

Thrombocytopenia and its Severity in Plasmodium Vivax Positive Patients

Mujtaba Shah¹, Shabnam Rani², Komal Kumari³, Nadeem Memon⁴, Zaheer Husain Memon⁵, Rutesh Kumar⁶

- 1 Senior Registrar, Department of Medicine, Liaquat University of Medical and Health Sciences, Jamshoro Pakistan
Data collection and write the first draft of manuscript
- 2 Assistant Professor, Department of Medicine, Muhammad Medical & Dental College, Mirpur Khas Pakistan
Data collection and methodology
- 3 MBBS Student, Islamabad Medical & Dental College, Islamabad Pakistan
Contribution in literature search and manuscript writing
- 4 Associate Professor, Department of Medicine, Muhammad Medical & Dental College, Mirpur Khas Pakistan
Guideline and finally approve the manuscript for publication
- 5 Associate Professor, Department of Medicine, Suleman Roshan Medical college, Tando Adam Pakistan
Contribution in manuscript writing
- 6 Medical Student, Agha Khan Medical University Karachi
Data analysis and formatting

CORRESPONDING AUTHOR

Dr. Mujtaba Shah

Senior Registrar, Department of Medicine,
Liaquat University of Medical and Health
Sciences, Jamshoro Pakistan
Email: mujtaba82shah@gmail.com

Submitted for Publication: 01-01-2023
Accepted for Publication 11-08-2023

How to Cite: Shah M, Rani S, Kumari K, Memon N, Memon ZA, Kumar R. Thrombocytopenia and its Severity in Plasmodium Vivax Positive Patients. APMC 2023;17(4):488-492. DOI: 10.29054/APMC/2023.1256

ABSTRACT

Background: Plasmodium vivax, one of the four species of human malaria parasites, is responsible for a considerable portion of malaria cases. While P. vivax is often considered less severe than Plasmodium falciparum, it is not without its complications. Thrombocytopenia is a common hematological complication associated with malaria infections, including those caused by P. vivax. **Objective:** To evaluate the severity of thrombocytopenia and relationship between thrombocytopenia and demographic factors, such as age and gender, in Plasmodium vivax positive patients. **Study Design:** Cross sectional study. **Settings:** Medicine OPD of Liaquat University of Medical and Health Sciences / Jamshoro and Muhammad Medical College, Mirpur Khas Pakistan. **Duration:** Six months from May 2022 to October 2022. **Methods:** Individuals aged over 12 years of either gender with a confirmed diagnosis of Plasmodium vivax were included. A single blood sample was collected from each participant for platelet count analysis, and demographic details and platelet counts were recorded using standardized data collection forms. Thrombocytopenia was defined as a platelet count below a predetermined threshold (e.g., <150,000 platelets/ μ L). All the information was collected via study proforma and SPSS version 26 was used for the analysis. **Results:** The participants had a mean age of 29.07 years. 122 individuals (61.3%) were male, and 77 individuals (38.7%) were female. Thrombocytopenia was highly prevalent in patients with a positive diagnosis of Plasmodium vivax, with a frequency of 83.4%. Among the affected individuals, 18.6% had mild thrombocytopenia, 38.2% had moderate thrombocytopenia, and 25.6% were observed with severe thrombocytopenia. According to the thrombocytopenia and its severity based on age and gender the p-values of 0.069 and 0.656 indicates no significant association of age and gender with thrombocytopenia severity. **Conclusion:** Study revealed a significant frequency of moderate to severe thrombocytopenia in individuals diagnosed with Plasmodium vivax infection and tends to be of moderate to severe intensity, without significant correlation of age and gender.

Keywords: Malaria, Vivax plasmodium, Platelets, Thrombocytopenia.

INTRODUCTION

Malaria is likely one of the oldest infectious diseases, influencing the trajectory of human evolution.¹ It is brought about by parasitic protozoa belonging to the genus Plasmodium and is naturally transmitted to humans via the bites of female Anopheles mosquitoes carrying the parasites.¹ Plasmodium vivax, the most widely distributed species among human malaria

parasites, impacts nearly 40% of the global population.²⁻⁴ The challenge lies in the undetectability of P. vivax's dormant liver stages using available diagnostic methods, potentially resulting in a significant underestimation of its true prevalence compared to P. falciparum.² Consequently, P. vivax parasites might be considerably more prevalent in numerous endemic areas than currently acknowledged.

