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Determination of Neutrophil-to-Lymphocyte Ratio, Monocyte-to-Lymhocyte Ratio in FIV Positive and Healthy Cats Associated with SIRS

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Abstract

This study aimed to reveal the diagnostic role of inflammatory biomarkers of neutrophil-to-lymphocyte ratio (NLR), monocyte-lymphocyte (MLR), and platelet-to-lymphocyte ratio (PLR) in cats infected feline immunodeficiency virus (FIV) and to investigate their usability in determining systemic inflammatory response syndrome (SIRS) in these cats. The study was divided into 2 different groups as FIV-positive and healthy groups. A total of 15 healthy and 15 FIV-positive cats of different breeds and ages were served to the current study. The FIV-positive group was categorised into two subgroups: SIRS positive and SIRS negative. While the median PLR value (p = 0.756) did not significantly differ between the groups, the median NLR (p = 0.049) and MLR (p = 0.019) values of FIV (+) cats were significantly higher than those of the healthy group. The average lymphocyte (p= 0.000) and PLT (p= 0.003) values of the SIRS (+) group were significantly lower compared to the healthy group. When comparing the NLR, MLR, and PLR values of the SIRS (+), SIRS (-), and healthy groups, the SIRS (+) group's median NLR (p=0.012) and MLR (0.030) values were significantly higher than the healthy group's, but the PLR values did not significantly between the three groups (p>0.05). In conclusion, NLR and MLR were significantly higher in FIV (+) cats compared to healthy cats. Furthermore, the significant increase in both parameters among SIRS-positive cats compared to SIRS-negative ones highlights the potential usefulness of MLR in identifying cats at risk for SIRS.

Keywords: FIV, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, SIRS.

Introduction

Feline immunodeficiency virus (FIV) was initially discovered in a California cat colony in 1986, and classified as a member in the Retroviridae family. Despite it having a structure similar to feline leukemia virus (FeLV), FIV is a lentivirus related to human immunodeficiency virus, is endemic in domestic cats causing an immunosuppressive disease that linked to a high morbidity rate and clinical symptoms of immunodeficiency, [1-3]. Lethargy and viremia are the primary hallmarks of infection, at the initial stage of illness; but in second stage of infection that lasts longer, infected cat seems to be healthy, without clinical symptoms. At third stage, symptoms of immunodeficiency, lymphoma, or other chronic illnesses may be shown [3, 4]. Weight loss, fever, anorexia, leukopenia, anaemia, gingivitis, stomatitis, neoplasia, upper respiratory tract infections, dermatitis, lymphadenopathy, chronic gastrointestinal problems, and persistent wounds could be seen as typical clinical indicators of FIV infection [5-8]. FIV infects domestic cats worldwide, is primarily transmitted through bites and saliva that containing the virus and FIV-infected white blood cells (WBCs), [5-9]. Geographical variations in the frequency of FIV are believed to be caused by global variations in cat populations and risk factors related to cat feeding [10]. For diagnosis, POC (point of care) tests based on ELISA or rapid immunomigration (RIM) methods, can detect the FIV antibodies in whole blood, serum, or plasma. Alternative methodologies, including immunofluorescence assay (IFA) and Western blotting (WB), may be utilised; however, they present challenges in terms of availability and technical complexity [9,11]. In unvaccinated cats

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against FIV, application of three point-of-care test kits for FIV have demonstrated strong sensitivity and specificity in an independent study conducted under Australian conditions. Anigen Rapid™ (BioNote, Gyeonggi-do, Korea), Witness™ (Zoetis Animal Health, Lyon, France) and SNAP Combo™ (IDEXX Laboratories, Westbrook, ME, USA) [12].

Complete blood count (CBC) can be used to quickly and affordably calculate the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). The total number of neutrophils, platelets and monocytes is divided by the total number of lymphocytes to determine NLR, PLR and MLR, respectively. In human and veterinary medicine, NLR, PLR and MLR have been used increasingly to quantify inflammatory responses [13,14].

