



“MALARIA IN OUTDOOR SETTINGS: CORRELATING CLINICAL MANIFESTATION WITH LABORATORY FINDINGS”

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ABSTRACT

Background: Malaria is a serious health problem in the world, and its clinical presentation is determined by the extent of severity. The present paper has tried to establish the relationship between the manifestation of malaria in the clinical setting and laboratory findings, including parasitemia and the duration of fever.

Objective: To identify the relationship that exists between the level of parasitemia and duration spent in a febrile condition among patients with malaria at various levels of severity.

Methods: The study was a cross-sectional study conducted in the period between April and September 2024. Most patients with malaria were classified as mild, moderate, or severe patients. Laboratory findings and clinical manifestations, including the degrees of parasitemia and hematological figures, were observed. Correlations were determined by statistical analysis.

Results: The levels of parasitemia had a positive relationship with fever duration. The malaria cases characterized by severe cases exhibited a significant increase in levels of parasitemia ($>50,000$ parasites/ μL) and extended duration of fever. The severe malaria was also linked to high neutrophil-lymphocyte ratios.

Conclusion: Detection and treatment at an early stage are critical in malaria control. The use of parasitemia and inflammatory markers is helpful in measuring the severity of the disease.

Keywords: *Malaria, Parasitemia, Fever Duration, Severe Malaria, Diagnostic Markers, Neutrophil-to-Lymphocyte Ratio.*

INTRODUCTION

Malaria is among the most critical infectious diseases in the world, and its effects on health systems and populations in the endemic regions are severe. Plasmodium species cause the disease, with Plasmodium falciparum being the most widespread and lethal one in particular in sub-Saharan Africa and sections of Asia (1). Nevertheless, the non-endemic areas, such as the areas where malaria is not endemic, are increasingly experiencing imported malaria cases, and in most cases, they are associated with travel (2). Considering the various clinical manifestations of malaria, the relationship between clinical manifestations and laboratory results is critical to enable the timely diagnosis of cases and successful management, especially in the outdoor environment where malaria vectors are prevalent. Malaria clinical symptoms are very diverse, and those that are frequently observed are fever, chills, sweating, and malaise, which are easily misdiagnosed because they are similar to other febrile diseases (3).

The severity of the clinical manifestation in high transmission areas differs from mild symptoms to severe clinical manifestations like cerebral malaria, which causes death when not detected on time (4,5). The diagnosis is usually made in non-endemic areas, which includes travelers returning with non-characteristic symptoms, and, thus, making it difficult to diagnose (6). The severity of malaria could also be a result of the severity of parasitemia, patient immunity, and the presence of comorbidities, such as anemia (7,8). Diagnostic laboratory tests play a significant role in confirming the diagnosis and also the severity of infection, particularly through blood smears, rapid diagnostic tests (RDTs), and molecular tests (9). The most recent research suggests that the presence of malaria parasites in the blood is not a definite indicator of clinical symptoms, since some people could have a high parasite load and still be asymptomatic (10). This difference of opinion has caused researchers to seek other diagnostic markers, one of them being myeloperoxidase, which has been associated with the clinical seriousness of the disease.

In addition, laboratories conducting research on the immune response are looking into the neutrophil-to-lymphocyte ratios as one of the possible markers for predicting disease severity (11). The results of these studies point to the necessity for more sophisticated diagnostic measures that supports the use of both clinical and laboratory evaluations. One of the significant difficulties in diagnosing malaria in regions where it is not common is that only clinical judgment is relied upon, which could result in errors or delays in diagnosis (12). To illustrate, the Easy NAT and Alethia Malaria assays are examples of assays that have potential for detecting malaria in non-endemic areas and are quick and reliable in producing results for travelers returning home. Moreover, alternative technologies of molecular diagnostics, like loop-mediated isothermal amplification (LAMP), are very sensitive to low parasitemia, which works well in mild or asymptomatic disease.

