Article

An Initial Investigation into the Interrelation of Systemic Inflammatory Response Syndrome (SIRS), Feline Coronavirus (FCoV), and Neutrophil-Lymphocyte Ratio (NLR) in Cats

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Simple Summary: Systemic inflammatory response syndrome (SIRS) is a clinical diagnosis based on abnormalities in patients' vital signs and white blood cell count. The neutrophil-ymphocyte ratio (NLR) is used as an easily accessible parameter to assess the patient's inflammatory status and stress. Feline coronavirus (FCoV) causes a fatal disease with a poor prognosis known as feline infectious peritonitis (FIP). In this study, in which the relationship between FCoV, NLR and SIRS was investigated, it was aimed to compare the relationship between SIRS (+) and SIRS (-) groups in the light of NLR in patients with high FCoV positivity. NLR as a diagnostic marker has been shown to differ between FCoV positive and healthy cats with high antibody titres. However, the diagnostic significance of NLR among FCoV positive cats with high antibody titres with SIRS (+) and SIRS (-) remains questionable. As a result of our study NLR can be used as a blood parameter in cats with high FCoV antibody titer and high probability of developing FIP.

Abstract: Systemic inflammatory response syndrome (SIRS) is a clinical diagnosis based on abnormalities in patients' vital signs and white blood cell count. Neutrophil-lymphocyte ratio (NLR) is used as an easily accessible parameter to assess the patient's inflammatory status and stress. There are some studies showing that NLR affected by the inflammatory response is a criterion to support the diagnosis of SIRS. In this study, it was aimed to compare the interrelation between SIRS (+) and SIRS (-) groups in patients with high positive feline coronavirus (FCoV) in the light of NLR. Based on the anamneses, physical examination findings, laboratory findings, enzyme immunoassay antibody test kit titer were included in the sick groups. These patients were further categorized based on the presence of SIRS symptoms, vital signs and laboratory findings. The NLR as diagnostic marker demonstrated to differ between high antibody titer FCoV positive and healthy cats. However the diagnostic significance of NLR remains questionable between the high antibody titer FCoV positive cats with SIRS (+) and SIRS (-). As a result of our study NLR can be used as a blood parameter like albumin/globulin ratio and elevated total bilirubin in cats with high FCoV antibody titer and high probability of developing FIP.

Keywords: neutrophil-to-lymphocyte ratio, feline infectious peritonitis, white blood cells, biomarker, FIP

1. Introduction

Feline coronavirus (FCoV) causes a fatal disease with a poor prognosis known as feline infectious peritonitis (FIP). FCoV, an alphacoronavirus, is common in approxi-

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mately 90% of both domestic and feral cat populations [1-2]. Coronaviruses can be transmitted by many ways: feco-oral route (direct), the indirect route, the aerosol route, and the consumption of contaminated food or water. Infected cats become chronic carriers and shed the virus throughout life [3]. Due to mutations in the spike protein gene of the FCoV biotype, FCoV causes changes in enterocytes and macrophages, thereby gaining the ability to infect macrophages and proliferate effectively, which usually does not cause any clinical symptoms, this situation causes lesion formation in organs with multi-organ involvement, necrosis and pyogenic granulomatous inflammation, leading to fatal systemic diseases [4-5]. Affected cats develop a variety of non-specific clinical signs, such as anorexia, malaise, weight loss, fever, and/or stomatitis. These symptoms are also accompanied by clinical and pathological changes such as anemia, microcytosis, lymphopenia, neutrophilia, thrombocytopenia, hyperglobulinemia, hypoalbuminemia and hyperbilirubinemia [6-7]. Lymphopenia is seen in 55-77% of patients as the most common hematological change. Hyperglobulinemia is observed in 89% of patients, and hypoalbuminemia or low-normal serum albumin level is observed in 64.5% of patients. A low albumin/globulin ratio (A/G) can be used to evaluate the diagnosis of FIP in patients with hyperglobulinemia and hypoalbuminemia [8]. FIP is difficult to diagnose because of non-specific clinical signs, non-pathognomonic hematological and biochemical abnormalities, and low sensitivity and specificity of tests used in the practical routine [9]. There are many tests used to detect FCoV with different methods. Comparing the detection of FCoV with different methods, the sensitivity and specificity of the test results controlled with the enzyme immunoassay kit [ImmunoComb® FCoV (FIP) Antibody Test Kit from Biogal Galed Laboratories, Israel] was determined 100%. In a study of Addie et al. (2014), the working principle of FCoV ImmunoComb® was described and different sample dilutions were used for different tests. Therefore, the results obtained by different antibody titers were categorized as borderline positive, low positive, moderately positive, high positive or very high positive and evaluated accordingly with a score between 0-5 [10-11].

