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RESEARCH ARTICLE

Determination of Hematological Indices in Dogs with Acute CDV Infection

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ABSTRACT

The objective of this study was to ascertain the hematological indices in canines that have been infected with the Canine Distemper Virus (CDV) in an acute phase. The study included ten dogs with acute CDV infection (n = 10) and ten healthy dogs (n = 10). The results of the study demonstrated a statistically significant elevation in the neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) in dogs acutely infected with CDV compared to the control group. In conclusion, different hematological responses can occur during the acute phase of CDV infection, and NLR ratios have the potential to be a good inflammatory marker for monitoring the acute phase.

Keywords: Canine distemper virus, Dog, Hematological indices, Neutrophil to lymphocyte ratio

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Akut Kanin Distemper Virüs Enfeksiyonlu Köpeklerde Hematolojik İndekslerin Belirlenmesi

ÖZ

Bu çalışmanın amacı akut Canine Distemper Virus (CDV) ile enfekte köpeklerde hematolojik indislerin belirlenmesidir. Çalışmaya 10 akut CDV enfeksiyonlu (n = 10) ve 10 sağlıklı köpek (n = 10) dahil edilmiştir. Çalışmanın sonuçlarına göre akut CDV ile enfekte köpeklerde kontrol grubuna göre kıyasla istatistiksel olarak önemli derecede yüksek nötrofil-lenfosit oranı (NLR) ve monosit lenfosit oranı (MLR) tespit edilmiştir. Sonuç olarak CDV enfeksiyonunun akut döneminde farklı hematolojik yanıtların oluşabileceği ve NLR oranlarının akut dönemi izlemede iyi bir yangısal belirteç olarak rol oynayabilme potansiyeline sahip olduğu tespit edilmiştir.

Anahtar Kelimeler: Canine distemper virus, Hematolojik indisler, Köpek, Nötrofil-lenfosit oranı

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INTRODUCTION

Canine distemper virus (CDV) constitutes one of the most highly transmissible viral pathogens affecting domestic canine populations globally. Furthermore, it presents a substantial menace to the persistence of a diverse array of endangered wildlife species across the world (Martinez-Gutierrez & Ruiz-Saenz 2016). The clinical presentation can vary substantially, ranging from asymptomatic infection to a fulminant multisystemic disease process. This variability is influenced by a multitude of factors, including the infected species, age, immunological competence of the host, and the virulence of the specific CDV strain (Deem et al. 2000). During the acute phase of the disease, respiratory and digestive system infections manifest prominently, whereas the nervous system exhibits involvement in the advanced stages (Martella et al. 2008). Furthermore, CDV infection demonstrably induces a state of immunosuppression within the host organism (Dik et al. 2023). This phenomenon stands in stark contrast to the inflammatory response typically observed in canine infectious diseases, where an increase in cytokine and acute-phase protein synthesis is a hallmark feature (Paul et al. 2023). This exceptional situation underscores the critical need for the utilization of alternative inflammatory markers for a more comprehensive evaluation of the host response in CDV.

Within this context, hematological indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and eosinophil-to-lymphocyte ratio (ELR) have emerged as prominent tools for evaluating inflammation in recent human studies (Langley et al. 2021; Buonacera et al. 2022). Given the inflammatory response observed in CDV infection, these readily available hematological indices hold promise as potential markers for assessing inflammation in canine patients with CDV.

Noteworthy developments in recent veterinary medicine have been the exploration of hematological indices as inflammatory markers. While the NLR has emerged as a promising indicator for intestinal inflammation in dogs (Becher et al. 2021), its efficacy in evaluating respiratory tract infections appears less conclusive (Conway et al. 2021). Intriguingly, while research on the PLR in veterinary medicine remains less compared to the NLR, existing studies suggest its potential as an inflammatory marker in various canine infectious diseases. More specifically, research has documented PLR as a significant inflammatory marker in canine sepsis (Pierini et al. 2020), and critically ill dogs (Dourmashkin et al. 2023). Furthermore, the MLR and ELR have garnered increasing attention in recent human studies as potential markers for detecting inflammatory processes (Vakhshoori et al. 2023).

