"THE MALARIA SEVERITY SCORE : A METHOD FOR SEVERITY ASSESMENT AND RISK PREDICTION OF HOSPITAL MORTALITY FOR FALCIPARUM MALARIA IN ADULTS"

Submitted By

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MD

in

General Medicine

Under the guidance of

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2012

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"THE MALARIA SEVERITY SCORE : A METHOD FOR SEVERITY ASSESMENT AND RISK PREDICTION OF HOSPITAL MORTALITY FOR FALCIPARUM MALARIA IN ADULTS"** is a bonafide and genuine research work carried out by me under the guidance of **DR.M.S.MULIMANI** **M.D.** Professor of Medicine.

Date:

Place: Bijapur.

DR. VINAYAK S. INGALAGI

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This is to certify that the dissertation entitled **"THE MALARIA SEVERITY SCORE : A METHOD FOR SEVERITY ASSESMENT AND RISK PREDICTION OF HOSPITAL MORTALITY FOR FALCIPARUM MALARIA IN ADULTS"**

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LIST OF ABBREVATIONS

AIDS	:	Acquired immune deficiency syndrome
ARDS	:	Adult respiratory distress syndrome
ARF	:	Acute renal failure
BC	:	Before Christ
CCF	:	Congestive cardiac failure
CN	:	cranial nerve
CPK	:	Creatinine phosphokinase
CSF	:	Cerebrospinal fluid
CT	:	Computed Tomography
CVP	:	Central venous pressure
DIC	:	Disseminated intravascular coagulation
ECG	:	Electrocardiogram
ELISA	:	Enzyme linked immunosorbant assay
FCT	:	Fever clearance time
G6PD	:	Glucose 6 phosphatase dehydrogenase
GIT	:	Gastrointestinal tract
HCO3	:	Bicarbonate
Hb-F	:	Foetal haemoglobin
HLA	:	Human leukocyte antigen
ICAM	:	Intra cellular adhesion molecule
LEA-1	:	Liver stageantigen
IgG	:	Immunoglobulin – G

IgM	:	Immunoglobulin – M
IL	:	Interleukin
IRMA	:	Indirect fluorescent antibody test
JVP	:	Jugular venous pressure
MP	:	Malarial parasite
IM	:	Intramuscular
IV	:	Intravenous
mmol/L	:	Millimol per litre
PCT	:	Parasite clearance time
PCV	:	Packed cell volume
PI	:	Parasite index
PEEMP-1	:	Plasmodium falciparum erythrocyte membrane protein – I
P.Vivax	:	Plasmodium vivax
P. falciparum	:	Plasmodium falciparum
Qbc	:	Quantitative buffy coat
RBC	:	Red Blood Cells
SC	:	Subcutaneous
TNF	:	Tumor necrosis factor
WHO	:	World Health Organization
μL	:	Microliter
μM	:	Micrometer
μmol/L	:	Micromol per litre

ABSTRACT

Background and objective

Malaria affects more than 2400 million people,over 40% of the worlds population, in more than 100 countries in the tropics from south America to the Indian peninsula study was conducted to study clinical feature ,complication,treatment and outcome of patients with falciparum malaria

Methodology

The present study was conducted in the dept of medicine ,BLDE Shri B.M.Patil medical college hospital,bijapur during the period of sept 2009 to sept 2011 among 100 patients of p.falciparum malaria with typical presentation and atypical presentation and were followed during the hospital stays and discharge or till the outcome.all patients were informed about the study and informed consent was obtained.detailed history and clinical examination was done on admission .peripheral smear for p.falciparum malaria parasite and QBC(MP) was done on admission.other investigation like CBC.LFT,mineral,urine examination,ECG and x-ray were done.parasite index on day 1,3,7 and 14 day of admission and or whenever was deemed necessary during follow up was done

Results

The results of the present study revealed that ,incidence in male is slighty higher (2.7:1) than females.incidence is equally common in adults upto age of 50 yrs and as the age advance it falls rapidly,parasite index did not correlate with the morbidity and mortality of p.falciparum,probably mature stage schizont in peripheral smear indicate

worst prognosis. Hepatic ,encephalopathy was observed in 12(12.%) patients. ARF/black water fever in 11 (11%) of the patients, ARDS was observed in 10 (10%) of the patients. Mortality Was 20% sixteen of these 18 patients had no spleenomegaly.

Conclusion

Assessment of severity of organ dysfunction required for risk stratification,prognostication and planning of treatment and to arrest in progression of disease and hence mortality on 1 day of admission

Key Words

Falciparum Malaria, Quantitative buffy coat, Adult respiratory distress syndrome, Acute renal failure.

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INTRODUCTION

Malaria is an important parasitic infection with considerable morbidity and mortality. This disease was almost eradicated in 1960's and has re-emerged as a major public health problem in the last few decades. Although exact statistics are not available, about 110 million cases are reported- The mortality in Malaria is due to plasmodium falciparum. The considerable mortality and morbidity in falciparum malaria is due to its protean manifestation, multiorgan involvement and delay in diagnosis and failure of administration of treatment promptly and adequately. The emergence of drug resistance adds to the seriousness of the problem.

Malaria affects more than 2400 million people, over 40% of the world's population, in more than 100 countries in the tropics from South America to the Indian peninsula. The tropics provide ideal breeding and living conditions for the anopheles mosquito, and hence this distribution. Every year 300 million to 500 million people suffer from this disease (90% of them in sub-Saharan Africa, two thirds of the remaining cases occur in six countries- India, Brazil, Sri Lanka, Vietnam, Colombia and Solomon Islands). WHO forecasts a 16% growth in malaria cases annually. About 1.5 million to 3 million people die of malaria every year (85% of these occur in Africa), accounting for about 4-5% of all fatalities in the world. One child dies of malaria somewhere in Africa every 20 sec., and there is one malarial death every 12 sec somewhere in the world. Malaria kills in 1 year what AIDS killed in 15 years. In 15 years, if 5 million have died of AIDS, 50 million have died of malaria.

Malaria ranks third among the major infectious diseases in causing deaths-after pneumococcal acute respiratory infections and tuberculosis. It is expected that by the turn of the century malaria would be the number one infectious killer disease in the world. It accounts for 2.6 percent of the total disease burden of the world. It is responsible for the loss of more than 35 million disability-adjusted life-years each year. Every year -' 30000 visitors to endemic areas develop malaria and 1% of them may die.

Since 1994 focal outbreaks malaria have been reported from various parts of the country with increased proportion of plasmodium falciparum. Hence a hospital based study of clinical profile of falciparum malaria is being carried out.

ANNEXURE –II

OBJECTIVE OF THE STUDY:

To develop a severity score for assessment of disease severity and risk prediction in adult patients of falciparum malaria on the day of admission.

ANNEXURE – III

REVIEW OF LITERATURE:

R. Helbok, et al studied in 2005 on the use of the multi-organ-dysfunction score to discriminate different levels of severity in severe and complicated plasmodium falciparum malaria, the prospective study was conducted at Bangkok hospital tor tropical disease in Bangkok, Thailand which includes 29 consecutive patients 15 yrs of age presenting with severe P. falciparum malaria as proposed by the study. Diagnosis was defined the presence of asexual forms of P. falciparum on blood smears.

