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RETROSPECTIVE STUDY

Retrospective evaluation of the neutrophil-to-lymphocyte ratio as a prognostic marker in cats with blunt trauma (2018–2021): 177 cases

Pavlos G. Doulidis DVM[1] | Yasamin Vali DVM[2] | Caroline Frizzo Ramos DVM[3] | Abigail Guija-de-Arespacochaga DVM, DECVCP[4]

[1]Department for Companion Animals and Horses, Division of Small Animal Internal Medicine, University of Veterinary Medicine of Vienna, Vienna, Austria

[2]Diagnostic Imaging, University of Veterinary Medicine, Vienna, Austria

[3]Clinical Unit of Anesthesiology and Perioperative Intensive Care, University of Veterinary Medicine, Vienna, Austria

[4]Department of Pathobiology, Clinical Pathology Platform, University of Veterinary Medicine, Vienna, Austria

Correspondence
Pavlos G. Doulidis, University of Veterinary Medicine of Vienna, Veterinaerplatz 1, 1210 Vienna, Austria.
Email: Pavlos.Doulidis@vetmeduni.ac.at

Partial results of this study were presented at the 24th Annual Congress ESVCP–ECVCP 2022, October 2022 in Belgrade, Serbia.

Abstract

Objective: To investigate the utility of the neutrophil-to-lymphocyte ratio (NLR) as a prognostic marker in cats with blunt trauma.

Design: Retrospective study from January 2018 to December 2021.

Setting: University teaching hospital.

Animals: Medical records of 177 cats admitted with blunt trauma were evaluated. History, clinical findings, blood cell count-based ratios, thoracic radiographs on presentation, and outcome were reviewed. The Animal Trauma Triage (ATT) score was assessed in each cat and classified as mild (1–3), moderate (4–7), and severe trauma ($\geq$8). Forty-eight healthy blood donor cats served as the control population. NLR, neutrophil counts, and lymphocyte counts were compared between cats with blunt trauma and controls, and among trauma patients.

Interventions: None

Measurements and Main Results: NLR, neutrophil counts, and lymphocyte counts significantly differ in cats with blunt trauma compared to controls ($p < 0.001$), and NLR was higher in patients with thoracic trauma ($p = 0.044$). Nonsurvivors had lower lymphocyte counts ($p = 0.041$), although those values do not appear to be clinically relevant. A significant increase in NLR was observed with increasing severity of trauma ($p < 0.001$). The NLR was not associated with the length of hospitalization, intensive care assistance, or mortality.

Conclusion: NLR is a widely available diagnostic tool, which can be used in addition to ATT to assess trauma severity, although in our study it was not predictive of the outcome.

KEYWORDS
feline, hematology, NLR, outcome, trauma severity score

Abbreviations: ATT, Animal Trauma Triage; HBC, hit by car; HRS, high-rise syndrome; MODS, multiple organ dysfunction syndrome; NLR, neutrophil-to-lymphocyte ratio.

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1 | INTRODUCTION

Blunt trauma, particularly as a result of high-rise syndrome (HRS) and trauma due to motor vehicle accidents, is common in feline emergency and critical care.[1–3] However, different patterns of injury severity have been described in different studies,[1–3] with thoracic trauma being prevalent in up to 63.5% of cases with HRS.[4] Trauma is one of the most common conditions related to ICU admission or euthanasia.[5–7] Even if survival rates of up to 97% have been reported in cats with HRS,[8] thoracic involvement in blunt trauma patients is associated with an increased risk of mortality[9]; therefore, prompt diagnosis and intensive treatment are crucial for these patients.

In human medicine, it has been demonstrated that dysregulation of the pro-inflammatory and anti-inflammatory response balance in the first hours after trauma is an important factor that influences mortality rates.[10] Tissue injury stimulates the production of pro- and anti-inflammatory mediators, primarily of the innate immune response cells such as neutrophils,[10] while a parallel decrease in blood lymphocytes can also be expected posttrauma.[11] An uncontrolled cytokine cascade in these patients can rapidly lead to complications like systemic inflammatory response syndrome and multiple organ dysfunction syndrome (MODS).[12] Accordingly in human medicine, the blood neutrophil-to-lymphocyte ratio (NLR) has been proposed as an early indicator of disbalance in inflammatory homeostasis and it has recently been shown to be a useful and simple prognostic tool in human patients presented with blunt trauma.[13,14] In veterinary medicine, NLR has been investigated as a diagnostic and prognostic marker in animals with neoplasia, inflammatory, endocrine, and infectious diseases among others[15–31]; however, to the authors' knowledge, no studies have evaluated its utility in cats with blunt trauma. Considering that CBC analysis is nowadays available to most veterinary practices, NLR is a simple and universally available tool for veterinarians and could be helpful in estimating prognosis for the feline blunt trauma patients. Therefore, the primary aim of this retrospective study was to investigate the utility of initial NLR in cats suffering from blunt trauma with and without thoracic injury and assess its prognostic value in this population.

