Original Article
DOI: https://doi.org/10.70749/ijbr.v3i2.585

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Frequency of Bicytopenia in Slide-Positive Malaria Patients

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ARTICLE INFO

Keywords

Thrombocytopenia, Malaria Patients, Haematological Complications and Recovery Duration.

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Declaration

Author's Contributions: All authors equally contributed to the study and approved the final manuscript.
Conflict of Interest: No conflict of interest.
Funding: No funding received by the authors.

Article History

Received: 19-12-2024
Revised: 21-01-2024
Accepted: 01-02-2025

ABSTRACT

Background: Malaria is a life-threatening parasitic disease that remains a significant global health concern, particularly in endemic regions. Haematological abnormalities such as bicytopenia, characterised by the reduction of two blood cell lines (red blood cells, white blood cells, or platelets), are commonly observed in malaria patients. **Methodology:** A cross-sectional study was conducted over six months at the Department of Hematology, Hayatabad Medical Complex, Peshawar. A total of 138 patients, aged 16–60 years, with confirmed Plasmodium falciparum or Plasmodium vivax malaria, were included. Bicytopenia was defined as a white blood cell count below 3,000/cmm and a platelet count below 150,000/mm³. Data on demographic, clinical, and laboratory parameters were collected and analysed using SPSS version 23. Stratification and post-stratification analyses were performed to identify significant associations, with a p-value <0.05 considered statistically significant. **Results:** Bicytopenia was observed in 32% of malaria patients. The most common pattern involved a reduction in white blood cells and platelets (91%), followed by a combination of white blood cells and red blood cells (7%), and platelet and red blood cell reduction (2%). Patients with bicytopenia were more likely to report symptoms such as fatigue (80%, p=0.048) and easy bruising (45%, p<0.001). Plasmodium falciparum was more frequently associated with bicytopenia compared to P. vivax, although the difference was not statistically significant (p=0.126). Laboratory findings showed significantly lower haemoglobin levels, white blood cell counts, and platelet counts in the bicytopenia group compared to the non-bi-cytopenia group (p<0.001 for all). **Conclusion:** This study highlights a significant burden of bicytopenia among malaria patients, with P. falciparum being a major contributor. The findings emphasise the importance of routine haematological evaluations in malaria management to identify and mitigate complications early.

INTRODUCTION

Malaria is a life-threatening parasitic disease transmitted through the bite of infected female *Anopheles* mosquitoes [1]. Despite advancements in healthcare, it continues to pose a significant global health burden, affecting millions of individuals annually. The disease is most prevalent in tropical and subtropical regions, where it remains a leading cause of morbidity and mortality[2]. Five species of *Plasmodium* are known to infect humans, with *Plasmodium falciparum* and *Plasmodium vivax* being the most commonly reported. The severity of malaria is influenced by factors such as parasite species, host immunity, and access to timely medical care[3].

The pathophysiology of malaria is complex and includes both immune and non-immune mechanisms[4]. The parasite infects red blood cells (RBCs), leading to their destruction, sequestration, and subsequent inflammatory response. In severe cases, complications such as cerebral malaria, multi-organ dysfunction, and severe anaemia may develop. These complications often arise due to the destruction of multiple cell lines, including RBCs, white blood cells (WBCs), and platelets[5].

Bicytopenia, defined as the reduction of two cell lines (RBCs, WBCs, or platelets), is a common haematological abnormality in malaria[6]. While pancytopenia has been extensively studied, literature on the frequency and patterns of cytopenia in malaria patients remains limited. This gap in knowledge highlights the need for focused research on this condition to improve our understanding of its clinical implications[7].

The haematological manifestations of malaria can vary depending on the species of *Plasmodium* involved. *P. falciparum* is more likely to cause severe bicytopenia due to its high parasitemia and propensity for capillary sequestration. In contrast, *P. vivax* infections are generally milder but may lead to significant haematological changes. Recognising these patterns can help clinicians identify patients at risk for complications and provide timely interventions[8].

This study aims to determine the frequency of bicytopenia in slide-positive malaria patients and explore its patterns in a tertiary care hospital setting. By understanding the haematological abnormalities associated with malaria, healthcare providers can better manage these patients, potentially reducing the burden of severe complications.

The findings from this research are expected to contribute to the limited body of evidence on bicytopenia in malaria, particularly in regions where the disease is endemic. Such data will help refine treatment protocols, improve patient outcomes, and guide future research efforts in this critical area.