Excludes 1) patients with previous malarial infection in the last 30 days before admission.2) patients known to be pregnant or lactating after child birth.3) patients with proven systemic infection other than malaria, and 4) patients transformed from other hospital already receiving specific antimalarial 'treatment. Additionally, for purpose of correlating the MODS with morbidity across the whole spectrum of clinical presentation of P, falciparum malaria-' 22 patients with uncomplicated P. falciparum malaria previously reported were used for statistical analysis. Patients from both groups (n=51) were prospectively enrolled during the same time period in a consecutive order.

21 healthy Thai volunteers served as control for determination of the serum TNF-a level. Results were reflects a continuum from asymptomatic to multi organ manifestation and death. Severe malaria is defined by WHO as qualitative variable. They used the multi organ dysfunction score (MODS) as a quantitative approach for

severity in 29 patients with severe and complicated P. falciparum malaria to lest its usefulness in discriminating different severity levels. The MODS on admission was highly correlated with the duration of symptoms after admission ($r=0.73$, $p<0.001$) and the serum level of TNF-a [$r=0.41$, $p=0.03$), MODS also correlated with liver and renal dysfunction during hospitalization. Thus, this score might provide a predictive value for morbidity in P. falciparum malaria.

Mishra SK. et al in their study of 248 severe malaria cases, 35 died. There were 212 adults (34 deaths) and 36 children (I death). The malaria score for adult was (MSA) =1 (severe anemia) +2 (acute renal failure) +3 (respiratory distress) +4 (cerebral malaria). The MSA ranges from 0-10. The mortality was 2% for MSA 0-2; 10% for MSA 3-4; 40% for MSA 5-6 and 90% for MSA 7 or more. The sensitivity is 89.9% and positive predictive value is 94.1% when 5 is taken as cut off value. From ibis study authors came to conclusion that MSA is a simple and sensitive predictor. It can be administered rapidly and repeatedly to prognosticate the outcome of severe malaria in adults. It can help the treating doctor to assess the patient as well as to communicate to the relatives of the patients about the prognosis. The score needs revalidation in other geographical areas.[2]

Mohapatra.M.K et al did A study of 2598 patients of P.falciparum malaria in 2009 were enrolled in this study of which 2089 patients were included as developmental and 509 patients as validation sample. Physiological variables were analyzed for defining and assessment of severity of organ dysfunction (OD). The severity level and corresponding severity score for each organ dysfunction were determined by logistic regression analysis that took both the relative severity among the organ system: the degree of severity within an organ system into account .Risk of

mortality has been calculated for each score.

Results were physiological variables defined dysfunction in 7 organ system with 3 levels of severity (I to III). Neurological renal dysfunction had 3 level of severity.

Hematologic, Cardiovascular and Respiratory dysfunction had 2 levels of severity where as hepatic and metabolic dysfunction had I level of severity. 1,3 and 5 points were assigned to level I,II and III severity of 'organ dysfunction respectively, Malaria without any abnormal physiological variables had been considered as no organ failure and assigned 0 score.

Criteria for diagnosis of organ dysfunction in malaria

Criteria	Parameters
a) General	1) Fever>101 F
	2) Presence of asexual form of P.falciparum
b) Specific organ system	parameters for defining dysfunction
1. Neurogenic	a) Glasgowcoma scale>13
2. Renal (one or more)	a) Urine output <750ml/24hr
	b) Serum-creatinine> 1.2mg/dl
	c) Blood.urea>36.0mg/dl
3. Hepatic	a) Serum. billirubin>2.0mg/dl
4. Respiratory	a) Respiratory rate>30/min
5. Cardiac (one or more)	a) systolic blood pressure<90mm hg
	b) Heart rate>120beats/mm
6. Metabolic	a) Blood. Glucose<60mg/min
7. Hematological (one or more)	a) Heamoglobin<10gm/dl
	b) Platelet count<80000/microlit
	c) Total leucocytes count<4000 or >12000/microlit

Range of variables to assess the level severity of organ dysfunction in malaria

Parameters of organ dysfunction	**level-0**	**level-I**	**level-II**	**level-III**
1. NeurologicGCS score	14-15	10-13	7-9	0--6
2. Renal Blood. urea Serum. creatinine Urine output	10-36mg/dl 0.6-1.2 mg/dl 750-3900 ml/24hrs	37-59mg/dl 1.3-1.9mg/dl 500-750 ml/24hrs	60-119mg/dl 2.0-4.9mg/dl 400--500 ml/24hrs	>120mg/dl >5.0mg/dl <500ml/24hrs
3 Cardiovascular heart rate/min systolic blood pressure	51-119/min 90-160mmhg	120-139/min 70-90mmhg	>140or<51/min 1-70 mmhg	
4. Respiratory respiratory rate	20-30/min	31-40/mi	>41/min	
5. Hematologic Hb TLC Platelet	10-13.9gm/dl 4001-16000/microlit 80000-250000/microlit	7-9.9gm/dl 2001-400/microlit <80000/microlit	<7 gm/dl <2000/microlit	
6 Hepatic Serum. bilirubin	<2.0mg/dl	> 2.0mg/dl		
7 Metabolic Blood glucose	60-110mg/min	< 60mg/min		

Malaria Severity score of each organ dysfunction with different level of severity.

Organ dysfunction and score	Level of Severity			
	0	I	II	III
Neurologic	Score – 0	Score – 1	Score – 3	Score – 5
Renal	Score – 0	Score – 1	Score – 3	Score – 5
Cardiovascular	Score – 0	Score – 1	Score – 3	Score – X
Respiratory	Score – 0	Score – 1	Score – 3	Score – X
Hematologic	Score – 0	Score – 1	Score – 3	Score - X
Hepatic	Score – 0	Score – 1	X	X
Metabolic	Score – 0	Score – 1	X	X

Malaria Severity Score and probability of Mortality

Severity of Malaria Score	Probability of Mortality
0	1.2
1	3.1
2	10.5
5	12
6	21.1
7	31.1
8	40.1
9	51.8
10	61.7
11	70.8

12	81.8
13	88.8
14	92
15	94.6
16	96.1
17	97.2
18	98.5
19	99.2
20	99.5
21	99.7

Malaria is the most important protozoan infection of the red blood cells in humans and the parasite is transmitted by the bite of a blood feeding female anophalese mosquito. The word malaria or ague has been known from antiquity. It is derived from the Roman word means literally "Bad Air". It is supposed to be due to offensive vapours emanating from tiberian marshes.

Hippocrates (400 D. C.) is credited with the first clear description of pattern of fever and in his aphorisms he described the regular paroxysms of intermittent fever,

The curative value of cinchona bark was known to Ameridians since an unknown period and was introduced to Europe in the middle of 17"' century.

The work of Meckel, Virchow and Frerich's had established that a pigment in the blood was identified in some patients with periodic fever.