2 | MATERIALS AND METHODS

Medical records of cats with a history of blunt trauma presented to our university clinic, between January 2018 and December 2021, were reviewed retrospectively. Cases were identified from the animal hospital information system (TIS) using the following keywords: "blunt trauma," "HBC" (Hit by Car), "hit by car," "HRS" (high-rise syndrome), and "High Rise Syndrome." Cats were included in the study if they had a posttrauma thoracic radiography and CBC performed within 24 hours after trauma as well as records available for evaluation. Cats with a questionable history of trauma, concurrent diseases unrelated to the trauma, medication prior to presentation, and lack of optimal treatment due to financial concerns of the owner were excluded. The control group consisted of client-owned blood-donor cats. Those cats were considered healthy based on physical examination as well as on hematology and serum biochemistry results and were not receiving any medications. Data were extracted and categorized by signalment, clinical, radiographic, and laboratory findings.

For each patient, retrieved information contained signalment (age, sex, breed), type of trauma (eg, HBC, HRS, blunt trauma of unknown origin), time since trauma event, initial physical examination findings (eg, heart rate, respiratory rate, type of breathing, thoracic auscultation results, perfusion status), injury type, intensive care requirement, hospitalization time (≤3, 4–7, and >8 d), need for blood transfusion or oxygen support (eg, oxygen cage), and outcome (survival to discharged vs died or euthanized). Based on these parameters at the time of presentation and before any medical intervention, an Animal Trauma Triage (ATT) score, a trauma localization system that indicated the location of the trauma (eg, head or neck, thorax, abdomen, extremities), and the severity of the injury (eg, none to mild to severe) were assessed. ATT score results were further summarized into mild trauma (ATT score 1–3), moderate trauma (ATT score 4–7), and severe trauma (ATT score 8).[4,32] ATT score has previously been evaluated in a large cohort of trauma feline patients and has shown excellent outcome predictive performance.[7] Abnormal thoracic radiograph findings were used to evaluate the presence and severity of thoracic trauma and included pneumothorax, pleural, and mediastinal effusion, rib and sternal fractures, as well as lung contusion. An automated complete blood cell count was performed within 24 hours of admission.[a] Blood smears were prepared and stained by an automated stainer using a modified Wright stain.[b] Numerical changes in total leukocyte counts, neutrophils, and lymphocytes exceeding 25% of the upper or the lower reference limit of the respective cell population and/or scatterplots indicating inappropriate cell separation prompted a microscopic slide evaluation by a senior technician to confirm abnormalities present in automatic counts, and if necessary, a microscopic count of 100 cells was carried out. Reference intervals for our laboratory for leukocytes are 6–18 × 10^9/L, neutrophils 3.6–12.75 × 10^9/L, and lymphocytes 0.9–5.1 × 10^9/L. The NLR was calculated as the ratio of the total neutrophil count (segmented and band neutrophils) to lymphocyte count.

2.1 | Statistical methods

The statistical analysis was done with a commercially available statistics program.[c] The distributions were assessed for normality with the Shapiro–Wilk test. Since most continuous variables were not normally distributed, nonparametric comparison tests were used for data analysis. Wilcoxon Mann–Whitney *U*-test was used to compare medians and data distribution from 2 groups of cats, while the Tukey–Kramer test was used for multiple comparison analysis. The associations between NLR, neutrophils, lymphocytes, and ATT with disease severity, the presence of thoracic trauma, course of disease (ICU stay, hospitalization period), and outcome were calculated accordingly. Differences were deemed significant at a *p*-value of <0.05.

TABLE 1 Total neutrophil count, lymphocyte count, and neutrophil-to-lymphocyte ratio (NLR) values (median and range) and comparison between Trauma and Control groups in both SI (international units) and US (conventional units).

	Trauma group ($n = 177$)	Control group ($n = 48$)	Reference interval	p-value
Neutrophil count, SI (US), $\times 10^9$/L ($\times 10^3$/µL)	9.7 (2.6–23.32)	4.58 (1.9–8.64)	3.6–12.75	<0.0001
Lymphocyte count, SI (US), $\times 10^9$/L ($\times 10^3$/µL)	1.14 (0.23–6.47)	1.7 (0.5–6.7)	0. 9–5.1	<0.0001
NLR	8.4 (0.43–57.13)	2.26 (0.4–9.3)		<0.0001

Abbreviation: NLR, neutrophil-to-lymphocyte ratio.

3 | RESULTS

The initial keyword search of the digital databases resulted in 2074 records of cats, presented to the university's small animal clinic with a history of blunt trauma during a 48-month period. After removing duplicates and filtering the abovementioned keywords to ensure proper diagnosis, we screened 430 cats. Of these cats, 243 were excluded due to incomplete medical history, missing laboratory data, or thoracic radiography (total $n = 138$); concurrent diseases ($n = 58$) (eg, dermatological disease [$n = 18$], chronic kidney disease [$n = 13$], diabetes mellitus [$n = 9$], hypertrophic cardiomyopathy [$n = 8$], feline leukemia virus infection [$n = 7$], and feline immunodeficiency virus infection [$n = 3$]); and prior medication administration ($n = 47$) (eg, nonsteroidal anti-inflammatory medication [$n = 25$], prednisolone [$n = 20$], and furosemide [$n = 2$]). Ten cats did not receive optimal treatment at the owner's request and were also excluded. The remaining 177 cats met the inclusion criteria and were included in the study as the trauma group. There were 109 (62%) males and 68 (38%) females. The median age in this group was 4 years (range: 0.6–17 y). Injury origin could be confirmed as HRS in 75 (42%), HBC in 21 (12%), and trauma of unknown origin in 81 (46%) of the patients. One hundred and fifty-nine (90%) cats survived, while 18 cats (10%) died or were euthanized. Forty cats (23%) needed short- or long-term oxygen supplementation, whereas 15 (8%) received a blood transfusion.

