

USE OF HEMATOLOGY INDICATORS TO DIFFERENTIATE BETWEEN MALARIA AND DENGUE FEVER

Original Research

Safia Sartaj^{1*}, Saima Zahir¹, Qurrat-ul-Ain², Syeda Bint e Zahra³, Rimsha Bashir¹

¹Department of Hematology, CMH, Multan, Pakistan.

²Department of Chemical Pathology, CMH, Multan, Pakistan.

³Department of Hematology, Ibne Siena Hospital, Multan, Pakistan.

Corresponding Author: Safia Sartaj, Department of Hematology, CMH, Multan-Pakistan, safiasartaj88@gmail.com

Acknowledgement: The authors acknowledge the laboratory staff at CMH Multan for their technical support.

Conflict of Interest: None

Grant Support & Financial Support: None

ABSTRACT

Background: Malaria and dengue fever are the two most widespread arthropod-borne infections, especially in tropical and subtropical regions where their endemic zones often overlap. Their clinical resemblance in early stages complicates timely diagnosis, leading to inappropriate treatment decisions and contributing to antimalarial resistance. Identifying distinguishing hematological markers can support early diagnosis and guide targeted therapeutic strategies in resource-limited settings.

Objective: To aid in the early differentiation of malaria and dengue using hematological parameters, thereby minimizing unnecessary diagnostic testing and inappropriate administration of antimalarials.

Methods: This cross-sectional study was conducted at the Department of Pathology, Combined Military Hospital, Multan, from February 2022 to March 2024. A total of 250 patients were enrolled, including 150 malaria and 100 dengue cases. Malaria diagnosis was confirmed through microscopy of thick and thin Leishman-stained peripheral smears or rapid diagnostic tests, while dengue diagnosis was based on NS1 antigen or IgM antibody positivity via ICT method. Complete blood counts were analyzed using Sysmex XN-1000. Statistical analysis was performed using SPSS v26. The independent sample t-test and chi-square test were applied, with $p < 0.05$ considered significant.

Results: Among malaria cases, *Plasmodium vivax* was identified in 84% ($n=126$), *P. falciparum* in 12.7% ($n=19$), and mixed infection in 3.3% ($n=5$). In dengue patients, NS1 antigen was positive in 96% ($n=96$). Malaria patients had significantly higher WBC counts (median: $5.50 \times 10^9/L$, IQR: 4.80–6.70) compared to dengue ($3.60 \times 10^9/L$, IQR: 2.82–4.50, $p = 0.000$). Conversely, dengue patients had higher RBC counts ($4.87 \times 10^{12}/L$, IQR: 4.55–5.31) and hemoglobin levels (14.0 g/dL, IQR: 12.50–14.80) than malaria patients ($p = 0.000$). NL ratio and ANC were significantly higher in malaria, while ALC and lymphocyte percentage were elevated in dengue.

Conclusion: Hematological profiling offers reliable support in the early differentiation of malaria and dengue. Leukopenia, lymphocytosis, hemoconcentration, and elevated RBC favor dengue, while neutrophilia, anemia, and high NL ratio suggest malaria.

Keywords: Anemia, Dengue, Hematologic Tests, Leukopenia, Malaria, Neutrophils, Thrombocytopenia.

