Original Article

Diagnostic significance of neutrophil-lymphocyte ratio (NLR) in dogs with chronic enteropathy: A meta-analytical study

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Abstract

This meta-analysis aimed to determine the diagnostic significance of the neutrophil-to-lymphocyte ratio (NLR) in dogs with chronic enteropathy (CE). This meta-analysis was constructed according to the PRISMA statement guidelines. The Web of Science, Sage, EBESCO, Ovid, Scopus, and Google Scholar databases were searched. Standardized mean difference (SMD) and odds ratio (OR) were calculated. Heterogenicity and publication bias were evaluated in this study. Five studies were found to be eligible for the assessment of the diagnostic significance of the NLR in dogs with CE. In total, 570 dogs (263 with CE and 307 healthy controls) were included in this study. NLR increased significantly in dogs with CE in comparison with healthy controls in fixed effect model (SMD 2.738; 95% CI: 1.96-3.8; $P < 0.001$). Hedges' G test indicated that there is significant evidence of diagnostic value of NLR in dogs with CE, where the pooled effect was 0.55 at fixed effect model. Moreover, the odds ratio (OR) reflects the significant diagnostic value of the NLR in dogs with CE. At fixed effects, the results indicated no significant evidence of heterogeneity (Cochran's Q Statistic :6.351, I2: 37.01 %). The variability of the true effect sizes represented by tau statistics indicated a very low level of heterogeneity (0.089). Publication bias analysis indicated no significant publication bias among the studies (Egger's test; Begg and Mazumdar rank correlation). The present meta-analysis implies that the NLR could be a reliable diagnostic biomarker for dogs with chronic enteropathy.

Keywords: canine, diagnostic value, enteropathies, epidemiology, meta-analysis

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Introduction

Chronic enteropathies (CE) are the main diseases in dogs and are caused by chronic inflammation of the intestine with long-lasting gastrointestinal symptoms for more than a few weeks (Impellizeri, 2010). The mechanism underlying this condition is complex, and an exaggerated immune reaction to luminal antigens appears to play a role in its pathogenesis (Jergens and Simpson, 2012).

Diarrhea and weight loss are the main characteristics of CE in dogs (Dandrieux, 2016). Therefore, CE is usually identified based on clinical signs (> 3 weeks) and histopathological findings in the intestinal mucosa (Jergens and Heilmann, 2022). Moreover, CE is difficult to diagnose without the need for invasive or expensive procedures. Therefore, identification of a noninvasive and repeatable biomarker is desirable. Several markers have been used to diagnose CE in dogs (Allenspach and Mochel, 2022; Dupouy-Manescau *et al*., 2024; Langlois *et al*., 2023).

The neutrophil-lymphocyte ratio (NLR) has emerged as a significant biomarker in various veterinary contexts, particularly in assessing inflammatory conditions in dogs (Becher *et al*., 2021). NLR has been found to be a convenient diagnostic technique in dogs with hypoadrenocorticism (Zeugswetter and Schwendenwein, 2014), dermatitis (Martins *et al*., 2018) sepsis (Hodgson *et al*., 2018) and cancer (Fernández and Chon, 2018; Macfarlane *et al*., 2016; Mutz et al., 2015; Rejec *et al*., 2017; Skor *et al*., 2017).

Distinctive leukogram alterations represented by the NLR have also been found to have diagnostic and prognostic value in inflammatory bowel disease (IBD) (Acarturk *et al*., 2015; Allenspach *et al*., 2007; Bertani *et al*., 2020). The literature on this topic provides a nuanced understanding of the diagnostic and prognostic value of NLR, particularly in the context of chronic enteropathy (CE) and related conditions (Acarturk *et al*., 2015).

