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Clinical and Hematological Criteria For Malaria Diagnosis In Endemic Area with Limited Resources

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ABSTRACT

Objective: To devise a clinical and hematological criteria for malaria diagnosis in endemic area with limited resources
Study Design: Prospective longitudinal study
Place and Duration of Study: Combined military hospital Chhor, Sindh Pakistan from Feb 2021-Jan 2022.
Methodology: 164 patients were enrolled using inclusion and exclusion criteria. Based on past experiences and unpublished data, specific clinical parameters of malaria were identified and given a score. Maximum score was 12. Clinical Score was calculated and verified for each patient by two clinicians. Later all the patients were subjected to Immuno-chromatographic tests by trained person to diagnose malaria. Clinical Score was then compared with subsequent ICT diagnosis of malaria. Cut-off was marked at score 7 as 151(92.7%) of patients presenting at and above this cut-off were confirmed cases of malaria.
Results: 164 fever cases were included in the study. Out of 164 cases, 143 males (87.02%) and rest 21 females (12.08%). Mean clinical score was 9 ± 2. Mean age of patients were 28 ± 6 years. 151(92.7%) cases presented at score ≥ 7.
Conclusion: Score ≥ seven be used in clinics of endemic area to assign cases suffering from malaria with confidence and can be treated empirically. This criteria can substitute ICT however cannot replace it. This criteria is very helpful where labs are not freely available or cannot be relied upon due to problems, specifically in peripheral health centre with limited resources.

Keywords: Clinical score, criteria, endemic, Malaria

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INTRODUCTION

Malaria is a significant health problem across the globe. Although ≤1% of malarial infections are life-threatening, this leads to significant amount of deaths annually.[1] As of 2018, malaria caused two-twenty eight million cases of which 4 million were fatal.[2] Malaria is known to be caused by five species of Plasmodia i.e P. falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi, but mixed infections do occur.[3] Pakistan being a part of WHO eastern Mediterranean zone showed reduced case incidence by forty percent or more in 2020 as compared to 2015 but still it's a viable threat.[4,5] with a cumulative API (annual parasite index) of 1.8 across Pakistan6.Smear microscopy is considered the gold standard method for malaria diagnosis but rapid diagnostic tests(RDTs) offer a convenient alternative for diagnosis in endemic areas.[4] However its pertinent to mention that all diagnostic methods have a ceiling beyond which it will not be possible to denote infected individuals.[5] The RDTs have grown significantly over the past fifteen years to diagnose malaria.[6] However, study of pattern of symptoms and signs identified a group of signs and symptoms which were strong predictors of malaria as opposed to other febrile illnesses.[7] Such differentiation of clinical diagnoses from other similar febrile illnesses based on patient's signs and symptoms may be challenging.[8] Another study showed that use of such clinical algorithm with emphasis on signs and symptoms only, resulted in thirty percent over-diagnosis of malaria.[9] Therefore, the accuracy of malaria diagnosis can be greatly enhanced by combining clinical and lab-based findings.[10]

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METHODOLOGY

Our study was carried out at Combined Military Hospital Chhor, Sindh Pakistan from Feb 2021 to Jan 2022 after the approval of Ethics Review Board (Ref no. 2021-12, dated Feb 1, 2021).Sample size was calculated using Raosoft® calculator (v2004) with confidence level = 95%, margin of error = 5%,

population proportion=0.5, reference population mean=14226, response distribution = 50% and recommended minimum sample size (n) = 104. Non-probability consecutive sampling was used.

Inclusion Criteria: Adults more than 12 years of age; Fever as a presenting complaint with duration ≤5 days and clinical and hematological

Exclusion Criteria: Patients less than 12 years; Undiagnosed and pyrexia of unknown origin cases; Chronic malaria cases; patients with history of recent travel within last 2 weeks and patients with any co-infection.

Patients fulfilling the inclusion criteria were selected. The patients were explained accordingly and informed written consent was taken after assuring them, benefits and risks of the study. Hospital registration number, name, age and gender were noted. Based on our past experience and unpublished data, the specific parameters of malarial fever were noted and assigned with score. Maximum score was 12 points. Each individual score was assigned relative to its frequency in malaria patients generally. In every patient the clinical score was calculated. Score was calculated by two clinicians independently. Higher score was used whenever there was dichotomy. Clinical and Lab criteria predicted Malaria fever patients were diagnosed by both peripheral smear examination and ICT kits simultaneously by trained technician or pathologist. The Tuber®Line Malaria Pf/Pv Rapid test Cassette (Whole Blood) was used. Complete blood cell counts were performed on automated haematology analyzer (XP-100 Sysmex, Japan). All the patients were investigated thoroughly for other causes of febrile illness with appropriate investigations. Data analysis was computer based with the use of SPSS-20. Mean and standard Deviation (SD) was calculated for quantitative variables like age and number of monthly cases. Frequency and percentage were used for qualitative variables like gender, fever, thrombocytopenia, alternative diagnosis less likely, rigors and chills and body aches. Independent sample t-test was applied to compare clinical score with clinical and hematological parameters. A *p*-value <0.001 was taken as significant.

