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Diagnostic Accuracy of Simple Clinical Parameters Predicting Non Severe Malaria in Pediatric Patients

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Keywords: Clinical parameters, children, diagnostic accuracy and malaria.

Abstract

Objective: To determine the diagnostic accuracy of simple clinical parameters predicting non severe malaria in pediatric patients.

Study Design: Cross sectional study

Place and duration of Study: This was conducted at Department of Paediatrics, Abbasi Shaheed Hospital, Karachi, from February 2018-August 2018 using Non probability consecutive sampling.

Material and Method: Significant clinical features were defined as presence of least three of the following clinical parameters, 1. Fever: body temperature; 37^0C of short duration with no focus of infection, 2.Anemia: Diagnosed by pallor of palm, tongue or conjunctive. 3. Spleenomegaly: Diagnosed when spleen was palpable on abdominal examination.4. Hepatomegaly: Diagnosed when spleen was palpable on abdominal examination. Sample of blood was taken and CBC was done, and thin and thick blood smears was prepared and stained with Giemsa stain (3% solution and 7.2 pH phosphate buffer) and reviewed by the researcher in the presence of a microbiologist with more than five years experience.

Results: Mean age in our study was 6.19±3.82 years. Moreover out of 211 patients, 109 (51.7%) were male and 102 (48.3%) were female. Mean duration of disease and weight in our study was 5.40±1.71 days and 31.78±9.41 kg respectively. 203 (96.2%) had fever, 199(94.3%) had shivering, 26 (12.3%) had hepatomegaly, 56(26.5%) had spleenomegaly and 89(42.1%) had anemia. CBC analysis showed that 205(97.1%) patients had thrombocytopenia, 127 (60.1%) had anemia, and 95(45%) had leucopenia. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of clinical parameters for diagnosing non-severe malaria by taking malarial parasite as gold standard was found to be 85.48%, 82.75%, 87.60%, 80% and 84.36% respectively.

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Conclusion: Assessment of clinical parameters in the initial diagnostic workup of patients presenting with febrile illness, particularly those presenting with suspicion of malaria, is highly accurate in its exclusion. If clinical parameters are assessed properly they can provide reassurance to patients and physicians.

Introduction

Malaria is a devastating epidemic in the world. It is a serious threat to public health and in 2020 it was estimated that 241 million malaria cases and 627 000 malaria deaths worldwide. Majority of the cases were reported in African Region (95%), followed by the South-East Asia Region (2%)[1]. Pakistan is among the countries where malaria is prevalent and continues to be a major public health problem[2]. Malaria is a protozoal disease caused by infection with parasites of the genus plasmodium and transmitted by female Anopheline mosquito[3]. Five species of plasmodium (plasmodium vivax, plasmodium falciparum, plasmodium malariae, plasmodium ovale, and plasmodium knowlesi) cause malaria in humans. P. falciparum and P.vivax are the most dangerous and common species[4]. Children of all ages are susceptible to malaria but under age of 5 years are most affected with 86% of deaths due to malaria are from under age of 5 years[5]. The common symptoms of malaria, are fever and flu-like syndrome[6]. Although fever is the classical feature, clinical findings in malaria vary widely ranging from mild headache to other serious complications which may be fatal[8]. The progression from simple fever to serious complications may occur very rapidly so, patient must be assessed and treated rapidly, with careful observations for early signs of systemic complications[9]. Several nonspecific symptoms like malaise, headache, myalgias, jaundice nausea; vomiting and diarrhea may lead physicians who see malaria infrequently to a wrong diagnosis, such as influenza predominantly during the seasonal epidemic flu, dengue, gastroenteritis, typhoid and other viral diseases[10]. Physicians should diagnose or exclude malaria, by performing microscopic examination of blood films. Appropriate treatment is critical to prevent morbidity and fatality.

In this study we aim determine the diagnostic accuracy clinical parameters in paediatric patients presenting at Abbasi Shaheed Hospital, Karachi in order to establish the local perspective as there is paucity of local data. The presumptive malaria diagnosis is based on clinical sign and symptoms. No study has been carried out to determine the sensitivity and diagnostic accuracy of simple clinical features of Malaria. Data from this study would explore the sensitivity, specificity, positive predictive value and negative predictive value of common clinical parameters used for diagnosing non-severe malaria. Thereby, timely and accurate diagnosis of malaria can be made and also help in formulating an effective management plan.

