higher compared to healthy dogs). No significant differences in means were observed among these groups of dogs. In dogs with babesiosis, the mean concentration of Hp was significantly lower than in these three groups of sick dogs but was significantly elevated compared to healthy animals. The distribution of individual values showed wide range of values and tendency of lower Hp values in most dogs affected by babesiosis compared to animals with other analyzed diseases (Fig. 1a). The average SAA values were significantly elevated in all groups of diseased dogs compared to the healthy dogs. Significant differences were observed also among the sick dogs, with higher mean concentrations in dogs suffering from parvoviral enteritis and pyometra, and lower mean values in dogs with babesiosis and acute pancreatitis. The mean SAA concentrations in dogs with parvoviral enteritis and pyometra were more than 200-fold higher than the mean value in healthy ones, while those in dogs with babesiosis and acute pancreatitis were approximately 120-fold higher compared to healthy animals. Furthermore, the mean SAA values obtained in dogs suffering from parvoviral enteritis and pyometra were almost 2-fold higher than those in dogs affected with babesiosis and acute pancreatitis. While distribution of individual values in dogs with babesiosis, acute pancreatitis and pyometra indicate a wider range of values, in dogs with parvoviral enteritis the range of values was markedly narrower (Fig. 1b).

The mean CRP values in all groups of sick animals were significantly higher compared to healthy dogs, and significant differences were also found among the sick animal groups. The lowest average concentration was recorded in dogs affected by babesiosis, the highest average CRP concentration was recorded in dogs suffering from parvoviral enteritis, which was about 50-fold higher compared to healthy dogs and almost 2-fold higher than the mean value found in dogs with babesiosis. Furthermore, the mean CRP concentrations in dogs with acute pancreatitis and pyometra were more than 30-fold higher compared to healthy animals, and more than 1.5 times higher compared to dogs with babesiosis. The distribution of individual results indicate wider range of values in all groups of sick animals (Fig. 1c).

DISCUSSION

It has been shown that acute phase proteins are one of the most sensitive markers of inflammation, with possible usefulness in the early diagnosis of inflammatory processes and in assessing response to treatment (Ceron et al. 2005). Increased concentrations of inflammatory markers (especially CRP) have been observed in various disease conditions of dogs, including most naturally or experimentally induced infectious diseases or organ disorders (Langhorn et al. 2014; Schmidt and Eckersall 2015; Yogeshpriya and Selvaraj 2020). The data presented in this study suggest that the magnitude and intensity of their increase differ according to the disease condition that induced an acute phase response. In the presented study marked differences were observed in the values of all measured inflammatory markers among the evaluated diseases of dogs. Parvoviral enteritis in dogs was found to induce a very high increase in the production of Hp, SAA and CRP, while the magnitude of increase of SAA concentrations was greater (more than 220-fold compared to healthy animals) than that of CRP (50-fold) and Hp (5-fold). Furthermore, the distribution of SAA concentrations showed a narrow range of measured values suggesting a strong systemic inflammatory response in all the evaluated dogs. Although significantly higher SAA values in dogs suffering from parvoviral enteritis in comparison to control animals were observed also by Ok et al. (2015), the differences were less marked compared to our results (approximately 2-fold higher). C-reactive protein has been found by Yamamoto et al. (1993) and Kocaturk et al. (2010) to be more markedly increased in canine parvoviral enteritis with more than 70-fold higher values in severely affected animals with leukopenia compared to healthy dogs. In a further study, Kocaturk et al. (2014) reported in severe cases of parvovirus enteritis CRP concentrations higher than 180mg/L that were related to secondary bacterial infection with a strong inflammatory response. Ceron et al. (2005) and Caldin et al. (2009) indicated that gastrointestinal diseases usually produce a very mild increase in the concentrations of CRP and very high values could be explained by complications due to concurrent bacterial infections and sepsis. Furthermore, the data presented by McClure et al. (2013) showed that CRP may be helpful in the differentiation of dogs that can survive from non-survivors within 24 hours after the beginning of treatment in the hospital. In our study, the high SAA and

