

THE SYSTEMIC-IMMUNE INFLAMMATION INDEX IN NATURALLY OBESE DOGS

GÜLTEN EMEK TUNA AND BÜLENT ULUTAŞ

Aydın Adnan Menderes University, Faculty of Veterinary Medicine, Department of Internal Medicine, Aydın, Türkiye

Received: 15 July 2023; **Accepted:** 18 October 2023

ABSTRACT

Obesity is one of the most prevalent health problems in the canine population. This study aimed to evaluate the clinical usability of the systemic immune inflammation index (SII) in obese dogs. A total of 25 obese dogs compared with 10 normal-weight dogs. Complete blood counts, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were measured in all dogs. The SII was calculated with the neutrophil count \times platelet count/lymphocyte count formula. C-reactive protein (CRP) concentrations were determined with dog-specific commercial ELISA test kits. The obese group had statistically higher WBC, neut, PLT, and SII than the control group. However, no significant difference between the groups in NLR, PLR, and CRP concentration. Additionally, a positive correlation between SII and serum CRP was determined. To the best of our knowledge, this is the first study to demonstrate the SII levels in obese dogs. Nevertheless, considering no statistical difference between inflammatory parameters such as NLR, PLR, and CRP between the two groups, large-scale studies are needed to reveal the reason for this increase in SII in obese dogs and understand its clinical utility.

Keywords: C-reactive protein, inflammation, obesity, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index

INTRODUCTION

Obesity is a pathological condition characterized by excessive fat storage that leads to changes in various body functions, and it usually occurs when the ideal body weight increases by 15% (Laflamme, 2001; Piantedosi *et al.*, 2016). It is the most common nutritional disease in dogs. Recently, the prevalence of overweight and obesity has been estimated to have increased

by approximately 37% in dogs, affecting almost 59.3% of the dog population (Vedrine *et al.*, 2021; Marchi *et al.*, 2022). Risk factors for obesity in dogs are multifactorial. It includes dog-related characteristics and owner-specific factors (Preet *et al.* 2021). The primary factor in dog-related characteristics is breed. Beagles, Cocker Spaniels, Dachshunds, Labrador Retrievers and Golden Retrievers breeds are more likely to be obese. Other risk factors for canine obesity include age, gender, neutering, types of food, activity, and feeding frequency (Preet *et al.*, 2021; Chiang *et al.*, 2022).

The life span and various body functions are affected by obesity in humans and animals.

Corresponding author: Gülten Emek Tuna

E-mail address: emektuna@adu.edu.tr

Present address: Department of Internal Medicine
Adnan Menderes University, 09100 Aydın, Turkey.
Tel: +902562470700-6250

Like humans, canine obesity can precipitate or exacerbate various clinical conditions such as osteoarthritis, metabolic diseases, certain types of cancer, and respiratory disease (Piantedosi *et al.*, 2016; Chiang *et al.*, 2022). It may also contribute to a shortened lifespan, increased risk of surgery, and exercise intolerance (German *et al.*, 2009; Piantedosi *et al.*, 2016; Shepherd, 2021). In humans, obesity is considered a chronic inflammatory condition that causes increased production and release of proinflammatory mediators accompanied by increases in white blood cells (WBC), lymphocytes (Lymph), and C-reactive protein (CRP) (Radakovich *et al.*, 2017; Barić Rafaj *et al.*, 2017). However, the relationship between inflammation and obesity in veterinary medicine is controversial (Veiga *et al.*, 2008; German *et al.*, 2009; Tvarijonaviciute *et al.*, 2012; Barić Rafaj *et al.*, 2017).

Recently, the components of complete blood count (CBC) and the parameters derived from them have been widely used in disease diagnosis, treatment follow-up, prognosis, and determination of systemic inflammation due to their cheap and easy accessibility (Pierini *et al.*, 2019; Park & Lee, 2022). Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are two of these parameters, and their clinical and diagnostic significance has recently been demonstrated in dogs with different diseases (Pierini *et al.*, 2019; Becher *et al.*, 2021; Neumann, 2021; Pierini *et al.*, 2021; Dinler Ay, 2022). The systemic immune-inflammation index (SII) is derived from CBC like NLR and PLR and reflects local immune response and systemic inflammation (Yazlık *et al.*, 2022). As a biomarker of the inflammatory process in human medicine, it has found its place as a prognostic factor in different malignancies (Sun *et al.*, 2020). The SII has been evaluated in dogs with few studies on different diseases such as oral melanoma, chronic enteropathy, pyometra and diabetes mellitus (Cristóbal *et al.*, 2022; Garcia *et al.*, 2022; Yazlık *et al.*, 2022).

