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Original article

Investigation of acute-phase protein concentrations in healthy and various diseased cats

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Abstract

This study aimed to evaluate the concentrations of α1-acid glycoprotein (AGP), haptoglobin (Hp), serum amyloid-A (SAA) and ceruloplasmin (Cp) in healthy and various diseased cats and establish reference intervals (RIs) for these acute phase proteins (APPs) in healthy cats. The animal material of the study consisted of 40 healthy cats and 152 cats with various diseases. The serum APPs in the diseased group were higher than those in the healthy group, and age affected Cp concentration in healthy cats. Also, the systemic inflammatory response syndrome (SIRS) positive (+) group had significantly higher AGP concentrations than the SIRS negative (-) group. In conclusion, this study contributes to the limited number of studies on RIs in serum APPs concentrations in healthy cats. The results of this study suggest that APPs are valuable diagnostic tools for identifying the inflammatory processes of various diseases, and AGP concentration could help determine the severity of the inflammatory condition.

Key words: acute phase protein, AGP, cat, Cp, Hp, SAA, SIRS

Introduction

Recently there have been studies investigating novel biomarkers capable of early clinical diagnosis and monitorisation of inflammatory conditions existing as several diseases. Early clinical diagnosis is important not only for humans but also for animals. Serum acute phase proteins (APPs) are considered highly sensitive biomarkers of inflammation that can be used to diagnose, manage, and prognosis various clinical conditions (Ceron et al. 2005, Eckersall et al. 2010, Silvestre-Ferreira et al. 2017). APPs are plasma proteins synthesised in the liver as part of the acute phase response (APR). APR is a nonspecific and systemic reaction to local or systemic disturbances induced by trauma, infection, stress, surgery, neoplasia or inflammation (Gruys et al. 2004, Kann et al. 2012, Rosa and Mestrinho 2019, Yuki et al. 2020).

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Synthesis, secretion and excretion of APPs differ according to animal species. The magnitude and duration of the increase vary in different species, and each has its major, moderate and minor APPs (Paltrinieri 2008, Glück et al. 2021). Major APPs increase a few hours after the inflammatory stimulus and remain elevated if the inflammation persists. The rise in moderate APPs is slower and returns to normal values with a gradual decrease (Ceron et al. 2005). Serum amyloid A (SAA) and alpha-1-acid glycoprotein (AGP) are major positive APPs, haptoglobin (Hp) is a moderate positive APP and ceruloplasmin (Cp) is a considered minor positive APP in cats (Paltrinieri 2008, Hazuchova et al. 2017, Rosa and Mestrinho 2019). Most studies in cats have concentrated on particularly SAA, AGP and Hp (Paltrinieri 2008). These three APPs are found to be increased in a variety of pathological conditions such as infectious diseases (e.g. *Dirofilaria immitis*, *Feline infectious peritonitis*), traumas, tumours (e.g. lymphoma), inflammatory diseases (e.g. pyometra, pancreatitis), endocrine disease (e.g. diabetes mellitus, hyperthyroid), heart diseases and hospitalisation (Eckersall and Bell 2010, Kann et al. 2012, Rosa and Mestrinho 2019).

There are limited data on APP concentrations in healthy cats, and to our knowledge, only one study determines the reference range (Duthie et al. 1997). Also, the results of studies reporting some APP concentrations in healthy cats show individual variations (Kajikawa et al. 1999, Giordano et al. 2004, Kann et al. 2012, Yuki et al. 2020). Thus, this study aimed to evaluate the serum concentrations of four positive APPs (AGP, Hp, SAA and Cp) in healthy and various diseased cats, establish reference intervals (RI) for these APPs concentrations in healthy cats, and determine the effect of health conditions, gender, and age on measured APPs concentrations.