Systemic inflammatory response syndrome (SIRS) is a clinical diagnosis based on abnormalities in patients' vital signs and white blood cell count [11]. SIRS refers to the clinical manifestations of a systemic proinflammatory response resulting from a series of interactions between inflammatory and endothelial cells that lead to the response of cytokines to trauma or infectious agents [12]. Immune reactions developing in patients with FIP lead to overproduction of proinflammatory cytokines, creating clinical symptoms and laboratory abnormalities. Therefore, SIRS is common in these patients [13]. The diagnosis of SIRS is established when three or more of the following criteria are fulfilled: rectal temperature ≥ 39.7°C or < 37.8°C, heart rate ≥ 225 beats per minute or ≤ 140 beats per minute, respiratory rate ≥ 40 breaths per minute, white blood cell count ≥ 19,500 WBC/μL or ≤ 5,000 WBC/μL, or a band neutrophil fraction ≥ 5% [14]. Although inflammation is a protective response against tissue damage, prolonged systemic inflammation may cause organ dysfunctions [11]. A study investigating the utility of leukocyte ratios in differentiating SIRS from sepsis in cats found that neutrophil-lymphocyte ratio (NLR) was associated with mortality in both SIRS and cats diagnosed sepsis [15].

NLR is used as an easily accessible parameter to assess the patient's inflammatory status and stress [16-17]. NLR is obtained by dividing the total neutrophil count by the lymphocyte count in the complete blood count (CBC) [18]. CBC provides the opportunity to calculate the relationships between blood cells easily and quickly, enabling the assessment of systemic inflammation [16]. NLR is a minimally invasive, inexpensive and routinely evaluated parameter that can be calculated by examining the CBC [19]. Increased neutrophil infiltration due to the altered balance of proinflammatory and anti-inflammatory cytokines is associated with cytotoxicity, angiogenesis, and tumor progression [20]. Lymphocytes are critical components of specific anti-inflammatory immunity and are crucial for generating an effective humoral and cellular response against the tumor [21]. Therefore, NLR is a biomarker of immune responses affected by inflammatory or neo-

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plastic diseases [20]. NLR is widely used as a powerful prognostic factor in human medicine for cardiovascular diseases, various types of cancer, inflammatory or infectious pathologies, and management of postoperative complications [22-23]. The correlation between NLR and disease outcomes or prognoses is thought to be based on the role of white blood cells in the production and secretion of various cytokines and growth factors affecting the inflammatory process [24]. In studies conducted on animals, it has been shown that NLR provides prognostic information in dogs with lymphoma, osteosarcoma, mast cell tumors, and soft tissue sarcomas [25-26]. In addition, NLR is a useful biomarker in the evaluation of diseases such as chronic enteropathy, IBD, protein-losing enteropathy and duodenal lymphangiectasia in dogs [27-28]. At the same time, it provides information about the course of the disease in cats and dogs with pancreatitis [24]. It can be used as a useful marker in the evaluation of the prognosis of hypertrophic cardiomyopathies in cats [17]. In response to an increase in glucocorticoids, a decrease in peripheral lymphocyte counts and an increase in neutrophil counts as well as an increase in the NLR are expected. In this way, NLR is a reliable method for assessing stress in cats and dogs [29].

