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**RESEARCH ARTICLE**

# Serum C-Reactive Protein, Procalcitonin, and Ceruloplasmin Concentrations in Dogs with Naturally Infected Ehrlichiosis

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**ABSTRACT**

This study aimed to evaluate the concentrations of C-reactive protein (CRP), Procalcitonin (PCT), and ceruloplasmin (Cp), which are potential biochemical markers of the inflammatory process in dogs naturally infected with Ehrlichiosis. A total of 20 dogs, 8 clinically healthy (Healthy group) and 12 mono-infected with *Ehrlichia* spp. (Ehrlichia group) were included in the study. Dogs in the Ehrlichia group were selected from those showing clinical signs of active infection, and their diseases were diagnosed with commercial test kits. Serum CRP and PCT levels were analysed by commercially available test kits, and Cp concentration was determined by colourimetric methods. The CRP concentration in the Ehrlichia group was significantly higher compared to the healthy group. There was no significant difference between the groups in serum PCT and Cp concentrations. As a result, the increase in serum CRP concentration can be used for detecting inflammatory processes in dogs with Ehrlichiosis. In addition, this study showed that PCT and Cp concentrations are not clinically useful markers for determining inflammatory status in dogs with Ehrlichiosis.

**Keywords: Key Words:** C-Reactive Protein, Ceruloplasmin, Dog, Ehrlichiosis, Procalcitonin

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# Ehrlichiosis ile Doğal Enfekte Köpeklerde Serum C-Reaktive Protein, Prokalsitonin ve Seruloplazmin konsantrasyonları

**ÖZ**

Bu çalışma, Ehrlichiosis ile doğal enfekte köpeklerde inflamatuar sürecin potansiyel biyokimyasal belirteçlerinden olan C-reaktif protein (CRP), Prokalsitonin (PCT) ve seruloplazmin (Cp) konsantrasyonlarını değerlendirmeyi amaçladı. Çalışmaya, klinik olarak sağlıklı 8 (Sağlıklı grup) ve *Ehrlichia* spp. ile mono enfekte 12 (Ehrlichia grubu) olmak üzere toplam 20 köpek dahil edildi. Ehrlichia grubundaki köpekler, klinik olarak aktif enfeksiyon belirtileri gösteren köpekler arasından seçildi ve hastalıkları, ticari test kitleri ile teşhis edildi. Serum CRP ve PCT seviyeleri köpek spesifik ticari ELISA test kitleri ile analiz edildi ve Cp konsantrasyonu kolorimetrik yöntemle belirlendi. Ehrlichia grubundaki CRP konsantrasyonu, sağlıklı grupla karşılaştırıldığında anlamlı olarak daha yüksekti. Serum PCT ve Cp konsantrasyonlarında gruplar arasında anlamlı fark yoktu. Sonuç olarak, serum CRP konsantrasyonundaki artış, Ehrlichiosis'li köpeklerde inflamatuar süreçlerin saptanmasında kullanılabilir. Ek olarak bu çalışma, PCT ve Cp konsantrasyonlarının Ehrlichiosis'li köpeklerde inflamatuar durumu belirlemek için klinik olarak yararlı belirteçler olmadığını göstermiştir.

**Anahtar Kelimeler:** C-reaktif protein, Ehrlichiosis, köpek, prokalsitonin, seruloplazmin

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## INTRODUCTION

Vector-mediated bacteria and parasites are important pathogens of domestic dogs and potentially important to public health (Chomel 2011, Maggi ve Krämer 2019). *Ehrlichia canis* (*E. canis*), *Ehrlichia chaffeensis* (*E. chaffeensis*) and *Ehrlichia ewingii* (*E. ewingii*) are gram-negative obligate intracellular bacterias transmitted by ticks and cause Ehrlichiosis in dogs (Ansari-Mood et al. 2010, Fonseca et al. 2017). Canine Ehrlichiosis has a worldwide distribution. However, only *Ehrlichia canis* species that cause canine monocytic Ehrlichiosis (CME) have been isolated from dogs in Türkiye (Duzlu et al. 2014, Aktas and Özübek 2019, Ayan et al. 2020). The clinical manifestation of CME shows a wide distribution due to several factors, such as the agent's strain, the dog's breed, the concurrent diseases and the state of the dog's immune system (de Castro et al. 2004, Harrus and Waner 2011). The disease is clinically divided into acute, subclinical, and chronic stages (Harrus and Waner 2011, Mylonakis et al. 2019). The acute phase of the disease is characterised by fever, depression, lethargy, anorexia, lymphadenomegaly, splenomegaly, eye lesions, and hemorrhagic disorders. In the subclinical period of the disease, no clinical findings may occur. In the chronic phase of the disease, the symptoms are very similar to the findings in the acute phase, but sometimes they can be much more severe (Moonarmart et al. 2014, Bhadesiya and Raval 2015, Mylonakis et al. 2019).