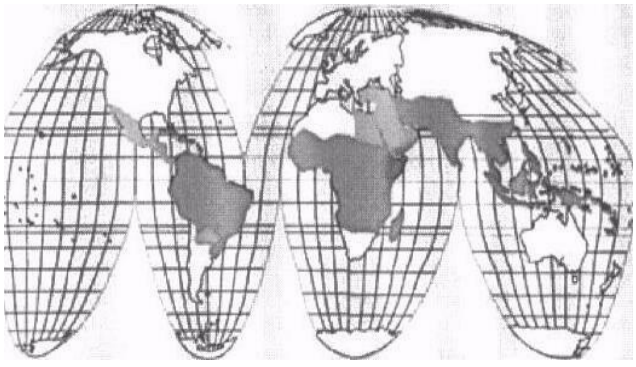
A French army surgeon working in Algeria was the first to come out with information that parasites caused malaria. On 20th October 1880 Charles Louis

Alphonse Laveran was examining the fresh blood of a patient with ague observed moving bodies (Probably watching gametocytes exflagellation) called parasites of RBC. The Transmission of infection in blood was proved by Gerbardt. The vector transmission of the plasmodium falciparum was first described by an young Scottish military physician Sir Ronald Ross on Aug. 20th 1897 while he was working in Secundarabad India and later in Calcutta.

The complete life cycle was described by Ross. For their contribution in the investigation of malaria both Ross and Laveran received nobcl prizes. In Rome Seirraleone Bignami et.al. confirmed the sporogony in anopheles mosquito and they succeeded in infecting a healthy volunteer with falciparum from mosquito bite. Approximately 270 million people suffer from malaria annually and there are between 1to 2.5 million deaths per year mostly in Tropical Africa. Almost all the deaths and severe diseases are caused by plasmodium falciparum of the four types of malaria in man.

GEOGRAPHICAL DISTRIBUTION

Malaria is found throughout the tropics. Plasmodium falciparum predominates in Africa, Papua New Guinea, Haiti and is alarmingly on rise in Indian sub continent and South East Asia, where it was mainly vivax malaria previously which was more prevalent.



EPIDEMIOLOGY

Female Anopheles Stephensi is the principal vector of transmission of malaria in India.[7] Anopheles culicifacies and anapheles fluviatilis are more common in rural areas and foothills of South India.

Malaria is often seasonal coinciding with the rainy season which provides water for mosquito breeding and increased humidity favoring mosquito survival. Malaria transmission does not occur at temperatures below 16°c or above 33 °c and at altitudes greater than 2000 mts. Because development in the mosquito (Sporogony) cannot take place. The optimum conditions for transmission are high humidity and an ambient temperature between 20 to 30°c.

Malaria transmission to man depends on following factors

1. Longevity of anopheles mosquito vector as sporogony (development of sporozoite parasite in the vector) takes over a week. The mosquito must survive for longer than this after feeding on a gametocyte carrying human if malaria is to be transmitted.

2. Malaria transmission is directly proportional to the density of the vector, the square of the number of .times each day that the mosquito bites man and the 10^{th} power of the probability of the mosquito surviving for one day - model described by Mc Donald though has certain theoretical limitation useful in control of the diseases.e.g.. Malaria transmission = K. x density of vector (D) x Square of number of times each day the mosquito bites man (S2) x 10th power of the probability of the mosquito survival for one day (p^{10}), where K is constant derived for that endemic area,

Human host

Human reservoir of gametocytes is required to transmit the infection. In areas of high transmission infants and young children are more susceptible than the more immune adults. Younger age group have high parasite density than old. The older age.group have asymptomatic infection and low parasite density due to immunity. Endemicity of malaria is defined traditionally in terms of spleen or parasite rates in children aged 2 to 9 yrs.

Hypo endemic - Spleen or parasite rate 0 - 10%.

Mesoendemic - Spleen or parasite rate 10 - 50%.

Hyperendemic - Spleen or parasite rate 50 - 75%. (Adult spleen rate high)

Holo endemic - Spleen or parasite rate> 75% (Adult Spleen rate low)

Where parasite rate is defined as the percentage of children between the age of 2-9 yrs. showing malaria parasites in their blood films in that particular area. The spleen rate is the percentage of children between 2-9 yrs. of age having an enlarged spleen.

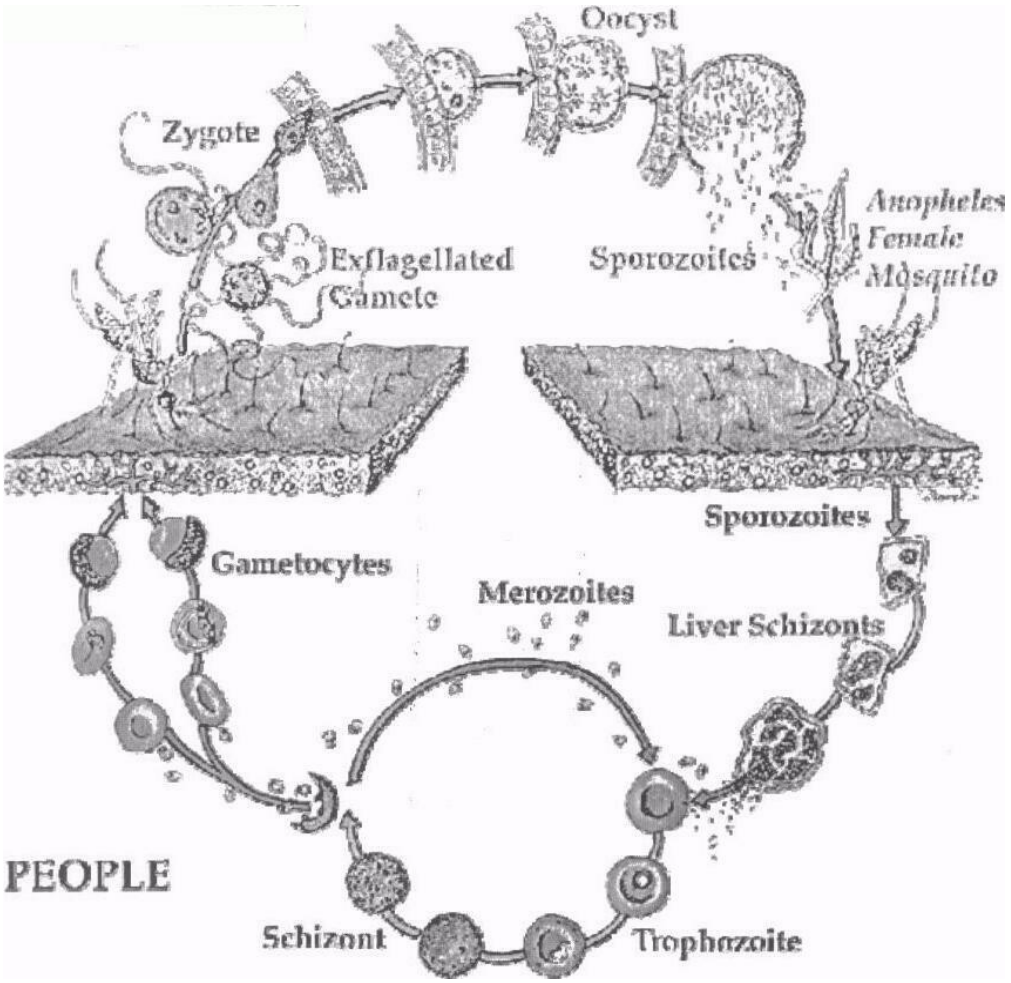
Falciparum malaria infection are more severe in non immune persons, and in pregnancy particularly primigravida and may be augmented by Iron supplementation.