Meta-analysis is a quantitative technique used to aggregate research findings from independent studies that address research hypotheses. This may result in improved generalizability of the findings and increased statistical power (Haidich, 2010). Furthermore, this may elucidate the robustness of the findings across different conditions. Moreover, while a single study may be affected by any bias from the investigators, a meta-analysis can assess whether unexplained inconsistencies may be due to various methods of measurement or study population characteristics (Moher *et al*., 2010). Clearly, one of the greatest motivations behind the development of meta-analytic techniques is the necessity to weigh the inconclusive or contradictory results. The advantages of aggregating results, rather than focusing on a small number of well-known studies, are that even small signals may become apparent, and the possibility of uncovering patterns across a number of studies increases. (Moher *et al*., 2009). Several meta-analytical studies have been conducted on the prognostic significance of the NLR in different disease conditions in humans (Huang *et al*., 2020; Ou *et al*., 2024; Saputra *et al*., 2022; Zhang and Lang, 2024). Although there have been numerous studies on the diagnostic and prognostic significance of NLR in dogs with various diseases, there is no available meta-analysis that provides a conclusion about its diagnostic significance in enteropathy. Therefore, the present meta-analysis provides a conclusion regarding the diagnostic value of the NLR in dogs with chronic enteropathy.

Materials and Methods

Ethical approval: This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Page *et al*., 2021). The PRISMA Checklist was followed for each section of the meta-analysis (https://www.prisma-statement.org/).

Reference dogs: The present meta-analysis included all articles that focused on the diagnostic value of the NLR in dogs with CE. The animals included in this study were clinically healthy and had chronic enteropathy. Enteropathy was confirmed by histopathological examination of affected animals.

Inclusion criteria: The inclusion criteria were (1) papers in English, (2) studies in which dogs with CE were designated based on the standard descriptions of the disease (Caulfield *et al*., 2021) and (3) studies providing NLR data for healthy dogs and those with CE.

Exclusion criteria: The exclusion criteria were as follows: (1) publications in languages other than English; (2) experimental studies; and (3) preprint, case reports, and review articles.

Search strategy: The objective of this study was to search for all publications that had been written about the NLR as diagnostic marker in dogs with CE. We searched the Web of Science, Sage, EBESCO, Ovid, Scopus, and Google Scholar databases using a combination of the following search terms: ("Neutrophil to lymphocyte ratio") ("Chronic enteropathy") (title/abstract) AND ("dogs") (title/abstract) AND ("sensitivity" "diagnostic value") (title/abstract) OR ("Dogs") (title/abstract). Preliminary screening of the articles was based on the title and abstract from the earliest data available by December 2024. Database outputs were integrated using EndNote software. The standard identification, selection, and eligibility criteria of the selected studies are shown (Fig. 1).

Quality control: This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher *et al*., 2010), the current meta-analysis was carried out. All available published publications on NLR in dogs with CE compared to control dogs were included to reduce publication bias. Subsequently, the articles were screened, data were extracted by two independent authors, and duplicates were removed. Conflicts between reviewers were resolved through discussion and agreement.

Statistical analysis: Data analysis was performed using a commercial software (Comprehensive Meta-Analysis ver. 2, USA). The standardized mean difference (SMDs) was used to adjust the differences in NLR values in the selected studies. The SMDs and the 95% confidence intervals (CIs) were also calculated to assess the variations in NLR among animals with chronic enteropathy. The Hedges' G value was calculated to evaluate the pooled effect size (Brydges, 2019). The results for the Hedges' G were interpreted as small (0.20), medium (0.5), or large (0.8). Odds ratios (OR) with 95% CIs were calculated to assess the diagnostic significance of NLR. Cochran's Q test and the inconsistency test (I2) were used to assess the heterogeneity among the studies. $P < 0.10$ or I2 ≥50% indicates significant heterogeneity (Higgins *et al*., 2019). Because there was no evidence of significant heterogeneity, a fixed-effects model was selected to calculate the pooled effects of SMD, weight, and OR. A funnel plot was constructed and evaluated to investigate publication bias using the Begg's and Egger's tests (Mueller *et al*., 2013). Statistical significance was defined as a two-tailed $P < 0.05$.