The control group constituted 48 healthy client-owned cats of which 33 (69%) were male and 15 (31%) were female with a median age of 4 years (range: 2–11 y). The best cutoff value for NLR between trauma patients and healthy cats based on receive operator characteristic (ROC) was 4.45 (sensitivity of 74% and specificity of 71%). Statistical analysis suggested that the NLR was significantly higher in the trauma group (median: 8.4, range: 0.43–57.13) than in the control group (median: 2.26, range: 0.4–9.3) ($p < 0.001$) (Figure 1). The total neutrophil count was also higher in cats with blunt trauma (median: 9.7×10^3/µL, range: 2.6–23.32) compared to the control group (median: 4.58×10^3/µL, range: 1.9–8.64) ($p < 0.001$), whereas the lymphocyte count was significantly lower in case of trauma (median: 1.14×10^3/µL, range: 0.23–6.47) than in healthy patients (median: 1.73×10^3/µL, range: 0.5–6.7) ($p < 0.001$) (Table 1).

Cats with thoracic trauma ($n = 134$) had a significantly higher NLR (median: 9.18, range: 0.88–57.13) than the cats in the trauma group without thoracic involvement ($n = 43$) (median: 6.4, range: 0.43–37.42) ($p = 0.04$) (Figure 2); however, no differences were found in total neutrophil and lymphocyte counts (Table 2). No significant difference was detected in patients with suspected abdominal involvement (ascites, peritonitis signs, hernias, concussions, hematomas, hematuria) ($p > 0.05$).

Sixty-two cats (35%) in the trauma group were hospitalized for 3 days or less, 75 cats (42.4%) between 4 and 7 days, and 40 cats (22.6%) for more than 8 days. The NLR and total neutrophil and lymphocyte counts did not differ significantly in cats within the different hospitalization periods ($p > 0.05$) (Table 2). No significant difference in total neutrophil and lymphocyte counts, as well as NLR, was detected between cats needing intensive care ($n = 25$) and those not requiring it ($n = 152$) ($p > 0.05$) (Table 2).

The difference in NLR and total neutrophil count between survivors ($n = 159$) and nonsurvivors ($n = 18$) was not statistically significant ($p = 0.13$ and 0.95, respectively), and while a difference ($p = 0.041$) was detected in lymphocyte count between the 2 outcome groups, as survivors (median: 1.19×10^9/L, range: 0.23–6.47) had significantly higher lymphocyte count than nonsurvivors, this difference is within measurement error levels and the median value remained within the normal limits (median: 0.91×10^9/L, range: 0.33–4.79) (Figure 3; Table 2).

The difference in the NLR of animals within the 3 different ATT score groups was statistically significant ($p < 0.0001$) (Figure 4). In detail, the NLR in cats with ATT scores of 1–3 (median: 3.98, range: 0.43–11.13) differed from the NLR in cats with ATT scores of 4–7 (median: 13.09, range: 2.37–57.13) ($p < 0.0001$) and from the NLR in cats with ATT score >8 (median: 28.21, range: 20.48–47.44) ($p < 0.0001$), while the difference in NLR between the ATT scores 4–7 and >8 was also significant ($p < 0.0001$). Likewise, it was observed that patients with higher ATT scores presented the highest NLR values (Figure 5).

4 | DISCUSSION

Blunt trauma is a common diagnosis in both human and veterinary emergency critical care medicine. It is a condition that has a favorable prognosis, with 80% of the cats with blunt trauma surviving to discharge in a recent study,[33] but can frequently be associated with long hospitalization periods, intensive care in up to 38% of the cases,[33] and high treatment costs. Hence, the need for reliable, rapidly available prognostic tools is of utmost importance. In human medicine, many simplified scoring systems have failed to demonstrate an adequate predictive capacity in patients with blunt trauma, in comparison to more complicated scoring systems, which require more time and resources.[34] The NLR is a simple, widely available, and rapidly accessible method for evaluating inflammation status, which can quickly provide valuable information about disease severity and potential