There is a prevailing agreement that the severity of *P. vivax* has been undervalued, especially when comorbidities are present.⁵ Despite notable deficiencies in the current understanding of *P. vivax* pathophysiology, there is a firm consensus that vivax malaria is linked to a strong systemic inflammatory response.^{5,6} Changes in blood characteristics can differ based on the degree of malaria prevalence, the presence of underlying hemoglobin disorders, nutritional status, demographic elements, and immunity to malaria. The precise cause of thrombocytopenia in malaria remains unclear; however, suggested mechanisms include elevated consumption or destruction of platelets, suppression of thrombopoiesis, or a combination of these factors.⁷ Despite significant gaps in our current understanding of *P. vivax* pathophysiology, it is firmly established that vivax malaria triggers a potent systemic inflammatory response.^{5,8}

This response is occasionally more pronounced than in infections with its counterpart, *P. falciparum*, where severe malaria is commonly observed. Research indicates the potential occurrence of tissue accumulation of *P. vivax*, with the hidden biomass being most substantial in severe cases and capable of driving systemic inflammation.^{5,9}

Rising evidence supports the role of platelets as agents of inflammation, owing to their ability to release various proteins either upon activation or through interactions with the endothelium or white blood cells. Most Pakistanis live in rural areas situated between tropical and subtropical regions, where malaria is widespread. In Pakistan, the highest incidence of malaria occurs during the peak months of July and August.¹⁰ However the significant complications of severe malaria, as outlined by the World Health Organization (WHO) in 2014, encompass conditions such as impaired consciousness, jaundice, pulmonary edema, acute renal failure, severe anemia, bleeding, acidosis, hyper parasitemia, respiratory distress, and hypoglycemia.^{11,12} These complications have the potential to manifest swiftly and escalate to a fatal outcome within a matter of hours or days.¹¹ Although it is crucial to investigate the malaria-related complications associated with evident cases of malaria. Several recent studies have indicated that thrombocytopenia, previously associated with *P. falciparum* malaria, is now observed in cases of *P. vivax* malaria as well.^{13,14} While certain research suggests that thrombocytopenia should be considered a complication of severe malaria, other studies disagree with this perspective.^{13,15}

As the thrombocytopenia is a frequent hematological occurrence in cases of malaria; however, there is insufficient local data in Pakistan regarding the correlation between the severity of thrombocytopenia

and the specific species of malaria.¹⁷ Therefore this study has been done to determine the severity of thrombocytopenia and relationship between thrombocytopenia and demographic factors, such as age and gender, in Plasmodium vivax positive patients.

METHODS

This cross-sectional study, was done at medicine OPD and ward of Liaquat University of Medical and Health Sciences/ Jamshoro and Muhammad Medical College MirpurKhas aimed to investigate the incidence of thrombocytopenia in individuals diagnosed with Plasmodium vivax infection. Study duration was Six months from May 2022 to October 2022. The inclusion criteria encompass individuals aged more than 12 years of either gender with the confirmed diagnosis of Plasmodium vivax, while exclusion criteria were excluded the patients with co-infections of other Plasmodium species or pre-existing hematological disorders and those who were not willing to participate in the study. After taking informed consent a single blood sample was collected from each participant for platelet count analysis, and demographic details, malaria diagnosis date, and platelet counts were recorded using standardized data collection forms. Thrombocytopenia was defined as a platelet count below a predetermined threshold (e.g., <150,000 platelets/ μ L), was assessed using standardized laboratory protocols. Further thrombocytopenia was categorized into mild (platelet counts ranging from 100,000 to 150,000/ μ L), moderate (platelet counts between 50,000 and 100,000/ μ L), and severe (platelet counts less than 50,000/ μ L).¹⁶ Data validation and quality control measures will be implemented to ensure the accuracy and reliability of the results. Statistical analyses, including the calculation of thrombocytopenia incidence and subgroup analyses based on demographic factors, was conducted to identify potential associations. Chi-square test was applied and a p-value <0.05 was considered as significant.