INTRODUCTION

Malaria and dengue fever are among the most prevalent arthropod-borne illnesses in tropical regions, particularly in Southeast Asia, where their endemic zones significantly overlap (1). As global health priorities have evolved, the prevention and control of these infectious diseases have become central targets, as exemplified by two major initiatives led by the World Health Organization (WHO): the Global Technical Strategy for Malaria 2016–2030 and the Global Strategy for Dengue Prevention and Control 2012–2021 (2). Despite decades of progress, malaria remains a pressing public health issue. It is an acute febrile illness transmitted through the bite of infected female *Anopheles* mosquitoes, which harbor *Plasmodium* parasites—five species of which are known to infect humans. Among them, *P. falciparum* and *P. vivax* are the most virulent (3). According to the WHO's 2023 report, malaria accounted for an estimated 249 million cases globally in 2022, with Pakistan contributing approximately 2.1 million cases, placing it among the highest-burden countries (4). Similarly, dengue fever represents a significant and rapidly escalating threat in endemic regions. Transmitted primarily by female *Aedes aegypti* mosquitoes and to a lesser extent by *Aedes albopictus*, the disease is caused by the dengue virus (DENV), a member of the flavivirus family (5). The WHO estimates that nearly 2.5 billion people live in areas at risk of dengue transmission, with approximately 50 million infections occurring annually (5,6). Clinically, dengue ranges from a self-limiting febrile illness to severe manifestations such as dengue hemorrhagic fever (DHF), which is characterized by plasma leakage, thrombocytopenia, and bleeding tendencies. Notably, the hallmark signs of DHF—such as hemoconcentration $\geq 20\%$, bleeding, and plasma leakage—typically emerge after the third or fourth day of fever (7,8).

The overlapping geographical distribution of malaria and dengue presents diagnostic and therapeutic challenges, as both diseases share similar early clinical presentations including fever, headache, and malaise. This overlap not only complicates clinical judgment but may also influence the transmission dynamics of each disease due to shared environmental risk factors, such as increased mosquito breeding in tropical climates (9). Furthermore, accurate diagnosis is essential, as both conditions can progress to severe, life-threatening stages if not promptly identified and managed. In laboratory settings, dengue is confirmed through direct detection of viral components like non-structural glycoprotein-1 (NS1) antigen or indirect serological markers such as IgM antibodies, while malaria is typically diagnosed via microscopic examination of thick and thin blood smears—a technique that is both time-intensive and reliant on skilled personnel (10). Given the significant public health burden posed by the co-endemicity of malaria and dengue, especially in resource-limited settings, there is a critical need for early and accurate differentiation between the two to guide appropriate treatment strategies. Misdiagnosis or over-reliance on empirical antimalarial therapy can lead to unnecessary drug exposure and foster resistance. Therefore, the objective of the present study is to support early and accurate laboratory-based differentiation of malaria and dengue fever, aiming to reduce unnecessary testing and inappropriate antimalarial administration, thereby improving patient outcomes and curbing drug resistance.

METHODS

This cross-sectional study was carried out at the Department of Pathology, Combined Military Hospital (CMH), Multan, Pakistan, from February 2022 to March 2024, following ethical approval from the Institutional Ethical Review Board (IERB No. 123/11). The study aimed to evaluate hematological parameters in patients with confirmed dengue or malaria infections to assist in their early differential diagnosis. A total of 250 participants were included, with the sample size calculated using the World Health Organization (WHO) sample size calculator to ensure appropriate statistical power. Inclusion criteria encompassed all patients who tested positive for *Plasmodium* species through thin film microscopy and those with dengue virus infection confirmed via NS1 antigen positivity using the immunochromatographic test (ICT). Exclusion criteria involved individuals receiving iron supplementation and those with known bleeding or coagulation disorders, as these conditions could confound hematological findings. Informed consent was obtained from all participants before sample collection (11).

Venous blood samples were drawn into EDTA tubes from each participant. For dengue diagnosis, NS1 antigen detection was performed using an ICT-based method due to its rapid turnaround time and practicality in the routine diagnostic setting. However, it is acknowledged that while ICT offers quick results, its sensitivity and specificity are lower than enzyme-linked immunosorbent assay (ELISA) or reverse transcription polymerase chain reaction (RT-PCR), particularly in cases of secondary dengue infections. Despite these limitations, ICT was employed as the primary diagnostic tool due to resource constraints and its widespread clinical use in the

local setting, providing a pragmatic approach to patient evaluation. Malaria diagnosis was primarily conducted using direct microscopic examination of Leishman-stained thick and thin peripheral blood smears, which remains the gold standard for detecting parasitemia. Thick smears were evaluated until 200 white blood cells (WBCs) were counted, and thin films were analyzed until 1,000 red blood cells (RBCs) were reviewed. In cases where microscopy was inconclusive—due to low parasitemia or equivocal findings—malaria antigen rapid diagnostic tests (RDTs) were used as an adjunct. This dual approach was implemented to enhance diagnostic accuracy, with microscopy serving as the confirmatory method wherever feasible. Clear preference was given to microscopy, and RDTs were only applied in cases where smear quality was suboptimal or results were delayed.