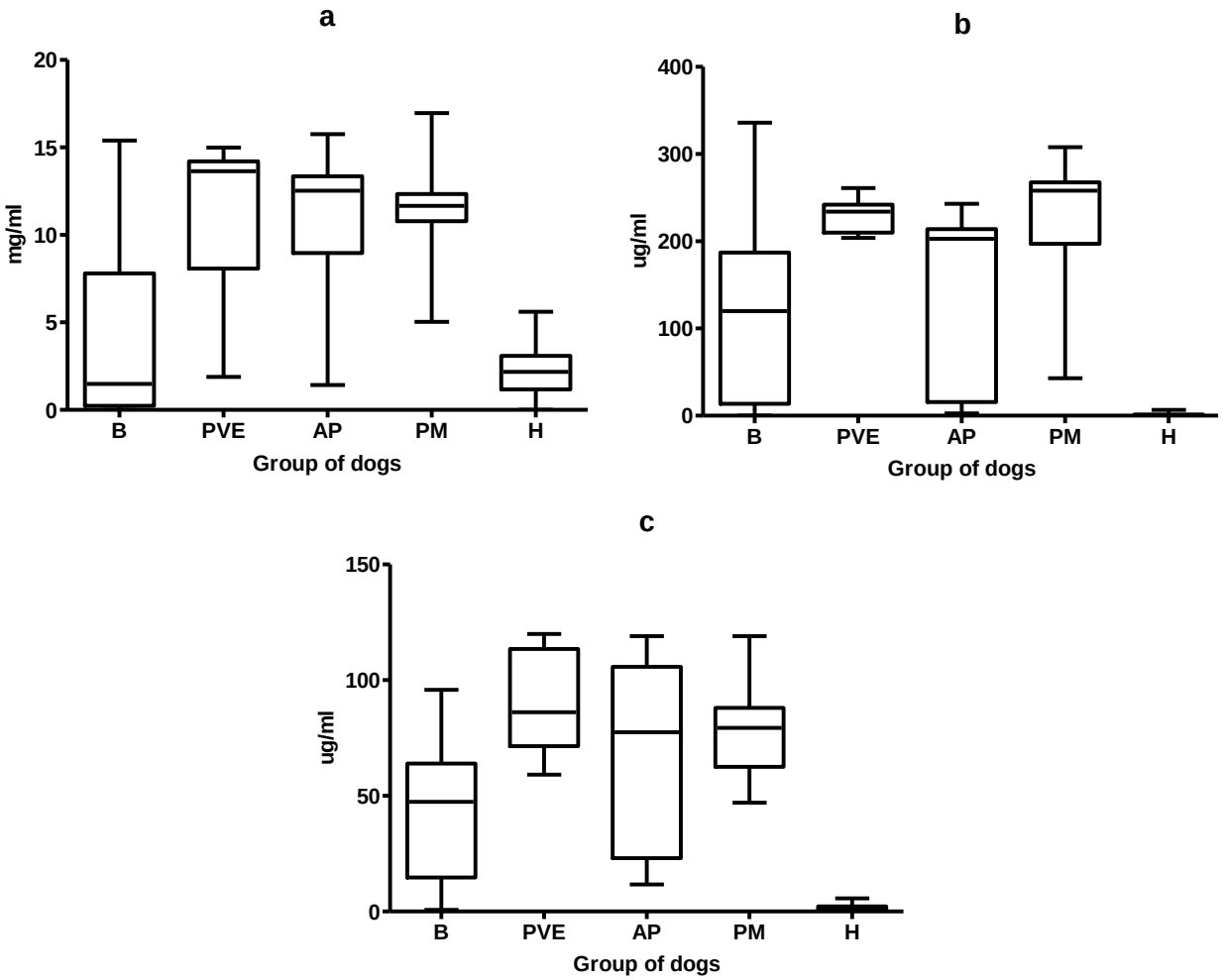

Fig. 1: Differences in the distribution of the concentrations of haptoglobin (a), serum amyloid A (b) and C-reactive protein (c) in dogs with various diseases (B - babesiosis, PVE - parvovirus enteritis, AP - acute pancreatitis, PM - pyometra) and clinical healthy dogs (H). The plots show the median (line within box), 25th and 75th percentiles (box), minimal and maximal values (whiskers)

Table 1: The concentrations of acute phase proteins in the evaluated groups of dogs (mean ± SD).

