*Original Article*

# Hematologic recovery in Ehrlichia-infected dogs: A meta-analysis of doxycycline's therapeutic impact

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## *Abstract*

Canine monocytic ehrlichiosis (CME), caused by *Ehrlichia canis*, is a globally prevalent tick-borne disease with significant hematologic manifestations, including anemia and thrombocytopenia. Doxycycline is the first-line treatment, but its effects on hematologic recovery remain inconsistently reported. This meta-analysis evaluates the impact of doxycycline on hematologic parameters in *E. canis*-infected dogs. A systematic search was conducted across PubMed, Scopus, Web of Science, and EMBASE. Five studies (one randomized controlled trial, four non-randomized trials) involving 116 dogs were included. Data on erythrocytes, leukocytes (neutrophils, eosinophils, monocytes, and lymphocytes), platelets, hemoglobin, and hematocrit were extracted. Heterogeneity was assessed using $I^2$ statistics, and random-effects models were applied where significant heterogeneity existed ($I^2 > 50\%$). Doxycycline significantly improved hemoglobin levels (MD: -1.98, 95% CI [-3.06, -0.9], $P = 0.003$), platelet counts (MD: -53.39, 95% CI [-74.94, -31.85], $P < 0.001$), and hematocrit (MD: -6.48, 95% CI [-8.88, -4.08], $P < 0.001$) compared to healthy controls. Infected treated dogs also showed higher platelet counts (MD: 53.1, 95% CI [24.63, 81.56], $P < 0.001$) and hematocrit (MD: 4.96, 95% CI [1.47, 8.45], $P = 0.005$) than untreated infected dogs. No significant differences were observed in leukocyte, neutrophil, monocyte, lymphocyte, or eosinophil counts ($P > 0.05$). Doxycycline effectively restores key hematologic parameters in CME, particularly platelets, hemoglobin, and hematocrit, reinforcing its role as the primary treatment. These findings support doxycycline's role in improving key hematologic alterations in CME; however, limited and inconsistent effects on leukocyte subsets and residual gaps versus healthy controls indicate the need for larger trials to consolidate the outcomes about hematologic recovery.


**Keywords:** biochemical markers, canine ehrlichiosis, doxycycline, hematological parameters, meta-analysis

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## Introduction

Canine monocytic ehrlichiosis (CME) is a prevalent disease caused by the gram-negative intracellular bacterium *Ehrlichia canis* (*E. canis*). The primary vector of *E. canis* is the brown dog tick (*Rhipicephalus sanguineus*), which affects mostly dogs (Dumler *et al.*, 2001). CME is widespread in tropical and subtropical areas with lower rates in other countries, the prevalence was 11.47% in central Thailand (Osathanon *et al.*, 2025), 6.9% in Bangladeshi pet dogs (Kabir *et al.*, 2024), 9.88% in China (Zu *et al.*, 2025), 41.46% in Eastern India (Chakraborty *et al.*, 2024), 0.9% in shelter dogs in Northern Portugal (Afonso *et al.*, 2024), 8.33% in Romania (Sandu *et al.*, 2025), 0.5% in Canada (Evason *et al.*, 2019) and 27% in Southern Europe (René-Martellet *et al.*, 2015). In CME cases, the animal may present with fever or hypothermia, depression, anorexia, lymphadenomegaly, splenomegaly, mucosal pallor, bleeding tendency, and eye abnormalities (Zhang *et al.*, 2023). Chronic CME may also include the above signs along with ulcerative stomatitis, necrotic glossitis, swelling, and central nervous system involvement signs such as seizures and ataxia (Aziz *et al.*, 2022; Pugliese *et al.*, 2022). Bleeding tendency is seen in both chronic and acute forms of the disease (Harrus and Waner, 2011; Mylonakis *et al.*, 2011). *E. canis* evades the immune system by disrupting the cellular environment and modulating cytokine production to sustain persistent infection (Lina *et al.*, 2016).

CME is a potentially fatal disease; medical treatment is necessary to hasten recovery and prevent clinical exacerbation or death (Harrus *et al.*, 1999). Doxycycline hydrochloride is the preferred medication for treating CME, with its effectiveness in infected dogs being well-documented (Fourie *et al.*, 2015; Cardoso *et al.*, 2023). Doxycycline, a semisynthetic tetracycline derivative, is widely employed for its antimicrobial properties (Holmes and Charles, 2009). It also possesses immunomodulatory and anti-inflammatory properties, suppressing the proliferation of blood leukocytes, cytokine production, and the activity of matrix metalloproteinase (MMP). Doxycycline also affects neutrophil functions, lymphocyte proliferation, and cytokine production (Liu *et al.*, 1999; Kuzin *et al.*, 2001; Zanjani *et al.*, 2006).