METHODOLOGY

This study was a cross-sectional analysis conducted in the Department of Haematology at Hayatabad Medical Complex, Peshawar. The study was carried out over six months from 15th June 2024 to 15th Dec 2024, following approval of the synopsis from the College of Physicians and Surgeons Pakistan (CPSP) Ref No: CPSP/ REU / HEM-2019-021-794. The purpose was to determine the frequency of bicytopenia in slide-positive malaria patients and identify its haematological patterns.

Ethical approval was obtained from the Institutional Review and Ethical Board (IREB) of Hayatabad Medical Complex Approval No: 1907. The study adhered to ethical principles as outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment. Participants were informed about the study's objectives, assured confidentiality, and notified that participation was voluntary, with no associated risks.

The sample size was calculated using the World Health Organization (WHO) sample size calculator. Assuming a 32% frequency of bicytopenia in malaria patients, an absolute precision of 7.8%, and a 95% confidence level, the required ‘sample size was determined to be 138’. ‘A consecutive non-probability sampling technique was used to recruit participants who met the’ inclusion criteria.

Inclusion and Exclusion Criteria

Participants were included in the study if they:

- Were aged between 16 and 60 years.
- Had a confirmed diagnosis of *Plasmodium vivax* or *Plasmodium falciparum* malaria through peripheral smear positivity.
- Presented to the hospital during the study period.

Exclusion criteria included:

- Patients with pre-existing blood dyscrasias, whether primary or secondary.
- Individuals diagnosed with autoimmune diseases or known haematological disorders.

Patients presenting to the hospital with fever and other symptoms suggestive of malaria were screened for eligibility. A detailed history and physical examination were conducted for all enrolled participants. Demographic data, including age, gender, residence, socioeconomic status, education level, and employment status, were recorded.

Malaria was diagnosed through a peripheral blood smear showing the presence of malarial parasites. Bicytopenia was defined as ‘a white blood cell (WBC) count of less than 3,000/cmm and a platelet count of less than 150,000/mm³’. These thresholds were determined using complete blood count (CBC) results performed on automated haematology analysers. Haemoglobin levels were also recorded for further haematological assessment.

The study employed a structured proforma to document clinical and laboratory findings systematically. Clinical symptoms such as fatigue, fever, easy bruising, and bleeding tendencies were noted. Laboratory parameters, including haemoglobin levels, WBC count, and platelet count, were measured to assess haematological abnormalities.

Data were analysed using SPSS version 23. Continuous variables, such as age, BMI, and duration of illness, were tested for normality using the Shapiro-Wilk test. Results were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on the data distribution. Frequencies and percentages were calculated for categorical variables, including gender, socioeconomic status, and the type of malaria.

Stratification was performed to control for effect modifiers such as age, gender, BMI, and disease duration. Post-stratification analysis was conducted ‘using chi-square or Fisher’s exact tests for categorical variables’. ‘A p-value of less than 0.05 was considered statistically significant’.

RESULTS

The participants' average age was slightly higher in the bicytopenia group (35 ± 10 years) compared to those without bicytopenia (32 ± 9 years), and this difference was statistically significant (p=0.041). Male participants were more prevalent in both groups, constituting 68% of

the bicytopenia group and 64% of the non-bicytopenia group, with no significant gender-based difference (p=0.675). Urban residents comprised 41% of the bicytopenia group, while 47% of those without bicytopenia lived in urban areas, showing no significant association between residence and bicytopenia (p=0.523). Regarding socioeconomic status, most participants in both groups fell into the lower socioeconomic tier (55% in the bicytopenia group and 54% in the non-bicytopenia group), with no significant disparity between groups (p=0.719). However, education and employment status were notably associated with bicytopenia. A smaller proportion of educated individuals was observed in the bicytopenia group (45%) compared to 64% in the non-bicytopenia group (p=0.029). Similarly, fewer individuals in the bicytopenia group were employed (50%) compared to the non-bicytopenia group (64%), a difference that was also significant (p=0.047).