RESULTS

Out of 164 cases, 143 males (87.02%) and rest 21 females (12.08%).Mean age of patients was 28 ± 6 years. Clinical score was calculated for all the patients as described above. Mean clinical score was 9±2. Out of 164 cases, 152 cases (92.7 %) presented at a cut off value of ≥7 on clinical score which was significant. Out of 164 cases, 162(98%) presented with fever, 155 cases (94.5%) had no evidence of alternate diagnosis clinically, 105 cases (64%) had thrombocytopenia, 89 cases (54.3%) presented with body aches and 83 cases (50.6%) presented with rigors & chills as shown in Table-II and Figure-1. 131(80%) cases presented in June till December corresponding the seasonal surge as shown in Table-III and Figure-2. It was observed that out of all the parameters of scoring system fever, rigors and chills and thrombocytopenia were statistically significant (*p*-value <0.001) as shown in Table-IV.

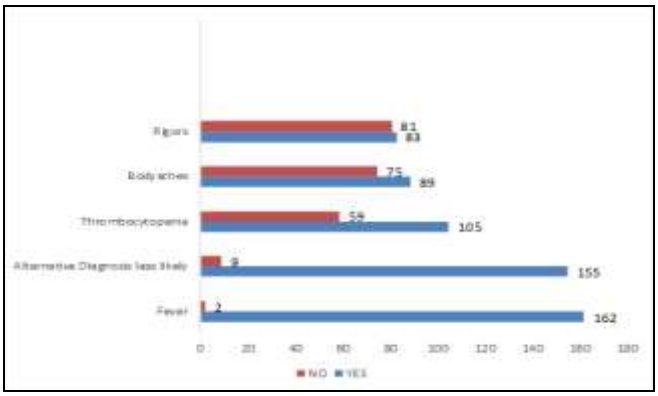

Figure-1: Frequency of Individual Clinical and Hematological Parameters

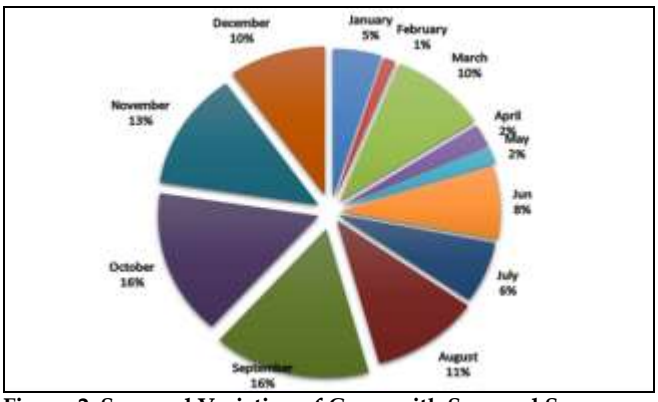

Figure-2: Seasonal Variation of Cases with Seasonal Surge

DISCUSSION

This is a unique study from a endemic area of Pakistan to derive a Clinical and hematological criteria to predict malarial fever. Malaria has significant effect on hematological parameters of patients such as Hemoglobin, Total Leucocyte Count & Platelets.[11] Plasmodium vivax malaria was more significantly associated with thrombocytopenia whereas Plasmodium falciparum more linked to anemia and leucopenia.

Seasonal variation provides important information for strict implementation of preventive measures during high transmission months.[12-14] Our study also proves seasonal surge of cases. The gold standard diagnostic tool for the malaria is peripheral film examination15. However, this facility is not widely available. Therefore, a rapid diagnostic test, such as RDTs are handy and valuable in peripheral health setups.[15]

Table-I: Clinical and Hematological Criteria for Malaria Diagnosis

Clinical and hematological Parameters	Scores
Fever (101o- 104oF) ≤5 days	3
Alternative diagnosis less likely*	3
Thrombocytopenia	2
Season/ epidemic period**	2
Rigors & Chills	1
Body Aches	1
Total score	12

**Alternative diagnosis less likely means "Clear throat, chest, Respiratory System and Cardiovascular system exam, absent massive splenomegaly, no neck rigidity, history of severe backache, conjunctival suffusion, rash, severe arthralgia/ myalgia, Respiratory rate>20 or continuous fever, postive Faget sign, no recent contact to a Covid-19 patient, recent travel within/from a pandemic/endemic area of a particular region or any LOCALISING feature of alternate diagnosis.*