Materials and Methods

Animals and inclusion criteria

This prospective study was conducted from 2013 through 2015 at the Aydın Adnan Menderes University Veterinary Teaching Hospital. One hundred and ninety-two owned cats of different gender, breeds, and ages were enrolled in this study. The cats were admitted to the hospital for vaccination, general control and clinical examination. All cat's signalment, medical histories, and physical examination findings were recorded. Cats were divided into healthy and diseased groups. Based on history, physical examination and laboratory results, 40 cats were considered healthy (healthy group), and 152 were considered diseased (diseased group). The healthy group were divided into subgroups according to gender and age. Twenty cats were female (female group), and 20 were male (male group). When healthy cats were evaluated according to their age, 14 were 0-6 months old (0-6 months group), 14 were 1-5 years old (1-5 years old group), and 12 were >5 years old (>5 years old group). Cats with various diseases were also classified according to the duration of illness and the presence of at least two or more of the systemic inflammatory response syndrome (SIRS) criteria (Brady et al. 2000). Regarding the disease duration, 65 cats had acute (acute group), and 87 had chronic (chronic group) disease. SIRS criteria included abnormal rectal temperature (≥39.7°C or ≤37.8°C), a heart rate (≥225 beats/min or ≤ 140 beats/min), a respiratory rate (≥40 breaths per min) and a white blood cell count (≥19.500/µl or ≤5000/µl). According to the SIRS criteria, 75 cats were SIRS positive (+), and 77 were SIRS negative (-). Cats were excluded from the study if they had recently taken any medication. Also, the study did not include cats with hemolysed and lipemic samples.

Laboratory analysis

Blood samples were taken from the *vena cephalica antebrachii* into the tubes with and without an anti-coagulant (K3-EDTA). Haematological analyses were performed using the Abacus Junior Vet haematology cell counter (Diatron MI Ltd, Hungary). Blood samples taken into without anti-coagulant tubes were centrifuged at 3000 g for 10 minutes, and the serum was separated. Routine serum biochemistry was measured using commercial test kits (Archem Diagnostic, Turkey) by autoanalyser (Sinnowa D 280, China). *FIV* antibodies, *Feline leukaemia virus (FeLV)* antigen and *FCoV* antibodies were tested with commercial immuno-chromatographic test kits (Witness, Zoetis, USA). Serum samples were stored at - 20°C until analysis for APPs. Serum AGP (Kamiya Biomedical Company. K-ASSAY, Seattle, USA), Hp (Tridelta Development LTD. Ireland) and SAA (Solid-phase sandwich ELISA kit Tridelta Development LTD. Ireland) concentrations were analysed using specific commercial kits according to the instruction manual. Serum Cp concentrations were measured on a spectrophotometer (Shimatzu UV1601, Japan) using the method reported by Sunderman and Numato (1970).

Statistical analysis

Reference intervals for healthy cats were analysed according to the American Society for Veterinary Clinical Pathology reference intervals guidelines (Friedrichs et al. 2012) using the Reference Value Advisor V2.1.

Table 1. Reference intervals of serum α1-acid glycoprotein, haptoglobin, serum amyloid-A, and ceruloplasmin in healthy cats, and serum concentrations of these acute phase proteins in diseased cats.

	Healthy cats	Diseased cats	p
N	40	152	
WBC (x10³/μL)	14.65 ± 4.92	21.00 ± 13.52	p<0.01
AGP (μg/mL)	616.01± 134.91	764.81 ± 141.18	
Median (IQR)	656.88 (602.22-695.17)	813.27 (667.90-889.75)	
Min-Max	172.53-748.32	299.60-972.80	
LRL (90% CI)	172.53-236.70	-	p<0.001
URL (90% CI)	712.68-748.32	-	
RI	381.20-776.70	-	
Hp (mg/mL)	2.7±1	3.42 ± 1.91	
Median (IQR)	2.6 (2.18-3.38)	3.14 (2.56-3.95)	
Min-Max	0.29-5.81	0.10-15.40	
LRL (90% CI)	0.3-1.5	-	p<0.01
URL (90% CI)	4.0-5.8	-	
RI	0.3-5.8	-	
SAA (μg/mL)	1.40 ± 1.10	11.45 ± 18.97	
Median (IQR)	1.40 (0.89-1.88)	2.96 (1.29-8.10)	
Min-Max	0-4.91	0-70.08	
LRL (90% CI)	0	-	p<0.001
URL (90% CI)	3.4-4.9	-	
RI	0-4.9	-	
Cp (mg/dL)	23.60 ± 12.50	32.82 ± 21.11	
Median (IQR)	21.10 (17.71-34.38)	29.74 (19.85-42.14)	
Min-Max	0.23-54.27	0.47-138.17	
LRL (90% CI)	0.2-8.5	-	p<0.01
URL (90% CI)	47.2-54.3	-	
RI	0.3-54.2	-	