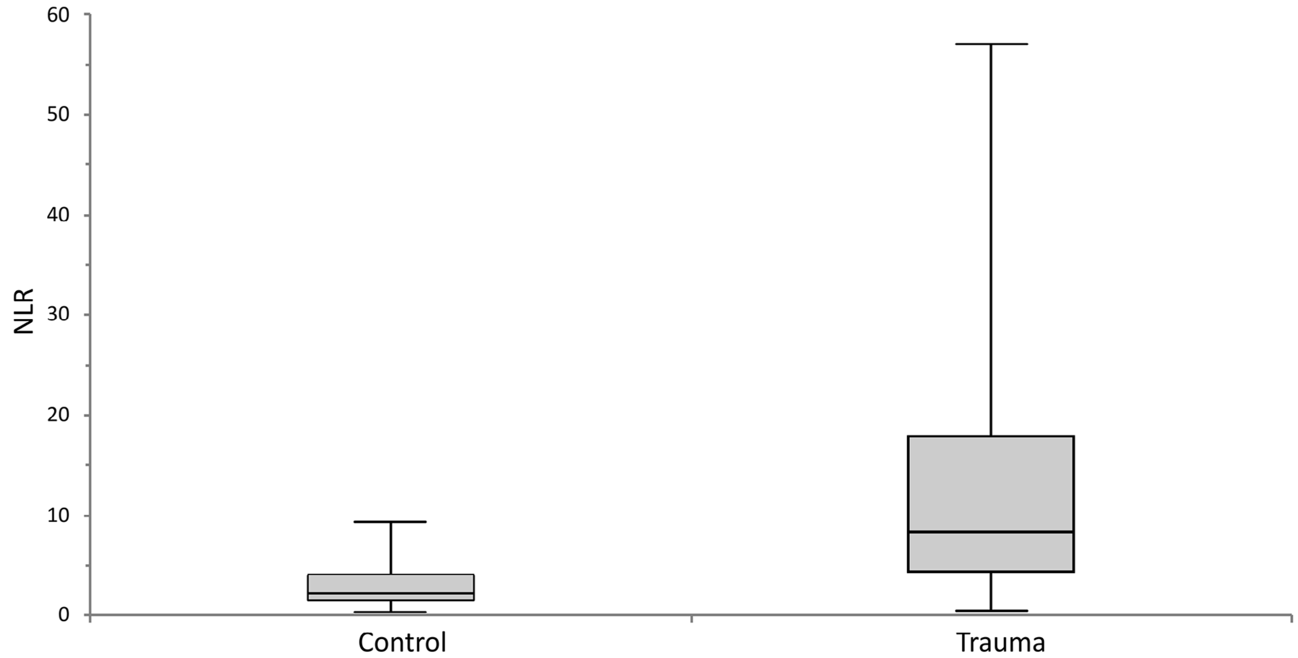

FIGURE 1 Box and whisker plot demonstrating the neutrophil-to-lymphocyte ratio (NLR) between Control ($n = 48$) and Trauma ($n = 177$) groups. The box represents the first and third quartile, and the central line represents the median. The outer extent of the whiskers represents maximum and minimum population values. Cats in the trauma group have significantly higher NLR than the cats in the control group ($p < 0.0001$).

TABLE 2 Total neutrophil count, lymphocyte count, and neutrophil-to-lymphocyte ratio (NLR) values (median and range) and comparison between different subgroups in both SI (international units) and US (conventional units).

	N	Neutrophil count, SI (US), $\times 10^9$/L ($\times 10^3$/µL)	*p*-value	Lymphocyte count, SI (US), $\times 10^9$/L ($\times 10^3$/µL)	*p*-value	NLR	*p*-value
Thoracic trauma							
Yes	134	10.20 (3.14–23.32)	>0.05	1.07 (0.23–6.47)	>0.05	9.17 (0.88–57.13)	0.0441
No	43	8.41 (2.60–22.12)		1.25 (0.37–6.05)		6.40 (0.43–37.42)	
Hospitalization days							
<3	62	10.09 (2.6–23.32)		1.15 (0.3–6.05)		7.98 (0.43–47.45)	>0.05
4–7	75	9.7 (3.15–22.6)	>0.05	0.97 (0.23–4.91)	>0.05	9.06 (0.9–50.52)	
>8	40	9.4 (3.6–17.48)		1.27 (0.23–6.47)		6.95 (0.88–57.13)	
ICU							
Yes	25	9.10 (3.14–23.32)	>0.05	0.94 (0.33–4.05)	>0.05	9.77 (1.79–36.76)	>0.05
No	152	9.81 (2.60–23.31)		1.14 (0.23–6.47)		8.37 (0.43–57.13)	
Outcome							
Survivors	159	9.70 (2.60–23.32)	>0.05	1.19 (0.23–6.47)	0.0415	8.09 (0.43–57.13)	>0.05
Nonsurvivors	18	9.22 (3.14–23.31)		0.91 (0.33–4.79)		9.51 (1.67–36.76)	

Abbreviation: NLR, neutrophil-to-lymphocyte ratio.

outcomes. The association between NLR and outcome has already been investigated in human medicine, suggesting a worse outcome with increasing NLR.[13,35,36]

In veterinary medicine, the utility of both canine and feline NLR received increased attention over the last years, especially in the fields of infectious, inflammatory, and neoplastic diseases.[15,17–31] These studies demonstrated that NLR can play an additional role in evaluating the inflammation status and possibly contribute to predicting the outcome.