Despite the widespread use of doxycycline as the first-line treatment for canine ehrlichiosis, there is considerable variability in the reported effects of this antibiotic on hematological and biochemical parameters in treated dogs. While certain studies describe noteworthy improvements in infected dogs following doxycycline therapy (Cardoso *et al.*, 2023; Wongtawan *et al.*, 2024), others show only marginal or inconsistent changes (Breitschwerdt *et al.*, 1998; Villaescusa *et al.*, 2015). This variability may be attributed to differences in study design, sample size, disease severity, dosage and duration of treatment, and geographical variations in Ehrlichia strains. Given these gaps, there is a pressing need for a systematic review and meta-analysis to systematically evaluate the effects of doxycycline on hematological and biochemical parameters in dogs diagnosed with ehrlichiosis. Such an analysis would enhance our knowledge about the drug's therapeutic impact and contribute to the development of more effective treatment strategies for canine ehrlichiosis.

## Materials and Methods

***Literature search:*** A thorough literature search was performed across four databases: PubMed, Scopus, Web of Science, and EMBASE. The search was conducted from inception to January 18, 2025. The search terms used were "Ehrlichia" or "Ehrlichiosis" and "Doxycycline" and "Canine" or "Dog". We also included the available MeSH terms in the search and performed a manual search to avoid any missing studies from the screening process. Eligible studies were screened on title and abstract first using the inclusion and exclusion criteria. We conducted and reported this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher *et al.*, 2009).

***Study selection:*** The study included only original comparative clinical trials written in English that assessed the effect of doxycycline treatment on different blood parameters in dogs infected with *E. canis*. Biomarkers published in more than two studies (>2) were eligible for inclusion in this review. There were no geographical restrictions on the studies included. A study on a nonplasmatic or calculation-derived biomarker and studies in humans, animals other than dogs, or dogs without confirmed infection were grounds for exclusion. We excluded non-English articles, observational studies, single-arm trials, reviews, systematic reviews, book chapters, as well as conference papers.

***Data extraction:*** Two reviewers independently extracted data using a double-check approach in a piloted and pre-established spreadsheet. If data were missing or incomplete, the respective paper authors were contacted for clarification. Disagreements arising between the reviewers were resolved through discussion with a third reviewer. In cases of studies with multiple arms or multiple papers reporting the same study, only the data of interest were extracted.

***Risk of bias assessment:*** Two reviewers independently assessed the risk of bias of the included studies, and in case of disagreement, a third reviewer was consulted. A critical appraisal of the risk of bias of included studies was performed; ROBINS-I was used for controlled, non-randomized clinical trials. We considered seven domains for ROBINS-I (selection bias, confounding, classification of interventions, deviations from intended interventions, missing data, measurement of the outcome, and bias in the selection of the reported result). We used the Cochrane risk of bias tool (ROB 2) for the randomized clinical trials, assessing five domains: randomization process, deviation from the intervention, selecting the reported outcomes, measuring the reported outcomes, and assessing the missing data of the outcomes (Higgins and Altman, 2008).

***Statistical analysis:*** Review Manager software (RevMan 5.4) was used for analysis. We used mean and standard deviation (SD) to represent the continuous data in the study. The statistical results were considered significant if the *P*-value did not exceed 5%. However, heterogeneity of the results was determined by the Chi-square *P*-value and the I2 value. The data were considered heterogeneous if the chi-square *P*-value was less than 0.1 and the I2 exceeded 50%. We selected the random effect model for the outcomes due to the heterogeneity between the studies. The outcomes showed significant heterogeneity, so sensitivity analysis was applied.

## *Result*

***Studies and patients' characteristics:*** After the comprehensive literature search, 925 results were retrieved from different databases, and 250 duplicates were removed. Based on a title and abstract review, irrelevant publications or those not fitting our inclusion criteria were excluded, resulting in 640 articles being excluded. Additionally, 30 studies were excluded from the full-text screening. Finally, five included studies were eligible for inclusion: one randomized clinical trial (Ranjithkumar *et al*., 2023) and four non-randomized clinical trials (Sharma *et al*., 2015; Pedreañez *et al*., 2021; Cardoso *et al*., 2023) (Fig. 1).

Table 1 provides a detailed summary of the characteristics of the studies eligible for inclusion in the meta-analysis. The five included studies, conducted in Brazil, India, Venezuela, and Spain, involved a total of 116 dogs—71 treated with doxycycline and 45 serving as controls. Study designs included four non-randomised clinical trials and one randomized controlled trial. The sample size for treated groups ranged from 5 to 24 dogs, while control groups ranged from 5 to 12, with most controls being healthy, and one study using healthy doxycycline-treated dogs. Doxycycline was administered orally in most studies at a consistent dose of 10 mg/kg, given every 12 or 24 hours over 20 to 28 days. Infection with *E. canis* was diagnosed primarily using rapid serological tests, with PCR confirmation in four studies. Co-medications were reported in only one study, while the study aims varied, focusing on hematological changes, cytokine profiles, oxidative stress, and overall treatment efficacy.