In Babies malaria is infrequent because of;

1. Passive transfer of immunity from the mother.

2. Presence of HbF in infant RBC which retards the parasite development. Malaria may also be transmitted by blood transfusion, bone marrow transplantation or through needle sharing among IV drug addicts.

LIFE CYCLE


Oocyst
Zygote
Anopheles
Female
Mosquito
Exflagellated
Gamete
Sporozoites
Sporozoites
Gametocytes
Merozoites
Liver Schizonts
PEOPLE
Schizont
Trophozoite

AETIOLOGY

Infection with human malaria begins when the female anopheles mosquito inoculates motile plasmodial sporozoites (8-15-100) at the time of feeding. Within 45 min. The sporozoites either enter the hepatocytes or have been cleared. Each sporozoite bore into hepatocyte and begins a phase of asexual reproduction.

- Exo erythrocytic hepatic phase of development- *5.5* days
- Erythrocytic cycle - 2 days
- Hypnozoitcs stage (relapses) -absent in falciparum,
- Number of merozoites per hepatic schizont -30,000.
- Erythrocyte preference - infects young RBC's mainly but can invade all Age RBC's.
- Maximum duration of untreated infection - 2 yrs.

The hepatic schizont ruptures to release merozoites into the blood stream. These merozites resembles sporozoites and are motile, ovoid and rapidly invade red cells.

The process of invasion involves attachment to the erythrocyte surface, orientation so that the apical organelle, the rhoptry abuts the red cell and then interiorization takes place by a wriggling or boring motion inside a vacuole composed of the invaginated erythrocyte membrane. The attachment of the merozoite to the red cell is mediated by a specific erythrocyte surface receptor which has not been identified. Unlike in P -vivax which is related to the duffy blood group antigen Fya or Fayb. The absence of these phenotypes in West Africans explain their resistance to infection with P. Vivax and the absence vivax malaria in West Africa.

During the early stage of development (<12 hrs.) the small "ring forms" appear like a pair of stereo head phones, with darkly staining chromatin in the nucleus, a circular rim of cytoplasm and a pale central food vacuole. Parasites arc freely mobile within the erythrocytes. As they grow they consume the erythrocyte content (hemoglobin).

Proteolysis of haemoglobin within the digestive vacuole releases amino acids which are taken up and utilized by the growing parasite for protein synthesis.

The haem that is freed from its protein scaffold oxidizes to toxic ferric form. Toxicity is avoided by spontaneous polymerization to an inert crystalline substance - haemozoin. The infected erythrocyte becomes progressively less elastic and deformable and most spherical as the parasite grows.

At 24-26 hrs, of development P. Falciparum parasite begin to exhibit a high molecular weight strain specific variant antigen on the surface of the infected red cell which mediates attachment to vascular endothelium. This is associated with knob like projection from the erythrocyte membrane. This red cells then disappear from the circulation by attachment or "cytoadherence" to the walls of venules and capillaries in the vital organs. This process is called Sequestration. High parasitemia (over 2%) are usually caused by P. Falciparum.

Approximately 36 hrs after merozoites invasion, repeated nuclear division takes place to form a segmenter or schizont. Eventually the growing parasite occupies the entire red cell which has become circular, rigid, depleted in haemoglobin and full of merozoites- This ruptures releasing 6- 36 merozoites which invade other red cells and start a new asexual cycle expanding the infection logarithmically. This asexual cycle takes 48 hrs, in P. Falciparum.

SEXUAL STAGE OF DEVELOPMENT IN THE MOSQUITO

After a series asexual cycles a sub population of parasites develop into sexual forms (gametocytes) which are long lived and motile. Gametogony takes more than 10 days. The Male: Female gametocyte sex ratio is 1:4. Following ingestion by the mosquito the male and female gametocytes become activated.

The male gametocyte under go rapid nuclear division and each of the eight nuclei formed associates with a flagellum (20-25 u,m long). The motile male microgamete then separates and seek female macrogamete. Fusion and meiosis takes place to form a zygote within 24 hrs. The enlarging zygote becomes motile and this forms the ookinete. Penetrates the wall of mosquito midgut where it encysts (as an oocyst). This spherical bag of parasites expand by asexual division to reach a diameter of approximately 500 UM

The oocyst finally burst to liberate myriads of sporozoites into coelomic cavity of the mosquito. Sporozoites then migrate to the salivary glands to await inocculation into the next human host during feeding.

The development of parasite in the mosquito is termed sporogony and takes between 8-35 days depending on the ambient temperature. The infection follows as long as the mosquito survives and remain alive. The mosquito transmits the infection after 12^{th} day following ingestion of infected blood- (The time taken for sporogony in mosquito and migration of sporozoites into salivary glands to await inoculation into the next human host).

MOLECULAR GENETICS

In P falciparum haploid and diploid generations alternate. The haploid genome is divided among 14 chromosomes. The sexual cycle is an obligatory part the opportunity for genetic diversity to arise from the recombination that occurs during meiosis in the mosquito. Self fertilization is common in P. Falciparum (i.e. the fusion of male and female gametocytes originating mitotically from the same haploid cell). But the extent to which self fertilization or heterozygous recombination occur in natural population is unresolved.

Antigen diversity is necessary for the parasite to elude the host immune system. The mechanism maintaining genetic diversity with in the parasite genome are many and complex. Some of the polymorphic antigens identified are encoded by single gene copies in the haploid genome and are characterised by tandem repeat sequences. Unequal crossing over during recombination can generate completely different sequences and their variation provides antigenic diversity.

Recent evidence suggests that the variant surface protein which mediates cyto-adherence (PFEMP1) is the main antigen determining the parasite population structure during chronic P. falciparum infection.

It has been suggested that the diversity of these immuno dominant variant repeat sequences interferes with the selection of high affinity antibody responses and perpetuates low affinity responses in malaria and this delays the development of effective immunity. Immune selection also provides the selective pressure to maintain diversity-in T and B cell epitopes through a high frequency of non synonymous base mutations during the asexual development of malaria parasites.

GENETIC FACTORS PROTECTING AGAINST MALARIA

JBS Haldane in 1949 suggested that people who were heterozygous for red cell abnormalities such as Thalassemia or Sickle cell disease might be protected against malaria. This would explain the high gene frequencies for the haemoglobinopathies in tropical areas.

The greatest protection is conferred by sickle cell trait and Melanesian ovalocytosis. These patients cells resists parasite invasion (in the case of sickle cell trait under low oxygen tensions) and once invaded the infected cells sickle readily, facilitating clearance by reticulo-endothelial system.