NLR has been previously investigated in cats and dogs with SIRS and it has been found that it can be used as a prognostic marker especially in cats with SIRS [15,23,30].

In this study, it was aimed to compare the interrelation between SIRS (+) and SIRS (-) groups in patients with high positive FCoV in the light of NLR. New markers are still rewarding in the diagnosis of FIP.

2. Materials and Methods

2.1. Study Population

Cats were categorized based on their clinical examination, and various symptoms and findings were referred to the Department of Internal Medicine, Faculty of Veterinary Medicine, Istanbul University-Cerrahpasa.

The anamneses of the cats were including at least one or more symptoms such as weakness, anorexia, vomiting, diarrhea, seizures, respiratory distress, litter eating, wall licking, and weight loss. Additionally, physical examination findings such as jaundice, incoordination, nystagmus, paralysis, paresis, abdominal effusion, pleural effusion, pericardial effusion, and enlarged lymph nodes were detected. Laboratory findings were also taken into account for categorization. Cats with laboratory findings such as non-regenerative anemia, microcytosis, lymphopenia, neutrophilia, thrombocytopenia, hyperglobulinemia, hypoalbuminemia, and hyperbilirubinemia were added in the categorization. Moreover, cats with high positive results from the enzyme immunoassay antibody test kit titer (S4, S5, and S6) using the commercially available enzyme immunoassay (Immuno-Comb®) were included in the sick groups, which were further categorized as SIRS (+) and SIRS (-).

In this study, 175 cats were examined at the Internal Medicine Department Clinic of Istanbul University Cerrahpaşa Faculty of Veterinary Medicine and classified into three distinct groups based on their characteristics. The SIRS (+) group (n:42) comprised cats that had high FCoV antibody titers and presented with SIRS, whereas the SIRS (-) group (n:78) consisted of cats that also had high FCoV antibody titers but were not afflicted with SIRS. Healthy cats were allocated to Group 3 (n:55) and were utilized as control group.

SIRS (+) group was defined as cats having at least three of the following four parameters: (1) abnormal body temperature (≤37.8°C or ≥39.7°C); (2) tachycardia (≥225 beats/min) or bradycardia (≤140 beats/min); (3) tachypnea (≥40 breaths/min); and (4) white blood cell abnormalities (WBC ≥19500 or ≤5000 k/μL). The remaining cats were included in SIRS (-) group. In order to eradicate the presence of Feline Immunodeficiency Virus (FIV), Feline Leukemia Virus (FeLV), and Toxoplasma gondii, with ELISA test (Anigen Rapid FIV Ab/FeLV Ag Test Kit, Anigen Rapid Feline Toxoplasma Ab Test Kit) were also detected. Cats with positive results were not included in the study.

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2.2. Sample Collection and Laboratory Analyses

Blood samples were obtained from the cephalic vein upon admission, with hematologic parameters being analyzed using the Mindray BC-5000 Vet Blood Counter after collection in EDTA tubes. For clinical chemistry, serum samples were collected in serum tubes and subjected to centrifugation at 3200g for 5 minutes, with subsequent measurement of clinical biochemical parameters using the Fuji Dri-Chem NX600V. FCoV antibody titers were assessed with the ImmunoComb® FCoV Antibody Test Kit. NLR were calculated as the absolute count of neutrophils divided by the absolute count of lymphocytes.

2.3. Statistical Analysis

The normality of the distribution of the continuous variables was tested using the Shapiro-Wilk test. Due to the non-normal distribution of the data, variables exhibiting such distribution were reported using their median values along with the minimum and maximum values. Group comparisons were conducted using the Kruskal-Wallis test. Comparisons of NLR between the diseased groups [SIRS (+) and SIRS (-)] and healthy group compared using Mann-Whitney U test. The analyses were performed using Javomi (Version 2.3) (https://www.jamovi.org).

3. Results

A total of 175 cats were included in the study.