Parameter	Groups of dogs					*P* value
	B	PVE	AP	PM	H	
Hp (mg/ml)	3.78±4.71^{a}	11.23±4.28^{b}	11.13±3.64^{b}	11.28±2.49^{b}	2.25±1.64^{c}	<0.001
SAA (ug/ml)	122.0±111.5^{a}	227.7±18.1^{ab}	131.3±101.8^{a}	220.2±71.5^{b}	1.0±1.7^{c}	<0.001
CRP (ug/ml)	41.1±29.2^{a}	89.5±21.3^{b}	68.2±40.0^{ab}	76.9±17.5^{b}	1.79±1.61^{c}	<0.001

B - babesiosis, PVE - parvovirus enteritis, AP - acute pancreatitis, PM – pyometra, H - clinical healthy dogs; P value – significance of the differences; a,b,c - means with different superscripts in rows differ significantly (P<0.05).

CRP concentrations were in dogs with PVE accompanied by high mean Hp concentration, but the individual values were distributed in a wider range. The lower Hp concentrations in some dogs with parvoviral enteritis might be related to possible gastrointestinal hemorrhage or hemolysis present in these cases when Hp binds to free hemoglobin in the blood (Ulutas et al. 2005).

Acute pancreatitis is a severe disorder in dogs associated with sudden inflammation of the pancreas together with the adjunctive tissues to varying extents, frequently accompanied by a systemic inflammatory response or multiple organ failures ((Mansfield 2012; Sato et al. 2017). In our study, the dogs with acute pancreatitis had significantly higher Hp, SAA, and CRP values. The mean SAA concentration was approximately 130-fold higher and the CRP values more than 30-fold higher compared to healthy ones, but the magnitude of increase was lower than in dogs with parvoviral enteritis or pyometra. There are relatively few studies dealing with the evaluation of SAA concentrations in dogs with pancreatitis, because of the time-consuming enzyme-linked immunoassays for its determination compared to point-of-care CRP tests (Christensen et al. 2013). In the study conducted by Yoon et al. (2020) the concentrations of SAA showed in all evaluated dogs with acute pancreatitis an elevation of 50-fold, which was positively correlated with CRP concentrations. Similar to our results, Kim et al. (2019) found in dogs with acute pancreatitis approximately 30-fold higher CRP concentrations than in healthy dogs, which significantly decreased after the recommended treatment. Although in the aforementioned study the concentrations of Hp in canine pancreatitis have been found to negatively correlate with the concentrations of CRP and SAA, our study presented significantly higher Hp values compared to healthy animals. However, its individual values showed a wider range that might be

associated with different stages or severity of the disorder at the collection of specimens. Lazarov et al. (2011) and Georgieva et al. (2011) reported that the Hp values in experimentally induced pancreatitis in dogs increased slowly compared to the values of CRP, reaching peak values later. The values of inflammatory markers in the presented study were determined only at the initial examination of dogs. Further investigations during the treatment and according to the severity of disease may help to better understand the possible importance of these inflammatory markers to monitor the disease progress in dogs.