The risk of bias for the non-randomized trials is summarized in Table 2, with a more comprehensive breakdown available in Supplementary Table 1. Additionally, the risk of bias for the single randomized controlled trial is illustrated in Figure 2.

***Hematological parameters:*** Four studies have reported the red blood cell count across two study arms: dogs infected with canine ehrlichiosis and a healthy control group. The resulting analysis showed MD: -0.54, 95% CI [-1.32, 0.23]. The pooled results showed significant heterogeneity ($P < 0.001$, $I^2 = 82\%$). Sensitivity analysis was applied to solve heterogeneity. The heterogeneity was resolved after removing Sharma 2015 (MD: -0.86, 95% CI [-1.45, -0.27], ($P > 0.05$, $I^2 = 26\%$) (Fig. 3).

Five studies have reported the leukocyte count in different study groups. The conducted analysis found no statistically significant effect of doxycycline regarding this outcome compared to the control group (MD: 0.08, 95% CI [-1.08, 1.23], $P > 0.05$ ($P = 0.03$, $I^2 = 64\%$)). Sensitivity analysis was applied to solve heterogeneity (MD: -0.38, 95% CI [-1.48, 0.71], ($P > 0.05$, $I^2 = 23\%$) (Fig. 4A). In two studies comparing the effect of doxycycline on the infected group compared to the non-treated group, there was a statistically significant difference between the groups (MD: 1.29, 95% CI [0.39, 2.19], $P = 0.005$) ($P > 0.05$, $I^2 = 0\%$) (Fig. 4A) Two studies have assessed the level of neutrophils in the group of dogs infected with CME and the healthy control group. The resulting analysis showed no statistically significant difference between the groups (MD: 0.39, 95% CI [-0.75, 1.52], $P > 0.05$, $I^2 = 0\%$) (Fig. 4B).

Two studies have reported the monocyte level in the affected group treated with doxycycline and the healthy control group. The pooled data analysis showed that there was no statistically significant difference between the groups (MD: 0.14, 95% CI [-0.11, 0.4], $P > 0.05$, $I^2 = 68\%$) (Fig. 4C).

The lymphocyte level was assessed in two studies comparing its level in dogs infected with CME and treated with doxycycline and the healthy control group. There was no statistically significant difference between the groups (MD: -0.56, 95% CI [-2.44, 1.32], $P > 0.05$, $I^2 = 77\%$ (Fig. 4D).

Regarding the eosinophil level across the groups, two studies addressed its level in the infected group treated with doxycycline and in the healthy control group. The resulting analysis showed no statistically significant difference (MD: 0.21, 95% CI [-0.26, 0.68], $P > 0.05$, $I^2 = 54\%$) (Fig. 4E).

Regarding hemoglobin levels, five studies addressed this outcome by comparing both the CME group treated with doxycycline and the control group. The resulting analysis reported a statistically significant difference between both groups (MD: -1.98, 95% CI [-3.06, -0.9], $P = 0.003$) ($P = 0.001$, $I^2 = 78\%$). To solve the significant heterogeneity, sensitivity analysis was applied (MD: -2.46, 95% CI [-3.11, -1.82], $P < 0.001$, ($P > 0.05$, $I^2 = 0\%$). The difference between the infected group treated with doxycycline and the untreated infected group was assessed in two studies. The resulting analysis showed a statistically significant difference between the groups (MD: 1.38, 95% CI [0.35, 2.42], $P = 0.009$) ($P > 0.05$, $I^2 = 0\%$) (Fig. 5).

Five studies have reported the platelet count comparing the groups. The resulting analysis assessing the difference between the infected group of dogs treated with doxycycline and the healthy control group showed a statistically significant difference between the groups (MD: -53.39, 95% CI [-74.94, -31.85], $P < 0.001$, ($P > 0.05$, $I^2 = 18\%$). To solve the heterogeneity, sensitivity analysis was applied (MD: -54.89, 95% CI [-72.5, -37.29], $P < 0.001$, $I^2 = 0\%$). In terms of assessing the difference between the infected treated group and the infected untreated group, the resulting analysis showed a statistically significant difference (MD: 53.1, 95% CI [24.63, 81.56], $P < 0.01$, $I^2 = 0\%$) (Fig. 6).

Four studies have assessed the hematocrit level in the study groups. The resulting analysis assessing the difference between the infected group of dogs treated with doxycycline and the healthy control group showed a statistically significant difference between

the groups (MD: -6.48, 95% CI [-8.88, -4.08], $P < 0.001$, $I^2 = 0\%$). In terms of assessing the difference between the infected treated group and the infected untreated group, the resulting analysis showed a statistically significant difference (MD: 4.96, 95% CI [1.47, 8.45], $P = 0.005$, $I^2 = 0\%$) (Fig. 7).