Complete blood counts (CBCs) were analyzed using the Sysmex XN-1000 hematology analyzer. This automated system provided comprehensive hematological profiles, including red blood cell indices such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), along with hemoglobin levels, hematocrit, platelet count, total leukocyte count, and differential counts of neutrophils, lymphocytes, monocytes, and eosinophils. Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 26. Descriptive statistics, including mean and standard deviation, were calculated for continuous variables. The independent sample t-test was used to compare the mean age between the two disease groups. Categorical variables such as gender distribution were presented as frequencies and percentages, and the chi-square test was employed to assess the association between gender and disease type. A p-value of less than 0.05 was considered statistically significant. By clarifying the diagnostic hierarchy and the rationale for using ICT and RDTs within resource-constrained settings, this methodological approach enhances both the transparency and reproducibility of the study while remaining grounded in practical realities.

RESULTS

The study population comprised 250 patients, of whom 60% (n=150) were diagnosed with malaria and 40% (n=100) with dengue fever. Among the malaria cases, *Plasmodium vivax* was the most commonly identified species, accounting for 84% (n=126), followed by *Plasmodium falciparum* in 12.7% (n=19), while mixed infections with both species were observed in 3.3% (n=5). In dengue cases, NS1 antigen positivity was the most frequent diagnostic marker, detected in 96% (n=96), while 3% (n=3) of cases were IgM antibody positive and 1% (n=1) had co-positivity for IgM and IgG, indicating a mix of acute and later-stage infections. The mean age of malaria patients was 30.6 ± 11.1 years, while dengue patients had a mean age of 32.5 ± 13.9 years. There was no statistically significant difference in mean age between the groups ($p = 0.242$). Gender distribution showed a male predominance in both groups but more pronounced in malaria cases, where 88% (n=132) were male compared to 74% (n=74) in the dengue group. Female representation was 12% (n=18) in malaria and 26% (n=26) in dengue cases. The association between gender and disease type was statistically significant ($p = 0.004$), indicating different gender susceptibility patterns.

Hematological comparisons revealed that malaria patients had significantly higher median total leukocyte counts ($5.50 \times 10^9/L$, IQR: 4.80–6.70) than dengue patients ($3.60 \times 10^9/L$, IQR: 2.82–4.50, $p = 0.000$). Conversely, dengue cases had higher median red blood cell counts ($4.87 \times 10^{12}/L$ vs. $4.57 \times 10^{12}/L$, $p = 0.000$) and hemoglobin levels (14.0 g/dL vs. 12.7 g/dL, $p = 0.000$), indicating hemoconcentration. Neutrophil percentage and absolute neutrophil count (ANC) were significantly elevated in malaria (73.0%, ANC: 417.4) compared to dengue (52.0%, ANC: 178.8, both $p = 0.000$), whereas lymphocyte percentage and absolute lymphocyte count (ALC) were markedly higher in dengue (36.0%, ALC: 1275.5) than in malaria (16.0%, ALC: 930.4, both $p = 0.000$). Other significant findings included higher monocyte counts and percentages in malaria, and a higher neutrophil-to-lymphocyte ratio (NLR) (median 4.6 in malaria vs. 1.45 in dengue, $p = 0.000$). The monocyte-lymphocyte ratio (MLR) was also elevated in malaria (0.47 vs. 0.25, $p = 0.000$). Platelet counts were slightly higher in dengue (median $101.5 \times 10^9/L$) compared to malaria ($100.0 \times 10^9/L$), but the difference was not statistically significant ($p = 0.051$). Other hematological parameters such as eosinophil count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW) did not show significant intergroup differences.