A typical inflammatory reaction characterized by elevated values of SAA, CRP, and Hp was also observed in our study in dogs with pyometra. The magnitude of increase was comparable to that found in dogs with parvoviral enteritis. Higher concentrations of the aforementioned proteins in dogs suffering from pyometra have been detected also by Yoon et al. (2021), but the differences between sick and healthy animals were less marked compared to our study (approximately 25-fold for CRP and 54-fold for SAA). Similar to our results, the aforementioned authors recorded a wider range of individual values suggesting differences in the reactivity of individual animals to the causative agent. Furthermore, the animals included into our study have been investigated at a different stage of the disease process which may explain the great variability among the measured acute phase protein concentrations. Jitpean et al. (2014) stated that SAA and CRP provide useful information in the diagnosis and prognosis of inflammatory states of the uterus. However, they are of varying importance. In the concentrations of these proteins, they observed significant differences between bitches with various types of pyometra. The SAA values were higher in bitches with septic pyometra than in bitches with non-septic pyometra (means 130.8 and 88.5mg/L, respectively). Significant differences in the concentrations of CRP between the groups of dogs were not observed. Furthermore, CRP, SAA, and Hp were found to be useful to distinguish infections with open cervix from that of closed cervix, with higher values in bitches with closed cervix pyometra (Dąbrowski et al. 2013). Dąbrowski et al. (2009) concluded that the inflammatory markers were found useful in bitches with surgically treated pyometra to monitor the postoperative period. The results observed in their study showed a repeated increase of CRP and SAA concentrations in bitches after ovariohysterectomy due to pyometra, while these complications were associated with infections caused by *Escherichia coli and Staphylococcus spp*. Furthermore, the high concentrations of Hp persisted throughout the whole observation.

In this study, infection with *Babesia canis* was not found to induce a strong acute phase response comparable to that observed in dogs with pyometra or parvoviral enteritis. Although the concentrations of SAA, CRP, as well as Hp in dogs suffering from babesiosis were significantly higher compared to healthy dogs, the magnitude of elevation was less pronounced than in other groups of sick animals. The results of the studies conducted by Matijatko et al. (2007) suggested that the natural *Babesia canis* infections were associated with strong inflammatory reactions with very high SAA values (approximately an 800-fold increase), while the values of CRP were approximately 30-fold higher. Their concentrations decreased daily after treatment and approached normal values by the eighth day suggesting that these inflammatory markers may be of importance to monitor the response to therapy. Elevated CRP values in naturally occurring *B. canis* infections have been found also by Barić Rafaj et al. (2013) presenting a mean CRP concentration of 154mgL, which remained significantly increased for 3 days after antiparasitic treatment. Higher CRP concentrations compared to our results were obtained also by Asawakam and Taweethavonsawat (2021), being in the range from 52.0 to 200.0mg/L (127.62mg/L on average). In addition, elevated production of fibrinogen and ceruloplasmin as part of inflammatory reactions was recorded in dogs infected with *B. canis*, while the concentrations of haptoglobin were lower compared to control dogs (Ulutas et al. 2005; Barić Rafaj et al. 2013). Although the concentrations of Hp in our study were significantly higher than those obtained in healthy dogs, the values were significantly lower compared to the other evaluated diseases probably reflecting intravascular hemolysis present in complicated cases (Zygner et al. 2011).

Conclusion

In conclusion, the data obtained in this study indicate marked differences in the activation of inflammatory responses to various canine diseases, expressed by differences in the values of major inflammatory markers among the evaluated diseases. Although higher concentrations compared to healthy dogs were obtained for SAA, CRP, as well as Hp, the magnitude of increase differed among the disease groups. Canine parvoviral enteritis and pyometra were found to evoke the most marked inflammatory response. In dogs with these diseases were recorded the highest mean concentrations of Hp, SAA, and CRP. On the other hand, canine babesiosis was associated with less marked alterations among the evaluated diseases of dogs. Furthermore, the obtained results suggest that the assessment of acute phase reactants during the diagnostic process as a single parameter is not possible, and should always be used in context with the interpretation of clinical findings and in combination with other laboratory parameters. Seeing that some inconsistent results exist, especially regarding the alterations of inflammatory proteins during the treatment process of various canine diseases, additional long-terming studies should be performed with a larger number of animals and repeated blood sampling to correctly explain the possible alterations.

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Author's contribution

Andrea Szarková: Investigation, Sample collection, Writing - original draft preparation. Csilla Tóthová: Conceptualization, Methodology, Formal analysis, Project administration, Writing - original draft preparation. Tatiana

Weissová: Investigation, Supervision. Branislav Lukáč: Investigation, Sample collection. Hana Turňa: Investigation, Sample collection. Lucia Kottferová: Investigation, Sample collection. Oskar Nagy: Conceptualization, Methodology, Formal analysis, Project administration, Data curation, Visualization, Supervision, Writing - review and editing. All authors have reviewed and approved the last submitted version.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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