The protective effect conferred by the Thalassemia or glucose-6-phosphate dehydrogenase deficiency (which share geographical distribution with malaria) is weaker and in some epidemiological studies has not been apparent.

Red cells from patients with alfa- Thalassemia are invaded normally by p. falciparum but they bind greater numbers of antibody molecules to the erythrocytes surface than infected normal cells and may therefore be cleared from the circulation more readily. Also rate of declined of haemoglobin F in the first year of life is slower in a & |3 Thalassemia heterozygotes. RBC with high Hb F do not support parasite growth. Melanesian ovalocytic erythrocytes both resist infection and provide a hostile intra erythrocytic ionic milieu for development.

Class I antigen HLA- BW 53 and class II ULA-DR B1 1302 may also confer protection against severe falciparum malaria. (Absence of duffy group antigen in certain African traits confer resistance especially only in P. Vivax).

INFECTION PATTERN AND IMMUNITY

When the hepatic schizont ruptures, they liberate approximately 10^5-10^6 merozoites, i.e. the product of 5-100 successful sporozoites into circulation. These invade young red cells immediately.

In non immune, the multiplication rate exceeds 10 fold (i.e. >50% efficiency) and often reach 20 fold per cycle. On an average parasite are detectable in the blood on the 11^{th} day after sporozoite inoculation. At this stage the host may be asymptomatic or may have vague non specific symptoms of malaise, headache, myalgia, weakness or anorexia.

On an average fever begins 2 days later, but in some fever precedes parasitemia. P. Falciparum has the capacity for untrammeled multiplication and parasitemia exceeds 50% in some cases.

Factors which limit parasite multiplication are

1. Specific and non specific immune defenses by hosts.
2. High fever damages parasite merozoites.
3. Lack of young RBC's —hence iron supplementation may help the diseases Process.

Although natural infections often contain two or more genetically different parasite strains development tends to be relatively synchronous from the outset. Further synchronization takes place in untreated infections in non immune subjects, such that merogony (sporulation) takes place within 1-2 hrs. This is associated with fever and rigors (the paroxysm). . Although one brood predominates in P. Falciparum

there is usually at least one minor brood or sub population cycling 24 hrs. out of phase with the major brood.

P. Falciparum is often synchronized to a daily fever spike (quotidian fever) presumably caused by two broods of approximately equal size oscillating each 24 hrs- or fails to synchronise at al.

The classic descriptions of malaria symptomatology derived largely from detailed clinical observations made 'in the late 19' and early 20' centuries, the experience with artificial infections in early chemo therapy studies, and the use of malaria therapy in the treatment neurosyphilis.

It was apparent from clinical observation and animal studies some strains of P. Flaciparum were more virulent than others. The virulence factor probably include - multiplication capacity, cytoadherence and resetting ability, the potential to induce cytokine release, antigenicity and anti malarial drug resistance.

In P. Falciparum the microscopist can see only the first half of the asexual life cycle. In the second half the parasitized cells are sequestered. As a consequence there may be large discrepancies between the number of parasites in the peripheral (circulating) blood and the number of parasites in the body. (The actual parasite burden).

This has often puzzled and misled the clinicians. Some patients appear to tolerate high parasitemia with little adverse effects, where as others die with low parasite counts. The clue to the discrepancy lies both in the immune status of the host and in the stage of development of parasites on the peripheral smear.

A predominance of more mature parasite indicates that a greater proportion are sequestered and carries a worst prognosis for any parasitemia than a predominance of younger forms. In synchronous P. Falciparum infections the peripheral blood parasite numbers fall at the time of sequestration and rise abruptly at the time of merogony (when a predominance of tiny rings are seen).

The other explanation for the ability to tolerate high parasitemia without apparent adverse effects relates to the development of antitoxic immunity.

The host adapts to repeated, infection by producing less cytokines for a given quantum of parasites. Eventually a stage is reached where infections are asymptomatic. This is called premunition (partial immunity),

Protective antibodies inhibit parasite expansion through co-operation with the monocyte-macrophage series by binding to parasitised erythrocytes and then activating this cells Fc receptors.'

Non specific effector mechanisms include the activation of phagocytic cells (including neutrophils) to release toxic oxygen species and nitric oxide, both of which are parasiticidal. The reaction of these oxygen intermediates with lipoproteins produces lipid peroxides. These are more stable cytotoxic molecules and are unaffected by antioxidants.

There is also augmentation of spleenic clearance function - both filtration and Fc receptor mediated phagocytosis are increased.

The parasite proteins expressed on the red cell surface undergo antigenic variation and this is probably instrumental in avoiding complete immune clearance and sustaining the infection.

The monocyte - macro phage series appears to be the most important immune effector cells in the direct attack on parasitised erythrocytes and merozoites.

Following natural infection there is transient humoral response to sporozoitcs antigens. Sporozoites antibodies decline with a half - life of 3- 4 weeks. The role of a cytotoxic T- cell immune response to the preerythrocytic liver stages in humas is not known, although several lines of evidence including the recent discovery that IILA-B53 is associated with protection from severe malaria- And that HLA-B53 restricted T-lymphocytes recognised a liver stage antigen LEA-1.

Strain specific immunity to the asexual stage parasites develops slowly during natural untreated infections but does provide good protection against rechallenge.

Infusion of hyper immune serum to patients with acute malaria can reduce or eliminate parasitemia, mainly through opsonization, phagocytic cell activation and cytotoxicity and augmentation of ring form infected erythrocyte clearance.

Immune serum also reduces parasite multiplication by agglutinating merozoites. It is of interest that malaria does not seem to be worsened by the acquired immune deficiency syndrome (AIDS).

PATHOPHYSIOLOGY

The pathophysiology of malaria results from:

1. Destruction of erythrocytes.

2. Liberation of parasite and erythrocyte material into the circulation.

3. The host reaction to these events.

4. Sequestration in microcirculation of vital organs interfering with micro circulatory flow and host metabolism.

Malaria parasites induce release of cytokines during schizont rupture. A glycolipid material with many of the properties of bacterial endotoxin is released on schizont rupture.

This material appears to be associated with the glycosyl phosphatidyl inositol anchor which covalently links proteins including the malaria parasite surface antigens to the cell membrane lipid bilayer. The parasite products like endotoxin, induce activation of the cytokine cascade.

Cells of the macrophage - monocyte series and endothelium are stimulated to release cytokines. Initially tumor necrosis factor (TNF) and Interleukin - I (IL-1) are produced and these induce release of other pro-inflammatory cytokines including IL-6 then IL-8.

Cytokines arc responsible for many of the symptoms and signs of the infections particularly fever and malaise. Plasma concentrations of cytokines are elevated, measured by ELISA or indirect fluorescent anti body test (1RMA). There is a positive correlation between cytokine levels and prognosis in severe falciparum malaria. Whether this is a cause or an effect of severe malaria is yet to be decided-

SEQUESTRATION

The process whereby erythrocytes containing mature forms of P. Falciparum adhere to microvascular endothelium (cytoadherence) and thus disappear from the circulation is referred to as sequestration. Cytoadherence begins at the middle of the parasites 48-hr. asexual life cycle involving matured forms.[1'] Sequestration occurs predominantly in the venules of vital organs -greatest in the white matter of brain and prominent in the heart, liver, kidneys, intestines and adipose tissue and least in the skin.

