

Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and C-reactive protein concentration in female domestic cats subjected to ovariohysterectomy

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Summary

This study assessed hematological parameters (especially the neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio) and the C-reactive protein concentration in the plasma of female cats subjected to ovariohysterectomy: prior to surgery as well as 2 and 10 days after surgery. The animals (n = 26) were patients of a private veterinary clinic between July 2019 and March 2021 and were brought there for ovariohysterectomies. The blood was sampled from the cephalic vein into two tubes. One of the tubes was sent to a commercial veterinary laboratory, where a hematological examination was performed. The second tube was centrifuged (2000 g, 10 min). After separation, plasma samples were stored at -80°C. Next, the CRP concentration was determined using an ELISA kit. We noted a statistically significant increase in NLR two days after surgery. The difference in the NLR value before the surgery and after a 10-day recovery period failed to reach statistical significance. Changes in PLR and the CRP concentration during the experiment were insignificant. The results indicate that NLR is an effective marker of stress and inflammation caused by surgery in female cats, whereas the CRP concentration is of no use in this species.

Keywords: hematology, NLR, PLR, CRP, inflammation, surgery

The neutrophil-to-lymphocyte ratio (NLR) is an easily measurable and relatively cheap hematological marker that is becoming more widely applied in human medicine, especially oncology. An increased NLR is associated with a worse prognosis in certain malignant tumors (10, 15, 28). Moreover, it has been reported that this marker is of great significance in cardiovascular diseases, such as coronary artery disease (CAD) or arterial hypertension (20). In such cases, an increased NLR is associated with a worse prognosis and a shorter survival time (20). A neutrophil-to-lymphocyte ratio

greater than 5.4 can indicate a higher risk of death and a lower survival time for patients suffering from severe fever with thrombocytopenia syndrome (38). NLR is also elevated in the course of chronic obstructive pulmonary disease (COPD) (14). It has been established that patients suffering from COPD show a positive correlation between NLR and the C-reactive protein (CRP) concentration in plasma (14), which proves that NLR can be used as an inflammation marker. However, studies on the application of this hematological marker in animals are scarce. It has been recognized as a reliable

stress marker in birds (35). It has also been discovered that this marker increases in dogs as a result of stress caused by transportation (4). In the case of laboratory mice and rats, NLR is associated with chronic stress exposure (16, 36). Moreover, NLR acts as an inflammatory marker that provides information on the severity of canine inflammatory bowel disease (3). Hodgson et al. (17) compared NLR in dogs with septic and non-septic systemic inflammatory diseases with NLR in healthy individuals and found that it was higher in the diseased dogs. It was also demonstrated that NLR was not associated with length of hospitalization, morbidity (based on the acute patient physiologic laboratory evaluation scoring system), or mortality. Gori et al. (13) investigated NLR in healthy cats and in those with systemic inflammation (SIRS) and sepsis. They observed that $\text{NLR} > 4.53$ had a sensitivity of 76% and a specificity of 93.4% in detecting SIRS/sepsis. NLR was also associated with mortality in sick cats. A study performed by Naito et al. (23) demonstrated that NLR could potentially be used as a preoperative prognostic factor for feline mammary tumors. Literature data regarding alterations in NLR in animals are limited and insufficient.

The platelet-to-lymphocyte ratio (PLR) is another indicator used in clinical hematology. It has been found that PLR in humans is elevated in end-stage renal disease (ESRD) (37). Furthermore, PLR has been found to be associated with poor prognosis in gastric cancer patients (39). Moreover, Raungkaewmanee et al. (33) demonstrated that PLR was a better prognostic indicator of survival for patients diagnosed with epithelial ovarian cancer (EOC) than thrombocytosis or NLR. According to Gasparyan et al. (11), interpreting PLR in combination with other hematological parameters is advisable for a more accurate diagnosis of inflammatory rheumatic diseases. Interestingly, the PLR of patients diagnosed with COVID-19 indicates the severity of cytokine storm and can be used to monitor patients suffering from this disease (32). There have not yet been many research papers on the significance of PLR in animals. A prospective study conducted by Neumann (25) showed that PLR was higher in dogs and cats with pancreatitis compared to healthy individuals.