Acute-phase proteins (APPs) are non-specific innate immune components potentially indicators of inflammation and tissue injury (Murata et al. 2004, Schmidt and Eckersall 2015). C-reactive protein (CRP) and ceruloplasmin (Cp) are positive APPs. In human and veterinary medicine, these non-specific markers can help diagnose, determine disease severity, and monitor response to treatment and prognosis in various diseases and conditions (Cray et al. 2009, Mylonakis et al. 2011, Schmidt and Eckersall 2015, Pardo-Marin et al. 2020). While CRP is important in protecting against infection, clearing damaged tissue, preventing auto-immunisation and regulating the inflammatory response (Waritani et al. 2020), Cp is an α-2 glycoprotein that carries copper and is essential for wound healing and protection. It protects cells and tissues against oxidant compounds (Cerón and Martínez-Subiela 2004).

Procalcitonin is a forerunner of calcitonin, a peptide (prohormone) released from parafollicular cells of the thyroid gland. Recently, PCT has been used in human medicine to diagnose bacterial infection as an acute-phase reactant (Goggs et al. 2018, Bassetti et al. 2019, Matur et al. 2021). PCT appears to be an earlier and better marker in sepsis and severe infections than inflammatory markers, for instance, CRP and white blood cell (WBC) count. It is also widely used to evaluate the efficacy of antibiotic therapy in humans (Schuetz et al. 2016). Procalcitonin rises markedly in two to four hours in severe systemic inflammation or bacterial infections and remains elevated until this pathological situation resolves. Therefore, PCT is important in rapidly diagnosing sepsis, minimising mortality, and reducing the redundant usage of antibiotics (Meisner 2015, Battaglia et al., 2020). There are a limited number of studies in dogs on serum procalcitonin levels, which are widely used in bacterial infections and sepsis in humans. With the increase in the number of dog-verified tests in recent years, the number of studies on procalcitonin is also increasing. Studies have focused especially on dogs with sepsis; significant differences were found between healthy dogs and dogs with sepsis (Yılmaz et al. 2008, Easley et al. 2020).

The CME caused by the Gram (-) bacterium *E. canis* causes a significant inflammatory response (Harrus and Waner 2011). However, there are limited studies on inflammatory and infection biomarkers in

dogs with Ehrlichiosis (Mylonakis et al. 2011, Karnezi et al. 2016, Matur et al. 2021, Singh et al. 2021). Therefore, this study aimed to evaluate serum CRP, PCT and Cp concentrations in dogs with naturally infected Ehrlichiosis and reveal their clinical availability.

## MATERIAL and METHODS

Ethical approval for the study was granted by The Animal Research Ethics Committee of the Aydın Adnan Menderes University (number 64583101/2022/007).

The study was conducted at Aydın Adnan Menderes University Faculty of Veterinary Medicine Animal Hospital. Twenty owned dogs, including 8 healthy and 12 dogs with Ehrlichiosis, were included in the study. The anamnesis, physical examination findings and laboratory results of all dogs were recorded.

The venous blood samples were taken from the cephalic vein into an anticoagulant (ethylenediaminetetraacetic acid) and clot activator tube. Complete blood counts (CBC) were performed with an automated blood analyser (Abacus Vet 5, Diatron MI LTD, Hungary) from blood samples with the anticoagulant. Serum was obtained from the samples collected in the clot activator tube. Blood samples taken into a clot activator tube were centrifuged at 3000 g for 10 minutes and separated serums. Some of the serum samples were used for vector-borne disease screening tests, and the remainder was stored at -20°C for CRP, Cp and PCT analysis.