Abbreviations: AGP: alpha 1-acid glycoprotein, CI: confidence interval, Cp: ceruloplasmin, Hp: Haptoglobin, IQR: interquartile range, LRL: lower reference limit, Min-Max: minimum-maximum, SAA: serum amyloid A, URL: upper reference limit.

by non-parametric methods (Geffré et al. 2011). RI with 90 % confidence intervals (CI) of the limits was determined using a bootstrap method. Statistical analysis was performed using SPSS version 19.0 for Windows (SPSS, Armonk, NY: IBM Corp). The Median, mean ($\bar{X}$), standard deviation (SD), interquartile range (IQR), and minimum-maximum (min-max) values of the data were determined. The distribution of numerical data was evaluated using the Shapiro-Wilk tests. One-way analysis of variance (ANOVA) was used to compare the normally distributed parameters. The transformation was applied to the data without normal distribution. The Kruskal-Wallis test compared the median values that did not provide normal distribution after transformation. Post-hoc Tukey test was used to investigate the differences between groups. Differences in $p<0.05$ value were considered statistically significant.

Results

Ethical Approval

The Animal Research Ethics Committee of the Aydın Adnan Menders University reviewed and approved all study procedures under protocol number B.30.2.ADÜ.0.00.00.00/050.04/2012/034**.**

Healthy cats

Descriptive statistics (mean, SD, median, IQR, minimum, maximum) of healthy and diseased cats are reported in Table 1. The reference intervals of APPs with lower and upper limits (90% CI) in healthy cats are also shown in Table 1.

Effects of gender and age

Serum AGP, Hp, SAA and Cp concentrations did not differ significantly between the gender groups ($p<0.05$ for all variables). While age affected serum Cp concentration ($p>0.05$), it had no significant effect

Table 2. Serum α1-acid glycoprotein, haptoglobin, serum amyloid-A, and ceruloplasmin concentrations of cats with various diseases and their statistical significance compared to the healthy group.