Results

Eligible studies: Fig. 1 shows the protocol used for the identification, screening, and eligibility of the studies. Finally, five studies were found to be eligible for the assessment of the diagnostic significance of the NLR in dogs with CE, and therefore were included in the meta-analysis (336 titles). In total, 570 dogs (263 dogs with CE and 307 healthy controls) were included in this study (Table 1).

Following the analysis, Fig. 2 shows that NLR increased significantly in dogs with CE in comparison with healthy controls with the fixed effect model (SMD 2.738; 95% CI: 1.96-3.8; $P < 0.001$). The Hedges' G test provided significant evidence of the diagnostic value of NLR in dogs with CE. In the fixed effects model, the pooled effect was 0.55 at fixed effect model. Moreover, Fig. 3 shows the odds ratio (OR), which reflects the significant diagnostic value of the NLR in dogs with CE. The pooled odds ratio in thein fixed effect model was 2.73 with 95% CI, 1-96-3.82, and $P < 0.001$

Heterogenicity and publication bias: Five studies included 570 dogs using NLR as a diagnostic biomarker. At fixed effects, the results indicated evidence of mild heterogeneity (Cochran's Q Statistic :6.351; I2, 37.01 %). The variability of the true effect sizes, represented by the Tau squared, indicated a very low level of heterogeneity (0.089). The analysis of publication bias is presented in Fig. 4. The results indicated no significant publication bias among the studies (Egger's test: $P = 0.03$; Begg and Mazumdar rank correlation: $P = 0.04$).

Table 1 Comparison of NLR between health and diseased dogs in five eligible studies for meta-analysis.

Study	Health		Diseased		*P* value
	Mean	Sample size	Mean	Sample size	
Benvenuti *et al*. (2020)	3.0	150	4.78	41	0.04
Becher *et al*. (2021)	2.0	44	5.5	93	0.001
Cristóbal *et al*. (2022)	2.11	20	4.58	16	0.001
Cagnasso *et al*. (2023)	2.42	68	5.74	53	0.035
Marchesi *et al*. (2024)	2.44	25	3.39	60	0.001

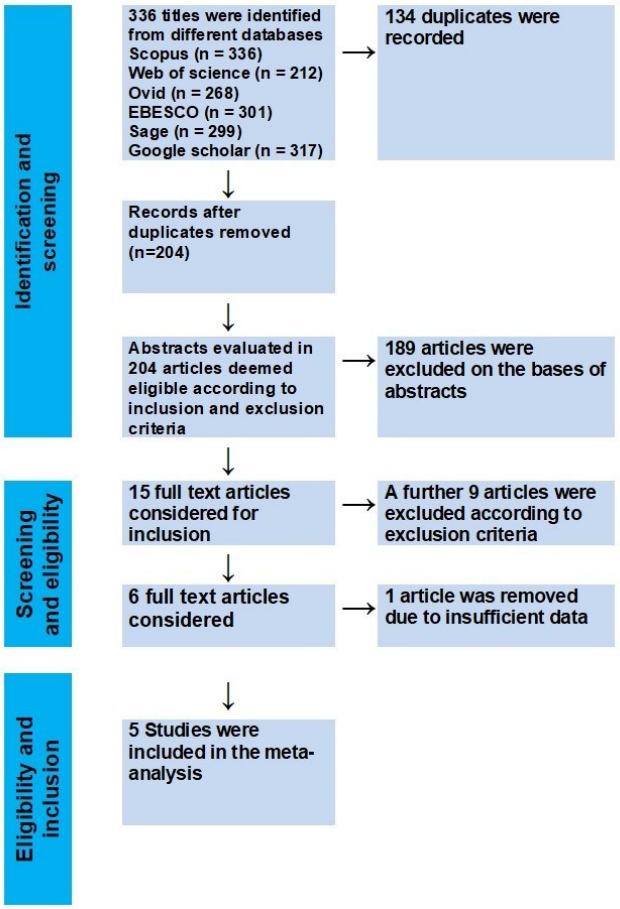


Figure 1 Schematic representation of literature search and inclusion regarding the diagnostic value of NLR in dogs with chronic enteropathy.