Subjects and Methods

This cross-sectional study was conducted at Department of Paediatrics, Abbasi Shaheed Hospital, Karachi from February 2018 till August 2018after approval of ethical review board. Informed consent was taken from the patients' parents for assigning them to the study and using their data in research. The sample size was calculated by taking, sensitivity 51%, specificity 72% and prevalence of malaria 63%, the margin of error d=9% for sensitivity and 10% for specificity and confidence interval 95%.Non probability consecutive sampling approach was employed. A total of 211 patients both male and female between ages of 6months-12 years having< 2% of erythrocytes infected with malarial parasite, along with absence of severe anemia (hemoglobin level < 5 g/dL), hypoglycemia (plasma glucose concentration < 70 mg/dl), respiratory distress, jaundice (total bilirubin >3 mg/dL), acidemia (arterial pH < 7.25), seizures (> 2 observed in 24 hours), renal failure (urine output 12 mL per kg in 24 hours), circulatory collapse (systolic BP < 50mmHg) or cerebral malaria (unarousable come not attributable to any other cause having Blantyre coma score ≤ 2) were included in the study. Non-consenting patients or patients having respiratory distress, coma, renal failure, and seizure were excluded from the study. Significant clinical features were defined as presence of least three of the following clinical parameters, 1.Fever: body temperature > 37^0C of short duration with no focus of infection. 2. Anemia: Diagnosed by pallor of

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palm, tongue or conjunctive. 3. Spleenomegaly: Diagnosed when spleen was palpable on abdominal examination. 4. Hepatomegaly: Diagnosed when spleen was palpable on abdominal examination.

Brief history was taken from the mother about the duration of illness and inquired about the presence or absence of clinical parameters was entered in the performa by the researcher. Sample of blood was taken and CBC was done, and thin and thick blood smears was prepared and stained with Giemsa stain (3% solution and 7.2 pH phosphate buffer) and reviewed by the researcher in the presence of a microbiologist with more than five years experience. Patients having positive MP were labeled as having malaria. Hemoglobin<12g/dl was defined as anaemia, platelets <100000/$mm^3$was defined as thrombocytopenia and leukocyte count < 4000 cells/ul was defined as leucopenia. Blood C/S, urine D/R + C/S. Dengue serology or antigen, chest x-ray to exclude other diseases like typhoid, UTI, dengue and pneumonia. Patients were labeled as True Positive: Patients with malarial parasite positive and clinical sign/symptoms positive. True Negative: Patients with malarial parasite negative and clinical sign/symptoms negative. False Positive: Patients with malarial parasite negative and clinical sign/symptoms positive. False Negative: Patients with malarial parasite positive and clinical sign/symptoms negative.

Data was analyzed on SPSS 21. Mean and standard deviation was calculated for continuous variables such as age, weight and duration of illness. Frequency and percentage was calculated for the quantitative variable like gender, and clinical parameters. Sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of clinical parameters predicting non-severe malaria taking malarial parasite as gold standard was calculated. Stratification was done with regards to age, gender, duration of illness, and weight to see the effect of these on outcome variable. Post stratification diagnostic accuracy was calculated.

Results

Out of 211 patients, age of the patients ranged from 02 to 12 years. Mean age in our study was 6.19 ±3.82 years. Mean duration of disease and weight in our study was 5.40±1.71 days and 31.78±9.41 kg respectively.203 (96.2%) had fever, 199(94.3%) had shivering26 (12.3%) had hepatomegaly, 56(26.5%) had spleenomegaly and 89(42.1%) had anemia.

Majority of patients 109 (51.7%) were males. Frequency distribution of age showed that 59 (28%), 76 (36%) and 76 (36%) patients were in age group 6months-4 years, 5-8 years and 9-12 years respectively. With respect to duration of symptoms, 47 (22.3%), 88 (41.7%) and 76 (36%) patients had the symptoms for < 4 days, 5-8 days and >8 days respectively. Most of the patients, 139 (65.9%) had weight> 25 kg rest of the patients were< 25 kg.