With the prevalence of obesity in dogs increasing worldwide, there is a need to determine how routine veterinary testing may be affected by obesity. The inflammatory state is controversial in dogs. Some researchers suggest that obesity may be associated with a chronic, low level of inflammation (German *et al.*, 2009; Barić Rafaj *et al.*, 2017). However, there is limited research regarding this condition in dogs (Veiga *et al.*, 2008; German *et al.*, 2009; Tvarijonaviciute *et al.*, 2012; Barić Rafaj *et al.*, 2017). Also, no studies evaluate the SII in obese dogs. Therefore, this study aimed to assess the clinical usability of SII in obese dogs, which has recently been used as an inflammatory biomarker in humans.

MATERIALS AND METHODS

Aydın Adnan Menderes University Animal Research Ethics Committee has reviewed and approved all study procedures with protocol number 64583101/2022/117.

Dogs

The present study was conducted on 35 dogs of different ages, sexes, and breeds brought to the Aydın Adnan Menderes University Veterinary Faculty Research and Practice Hospital. The dogs' body condition scores (BCS) were evaluated on a 9-point scale (Laflamme, 2001). The dogs of the control group (n=10) were clinically healthy based on physical examination and laboratory findings. Moreover, these dogs were brought for annual routine control, vaccination and selective operation (Castration or ovariohysterectomy). The BCS of these dogs ranged from 4 to 5 points. Dogs with BCS > 7 were included in the obese group (n=25). All dogs show the exclusion criteria (diagnosed comorbidities such as inflammatory disease, neoplasm and endocrinopathies and ongoing treatment etc.) were removed from the study.

The control group included 4 Crossbreeds, 2 Golden retrievers, 2 Terriers, and 2 Cavalier King Charles breeds dogs. In the obese group,

there were 11 Crossbreds, 4 Golden retrievers, 3 Terriers, 2 Cockers, 2 Labrador retrievers, 2 cavalier King Charles and 1

French bulldog. The characteristics of dogs in the control and obese groups are shown in Table 1.

Table 1: Characterization of the study population.

	Control group	Obese group
Number of dogs	10	25
Number of male/female (%) dogs	3 (30%) / 7 (70%)	4 (16%) / 21 (84%)
Neutered/spayed (%)	5 (50%)	20 (80%)
Age (years)	5.9±2.07	6.68±1.33
Body weight (kg) (mean±SD) (Min-Max)	14.96±10.44 (3-29)	23.47±12.32 (6-43)
Body condition score	4-5	> 7

Abbreviation: SD, standard derivation; Min, minimum; Max, maximum

Laboratory Analysis

Blood samples from dogs were collected via cephalic vein puncture into serum separator tubes and anticoagulant tubes containing K3-ethylenediaminetetraacetic acid (EDTA). CBC of dogs was performed with an automated blood cell counter (Abacus Vet5, Diatron, Budapest, Hungary) using samples with EDTA within 15 min after blood collection. WBC, neutrophil (Neut), Lymph, and platelet (PLT) counts were recorded directly from CBC. NLR and PLR were calculated as the ratio of absolute neut, and PLT counts to the absolute Lymph count, respectively. SII was calculated with the formula of neutrophil count x platelet count/lymphocyte count. Blood samples within the serum separator tubes were centrifuged after clot retraction at 2000 g for 10 min to obtain sera. Serum samples were stored at -20°C until the CRP analysis (within 1-2 months). Serum CRP concentrations were determined using a dog-specific ELISA commercial assay (Tridelta, Ireland).

Data analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) 19.0 (Armonk, USA). WBC, neut, and PLT were normally distributed according to the Shapiro-Wilk test, while Lymph, NLR, PLR, SII, and CRP did not show normal distribution. However, considering the sample size of the groups, the nonparametric

Mann-Whitney U test was used. Spearman correlation coefficient (rho) was determined to evaluate the correlation between SII and CRP.