*** from June till december*

Table-II: Frequency of Clinical and Hematological Parameters

Age	27.89±6.33 [15-44]
Variables	Frequency (%)
N	164
Gender (Male/Female)	143/21(87.2%/12.8%)
Fever	162(98.8%)
Alternative diagnose less likely	155(94.5%)
Thrombocytopenia	105(64%)
Rigors & Chills	83(50.6%)
Body Aches	89(54.3%)
Previous history of Malaria	63(38.4%)
Leucopenia	15(9.1%)
Clinical Scoring	9.73±1.69 [1-12]

Table-III: Monthly Presentation of Cases (%) Along with Relevant Clinical Score

	Frequency (%)	Clinical Score: mean±SD [Min-Max]
January	8(4.88%)	8.00±1.69 [5-10]
February	2(1.22%)	8.00±1.41 [7-9]
March	16(9.76%)	8.19±2.07 [1-10]
April	4(2.44%)	9.00±1.41 [7-10]
May	3(1.83%)	9.67±0.57 [9-10]
June	13(7.93%)	9.92±1.49 [8-12]
July	11(6.71%)	10.18±1.66 [8-12]
August	18(10.98%)	9.94±1.69 [5-12]
September	26(15.85%)	9.92±1.52 [7-12]
October	26(15.85%)	10.23±1.55 [6-12]
November	21(12.80%)	10.33±1.15 [8-12]
December	16(9.76%)	9.88±1.62 [6-12]
Total	164(100%)	9.73±1.69 [1-12]

Table-IV: Comparison of Clinical scoring with individual clinical parameters

Variable	Categories	Mean±SD	*p*-value(a)
Gender	Male	9.76±1.66	0.473
	Female	9.48±1.94	
Fever	Yes	9.81±1.51	<0.001*
	No	3.00±2.82	
Thrombocytopenia	Yes	10.52±1.21	<0.001*
	No	8.31±1.50	
Rigors & Chills	Yes	10.22±1.53	<0.001*
	No	9.22±1.71	
Body Aches	Yes	10.08±1.96	0.002*
	No	9.31±1.19	
	No	9.79±1.54	

Note: (a): Independent sample t-test, p-value<0.05 (statistically significant)

A recent study displayed comparable efficacy between Microscopy and RDT (e.g ICT) and demonstrated a reasonable basis for use of ICT as a cost-effective tool in periphery and for clinicians who can proceed with empiric treatment of malaria patients.[14,15] However, RDT for malaria has its own limitations16. Therefore, a more accurate additional diagnostics may be needed for malaria diagnosis in the field. RDT, among all available current and future diagnostic methods is still the most feasible test because it is easy to use, fast and does not require expensive equipment.[17]

Anti-malarials such as chloroquine and hydroxychloroquine can prolong the QT interval that could initiate ventricular arrhythmias. Use of empirical antimalarials is rampant in Pakistan which has led to anti-malarial resistance.[18] Empirical use is not justified as it may results in over use of drugs, side effects, development of resistance and cost. Therefore, the clinical & hematological criteria is of prime importance in the area where facilities are sparse & lack of availability of trained staff.[19]

Our study showed majority of the patients (>90%) having score ≥7 were found to have malarial fever on RDT. The most prevalent clinical parameter was found to be fever (*p*-value <0.001) followed by thrombocytopenia, rigors and chills (*p*-value <0.001), and body aches20, also demonstrated by contemporary studies of African population. Fever has been the main symptom of enquiry in predicting malaria.[20] Past history of malaria was also found to be contributive but not significant.[21] Apart from fever, other symptoms like body aches, rigors and chills were also reported in few studies.[21,22]

As per our study, 98% of the patients presented with fever as a presenting feature also reported by local study.[23] Similar study by Plucinski MM *et al* also demonstrated fever in 100% of malaria-positive patients as a presenting feature, hence we included fever in our criteria.[24] A local study in an endemic area also demonstrated some connection of presenting clinical parameters with the diagnosis of malaria.[25]

Our research revealed that with suggested clinical and hematological criteria, patients scoring ≥7 can be predicted as case of malaria pending lab confirmation and can be empirically treated.

LIMITATION OF STUDY

1) This criteria should not be applied to children.

2) The smear is gold standard for diagnosis however this criteria should be viewed as helping tool for physicians working in area where availability of lab confirmation is uncertain.

3) As the study was conducted on a limited population of Chhor, large trial is needed to prove its effectiveness.

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CONCLUSION

The Clinical and Hematological Criteria may be helpful in epidemics or peripheries of endemic countries having diagnostic challenges. The finding of this study can be pursued further for research.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SZ: & RSAK: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

ARJ: & SARZ: Data acquisition, data analysis, approval of the final version to be published.

MNK: & MS: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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