CBC analysis showed that 205(97.1%) patients had thrombocytopenia, 127 (60.1%) had anemia, and 95(45%) had leucopenia.

Diagnosing on the basis of clinical parameters showed that 124 (58.8%) had non-severe malaria and 87 (41.2%) and did not have non-severe malaria. While 121 (57.3%) were positive for malarial parasite on thick and thin films, and 90 (42.7%) were negative for malarial parasite on thick and thin blood films. In our study, 106 cases were true positive while only 15 cases were found to be false positive, on the basis of clinical parameters as presented in Table 1.

Table 1: Frequency of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) on the basis of clinical parameters for diagnosis of non-severe malaria by taking malarial parasite as gold standard.

MALARIAL PARASITE	CLINICAL PARAMETERS		TOTAL
	POSITIVE	NEGATIVE	
POSTIVE	106(TP)	15(FP)	121
NEGATIVE	18(FN)	72(TN)	90
TOTAL	124	87	211

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The diagnostic accuracy of clinical parameters for diagnosing non-severe malaria by taking malaria parasite as gold standard was found to be 84.36%.Sensitivity, specificity, positive predictive value, negative predictive value were found to be85.48%, 82.75%, 87.60%, and 80% respectively. With respect to stratification for age highest diagnostic accuracy, (90.7%) was found to be in 5-8 years group. With respect to stratification for gender, females had higher diagnostic accuracy (88.2%) clinical parameters than males (80.7%). With respect to stratification for duration of illness, the diagnostic accuracy of clinical parameters for diagnosing non-severe malaria was found to be 68% in < 4 days, 88.6% in 5-8 days and 89.4% n > 8 days. Diagnostic accuracy was roughly similar for both weight groups as shown in table 2.

Table 2: Diagnostic accuracy of clinical parameters for diagnosis of non-severe malaria according to gender, age, duration of illness and weight.n=211.

Variables	**Malarial Parasite**	**Clinical Parameters**			
Gender		**Positive**	**Negative**		
Male	Positive	37(TP)	13(FP)	50	**SEN 82.2%**
	Negative	8(FN)	51(TN)	59	**SPE 79.6%**
	Total	45	64	109	**PPV 74%**
					NPV 86.4%
					DA 80.7%
Female	Positive	69(TP)	2(FP)	71	**SEN 87.3%**
	Negative	10(FN)	21(TN)	31	**SPE 91.3%**
	Total	79	23	102	**PPV 97.1%**
					NPV 67.7%
					DA 88.2%
Age					
6mn-4yrs	Positive	35(TP)	3(FP)	38	**SEN 83.3%**
	Negative	7(FN)	14(TN)	21	**SPE 82.3%**
	Total	42	17	59	**PPV 92.1%**
					NPV 66.6%
					DA 83%
5-8 yrs	Positive	33(TP)	3(FP)	36	**SEN 89.1%**
	Negative	4(FN)	36(TN)	40	**SPE 92.3%**
	Total	37	39	76	**PPV 91.6%**
					NPV 90%
					DA 90.7%
9-12 yrs	Positive	38(TP)	9(FP)	47	**SEN 84.4%**
	Negative	7(FN)	22(TN)	29	**SPE 70.9%**
	Total	45	31	76	**PPV 80.5%**
					NPV 75.8%
					DA 78.9%
Duration of Illness					

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< 4**Days**	Positive	11(TP)	6(FP)	17	**SEN 55%**
	Negative	9(FN)	21(TN)	30	**SPE77.7%**
	Total	20	27	47	**PPV 64.7%**
					NPV 70%
					DA 68.1%
5-8Days	Positive	42(TP)	6(FP)	48	**SEN 91.3%**
	Negative	4(FN)	36(TN)	40	**SPE 85.7%**
	Total	46	42	88	**PPV 87.5%**
					NPV 90%
					DA 88.6%
> 8Days	Positive	53(TP)	3(FP)	56	**SEN 91.3%**
	Negative	5(FN)	15(TN)	20	**SPE 83.3%**
	Total	58	18	76	**PPV 94.6%**
					NPV 75%
					DA 89.4%
Weight					
< 25 KG	Positive	51(TP)	4(FP)	55	**SEN 87.93%**
	Negative	7(FN)	10(TN)	17	**SPE 71.42%**
	Total	58	14	72	**PPV 92.72%**
					NPV 58.82%
					DA 84.72%
> 25 KG	Positive	55(TP)	11(FP)	66	**SEN 83.33%**
	Negative	11(FN)	62(TN)	73	**SPE 84.93%**
	Total	66	73	139	**PPV 83.33%**
					NPV 84.93%
					DA 84.17%