RESULTS

The participants had a mean age of 29.07 years, with a standard deviation of 16.2 years. Out of the total sample size of 199, 122 individuals (61.3%) were male, and 77 individuals (38.7%) were female. The gender distribution reveals a slight predominance of males in the studied population. Table.1

Table 1: Mean age and gender of the patients (n=199)

Variables		Frequency	Percent
Gender	Male	122	61.3%
	Female	77	38.7%
	Total	199	100.0%
Age (mean \pm SD)		29.07 \pm 16.2 years	

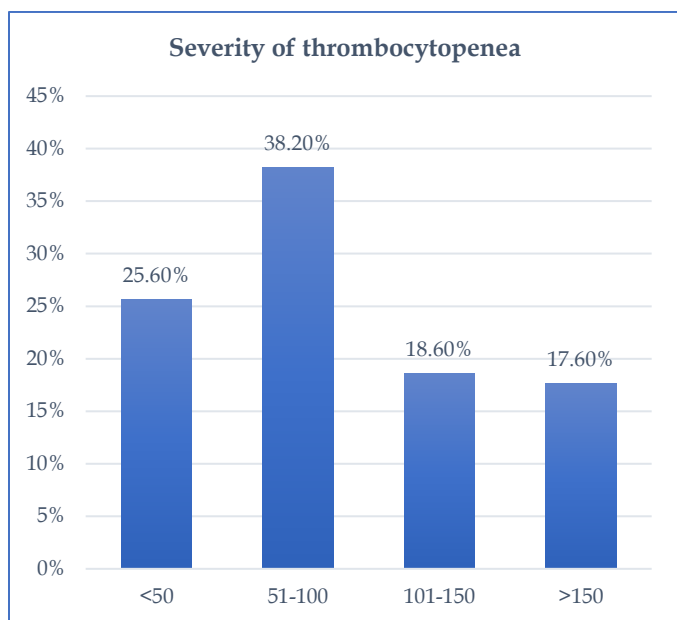
The mean values indicate the average levels of various hematological parameters, with red blood cell count (RBC) averaging at 4.14, hemoglobin at 11.15, leucocytes at 5.52, and platelets at 53.42, as shown in table 2.

Table 2: Descriptive statistics of hematological patterns (n=199)

Statistics	RBC	Hemoglobin	Leucocytes	Platelets
Mean	4.14	11.15	5.52	53.42
Std. Deviation	0.911	5.61	2.84	35.23
Minimum	1.39	3.20	1.10	10.00
Maximum	6.62	82.00	18.30	284.00

Thrombocytopenia was highly prevalent in patients with a positive diagnosis of Plasmodium vivax, with a frequency of 83.4%. Among the affected individuals, 18.6% had mild thrombocytopenia, 38.2% had moderate thrombocytopenia, and 25.6% were observed with severe thrombocytopenia. Fig:1

Figure 1: Frequency thrombocytopenia and its severity (n=199)



The table presents an analysis of thrombocytopenia and its severity based on age and gender in a cohort of 199 individuals. The p-value of 0.069 suggests no statistically significant association between age and thrombocytopenia severity. Further, the analysis includes gender-based thrombocytopenia severity, the p-value of 0.656 indicates no significant association between gender and thrombocytopenia severity, as shown in table 3.

Table 3: Thrombocytopenia and its severity according to age and gender (n=199)

Variables		Severity of thrombocytopenia				Total	p-value
		<50	51-100	100-150	>150		
Age group	12-20 years	11	30	17	13	71	0.069
		5.5%	15.1%	8.5%	6.5%	35.7%	
	21-30 years	19	28	11	8	66	
		9.5%	14.1%	5.5%	4.0%	33.2%	
	31-40 years	5	12	3	2	22	
		2.5%	6.0%	1.5%	1.0%	11.1%	
	41-50 years	6	4	5	6	21	
		3.0%	2.0%	2.5%	3.0%	10.6%	
	51-60 years	6	1	0	1	8	
3.0%		0.5%	0.0%	0.5%	4.0%		
61-70 years	2	1	1	3	7		
	1.0%	0.5%	0.5%	1.5%	3.5%		
>70 years	2	0	0	2	4		
	1.0%	0.0%	0.0%	1.0%	2.0%		
Total		51	76	37	35	199	
		25.6%	38.2%	18.6%	17.6%	100.0%	
Gender	Male	31	47	20	24	122	0.656
		15.6%	23.6%	10.1%	12.1%	61.3%	
	Female	20	29	17	11	77	
		10.1%	14.6%	8.5%	5.5%	38.7%	
Total		51	76	37	35	199	
		25.6%	38.2%	18.6%	17.6%	100.0%	

