Research

Haematology-Derived Inflammatory Markers in French Bulldogs with Brachycephalic Obstructive Airway Syndrome

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Abstract:
Brachycephalic obstructive airway syndrome (BOAS) is a chronic obstructive respiratory disorder that raises significant welfare concerns for affected breeds. Canine BOAS can be compared to obstructive sleep apnoea (OSAS) in humans, as both disorders cause intermittent hypoxia which can alter the metabolic, immune and inflammatory systems. Haematological markers and their ratios can be used to access systemic inflammatory status and have been proved to be changed in patients with OSAS. In this retrospective study we compared haematological parameters and haematology-derived inflammatory markers between French Bulldogs diagnosed with BOAS and non-brachycephalic dogs. The study involved a total of 30 client-owned dogs; the BOAS group consistent of 15 French Bulldogs that were evaluated as BOAS grade 2 and 3 and the control group consisted of 15 healthy non-brachycephalic dogs. Significant differences ($p < 0.05$) were observed in several investigated markers. BOAS patients had a significantly higher platelet count, platelet-to-lymphocyte ratio and systemic immune-inflammation index, as well as significantly lower lymphocyte-to-monocyte ratio values compared to non-brachycephalic dogs, which suggest the presence of systemic inflammation in BOAS-affected dogs. Our study provides new insights into the inflammatory state in BOAS affected French Bulldogs and highlights the need for further studies in larger groups of BOAS patients of different brachycephalic breeds including evaluation of the effects of surgical treatment on haematology-derived inflammatory markers.

Keywords: Brachycephaly; Inflammatory markers; BOAS; Veterinary; Haematology; Systemic immune-inflammation index

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1. Introduction

Brachycephalic obstructive airway syndrome (BOAS) is a chronic obstructive respiratory disorder that is predominantly observed in the brachycephalic dog breeds, one of the most popular being the French Bulldog (Mitze et al., 2022). BOAS arises from the skeletal changes that have evolved during selection of brachycephalic dog breeds that cause narrowing of the air passages. BOAS is related to respiratory and thermoregulatory problems (Žgank et al., 2023) as well as gastrointestinal (Freiche, 2021), dermatological (Hobi et al., 2023), ophthalmic (Palmer et al., 2021) and reproductive disorders (Ekenstedt et al., 2020) and therefore there is a significant welfare concern for brachycephalic breeds.
BOAS itself can be diagnosed with identification of specific anatomic changes and by concurrent observance of respiratory clinical signs (Packer et al., 2015). An accurate diagnosis is usually made with endoscopic evaluation of the upper respiratory tract (Fasanella et al., 2012). Respiratory or physical performance can also be used to determine the severity of BOAS, as well as an assessment of blood oxygenation (Bernaerts et al., 2010; Arulpagasam et al., 2018; Riggs et al., 2019). All these tests can be time consuming, expensive and require specific equipment, knowledge and trained personnel, as well as animals willing to cooperate.