Logistic regression analysis showed that leukopenia (WBC < 4000) was significantly associated with dengue, with an odds ratio (OR) of 10.6 ($p = 0.029$). Neutropenia (ANC < 2800) and low NLR (< 2.8) were also predictive of dengue, with ORs of 9.3 ($p = 0.011$) and 22.8 ($p < 0.001$), respectively. Hemoconcentration (hematocrit > 40%) increased the odds of dengue by 15.1 times ($p < 0.001$). In contrast, anemia (Hb < 11.5 g/dL) and lower RBC count (< 4.0 million/ μL) were strongly associated with malaria, with ORs of 15.4 ($p = 0.007$) and 0.1 ($p = 0.048$), respectively. Thrombocytopenia (platelet count < 100,000/ μL) was observed in both conditions but did not reach statistical significance ($p = 0.056$). Parameters such as ALC, MLR, MCV, MCH, and MCHC did not significantly differentiate between the two groups ($p > 0.05$). Analysis of clinical symptomatology and patient outcomes revealed several notable differences

between malaria and dengue cases. The mean duration of fever was slightly longer in dengue patients (6.1 ± 1.5 days) compared to those with malaria (5.2 ± 1.3 days). Bleeding manifestations were significantly more common in dengue, observed in 19% of cases, whereas only 5.3% of malaria patients experienced bleeding symptoms. Hepatosplenomegaly was more frequently reported in malaria cases (22.7%) than in dengue (7.0%), reflecting organ-specific pathophysiological responses. The average hospital stay was comparable between both groups, with malaria patients staying a mean of 4.1 ± 1.0 days and dengue patients 4.4 ± 1.2 days. Recovery outcomes were favorable in both groups, with full recovery achieved in 96% of malaria and 98% of dengue patients. However, complications were slightly more common in malaria cases (4.0%) than in dengue (2.0%). These findings complement the hematological data by emphasizing the differing clinical presentations and outcomes, further supporting the importance of integrated diagnostic approaches for early and accurate differentiation between the two infections.

Table 1: Distribution of Malaria and Dengue Cases with Subclassification Based on Pathogen Type and Diagnostic Markers

Disease	Frequency	Percentage
Malaria	150	60%
Dengue	100	40%
Malaria Parasite Species		
Plasmodium falciparum	19	19
Plasmodium vivax	126	126
Both P. vivax and P. falciparum	5	5
Dengue Diagnostic Markers		
NS1 antigen	96	96.0
IgM antibodies	3	3.0
IgM and IgG co-positivity	1	1.0

Table 2: Comparison of Age Distribution Between Malaria and Dengue Cases

Disease Groups	Mean	SD	Minimum	Maximum	p-value
Malaria	30.6	11.1	3.0	66.0	0.242
Dengue	32.5	13.9	14	65	

Table 3: Association Between Gender and Disease Type

Disease Groups		Gender		p-value
		Males	Females	
Malaria	n	132	18	0.004*
	%	88.0%	12.0%	
Dengue	n	74	26	
	%	74%	26%	

Table 4: Comparison of Hematological Parameters Between Malaria and Dengue Patients