Notably, recent human studies emphasize the importance of evaluating these indices at different disease stages for a more comprehensive understanding of the immune response (Zhou et al. 2023; Tan et al. 2024). This emphasis on staged evaluation in human medicine resonates with the importance of considering disease stage when assessing hematologic indices in CDV infection. By evaluating these indicators throughout the disease process, it is possible to gain a more complete understanding of the immune response and potential inflammatory processes associated with CDV infection. Building upon the growing recognition of the value of staged evaluation of hematologic indices in human medicine, this study aimed to determine the specific profile of these indices in dogs acutely infected with CDV.

MATERIALS and METHODS

Animals

The study was approved by the Atatürk University Local Ethics Committee (Decision Number: 2024/19). A prospective, case-controlled observational study was performed in unvaccinated dogs with upper respiratory tract symptoms and/or diarrhea. The G*Power program, version 3.1, developed by Franz Faul at the University of Kiel, Germany, was used to determine the minimum sample size for each group based on NLR data (Thomas, 2014). The calculation was performed using information about NLR from a previous study conducted by Durán-Galea et al (2024) on dogs with leptospirosis, with the following parameters: effect size = 1.4032928, significance level = 0.05, and power = 0.90. The analysis determined that at least 10 dogs should be included in each group. Therefore, the study included 10 dogs (n = 10) of any breed or gender presenting with clinical signs suggestive of CDV infection, including diarrhea, lethargy, vomiting, sneezing, and ocular discharge. Dogs exhibiting neural signs suggestive of a chronic infection were excluded from the study. Moreover, dogs were unvaccinated for CDV and had no prior medical intervention. The initial stage involved a comprehensive patient evaluation, encompassing a thorough review of medical records, a detailed physical examination, and the analysis of fecal samples using flotation techniques. Screening for CDV infection in suspect dogs was performed using a rapid CDV antigen test kit (Anigen, Antigen-USA). Post-CPV screening, additional examinations for canine coronavirus (CCV) and parvovirus (CPV) were performed. Dogs diagnosed with co-infections (CCV or CPV) were excluded to maintain the study's focus on CDV.

Following the recruitment of the CDV-infected group, 10 control dogs (n = 10) were included to

ensure age-matched cohorts in the study. These control dogs underwent a comprehensive health evaluation, including a review of their medical history, a thorough physical examination, complete blood count analysis, and confirmation of their CDV-negative status.

Blood Sampling and Complete Blood Count Analysis

Prior to the commencement of treatment, blood samples were obtained via the use of 21-gauge needles, with some samples collected from the cephalic vein and the remainder obtained through jugular venipuncture and distributed into anticoagulant (EDTA) tubes (K2EDTA Vacuette, Shanghai, China). Whole blood counts were subsequently evaluated using an automated hematology analyzer (Abacus Junior Vet5®, Hungary). The NLR, PLR, MLR, and ELR were determined using the following formulas:

NLR = absolute counts of neutrophils/absolute counts of lymphocytes,

PLR = absolute counts of platelets/absolute counts of lymphocytes,

MLR = absolute counts of monocytes/absolute counts of lymphocytes,

ELR = absolute counts of eosinophils/absolute counts of lymphocytes.

Statistical Analysis

The Shapiro-Wilk normality test was employed to ascertain whether the data were normally distributed. As the results of the normality test indicated that the data obtained in this study did not exhibit normal distribution, a statistical analysis of the data was conducted using the Mann-Whitney U test, a non-parametric test suitable for comparing two groups (control and CDV) (Despande et al. 2018). Data are expressed as median (1st quartile-3rd quartile). SPSS 27.0 software was used to perform the Mann-Whitney U test, with significance set at $p < 0.05$ to identify statistically significant differences between the control and CDV groups.

RESULTS

The results of the study revealed that both the CDV-infected (n = 10; median age: 4 months, range: 3.0–6.0 months) and control groups (n = 10; median age: 4.5 months, range: 3.0–6.0 months) had similar median ages. Importantly, there was no statistically significant difference in the age distribution between the groups. The clinical signs observed in the canines included in the study were fever (6/10), dehydration (7/10), vomiting (2/10), diarrhea (7/10), cough (5/10), nasal discharge (9/10), and lacrimation (7/10).