Table 1

Demographic and Socioeconomic 'Characteristics of Participants' with and without Bicytopenia

Characteristic	Bicytopenia Present (n=44)	Bicytopenia Absent (n=94)	Total (n=138)	Statistical Significance
Average Age (years)	35 ± 10	32 ± 9	33 ± 9.5	0.041
Gender				
Male (%)	30 (68%)	60 (64%)	90 (65%)	0.675
Female (%)	14 (32%)	34 (36%)	48 (35%)	
Living Area				
Urban (%)	18 (41%)	44 (47%)	62 (45%)	0.523
Rural (%)	26 (59%)	50 (53%)	76 (55%)	
Economic Tier				
Upper Class (%)	5 (11%)	9 (10%)	14 (10%)	0.719
Middle Class (%)	15 (34%)	34 (36%)	49 (36%)	
Lower Class (%)	24 (55%)	51 (54%)	75 (54%)	
Education Level				
Educated (%)	20 (45%)	60 (64%)	80 (58%)	0.029
Uneducated (%)	24 (55%)	34 (36%)	58 (42%)	
Employment Status				
Employed (%)	22 (50%)	60 (64%)	82 (59%)	0.047
Unemployed (%)	22 (50%)	34 (36%)	56 (41%)	

The median duration of illness was significantly 'longer in the bicytopenia group (10 days, IQR 8–12) compared to the non-bicytopenia group (8 days, IQR 6–10; p=0.032)'. The distribution of malaria types showed that *Plasmodium falciparum* was more common among bicytopenic patients (57%) than non-bicytopenic ones (43%), although 'this difference did not reach statistical significance' (p=0.126). Conversely, *Plasmodium vivax* was more frequently identified in the non-bicytopenia group (57%) than the bicytopenia group (43%). All participants in both groups reported fever, but other symptoms differed significantly. Fatigue 'was more prevalent in the bicytopenia group (80%) than the non-bicytopenia group' (64%; p=0.048). Easy bruising was markedly more common in the bicytopenia group (45%) compared to only 11% in the non-bicytopenia group p<0.001 ().

Table 2

Clinical Characteristics of Patients Based on Bicytopenia Status

Clinical Parameter	Bicytopenia Present (n=44)	Bicytopenia Absent (n=94)	p-value
Disease Duration (days)	Median 10 (IQR 8–12)	Median 8 (IQR 6–10)	0.032
Malaria Type			
Plasmodium falciparum (%)	25 (57%)	40 (43%)	0.126
Plasmodium vivax (%)	19 (43%)	54 (57%)	
Mixed Infection (%)	0	0	
Symptomatic Presentation			
Fatigue (%)	35 (80%)	60 (64%)	0.048
Easy Bruising (%)	20 (45%)	10 (11%)	<0.001
Fever (%)	44 (100%)	94 (100%)	—

Laboratory findings revealed significant differences between the groups. Patients with bicytopenia had lower mean hemoglobin levels (10.5 ± 1.8 'g/dL) compared to those without bicytopenia (11.8 ± 1.2 g/dL; p<0.001)'. The median white blood cell (WBC) count was significantly reduced in the bicytopenia group (2,500 cells/cmm; IQR 2,000–2,900) compared to the non-bicytopenia group (5,600 cells/cmm; IQR 4,800–6,200; p<0.001). Platelet counts followed a similar pattern, with a median of 80,000/mm³ (IQR 60,000–100,000) in the bicytopenia group, substantially lower than 210,000/mm³ (IQR 180,000–240,000) in the non-bicytopenia group (p<0.001).

Table 3

Laboratory Parameters in Patients with and without Bicytopenia

Lab Parameter	Bicytopenia Present (n=44)	Bicytopenia Absent (n=94)	p-value
Hemoglobin (g/dL)	10.5 ± 1.8	11.8 ± 1.2	<0.001
WBC Count (cells/cmm)	Median 2,500 (IQR 2,000–2,900)	Median 5,600 (IQR 4,800–6,200)	<0.001
Platelet Count (/mm³)	Median 80,000 (IQR 60,000–100,000)	Median 210,000 (IQR 180,000–240,000)	<0.001

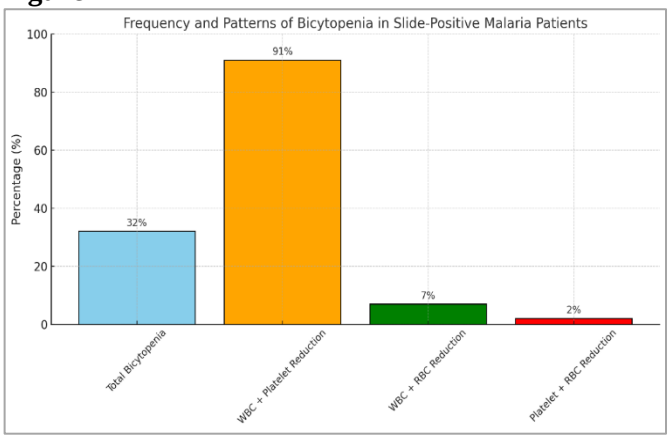
The overall frequency of bicytopenia among the studied participants was 32% (n=44). The most common pattern observed was a reduction in WBC and platelet counts, present in 91% of bicytopenic patients (confidence interval: 85%–97%; p<0.001). A combination of reduced WBC and red blood cell (RBC) counts occurred in 7% of cases (confidence interval: 2%–15%; p=0.015), while a reduction in platelet and RBC counts, was the least frequent, observed in only 2% of cases (confidence interval: 0.1%–7%; p=0.045).