The SIRS (+) group comprised of 42 cats, with the majority (24 out of 42) being domestic shorthairs, making up 57% of the group. British Shorthair was the second most common breed, observed in 13 out of 42 cats, accounting for 30% of the group. The remaining 5 cats belonged to different breeds, including 3 Scottish Folds, as well as one each of the Bombay cat and Van cat breeds. In terms of gender distribution, there were 23 females and 19 males with the proportion of spayed and castrated cats unknown. The median age of the cats was determined to be 2.7 years.

A total of 78 cats were identified as belonging to the SIRS (-) group. Among them, the majority (51/78) were domestic shorthairs, making up 65% of the group. The re-maining 27 cats represented various breeds, including 11 British Shorthairs, 9 Scottish Folds, 3 Persians, and one each of the Exotic Shorthair, Himalayan, Maine Coon, and Ragdoll breeds. In terms of gender distribution, there were 40 females, with the proportion of spayed cats unknown. Additionally, there were 38 males, and the proportion of castrated cats among them was not specified. The median age of the cats in this group was determined to be 2.2 years.

The healthy group comprised a total of 55 cats. The majority of the group, accounting for 70%, were domestic shorthairs, with 30 out of the 55 cats belonging to this breed. The remaining 25 cats were of different breeds, including 11 Scottish Folds, 8 British Shorthairs, 5 Persians, and 1 Himalayan. Out of the 55 cats, 29 were females, and it is unknown what proportion of them were spayed. Additionally, there were 26 males, and the information regarding the proportion of castrated cats among them was not specified. The median age of the cats in the healthy group was determined to be 1.9 years.

According to reader results out of the 175 cats, 21 exhibited S4 FCoV antibody titers, 24 exhibited S5 FCoV antibody titers, and 75 exhibited S6 FCoV antibody titers (Table 1). Level 4 were classified as low positive, while those observed at level 5 were categorized as medium positive. Level 6 were considered strongly positive.

There have been no significant changes observed among the SIRS (+), SIRS (-), and healthy groups over the years, with values of 2.2, 2.7, and 1.9, respectively ($p = 0.204$).

The values of NLR are reported in Table 2. In summary, there were significant differences observed in NLR between the SIRS (+) and healthy groups, as well as between the SIRS (-) and healthy groups. However, no significant differences were found between the SIRS (+) and SIRS (-) groups ($p < 0.366$).

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Table 1. Number of patients by FCoV Antibody Titers in SIRS (+) and SIRS (-) groups.

FCoV Antibody Titer	Groups		Total
	SIRS (+) (*n*=42)	SIRS (-) (*n*=78)	
S4	10	11	21
S5	5	19	24
S6	27	48	75

Table 2. NLR in healthy, SIRS (+) and SIRS (-) groups. Data are presented as median along with the minimum and maximum values.

Parameter	Groups			*p*-value
	SIRS (+) (*n*=42)	SIRS (-) (*n*=78)	Healthy (*n*=55)	
NLR	3.44 (0.13-122) [1,2]	3.75 (0.01-40.4) [1,2]	1.2 (0.15-3.87)	< 0.001

[1] Significantly different from healthy; $p < 0.001$. [2] No significant differences were found between the SIRS (+) and SIRS (-) groups, $p < 0.366$.

When the combined diseased groups [SIRS (+) and SIRS (-)] were compared to the healthy group, a statistically significant difference was observed in the NLR ($p < 0.001$) (Table 3). Conversely, no statistically significant difference was found in the NLR when comparing based on the titers ($p < 0.793$) (Table 4).

Table 3. Comparisions of NLR between the diseased groups [SIRS (+) and SIRS (-)] and healthy group. Data are presented as median along with the minimum and maximum values.

Parameter	Groups		*p*-value
	SIRS (+) and (SIRS (-) (*n*=120)	Healthy (*n*=55)	
NLR	3.73	1.2	< 0.001

Table 4. Comparisions of NLR based on the titers. Data are presented as median along with the minimum and maximum values.

