ORIGINAL RESEARCH

Investigating the association between various platelet indices and different clinical sub-groups of severe malaria

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Abstract

Aim

To evaluate the ability of platelet count, mean platelet volume, platelet distribution width, and platelet mass index to predict the severity of malaria.

Materials and Methods

This study was conducted as a retrospective cohort study at a tertiary hospital in Somali. Patients grouped as severe and non-severe malaria. We compared groups in terms of platelet count, mean platelet volume, platelet distribution width, and platelet mass index.

Results

A total of 131 patients were included in the final analysis. Of the patients, 77 (58.7%) had non-severe malaria, and 54 (41.3%) had severe malaria. The multivariate analysis revealed that there was no significant difference between the groups in terms of platelet count, mean platelet volume, platelet distribution width, and platelet mass index (p: 0.183, 0.323, 0.204, and 0.139, respectively). In the receiver operating characteristic analysis, the area under the curve values for platelet count, mean platelet volume, platelet distribution width, and platelet mass index were 0.699, 0.619, 0.504, and 0.675, respectively.

Conclusion

Of the platelet indices, platelet count, mean platelet volume, platelet distribution width, and platelet mass index were not clinically significant markers that could be used to predict the severity of malaria.

Keywords: Malaria; platelet; mortality; severity

Background

Malaria is a disease that has been known since ancient times and is seen in 300-500 million people per year in developing countries in tropical regions. It has been reported that 2-3 millions of these patients die, and malaria ranks sixth to eighth among infectious diseases[1]. It is known that malaria affects many organs and systems, especially the hematopoietic system, and complications related to these systems are responsible for mortality and morbidity. Changes in the hematological system, especially erythrocyte count and platelet count have been associated with mortality[2,3].

Platelets are non-nucleated cells with a diameter of 2 µ, which are produced by megakaryocytes in the bone marrow and play a key role in hemostasis 849. The life span of platelets is eight to 10 days, and there are approximately 1 trillion platelets in adults. Platelets perform many functions other than hemostasis through biologically active molecules they store inside the cell. While bioactive mediators and adhesive proteins secreted from activated platelets provide interaction between platelets and regulate their interaction with other immune system cells[4,5]. Activated platelets facilitate the adhesion of neutrophils to the endothelium and regulate the pro-inflammatory functions of neutrophils. Thus, platelets play an important mediating role in intercellular communication in the inflammatory response. Therefore, changes in platelet shape, number, and volume have been associated with many infectious and inflammatory processes, such as sepsis[5,6]. Thrombocytopenia is already a well-known characteristic of malaria (both uncomplicated malaria and severe malaria). Some previous studies have shown an association between lower-than-normal platelet counts and transition from uncomplicated malaria to severe malaria[7,8]. In this study, we aimed to investigate the role of initial platelet indices in predicting severe malaria.

Materials and Methods

Study design

This study was conducted as a retrospective cohort study in a tertiary education hospital in Somali (Mogadishu Somalia Turkish Training and Research Hospital), equipped with 300 beds (50 for critical care) and receiving 350 daily emergency admissions (annual average of the study period). The data of patients who presented to the emergency department between January 1, 2017, and January 1, 2020, were retrospectively collected.

Study population

The population of the study consisted of adult patients who

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presented to the emergency department with symptoms of malaria during the study period. Patients who were diagnosed with malaria or who had symptoms and signs of malaria were identified through the hospital computerized medical and laboratory record system. Rapid Diagnostic Kit-Rapid Diagnostic Test (RDT) for malaria was used as the diagnostic test of the study population. RDT is using to diagnose malaria by detecting evidence of malaria parasites (antigens) in human blood. These tests require a drop of peripheral blood. Patients presenting with cerebral malaria, shock or circulatory collapse, severe acidosis, pulmonary edema, severe malarial anemia, spontaneous bleeding, renal failure, or clinical evidence of jaundice, and vital organ dysfunction were considered to have severe malaria. Based on WHO guidelines, patients with cerebral malaria are supposed to have a Glasgow Coma Score (GCS) of <11, with unarousable coma not attributable to any other cause and who are unable to localize stimuli and are incomprehensible to sounds while those presenting with uncomplicated malaria or other forms of severe malaria should have a GCS score of greater than 11 at both times. Patients with missing data were excluded from the study. The flowchart of the study is shown in Figure 1.