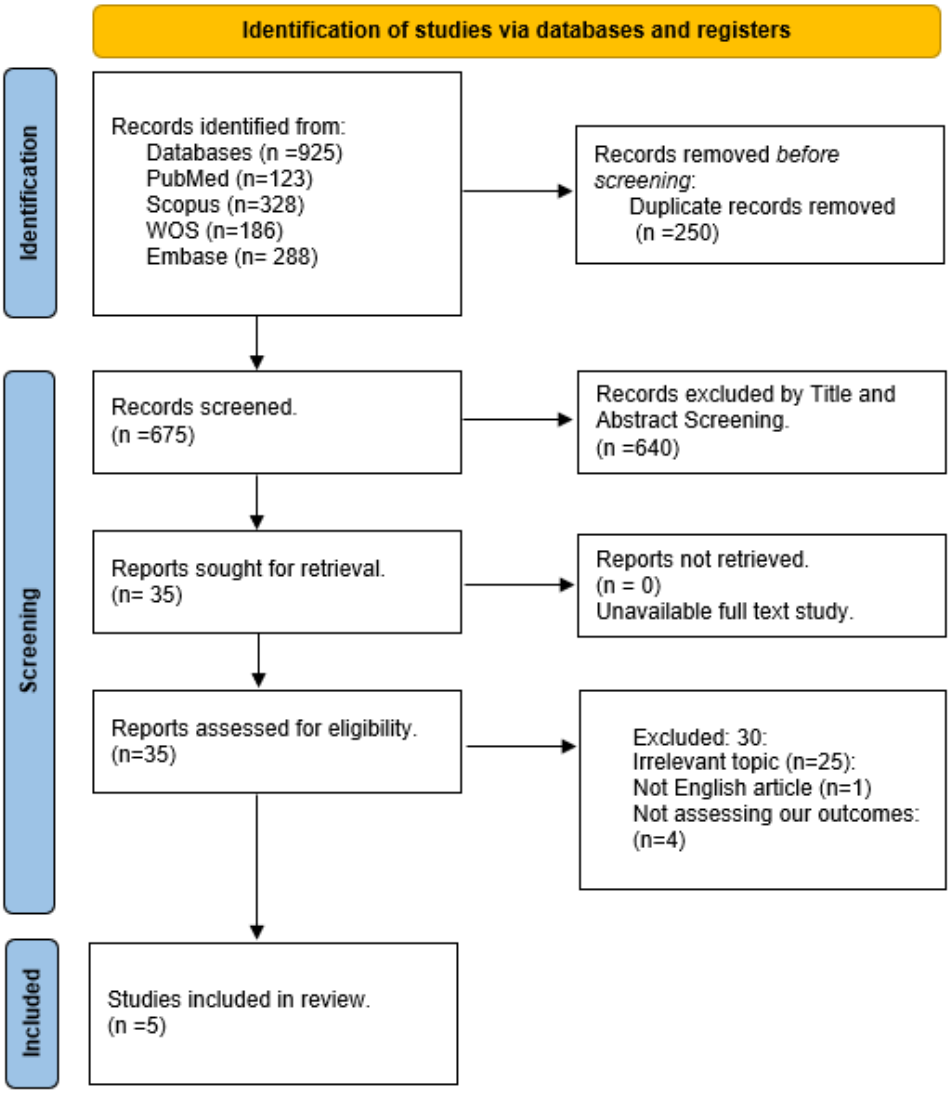


**Figure 1** PRISMA flow diagram.

**Table 1** Baseline characteristics and summary of included studies.

| Study | Location | Study design | Intervention | | Comparison | | Mode of administration | Treatment duration | Dose | Diagnosis of infection | Co-medications | Aim of the study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Name | No. | Name | No. | | | | | | |
| Cardoso *et al*. 2023 | Brazil | Non-randomised CT | Doxycycline | 7 | Control (healthy) | 11 | n/a | 28 days | 10 mg/kg every 12 hours for 28 days | *E. canis* infection positive in rapid serological tests and confirmed by PCR | n/a | To analyze the hematological parameters, blood viscosity, and cytokines of dogs infected by *E. canis*, untreated and treated with doxycycline |
| Ranjithkumar *et al*. 2023 | India | RCT | Doxycycline | 24 | Control (healthy) | 9 | Oral | 28 days | 10 mg/kg every 24 hours for 28 days | *E. canis* infection positive in rapid serological tests and confirmed by PCR | n/a | To evaluate the effectiveness of parenteral doxycycline in treating natural cases of CME over a shorter duration of 15 days, compared to the standard 28-day course of oral doxycycline |
| Pedreañez *et al*. 2021 | Venezuela | Non-randomised CT | Doxycycline | 15 | Control (healthy) | 8 | n/a | 28 days | 10 mg/kg every 24 hours for 28 days | Positive serology for E. canis | n/a | To evaluate nitric oxide (NO) levels and lipid peroxidation (Malondialdehyde: MDA) in the plasma of dogs naturally infected by Ehrlichia canis, and to determine the effect of doxycycline on clinical, hematological, and oxidative parameters. |