	N	AGP (µg/mL)	Hp (mg/mL)	SAA (µg/mL)	Cp (mg/dL)
Gastroenteritis	17	870.85 (812.11-918.07)**	2.76 (2.21-3.42)	3.25 (2.06-14.73)**	36.74 (25.71-43.25)**
URTD	16	875.90 (841.74-903.60)**	3.41 2.39-4.34)*	3.85 (1.17-5.19)*	45.15 (24.11-59.31)**
Coccidiosis	12	895.13 (833.18-925.19)**	3.39 (2.57-4.21)*	6.30 (2.57-31.60)**	33.28 (21.69-45.56)*
FIV	11	683.90 (676.40-703.87)*	3.11 (2.56-3.46)	1.91 (0.83-3.12)	32.23 (17.06-52.14)
Gingivostomatitis	11	874.42 (860.72-900.85)**	3.04 (2.64-3.87)*	1.30 (0.78-3.47)	34.84 (29.39-40.29)*
Constipation	10	864.47 (785.61-904.93)**	3.56 (2.73-4.20)*	2.25 (0.93-33.91)*	25.00 (13.39-40.47)
LRTD	9	861.52 (823.03-939.05)**	3.80 (2.68-4.50)*	3.20 (2.52-5.84)**	33.89 (26.54-52.61)*
LUTD	9	663.80 (596.82-674.05)	2.72 (2.26-3.38)	1.99 (0.40-30.22)	20.86 (15.64-32.82)
Cholangiohepatitis	9	680.43 (651.60-711.74)	3.08 (1.58-4.99)	3.43 (0.58-28.23)	28.44 (15.40-44.67)*
M. haemofelis	8	706.57 (695.65-713.23)**	1.53 (0.63-2.57)*	4.68 (0.66-22.19)*	23.10 (11.85-32.94)
FCoV	7	661.77 (531.80-683.95)	3.12 (2.73-3.46)	3.42 (1.60-13.84)*	27.49 (16.59-42.19)
Neoplasia	7	652.15 (635.78-674.74)	2.88 (2.44-3.47)	7.24 (0.61-54.91)*	40.29 (19.43-48.59)
Renal disease	7	668.11 (569.77-902.71)	3.31 (1.38-3.95)	4.21 (2.64-63.19)*	18.25 (11.38-35.31)
Extremity fractures	6	884.52 (829.13-923.61)**	3.06 (2.68-3.76)	3.31 (1.37-23.07)*	31.28 (20.32-53.15)
Dermatitis	5	667.84 (525.56-692.91)	2.94 (1.84-3.36)	0 (0-18.70)	21.80 (18.96-30.45)
Diabetes mellitus	5	602.12 (558.51-636.88)	6.86 (4.45-11.01)*	3.40 (1.60-23.98)**	21.33 (9.72-33.32)
H. diaphragmatica	3	866.76±36.97	3.42±1.93	1.89±1.64	35.47±29.38

Abbreviation: URTD, upper respiratory tract disease; *FIV*, *Feline immunodeficiency virus*; LRTD, lower respiratory tract disease; LUTD, lower urinary tract disease; *M. Haemofelis*, *Mycoplasma haemofelis*; *FcoV*, *Feline coronavirus*; H. diaphragmatica, hernia diaphragmatica.* $p<0.05$, ** $p<0.001$.

on the other three APPs concentrations ($p<0.05$ for all variables). Serum Cp concentration was significantly higher in 1-5 years old cats (30.92±9.53 mg/dL) compared to 0-6 months old (18.01±14.32 mg/dL) and >5-year-old cats (21.43±9.55 mg/dL) animals.

Diseased cats

The median WBC counts, serum AGP, Hp, SAA and Cp concentrations were significantly higher in diseased cats than in the healthy cats ($p<0.01$, $p<0.001$, $p<0.01$, $p<0.001$ and $p<0.01$, respectively) (Table 1).

The diseased group included cats with gastroenteritis (n=17), upper respiratory tract disease (n=16), coccidiosis (n=12), *Feline immunodeficiency virus (FIV)* (n=11), gingivostomatitis (n=11), constipation (n=10), lower urinary tract disease (n=9), lower respiratory tract disease (n=9), cholangiohepatitis (n=9), *Mycoplasma haemofelis* (*M. haemofelis*) (n=8), *Feline coronavirus (FCoV)* (n=7), neoplasia (n=7), renal disease (n=7), extremity fractures (n=6), dermatitis (n=5), diabetes mellitus (n=5), hernia diaphragmatica (H. diapragmatica) (n=3).

Serum concentrations of AGP, Hp, SAA and Cp of the cats with various diseases and statistical significance compared to the healthy group are presented in Table 2 (shown as median with IQR). Since the numbers of cats with H. diaphragmatica in the disease group were too low to be evaluated statistically, they were not considered as a separate disease group. Therefore, their values are given as means (±SD) in Table 2, unlike other disease groups.

Changes depending on the duration of the disease

Compared to healthy cats, serum AGP ($p<0.001$) and SAA ($p<0.01$) concentrations were significantly higher in the acute and chronic groups (Fig. 1). Nevertheless, there was no statistical significance between serum APPs concentrations in the acute and chronic groups ($p>0.05$).