Parameter	Groups			*p*-value
	S4	S5	S6	
NLR	3.13 (0.75-32.01)	3.93 (0.71-39.23)	3.71 (0.17-122.1)	0.793

4. Discussion

In this study the presence of FCoV was investigated with SIRS and NLR in cats. The NLR can be as diagnostic biomarker demonstrated to differ between high antibody titer FCoV positive and healthy cats. Cats with high antibody titer are prone to develop FIP.

However the diagnostic significance of NLR remains questionable between the high antibody titer (S4, S5 and S6) FCoV positive cats with SIRS (+) and SIRS (-) ($p = 0.793$). We evaluated this parameter in feline SIRS (+), SIRS (-) and healthy cats because they have demonstrated their diagnostic utility in both cats and dogs [15,23,30]. The NLR resulted able to discriminate cats with high antibody titer FCoV positive cats from healthy cats ($p < 0.001$) but cannot discriminate SIRS (+) from SIRS (-) cats ($p < 0.366$).

FCoV is widespread among cat populations [1-2] and is responsible for the onset of a fatal condition known as FIP. The diagnosis of FIP poses challenges due to the presence

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of nonspecific clinical symptoms, as well as hematological and biochemical abnormalities, along with the limited sensitivity and specificity of commonly used diagnostic tests in practical settings [9]. Multiple tests employing different methods are available for FCoV detection. The study conducted using ImmunoComb® yielded results demonstrating 100% sensitivity and specificity [10-11]. Cats with FCoV antibody titers of S4 or higher are considered to have an increased risk of developing FIP [10-11]. Given the diagnostic difficulties associated with FIP, the ImmunoComb® test was employed in patients suspected of having FIP, as mentioned earlier. Consequently, cats with FCoV antibody titers of S4, S5, and S6 were included in the study. These patients were further categorized based on the presence of SIRS symptoms.

Cats suffering from FIP exhibit a diverse range of nonspecific clinical indications, including anorexia, malaise, weight loss, fever, and/or stomatitis. In this study, the previously mentioned clinical symptoms were documented, and in addition to these, frequent occurrences of symptoms such as ingestion of litter, wall licking, presence of abdominal and pleural effusion, ataxia, and nystagmus were observed.

Immune reactions developing in patients with FIP lead to overproduction of proinflammatory cytokines, creating clinical symptoms and laboratory abnormalities. Therefore, SIRS is common in these patients [13]. Neutrophilia and lymphopenia, which are hematological abnormalities of FCoV [31] can also be seen in SIRS patients [30]. Neutrophils are responsible for direct killing of pathogens, release of inflammatory mediators and activation of T cells via phagocytosis and are an important component of the immune system [18]. Due to the change in the balance of proinflammatory and anti-inflammatory cytokines, neutrophil infiltration increases [20]. Lymphocytes are critical components of specific anti-inflammatory immunity and are crucial for generating a humoral and cellular response [21]. For this reason, NLR is considered a biomarker of innate and adaptive immune responses triggered by inflammatory or neoplastic diseases [20]. As far as we know, there is no study on NLR evaluation in FCoV patients according to SIRS criteria so far. Therefore, in this study, it was aimed to analyze how the NLR would change in patients suspected of FIP and SIRS symptoms, which exhibit comparable hematological irregularities and the potent of NLR patients with FCoV.

NLR, in human medicine, serves as a readily available parameter for assessing various conditions including cardiovascular diseases, different types of cancer, inflammatory or infectious pathologies, as well as postoperative complications management [22- 23] The association between NLR and disease outcomes or prognoses is believed to stem from the involvement of white blood cells in the production and secretion of diverse cytokines and growth factors that influence the inflammatory process [24]. As a result of studies conducted in patients with coronavirus disease (COVID-19) in recent years, it is thought that NLR may indicate the presence of underlying endothelial dysfunction, which will support cellular damage and subsequent endothelial cell damage due to viral infection. Endothelial dysfunction may play an important role in explaining the progression of the disease leading to multi-organ failure [32].