Dogs with Ehrlichiosis were selected from dogs that showed clinical (such as fever, generalised lymphadenopathy, anorexia, splenomegaly, lethargy, petechiae, epistaxis, eye lesion) and laboratory findings (such as thrombocytopenia, anaemia) consistent with the disease. These dogs were simultaneously screened with the SNAP 4Dx Plus (IDEXX Laboratories, Inc., USA) assay kit for *E. canis*, *E. ewingii* (for *Ehrlichia* spp. 97.1% sensitivity and 95.3% specificity), *Borrelia burgdorferi* (*B. burgdorferi*), *Anaplasma phagocytophilum* (*A. phagocytophilum*), *Anaplasma platys* (*A. platys*) and *Dirofilaria immitis* (*D. immitis*). Dogs were also screened for Leishmaniasis with the commercial test kit SNAP Leishmania (IDEXX Laboratories, Inc., USA). In addition, blood smears were made from anticoagulant blood taken from dogs, and *Babesia* spp., *Hepatozoon* spp. and *Hemotropic Mycoplasmas* were examined. Only *Ehrlichia* spp. mono-infected dogs were included in the study. Dogs with concurrent disease, inflammatory conditions, and the use of any medication (such as antibiotics and anti-inflammatories) were excluded from the study.

Healthy dogs were selected from dogs brought in for annual routine control, vaccination and elective surgery (ovariohysterectomy or castration). According to clinical examination and laboratory findings (CBC and routine serum biochemistry), these dogs did not show any signs of disease. Also, blood smear, SNAP4DxPlus, and Snap Leishmania results were negative. Thus, these dogs were considered healthy and included in the study as the healthy group.

Procalcitonin (Sun Red Bio. Shanghai, China) and CRP concentrations (Solid phase sandwich ELISA kit Tridelta Development LTD, Ireland) from serum samples were determined with canine-specific solid sandwich ELISA commercial test kits. Serum Cp concentrations were measured spectrophotometrically in a spectrophotometer device (Shimadzu UV-1601, Japan) using the method reported by Sunderman and Numato (1970).

Numerical data obtained from *Ehrlichia* spp. seropositive and healthy dogs were analysed using the SPSS package program 19.0 (SPSS, Armonk, NY: IBM Corp). Although PCT and WBC showed normal distribution according to the Shapiro-Wilk normality

test results, non-parametric tests were used for all parameters considering the sample size. The median values of WBC, CRP, PCT and Cp were compared with the non-parametric Mann-Whitney U test. For all assessments, p-value less than 0.05 suggested that the difference was statistically significant.

## RESULTS

Based on history, physical examination and laboratory results, eight dogs were healthy (Healthy group), and 12 were *Ehrlichia spp.* seropositive (Ehrlichia group). The mean age of the healthy group was 3.25 ± 1.04 years (between 1 and 5 years), and there were five male dogs and three female dogs. Several breeds were included in the healthy group: Golden Retriever (n = 3), Maltese Terrier (n = 2), mixed breed (n = 2), and Dobermann Pinscher (n = 1).

The mean age of the Ehrlichia group was 2.67 ± 1.17 years old. Eight of these dogs were male, and 4 of them were female. The most common breeds were Golden Retriever (n = 3) and Crossbreed (n = 3), followed by Maltese Terrier (n = 2), Anatolian shepherd dog (n = 9), Pekingese (n = 1) and Pug (n = 1). In this group, all dogs had at least two or three clinical and laboratory findings of active disease. These clinical and haematological findings are presented in Table 1.

The mean serum CRP concentration of the Ehrlichia group was significantly (p= 0.002) higher than the healthy group (Figure 1B). There was no statistical significance between the groups in WBC counts (p= 0.217), serum PCT (p= 0.939) and Cp (p= 0.615) concentrations (Figure 1A, C, D).