Changes according to inflammatory status

SIRS (+) and SIRS (-) cats had higher serum AGP ($p<0.001$ for two groups) and SAA ($p<0.05$ for two groups) concentrations compared to healthy cats (Fig. 2). In addition, serum Cp concentrations in SIRS (+) cats were higher than in healthy cats ($p<0.05$). There was a significant difference in serum AGP concentra-

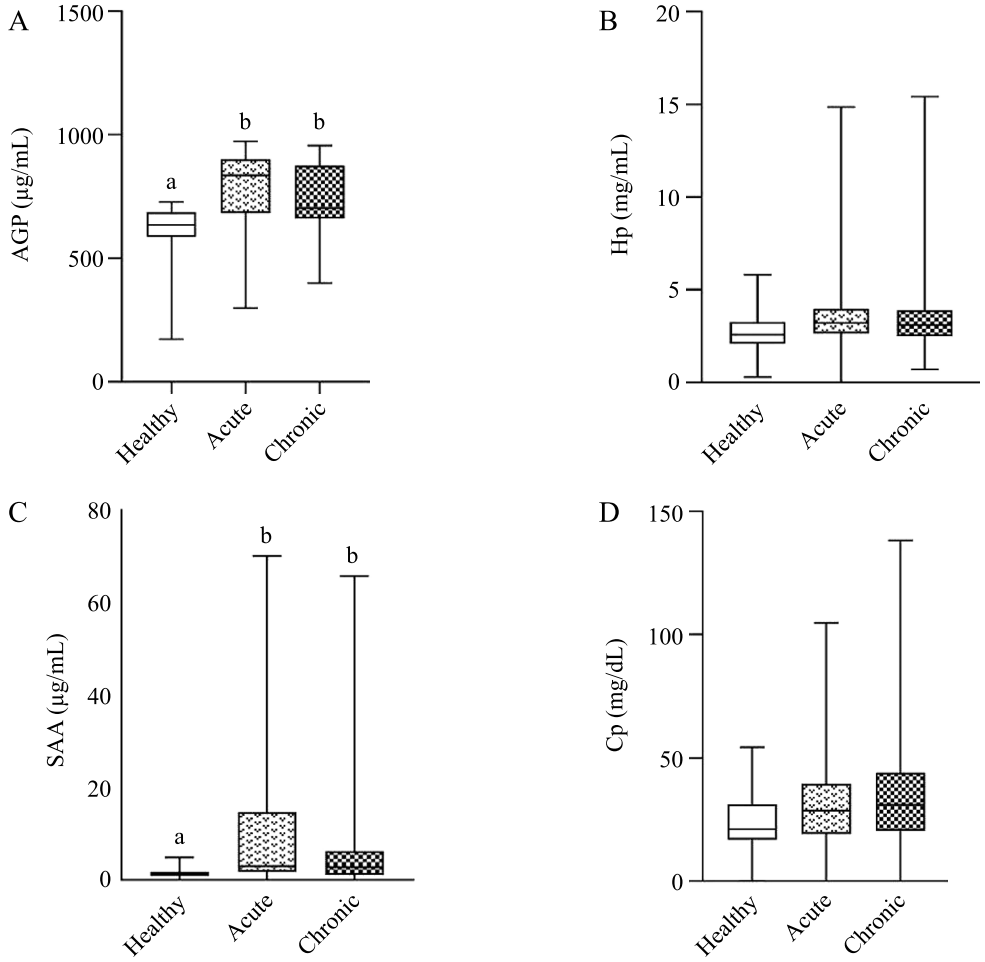

Fig. 1. Serum (A) α1-acid glycoprotein, (B) haptoglobin, (C) serum amyloid-A and (D) ceruloplasmin concentrations in healthy, acute and chronic groups. Different letters indicate statistical significance ($p<0.05$).

tion between SIRS (+) and SIRS (-) cats ($p<0.001$). There were no statistically significant differences between the two groups in serum Hp, SAA and Cp concentrations ($p>0.05$).