Data collection

The patients' demographic data, signs, and symptoms, laboratory findings, emergency department outcomes, and mortality due to malaria were obtained from the hospital system. Signs and symptoms were recorded as headache, vomiting, cough, diarrhea, pallor, icterus, hepatomegaly, and splenomegaly. The laboratory parameters were documented as creatinine, blood urea nitrogen, alanine transaminase, aspartate transaminase, total bilirubin, direct bilirubin, indirect bilirubin hemoglobin, hematocrit, white blood cell count, platelet, mean platelet volume, plateletcrit, platelet distribution width, and platelet mass index. The platelet mass index was calculated by multiplying the platelet count and the mean platelet volume. Emergency department outcomes were noted as discharge, admission to ward, and admission to the intensive care unit. The mortality status of the patients was questioned by phone calls using the patients' contact numbers registered in the hospital system.

Statistical analysis

We used IBM SPSS Statistics for Mac, NY, IBM Corp, Version 27.0. Armonk to perform statistical analyses. To evaluate the conformance of variables to the normal distribution, the Kolmogorov-Smirnov test was conducted. The non-normally distributed data were expressed as median and 25th-75th percentile values, and the data that conformed to the normal distribution were presented with mean and standard deviation values. Categorical data were presented as the number of cases and percentages. For the comparison of qualitative and quantitative data between two groups, the chi-square and Mann-Whitney U tests were used.

To demonstrate the ability of initial platelet indices, the receiver operating characteristic (ROC) analysis was performed.