SEN:Sensitivity, SPE:specificity, PPV:positive predictive value, NPV:negative predictive value, DA:diagnostic accuracy**.**

Sensitivity:TP/TP+FN x 100, Specificity:TN/TN+FP x 100, PPV:TP/TP+FP x 100, NPV:TN/FN+TN x 100, DA:TP + TN/Total Patients x 100

Discussion

Malaria is known to cause more than 0.4 million deaths in the world every year, of these 67% were children[11]. World Health Organization (WHO) eastern Mediterranean region comprises of twenty two countries, out of which six (including Pakistan) bear 95% of the disease burden[12]. Every year Pakistan is threatened by malaria epidemic in post monsoon seasons resulting in loss of many precious lives, which can be minimized by prompt diagnosis and implementation of correct treatment. In 2004, reported annual parasite incidence of malaria in Pakistan was 5.6% and plasmodium falciparum ratio was 33%[13]. Rural Sindh and Balochistan are the areas having major disease burden in Pakistan[14-15].

In our study mean age was 6.19±3.82years. 109 (51.7%) were male and 102 (48.3%) were female. 203(96.2%) had fever, 199(94.3%) had shivering 26(12.3%) had hepatomegaly, 56(26.5%) had spleenomegaly and 89(42.1%) had anemia.

Another study which included 32 cases reported fever was the commonest presenting symptoms present in 100% of cases, 50% had pallor, cough, 9.3 % had dysuria as additional presenting symptoms[16]. In the current study anemia was the commonest CBC finding followed by thrombocytopenia and leucopenia. These results are concordant with other researches done in Korea and Karachi[17-18].

Moreover out of 211 patients, sensitivity, specificity, positive predictive value, negative

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predictive value and diagnostic accuracy of clinical parameters for diagnosing non-severe malaria by taking malarial parasite as gold standard was found to be 85.48%, 82.75%, 87.60%, 80% and 84.36% respectively. We found out that clinical parameters were more sensitive than specific. In this condition sensitivity is more important than specificity because majorly because malaria is very easily treatable which may be fatal if not diagnosed in time. The results of our study are in concordance with another study done in Africa which showed sensitivity of clinical diagnosis was very high 97.0%, specificity 66.7%, and positive predictive value was reported to be 37.4%[19].

In addition to this when we analyzed the effect of gender on diagnostic accuracy of clinical parameters; we found that sensitivity, specificity and diagnostic accuracy was better in female patients. With respect to age lowest performance was noted in 6months-4years age group. This may be due to the fact that younger children tend to be more asymptomatic in various illnesses. Highest sensitivity, specificity and diagnostic accuracy were noted in 5-8 years age group. An other researcher also reported high percentage of asymptomatic malaria patients in lower age group[20].

The results of our study showed that diagnostic accuracy of clinical parameters increased from 68.1% to 89.4% as the duration of illness increased from <4days to >8 days. This means that using only clinical parameters in young children may miss out on correct diagnosis of malaria. So other diagnostic tools like blood tests must be used along with simple clinical parameters especially in younger children.

In recent years, the clinical pattern of malaria has changed. Severe and non-sever malaria is now very common with increasing mortality. Not only the number, but also the type of presentation influences the outcome of malaria. Properly trained medical and paramedical staff can make use of these simple clinical parameters for prompt diagnosis and initiation of treatment of malaria so mortality and morbidity can be curtailed.

Conclusions

Assessment of clinical parameters in the initial diagnostic workup of patients presenting with febrile illness, particularly those presenting with non severe malaria, is highly accurate in its exclusion and can provide reassurance to patients and physicians. However, care must be exercised as diagnostic performance of clinical parameters may be influenced by prevalence of malaria in the region. The accuracy of malarial diagnosis can be greatly increased by combining both clinical and laboratory based tests.

Conflict of Interest

Authors have no conflict of interest and no grant/funding from any organization.

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