Discussion

Our study aimed to evaluate four positive APPs (AGP, Hp, SAA and Cp) in healthy and various diseased cats, establish reference intervals for these APPs concentrations in healthy cats, and determine the effect of health conditions, gender, and age on measured APPs concentrations.

Reference intervals used in evaluating laboratory results allow separating sick individuals from the healthy population. The variety and interpretation of tests increase the importance of RI (Kann et al. 2012). To our knowledge, only one study has established a reference range for APPs concentrations in healthy cats. This study is limited to only AGP (100-480 µg/mL) and Hp (0.04-3.84 mg/mL) concentrations (Duthie et al. 1997). However, there are different studies on APPs concentrations in healthy cats. These studies show individual differences (Kann et al. 2012, Yuki et al. 2020, Love et al. 2021). In this study, the reference intervals of serum AGP, Hp, AGP and Cp concentrations in healthy cats were 381.17-776.74 µg/mL, 0.3-5.8 mg/mL, 0-4.9 µg/mL and 0.3-54.2 mg/dL, respectively. The reference intervals of the AGP and Hp concentrations detected in this study (Table 1) differed from those determined by Duthie et al. (1997). There were also differences between mean/median serum concentrations of AGP, Hp, SAA, and Cp in healthy cats revealed in this study (Table 1) and different other studies (Andrews et al. 1994, Kajikawa et al. 1999, Giordano et al. 2004, Kann et al. 2012, Love et al. 2021). It is thought that the differences in APPs concentrations reported in healthy cats in the present and previous studies may be due to the use of different methods, the characteristics of the antibodies used, and the lack of suitable materials for standardisation of the tests, as reported by Kann et al. (2012).

Limited studies in healthy cats have evaluated the relationship between age and serum APPs concentra-