| Villaescusa *et al*. 2015 | Spain | Non-randomised CT | Doxycycline (infected) | 20 | Doxycycline (healthy) | 12 | Oral | 28 days | 10 mg/kg every 24 hours for 28 days | *E. canis* infection positive in rapid serological tests and confirmed by PCR | n/a | To investigate whether these changes were caused by antimicrobial or nonantimicrobial properties of doxycycline, using healthy doxycycline-treated dogs as a control group |
| Sharma *et al*. 2015 | India | Non-randomised CT | Doxycycline | 5 | Control (healthy) | 5 | Oral | 20 days | 10 mg/kg every 12 hours for 20 days | n/a | Paracetamol 10 mg/kg tab. as needed. Pantaprazole 20 mg once daily. Silymarins syrup | To evaluate the efficacy of doxycycline with whole blood transfusion in anemic and thrombocytopenic cases of canine ehrlichiosis |

**Table 2** Risk of bias assessment of the non-randomized trials according to the ROBINS-I tool.

| Study | Bias due to confounding | Bias in the selection of participants into the study | Bias in the classification of interventions | Bias due to deviations from intended interventions | Bias due to missing data | Bias in the measurement of outcomes | Bias in the selection of the reported result | Overall bias |
|---|---|---|---|---|---|---|---|---|
| Sharma *et al*. 2015 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Villaescusa *et al*. 2015 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Pedreañez *et al*. 2021 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Cardoso *et al*. 2023 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |

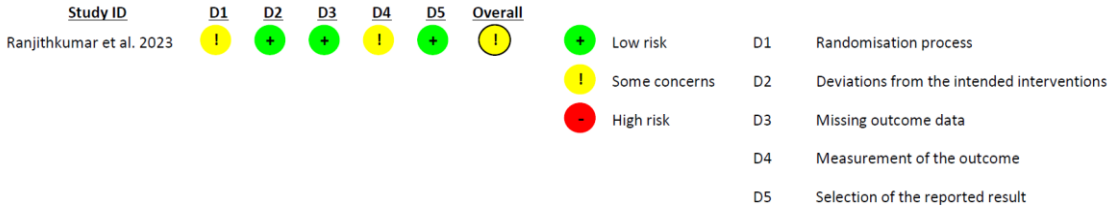


**Figure 2** Risk of bias assessment for Ranjithkumar *et al*. (2023) using the Cochrane RoB 2.0 tool. Judgments are shown across five domains with an overall risk level indicating some concerns.