**Table 1.** Clinical and haematological findings in dogs in the Ehrlichia group.

| Clinical abnormality | n (%) | Haematological abnormality | n (%) |
|---|---|---|---|
| **Depression or lethargy** | 12 (100) | **Thrombocytopenia** | 10 (83.33) |
| **Anorexia** | 12 (100) | **Anaemia** | 8 (66.67) |
| **Lymphadenomegaly** | 10 (83.33) | **Leucocytosis** | 3 (25) |
| **Fever (>39.5$^0$C)** | 9 (75) | **Leucopenia** | 3 (25) |
| **Mucosal pallor** | 8 (66.67) | **Lymphopenia** | 3 (25) |
| **Tick infestation** | 7 (58.33) | | |
| **Ocular lesion** | 6 (50) | | |
| **Bleeding tendency** | 1 (8.33) | | |

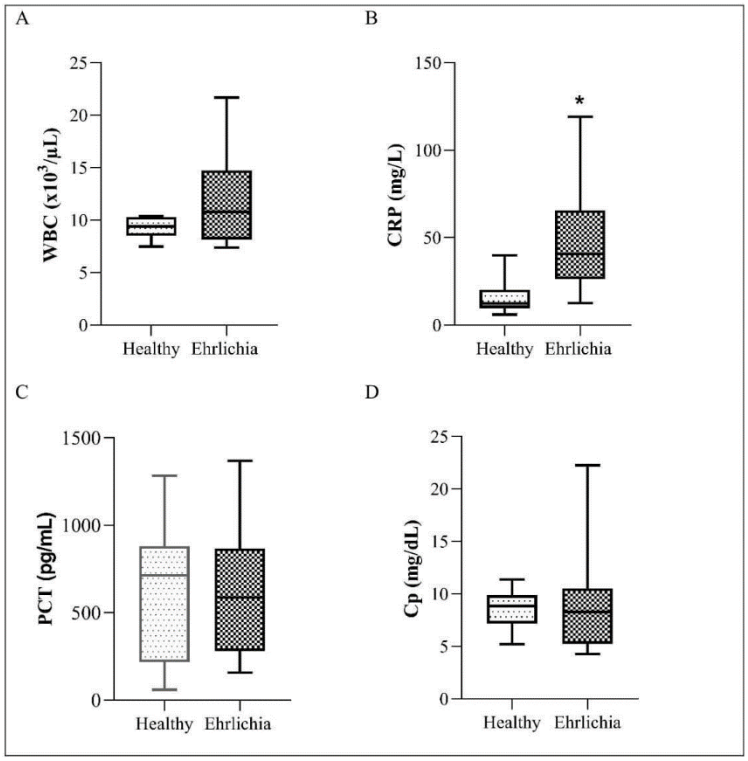


**Figure 1.** Box and whisker plot showing (A) WBC count, (B) CRP, (C) PCT and (D) Cp concentration in healthy and Ehrlichia groups. Abbreviation: Cp: ceruloplasmin, CRP: C-Reactive Protein, PCT: Procalcitonin, WBC: White blood cells, *: statistically significant differences at $p< 0.05$.

## DISCUSSION

Canine Ehrlichiosis is a worldwide vector-borne disease caused by the gram (-) bacteria *Ehrlichia* species. It is reported that CME causes a marked inflammatory response (Harrus and Waner 2011, Karnezi et al. 2016, Singh et al. 2021). Thus, the current study aimed to evaluate the concentration and clinical usability of inflammatory markers such as CRP, PCT and Cp in dogs with Ehrlichiosis. This study found that the serum CRP concentration is statistically significantly higher in the Ehrlichia group than in the healthy group ($p= 0.002$). Nevertheless, there was no statistical difference between the groups in serum PCT and Cp concentrations ($p> 0.05$).

In dogs, CRP is considered the major acute-phase protein and serum/plasma CRP concentration is increased in various inflammatory diseases (Nakamura et al. 2008, Asawakarn et al. 2021). Some researcher reported that CRP concentration (Rikihisa et al. 1994, Nakamura et al. 2008, Mylonakis et al. 2011, Munhoz et al. 2012, Asawapattanakul et al. 2021, Singh et al. 2021, Jaheen et al. 2022). Rikihisa et al. (1994) and Asawapattanakul et al. (2021) reported that the serum CRP concentrations in dogs with naturally infected *E. canis* were higher than in healthy dogs. Mylonakis et al. (2011) have shown that the CRP concentrations in dogs with and without myelosuppression were significantly higher than in healthy dogs. They have also correlated myelosuppression with chronic CME and reported that the increase in CRP concentration in these dogs was much higher than in dogs with acute disease. The study mentioned above has also noted that using CRP and some APPs with other tests may help assess the clinical severity of CME. Also, one experimental study showed that CRP concentration increases significantly between 4-16 days after