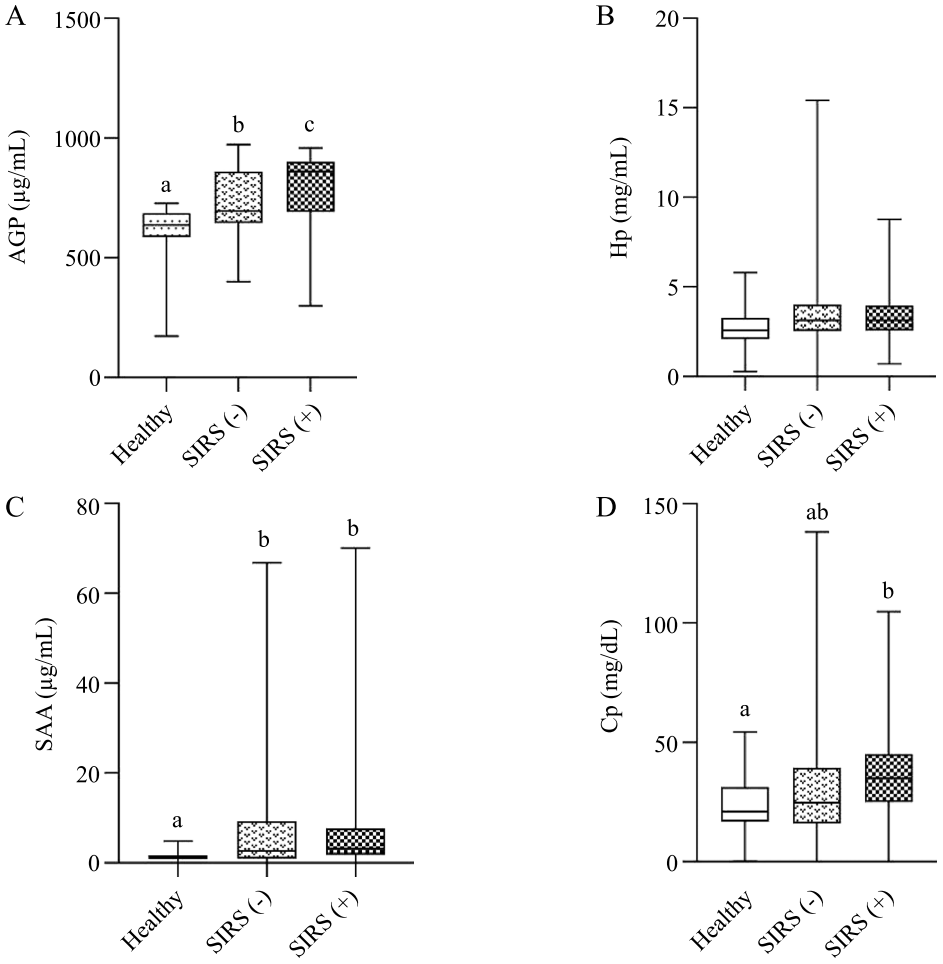

Fig. 2. Serum (A) α1-acid glycoprotein, (B) haptoglobin, (C) serum amyloid-A and (D) ceruloplasmin concentrations in healthy, SIRS (+) and SIRS (-) groups. Different letters indicate statistical significance ($p<0.05$).

tions (Campbell et al. 2004, Kann et al. 2012, Coşkun et al. 2021). While some researchers (Campbell et al. 2004, Yuki et al. 2020) reported no relationship between age and serum APPs concentrations, others (Kann et al. 2012, Coşkun et al. 2021) determined a relationship between age and some APPs concentrations. Kann et al. (2012) reported that the SAA concentration was higher in older cats. It is emphasised that this situation may be associated with a higher risk of subclinical infection in the older animals. Coskun et al. (2021) reported that the plasma AGP concentration in cats under one year old was significantly higher than in cats aged 2-2.5 years; they did not explain the reason for this difference. No relationship was found between age and serum AGP, Hp and SAA values in the present study. However, serum Cp concentration was significantly higher in cats aged 1-5 years than in the other age groups ($p<0.05$). In the present study, the age-related change in Cp concentration may be related to the adaptation of the organism to free radical activation and peroxidation processes, as reported by some authors (Murata et al. 2004, Kim 2008).

Many feline APP studies (Paltrinieri 2008, Troìa et al. 2017, Rosa and Mestrinho 2019) have been focused on AGP, SAA and Hp, and there are few studies of Cp (Silvestre-Ferreira et al. 2017, Liu et al. 2020). Most of these studies reported that serum/plasma APPs concentrations increase in various pathophysiological conditions such as inflammatory and infectious diseases, endocrinological disorders, neoplasms, trauma, hospitalisation, surgical intervention and renal failure in cats (Paltrinieri 2008, Kann et al. 2012, Troìa et al. 2017, Rosa and Mestrinho 2019). In the present study, serum APPs concentrations of diseased cats were significantly higher than in healthy cats (Table 1). These results are similar to those obtained in previous studies suggesting that the condition is associated with APR during illness and that APPs may be a useful biomarker in various diseases and disorders (Kann et al. 2012, Rosa and Mestrinho 2019). Furthermore, the concentration of SAA in 11, serum AGP in 9, serum Hp in 6 and serum Cp in 6 of 16 disease groups was significantly higher than found in the healthy cats, and serum Hp concentration was lower than in the healthy cats in one

disease group (Table 2). This result suggests that AGP and SAA, the major APPs in cats, may be considered safer biomarkers than other APPs in identifying inflammatory states in different diseases.