RESULTS

The mean WBC, neut, Lymph and PLT values and statistical comparisons of the obese and control groups are shown in Figure 1. In both groups, these four parameters were within the normal reference ranges reported for dogs. Nevertheless, the mean WBC ($p = 0.026$), neut ($p = 0.022$), and PLT ($p = 0.024$) values of the obese group were statistically significantly higher than the control group. There was no statistically significant ($p > 0.05$) difference between these two groups regarding the mean lymphocyte counts (Figure 1).

The NLR, PLR, SII and serum CRP concentrations and statistical comparisons of the two groups are shown in Figure 2. The obese and control groups had no statistical differences in serum CRP concentration, NLR, and PLR values ($p > 0.05$ for each parameter). Nevertheless, SII was significantly higher in the obese group than in the control group ($p = 0.028$). Also, the Spearman correlation coefficient results showed a significant positive association between CRP and SII ($\rho = 0.681$; $p = 0.000$) (Figure 3).

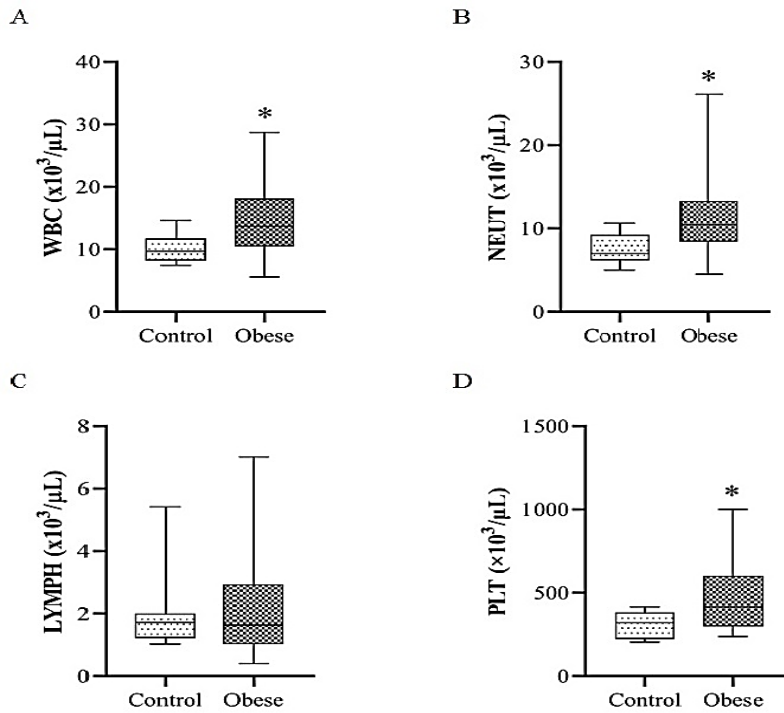


Figure 1: Box plot graphs showing the WBC (A), Neut (B), Lymph (C), and PLT (D) comparison between control and obese groups. “*” is statistically significant ($p < 0.05$). Abbreviations: LYMPH, lymphocyte; NEUT, neutrophil; PLT, platelet; WBC, white blood cell.