Table 1. Comparisons of hematological analyses of canine distemper virus infected and control dogs.

Variables	Study Group (n=10)	Control Group (n=10)	P Value	Reference range (Khan et al., 2011; MSD Manual)
WBC (10^9/l)	16.29 (13.08-26.98)	7.61 (4.65-11.19)	<0.001	5.9-16.6
Lymph (10^9/l)	0.85 (0.23-2.21)	1.31 (0.52-3.60)	0.218	0.4-2.9
Mono (10^9/l)	0.87 (0.72-1.26)	0.55 (0.11-0.88)	0.005	0.1-1.4
Neut (10^9/l)	14.64 (11.04-24.99)	5.41 (3.11-9.00)	<0.001	2.9-12
Lymp (%)	5.2 (1.3-11.9)	14.18 (11.18-49.86)	<0.001	8-21
Mono (%)	5.45 (3.7-7.0)	6.12 (1.04-18.49)	0.436	1-9
Neut (%)	87.75 (81.1-92.8)	72.93 (44.32-84.83)	<0.001	51-84
Eos (%)	0.35 (0.2-2.0)	1.22 (0-4.47)	0.165	0-9
RBC (10^{12}/l)	5.73 (4.19-5.96)	7.39 (5.24-8.29)	<0.001	5.5-8.5
Hgb (g/dl)	9.75 (8-11.8)	16.5 (10.9-18.2)	<0.001	14.2-19.2
Hct (%)	33.48 (24.66-42.78)	50.16 (36.36-59.3)	<0.001	35-57
MCV (fl)	64.5 (53-73)	69 (68-75)	0.035	65-80
MCH (pg)	18.9 (15.9-20.4)	21.3 (19-24.5)	<0.001	12.2-25.4
MCHC (g/dl)	28.6 (26.90-33.60)	31.2 (28-36.3)	0.035	32-36
PLT (10^9/l)	459.5 (251-873)	389 (260-690)	0.218	211-621
MPV (fl)	10.9 (9.4-19.80)	7.95 (6.4-10.3)	<0.001	6.1-10.1

Eos; eosinophil, **Hct;** hematocrit, **Hgb;** hemoglobin concentration, **Lymph**; lymphocyte, **Neut**; neutrophil, **Mono**; monocyte, **MCV**; mean corpuscular volume, **MCH**; mean corpuscular hemoglobin volume, **MCHC;** mean corpuscular hemoglobin concentration, **MPV**; mean platelet volume, **PLT**; platelet, **RBC;** Red Blood Cell, **RDW**; red cell distribution, **WBC**; white blood cell.

The results of the hematological analysis are presented in Table 1. The findings of the hematological analyses indicated a statistically significant increase in white blood cell, monocyte, neutrophil count and percentage, and mean platelet volume, and a statistically significant decrease in lymphocyte percentage, red blood cell, hemoglobin, mean corpuscular hemoglobin concentrations, and hematocrit levels in CDV dogs in comparison to the control group. However, only neutrophil count, neutrophil percentage, and mean platelet volume were found to be not within the reference values.

Figure 1 presents the concentrations of NLR, PLR, MLR, and ELR ratios in the control and CDV groups. The NLR showed a significant increase ($p < 0.001$) in CDV-infected dogs (median: 16.84, interquartile range [Q1-Q3]: 8.53-30.30) compared to the control group (median: 5.42, interquartile range [Q1-Q3]: 3.04-6.06).

Similarly, MLR levels were significantly higher in CDV-infected dogs (median: 1.09, interquartile range [Q1-Q3]: 0.58-1.50, $p = 0.023$) compared to controls (median: 0.39, interquartile range [Q1-Q3]: 0.12-0.85). While PLR also tended to be higher in the CDV group (median: 616.11, interquartile range [Q1-Q3]: 311.92-856.76) compared to controls (median: 397.36, interquartile range [Q1-Q3]: 172.32-616.52), this increase was not statistically significant ($p = 0.247$).