The diagnostic and prognostic value of NLR in feline patients suffering blunt trauma has not yet been established. Therefore, our aim was to investigate the changes of the NLR in feline blunt trauma patients of different trauma severity versus controls, analyze the relationship between the NLR and outcome, and, finally, evaluate the utility of the

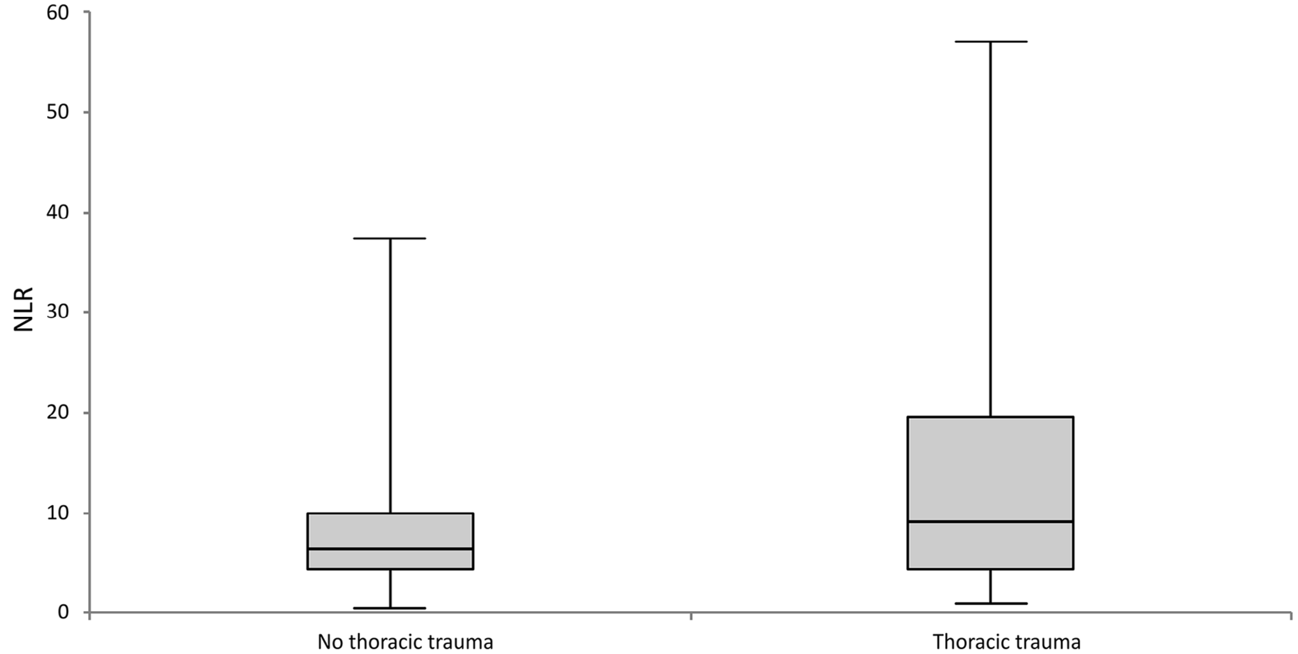

FIGURE 2 Box and whisker plot demonstrating neutrophil-to lymphocyte-ratio (NLR) of cats with traumatic thoracic changes ($n = 134$) and cats without evidence of thoracic changes ($n = 43$). The box represents the first and third quartile, and the central line represents the median. The outer extent of the whiskers represents maximum and minimum population values. Cats with thoracic changes have significantly higher NLR than the cats without ($p < 0.0001$).