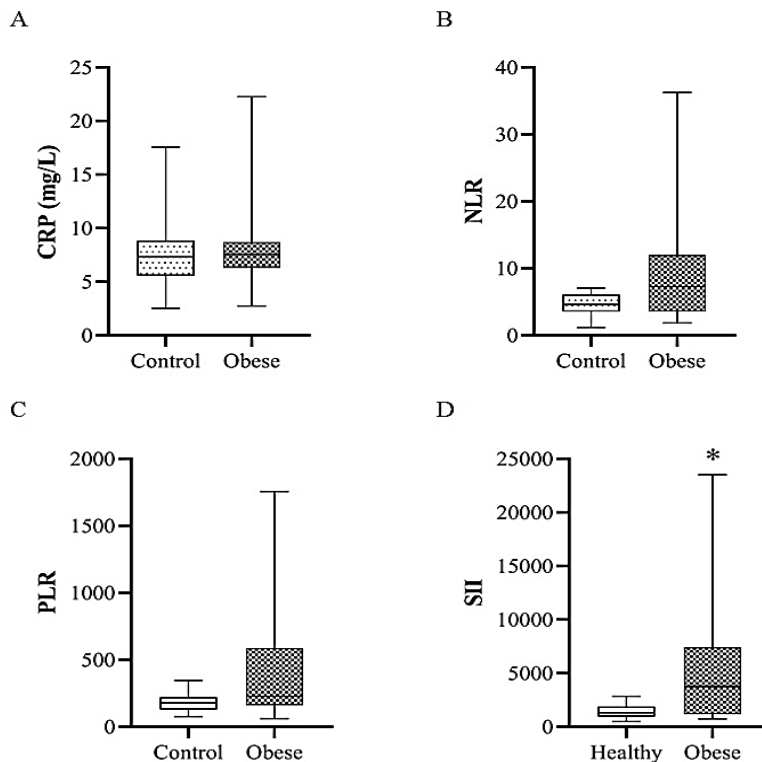


Figure 2: Box plot graphs showing the CRP (A), NLR (B), PLR (C) and SII (D) comparison between control and obese groups. “*” is statistically significant ($p < 0.05$). Abbreviations: CRP, C reactive protein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index.

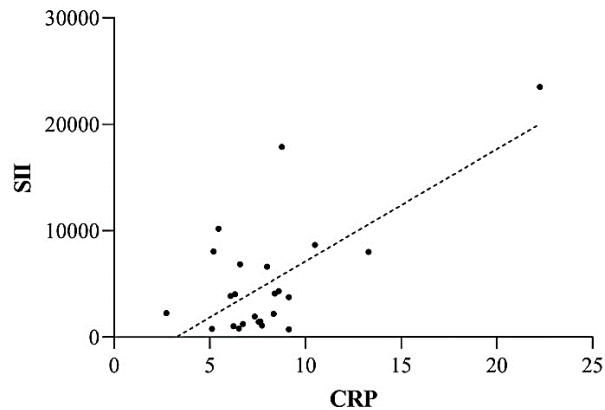


Figure 3: The scatter plot for the relationship between CRP and SII ($p = 0.00$; $\rho = 0,681$). Abbreviations: CRP, C reactive protein; SII, systemic immune inflammation index.

DISCUSSION

Recently, the incidence of obesity has been increasing in pets and humans. This situation is a major concern in clinical practice as it can cause serious health problems (Barić Rafaj *et al.*, 2017). The inflammatory state of obesity in dogs has still not been fully elucidated, and there are different opinions on this issue (Tvarijonaviciute *et al.*, 2012; Barić Rafaj *et al.*, 2017).

There are several studies on CBC components in obese dogs (German *et al.*, 2009; Barić Rafaj *et al.*, 2017; Martins *et al.*, 2019). These studies demonstrated that clinically healthy overweight/obese dogs had a variety of haematological parameters that differed significantly from healthy control dogs (Radakovich *et al.*, 2107). Leukocytosis can be expected in obese dogs because of granulopoiesis and lymphopoiesis induced by interleukins and interferons. However, most studies show that the mean WBC, neut and lymph counts were within reference limits in obese dogs, although higher than in dogs with normal body weight (German *et al.*, 2009; Radakovich *et al.*, 2017; Barić Rafaj *et al.*, 2017; Martins *et al.*, 2019). Similar to these studies, the total and differential leukocyte counts of the obese group were within the reference ranges in the current study. Also, WBC and neut counts were statistically significantly higher than the control group.

German *et al.* (2009) reported that obesity might predispose dogs to subclinical inflammatory conditions since the mean leukocyte counts of obese dogs are at the upper limit of the reference range and decrease significantly after weight loss. However, the exact role of proinflammation in canine overweight and obesity is currently unknown. On the other hand, studies in obese humans and dogs have shown that neutrophils are positively correlated with increased visceral fat (Ryder *et al.*, 2014; Barić Rafaj *et al.*, 2016), and an increase in total cholesterol causes increases in neutrophil counts. In the current study, WBC and neut counts of the obese group were statistically higher than the control group. Considering that other inflammatory markers such as NLR, PLR and CRP were normal in the obese group, this elevation may be associated with increased visceral fat, as mentioned by the authors above. Also, a possible stress response may have caused a rise in these two parameters.

It has been reported that the platelet count increases in overweight dogs and that primary hemostasis is affected by this condition (Pasquini *et al.*, 2013; Barić Rafaj *et al.*, 2017). Barić Rafaj *et al.* (2017) report that the increase in PLT value in obese dogs may be associated with chronic low inflammation. Pasquini *et al.* (2013) also emphasize that the PLT value decreases after dieting in overweight dogs, and this is not related to the

inflammatory condition reported in humans since there is no change in CRP concentration. Similar to Pasquini *et al.* (2013), although the PLT values of the obese group were significantly higher than the control group in this study, there was no difference between the groups regarding CRP, the major acute phase protein (APP). Therefore, the increase in PLT may be associated with visceral adipose tissue becoming an additional source of thrombopoietin and increased thrombopoietin production (Purdy & Shatzel, 2021).