Systemic inflammatory response syndrome (SIRS) is a clinical condition that diagnosed based on clinical symptoms (high rectal temperature, high heart rate, high respiratory rate etc.). The diagnosis is fundamentally established based on deviations in WBC counts and alterations in vital signs [15]. NLR is used as an easily accessible parameter to assessing the inflammation status and physiological stress in the patients [16,17]. Although inflammation in response to tissue damage is a protective response, prolonged systemic inflammation can lead to organ dysfunction [15]. The neutrophil-to-lymphocyte ratio has previously been evaluated in both canine and feline patients diagnosed with systemic inflammatory response syndrome (SIRS), and its prognostic significance has been well documented, particularly in feline cases, where it has demonstrated considerable value as a predictive biomarker for clinical outcomes. [18,19].

The study aims to determine the diagnostic value of inflammatory biomarkers derived from CBC, namely the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio, in FIV-seropositive cats. Furthermore, the study seeks to evaluate the clinical utility of these biomarkers in detecting systemic inflammatory response syndrome in these patients, and to assess whether these parameters could serve as supportive tools in clinical decision-making processes for cats with FIV infection. Furthermore, the study aims to evaluate the interaction between FIV infection, NLR and SIRS, particularly through comparative analysis of NLR, MLR and PLR values between SIRS positive and SIRS negative cat groups.

Material and Methods

Animals

Study animals were divided into 2 groups as FIV positive and healthy animals. The FIV positive group was divided into two subgroups as SIRS positive and SIRS negative. The study material consisted of 15 FIV positive and 15 healthy a total of 30 cats of various breeds and ages (1–8 years old), including both males and females were brought to Small Animal Clinic of University Animal Hospital for examination, treatment, and general control. All clinical examination findings of each patient were recorded.

Blood samples and laboratory analaysis

Samples of blood were drawn from the vena cephalica antebrachii and collected into serum separator tubes and anticoagulant (K3-EDTA) tubes. Hematology Analyzer (Abacus Junior Vet, Diatron MI LTD, Hungary) was used to perform complete blood counts. From the anticoagulated blood, blood smears were prepared and microscopically evaluated to verify the hematology results. Serum samples were obtained by centrifuging the blood collected in serum separator tubes for 10 minutes at 3000 g. FIV antibodies were detected in serum samples from the cats using commercial immuno-chromatographic test kits and samples that gave a positive test result were considered FIV (+) and others were considered FIV (-) (FeliCheck-3, Anigen, Korea; sensitivity 96%, specificity 97.9%) [12,20].

The diagnosis of SIRS was established when three or more of the following criteria were met: rectal temperature ≥ 39.7°C or < 37.8°C; heart rate ≥ 225 beats/min or ≤ 140 beats/min; respiratory rate ≥ 40 breaths/min; white blood cell count ≥ 19,500 WBC/μL or ≤ 5,000 WBC/μL or band neutrophil fraction ≥ 5%, those with less than 3 criteria were considered SIRS (-). [21].

Statistical analysis

Statistical analyzes were performed using SPSS software (version 19.0, IBM Corporation), and A significance level of $p < 0.05$ was considered. Shapiro-Wilk test were used to assess the data's distribution. One-way analysis of variance (ANOVA) was used to evaluate normally distributed data, while the non-parametric Kruskal Wallis test was employed to express non-normal data. Two groups were compared using the Mann-Whitney U test, and three groups (healthy, SIRS (+) and SIRS (-) groups) were compared using the Kruskal-Wallis test. To determine the optimal diagnostic cut-off settings, receiver operating characteristic (ROC) curves were generated. Chi-square test was used to evaluate the relationship between FIV status and categorical variables.

Results

Study Population

The 15 cats included in the study were considered healthy based on their anamnesis, clinical, and laboratory findings. In the healthy group, there were the most mixed-breed cats (n=6) and turkish van cats (n=5). These were followed by tricolor (n=2), persian

(n=1), and british shorthair (n=1) cats. The average age of the healthy cats was 3.87 ± 2.09 (1-8 years), with 9 males and 6 females. While 4 of these cats lived indoors, 11 had a lifestyle associated with the outdoors. All of FIV (+) cats were presented to the clinic with clinical signs including gingivitis, oral-nasal lesions, cough, and eye and nasal discharge. Of these cats, 13 were mixed breed, , 1 was tricolor, , and 1 was persian. The age range of the cats varied between 1.5 and 7 years (3.53±1.73), with 7 cats (46.7%) being female and 8 cats (53.3%) being male. Additionally, one of these cats lived solely indoors, while 14 cats had direct exposure to the outdoors (Table 1). When the relationship between FIV positivity and risk factors such as age, breed, gender, and living environment was evaluated, no statistical significance was found (p>0,05). Chi-square test was used to evaluate the relationship between FIV status and categorical variables.