The c-reactive protein (CRP) concentration is measured in clinical laboratories as a marker of inflammation (26). C-reactive protein is a “positive” acute-phase protein because its concentration increases during inflammation (30). Many researchers have demonstrated that the CRP level changes in various pathological states. Nakamura et al. (24) observed increased CRP levels in dogs diagnosed with pyometra, panniculitis, acute pancreatitis, polyarthritis, and hemangiosarcoma. Mischke et al. (22) noted that CRP concentrations were higher in dogs with malignant multicentric lymphoma, acute lymphoblastic leukemia, chronic lymphocytic leukemia, and multiple myeloma. Dąbrowski et al.

(9) showed that CRP concentrations were elevated in healthy bitches and those with pyometra immediately after ovariohysterectomy and diminished thereafter. CRP concentrations were also higher in dogs shortly after experimentally induced acute gastric injury and returned to nearly the previous level within 2 weeks (29). Ohno et al. (27) demonstrated that the CRP concentration was increased in dogs with idiopathic polyarthritis at the time of diagnosis and decreased in response to the initial corticosteroid treatment. According to Christensen et al. (8), canine CRP is a marker of the degree of surgical trauma, but the evidence for this is limited.

This study aimed to determine whether NLR, PLR, and the CRP concentration in the blood plasma of female cats can be used as markers of inflammatory response to a surgical procedure (ovariohysterectomy). Furthermore, basic hematological parameters were assessed.

Material and methods

Animals. Twenty-six privately owned intact, clinically healthy female European shorthair cats (*Felis catus*) were used in this study. The animals were patients of a private veterinary clinic in Kraków (Poland) between July 2019 and March 2021 and were brought there for ovariohysterectomies. Permission for the study was obtained from the Local Ethics Committee (Resolution No. 117/2019 of 30.05.2019). The owners expressed written consent for their queens to participate in the study.

The age of the queens was 14.33 ± 7.94 (mean $\pm$ SE) months, and they had never been pregnant. All the animals in the study underwent a thorough clinical examination and were confirmed to be clinically healthy. The examinations were carried out by an experienced veterinarian. After the surgery, all patients received antibiotic (ampicillin in Albi-pen La 100 mg/ml inj., Intervet International B.V.) and anti-inflammatory drug treatment (tolfenamic acid in Tolfedine 4% inj., Vetoquinol). The animals were not given any anti-inflammatory drugs for at least 4 weeks prior to the study.

Blood analysis. The blood for hematological evaluation and C-reactive protein (CRP) concentration analysis was collected three times: before the ovariohysterectomy, as well as 2 and 10 days after the surgery. The blood was sampled from each individual from the cephalic vein (with a 0.8×40 mm needle) into two polypropylene tubes with EDTA, V – 1 ml. One of the tubes was sent to a commercial veterinary laboratory (Labwet, Kraków, Poland), where a hematological examination was performed with a Nihon Kohden MEK-6550 analyzer (Haryana, India). The samples were tested for the following parameters: red blood cell (RBC) count, hemoglobin (Hb) concentration, hematocrit (Ht) value, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), white blood cell (WBC) count, differential leukocyte count (leukogram), and platelet (PLT) count. The second tube was centrifuged for 10 min at $\text{RCF} = 2000$ g. After separation, the plasma

samples were pipetted into Eppendorf tubes and stored at -80°C . Next, the CRP concentration was determined with a Cat CRP ELISA kit (catalog number E0061Cat, Bioassay Technology Laboratory, Jiaxing, China) on an EPOCH 2 fluorescence microplate reader (Biotek Instruments, Inc., Vermont, USA). Optical density was determined at 500 nm wavelength. NLR and PLR were calculated using standard formulas:

$\text{NLR} = (\text{segmented neutrophils} + \text{band neutrophils}) / \text{lymphocytes}$

$\text{PLR} = \text{platelets} / \text{lymphocytes}$

Statistical analysis. The compliance of the results with the normal distribution was verified using the Shapiro-Wilk test. Due to the lack of compliance, Friedman's rank test was applied. Post hoc analysis was carried out using the Wilcoxon test with Bonferroni correction. The level of significance was set at $\alpha = 0.05$. The statistical analysis was performed using the R software.