Acute phase proteins are proteins that concentrations rise quickly in the blood in texture demolition and inflammation. In recent years, they have been used in veterinary medicine for the differential diagnosis of many diseases and inflammatory conditions, evaluation of prognosis and determination of therapeutic efficacy (Eckersall & Bell, 2010). Some researchers suggest that obesity may be associated with chronic, low-grade inflammation. They also revealed that adipocytes have roles similar to T cells and macrophages in complement activation and proinflammatory cytokine production (German *et al.*, 2009; Barić Rafaj *et al.*, 2017). It has been reported that CRP concentration increases in obese people (Park *et al.*, 2005). However, there are conflicting data on CRP concentration in dogs. German *et al.* (2009) and Barić Rafaj *et al.* (2017) report that APP levels are increased in obese dogs. However, while Tvarijonavičiute *et al.* (2011) emphasized no significant difference in APP levels in experimentally induced obesity in dogs, Veiga *et al.* (2008) reported that CRP concentration decreased in obese dogs. This study showed no statistical difference in CRP concentration between the obese and control groups. This result suggests that inflammation is not an important component in the canine obesity model, similar to the study of Tvarijonavičiute *et al.* (2011).

The SII is one of the new inflammatory markers obtained from CBC, such as NLR

and PLR (Zhang *et al.*, 2021; Ji & Wang, 2022). It has been demonstrated that high SII values in humans are associated with disease severity and poor prognosis in many diseases and malignancies (Zhang *et al.*, 2021; Ji & Wang, 2022). There are a few studies on dogs with chronic enteropathy, melanoma and pyometra in veterinary medicine (Cristóbal *et al.*, 2022; Garcia *et al.*, 2022; Yazlık *et al.*, 2022). It has been demonstrated that SII can be used as a diagnostic parameter in dogs with pyometra (Yazlık *et al.*, 2022). In dogs with chronic enteropathy, SII reductions have also been reported with treatment (Cristóbal *et al.*, 2022). There are no studies regarding SII in obese dogs. In humans, it has been shown that SII is significantly affected by body mass index, and SII is higher in obese adults/children than in individuals with normal weight (Furuncuoğlu *et al.*, 2016). Similar to human research, the obese group had significantly higher SII levels than the control group in our study. No statistical difference between the obese and the control groups in inflammatory parameters such as CRP, NLR and PLR suggests that this increase may reflect the increase in platelet and neutrophil counts, not caused by inflammation. More extensive research is needed to understand the reason for this rise in SII.

There are several limitations to our study. First, the relatively low number of dogs included in the study. Many obese dogs were excluded from the study because of concurrent disease (e.g. another inflammatory or metabolic disease, cardiovascular problem) and lost data. Second, the number of pure breeds was low; It was not possible to statistically compare the data of obese and healthy dogs of the same breed. Finally, only CRP, the major APP in dogs, was evaluated to support the assessment of the inflammatory state in dogs due to the limited budget. Other APPs could not be evaluated.

CONCLUSION

In conclusion, the present study has shown that the SII is elevated in obese dogs, and

there was no difference in NLR, PLR and CRP concentrations. Furthermore, there was a positive correlation between SII and CRP. Large-scale studies are needed to reveal the reason for this increase in SII in obese dogs and to demonstrate its clinical utility.