Cytoadeherence and the related phenomenon of rosetting leads to microcirculatory obstruction leading to reduced oxygen and substrate supply resulting in anerobic glycolysis and lactic acidosis.

CYTOADHERENCE

Cytoadherence is mediated by a family of strain specific high molecular weight parasite derived proteins termed P. Falciparum erythrocyte membrane protein 1 orPFEMP1

This protein is anchored on the surface of RBC through accredition -which causes knobs on the surface of the red cell and these are attached to vascular endothelium. A protein similar to PFEMP1 called sequestrin has recently been identified on the surface of infected RBC.

Cytoadherence is also mediated by altered red cell membrane components and may be modulated by spleen.

Parasitised RBC's do not cytoadhere in splenectomised monkeys. occasionally patients who have had splenectomy developed falcipamm malaria, and in some of these cytoadherence does not occur and all stages of the parasite are seen in the peripheral blood smears.

In presence of a low pH of <7 and high calcium, CD36 - the leucocyte differentiation antigen protein which is present on vascular endothelium (except brain endothelium) and monocyte-macrophages favor cytoadherence. The intercellular adhesion molecule ICAM| (which is also the receptor for rhinovirus attachment) will also bind parasitised erythrocytes. This is up regulated by cytokines mainly TNF i.e. cytokine release enhance cytoadherence mainly in cerebral endothelium. The relative importance of the various potential vascular ligands in the pathophysiology of severe P. Falcipamm malaria and precise role of spleen remains to be determined,

As there is considerable variability in the cytoadherence determinants in both parasite and the host, severe malaria and the pattern of organ involvement may reflect the result of a particular host- parasite combination.

ROSETTING

Erythrocytes containing mature parasites also adhere to uninfected erythrocytes. This process leads to the formation of "Rosettes'.

Resetting shares some characteristics of cytoadherence. It occurs mainly at the middle of the asexual life cycle and it is trypsin sensitive. Unlike cytoadherence resetting is inhibited by certain heparin sub fractions and calcium chelators. Resetting in P. Falcuparum is associated with cerebral malaria and increased cytoadherence with other vital organ dysfunction.

It has been suggested that rosetting might encourage cytoadherence by reducing flow (shear rate) which would enhance anerobic glycolysis. reduce pH and facilitate adherence of infected RBC's to venular endothelium. The mechanical obstruction or static hindrance would be compounded by the lack of deformability of the adherent and circulating parasitised red cells.

As the parasite mature inside the erythrocyte, the normally flexible biconcave disc becomes progressively more spherical and rigid. The reduction in deformabilily results from reduced membrane fluidity, increasing sphericity and the enlarging and relatively rigid intra erythrocytic parasite.

Severe malaria e.g., cerebral malaria specific immune mediated damage is unlikely as there is no pathological evidence for vasculitis with a cellular infiltrate in or around the cerebral vessels.

Although some glomerular abnormalities have been noted in fatal malaria, the clinical and pathological findings indicate acute tubular necrosis and not glomerular nephritis is the cause of renal dysfunction.

The pathogenesis of pulmonary oedema/ARDS is uncertain. Recent evidence suggest a high permeability oedema secondary to microvascular dysfunction. The endothelial cells showed marked cytoplasmic swelling, dilated rough endoplasmic reticulum and swollen mitochondria. Macrophages containing phagocytized malarial pigment filled capillary lumens and infiltrated the interstitium TNF and interlcukin - 1 has been attributed to this.

Acute malaria infections are associated with malaria antigen specific unresponsiveness. This selective paresis is one of the factors contributing to the slow development of an effective and specific immune response in malaria.

Acute malaria is characterized by non specific polyclonal B - cell activation. There is a reduction in circulating T cells with an increase in the o/y T - cell subset but other T-cell proportions are usually normal.

Although residents of hyper endemic or holoendemic malarious areas have hyper gamma globulinemia most of this anti body is not directed against malaria antigens.

In non immune individuals, the acute anti body response to infection often comprises IgM or IgG2 isotypes which are unable to arm cytotoxic cells and thus kill asexual malaria parasites.

These observation suggested immunological basis with specific cellular immune response. In severe malaria there is evidence of a broader immune suppression with defects in monocyte and neutrophil chemotaxis. reduced monocytic phagocytic function and a tendency to bacterial super infection.

There is evidence of a mild generalised increase in systemic vascular permeability in severe malaria. It is now clear form imaging studies, in majority of cerebral malaria there is no cerebral oedema, if at all slight brain swelling is present it is because of an increased cerebral blood flow and hence volume, independent of permeability. This is due to considerable sequestration of microvasculature necessitating increased cerebral permission required for ischemic brain.

Coma

The cause of coma in cerebral malaria is not known. It is not caused by raised intracranial pressure. Low arterial oxygen content in cerebral blood flow with increased cerebral anaerobic glycolysis leading to accumulation of lactate may be one of the key factors. Severe hypoglycemia may be another contributing factor.

Presumably the metabolic milieu created adjacent to the sequestered and highly metabolically active parasites interferes with neuro transmission.Cytokines increase production of nitric oxide, a potent inhibitor of neuro transmission by leucocytes, smooth muscle cells, microglia and vascular endothelium through induction of, the enzyme nitric oxide synthase. Local synthesis of nitric oxide could well be relevant to the impairment of consciousness.

Renal failure

Two mechanisms are known in the pathogenesis:

Specific effect of parasitised erylhrocytes with haemorrhagic changes and non specific inflammatory and associated factors like –

1. Hypovolemia due to sweating, vomiting and diarrhoea,
2. Renal cortical vasoconstriction and consequent hypoperfusion due to Kinin release.
3. Renal micro vascular obstruction in glomeruli and tubule due to sequestration leading to acute tubular necrosis.
4. Massive haemolysis - leading to accumulation of malaria pigment and hemoglobin nephropathy as a consequence of Black Water Fever.
5. Intravascular coagulation, catecholamine effects, endotoxemia and jaundice Glomerulo nephritis is rare.

Black Water fever

Black water fever is the result of massive intravascular haemolysis and the passage of "Coca-cola" colored urine. Pathogenesis is poorly understood. It occurs in three circumstances;

1. When patients with G6PD deficiency take oxidant drugs irrespective of whether they have malaria or not.
2. Patients with G6PD deficiency having malaria and on quinine therapy.
3. Normal P. Falciparum patients treated with quinine.

G6PD deficient red cells are particularly susceptible to oxidant stress as they are unable to synthesize adequate quantities of NADPH through the pentose shunt. This leads to low intraerythrocytic levels of reduced glutathione and both alterations in the erythrocyte membrane and increased susceptibility to organic peroxides.

Fluid and electrolyte changes

Total body water and extra cellular volume are normal. Plasma renin activity, aldosterone and anti-diuretic hormone concentrations are elevated reflecting an appropriate activation of homeostatic mechanism to maintain adequate circulating volume in the presence of general vasodilatation and a falling haematocrit. Mild hyponatremia and hypochloraemia are common but serum potassium are usually normal.