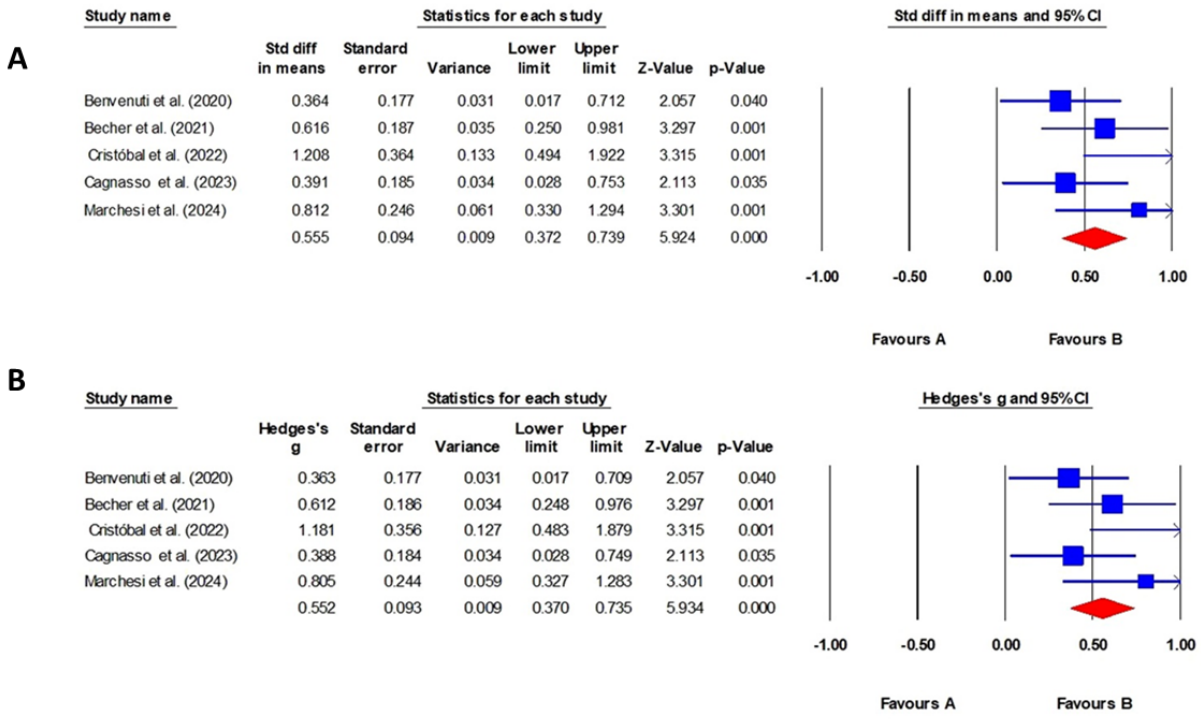


Figure 2 A: Pooled effect size and standardized mean differences (SMD) in dogs for the diagnostic value of NLR in dogs with chronic enteropathy at fixed model effect. B: Hedges' G test and confidence interval.