Results and discussion

NLR was significantly higher 2 days after the surgery (sampling II) in comparison to samplings I ($p = 0.001$) and III ($p = 0.037$). PLT was significantly lower in sampling II compared to samplings I ($p = 0.000$) and III ($p = 0.000$). The percentage of lymphocytes was significantly lower in sampling II in comparison to sampling I ($p = 0.001$). The percentage of segmented neutrophils was significantly higher in sampling II in comparison to samplings I ($p = 0.001$) and III ($p = 0.013$). The percentage of eosinophils was significantly higher in sampling III compared to samplings I ($p = 0.003$) and II ($p = 0.020$). The other hematological parameters (Tab. 1) and the CRP concentration (Fig. 1) did not change significantly during the study.

The results obtained in our study suggest that the neutrophil-to-lymphocyte ratio is a reliable marker of stress/inflammation due to ovariohysterectomy in female cats. After a 10-day recovery period, the value of this indicator fell almost to the baseline (established before the ovariohysterectomy). Previous research papers on NLR in animals deal mostly with cancers. Rejec et al. (34) evaluated retrospectively selected hematological indices in dogs with oropharyngeal tumors (OT) compared with healthy animals. That study demonstrated that NLR was significantly higher in dogs with OT in comparison to healthy animals. Chiti et al. (7) found that NLR was correlated with tumor size and the histological pattern of tumor growth in cats diagnosed with feline injection-site sarcoma (FISS). The authors noted that preoperative NLR may be useful in identifying cats at a higher risk of local recurrence of sarcoma. Moreover, Naito et al. (23) showed that higher NLR was significantly associated with a shorter survival time in cats with feline mammary tumors (FMT). Becher et al. (2) evaluated NLR in 93 dogs with chronic enteropathy (CE) and demonstrated that it was significantly higher in CE dogs with severe clinical disease than in dogs with mild clinical disease.

Tab. 1. Hematological parameters in female domestic cats before and after castration (mean $\pm$ SD)

Parameter	Sampling I	Sampling II	Sampling III
NLR	1.18 ± 0.57^a	2.07 ± 1.33^b	1.27 ± 0.67^a
PLR	9.90 ± 4.39^a	10.54 ± 6.08^a	12.31 ± 5.89^a
RBC [T/l]	8.77 ± 0.91^a	8.67 ± 0.97^a	8.98 ± 0.81^a
Ht [l/l]	0.41 ± 0.04^a	0.41 ± 0.04^a	0.42 ± 0.04^a
Hb [mmol/l]	8.55 ± 0.89^a	8.51 ± 0.86^a	8.73 ± 0.79^a
MCV [fl]	46.31 ± 2.85^a	46.85 ± 2.63^a	46.62 ± 2.76^a
MCH [fmol]	0.98 ± 0.06^a	0.99 ± 0.07^a	0.98 ± 0.06^a
MCHC [mmol/l]	21.12 ± 0.68^a	21.07 ± 0.76^a	20.93 ± 0.77^a
RDW [%]	21.69 ± 0.84^a	21.85 ± 0.92^a	22.08 ± 0.84^a
MPV [fl]	16.00 ± 1.18^a	15.65 ± 1.41^a	15.69 ± 1.19^a
PLT [G/l]	421.62 ± 119.44^a	322.54 ± 88.49^b	490.96 ± 181.41^a
WBC [G/l]	7.72 ± 3.04^a	9.17 ± 3.45^a	8.52 ± 3.53^a
Segm [%]	48.35 ± 12.92^a	58.46 ± 14.46^b	47.04 ± 14.75^a
Band [%]	0.23 ± 0.43^a	0.23 ± 0.59^a	0.35 ± 0.49^a
Lym [%]	46.54 ± 11.97^a	35.65 ± 12.73^b	43.42 ± 13.71^{ab}
Mono [%]	0.46 ± 0.95^a	0.46 ± 0.33^a	0.31 ± 0.27^a
Eos [%]	4.35 ± 3.03^a	4.96 ± 3.78^a	8.65 ± 6.19^b
Baso [%]	0.08 ± 0.27^a	0.23 ± 0.43^a	0.23 ± 0.51^a

Explanations: NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; RBC – red blood cell count; Ht – hematocrit value; Hb – hemoglobin concentration; MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; RDW – red blood cell distribution width; MPV – mean platelet volume; PLT – platelet count; WBC – white blood cell count; Segm – segmented neutrophils; Band – band neutrophils; Lym – lymphocytes; Mono – monocytes; Eos – eosinophils; Baso – basophils; sampling I – before surgery; sampling II – 2 days after surgery; sampling III – 10 days after surgery; values in rows marked with different letters (a or b) differ significantly ($p < 0.05$)