Hematological profile

The pathogenesis of anemia is multifactorial. In severe malaria anemia develops rapidly due to accelerated destruction of non parasitized red cells, with the obligatory destruction of red cells containing parasites at merogony leading to severe decline in the haematocrit,

The haemolytic anemia is compounded by bone-marrow dysfunction. Dyserythropoiesis persist for days or weeks following acute malaria and reticulocyte counts are usually low in the acute phase of the diseases.

Although there is evidence of a lowered threshold for spleenic clearance of abnormal erythrocytes the factors that trigger removal of uninfected erythrocytes have not been identified. The role of antibody i.e. Coomb's positive haemolysis in anemia is unresolved.

There is accelerated coagulation cascade activity with accelerated fibrinogen turnover, consumption of antithrombin III. and increased concentrations of fibrin degradation products.

In severe infection the prothrombin and partial thromboplastin times are prolonged and in 5% of patients bleeding may be significant.

Thrombocytopenia is caused by increased spleenic clearance. The rote of platelet bound antibody in this process is not yet determined. Infected erythrocytes may activate the coagulation cascade - directly and cytokine release is also procoagulant and this is directly proportional to the disease severity.

Spleen

There is considerable spleenic enlargement in malaria and an increased capacity to clear red cells from the circulation both by Fc receptor mediated immune mechanisms and by recognition of reduced deformability.

The spleen may also modulate cytoadherence. It plays a central role in limiting the acute expansion of the malaria infection by removing parasitised erythrocytes and this has led to the suggestion that a failure to augment splenic clearance sufficiently rapidly may .be a factor in the development of severe malaria.

Liver dysfunction

Jaundice is common in falciparum malaria and there is evidence of hepatic dysfunction with reduced clotting factor synthesis, reduced metabolic clearance of anti malarial drugs and a failure of gluconeogenesis which contributes to lactic acidosis and hypoglycemia. Jaundice appears to have haemolytic, hepatilic and

cholestatic components. There is sequestration in the hepatic microvasculature and in severe malaria liver blood flow is reduced.

The degree of hepatic damage depends on the severity of falciparum infection. Recession of asexual parasite from peripheral circulation to the capillary blood vessels of liver for later stages of schizogony and adhesiveness of infected RBC's in relation to vascular endothelium cause - capillary blockade and ischemia.

Hyper bihrubinacmia results trom;

- Intravascular hemolysis of parasitised erythrocytes.
- Hepatic dysfunction.
- Micro angiopathic hemolysis associated with D1C.
- Liver function impairment associated with septicemia.
- Associated viral hepatitis.

Unconjugated bilirubinaemia is caused by haemolysis, conjugated bilirubin in hepatocyte dysfunction and cholestasis seen in black water fever.

GIT dysfunction

Gut sequestration and visceral vasoconstriction reduces splanchnic perfusion leading to malabsorption of sugars, fats and amino acids. There is increased gut permeability and reduced local defenses against bacterial toxins. Minor stress ulcerations of the stomach and duodenum is common. Antimalarial drug absorption is remarkably unaffected in uncomplicated malaria.

Metabolic dysfunction

In severe malaria arterial, capillary, venous and CSF concentrations of lactate rise in direct proportions lo disease severity. Venous lactate concentration 4 hrs. after admission lo hospital is the best prognostic indicator in severe malaria- lactic acidosis is an important cause of death. It is caused by;

1. Tissue anaerobic glycolysis consequent upon microvascular obstruction.
2. Failure of hepatic and renal lactate clearance.
3. Production of lactate by the parasite. Mature malaria parasites consume up to 70 times as much glucose as uninfected cells and over 90% of this is converted to L+ lactic acid as P. Falciparum do not have the necessary enzymes for citric acid cycle.
4. Lactate levels also rise after generalized convulsions due to release from Muscles,
5. Hyper lactemia is accompanied by hyperalaninemia reflecting the impairment of gluconeogenesis through the cori cycle.

Triglyceride and free fatty acid levels are also elevated and plasma concentration of ketone bodies arc raised in patients who have been unable to eat. in severe malaria there is dysfunction of all organ systems. Particularly those with obligatory high metabolic rates.

Pituitary

Thyroid axis abnormalities result in the sick euthyroid syndrome and parathyroid dysfunction. Mild hypocalcemia is common and hypophosphatemia may be profound. Pituitary - adrenal axis appears normal in acute malaria.

Hypoglycemia

Causes of hypoglycemia are;

- Increased utilisation of glucose (anaerobic glycolysis-the pasteur effect) by malaria parasite and increased metabolic demand of febrile illness.
- Reduced liver gluconeogenesis due to micro vascular obstruction and glycogenolysis (reduced supply)-
- Insulin release from pancreatic Islets by quinine or quinidine used in treatment.

Hyperinsulinemia is balanced by reduced tissue sensitivity to insulin which returns to normal as the patient improves. This probably explains why quinine induced hyperinsulinemic hypoglycemia tends to occur after the first 24hrs, of treatment, where as malaria related hypoglycemia (with appropriate suppression of insulin secretion) is .often present when the patient with severe malaria is first admitted. Hypoglycemia leads to nervous system dysfunction and in cerebral malaria causes residual neurological deficits in survivors.

Placental dysfunction

Pregnancy increases susceptibility to malaria. This is probably caused by a suppression of systemic and placental cell mediated immune response.

There is intense sequestration of P.Falciparum infected erythrocytes in the placenta and maternal anemia leading to placental insufficiency and foetal growth retardation-In areas of intense transmission low birth weight and a possible increase in the risk of still birth arc confined to primigravidae. With lower levels of transmission i.e. less immunity the risk extends to other pregnancies and there is a propensity to develop severe malaria with a high incidence of foetal death.

BACTERIAL INFECTION

Patients with severe malaria are vulnerable to bacterial infections. Particularly of the lungs and urinary tract (following catheterisation). Postpartum sepsis is common. Spontaneous gram negative septicemia occurs but rare.

PATHOLOGY

In Falciparum malaria the microvasculature of the vital organs is packed with erythrocytes containing mature form of the parasite. There is abundant intra and extra erythrocytic pigment and organs such as liver, spleen and placenta may be grey- black in colour. Sequestration is not uniformly distributed. It tends to be greatest in the brain and heart followed by the gut, kidney, adipose tissue, liver. lungs and least of all in bone marrow and skin.

BRAIN

The brain is swollen with multiple small petechial hemorrhages throughout the white matter. Hemorrhages are unusual in the grey matter. There is no evidence of tentorial or foramen magnum nemiation is seen- Nearly every capillary and venule is packed with erythrocytes containing mature forms of the parasite (where as these are rarely seen in peripheral smear). The sequestration is particularly prominent in the

white matter although the tissue is much less vascular than grey matter.

The degree of cerebral sequestration and the intensity of erythrocyte packing is greater in cerebral malaria than in fatal malaria in which the patient was not comatose. In the while matter accumulation of glial cells are seen surrounding hemorrhagic foci (Durck's granuloma) where vessels appear to have been occluded by a mass of parasitised ceils and then ruptured,

At the ultra structural level the erythrocytes are seen to be packed closely together and the infected red cells are adherent to the vascular endothelium by attachment of knob like surface projections to the endothelial surface.