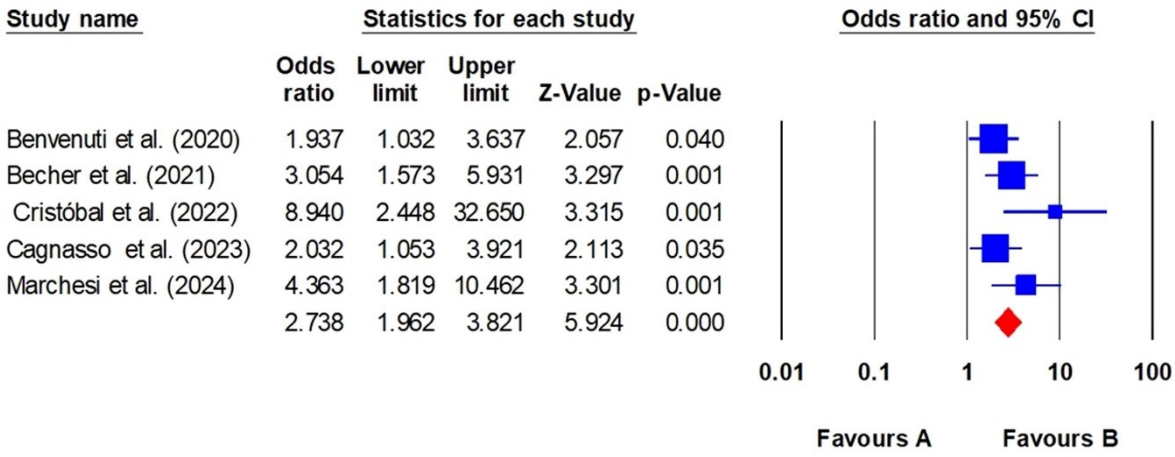


Figure 3 Odds ratio (OR), confidence interval (CI) for the diagnostic value of NLR in dogs with chronic enteropathy at fixed model effect.