Increased concentrations of APPs have been reported in various acute and chronic inflammatory diseases (Petersen et al. 2004, Vilhena et al. 2018, Mestrinho et al. 2020). While the acute inflammatory process is generally reversible, the prognosis of chronic inflammation is poor. Therefore, it is clinically significant to distinguish between these two disease stages. Concentrations of APPs usually reach their maximum blood concentration within 24-48 hours following APR, and their concentrations decline, coinciding with recovery from infection or inflammation. However, after repeated stimulation, APR can become chronic. It has also been reported that positive APPs concentrations remain higher than normal values during chronic inflammation or infection and can be used for diagnostic purposes (Gruys et al. 2005, Jain et al. 2011). However, this elevation is higher in the acute stage of inflammation or infection than in the chronic stage. Although some researchers (Alsemgeest et al. 1994, Horadagoda et al. 1999) reported that APPs could be used as a marker to differentiate acute and chronic infections, no statistical significance was determined between acute and chronic groups in the present study (Fig. 1). However, serum AGP and SAA concentrations found in the acute and chronic groups were significantly higher than those in the healthy cats ($p<0.001$ and $p<0.05$, respectively). As reported by various researchers (Gruys et al. 2005, Jain et al. 2011), it is thought that the rising APPs concentrations after an inflammatory stimulus remain high as the stimulation continues.

Acute-phase response emerges as a complex reaction characterised by local and systemic changes initiated by inflammatory mediators in areas of tissue destruction. Local inflammation is the immune system's first response to harmful stimuli. The organism responds with a wide-ranging systemic reaction if the local defence system cannot stop infection or tissue damage. This includes physiological, biochemical and behavioural changes in many organs and tissues far from the inflammation area (Petersen et al. 2004, Ceciliania et al. 2012). It has been reported that the determination of systemic inflammation in humans and animals has important effects on the prognosis of the disease, and systemic inflammation has an adverse impact on the prognosis (Tamamoto et al. 2013, Torrente et al. 2015). Therefore, APPs have a significant role in classifying the severity of the inflammatory status and revealing local and systemic inflammatory conditions (Hooijberg et al. 2014, Troìa et al. 2017, Petini et al. 2020). SIRS describes a clinical condition characterised by widespread inflammatory system activation secondary to a sterile inflammatory disease or infectious insult. SIRS has been associated with significant disease effects and mortality (Troìa et al. 2017, Gori et al. 2021). There are limited studies of serum APPs concentrations in cats with SIRS (Sasaki et al. 2003, Troìa et al. 2017). Troìa et al. (2017) reported that cats with an infectious and non-infectious origin SIRS had a significantly higher SAA concentration than the healthy control. In our study, both SIRS (-) and SIRS (+) groups had higher serum AGP and SAA concentrations than healthy cats. The increase in serum AGP concentration of the SIRS (+) group was significantly higher than that found in the SIRS (-) group (Fig. 2). In addition, serum Cp concentrations in SIRS (+) cats were significantly higher than in healthy cats. In light of these findings, we believe that the increase in serum AGP, SAA and Cp concentrations can be used to determine the inflammatory state. Also, increased serum AGP concentration can be used as a biomarker in classifying the severity of the inflammatory condition, but more sampling is needed.

There are some limitations to our study. Firstly, the number of cats in some disease groups is too small. Secondly, the effect of breeds on APPs concentration was not performed due to the small sample sizes. Third, in the SIRS (+) group, no distinction was made between infectious (sepsis) and non-infectious causes. Finally, blood sampling was taken from cats once they were first brought to the clinic. Monitoring the APPs investigated in the diseased group over time could be important in evaluating the response to treatment and determining the prognostic value.

In conclusion, this study contributes to the limited number of research studies on reference intervals in serum APPs concentrations in healthy cats. Establishing reference intervals for these APPs can help diagnose the inflammatory process and monitor therapy. Also, age could be affected when evaluating the results of serum Cp concentrations in cats. Our results support that diseased cats have higher serum APPs than healthy cats. Therefore, APPs can be used as valuable diagnostic tools to identify the inflammatory processes of various diseases. Furthermore, it also reveals that serum AGP and SAA concentrations in SIRS (-) cats and serum AGP, SAA and Cp concentrations in SIRS (+) cats were higher than in healthy cats. The increase in serum AGP concentration in SIRS (+) cats is significantly higher than in SIRS (-) cats suggesting that serum AGP concentration could help determine the severity of the inflammatory condition. However, more detailed studies are needed.

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