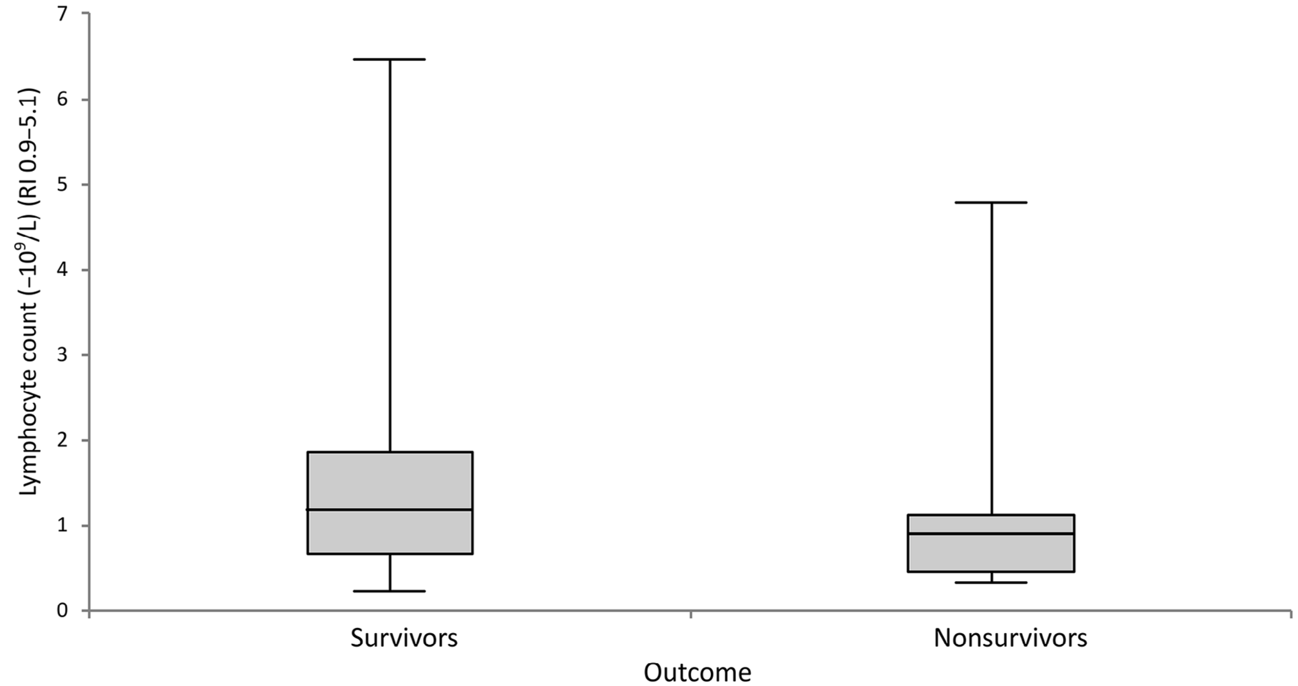

FIGURE 3 Box and whisker plot demonstrating the lymphocyte count of cats with blunt trauma that survived ($n = 159$) and cats that were euthanized or died ($n = 18$). The box represents the first and third quartile, and the central line represents the median. The outer extent of the whiskers represents maximum and minimum population values. Cats that survived show significantly higher lymphocyte count than the cats that did not ($p < 0.0415$).

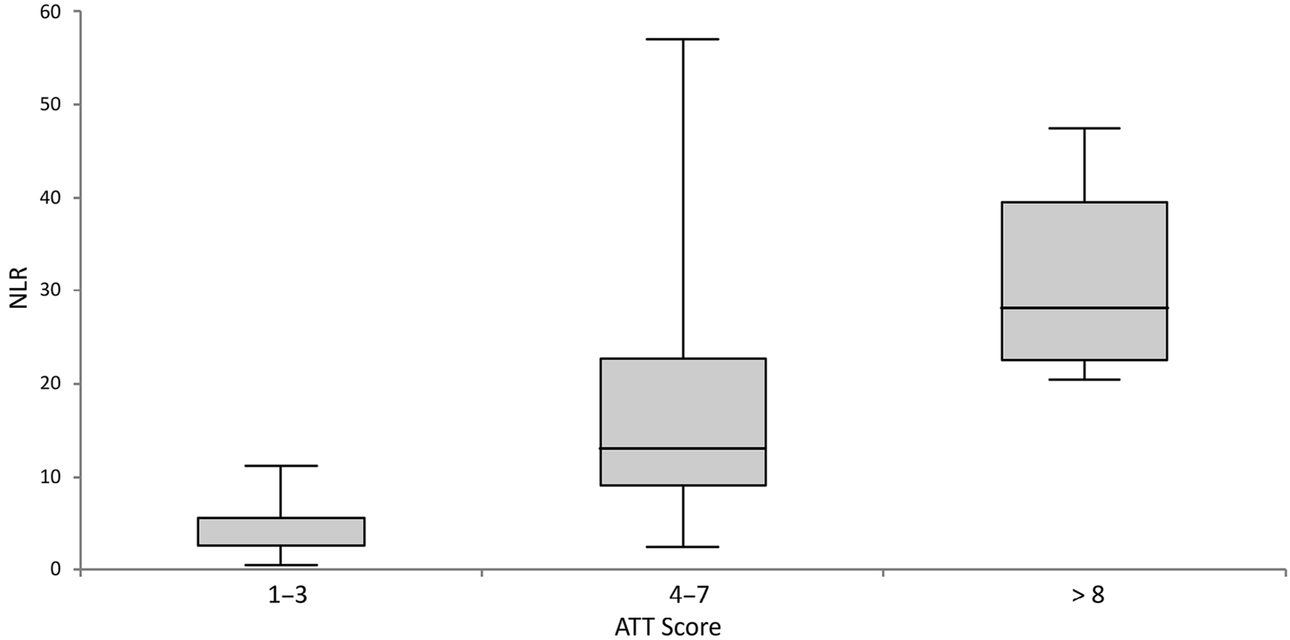

FIGURE 4 Box and whisker plot of the neutrophil-to lymphocyte-ratio (NLR) between the 3 Animal Trauma Triage (ATT) score groups. The box represents the first and third quartile, and the central line represents the median. The outer extent of the whiskers represents maximum and minimum population values. Cats with ATT score between 1 and 3 (median: 3.98, range: 0.43–11.13) have a lower NLR in comparison to cats with ATT score 4–7 (median: 13.09, range: 2.37–57.13) and >8 (median: 28.21, range: 20.48–47.44), while cats with ATT score >8 have a higher score, when compared to cats with ATT score 4–7. The differences between all groups are statistically significant ($p < 0.0001$ for all pairwise testing).