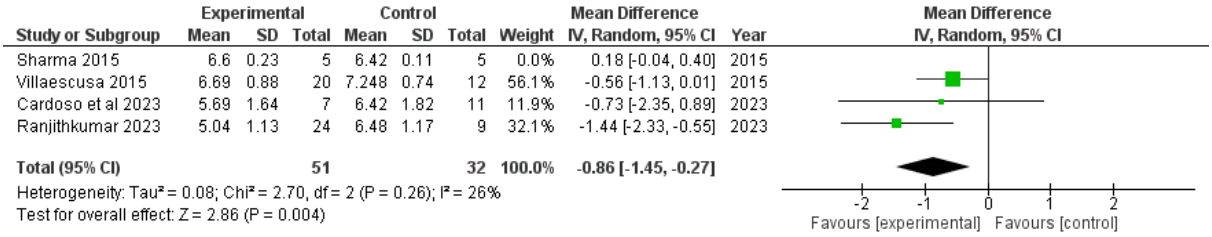


**Figure 3** Forest plot showing the mean difference in red blood cell count.

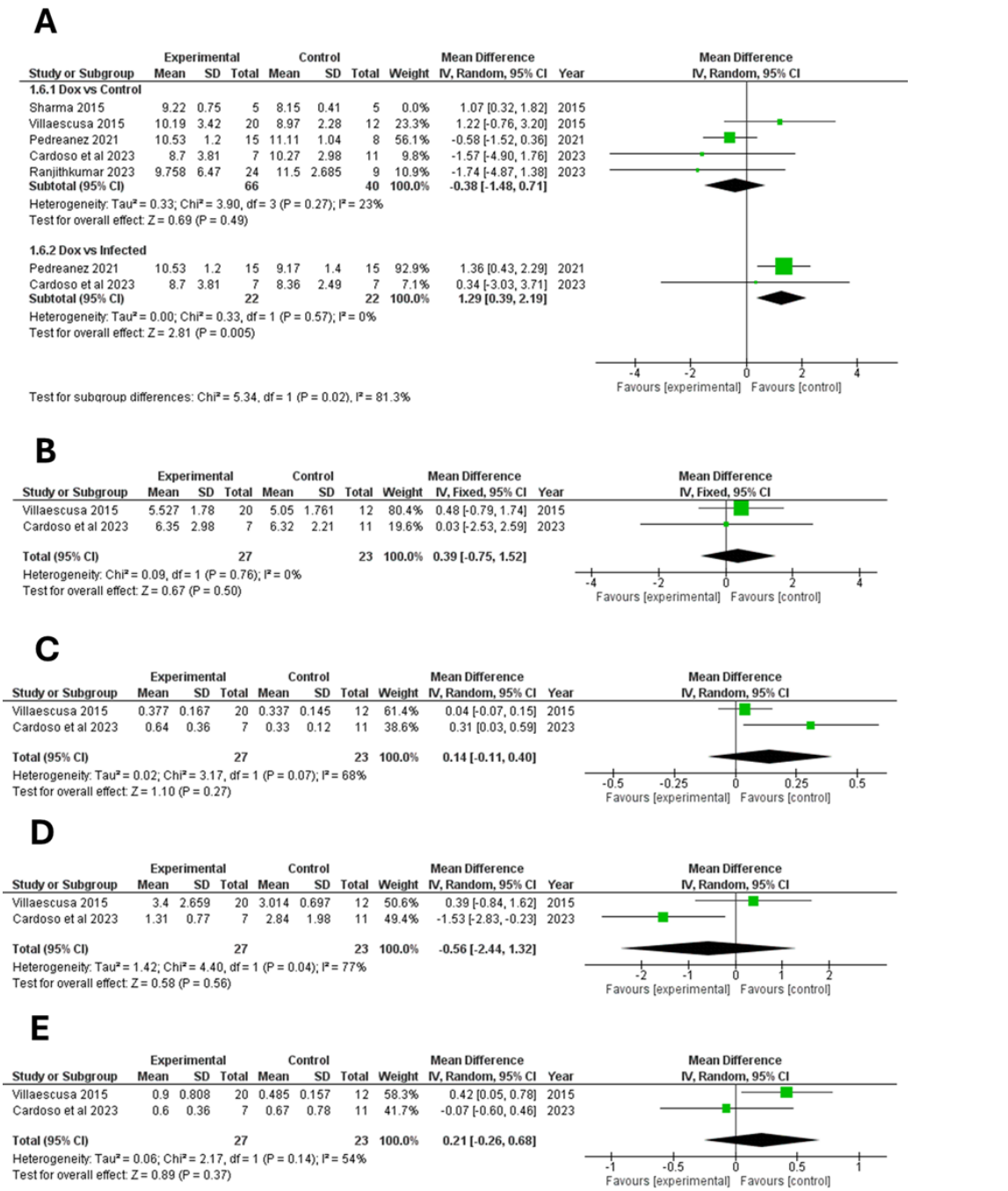


**Figure 4** Forest plot showing the mean difference in the counts of A) leukocytes, B) neutrophils, C) monocytes, D) lymphocytes, and E) eosinophils.