All hematological parameters of healthy cats and the average WBC, lymphocyte, monocyte, and neutrophil counts, as well as the RBC, Hg, Hct, and PLT values of FIV (+) cats, were within the reported reference values for cats. The mean lymphocyte percentage was significantly lower in FIV (+) cats compared to healthy cats ($p < 0.05$). The average lymphocyte percentage in FIV (+) cats was low, while the average monocyte and neutrophil percentages were high. Leukocytosis was defined as WBC > 19,500/µL; leukopenia as WBC < 5,000/µL, based on Babyak and Sharp [21]. The mean neutrophil percentage in FIV (+) cats was 78.5 ± 6.2%, which exceeds the upper limit of the reference range (60%). However, although it did not reflect in the average, 6 cats had leukocytosis (40%), 4 cats had leukopenia (27%), 4 cats had anemia (2 cats had mild and 2 cats had moderate) (27%), and 5 cats (3 cats had severe and 2 cats had moderate) had thrombocytopenia (33%). Korman and colleagues classified the severity of anemia in cats according to the packed cell volume (PCV)/haematocrit (HCT) ratio; mildly anemic (HCT/PCV 20–24.9%), moderately anemic (HCT/PCV 14–19.9%), and severely anemic (HCT/PCV 11–13.9%) [22].

When comparing the NLR, MLR, and PLR values of healthy cats and FIV (+) cats, the median NLR ($p= 0.049$) and MLR ($p=0.019$) values of FIV (+) cats were significantly higher than those of healthy group; while no significant difference were shown between the median PLR value ($p = 0.756$) of study groups (Figure 1).

When FIV-positive cats were evaluated according to the SIRS criteria [21], 10 of 15 FIV-positive cats (66.7%) were classified as SIRS (+). WBC, monocyte, and neutrophil counts did not differ statistically significantly between the SIRS (+), SIRS (-), and healthy groups (p>0.05); however, the SIRS (+) group's average lymphocyte ($p < 0.001$) and PLT ($p=0.003$) values were significantly lower than those of the healthy group (Figure 2). The mean lymphocyte (1.20 ± 0.67) and PLT count (200.41 ± 63.38) of the SIRS (+) group were significantly lower than the mean lymphocyte (3.32 ± 1.15) and PLT count (469.20 ± 153.70) of the healthy group (Figure 2) ($p= 0.000$ and $p= 0.003$, respectively).This significant decrease may reflect immune suppression and thrombocytopenic tendencies in SIRS (+) FIV-infected cats. As shown in Figure 2, the boxplots illustrate the significant decrease in lymphocyte and PLT counts in the SIRS (+) group compared to the healthy group.

There was no significant difference in PLR values among the three groups ($p > 0.05$)., The median NLR ($p=0.012$) and MLR (0.030) values of the SIRS (+) group were significant higher than observed in healthy group when comparing the NLR, MLR, and PLR values of the SIRS (+), SIRS (-), and healthy groups (Figure 3). Additionally, the best cutoff value of MLR for predicting SIRS was > 0.27 with 80.00% sensitivity and 75.00% specificity ($P = 0.026$; AUC 0.753; 95% CI 0.5308 - 0.9742) (Figure 4). NLR did not show significant predictive value for SIRS ($p = 0.1083$).. As shown in Figure 3, the boxplots demonstrate a significantly higher median MLR and NLR in SIRS (+) cats compared to the healthy group. ROC curve analysis for MLR is presented in Figure 4.

Discussion

Inflammatory biomarkers derived from complete blood counts, such as NLR, MLR, and PLR, were used in this investigation to determine the diagnostic value of these biomarkers in FIV seropositive cats and to examine their potential for detecting SIRS in these cats. Based on the outcomes of the present study, the median NLR and MLR values in FIV(+) and SIRS(+) cats were found to be significantly elevated in comparison to those of the healthy control group.