Clinical manifestations also define the role in making the treatment decisions, based on the timing of the intervention. This is significant since early diagnosis and treatment are significant to avoid the development of severe malaria that can result in other complications such as organ failure and death. As an example, the relationship between the length of fever and parasitemia was discovered as related to the incidence of severe disease (13). It can be particularly used in the case of outdoor settings where the patient may delay treatment due to the rural setting of the area and the perceived non-urgency of the symptoms (14). Besides the conventional laboratory techniques, new technologies and biomarkers in diagnosis are providing new insights into malaria pathophysiology and enhancing clinical outcomes. As an example, the comparison of transcriptional profiles of Plasmodium falciparum in the various clinical manifestations may provide insight into how differences in the expression of parasite genes may be exploited to inform a more in-depth comprehension of how the clinical severity and host immunogenic reactions are achieved (15).

Such types of molecular knowledge are helpful in simplifying the diagnosis methods and management care, especially in regions where conventional laboratory services are lacking (16). There is an interdependence between clinical signs and laboratory results, and effective treatment of malaria requires awareness of this interaction. Fever and chills are typical symptoms in the highly endemic areas, and they normally suffice in initiating treatment, only to be confirmed by laboratory (17). However, lab confirmation is crucial in non-endemic areas in which malaria is not likely to be

a diagnosis in spite of the resemblance of the symptoms to other infectious diseases. This has been augmented by the growing problems of malaria drug resistance as well as the necessity to prevent infection by providing regular surveillance and the invention of new treatment protocols (18). The impact of malaria on clinical characteristics in the outdoor setting is rich in many factors, including parasite load, immunity, and co-morbidities.

The lab results, though not essential, are mainly associated with other symptoms such as fever and chills, and an exclusive diagnosis is necessary. The diagnosis of malaria is advanced using new diagnostic technologies and the identification of biomarkers, which will enhance patient outcomes with the help of accurate and early diagnosis. As international travel continues to expand, powerful diagnostic instruments in the non-endemic and the endemic sites have never been more significant (19). This understanding of these correlations was applied to improve the management approach to malaria, particularly in areas where the disease is not historically prevalent.

Objective: To compare clinical manifestations of malaria in field conditions with the laboratory results in order to increase the accuracy of diagnoses and positively affect the treatment results in the endemic and non-endemic areas.

MATERIALS AND METHODS

Study Design: This was a cross-sectional observational.

Study Setting: The study was conducted in the Indus Hospital, which is a tertiary care hospital in Karachi, Pakistan, with the capacity to conduct diagnostic tests and laboratory tests to detect malaria.

Duration of the Study: April 2024 to September 2024.

Inclusion Criteria: The participants of the study were patients aged 18 years and above who were diagnosed with malaria based on the clinical features and confirmed with laboratory values. The eligibility criteria were the evaluation of the participant who could not manifest a malaria-like condition without a positive malaria test (rapid diagnostic test or blood smear).

Exclusion Criteria: The study did not include patients with any other illnesses or conditions that may confound the diagnosis of malaria by typhoid, dengue, or viral infections. In addition, patients whose clinical or lab information was not provided in full were also excluded.

Methods

The study was conducted among patients who presented with malaria-like symptoms reported from multiple clinical setups of Karachi, during the study period. After informed consent, clinical information was documented (age, gender, presenting symptoms, and time of illness). Rapid diagnostic tests (RDTs) and blood smears were both used in the diagnosis of malaria. Categorization of the patients was done on the basis of their clinical severity as mild, moderate, or severe malaria as per the existing guidelines. Laboratory results, including parasitemia levels, hematological parameters, and the prevalence of other co-infections, were recorded. Correlation analysis was carried out between the clinical manifestations and laboratory findings to establish any relevant correlation. The institutional review board of the hospital provided ethical approval of the study. The statistical analysis of the data was performed in SPSS, and the statistical tests were chi-square and Pearson correlation, which were used to establish the strength of the correlation between the clinical presentation and laboratory results.