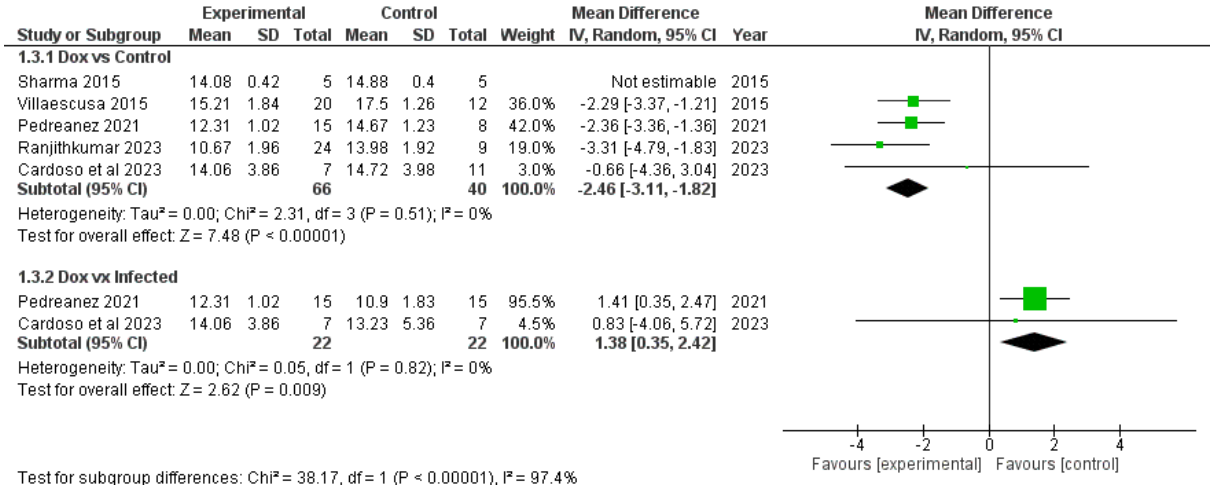


**Figure 5** Forest plot showing the mean difference in hemoglobin level.

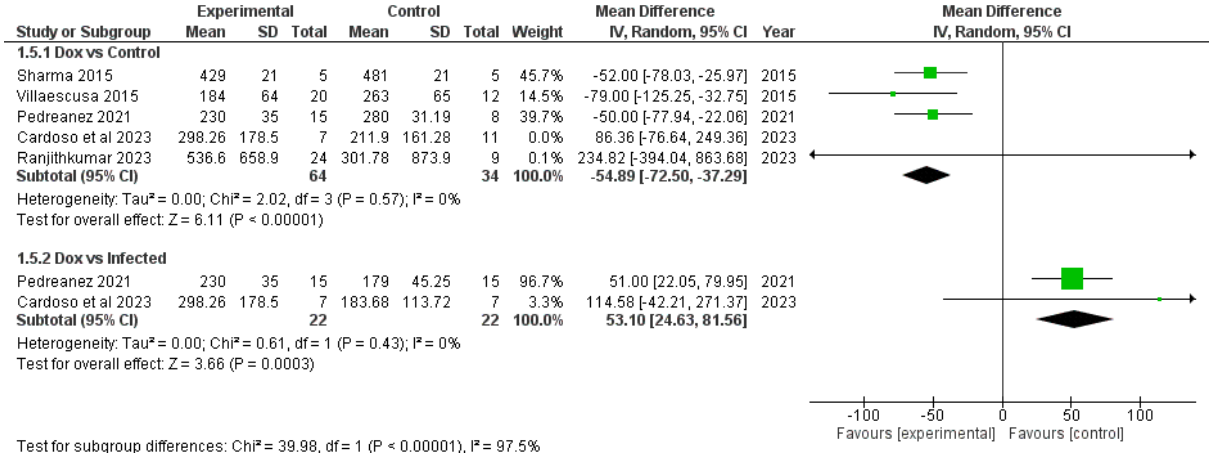


**Figure 6** Forest plot showing the mean difference in platelet count.

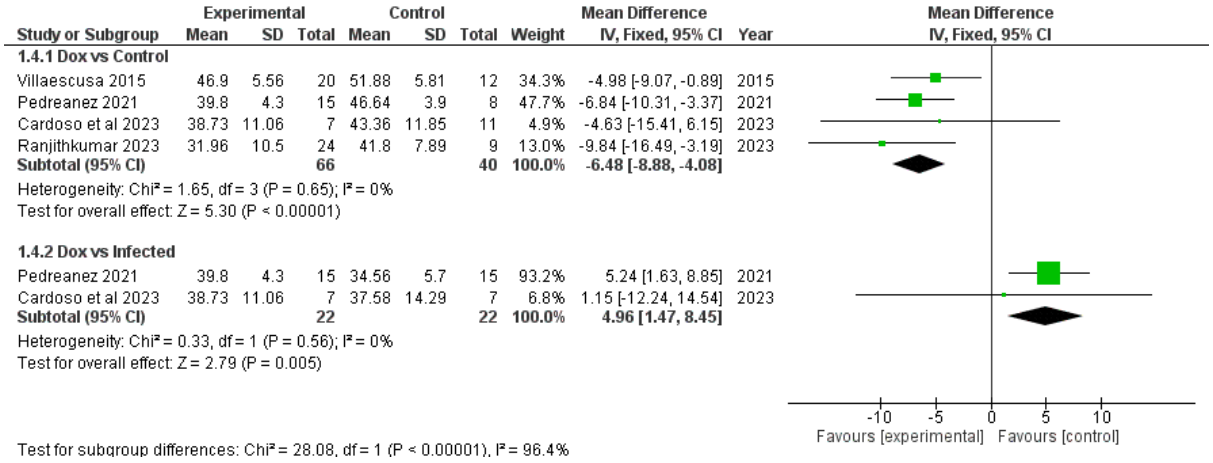


**Figure 7** Forest plot showing the mean difference in hematocrit level.

## *Discussion*

This study assessed the therapeutic impact of doxycycline on dogs infected with CME by comparing outcomes among doxycycline-treated infected dogs, untreated infected dogs, and healthy controls. The analysis revealed that doxycycline significantly improved several hematological parameters in infected dogs relative to the untreated group. The meta-analysis revealed that doxycycline treatment significantly improved key hematological parameters in dogs infected with *E. canis*. Notably, hemoglobin levels, platelet counts, and hematocrit values showed marked increases post-treatment, underscoring doxycycline's efficacy in restoring hematologic health. These findings align with previous studies highlighting the antibiotic's role in mitigating the pathogenic effects of *E. canis*, such as bone marrow suppression and immune evasion. The observed improvements in platelet counts are particularly