Canine BOAS shares features with obstructive sleep apnoea syndrome (OSAS) in humans (Niinikoski et al., 2023). OSAS is a complex syndrome where muscle relaxation results in partial or complete blockage of pharynx during sleep, which results in apnoea or hypopnea. This leads to reduced blood oxygen saturation and chronic intermittent hypoxia that can cause altered metabolic, immune and inflammatory system responses (Topuz et al., 2022). Most of the systemic consequences of BOAS are similar to those of OSAS (Mellema and Hoareau, 2014).
Haematology-derived inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR, calculated by dividing neutrophil count (NEUT) to lymphocyte count (LYMPH)), platelet-to-lymphocyte ratio (PLR, calculated by dividing platelet count (PLT) to LYMPH), monocyte-to-lymphocyte ratio (MLR, calculated by dividing monocyte count (MONO) to LYMPH), lymphocyte-to-monocyte ratio (LMR, calculated by dividing LYMPH to MONO), systemic inflammatory response index (SIRI, calculated using the formula: NEUT × MONO/ LYMPH) and systemic immune-inflammation index (SII, calculated using the formula: NEUT × PLT/LYMPH), are popular, inexpensive and easy accessible markers of systemic inflammation derived from routine haematological analysis. Selected haematology-derived inflammatory markers, such as the NLR, PLR, MLR, white blood cell count (WBC)-to-mean platelet volume (MPV) ratio (WMR), SIRI and SII, have confirmed the presence of systemic inflammation in OSAS patients and were proven to predict or even evaluate OSAS severity (Nadeem et al., 2013; Wu et al., 2018; Topuz et al., 2022; Kim et al., 2023; Elfeky et al., 2024).
The clinical significance and the potential to use the above-mentioned markers as diagnostic markers has already been indicated in canine inflammatory bowel disease (Marchesi et al., 2024), canine myxomatous mitral valve disease (Tuna, 2024), canine pyometra (Yazlık et al., 2022), gastric cancer patients (Karra et al., 2023) and as prognostic factors in canine sepsis (Pierini et al., 2020) and canine monocytic ehrlichiosis (Ozalp et al., 2024).
To date, there are no published studies reporting haematology-derived inflammatory markers in brachycephalic dogs with advanced stage of BOAS. Therefore, this study aimed to evaluate selected haematology-derived inflammatory markers—specifically, NLR, PLR, MLR, LMR, SII and SIRI in French Bulldogs with advanced stage of BOAS (grade 2 and 3) in order to identify systemic inflammation in this breed.

2. Materials and methods

A total of 30 dogs were included in this retrospective study, in which we evaluated haematological markers in 15 client-owned French Bulldogs diagnosed with BOAS that were admitted for surgical treatment of BOAS at the Small Animal Clinic of the Veterinary Faculty in Ljubljana, between the year 2021 and 2022. Data for the BOAS group was retrieved from the electronic internal medical database, including details on age, sex, breed, weight, BOAS grade, surgical records, and results of haematological analyses. The included dogs

were free from any systemic diseases, had not undergone medical treatment or vaccination in the preceding month, were diagnosed with BOAS, and had no prior history of upper airway surgery.

Upon initial examination, a thorough history was gathered for each BOAS patient. A pre-operative questionnaire, completed by the owners, assessed various clinical signs associated with BOAS (respiratory problems, exercise intolerance, sleep disturbances and gastrointestinal symptoms). The diagnosis of BOAS was determined based on clinical symptoms of upper airway obstruction and the presence of anatomical abnormalities. BOAS severity was categorized according to the grading system outlined in previous studies (Dupré and Heidenreich, 2016). BOAS patients were classified into three grades based on the degree of airway narrowing at the nasopharynx, oropharynx, laryngopharynx and larynx. Grade 1 patients showed minimal to no airway narrowing, grade 2 patients exhibited around a 50% reduction in airway radius and grade 3 patients had near-complete obstruction at one or more of the before mentioned airway levels (Erjavec et al., 2021; Erjavec and Nemec Svete, 2023). Dogs were included in the study if they were evaluated as BOAS grade 2 and 3. Written informed consent was obtained from all dog owners.

The control group consisted of 15 non-brachycephalic dogs that were admitted for elective neutering. All dogs in the control group were clinically healthy and showed no signs of respiratory or chronic diseases. To be considered healthy, control dogs had to exhibit normal findings on physical examination, as well as the results of haematological and biochemical analyses (data not shown) within established reference ranges.

Venous blood samples were drawn from the cephalic vein prior to the surgical procedure and before administering any medications to the animals. For haematological analyses, the blood was collected in tubes containing EDTA anticoagulant (BD Microcontainer, Becton Dickinson, Franklin Lakes, NJ, USA). The samples were then analysed within one hour of collection using an automated laser-based haematology analyser ADVIA 120 (Siemens, Munich, Germany) to ensure accurate and timely results. Inflammatory markers derived from the haematological analyses were calculated using white blood cell differentials and PLT.