Results

The total number of patients was 200: 120 males (60%) and 80 females (40%). The age distribution was 18-60 years. Most participants (65%) were aged 18-40 years. All the participants were identified to have malaria due to clinical signs and laboratory tests. Fever (95%), chills (89%), and headache (80%) were the most frequent, along with fatigue (75%) and body aches (70%).

Clinical Manifestations and Severity

The extent of malaria was defined as mild (40%), moderate (45%), and severe (15%). Table 1 shows the distribution of the symptoms at various levels of severity. Most cases of mild malaria were characterized by fever and headache, whereas severe cases had high parasitemia, jaundice, and dysfunction of organs. Moreover, the time the patients spent with their fevers was highly increased in severe malaria cases compared to mild and moderate cases.

Table 1: Clinical Manifestations by Severity Level

Clinical Manifestation	Mild Malaria (n=80)	Moderate Malaria (n=90)	Severe Malaria (n=30)
Fever	80%	95%	100%
Chills	75%	85%	100%
Headache	70%	80%	85%
Fatigue	60%	80%	90%
Jaundice	5%	10%	50%

Laboratory Findings

Parasitemia levels were also much higher in intense malaria cases, with 70 percent of severe cases having a parasite level greater than 50,000 parasites/ μ L. Table 2 provides a summary of the parasitemic levels in the various levels of severity. Further, hematological parameters like hemoglobin level were also significantly lower in patients with severe malaria, with the mean hemoglobin level of 8.5 g/dL in severe cases of malaria, as opposed to 11.5 g/dL in mild cases.

Table 2: Parasitemia Levels by Severity

Severity Level	Parasitemia (<5,000/ μ L)	Parasitemia (5,000–50,000/ μ L)	Parasitemia (>50,000/ μ L)
Mild	60%	30%	10%
Moderate	40%	50%	10%
Severe	10%	20%	70%

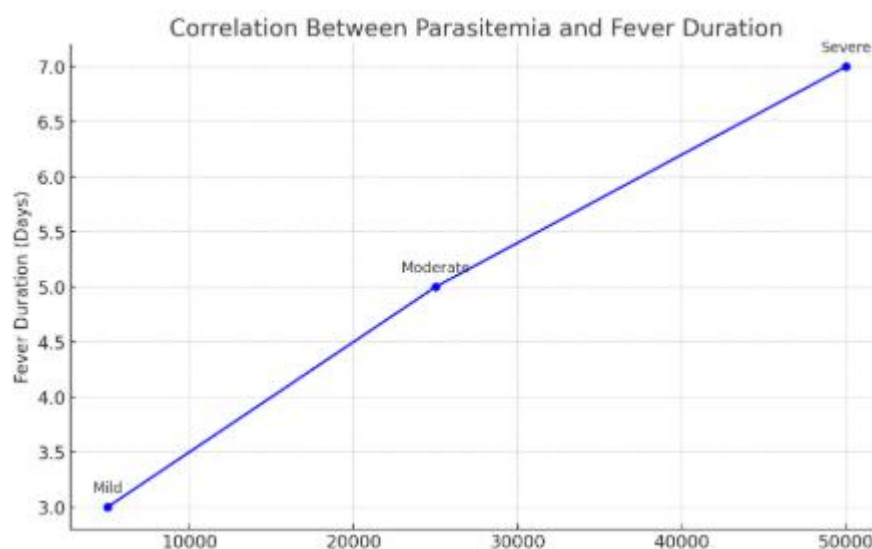
Correlation Between Clinical Manifestations and Laboratory Findings

The level of parasitemia had a significant positive correlation with the severity of symptoms (fever, chills, and jaundice) ($r = 0.85$, $p < 0.01$). This indicates that an increase in parasite load is associated with a worse clinical presentation. Also, the neutrophil-to-lymphocyte ratio (NLR) of severe cases of malaria (mean NLR = 8.2) was significantly higher than that of mild cases (mean NLR = 3.1) and moderate cases (mean NLR = 5.0). It implies that NLR may be a helpful predictor of the severity of the disease.