critical, as thrombocytopenia is a hallmark of ehrlichiosis and a major contributor to the bleeding tendencies seen in infected dogs. The consistency of these results across multiple studies, despite geographical and methodological variations, reinforces doxycycline's status as a first-line treatment for CME.

Several studies have investigated the efficacy of doxycycline in treating CME across different disease phases. McClure *et al*. (2010) showed that doxycycline treatment significantly improved hematological parameters in dogs with acute, subclinical, and chronic CME. Leukocytes, platelets, and hematocrit values dropped during disease progression but recovered substantially after treatment initiation, with near or full return to baseline levels depending on the disease phase. In a 28-day course, doxycycline significantly improved hematologic parameters in dogs during the acute and subclinical phases of CME, with notable increases in platelet count (94.9%), leukocyte count (124.5%), and hematocrit (100.7%) (McClure *et al*., 2010). Similarly, Kumar *et al*. (2023) evaluated the effects of both doxycycline and minocycline, reporting that doxycycline effectively improved CME-altered biohematological parameters (Kumar *et al*., 2023). In a study by Niwetpathomwat (2006), doxycycline demonstrated effective curative action in dogs with concurrent ehrlichiosis and babesiosis, based on a retrospective study of 70 cases of ehrlichiosis and 12 co-infection cases. Post-treatment, red blood cell indices and platelet count significantly improved ($P < 0.05$). The findings support doxycycline as a recommended treatment for both single and concurrent infections in veterinary settings (Niwetpathomwat, 2006). Consistent with these findings, Chaurasia et al. reported significant hematological recovery in all doxycycline-treated dogs in their study (Chaurasia *et al*., 1999). All animals showed marked improvement in hematological values and clinical signs by day 14. By day 21, a 100% recovery rate from ehrlichiosis was achieved in both treatment groups. These findings indicate the strong efficacy of the medication regimen.

However, the analysis also identified variability in the response of other hematologic parameters, such as leukocyte and neutrophil counts, which did not show statistically significant changes post-treatment. This inconsistency may stem from differences in disease severity, timing of treatment initiation, or co-infections in the studied populations. The lack of significant changes in these parameters suggests that while doxycycline effectively targets the underlying infection, its impact on certain immune cells may be limited or context dependent. Several factors may explain the limited differences observed in total WBC and differentials beyond direct immunomodulation. Disease phase and sampling timing influence leukogram patterns in CME: acute infection may induce transient neutrophilia or mild leukocytosis, whereas subclinical/chronic phases can feature bone-marrow suppression with normal or low-normal totals, masking treatment effects at aggregated timepoints. In addition, co-infections (e.g., babesiosis, anaplasmosis) and medications (e.g., NSAIDs). Further research is needed to explore these observations and optimize treatment protocols for diverse clinical conditions.

In conclusion, this meta-analysis confirms that doxycycline effectively improves key hematological parameters—such as platelet count, hematocrit, and hemoglobin levels—in dogs infected with *E. canis*. While treated dogs showed significant recovery compared to untreated infected dogs, their values remained below those of healthy controls, suggesting that doxycycline may not fully restore pre-infection hematological health. The findings support its use as a first-line treatment for acute and subclinical CME but indicate potential limitations in reversing chronic infection-related deficits. Variability in study designs, small sample sizes, and inconsistent treatment protocols highlight the need for further research to refine therapeutic approaches.

***Limitations of this study:*** The limited number and small sample sizes of the included studies have restricted the generalizability of our findings. Additionally, the exclusion of non-English publications may have led to the omission of relevant data. Considerable heterogeneity and variability in treatment durations and dosages further prevented statistical comparisons, limiting our ability to recommend an optimal doxycycline regimen.

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## *CRediT authorship contribution statement*

**Mahmoud Kandeel**: Conceptualization, Data curation, Methodology, Resources, Software, Writing—original draft preparation. **Mohamed Marzok**: Conceptualization, Data curation, Methodology, Writing—review and editing. **Maryam Mahmoud**: Conceptualization, Data curation, Formal analysis, Methodology, Writing—review and editing. **Khalid Al Khodair**: Conceptualization, Data curation, Formal analysis, Writing—review and editing.

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