Table 4

Frequency and Patterns of Bicytopenia in Slide-Positive Malaria Patients

Parameter	Cases (%)	Confidence Interval	p-value
Total Cases of Bicytopenia	44 (32%)	25%–40%	—
WBC and Platelet Reduction	40 (91%)	85%–97%	<0.001
WBC and RBC Reduction	3 (7%)	2%–15%	0.015
Platelet and RBC Reduction	1 (2%)	0.1%–7%	0.045

Figure 1



The bar graph depicts the frequency and patterns of bicytopenia in slide-positive malaria patients. Overall, 32% of patients were found to have bicytopenia. Among these, the most frequent pattern was a combination of white blood cell (WBC) and platelet reduction, observed in 91% of cases. A much smaller proportion, 7%, exhibited a combination of WBC and red blood cell (RBC) reduction. In contrast, the least common pattern, involving platelet and RBC reduction, was identified in only 2% of patients. This visualisation highlights that WBC and platelet reduction are this population's predominant manifestations of bicytopenia.

DISCUSSION

This study evaluated the frequency and patterns of bicytopenia in slide-positive malaria patients. The findings revealed that 32% of malaria patients exhibited bicytopenia, with WBC and platelet reduction being the most common combination. These results underscore the haematological impact of malaria, mainly its potential to cause significant blood cell line abnormalities.

The observed frequency of bicytopenia aligns with findings from previous studies conducted in malaria-endemic regions. Studies reported a similar prevalence of bicytopenia among malaria patients, emphasising the consistent association of malaria with haematological abnormalities in different settings [9-11]. The predominance of WBC and platelet reduction in our study was also consistent with prior literature, which attributes this pattern to immune-mediated destruction and splenic sequestration caused by *Plasmodium* infection[12, 13].

The role of *Plasmodium falciparum* in contributing to severe haematological abnormalities was evident in our study, where this species was more frequently associated with bicytopenia than *P. vivax*. This finding was supported by previous research indicating that *P. falciparum* infections are often associated with higher parasitemia and more significant sequestration of infected red blood cells, leading to increased bone marrow suppression and peripheral destruction of blood cells [14, 15]. Conversely, *P. vivax* infections were less likely to cause bicytopenia, consistent with its typically milder disease course[16].

In our study, patients with bicytopenia had significantly lower WBC and platelet counts than those without bicytopenia. This aligns with a study by Studies thar reported profound reductions in WBC and platelet counts in patients with malaria-induced bicytopenia. The immune activation and inflammatory response triggered by malaria contribute to this phenomenon. Cytokine release, particularly interleukin-6 and tumour necrosis factor-alpha, plays a pivotal role in blood cells' peripheral destruction and sequestration[17, 18].

Clinical symptoms such as fatigue and easy bruising were more common in the bicytopenia group, highlighting the clinical relevance of these hematological changes. These findings corroborate reports from studies that have linked bicytopenia to symptoms of anemia and thrombocytopenia, which are common in malaria patients. The extended duration of illness observed in bicytopenic patients in our study may reflect the added burden of hematological complications on recovery [13, 19, 20].

The implications of these findings are significant for clinical practice. Early recognition of bicytopenia in malaria patients can aid in identifying those at risk of severe complications, such as bleeding tendencies or severe anemia. Routine haematological evaluation in malaria patients, including complete blood count (CBC), should be emphasised to guide timely management and improve outcomes.

‘While this study provides valuable insights, certain limitations must be acknowledged. The cross-sectional design precludes an assessment of causality between

malaria and bicytopenia'. Additionally, 'the study was conducted at a single tertiary care hospital, which may limit the generalizability of the findings to other populations or healthcare settings'.

CONCLUSION

This study highlights the significant burden of bicytopenia among malaria patients, with *Plasmodium falciparum* being a major contributor. The findings emphasise the need for routine haematological assessment in malaria management to address potential complications early. Future research should explore the long-term outcomes of patients with malaria-induced bicytopenia and evaluate interventions aimed at mitigating its impact.

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