

Received Date: December 26, 2024**Accepted Date: January 12, 2024****Published Date: February 1, 2024**

Malaria and Thrombocytopenia: A Systematic Review and Meta-Analysis

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Abstract- Thrombocytopenia is a frequently reported hematological abnormality in malaria. However, its precise prevalence, diagnostic utility, and prognostic value across different *Plasmodium* species remain inadequately synthesized. To determine the pooled prevalence of thrombocytopenia in malaria, its accuracy in diagnosing malaria in febrile patients, and its association with severe

disease and mortality. A systematic search of MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials was conducted from inception to May 2023. Observational studies (cohort, cross-sectional, case-control) reporting platelet counts or the prevalence of thrombocytopenia in patients with smear-positive or rapid diagnostic test (RDT)-confirmed malaria were included. Two independent reviewers extracted data on study characteristics,

patient demographics, parasite species, platelet counts, and clinical outcomes. The quality of studies was assessed using the Newcastle-Ottawa Scale. 127 studies involving 98,451 malaria patients were included. The pooled prevalence of thrombocytopenia (platelet count $<150,000/\mu\text{L}$) was 74% (95% CI, 71-77%; $I^2=94\%$). Prevalence was high in both *P. falciparum* (72%, 95% CI 68-75%) and *P. vivax* (78%, 95% CI 74-81%) infections. The pooled mean platelet count was $89,500/\mu\text{L}$ (95% CI $85,200-93,800/\mu\text{L}$). For diagnosing malaria in febrile patients, thrombocytopenia had a pooled sensitivity of 0.75 (95% CI 0.71-0.79), specificity of 0.81 (95% CI 0.77-0.84), and a diagnostic odds ratio of 14.2 (95% CI 10.5-19.1). Patients with severe thrombocytopenia ($<50,000/\mu\text{L}$) had a significantly higher risk of severe malaria (Pooled Relative Risk 3.45, 95% CI 2.68-4.44) and mortality (Pooled RR 2.91, 95% CI 1.98-4.27). Thrombocytopenia is a highly prevalent and salient feature of both *P. falciparum* and *P. vivax* malaria. It serves as a strong diagnostic marker for malaria in febrile illness and is a significant prognostic indicator for disease severity and mortality.

1. Introduction

Malaria, a life-threatening disease caused by *Plasmodium* parasites, continues to impose a significant global health burden. [1] While peripheral blood smear microscopy remains the diagnostic cornerstone, the identification of characteristic hematological abnormalities can provide crucial supportive evidence and guide clinical management. Among these, thrombocytopenia has emerged as one of the most consistent laboratory findings. [2]

The pathophysiological mechanisms underlying malarial thrombocytopenia are multifactorial, involving peripheral destruction, sequestration, and impaired production. Proposed mechanisms include immune-mediated platelet destruction with splenic clearance, platelet activation and consumption due to endothelial adherence, and dysmegakaryopoiesis within the bone marrow. [3, 4] Despite its clinical frequency, the reported prevalence of thrombocytopenia varies widely across different geographical regions and patient populations.

Several narrative reviews have highlighted this association, but a comprehensive, quantitative synthesis of the global evidence is lacking. This systematic review and meta-analysis aims to consolidate the available data to provide precise estimates of the prevalence of thrombocytopenia in malaria, evaluate its diagnostic accuracy in distinguishing malaria from other febrile illnesses, and quantify its association with severe disease and mortality.

2. Methods

2.1 Search Strategy and Selection Criteria

We conducted this systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. [5] A systematic literature search was performed in MEDLINE, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials from database inception to May 2023. The search strategy used a combination of Medical Subject Headings (MeSH) terms and keywords: ("Malaria" OR "Plasmodium falciparum" OR "Plasmodium vivax") AND ("Thrombocytopenia" OR "Platelet Count" OR "Platelets"). The reference lists of retrieved articles and relevant review articles were manually screened for additional studies.

Studies were included if they met the following criteria: (1) enrolled patients with confirmed malaria diagnosis by smear or RDT; (2) reported quantitative platelet count data or the frequency of thrombocytopenia (defined as platelet count $<150,000/\mu\text{L}$); and (3) were observational studies (cohort, cross-sectional, or case-control). Exclusion criteria were: (1) case reports, reviews, or editorials; (2) studies with fewer than 20 patients; (3) studies involving only special populations (e.g., only pregnant women) without general patient data; and (4) studies not published in English.

2.2 Data Extraction and Quality Assessment

Two investigators independently extracted data using a standardized form. Any discrepancies were resolved by consensus or consultation with a third reviewer. The extracted data included: first author, year of publication, country, study design, *Plasmodium* species, total number of patients, patient age, mean/median platelet count, prevalence of thrombocytopenia, and number of patients with severe malaria and/or mortality.

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. [6] A score of ≥ 7 was considered high quality.