DISCUSSION

Plasmodium vivax stands as the most prevalent malarial parasite affecting humans.¹⁸ Mild thrombocytopenia is a typical characteristic of acute P. vivax-induced malaria, irrespective of the infection's intensity, and it has the potential to develop into severe thrombocytopenia.¹⁸ This study aimed to evaluate the severity of thrombocytopenia and explore its correlation with demographic factors, specifically age and gender, among individuals who tested positive for Plasmodium vivax. The study included 199 malaria cases, with a mean age of 29.07 years. Among these cases, 122 individuals (61.3%) were male, while 77 individuals (38.7%) were female. These findings were correlated with Ahmad S *et al*¹⁷ as the mean age of the patients with malaria was 40.85 ± 15.6 years and males were 56.6% and females were 43.3%. Consistently Iqbal S *et al*¹⁸ also reported that the males were 40 (71.43%) males and 16 (28.57%) females, while inconsistently they found mean age of the patients 6.3 years, which was markedly lower compared to this study and this may be because, their study population was children. These findings were also

corelated with the study by Gopalakrishnan NT *et al*¹⁹ as male to female ratio of 5:1 and they found most of the cases 31.6 % with age group of 21-30 years.

In this study, thrombocytopenia was highly prevalent among patients with a positive diagnosis of Plasmodium vivax, with a frequency of 83.4%. Among the affected individuals, 18.6% had mild thrombocytopenia, 38.2% had moderate thrombocytopenia, and 25.6% were observed with severe thrombocytopenia. This aligns with the findings of Iqbal S *et al.*¹⁸, who reported thrombocytopenia in 82.14% of cases, with 26.7% having mild thrombocytopenia, 41.07% having moderate thrombocytopenia, and 14.29% having severe thrombocytopenia. Gopalakrishnan NT *et al.*¹⁹ documented thrombocytopenia in 90.8% of cases, with a predominant occurrence of moderate to severe thrombocytopenia (80.7%). In a comparative study, Ahmad S *et al.*¹⁷ reported that thrombocytopenia manifested in 73% of all malaria patients. Among them, 35.23% experienced mild thrombocytopenia, while 31.82%, 23.86%, and 9.09% developed moderate, severe, and very severe thrombocytopenia, respectively. In a related study, Khan HU *et al.*²⁰ focused on pediatric cases of Plasmodium vivax malaria and found that out of the 172 participants, 68% exhibited thrombocytopenia. In contrast, Krishna P *et al.*⁷ reported thrombocytopenia in 81% of cases, with 30% having mild thrombocytopenia, 31% having moderate thrombocytopenia, and 20% having severe thrombocytopenia. Additionally, 19 subjects in Krishna P *et al.*'s study had normal platelet counts.⁷ In this study thrombocytopenia and its severity based on age and gender in a cohort of 199 individuals. The p-value of 0.069 suggests no statistically significant association between age and thrombocytopenia severity. Further, the analysis includes gender-based thrombocytopenia severity, the p-value of 0.656 indicates no significant association between gender and thrombocytopenia severity.

While thrombocytopenia was more prevalent in our study, it is essential to consider contextual factors. Most patients in this study had experienced previous flood conditions in Sindh, and a significant portion were admitted with delays and in severe conditions. Unfortunately, the duration of the disease was not documented in this study, which may have influenced the severity of thrombocytopenia. The delayed admissions and severe conditions could have contributed to the higher incidence observed in our study. To enhance the understanding of thrombocytopenia in Plasmodium vivax malaria, further large-scale studies should be conducted, stratifying demographic characteristics. This approach would provide a more nuanced perspective on the factors influencing thrombocytopenia and contribute

to the development of targeted interventions and treatment strategies.

CONCLUSION

The findings reveal a notable frequency of moderate to severe thrombocytopenia in individuals diagnosed with Plasmodium vivax infection and tends to be of moderate to severe intensity, without significant correlation of age and gender. This underscores the importance of vigilant monitoring and timely intervention for patients presenting with Plasmodium vivax infection, particularly in regions where this malaria species is prevalent.

LIMITATIONS

The study's sample size is relatively small, potentially limiting the generalizability of the results to a broader population. A larger and more diverse sample would enhance the external validity of the study. Additionally, the study did not stratify the data based on the duration of the disease and other demographic characteristics, which are assumed to be crucial factors in understanding the dynamic nature of thrombocytopenia in Plasmodium vivax malaria

SUGGESTIONS / RECOMMENDATIONS

Further large-scale studies should be conducted, stratifying demographic characteristics.

CONFLICT OF INTEREST / DISCLOSURE

None.

ACKNOWLEDGEMENTS

We extend our sincere gratitude to all those who contributed to the completion of this research article. Our heartfelt thanks go to the study participants whose cooperation and willingness to contribute their time and experiences made this research possible.