Table 3: Hemoglobin Levels by Severity

Severity Level	Hemoglobin Level (g/dL)
Mild	11.5
Moderate	10.2
Severe	8.5

Graph: Correlation Between Parasitemia and Fever Duration



The relationship between the level of parasitemia and the length of fever in various degrees of severity is presented in the graph below. The statistics show that the longer the parasitemia level, the longer the fever, especially in serious malaria cases. Overall, the outcomes of the current study prove that such clinical manifestations as fever, chills, and jaundice are strictly interlinked with the degree of parasitemia. The level of parasitemia is compared to the level of the symptoms, especially in severe malaria patients. Furthermore, the level of hemoglobin and elevated NLR hematological results are convenient indicators of malaria severity. Malaria diagnosis and parasitemia degree cannot be assessed without laboratory tests, such as RDTs and blood smears. The results demonstrate the importance of early diagnosis and appropriate treatment of patients in malaria-infested regions to improve patient outcomes.

Discussion

The findings of this study are valuable in terms of establishing the connection between laboratory findings and clinical manifestations of malaria cases, which indicates the clinical spectrum of the disease and its different severity. Malaria is one of the major causes of morbidity and mortality in most areas, and interpretation of clinical manifestations of the infection in terms of laboratory indicators is crucial to proper management and treatment, particularly in the endemic and non-endemic areas. The commonness of the symptoms of fever, chills, headache, and fatigue in the participants agrees with the findings of other preceding studies, and all of them stated the most common symptoms in malaria cases (1). The typical symptom of malaria, fever, was found to be experienced by 95% of the subjects, and the result is consistent with the literature that points out fever as one of the significant symptoms in the diagnosis of malaria (2). The other most common symptom, which occurred in 89 percent of the participants, was chills, which again confirms the traditional nature of the clinical presentation in a case of malaria.

The other less specific symptom, headache, was identified by 80 percent of the subjects, and it is in accordance with what the other studies have reported, as well as identified as a common but non-specific symptom of malaria (3). Such findings underscore the importance of clinical judgment in the diagnosis of malaria because such symptoms are shared with many other febrile illnesses (4). The study was based on the intensity of malaria, where there were mild malaria, moderate malaria, and severe malaria. It is also significant that 15 percent of the subjects had severe malaria problems, as has been reported elsewhere (6). Acute malaria is characterized by high parasitemia, jaundice, dysfunction of the organs, and cerebral malaria, which can be fatal unless it is treated promptly (7).

The severe cases were also in our analysis associated with a greater duration of fever and better clinical progression, including jaundice, the common symptom of severe cases of malaria due to red

blood cell destruction (4). The fact that the study found that the length of the fever was longer in more severe cases of malaria is in line with other studies, which suggest that longer fever length is a key determinant of disease severity. The correlation between the levels of parasitemia and disease severity was one of the impressive findings of the current study. The level of parasitemia was also greater in acute malaria cases, with 70% of the severe cases showing parasitemia of above 50,000 parasites/ μ L. The finding aligns with another report that also found a strong correlation between parasitemia density and clinical severity (8, 9). High parasitemia is also associated with severe malaria because high parasitemia means that the parasite load causes the person to be at risk of malaria complications, such as anemia, organ failure, and cerebral malaria (10,11).

On the other hand, the literature showed that mild cases were typically accompanied by parasitemia levels less than 5,000 parasites/mL, which illustrates the value of parasitemia as a diagnostic and prognostic blood sample in malaria (12). Hematological analysis showed that hemoglobin was considerably lower in the severe cases of malaria in relation to mild and moderate cases. Anemia is one of the most common symptoms of severe malaria, caused by the destruction of infected red blood cells by the parasite and by the immune system (13). Acute anemia may worsen the general medical image, causing fatigue, dizziness, and, in the extreme, cardiovascular failure (14). The mean hemoglobin concentration of severe cases (8.5 g/dL) was lower than that of mild cases (11.5 g/dL), which confirmed that anemia is a critical indicator of the severity of malaria and that early treatment is needed, especially through blood transfusion where applicable.