In contrast to the other parameters, ELR levels in CDV-infected dogs (median: 0.07, interquartile range [Q1-Q3]: 0.05-0.17) tended to be lower compared to the control group (median: 0.09, interquartile range [Q1-Q3]: 0.03-0.16). However, this decrease was not statistically significant ($p = 0.631$).

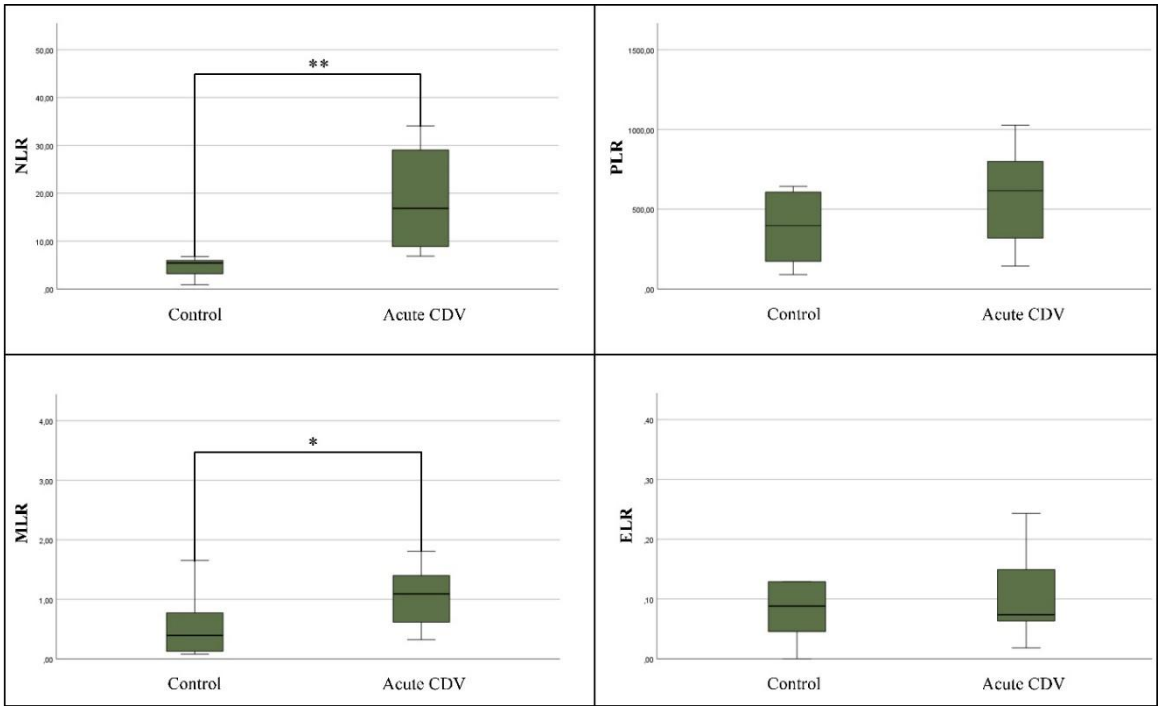

Figure 1. Comparisons of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and eosinophil-to-lymphocyte ratio in dogs acutely infected with CDV with ones in control group. (* = $p<0.05$, ** = $p< 0.01$).

DISCUSSION

A comparative analysis of hematological parameters was conducted in canines experiencing acute CDV infection. Results revealed a statistically significant elevation in the NLR among CDV-infected dogs (median: 16.84, interquartile range [Q1-Q3]: 8.53-30.30) compared to controls (median: 5.42, interquartile range [Q1-Q3]: 3.04-6.06). This finding aligns with previous research documenting increased NLR in chronic CDV cases (Pekmezci et al. 2022). However, the present study identified notably higher NLR values than those reported previously. This discrepancy can be attributed to pronounced neutrophilia, rather than solely lymphopenia, which has been associated with lymphoid apoptosis in acute CDV infection (Schobesberger et al. 2005). In contrast to the neutropenia typically observed in canine viral diseases (Gülersoy et al. 2022), the present study identified neutrophilia as a prominent feature of acute CDV infection. Considering the inverse relation between neutrophil count and disease severity (Goddard et al. 2008), an elevated NLR emerges as a potentially more sensitive inflammatory biomarker in acute CDV cases.