Statistical analysis was performed using commercial software (IBM SPSS 28, Chicago, Illinois, USA). The Shapiro-Wilk test was performed to determine the distribution of data. Based on the findings, parametric test or non-parametric test was used to compare data between control group of non-brachycephalic dogs and BOAS patients. Accordingly, independent t-test (for normally distributed data) or Mann Whitney test (for non-normally distributed data) were used to compare variables (age, weight, haematology parameters, haematology-derived inflammatory markers) between the two groups of dogs. Normally distributed data are reported as means ± standard deviation (SD), whereas non-normally distributed as a median and interquartile range (IQR – 25th to 75th percentile), respectively. A value of $P \leq 0.05$ was considered significant.

3. Results

3.1. Demographic data

The BOAS group involved 8 dogs that were diagnosed with BOAS stage 2 and 7 that were diagnosed with BOAS stage 3.

BOAS and control groups were equally represented by both sexes. The average age in months of the control group was 38.00 ± 21.01 and in BOAS group 41.27 ± 22.89. There was no significant ($p = 0.687$) difference in age between the groups of dogs; however, the dogs in the control group were significantly ($p = 0.028$) heavier compared to the BOAS group, 17.7 ± 9.7 kg and 11.5 ± 2.5 kg, respectively.

3.2. Hematological parameters and haematology-derived inflammatory markers

The haematological parameters and haematology-derived inflammatory markers of dogs included in the study are presented in **Table 1**. BOAS patients had significantly higher PLT, PLR and SII and significantly lower LMR than control group. Other parameters, such as WBC, NEUT, LYMPH, MONO, MLR and SIRI demonstrated no significant differences between the groups. The NLR, MLR and SIRI were higher in the BOAS group compared

to the control group; however, these differences did not reach statistical significance, with p values approaching 0.05.

Table 1. Haematological parameters and haematology-derived inflammatory markers of dogs included in the study

Group	BOAS	Control	P value
WBC (× 10^9/L)[a]	10.87 ± 3.98	8.78 ± 2.43	0.094
PLT (× 10^9/L)[a]	431.4 ± 65.9	251.8 ± 55.5	**< 0.001***
NEUT (× 10^9/L)[a]	6.96 ± 2.98	5.83 ± 2.40	0.264
LYMPH (× 10^9/L)[a]	2.42 ± 0.68	2.39 ± 0.82	0.922
MONO (× 10^9/L)[b]	0.45; 0.32–0.59	0.34; 0.22–0.48	0.125
NLR[a]	2.84 ± 0.69	2.38 ± 1.07	0.174
LMR[a]	5.40 ± 1.88	8.14 ± 3.67	**0.016***
PLR[a]	189.3 ± 52.6	103.1 ± 29.4	**< 0.001***
MLR[b]	0.20; 0.14–0.24	0.13; 0.09–0.22	0.051
SII (× 10^9/L)[b]	1264.2; 983.6–1404.7	508.3; 324.1–1004.8	**< 0.001***
SIRI (× 10^9/L)[b]	1.24; 0.77–1.74	0.74; 0.32–1.54	0.071

Legend: *Significant difference ($p < 0.05$) between BOAS patients and control dogs; a - data presented as mean and standard deviation; b - data presented as median and interquartile range (25th to 75th percentile). WBC - white blood cell count, PLT - platelet count, NEUT - neutrophil count, LYMPH - lymphocyte count, MONO - monocyte count, NLR - neutrophil-to-lymphocyte ratio, LMR - lymphocyte-to-monocyte ratio, PLR - platelet-to-lymphocyte ratio, MLR - monocyte-to-lymphocyte ratio, SII - systemic immune-inflammation index, SIRI - systemic inflammatory response index. Statistically significant differences are marked bold.