In animal studies, NLR has demonstrated prognostic value in dogs diagnosed with lymphoma, osteosarcoma, mast cell tumors, and soft tissue sarcomas [25-26]. Furthermore, NLR serves as a valuable biomarker for evaluating diseases such as chronic enteropathy, inflammatory bowel disease (IBD), protein-losing enteropathy, and duodenal lymphangiectasia in dogs [27-28]. Additionally, NLR offers insights into the disease progression in cats and dogs with pancreatitis [24], and it can serve as a useful marker for assessing the prognosis of hypertrophic cardiomyopathies in cats [17].

In response to elevated glucocorticoid levels, a decrease in peripheral lymphocyte counts, an increase in neutrophil counts, and an elevated NLR are anticipated. There-fore, NLR represents a reliable method for evaluating stress levels in cats and dogs [29]. Another potential explanation could be the existence of a "stress leukogram" pattern, which has not been reported in human patients [33]

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A study involving 209 cats aimed to investigate potential variations in leukocyte ratios (NLR, BLR, and BNLR) among healthy cats, cats with SIRS, and cats with sepsis. It was observed that cats with an NLR > 4.53 had a 44 fold increased likelihood of having SIRS or sepsis. Furthermore, the study revealed a significant association between NLR and mortality in sick cats [15]. A significant difference between the SIRS (+) and SIRS (-) groups was not observed in our research. Obtaining a larger sample size and conducting a reevaluation of the study may yield more precise outcomes.

A study was undertaken to evaluate the NLR in dogs diagnosed with septic peritonitis and nonseptic systemic inflammatory diseases, as well as in a group of healthy dogs. The results indicated that a NLR value of ≥6 displayed a sensitivity of 84.39% and specificity of 86.95% in detecting dogs with systemic inflammatory diseases [18].

In the context of SIRS, there is an elevation in white blood cell (WBC) count, neutrophil count, and monocyte count, accompanied by a concurrent reduction in lymphocyte count and eosinophil count [30]. Neutrophilia and lymphopenia were also observed in our study, which is generally with the typical hematological changes seen in viral infections.

In another study involving the assessment of 22 dogs with SIRS to evaluate the NLR, nucleated red blood cells, and erythrocyte abnormalities, the median NLR was determined as 11.69. The findings of this study indicated that NLR could serve as a novel tool for evaluating dogs with SIRS. Furthermore, it was observed that the septic group exhibited a significantly lower NLR compared to the non-septic group [30].

In a study involving 57 dogs diagnosed with sepsis and 57 dogs with non-septic SIRS, it was observed that septic dogs exhibited a significantly lower NLR ($p = 0.04$) in comparison to dogs with SIRS [23].

NLR has been found to be a parameter with good predictive values for disease severity and mortality in patients with COVID-19 infection [34]. Despite the differences in pathogenesis, SIRS develops in both COVID-19 and FIP. The immune response that develops in FIP triggers an excessive production of proinflammatory cytokines which known as cytokine storm that lead to important clinical and laboratory changes. This cytokine storm may contribute to the high mortality observed in critically ill patients with both COVID-19 and FIP, resulting in multi-organ failure [13]. This study suggests that high NLR levels detected in cats with high positive FCoV antibody titers may be attributable to the cytokine storm that also occurs in COVID-19.

5. Conclusions

FCoV, which is frequently seen in our country and worldwide, poses a big threat to cats because it leads to FIP. Research on new diagnostic methods and biomarkers related to the diagnosis of FIP, continues intensively. As a result of our study, although there were no significant results detected between SIRS (+) and SIRS (-) groups, NLR showed a significant difference between high positive coronavirus cats and healthy cats. NLR can be used as a blood parameter like A/G ratio and elevated total bilirubin in cats with high FCoV antibody titer and high probability of developing FIP. To the authors' knowledge, it is the first study enlighting relationship between FCoV, SIRS and NLR and may enlighten new researchs that has been conducted in this perspective.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author. The data are not publicly available due to other project involvement.

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