Additionally, in the determination of SIRS, an MLR > 0.27 was identified as the cut-off value with 80% sensitivity and 75% specificity ($p = 0.026$). Retroviruses are infectious agents of great importance for both human and animal health. FIV, one of the feline retrovirus agents, is one of the most important pathogens in cats and is one of the main reasons why cats get infections [9]. Many studies report that in cats, gender (male cats are more susceptible than female cats), age (the FIV (+) rate increases with age), and the environment they live in (outdoor environment) are risk factors for FIV (+) [6,8,23-26]. In line with the above studies, in this study as well, the majority of FIV (+) cats were male, with the cats' age range fluctuating from 1.5 and 7 years, and 14 cats had a relationship with the outdoor environment. However, no relationship was found between FIV (+) and risk factors such as age, breed, gender, and living environment. The lentivirus

known as FIV produces modest haematological abnormalities in most cats, including anaemia, lymphopenia, and neutropenia [27-29]. Many studies report that FIV-Ab (+) cats show a tendency towards neutrophilia, monocytosis, leukocytosis, neutropenia, lymphopenia, thrombocytopenia, and monocytopenia [24,26,27,30,31]. However, it has also been reported that these hematological changes are only significantly observed in the symptomatic and terminal phases [29,32]. Similar to the aforementioned studies, in this study, leukocytosis was present in 6 FIV (+) cats, leukopenia and anemia in 4, and thrombocytopenia in 5, and all of these cats were in the symptomatic phase. In FIV (+) cats, there were respiratory system symptoms such as gingivitis, oral-nasal lesions, cough, and eye and nasal discharge. Additionally, compared to healthy cats, the average lymphocyte percentage in FIV (+) cats was low, while the average monocyte and neutrophil percentages were statistically significantly high. Hemogram-derived inflammation markers, including NLR, MLR, and PLR, are new, widely used, reasonably priced, and conveniently accessible markers of systemic inflammation that come from regular hemogram examinations. Recently, these parameters have been evaluated in the inflammatory [18,33-36] and neoplastic [37,38] diseases of felidae and have been suggested as diagnostic and prognostic markers for some inflammatory and neoplastic conditions [39,40]. However, there is only one study evaluating these parameters in FIV-positive cats [29]. Rossi et al. [29] stated that there was no significant difference comparing cats with FIV-Ab and control cats in terms of NLR, MLR, and PLR ratios, explaining this by the lack of a statistical difference in the hematological parameters used for calculations in both groups. Additionally, they noted that the FIV infection stage was not taken into account and that hematological changes were only significant in the symptomatic and terminal phases. Rossi et al. [28], who included asymptomatic cats, our study focused on symptomatic FIV-positive cats, which may explain the differences in hematologic profiles. In this study, the median NLR and MLR values of FIV (+) compared to the healthy group, cats were statistically substantially higher, although there was no discernible difference between the groups in terms of median PLR value, similar to Rossi et al. [29]. All FIV (+) cats in our study had different hematological findings due to being symptomatic, and when compared to healthy cats, the FIV (+) cats had significantly lower lymphocyte counts and significantly higher neutrophil and monocyte counts. This situation can be explained by the observation of lymphopenia due to direct viral replication of CD4+ lymphocytes in the chronic stages of infection in FIV (+) cats [41,42] and the presence of neutrophilia and monocytosis due to the direct cytopathic effect of the virus on the bone marrow or chronic inflammation [30,43-46]. As a result, the low lymphocyte count and high monocyte and neutrophil counts in FIV (+) cats lead to higher MLR and NLR compared to healthy cats. Based on anomalies in the patient's vital signs and WBC count, SIRS is a clinical diagnosis that is defined by broad activation of the inflammatory system caused by an infectious agent or a sterile inflammatory disease [47, 48]. Several studies in humans and animals have highlighted the value of NLR and MLR in predicting SIRS [13,14,49,50]. Few studies, meanwhile, have examined these characteristics in cats with sepsis and SIRS [18,36,39]. An NLR value of $\geq$ 4.53 offers 76% sensitivity and 93.4% specificity in detecting SIRS+ septic cats, according to Gori et al. [18]. Gori et al. [18] reported that NLR may be used as a prognostic parameter in cats with SIRS. Similarly, in our study, the NLR value was significantly higher in the SIRS positive group than in the healthy group. Tuna and Kırkulak [35] reported that MLR and NLR values were noticeably greater in *Cystoisospora spp*. infected, diarrhea-positive SIRS cats compared to the healthy group. Additionally, they stated that an NLR value greater than 1.67 would be a helpful indicator for anticipating SIRS with 92.86% sensitivity and 84.62% specificity. In this study, parallel to the mentioned studies in SIRS (+) cats, the NLR and MLR values of SIRS (+) cats were significantly higher compared to SIRS (-) cats. The decline of the CD4+ T lymphocyte count associated with chronic lentivirus infection below a certain number, along with secondary and opportunistic infections, makes immune dysfunction evident. Thus, in addition to lymphopenia, monocytosis, and neutrophilia observed in chronic FIV infection, there are also increases in neutrophil and monocyte counts due to SIRS, which particularly contributes to secondary infections, along with decreases in lymphocyte counts [51,52]. We believe that the increases in NLR and MLR values in SIRS (+) cats in our study are related to this condition. However, unlike the above studies, this study found that NLR had diagnostic role in determining SIRS, while the best cutoff value for MLR in predicting SIRS was found to be > 0.27 with 80.00% sensitivity and 75.00% specificity.