experimental infection and reaches peak points between 1-6 weeks (Shimada et al. 2002). Similar to the studies performed in experimental and naturally infected dogs with Ehrlichiosis, the serum CRP concentration in the Ehrlichia group was statistically significantly higher than the healthy group in our study. It is known that CME causes infiltration of mononuclear cells, macrophages and plasma cells in the subendothelial layer and perivascular region of many organs in dogs, leading to a marked inflammatory reaction (Abiramalatha et al. 2018, Singh et al. 2021). The increased serum CRP concentration in the Ehrlichia group in this study may also be associated with the abovementioned inflammatory reaction. In the studies conducted, the relationship between the severity of the disease and the CRP concentration was evaluated according to the presence of myelosuppression (Mylonakis et al. 2011). Since no dogs with myelosuppression were in the Ehrlichia group, this study could not evaluate the correlation between disease severity and CRP.

Increased PCT in bacterial infections has been reported in human and veterinary medicine (Reitman et al. 2012, Liu et al. 2015, Cho et al. 2021). This increase is more sensitive and specific than other inflammatory markers, such as an APP, in differentiating bacterial infections from non-infectious diseases (Schuetz et al. 2012, Cho et al. 2021). There are limited studies of PCT in dogs infected with the gram-negative bacteria *Ehrlichia* spp. (Matur et al. 2021, Jaheen et al. 2022). Matur et al. (2021) showed that the PCT concentration was not statistically significant between dogs with Ehrlichiosis and the control group. In contrast to this study, Jaheen et al. (2022) determined that the PCT concentration in dogs with Ehrlichiosis was significantly higher than in the control group. They also reported that PCT as an inflammatory biomarker was more diagnostic than CRP and leukocyte count in dogs with Ehrlichiosis. In the bloodstream, PCT has a half-life of about 25-30 hours (Nakamura et al. 2013, Matur et al. 2021). Different conditions (duration and severity) associated with diseases affect procalcitonin levels (Schuetz et al. 2012, Seo et al. 2015, Sitar et al. 2019, Cho et al. 2021). In this study, no distinction was made between acute and chronic diseases in the Ehrlichia group. Only dogs with clinical and laboratory findings of active disease (non-subclinical) were included in the study. Therefore, the disagreement between studies may be related to the stage of the disease. In addition, the severity of the disease, study population, bacterial load and sepsis may also have contributed to this difference.

To our knowledge, there is only one study of Cp concentration in dogs with Ehrlichiosis. That study was also carried out experimentally. Munhoz et al. (2012) indicate that the ceruloplasmin level increased gradually on the 3rd day after inoculation, peaked on the 6th and 12th days, and decreased substantially until the 30th. Also, Cp concentrations on the 6th and 12th days were significantly higher than in the control group. They reported that Cp levels were elevated before clinical signs and laboratory findings and could be an early indicator of the onset of inflammatory processes. Our study showed no statistically significant difference between serum Cp concentrations of the healthy and Ehrlichia groups. In contrast to the above study, this study included naturally infected dogs, and all dogs had clinical and laboratory findings. In CME, mild clinical and laboratory findings appear 8-20 days after exposure (Rikihisa et al. 1994). Therefore, the difference between the results of the studies may be related to dogs being in different periods of the disease and the study design.

There are several limitations to this study. First, the relatively low number of dogs included in the study. Many dogs with Ehrlichiosis were excluded from the study because of concomitant diseases (e.g. leishmaniasis, dirofilariasis and hemotropic mycoplasmas). Second, the diagnosis of Ehrlichiosis in dogs was made only with point-of-care test kits.

However, these tests had 97.1% sensitivity and 95.3% specificity for *Ehrlichia* spp. In addition, these dogs had clinical and laboratory findings related to active disease. Third, CRP, PCT and Cp concentrations were analysed from blood taken from dogs at the initial examination and are based on a single measurement.

## CONCLUSION

In conclusion, our data suggest that serum CRP concentration is increased in dogs naturally infected with *Ehrlichia* spp., and serum CRP concentration could be used as a helpful biomarker for determining the inflammatory processes in dogs with Ehrlichiosis. However, more detailed studies are needed to assess serum PCT and Cp concentrations and reveal their clinical roles in dogs infected with *Ehrlichia* spp.

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