Blood Parameters	Disease Groups	Median (Q1 – Q3)	Minimum	Maximum	p- value
WBC (×10 ¹² /L)	Malaria	5.50 (4.80 – 6.70)	1.9	12.7	0.000*
	Dengue	3.60 (2.82 – 4.50)	1.9	7.6	
RBC (×10 ¹² /L)	Malaria	4.57 (4.16 – 5.04)	2.7	6.5	0.000*
	Dengue	4.87 (4.55 – 5.31)	2.9	6.8	
Neutrophils (%)	Malaria	73.0 (66.8 – 80.0)	39.2	92.0	0.000*
	Dengue	52.0 (44.3 – 58.0)	20.0	83.0	
ANC	Malaria	417.4 (336.0 – 507.4)	100.0	914.4	0.000*
	Dengue	178.8 (122.4 – 253.2)	71.3	539.6	
Lymphocytes (%)	Malaria	16.0 (12.0 – 22.0)	6.0	48.0	0.000*
	Dengue	36.0 (31.0 – 42.8)	9.0	69.0	
ALC	Malaria	930.4 (614.3-1306.5)	114.0	3164.0	0.000*
	Dengue	1275.5 (1003.8 –1576.8)	392.0	4560.0	
AMC	Malaria	47.8 (29.3 – 62.01)	3.8	111.6	0.000*
	Dengue	30.5 (20.6 – 49.1)	8.0	151.8	
Monocytes (%)	Malaria	8.0 (5.0 – 10.0)	2.0	18.0	0.000*
	Dengue	10.0 (6.0 – 12.0)	2.0	69.0	
Eosinophils (%)	Malaria	2.0 (1.0 – 2.0)	0.0	8.0	0.307
	Dengue	2.0 (1.0 – 3.0)	0.0	7.0	
NL Ratio	Malaria	4.6 (3.2 – 6.7)	0.8	15.3	0.000*
	Dengue	1.45 (1.07 – 1.84)	0.3	7.8	
ML Ratio	Malaria	0.47 (0.30 – 0.61)	0.1	1.5	0.000*
	Dengue	0.25 (0.17 – 0.35)	0.1	2.0	
Hemoglobin (g/dL)	Malaria	12.7 (11.58 – 13.6)	5.8	17.9	0.000*
	Dengue	14.0 (12.50 – 14.8)	8.2	18.8	

Blood Parameters		Disease Groups	Median (Q1 – Q3)	Minimum	Maximum	p- value
Hematocrit		Malaria	0.38 (0.34 – 0.40)	0.2	0.5	0.000*
		Dengue	0.41 (0.40 – 0.44)	0.2	0.6	
Mean Corpuscular Volume (fL)		Malaria	82.0 (77.8 – 84.4)	57.6	102.6	0.006*
		Dengue	82.9 (80.6 – 86.1)	65.3	97.0	
Mean Corpuscular Hemoglobin (pg)		Malaria	27.6 (25.8 – 29.5)	16.8	35.0	0.772
		Dengue	27.7 (26.4 – 29.1)	20.3	39.1	
Mean Corpuscular Hemoglobin Concentration (g/dL)		Malaria	33.6 (32.7 – 34.8)	27.5	37.7	0.670
		Dengue	33.9 (33.1 – 34.7)	30.1	36.8	
Red Cell Distribution Width		Malaria	40.8 (39.5 – 43.2)	36.9	52.1	0.765
		Dengue	40.8 (39.6 – 42.8)	36.4	52.1	
Platelets (×1012/L)		Malaria	100.0 (80.0 – 130.0)	23.0	224.0	0.051*
		Dengue	101.5 (90.3 – 147.5)	15.0	300.0	

Table 5: Hematological Markers for Differentiating Dengue and Malaria
95% Confidence Interval

Parameter	OR	Lower	Upper	p-value
WBC<4000	10.6	1.3	87.7	0.029
RBC<4.0 Mn	0.1	0.0	1.0	0.048
NC<2800	9.3	1.7	51.3	0.011
ALC<800	0.6	0.1	3.9	0.625
NLR<2.8	22.8	4.8	106.8	0.000
MLR<0.25	2.7	0.8	9.5	0.112
Hb<11.5 g/dl	15.4	2.1	111.9	0.007
HCT>40	15.1	3.6	64.3	0.000
MCV>80	2.2	0.4	12.8	0.369
MCH>25	0.4	0.0	3.6	0.385
MCHC>33	4.0	0.7	23.0	0.118
PLt<100000/ul	0.3	0.1	1.0	0.056