Conclusion

In conclusion, FIV (+) cats had significantly higher NLR and MLR than healthy cats. Additionally, these two parameters were significantly greater among SIRS (+) cats than SIRS (-) cats, indicating that MLR could be a useful indicator in predicting SIRS. But, NLR could be considered a prognostic marker in feline cases with SIRS. Although the present findings highlight the potential clinical value of NLR and MLR as supportive diagnostic indicators in FIV(+)and SIRS (+) cats, further large-scale, prospective studies are indispensable to validate their diagnostic accuracy

and clinical applicability in routine veterinary practice.

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TABLE 1. Assessment of Biological and Behavioral Parameters in Healthy and FIV-Positive Cats

Feature	Healthy Group	FIV-Positive Group
Cat Breeds		
Mixed Breed	6	13
Turkish Van	5	0
Tricolor	2	1
Persian	1	1
British Shorthair	1	0
Average Age (years)	3.87 ± 2.09 (range 1–8)	3.53 ± 1.73 (range 1.5–7)
Gender		
Male	9	8
Female	6	7
Lifestyle		
Indoor	4	1
Outdoor	11	14

Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical of approval

The Animal Research Ethics Committee of the Aydın Adnan Menders University reviewed and approved all study procedures under protocol number 64583101/2019/047.

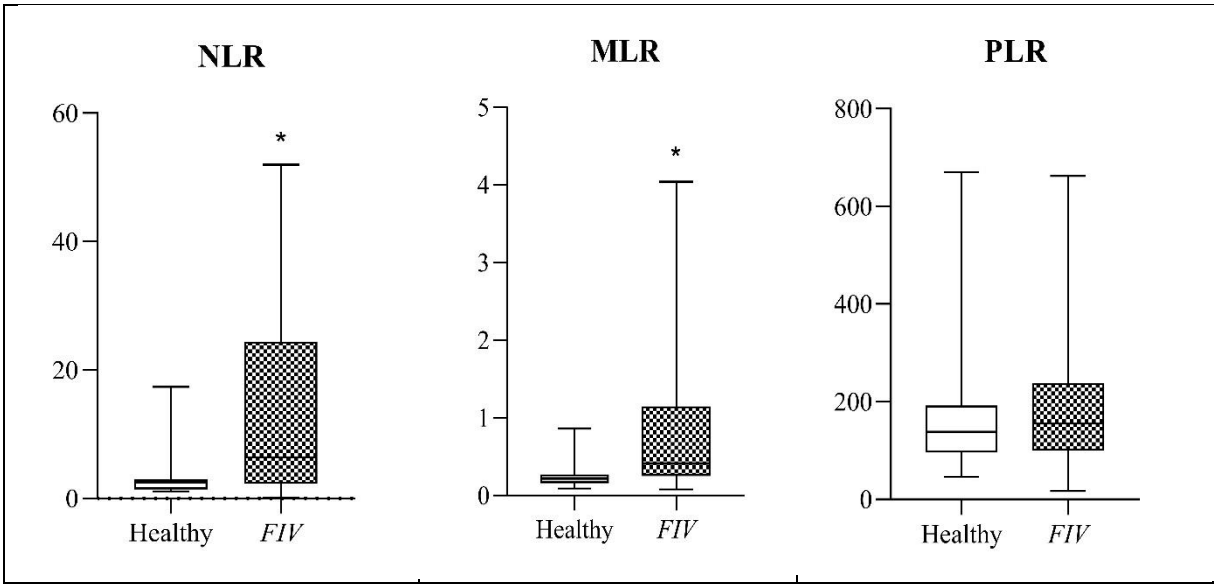

Fig. 1. Box plot graphs comparing the NLR (neutrophil-to-lymphocyte ratio), MLR (monocyte-lymphocyte ratio), and PLR (platelet-to-lymphocyte ratio) values of healthy and FIV (feline immunodeficiency virüs) (+) cats.
*: significant value

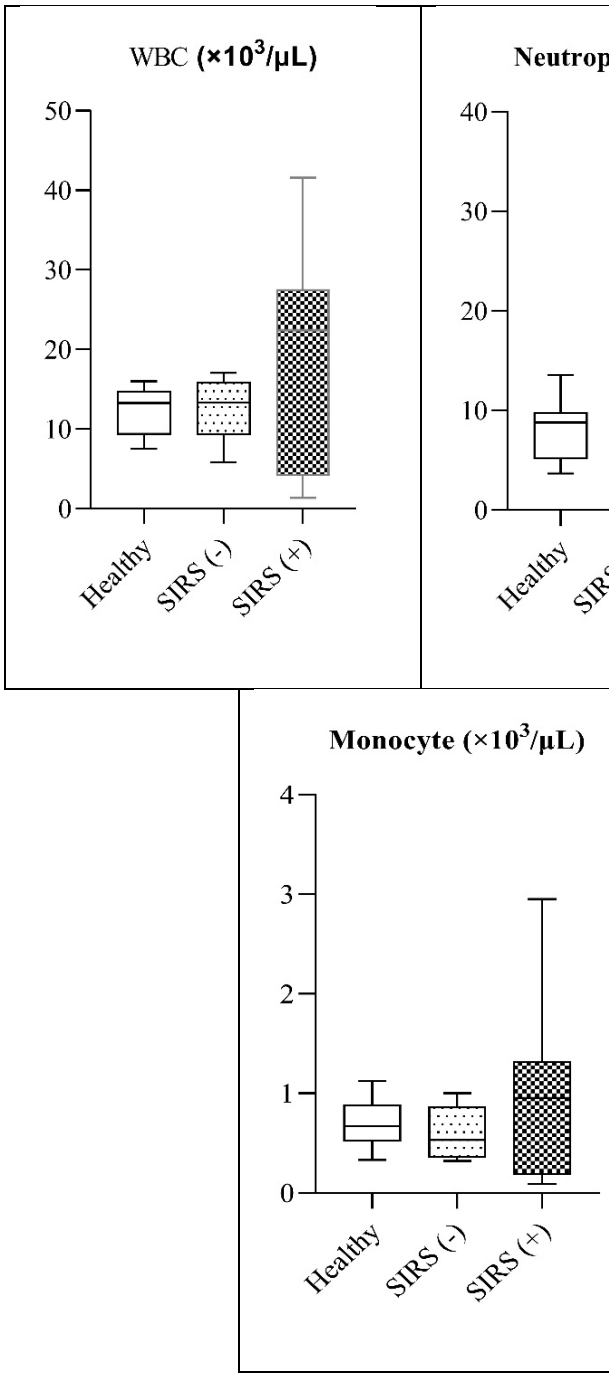

Fig. 2. Box plot graphs of WBC (white blood count), neutrophil, lymphocyte, monocyte, and PLT (platelet) values for healthy, SIRS (systemic inflammatory response syndrome) (-), and SIRS (+) groups.