Figure 1. Flowchart of the study

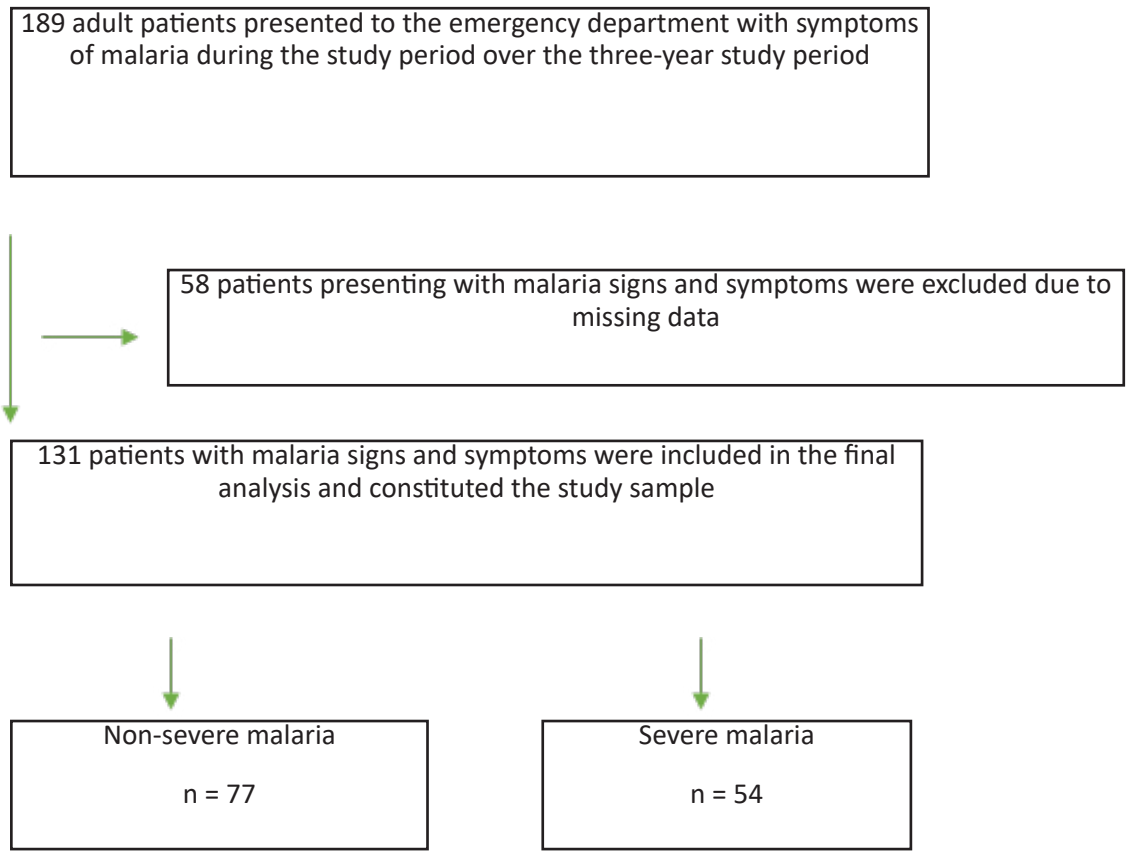

Table 1. Baseline characteristics of the enrolled patients and their distribution according to the severity of malaria

	Total	Non-severe	Severe
	n = 131	n = 77	n = 54
Age, years	33 (18-80)	29 (18-80)	40 (18-68)
Gender			
Male	86 (65.6%)	47 (61%)	39 (72.2%)
Female	45 (34.4%)	30 (39%)	15 (27.8%)
Signs and symptoms			
Fever	59 (45%)	28 (36.4%)	31 (57.4%)
Headache	46 (35.1%)	25 (32.5%)	21 (38.9%)
Vomiting	30 (22.9%)	15 (19.5%)	15 (27.8%)
Cough	19 (14.6%)	13 (16.9%)	6 (11.3%)
Diarrhea	40 (30.8%)	23 (30.3%)	17 (31.5%)
Pallor	18 (13.7%)	7 (9.1%)	11 (20.4%)
Icterus	27 (20.6%)	8 (10.4%)	19 (35.2%)
Hepatomegaly	16 (12.2%)	13 (16.9%)	3 (5.6%)
Splenomegaly	8 (6.1%)	0	8 (14.8%)
Laboratory findings			
Aspartate aminotransferase	32.5 (22-57)	28 (21-44)	52 (30.84-77)
Alanine aminotransferase	24.34 (15-52)	20.69 (11-45)	35 (20.69-58)
Total bilirubin	0.67 (0.42-2.69)	0.48 (0.35-0.66)	2.69 (1.48-7.53)
Direct bilirubin	0.46 (0.14-2)	0.27 (0.14-0.35)	1.91 (0.6-4)
Creatinine	0.79 (0.53-1.12)	0.7 (0.5-0.94)	1.02 (0.57-2.22)
Blood urea nitrogen	14 (8-30)	9 (6-16)	25 (14-40)
Hemoglobin	11.9 (10.1-13.2)	12.1 (10.9-13.9)	10.1 (6.1-13.1)
Hematocrit	34.4 (27.6-40)	35.7 (32.4-41)	33 (22-38.8)
White blood cell count	6.32 (4.7-8.22)	5.75 (4.52-7.5)	8 (6.51-13.68)
Platelet count	203 (102-294)	220 (157-301)	118 (54-199)
Mean platelet volume	8 (7.2-9)	8.2 (7.9-9)	8 (7-9)
Platelet distribution width	15.8 (14-16.8)	15 (14-16.3)	16 (14-17)
Platelet mass index	1749.2 (1029.2-2500)	1909.6 (1552.5-2616.6)	1029.2 (720-2220)
Emergency department outcomes			
Discharge	70 (53.4%)	70 (90.9%)	0
Admitted to ward	38 (29%)	7 (9.1%)	31 (57.4%)
Admitted to intensive care unit	20 (15.3%)	0	20 (37%)
Mortality	16 (12.2%)	0	16 (29.6%)

The results of ROC were presented with the area under the curve (AUC), cut-off, sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive value, accuracy, 95% confidence interval, and p value. An AUC value greater than 0.7 was considered to be a significance value for a possible predictor[9]. A p value of 0.05 was considered as the cut-off point for statistical significance. The study was determined as 122 with G-power by taking impact size 0.6 and α=0.005, power (1- β) =0.95 at a confidence level 95%.

Ethics

Ethical approval for the study was received from the ethics committee of Mogadishu Somalia Turkish Training and Research Hospital with 11.22.2021 date and 449 number. We retrospectively reviewed secondary data recorded from the computer-based hospital information system, and these data did not include any personal identifiable information; therefore, informed consent was waived within the knowledge of the ethics committee.