REFERENCES

- Barić Rafaj, R.; Kuleš, J.; Marinculić, A.; Tvarijonavičute, A.; Ceron, J.; Mihaljević, Ž.; Tumpa, A. and Mrljak, V. (2017):* Plasma markers of inflammation and hemostatic and endothelial activity in naturally overweight and obese dogs. *BMC Veterinary Research*, 13(1), 13.
- Barić Rafaj, R.; Kuleš, J.; Turković, V.; Rebselj, B.; Mrljak, V. and Kučer, N. (2016):* Prospective hematological and biochemical evaluation of spontaneously overweight and obese dogs. *Veterinarski arhiv*, 86(3), 383-394.
- Becher, A.; Suchodolski, J.S.; Steiner, J.M. and Heilmann, R.M. (2021):* Blood neutrophil-to-lymphocyte ratio (NLR) as a diagnostic marker in dogs with chronic enteropathy. *Journal of Veterinary Diagnostic Investigation*, 33(3), 516-527.
- Chiang, C.F.; Villaverde, C.; Chang, W.C.; Fascetti, A.J.; Larsen, J.A. (2022):* Prevalence, Risk Factors, and Disease Associations of Overweight and Obesity in Dogs that Visited the Veterinary Medical Teaching Hospital at the University of California, Davis from January 2006 to December 2015. *Topics in companion animal medicine*, 48, 100640.
- Cristóbal, J.I.; Duque, F.J.; Usón-Casaús, J.; Barrera, R.; López, E. and Pérez-Merino, E.M. (2022):* Complete Blood Count-Derived Inflammatory Markers Changes in Dogs with Chronic Inflammatory Enteropathy Treated with Adipose-Derived Mesenchymal Stem Cells. *Animals (Basel)*, 12(20), 2798.
- Dinler Ay, C. (2022):* Neutrophil to lymphocyte ratio as a prognostic biomarker in puppies with acute diarrhea. *Journal of Veterinary Emergency and Critical Care*, 32(1), 83-89
- Donma, M.M. and Donma, O. (2018):* Evaluation of Systemic Immune-Inflammation Index in Obese Children. *International Journal of Medical and Health Sciences*, 12, 362-365.
- Eckersall, P.D. and Bell, R. (2010):* Acute phase proteins: Biomarkers of infection and inflammation in veterinary medicine. *Veterinary Journal*, 185(1), 23-7.
- Furuncuoğlu, Y.; Tulgar, S.; Dogan, A.N.; Cakar, S.; Tulgar, Y.K. and Cakiroglu, B. (2016):* How obesity affects the neutrophil/lymphocyte and platelet/lymphocyte ratio, systemic immune-inflammatory index and platelet indices: a retrospective study. *European Review for Medical and Pharmacological Sciences*, 20(7), 1300-6.
- Garcia, J.S.; Nowosh, V.; López, R.V.M. and Massoco, C.O. (2022):* Association of Systemic Inflammatory and Immune Indices With Survival in Canine Patients With Oral Melanoma, Treated With Experimental Immunotherapy Alone or Experimental Immunotherapy Plus Metronomic Chemotherapy. *Frontiers in Veterinary Science*, 9, 888411.
- German, A.J.; Hervera, M.; Hunter, L.; Holden, S.L.; Morris, P.J.; Biourge, V. And Trayhurn, P. (2009):* Improvement in insulin resistance and reduction in plasma inflammatory adipokines after weight loss in obese dogs. *Domestic Animal Endocrinology*, 37, 214-226.
- Ji, Y. and Wang, H. (2020):* Prognostic prediction of systemic immune-inflammation index for patients with gynecological and breast cancers: a meta-analysis. *World Journal of Surgical Oncology*, 18(1),197.
- Laflamme, D.P. (2001):* Determining metabolizable energy content in