*a, b, ab: It expresses statistical significance. There is a statistical difference between a and b, but not between a or b and ab.

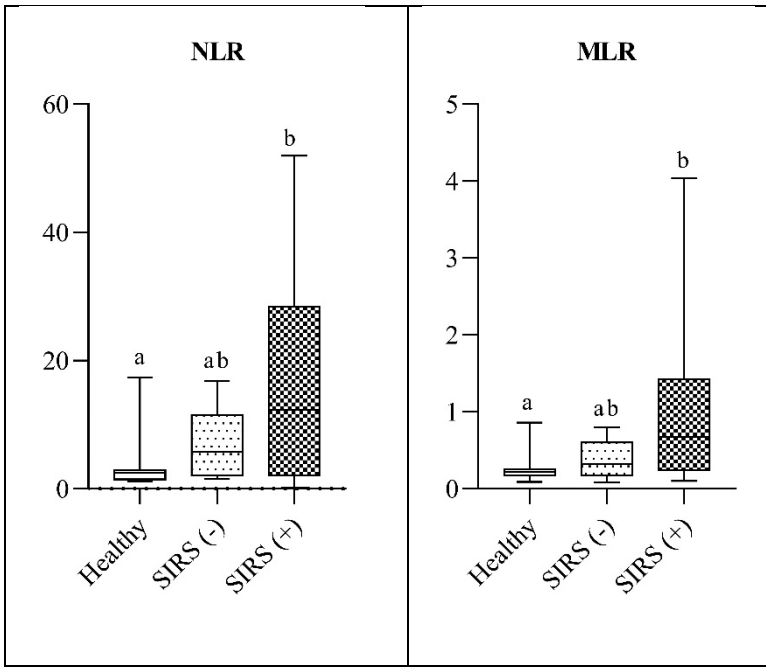

Fig. 3. Box plot graphs of NLR (neutrophil-to-lymphocyte ratio), MLR (monocyte-lymphocyte ratio), and PLR (platelet-to-lymphocyte ratio) values for healthy, SIRS (systemic inflammatory response syndrome) (-), and SIRS (+) groups.

*a, b, ab: It expresses statistical significance. There is a statistical difference between a and b, but not between a or b and ab.

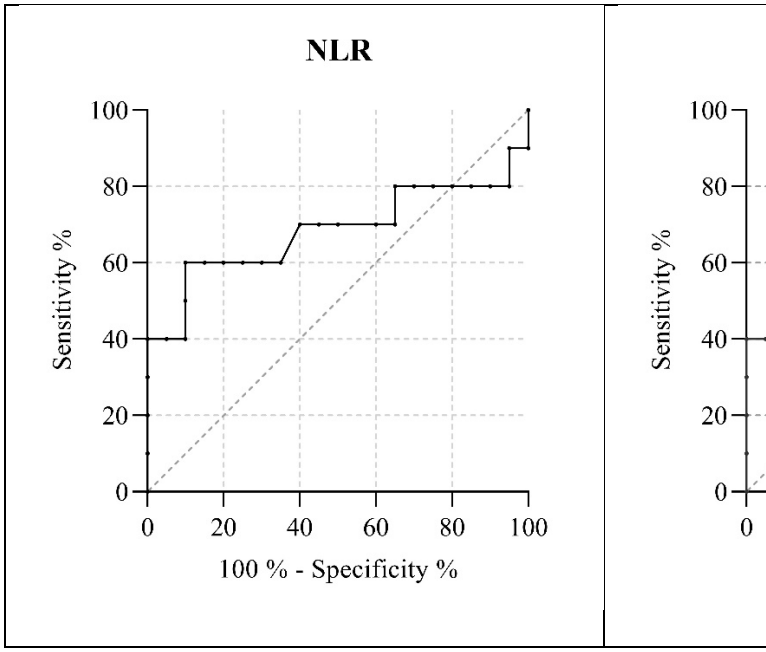

Fig. 4. Receiver operating characteristic of NLR (neutrophil-to-lymphocyte ratio) and MLR (monocyte-lymphocyte ratio) to predict SIRS (systemic inflammatory response syndrome).

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