Results

A total of 131 patients were included in the final analysis. Forty-five (34.4%) patients were female. Of the patients, 77 (58.7%) were considered to have non-severe malaria and 54 (41.3) severe malaria. A total of 16 (12.2%) patients died due to malaria-related causes. Sixteen (12.2%) patients had cerebral malaria, 16 (12.2%) patients had shock or circulatory collapse, 15 (11.4%) had severe acidosis, 15 (11.4%) had pulmonary edema, 33 (25.1%) had severe malarial anemia, eight (6.1%) had spontaneous bleeding, 19 (14.5%) had renal failure, and 23 (17.5%) had clinical evidence of jaundice and vital organ dysfunction. The baseline characteristics of the study population and their distribution according to the severity of malaria are shown in Table 1. To compare the severe and non-severe malaria groups, we first performed a univariate analysis. As a result of this analysis, we found a significant difference between the severe and non-severe malaria groups in terms of all parameters except the platelet distribution width, which is one of the laboratory parameters examined in our study (Table 2). Our multivariate analysis revealed no significant difference between the groups in terms of the investigated parameters (Table 2).

We performed the ROC analysis to demonstrate the ability of initial platelet indices to predict severe disease.

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Table 2. Univariate and multivariate logistic regression analyses of patients with non-severe and severe malaria

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age, years		0.136	0.973 (0.87-1.08)	0.629
Age, ≥50 vs. <50	1.639 (0.756-3.553)	0.211		
Fever, ≥37.8 vs. <37.8	2.359 (1.158-4.806)	0.018	0.033 (0.001-1.25)	0.066
Blood urea nitrogen		<0.001	1.021 (0.92-1.12)	0.681
Aspartate aminotransferase		<0.001	1.012 (0.98-1.03)	0.291
Total bilirubin		<0.001	2.903 (0.60-13.84)	0.181
Hemoglobin		0.001	0.789 0.39-1.57)	0.502
White blood cell count		<0.001	1.025 (0.90-1.15)	0.684
Platelet count		<0.001	1.061 (0.97-1.15)	0.183
Mean platelet volume		0.038	4.007 (0.25-62.90)	0.323
Platelet distribution width		0.949	0.557 (0.22-1.37)	0.204
Platelet mass index		0.002	0.991 (0.97-1.003)	0.139

OR: odds ratio; CI: confidence interval

Table 3. Accuracy of the platelet count, mean platelet volume, platelet distribution width, and platelet mass index in predicting severity in patients with malaria

	AUC	Cut-off	Sensitivity	Specificity	+LR	-LR	+PV	-PV	Accuracy	95% CI	p-value
Platelet count	0.699	≤199	76	67.5	2.34	0.36	60.3	81.3	43.53	61.1-77.7	≤0.001
Mean platelet volume	0.619	≤7.4	48.7	78.1	2.22	0.66	54.3	74	26.80	52.2-70.9	0.046
Platelet distribution width	0.504	≤22.2	94.9	15.9	1.13	0.32	38.9	84.6	10.81	40.6-60.1	0.949
Platelet mass index	0.675	≤1228.3	66.7	86.3	4.87	0.39	72.2	82.9	52.97	58-76	0.004

patients with malaria

AUC: area under the curve; PV: positive predictive value; CI: confidence interval; LR: likelihood ratio

As a result of the ROC analysis, the AUC values for platelet count, mean platelet volume, platelet distribution width, and platelet mass index were determined as 0.699, 0.619, 0.504, and 0.675, respectively (p: <0.001, 0.046, 0.949, and 0.004, respectively) (Table 3, Figure 2).