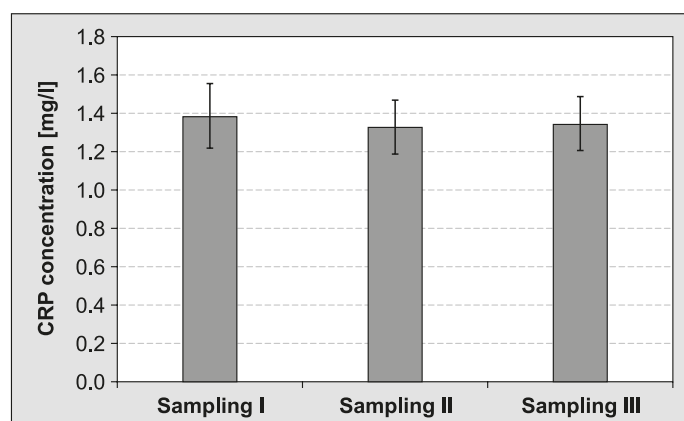


Fig. 1. CRP concentration in female domestic cats before and after castration (sampling I – before surgery, sampling II – 2 days after surgery, sampling III – 10 days after surgery)

The authors noted that NLR can be easily assessed during routine hematology tests and can potentially aid the classification of individuals diagnosed with CE based on the response to treatment. It is worth noting that the main advantages of using this marker are its

simplicity, quick measurement, and low cost. It seems that NLR could be used as an effective auxiliary tool in clinical diagnostics.

The platelet-to-lymphocyte ratio (PLR) did not significantly change throughout the study. Knowledge on the use of this parameter for diagnosing animals is limited. Akpovona and Onoagbe (1) examined the effects of aqueous and ethanol extracts of *Terminalia macroptera* stem bark (TMSB) on the blood parameters of rats. They noted that PLR was significantly lower in rats dosed with 1200 mg/kg aqueous extract compared to control animals, and significantly higher in those treated with ethanol extracts at 1000 mg/kg and 1200 mg/kg compared to the control value. According to Pierini et al. (31), PLR was not associated with endoscopic and histopathological scores and seemed unhelpful in predicting response to treatment or relapse of enteropathy in dogs. Neumann (25) investigated 67 dogs and 41 cats diagnosed with acute pancreatitis, and used 17 healthy animals as the control. The severity of the disease was determined using a modified “bed-side index of severity in acute pancreatitis” score in humans. The results showed that PLR was higher in dogs and cats with pancreatitis compared to healthy ones. However, no significant relationship between PLR and the severity of the disease was found. Despite this fact, the author concluded that increased PLR provides information regarding the course of pancreatitis in dogs and cats.

As far as the number of platelets is concerned, the statistically significant decrease in platelet count that we noted 2 days after surgery could have been related to the surgical procedure itself, hemostatic response (5), or the antibiotic treatment provided (12).

This study has revealed a statistically significant increase in the percentage of segmented neutrophils and a significant reduction in the percentage of lymphocytes. These changes may be indicative of inflammation caused by surgical intervention, as this increase in the neutrophil level is typical of acute inflammation (5, 21). It must be noted, however, that the values of both markers determined in our study (after being recalculating into absolute values) fall within feline reference intervals (19).

The fluctuations in the CRP concentration recorded in this study failed to reach the level of significance. Kajikawa et al. (18) measured the concentrations of CRP in the serum of clinically healthy and diseased cats, those with experimentally induced inflammation, and those subjected to surgery for urinary diversion. They observed that the CRP level was not significantly different between the groups. Cerón et al. (6) noted that information on CRP in cats is scarce because CRP does not seem to be involved in the acute phase response in this species. Our experiment supports this thesis.

The results of the present study should be regarded as preliminary, as it is possible that ampicillin and tolf-

enamic acid, both of which were administered to the cats after the surgery, influenced the results. However, omitting antibiotic or anti-inflammatory treatment could raise ethical concerns.

The results presented in this paper suggest that NLR is a reliable hematological marker that reflects inflammation response to surgical procedures in cats and it may gain significance in clinical practice in the future. The usefulness of PLR in this respect was not confirmed. The results obtained in this study support earlier reports that the assessment of the CRP concentration in cat blood has no clinical application.

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