2.3 Statistical Analysis

Statistical analysis was performed using R software (version 4.2.0) with the 'meta' and 'metafor' packages. The primary outcome was the pooled prevalence of thrombocytopenia. Secondary outcomes included pooled mean platelet count, diagnostic test accuracy (sensitivity, specificity, diagnostic odds ratio) for malaria in febrile patients, and the association between thrombocytopenia and severe malaria/mortality.

Pooled prevalence and mean platelet counts were calculated using a random-effects model with the DerSimonian-Laird method. Heterogeneity was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity. For diagnostic accuracy, we calculated pooled sensitivity, specificity, and diagnostic odds ratio (DOR) using a bivariate random-effects model. The association between severe thrombocytopenia ($<50,000/\mu\text{L}$) and clinical outcomes was expressed as a pooled relative risk (RR) with 95% confidence intervals (CI). Publication bias was assessed visually using funnel plots and statistically using Egger's test.

3. Results

3.1 Study Selection and Characteristics

The initial search yielded 3,458 records. After removing duplicates and screening titles and abstracts, 327 full-text articles were assessed for eligibility. A total of 127 studies involving 98,451 patients with confirmed malaria were included in the final meta-analysis. The included studies comprised 84 cross-sectional studies, 32 cohort studies, and 11 case-control studies. The mean NOS score was 7.4, indicating overall high quality.

3.2 Prevalence of Thrombocytopenia

The pooled prevalence of thrombocytopenia in all malaria patients was 74% (95% CI, 71-77%). Significant heterogeneity was observed ($I^2 = 94\%$). In subgroup analysis, the prevalence was 72% (95% CI 68-75%) for *P. falciparum* and 78% (95% CI 74-81%) for *P. vivax* (Figure 1). The pooled mean platelet count across all studies was 89,500/ μL (95% CI 85,200-93,800/ μL).

3.3 Diagnostic Accuracy of Thrombocytopenia

Forty-two studies, including 25,887 febrile patients (malaria and non-malaria), provided data for diagnostic accuracy analysis. The pooled sensitivity of thrombocytopenia for diagnosing malaria was 0.75 (95% CI 0.71-0.79), and the pooled specificity was 0.81 (95% CI 0.77-0.84). The pooled diagnostic odds ratio was 14.2 (95% CI 10.5-19.1), indicating a strong ability to distinguish malaria from other febrile illnesses.

3.4 Thrombocytopenia as a Prognostic Marker

Fifty-eight studies reported on the association between thrombocytopenia and severe malaria. Patients with severe thrombocytopenia ($<50,000/\mu\text{L}$) had a significantly higher risk of severe malaria compared to those with higher platelet counts (Pooled RR 3.45, 95% CI 2.68-4.44). Furthermore, severe thrombocytopenia was associated with a significantly

increased risk of mortality (Pooled RR 2.91, 95% CI 1.98-4.27), based on data from 28 studies.

3.5 Publication Bias

The funnel plot for the primary outcome (prevalence) was asymmetrical, and Egger's test was significant ($p < 0.01$), suggesting potential publication bias.

4. Discussion

This systematic review and meta-analysis, encompassing nearly 100,000 patients, provides a comprehensive quantitative synthesis of the relationship between malaria and thrombocytopenia. Our findings confirm that thrombocytopenia is a highly prevalent complication, affecting approximately three-quarters of all malaria patients. The high prevalence in both *P. falciparum* and *P. vivax* challenges the traditional view of *P. vivax* as a "benign" infection and underscores its significant hematological impact. [7]

The high diagnostic odds ratio of 14.2 establishes thrombocytopenia as a powerful, readily available bedside marker to raise the index of suspicion for malaria in a febrile patient in an endemic area. Its high specificity (81%) means that a low platelet count in this context is strongly indicative of malaria, though its moderate sensitivity (75%) means a normal platelet count cannot reliably rule it out.

Most critically, our analysis demonstrates that severe thrombocytopenia is not merely a laboratory curiosity but a robust prognostic indicator. The three-fold increased risk of severe malaria and mortality associated with a platelet count below 50,000/ μL highlights its utility in risk stratification. This finding should prompt clinicians to intensify monitoring and management in such patients. The pathophysiological link likely involves increased sequestration and consumption of platelets in the microvasculature, reflecting the underlying severity of the parasitic infection and the host's inflammatory response. [3, 4]

4.1 Limitations

The conclusions of this review are tempered by several limitations. The high statistical heterogeneity is likely due to variations in patient demographics, baseline immunity, and local definitions of thrombocytopenia. The presence of publication bias suggests that smaller studies not finding a significant association may be missing from the literature. Furthermore, many studies did not adjust for potential confounders in the prognostic analysis.

5. Conclusion

This meta-analysis provides conclusive evidence that thrombocytopenia is a salient feature of malaria, with high prevalence across *Plasmodium* species. It serves as a valuable diagnostic and, more importantly, a prognostic marker. The routine assessment of platelet count in the management of febrile patients in malaria-endemic regions is a simple, cost-effective strategy to aid diagnosis and identify those at high risk for severe complications.

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