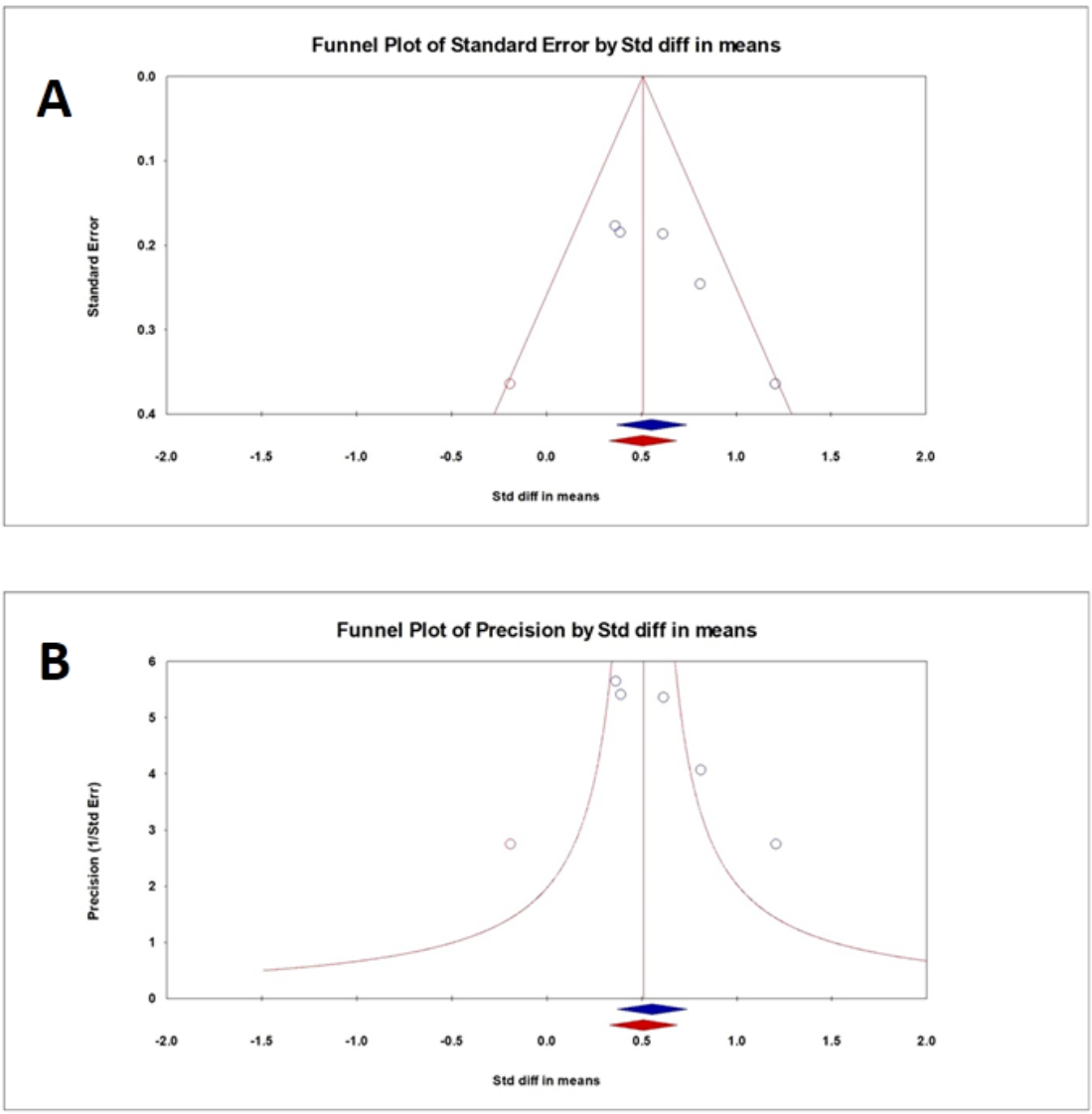


Figure 4 Funnel plot of standard error(A) and of precision (B) for the diagnostic value of NLR in dogs with chronic enteropathy at fixed model effect.

Discussion

The NLR has gained interest in assessing disease severity and predicting outcomes in dogs (Alaimo *et al*., 2023; Becher *et al*., 2024; Chiti *et al*., 2021). However, those studies provided inconclusive and complicated results. Accordingly, the present meta-analysis is the initial report to assess the role of NLR in the diagnosis of chronic enteropathy in dogs. Here, five studies were found eligible according to inclusion and exclusion criteria. In these studies, 570 dogs were included (263 dogs with CE and 307 healthy controls). We found that the NLR increased significantly in dogs with CE compared with that in control dogs. Thus, the pooled effect size showed a significant diagnostic value for the NLR in dogs with chronic enteropathy.

These findings are supported by the results of a meta-analysis on the diagnostic significance of NLR in humans with sepsis (Huang *et al*., 2020), heart failure (Vakhshoori *et al*., 2023), cancer (Naszai *et al*., 2021) and inflammatory conditions (Hajibandeh *et al*., 2020).

Similarly, the investigation by Becher *et al.* (2024) examined the diagnostic and prognostic capabilities of NLR in dogs with congenital portosystemic shunts. Their study found that while the NLR was associated with systemic inflammation, it could not differentiate between various disease states, including portosystemic shunts and other hepatic conditions. This suggests that while the NLR can serve as an indicator of inflammation, it may lack the specificity needed for precise diagnostic purposes to distinguish between overlapping clinical presentations.

Expanding the discussion on NLR, Samuels *et al*. (2024) highlighted its role as an objective biomarker, reflecting prognosis in various clinical settings. This perspective invites a comparative analysis of NLR's applicability of NLR across species, suggesting that insights from human studies might inform veterinary practice.

A retrospective evaluation of NLR in dogs diagnosed with inflammatory protein-losing enteropathy (IRE-PLE) compared to healthy controls was conducted, and the results revealed that dogs with IRE-PLE exhibited significantly higher NLR values than healthy dogs, indicating a potential association between elevated NLR and inflammatory conditions (Cagnasso *et al*., 2023). However, the study also highlighted limitations, such as the lack of significant correlations between NLR and clinical disease severity, as measured by the canine chronic enteropathy clinical activity index (CCECAI). This raises questions regarding the clinical utility of NLR as a standalone diagnostic tool in this population, suggesting that while it may reflect systemic inflammation, its sensitivity and specificity remain suboptimal for predicting treatment outcomes shortly after diagnosis.