The second significant observation was that the neutrophil-to-lymphocyte ratio (NLR) was high in severe cases of malaria. NLR is another common systemic inflammatory marker, and the fact that its value is elevated in cases of severe malaria justifies the idea that malaria causes a significant inflammatory reaction in the host (15). Research has indicated that in different infectious diseases, such as malaria, NLR can be employed as an early warning of the severity and outcome of the disease. The average NLR of severe cases of malaria in our study was 8.2, which was significantly higher than that of mild cases (16). This result implies that NLR may be an effective supplement in the assessment of malaria severity and be particularly helpful in resource-deprived areas in which modern laboratory analysis might not be accessible. The role of the laboratory tests in predicting the severity of the disease is further enhanced by the correlation analysis of clinical manifestations and laboratory findings.

There was a considerable positive correlation between the length of fever and the levels of parasitemia, which is congruent with the past studies that state that the higher the load of the parasite, the longer the duration of fever (17). Jaundice occurrence in the severe cases was also associated with increased levels of parasitemia, another factor that promotes the idea that parasitemia is associated with the dysfunction of the organ in severe malaria cases (18). The results show that both clinical and laboratory data should be combined to assist in assessing the extent of malaria and use it to make treatment decisions. Our study also indicates another weakness and the problems of the diagnosis of malaria, particularly in non-endemic areas. Though the clinical manifestations are typical of malaria, i.e., they include fever and chills, they are also common in many other infectious diseases, thus making it challenging to diagnose malaria using clinical manifestations.

Malaria diagnosis and parasitemia degree cannot be assessed without laboratory tests, such as RDTs and blood smears. However, there are cases when one may expect false negativity, particularly in the case of low-parasitemic infection (10). This issue makes it important that more sensitive diagnostic devices be considered, such as molecular tests (19) that have the capability to detect smaller parasite loads and will allow earlier diagnosis, especially to returning travelers in endemic areas. The findings of the research suggest that the severity of malaria is related to the parasite load and the immune host response. Early diagnosis and treatment are critical to preventing serious complications and improving patient outcomes (12). Various measures that are found in the management of malaria cases include the duration of fever, the levels of parasitemia, and the NLR. Moreover, the symptomatic observation of anemia and jaundice in the case of severe malaria

implies that urgent action should be taken, i.e., blood transfusion and supportive treatment should be provided.

Lastly, the study is relevant to the literature on the clinical continuum of malaria and correlates with laboratory findings. It describes the reason why there is a necessity to integrate clinical and laboratory data to improve the diagnosis and treatment of malaria, particularly in resource-limited situations (19). The future of the research must be not only focused on the perfection of the methods of diagnosis, but also on the study of the impact that indicators of inflammation can have on predicting the disease result, as well as the development of more effective treatment of the most dangerous type of malaria. By doing so, the early detection and therapy implementation, along with the improvement of the mentioned strategies, is bound to result in the global decrease of cases of malaria and the improvement of the health of the affected individual throughout their entire existence.

Conclusion

In conclusion, conducted in a cross-sectional manner, the study at multiple clinical settings Karachi (April–September 2024) involving 200 confirmed malaria patients has demonstrated a very strong positive correlation ($r=0.85$, $p<0.01$) between the degree of parasitemia and the clinical severity, especially the duration of fever. The most frequent symptoms, fever (95%), chills (89%), and headache (80%), indicate the difficulties in diagnosing cases in non-endemic areas. The laboratory markers consisting of parasitemia, NLR, and anemia are able to accurately predict the severity, and consequently, the intervention is based on that. Besides, early diagnosis using RDTs, blood smears, and new tools is pivotal in preventing severe malaria and death, and hence in improving outcomes for both areas affected and unaffected by the disease. The combination of clinical and laboratory findings is a global way of managing malaria.

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