The results demonstrated an elevation in PLR levels in CDV-infected canines (median: 616.11, interquartile range [Q1-Q3]: 311.92-856.76) when compared to the control group (median: 397.36, interquartile range [Q1-Q3]: 172.32-616.52). However, this increase did not attain a statistically significant level. It is beneficial to highlight the increase in platelet count as the primary reason for the observed elevation in PLR levels, rather than lymphopenia. However, this finding is inconsistent with previous reports of thrombocytopenia in CDV infection (Jesus et al. 2021). In light of these findings, it can be postulated that the dogs were in the acute phase of the disease. Some studies in human medicine indicate that certain viruses can directly interact with platelets during the acute phase of infection, leading to their activation (Chaipan et al. 2016). Additionally, it has been demonstrated that cytokine release during the course of infection may result in platelet activation (Goeijenbier et al. 2012). In this context, although platelet activation is seen as a plausible cause in our results, it is important to note that these are only hypotheses and that the underlying cause should be determined with greater precision. Although no statistical difference was detected, this may be attributed to the small sample size. In future studies, it is strongly recommended that platelet levels in dogs acutely infected with CDV be investigated with a larger sample size.

A statistically significant elevation in the MLR was observed in CDV-infected dogs (median: 1.09, interquartile range [Q1-Q3]: 0.58-1.50, $p = 0.023$) compared to controls (median: 0.39, interquartile range [Q1-Q3]: 0.12-0.85). This finding is consistent with the established role of monocytes in orchestrating rapid pro-inflammatory and antiviral responses during acute viral infections (Nikitina et al., 2018). Notably, the signaling lymphocyte activation molecule (SLAM), a primary CDV receptor (Seki et al., 2003), can be rapidly upregulated on monocytes (Beineke et al. 2009), suggesting a potential mechanism for the observed increase in MLR. The enhanced monocyte activation, possibly mediated by SLAM engagement, may contribute to the amplified inflammatory response characteristic of acute CDV infection. These results suggest that MLR may serve as a valuable prognostic indicator of inflammation in dogs with acute CDV.

In contrast to other hematological parameters, a non-significant decrease in ELR was observed in CDV-infected dogs (median: 0.07, interquartile range [Q1-Q3]: 0.05-0.17) compared to healthy dogs (median: 0.09, interquartile range [Q1-Q3]: 0.03-0.16). This finding suggests a potential redistribution of eosinophils from the peripheral circulation to extravascular tissues. Corroborating this hypothesis, previous research has documented the presence of eosinophilic inclusion bodies within the bladder, stomach, kidneys, and lungs of CDV-infected canines (Headley & Graça 2000). The observed decrease in circulating eosinophils may reflect an early phase of this extravasation process, resulting in a non-significant difference in ELR.

The present study is subject to certain limitations. Firstly, due to financial constraints, molecular confirmation of CDV infection, such as PCR, was not possible. Secondly, the sample size was relatively small. However, it is important to note the low prevalence of CDV in the study region. Future research should prioritize the molecular diagnosis of CDV and employ a larger sample size to enhance the robustness of findings.

CONCLUSIONS

In conclusion, this study investigated the utility of hematological indices in monitoring inflammation during acute CDV infection. NLR and MLR may be important parameters to assess inflammation in this context. Given their cost-effectiveness, accessibility and widespread clinical application, NLR and MLR show promise as valuable tools for monitoring treatment response in dogs with acute CDV.

Conflict of interest: The authors have no conflicts of interest to report.

Authors' Contributions: KEY and ŞD contributed to the project idea, design and execution of the study. KEY, ŞD and MK contributed to the acquisition of data. KEY and ŞD analysed the data. KEY drafted and wrote the manuscript. KEY, ŞD and MK reviewed the manuscript critically. All authors have read and approved the finalized manuscript.

Ethical approval: This study was carried out at Atatürk University Animal Hospital. This research was approved by Atatürk University Local Ethics Committee (Decision Number: 2024/19)

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