Table 6: Clinical Symptomatology and Patient Outcomes

Clinical Feature / Outcome	Malaria	Dengue
Duration of Fever (days)	5.2 ± 1.3	6.1 ± 1.5
Presence of Bleeding (n, %)	8 (5.3%)	19 (19.0%)
Hepatosplenomegaly (n, %)	34 (22.7%)	7 (7.0%)
Hospital Stay (days)	4.1 ± 1.0	4.4 ± 1.2
Full Recovery (n, %)	144 (96.0%)	98 (98.0%)
Complications (n, %)	6 (4.0%)	2 (2.0%)

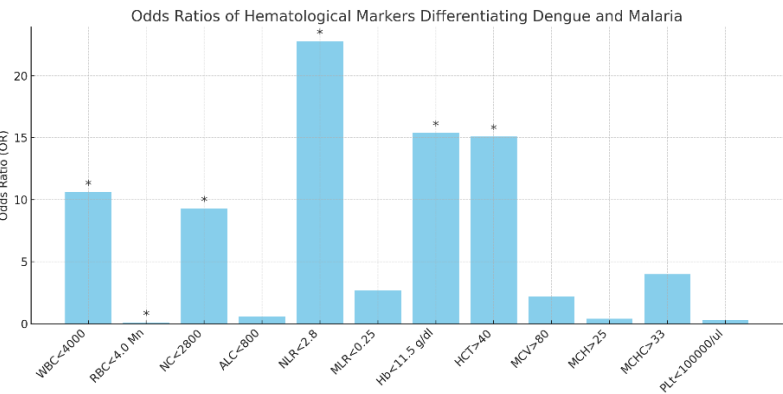


Figure 1 Odds Ratios of Hematological Markers Differentiating and Malaria

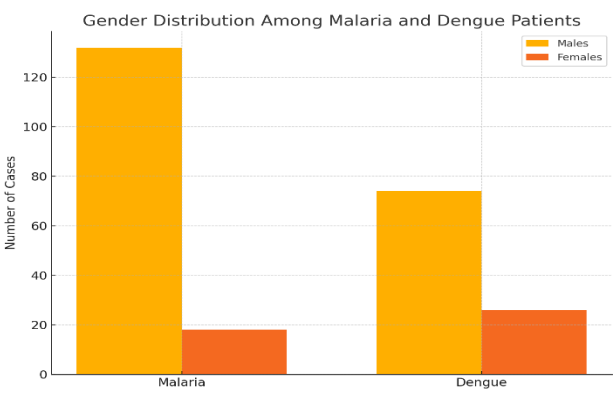


Figure 2 Gender Distribution Among Malaria and Dengue Patients

DISCUSSION

The findings of the present study offer valuable insights into the hematological and demographic characteristics distinguishing malaria from dengue fever in an endemic setting. The mean age of patients did not differ significantly between the two groups ($p = 0.242$), with dengue patients averaging 32.5 years and malaria patients 30.6 years. This contradicted earlier reports where dengue fever was more common in younger individuals, including children under 15 years of age (12,13). The observed age distribution in the current study may reflect evolving transmission dynamics or healthcare-seeking behavior, and may also be influenced by the increased exposure of older adults in occupational settings. The diminished malaria incidence with age reported in other endemic regions may relate to acquired immunity and age-associated changes in immune response to *Plasmodium* species (14). Conversely, although dengue was more prevalent in older adults in the present cohort, previous studies noted that children face a higher risk of developing severe dengue due to their relatively immature immune responses (15,16). A marked male predominance was observed in both malaria and dengue cases, more pronounced in malaria (88%) than dengue (74%). This trend was consistent with previous observations and may be attributed to gender-specific differences in mosquito exposure, with males often engaged in outdoor activities or occupations that increase their contact with mosquito vectors (17). The gender-based distribution observed adds a sociobehavioral dimension to disease prevalence, emphasizing the role of occupational and environmental exposure patterns.