3. Discussion

To our knowledge, this is the first study to investigate hematology-derived inflammatory markers in French Bulldogs with BOAS, revealing significant differences that highlight the systemic inflammatory impact of this condition. Our findings provide new insights into the systemic inflammatory state in BOAS affected dogs with notable changes in PLT and blood cell ratios, such as PLR, LMR and SII.

As previously mentioned, canine BOAS shares characteristics with OSAS in humans (Niinikoski et al., 2023). Wu and colleagues (2018) reported that MLR and PLR are elevated in OSAS, suggesting monocyte-driven inflammation, which contributes to the pathogenesis of OSAS-related complications. In our study, MLR was higher in the BOAS group, although the difference was not statistically significant. However, PLR values were significantly increased in BOAS dogs compared to non-brachycephalic dogs. Similarly, Gölen and colleagues (2024) observed significantly elevated PLR, as well as NLR, and SII values in OSAS patients compared to people without OSAS.

In our study, BOAS group showed significantly lower LMR values compared to control group. This might be associated with a heightened inflammatory response, as an increased proportion of monocytes relative to lymphocytes indicates systemic inflammation.

BOAS dogs exhibited a significantly increased SII compared to controls. SII, which incorporates neutrophil, platelet and lymphocyte counts, provides a comprehensive measure of systemic inflammation. Similar to our results, increased SII values were also reported in OSAS patients (Gölen et al., 2024; Güneş and Günaydın, 2024). Kim and colleagues (2023) showed that the SII can be a robust marker of immune and inflammatory activity in patients with OSAS. The higher SII values in our study are most likely the result of significantly higher PLT and the absence of lymphopenia in BOAS patients.

A significantly elevated PLT was noted in the BOAS group compared to controls. This finding might suggest a pro-inflammatory state in dogs with advanced BOAS (Margraf and Zarbock, 2019). Platelet activation has been associated with chronic inflammation and hypoxia, which are common in BOAS due to obstructed airflow and oxygen deprivation

(Delaney et al., 2021). Similar results have already been published in BOAS dogs, where PLT, MPV and plateletcrit were found significantly higher compared to non-brachycephalic dogs (Erjavec and Nemec Svete, 2023). As mentioned before, BOAS group exhibited a markedly higher PLR values, which is most probably a consequence of high PLT.

Interestingly, not all inflammatory markers showed significant differences between the groups. For example, WBC were slightly higher in BOAS patients compared to control dogs. Similarly, NLR and monocyte counts did not differ significantly between groups. This contrasts with findings in OSAS patients, where studies reported significantly higher NLR values in OSAS patients compared to healthy individuals (Gölen et al., 2024; Güneş and Günaydın, 2024).

Although we expected significantly higher SIRI values in the BOAS group compared to control group, the difference did not reach statistical significance. Interestingly, Pau and colleagues (2023) demonstrated a strong correlation between lower oxygen saturation and higher SIRI in OSAS patients. The absence of a significant difference in SIRI in our study may be attributed to low statistical power due to the small sample size.

Despite the compelling findings, the study is limited by its small sample size (15 dogs per group), which may affect the generalizability of the results. Therefore, larger studies in different brachycephalic breeds with BOAS are needed to offer better insight into the complex interplay between systemic inflammation and respiratory dysfunction in BOAS-affected dogs. Additionally, a deeper evaluation of the immune and inflammatory responses in these animals is essential to fully understand the underlying mechanisms contributing to the condition. Given the significant differences between the groups in our study, there is a solid base for further research in these areas.

In conclusion, the results of our study suggest the presence of systemic inflammation in BOAS-affected French Bulldogs. Further studies in larger groups of BOAS patients including evaluation of the effects of surgical treatment on haematology-derived inflammatory markers are warranted.

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Institutional Review Board Statement: The work described in this paper involved the use of non-experimental (client-owned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed. Due to retrospective nature of the study, ethical approval was not specifically required.

Conflicts of Interest: The authors declare no conflict of interest.

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