As a secondary outcome we evaluated mortality data. All non-survivor patients were from the severe malaria group. Significant differences were observed between the survivor and non-survivor groups in relation to creatinine [1.15 (0.85-2.80) versus 0.44 (0.35-1.05), p = 0.007], hemoglobin [9.9 (6.1-12.1) versus 13.2 (11.7-13.2), p = 0.013], and hematocrit [27.6 (20.2-34.6) versus 40.7 (34.4-40.7) %, p = 0.009] (Mann Whitney U test). There were no significant differences between the survivor and non-survivor groups in laboratory parameters: aspartate aminotransferase [48 (27.06-70.5) versus 57 (57-77), p = 0.114], alanine aminotransferase [43 (18-69) versus 35 (20.69-58), p = 0.999], total bilirubin [2.69 (1.53-7.53) versus 5.73 (0.42-25.42), p = 0.936], direct bilirubin [1.96 (0.66-4) versus 0.09 (0.05-17.57), p = 0.540], blood urea nitrogen [29 (13-44) versus 18 (14-26), p = 0.219], white blood cell count [9 (6.9-14.21) versus 7.85 (5.2-7.87), p = 0.094], platelet count [133 (46-278) versus 87 (54-166), p = 0.153], mean platelet volume [8 (7-9) versus 6.2 (6.2-9.1), p = 0.197], platelet distribution width [16 (14.2-17) versus 14.6 (12.6-15.8), p = 0.066], and platelet mass index [1046.5 (414.2-2220) versus 1029.2 (928.2-1039.2), p = 0.068] (Mann Whitney U test).

Discussion

In this retrospective study, we evaluated the ability of platelet count, mean platelet volume, platelet distribution width, and platelet mass index to predict the severity of malaria. According to the results of our sample, the ability of these platelet indices to predict severe malaria was not clinically significant. To the best of our knowledge, this is the first study in the literature to evaluate the relationship between the platelet mass index and severe malaria.

Although the primary function of platelets is hemostasis, they also play a role in immunity. The effect of platelets in malaria is through immunity. The immune role of platelets, like immune cells, is to express different receptors that

bind antibodies and cytokines, and Toll-like receptors that bind microbial products. The binding of PF erythrocyte membrane protein produced by plasmodium and CD36 expressed from platelets is an important step in the immune response to the parasite[10,11].

In the literature, there are studies on the relationship between malaria and platelet. In a study examining the effect of hematological parameters, Awoke and Arota reported that thrombocytopenia was associated with severe disease. The authors compared malaria-positive and malaria-negative cases and evaluated only correlation in the statistical analysis[12]. In a review by Lacerda et al., complicated malaria cases with thrombocytopenia were evaluated, and it was suggested that thrombocytopenia might be associated with complicated cases[13]. In the current study, the platelet count was significantly lower in patients with severe malaria according to the results of the univariant analysis. However, the multivariate analysis did not validate this finding. Although the platelet count seems to be lower in severe cases, this is not sufficient to claim that it is an independent predictor of clinically severe malaria.

The mean platelet volume is one of the well-known platelet parameters that has been associated with malignancy, infection, and inflammation in many studies[14-16]. Ali et al. reported that the mean platelet volume was the platelet index that best predicted malaria (AUC: 0.726 and odds ratio: 2.21)[15]. Although these results are statistically significant, we consider that they are not clinically significant[17]. Sakzabre et al., in their study in Ghana, found that patients with high parasite density had a lower mean platelet volume[16]. In the current study, a low mean platelet volume was associated with severe malaria. However, we were not able to validate this result by the multivariate analysis, as was the case with the platelet count. The common result of all these studies indicate that the mean platelet volume is not a platelet index that can be used in clinical decision-making.

The platelet mass index is the total platelet volume per unit volume. It is calculated by multiplying the platelet count and the mean platelet volume. This index is a new predictor that has been investigated in rheumatological diseases and neonatal sepsis[18,19]. It has been reported to be unrelated to mortality in patients with COVID-19[6]. In the current study, the severity of the platelet mass index disease was found to be unrelated. A logical explanation for this may be that both parameters constituting the platelet mass index were insufficient to predict the severity of the disease in our sample. To the best of our knowledge, the current study is the first to evaluate the role of the platelet mas index in predicting the severity of malaria.

Limitations

The main limitation of our study was its retrospective nature; thus, there may have been other risk factors that could not be measured. Retrospective studies cannot determine causation; they only evaluate association. Secondly, our study was conducted in a hospital with relatively high treatment costs in sub-Saharan Africa. The patient population admitted to the hospital may have been affected by socioeconomic reasons. This may have resulted in a bias in the selection of the study population. Lastly, our study had a single-center design, and therefore our results cannot be generalized to other healthcare institutions.

In conclusion, our results indicated that of the platelet indices, platelet count, mean platelet volume, platelet distribution width, and platelet mass index were not clinically significant markers that could be used to predict the severity of malaria. We recommend that multicenter studies be carried out to verify the data obtained from our study and increase their generalizability.

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