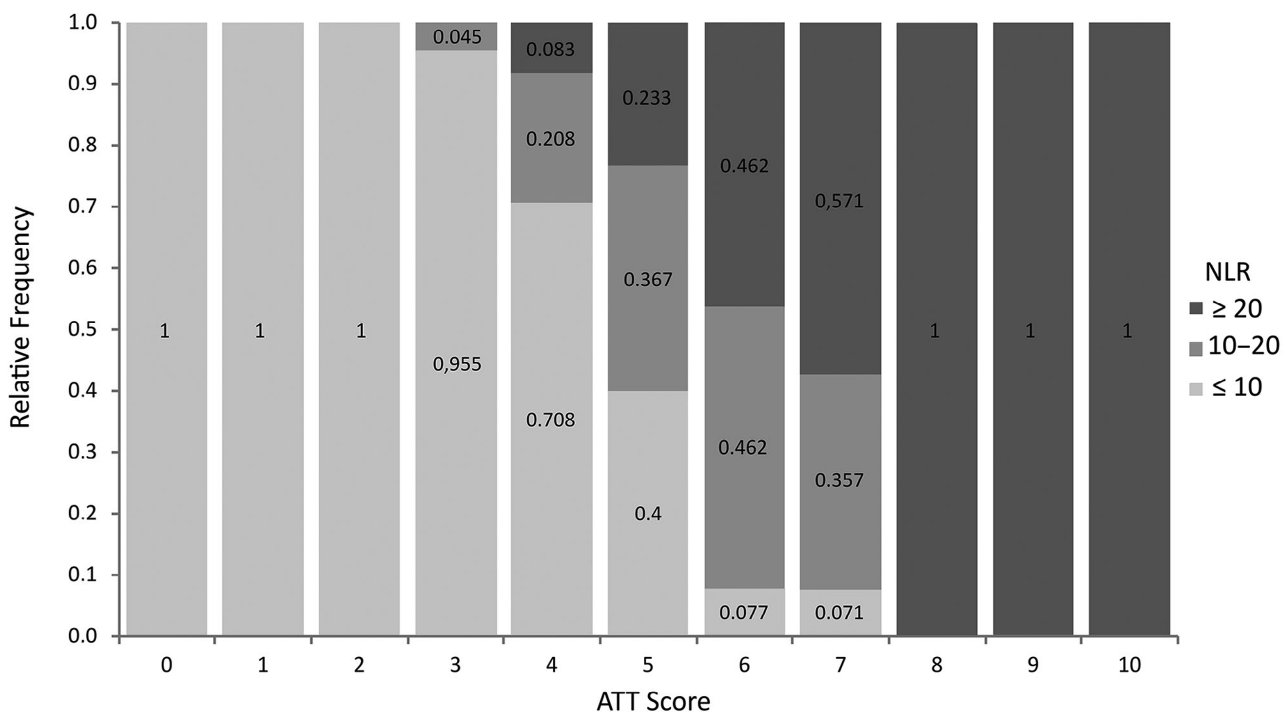

FIGURE 5 Mosaic plot illustrating the relationship between neutrophil-to-lymphocyte ratio (NLR) and Animal Trauma Triage (ATT) score. Patients with a higher ATT score demonstrate a higher NLR.

NLR, total neutrophil, and lymphocyte counts in predicting outcome in patients with thoracic involvement.