The Hedges' G/standard error for the relevant model is typically used to determine the z-value, which is used to test the null hypothesis (Higgins, 2019). In our results, a Hedges' G result of 0.55 ($P < 0.001$) indicates a moderate effect size in the context of meta-analysis. This result suggests that the NLR has a significant diagnostic value in dogs with CE. The hedge value indicates that when there is a larger difference, the evidence is greater and, consequently, the model is significant.

Regarding heterogeneity at fixed effects, the results showed evidence of mild heterogeneity (Cochran's Q Statistic:6.351 and I2: 37.01 %). Cochran's Q statistic measures the presence or absence of heterogeneity across the studies. This helps to determine whether the variations in the study results are due to chance or other reasons. A Q value significantly greater than the degrees of freedom (df) suggests the presence of heterogeneity among the studies (Thompson, 1994). However, if the Q-statistic provides no effect size dispersion, I2 and tau-squared can provide alternative interpretations (Schulz *et al*., 1995).

In the present study, an I^2 value of 37.01% suggests that approximately 37% of the variation in effect estimates can be attributed to heterogeneity among the studies, whereas the remaining 63% was due to sampling error. This level of heterogeneity can be considered moderate, meaning that while some variation exists among the study results, it is not excessively high. These results suggested a mild level of heterogeneity among the studies included in the meta-analysis. The differences among studies may be attributed to differences in the study design, population characteristics, interventions, or outcome measurements (van Aert *et al*., 2019). The heterogeneity test also explains the differences among studies owing to sampling errors (Borenstein *et al*., 2021). In this case, a low p-value indicates that there may be an unidentified degree of heterogeneity (Duffield *et al*., 2008).

Regarding publication bias, the results indicated no significant publication bias among the studies. Publication bias is usually found in studies with small sample sizes (Joober *et al*., 2012). Accordingly, identifying bias is an important issue as it has a determinantal effect on the conclusions of systematic meta-analyses (Sutton *et al*., 2000). A funnel plot was created to indicate evidence of publication bias. In this plot, the effect size is usually shown against standard errors or precision (J. Light and B. Pillemer, 1986). In the present study, the funnel plot was symmetric and there was no indication of publication bias. From the statistical meta-analysis, a lack of bias was identified by a zero level of the regression slope (Rothstein HR, 2005). A strong correlation in the Begg test implies the presence of publication bias (Begg and Mazumdar, 1994).

In this study, the trim-and-fill outcome indicated no bias. The trim-and-fill test estimates the total effect size and tests for publication bias (Duval and Tweedie, 2000). A constant procedure was used to eliminate small studies at the extreme ends of positive funnel plots. The trimming and filling procedures were repeated until the funnel plot was symmetrical. Orwin's fail-safe N proposes that 470000 missing studies are needed to change the effect size and accomplish the outcome of the study is significant. Additionally, criterion for a 'trivial' std diff in means in this test was 0.000. This test is usually used in meta-analyses to assess instability in results, but the power of the study should be considered to avoid misinterpretation (Peters *et al*., 2006, 2007; Rücker *et al*., 2008; Sterne *et al*., 2000; Terrin *et al*., 2003).

The limitation of this meta-analysis was the small number of studies included. Generally, studies on chronic enteropathy are not large because a definite diagnosis of the disease depends mainly on histological examination. In our study, the results of Hedges' G, presence of mild heterogeneity, and absence of publication bias supported the reliability of this meta-analysis. Here, we followed the standard steps of analysis when there are a few numbers of included studies (Schulz *et al*., 2022). Moreover, several meta-analytical studies in humans and veterinary medicine included few numbers of studies and provided a reliable conclusion (Pang *et al*., 2018; Calzetta *et al*., 2020; Zhang *et al*., 2022).

In conclusion, the results of this meta-analysis on the NLR in dogs with chronic enteropathy emphasize its potential as a biomarker for assessing inflammatory conditions. However, these conclusions should be interpreted with caution due to the limited number of clinical studies.

Conflict of interest: Authors declare that there is no conflict of interest.

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