Regarding hematological parameters, dengue patients had significantly higher RBC counts and hemoglobin levels compared to those with malaria. This observation aligns with the understanding that dengue, particularly in its early stages, may present with hemoconcentration due to plasma leakage—a hallmark of dengue hemorrhagic fever (18). In contrast, anemia was more common in malaria patients, which is expected due to the parasitic destruction of RBCs and suppression of erythropoiesis. The destruction of parasitized as well as non-parasitized erythrocytes contributes to the observed reduction in RBC indices in malaria. Anemia, particularly in *P. falciparum* infections, reflects both the high parasite burden and immune-mediated clearance mechanisms (15,19). These patterns support the utility of hematological indices as differential diagnostic tools. The raised hematocrit observed in dengue cases further supports the diagnostic criterion of hemoconcentration, which is indicative of plasma leakage and vascular permeability changes during infection. The hematocrit levels in malaria patients, though lower, are consistent with the anemia associated with parasitemia (8,14). Although thrombocytopenia was prevalent in both groups, its diagnostic value was limited by the lack of statistical significance ($p =$

0.056). While platelet counts below 100,000/ μ L were more frequent in malaria (66%) compared to dengue (74%), this finding reinforces previous literature suggesting that thrombocytopenia is a common but nonspecific finding in both diseases (19,20). This study presents several strengths, including a well-defined patient population, comprehensive hematological profiling, and comparative analysis across multiple clinical parameters. It effectively highlights hematological markers that can aid in the early differentiation between malaria and dengue, potentially guiding timely and targeted treatment interventions. However, the study also faced notable limitations. Being a single-center study with a modest sample size, the generalizability of the findings is restricted. The cross-sectional design did not allow for the assessment of disease progression over time, limiting the understanding of how hematological markers evolve throughout the clinical course. Furthermore, financial and logistical constraints limited the inclusion of more advanced diagnostic modalities such as ELISA or PCR, which could have added diagnostic precision. The absence of detailed temporal data linking symptom onset to laboratory changes also represents a missed opportunity to explore dynamic changes in hematological profiles. Future research should incorporate multicenter participation with larger cohorts to validate the diagnostic utility of the identified hematological markers. Longitudinal designs examining temporal trends in laboratory parameters and clinical progression would offer deeper insights into the pathophysiology and prognostic value of hematological indices. Expanding the scope to include pediatric populations, varying geographic settings, and co-infection scenarios would also enhance the applicability of the findings. Integrating clinical, hematological, and molecular diagnostic tools in future studies will pave the way for more accurate and timely differentiation between these clinically overlapping vector-borne illnesses.

CONCLUSION

In conclusion, this study demonstrated that hematological profiling serves as a valuable diagnostic tool in distinguishing between malaria and dengue, particularly in regions where both diseases are co-endemic and present with overlapping clinical features. Key hematological indicators such as leukopenia, lymphocytosis, elevated red blood cell indices, and hemoconcentration were more indicative of dengue, while neutrophilia, anemia, and a raised neutrophil-to-lymphocyte ratio favored malaria. These findings emphasize the practical utility of simple, accessible blood parameters in guiding early and accurate diagnosis, thereby minimizing diagnostic uncertainty, reducing the unwarranted use of antimalarial drugs, and ultimately contributing to better patient outcomes and antimicrobial stewardship.

Author Contribution

Author	Contribution
Safia Sartaj*	Substantial Contribution to study design, analysis, acquisition of Data
	Manuscript Writing
	Has given Final Approval of the version to be published
Saima Zahir	Substantial Contribution to study design, acquisition and interpretation of Data
	Critical Review and Manuscript Writing
	Has given Final Approval of the version to be published
Qurrat-ul-Ain	Substantial Contribution to acquisition and interpretation of Data
	Has given Final Approval of the version to be published
Syeda Bint e Zahra	Contributed to Data Collection and Analysis
	Has given Final Approval of the version to be published
Rimsha Bashir	Contributed to Data Collection and Analysis
	Has given Final Approval of the version to be published

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