In our study, cats with blunt trauma had a significantly higher NLR and total neutrophil count and a lower lymphocyte count compared to the control group. However, in contrast to human studies where an increased NLR was associated with higher mortality in critically ill trauma patients,[13,14] a significant predictive value of NLR regarding outcome could not be demonstrated in our study. The interpretation of these findings must be made cautiously, as the number of nonsurvivors (10.2%) is low, and the distribution of the outcome groups is noticeably uneven. Neutrophils compose the first line of defense against microorganisms by means of degranulation, phagocytosis, and generation of extracellular traps. Alterations in neutrophil count and in multiple of its functions, like phagocytizing and oxidative burst, have been observed at various time points after trauma in people,[37–39] potentially contributing to the development of complications. A shift from the marginated to circulating pool is based on inflammatory cytokines like (IL-1, TNF, IFN-γ) and other chemical mediators (LTBA4, PAF) that equate to a more severe inflammatory response.[40] Hospitalized trauma patients have an increased susceptibility to secondary infections, probably because of neutrophil sequestration in remote bystander organs, leading to the development of both acute respiratory distress syndrome and MODS.[41] Additionally, the release of multiple endogenous damage-associated molecular patterns through tissue damage has been recognized as the initiator of systemic inflammatory response syndrome.[42] Elevated plasma levels of inflammatory cytokines, such as IL-6, IL-8, and TNF-α among others, have been reported in humans with acute lung injury and have been associated with increased mortality among these patients.[43] Nonetheless, here we observed that nonsurvivors have a significantly lower lymphocyte count compared to survivors, although the difference is not clinically significant and within the error levels. Conway et al reported significant differences in lymphocyte count in dogs with pneumonia. Lymphocytes are a major cellular component of both the cell-mediated and humoral immune response. It has been shown that both T- and B-lymphocytes are negatively affected in trauma and hemorrhage models. Irregularities in the Th1 immune response are associated with a decrease in the count of CD4+ T cells and natural killer cells. Lymphopenia is a commonly reported finding in patients with sepsis, burns, and MODS.[44] Furthermore, studies in people and animal models have shown that lymphocyte loss, apoptosis, or dysfunction can rapidly occur after trauma[11,45,46] and specifically after acute lung injury.[47] Moreover, persistent lymphopenia has been shown to be associated with an increased mortality rate in severely injured patients compared to those whose lymphocyte levels returned to normal values after 4 days.[11,45] A continued cellular loss, exhaustion, desensitization, and downregulation of the lymphocytes may explain the failure of the immune system to normalize their count, leading to a lower associated survival in these patients.[46] In alignment with these data, the fact that in our study cats with thoracic injury showed a significantly higher NLR when compared to patients without thoracic injury hints that a more severe inflammatory response can follow also in feline trauma patients with thoracic involvement. However, this should be interpreted with caution, since the higher marginated leukocyte pool (estimated in cats to be 70%) may be responsible for more variable leukocyte counts compared to dogs and humans and consequently higher NLR.[48] Additionally, lack of precision in the measurement of leukocytes must be considered, especially in those samples where bands and toxic cells are present, which can lead to errors in cell differentiation Therefore, it must be highlighted that these ratios should be critically interpreted since their result depends directly on the precision of the hematological instruments for neutrophils and lymphocytes used for the analysis and the experience of the technicians in case a manual differentiation is required. Microscopic evaluation of blood smears should always be performed in patients with pathological results and altered graphics. An ATT score was retrospectively assigned to our trauma study cohort. The ATT scoring system is used to utilize information gathered from the physical examination performed at presentation for emergency care, prior to further extensive diagnostic and therapeutic intervention.[32] Rockar et al also showed a correlation between an ATT score >7 and a decreased survival rate. We hypothesized that NLR will positively correlate with the ATT and this correlation might strengthen the severity and prognosis assessment and provide the clinician with an additional tool in deciding the trauma severity. In our study, we found a significant difference in the NLR value between the ATT score groups; in addition, an increase in NLR parallel to the ATT was observed. The fact that more severely injured patients have a higher NLR score is in alignment with data in the literature that support increased disease severity, due to a greater stress response, more pronounced neutrophilia, and a decrease in lymphocyte count, all connected to higher NLR.[13,14,18,19]

Based on the retrospective design of the study, there are some limitations that are unavoidable and may have affected the result. For example, initial clinical assessment, re-checks, and treatment of the patients were performed by various veterinarians, which may have affected the history and ATT scoring. The study population was composed only of animals that received a thoracic radiograph and a blood examination within 24 hours after trauma. However, the exact procedures and the exact point of sample testing may play an additional role in the NLR fluctuation. Another limitation is the method by which the cell populations were determined in the samples, with most identified automatically; however, in cases flagged by the instrument, the count was carried out manually. Other inflammation markers (such as Serum Amyloid A) were only occasionally available. Furthermore, in our population of 177 cats, 159 (89.8%) survived, while only 18 (10.2%) passed away or were euthanized. This uneven distribution, because of the restricted size of the nonsurvivors' group, should be considered when interpreting results. Finally, NLR was available only on patient admission since regular analyses were not available for all patients.

Therefore, it is possible that NLR provides better information about the prognosis and outcome in feline trauma patients using serial measurements over time, as in humans, serial measurements of NLR have shown promising potential.[19,49]

5 | CONCLUSIONS

Cats that suffer from blunt trauma have a higher initial NLR compared to the control group. Similarly, thoracic trauma was associated with higher NLR. NLR during the first 24 hours of admission does not offer predictive value about the outcome when used alone, but it provides useful information about trauma severity, as we report a higher initial NLR in cats with increased ATT scores. Prospective studies are needed to further evaluate the prognostic quality of NLR and to investigate possible correlations with other clinical or hematological parameters, as it should not be used alone as a marker for predicting outcomes.

AUTHOR CONTRIBUTIONS

Pavlos G. Doulidis: conceptualization; data Curation; investigation; methodology; project Administration; writing Original Draft; writing Review Editing. **Yasamin Vali**: conceptualization; investigation; methodology; writing Original Draft; writing Review Editing. **Caroline Frizzo Ramos**: conceptualization; data Curation; investigation; methodology; writing Original Draft; writing Review Editing. **Abigail Guija-de-Arespacochaga**: data Curation; formal Analysis; investigation; methodology; project Administration; software; supervision; writing Original Draft; writing Review Editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ORCID

Pavlos G. Doulidis DVM https://orcid.org/0000-0001-8731-2936
Yasamin Vali DVM https://orcid.org/0000-0002-6090-0663

ENDNOTES

[a] ADVIA 2120i, Siemens Healthcare Diagnostics GmbH, Vienna, Austria.
[b] Hematek and Hematek Stain Pack, Modified Wright; Siemens Healthcare Diagnostics GmbH, Vienna, Austria.
[c] Analyse It Software for Microsoft Excel 5.92, Leeds, UK.

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