- commercial pet foods. *Journal of Animal Physiology and Animal Nutrition*, 85, 222-230.
- Marchi, P.H.; Vendramini, T.H.A.; Perini, M.P.; Zafalon, R.V.A.; Amaral, A.R.; Ochamoto, V.A.; Da Silveira, J.C.; Dagli, M.L.Z.; Brunetto, M.A. (2022). Obesity, inflammation, and cancer in dogs: Review and perspectives. *Frontiers in veterinary science*, 9, 1004122.
- Martins, C.R.; Noletto, P.G.; De Miranda, R.L. and Mundim, A.V. (2019): Blood profile of obese and aged dogs (*Canis familiaris*). *Acta Veterinaria Brno*: 88(1), 33-41.
- Neumann, S. (2021): Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in dogs and cats with acute pancreatitis. *Veterinary Clinical Pathology*, 50(1), 45-51.
- Park, H.S.; Park, J.Y. and Yu, R. (2005): Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. *Diabetes Research and Clinical Practice*, 69(1), 29-35.
- Park, S.H. and Lee, H. (2022): Obesity, Leukocytes, and High-Sensitivity C-Reactive Protein Biomarkers Associated with Type 2 Diabetes Mellitus in South Korean Adults. *Iranian Journal of Public Health*, 51(8), 1827-1835.
- Pasquini, A.; Roberti, S.; Meucci, V.; Luchetti, E.; Canello, S.; Guidetti, G. and Biagi, G. (2012): Association between Body Condition and Oxidative Status in Dogs. *Food and Nutrition Sciences*, 4, 191-6.
- Piantedosi, D.; Di Loria, A.; Guccione, J.; De Rosa.; Fabbri, S.; Cortese, L.; Carta, S. and Ciaramella, P. (2016): Serum biochemistry profile, inflammatory cytokines, adipokines and cardiovascular findings in obese dogs. *The Veterinary Journal*, 216, 72-78.
- Pierini, A.; Esposito, G.; Gori, E.; Benvenuti, E.; Ruggiero, P.; Lubas, G. And Marchetti V. (2021): Platelet abnormalities and platelet-to-lymphocyte ratios in canine immunosuppressant-responsive and non-responsive enteropathy: A retrospective study in 41 dogs. *Journal of Veterinary Medical Science*, 83(2), 248-253.
- Pierini, A.; Gori, E.; Lippi, I.; Ceccherini, G.; Lubas, G. and Marchetti, V. (2019): Neutrophil-to-lymphocyte ratio, nucleated red blood cells and erythrocyte abnormalities in canine systemic inflammatory response syndrome. *Research in Veterinary Science*, 126, 150-154.
- Preet, G.S.; Turkar, S.; Gupta, S.; Kumar, S. (2021): Dog obesity: Epidemiology, risk factors, diagnosis and management: A review paper. *The Journal of Pharmaceutical Innovation*, 10, 698-705.
- Purdy, J.C. and Shatzel, J.J. (2021): The hematologic consequences of obesity. *European Journal of Haematology*, 106(3), 306-319.
- Radakovich, L.B.; Truelove, MP.; Pannone, S.C.; Olver, C.S. and Santangelo, K.S. (2017): Clinically healthy overweight and obese dogs differ from lean controls in select CBC and serum biochemistry values. *Veterinary clinical pathology*, 46(2), 221-226.
- Ryder, E.; Diez-Ewaldm, M.; Mosquera, J.; Fernández, E.; Pedrañez, A.; Vargas, R.; Peña, C. and Fernández, N. (2014): Association of obesity with leukocyte count in obese individuals without metabolic syndrome. *Diabetes & metabolic syndrome*, 8(4), 197-204.
- Shepherd, M. (2021): Canine and Feline Obesity Management. *The Veterinary clinics of North America Small animal practice*, 51(3), 653-667.
- Sun, Y.; Li, W.Q, Li, A.J.; Su, H.C.; Yue, J.B. and Yu, J.M. (2019): Increased systemic immune inflammation index independently predicts poor survival for hormone receptor-negative, HER2-positive breast cancer patients. *Cancer Management and Research*, 11, 3153-62.

- Tvarijonavičiute, A.; Martinez, S.; Gutierrez, A.; Ceron, J.J. and Tecles, F. (2011):* Serum acute phase proteins concentrations in dogs during experimentally short-term induced overweight. A preliminary study. *Research in veterinary science*, 90(1), 31-34.
- Tvarijonavičiute, A.; Tecles, F.; Martínez-Subiela, S. and Ceron, J.J. (2012):* Effect of weight loss on inflammatory biomarkers in obese dogs. *Veterinary Journal*, 193, 570-72.
- Vedrine, B.; Fernandes, D.; Gérard, F.; Fribourg-Blanc, L.A. (2021):* Use of an intragastric balloon for management of obesity in a dog. *The Journal of Small Animal Practice*, 62(9), 816–821.
- Veiga, A.P.; Price, C.A.; de Oliveira, S.T.; Dos Santos, A.P.; Campos, R.; Barbosa, P.R. and González F.H. (2008):* Association of canine obesity with reduced serum levels of C-reactive protein. *Journal of Veterinary Diagnostic Investigation*, 20(2), 224-228.
- Yazlık, M.O.; Mutluer, İ.; Yıldırım, M.; Kaya, U.; Çolakoğlu, H.E. and Vural, M.R. (2022):* The evaluation of SIRS status with hemato-biochemical indices in bitches affected from pyometra and the Usefulness of these indices as a potential diagnostic tool. *Theriogenology*, 193, 120-127.
- Zhang, M.H.; Wang, H.; Wang, H.G.; Wen, X. and Yang, X.Z. (2021):* Effective immune-inflammation index for ulcerative colitis and activity assessments. *World Journal of Clinical Cases*, 9, 334-343.