REFERENCES

1. Foko LP, Arya A, Sharma A, Singh V. Epidemiology and clinical outcomes of severe Plasmodium vivax malaria in India. *Journal of Infection*. 2021 Jun 1;82(6):231-46.
2. Naing C, Whittaker MA. Severe thrombocytopenia in patients with vivax malaria compared to falciparum malaria: a systematic review and meta-analysis. *Infectious Diseases of Poverty*. 2018;7:1-0.
3. Howes RE, Battle KE, Mendis KN, Smith DL, Cibulskis RE, Baird JK, et al. Global epidemiology of plasmodium vivax. *Am J Trop Med Hyg*. 2016;95:15-34
4. Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Vivax malaria: neglected and not benign. *Am J Trop Med Hyg*. 2007;77:79-87
5. Santos ML, Coimbra RS, Sousa TN, Guimarães LF, Gomes MS, Amaral LR. The interface between inflammatory mediators and MicroRNAs in plasmodium vivax severe thrombocytopenia. *Frontiers in Cellular and Infection Microbiology*. 2021;15:11:631333.

6. Antonelli LR, Junqueira C, Vinetz JM, Golenbock DT, Ferreira MU, Gazzinelli RT. The immunology of Plasmodium vivax malaria. Immunological reviews. 2020 Jan;293(1):163-89.
7. Krishna P, Chalamalasetty MK. Thrombocytopenia in malaria and its diagnostic significance: A prospective study. Journal of Clinical and Scientific Research. 2023 Jul 1;12(Suppl 1):S1-4.
8. Antonelli LR, Junqueira C, Vinetz JM, Golenbock DT, Ferreira MU, Gazzinelli RT. The immunology of Plasmodium vivax malaria. Immunological reviews. 2020 Jan;293(1):163-89.
9. Silva-Filho JL, Lacerda MV, Recker M, Wassmer SC, Marti M, Costa FT. Plasmodium vivax in hematopoietic niches: hidden and dangerous. Trends in parasitology. 2020 May 1;36(5):447-58.
10. Khalid M, Iqbal K, Nadeem M, Khan K, Kousar A, Rao S, Abrar M, Abbas F. Frequency of Thrombocytopenia in Malaria Patient at Tertiary Care Hospital. Pakistan Journal of Medical & Health Sciences. 2022 Dec 6;16(10):362-.
11. Kotepui M, Kotepui KU, Milanez GD, Masangkay FR. Prevalence and risk factors related to poor outcome of patients with severe Plasmodium vivax infection: A systematic review, meta-analysis, and analysis of case reports. BMC Infectious Diseases. 2020 Dec;20(1):1-4.
12. World Health Organization. Guidelines for the treatment of malaria. Geneva: World Health Organization; 2015
13. Bansal Y, Maurya V, Aggarwal N, Tak V, Nag VL, Purohit A, Goel AD, Bohra GK, Singh K. Thrombocytopenia in malaria patients from an arid region of Western Rajasthan (India). Tropical Parasitology. 2020 Jul;10(2):95.
14. Muley A, Lakhani J, Bhirud S, Patel A. Thrombocytopenia in Plasmodium vivax malaria: How significant? J Trop Med. 2014;2014:567469
15. Hanson J, Phu NH, Hasan MU, Charunwatthana P, Plewes K, Maude RJ, et al. The clinical implications of thrombocytopenia in adults with severe falciparum malaria: A retrospective analysis. BMC Med. 2015;13:97.
16. Gebreweld A, Erkihun Y, Feleke DG, Hailu G, Fiseha T. Thrombocytopenia as a diagnostic marker for malaria in patients with acute febrile illness. Journal of Tropical Medicine. 2021 Apr 10;2021;1-6
17. Ahmad S, Rehman SU, Ikramullah Q, Ahmad I. Frequency of Thrombocytopenia in malaria and its prognostic significance. Journal of University Medical & Dental College. 2023;14(1):545-548
18. Iqbal S, Riaz L, Shaukat F, Aslam M. Frequency of Thrombocytopenia in Plasmodium vivax malaria. Proceeding SZPGMI. 2014;28(1):13-7.
19. Gopalakrishnan NT, Papaiah S, Soman S. A clinicopathological study of thrombocytopenia in malaria cases with its evaluation in different types of malaria. J Evolution Med Dent Sci 2021;10(33): 2707-2711,
20. Khan HU, Jehanzeb S, Mehreen B, Shaheen R, Rehman SU, Babar MF. Frequency of Thrombocytopenia in Plasmodium VIVAX Malaria Among Children. Pakistan Journal of Medical & Health Sciences. 2023 Apr 30;17(03):476-.