Occasional fibrin strands are seen but there is a striking absence of platelets and no evidence for leucocytes aggregation i.e. there is no evidence of thrombus formation or vasculitis.

HEART AND LUNGS

Despite intense sequestration in the myocardial vasculature in heart is remarkably normal. In anemic patients it may be pale and dilated. Evidence of pulmonary oedema with hyaline membrane formation suggesting leakage of proteinaceous fluid may be seen. Moderate sequestration and leucocytes aggregation may be seen.

LIVER AND SPLEEN

Liver is enlarged and may be black due to malaria pigment. There is congestion of the centrilobular capillaries with sinusoidal dilatation and kupficr cell hyperplasia. Sequestration of parasitised erythrocytes is associated with variable cloudy swelling

of the hepatocytes and perivenous ischemic changes and sometime centrizonal necrosis.

Spleen is dark from malaria pigment, enlarged, soft and friable. It is full of erythrocytes containing mature and immature parasites. There is evidence of reticular hyperplasia and architectural reorganisation. The soft and acutely enlarged spleen of acute lethal infections contrasts with the hard fibrous enlargement associated with repeated malaria.

KIDNEY

Kidneys are slightly swollen. Tubular abnormalities are consistent with ischemia. There is sequestration in glomerular capillaries and sometimes mesangial and endothelial ce11 Proliferative changes are seen. Immuno fluorescent studies show immunoglobulin deposition on the glomerular capillary basement membranes.

ALIMENTARY TRACT

Upper GI bleeding from erosions may be seen. Intense sequestration in the gut and the visceral ischemia explain the acute abdomen. Despite this drug absorption is often remarkably normal.

BONE MARROW

Dyserythropoietic changes are prominent. Bone marrow macrophages contain pigment erythrophagocytosis and malaria parasites may be seen.

PLACENTA

May be black due to malaria pigment and a large number of mature parasites are seen although peripheral smear may be negative. There is often trophoblastic thickening, macrophage infiltration and perivillous fibrin deposition.

CLINICAL FEATURES

The clinical manifestation of falciparum malaria are dependeal on the previous immune status of the host. In areas of intense transmission asymptomatic parasitemia is usual in adults due to premunition (partial immunity). The incubation period depends on previous immunity status of the individual - effective immunity both reduces effective multiplication which prolongs the incubation period. The incubation period is 9-14 days, the average being 12 days,

The clinical picture of falciparum malaria is variable from mild to severe leading to death. The severity depends on the quantum of parasitemia, the patient's state of immunity and also .the presence of concomitant conditions such as malnutrition, diabetes mellitus or other diseases which compromise immunity. The high risk individuals are immunocompromised pregnant women and children. The duration of incubation period may be prolonged by prophylaxis which may be inadequate to destroy developing parasites. The prodromal symptoms are malaise, anorexia, lassitude, body- aches, headache, vague abdominal discomfort; vomiting, lethargy and dysphoria often precede fever by two days.

Malaria may mimic any febrile illness. The primary fever in the beginning is usually irregular but may be continuous before the classical 48 hrs. Periodicity becomes established. The paroxysms are not regular as in vivax malaria. The typical

attack may have three distinct stages provided the patient has not consumed antipyretic drugs. these are the cold stage, hot stage and sweating stage .these stages are however seen less frequently now days

The cold stage - The prodromal symptoms after some time are followed by rigors, which at times can be very severe. The fever rises quickly to 39-41°C (102 to !06°F) accompanied by an appropriate rise in pulse rate. Headache may be quite severe. Parasites are usually seen in the blood. It is followed in half to two hour's lime by hot stage.

HOT STAGE

The patient now feels warmth and the skin is hot and dry to touch. Headache can still be quite intense. This stage lasts for half to six hrs.

THE SWEATING STAGE

Profuse sweating occurs and the temperature rapidly comes down to normal or subnormal level. The skin feels cold and moist. The patient becomes comfortable.

After the primary attack of fever, there is often an interval of 48-72hrs. And then other attacks similar to the first occur and each attack is followed by afebrile period of 4S-72 hrs. But in non immune or partially immune persons within 24 hrs. The patient may become severely ill with delirium or coma. The classical malaria fever charts like tertian i.e. fever recurring every third day described in earlier days of 20th century, the rigors and profuse sweating that characterizes the paroxysms are relatively unusual today because of rapid therapy.

Hepatospleenomegaly occurs associated with hemolytic anemia and Jaundice. Acute abdomen or abdominal discomfort associated with constipation or diarrhea may occur, in pregnancy there is increased risk of falciparum malaria during second and third trimester. It may be asymptomatic in immune with severe anemia leading to low birth weight babies. In non immune fetal loss is common and maternal mortality is high. Acute pulmonary oedema and hypoglycemia are usual complications- The mortality *of* cerebral malaria in pregnancy is approximately 50% compared to 20% in non pregnant adults because of altered or reduced immunity.

SEVERE MALARIA

The following definition of severe falciparum malaria has been proposed by a working group convened by the World Health Organisation (WHO). '

• Cerebral malaria - Unarousable coma not attributable to any other cause in a patient with falciparum malaria. The coma should persist for atleast 30 min- after a generalised convulsion 10 make the distinction from transient postictal coma.

• Severe anemia - Normocytic anemia with haematocrit < 15% or haemoglobin < 5gm% in the presence of parasitemia >]0.000/ul.. If anemia is microcytic and hypochromic. iron deficiency and thalassemia or haemoglobinopathy must be excluded. A parasitemia of > 10.000/uL is diagnostic.

• Renal failure - defined as a urine out put of< 400ml in 24 hrs. in adults or 12 ml/kg in 24 hrs. in children, failing to improve after rehydration, and serum creatinine of>265 umol/L (>3mg%).

• Pulmonary edema or adult respiratory distress syndrome (ARDS).

• Hypoglycemia - defined as a whole blood glucose concentration of <2.2mmol/L (40mg %)

• Circulatory collapse or shock - hypotension (systolic blood pressure < 50 mm Hg in children 1-5 yrs. or <70mmHg in adults) with cold clammy skin or core-skin temperature difference of>10° C.

• Spontaneous bleeding from gums, nose and gastrointestinal tract etc. and or substantial laboratory evidence of disseminated intravascular Coagulation (DIC).

• Repeated convulsions more than 2 observed with in 24hrs-dcspitc cooling of fever.

• Acidemia - defined as an arterial pH <7, 25 or acidosis defined as a plasma bicarbonate concentration <15mmol/L.

• Macroscopic haemoglobinuria - if definitely associated with acute malaria infection and not merely the result of oxidant anti malarial drugs in patients with erythrocyte enzyme defects e.g., G6 PD deficiency,

• Postmortem confirmation *of* diagnosis - in fatal cases by histological examination of needle necropsy of the brain.

The characteristic features found especially in cerebral grey mailer are venules or capillaries packed with erythrocytes containing mature trophozoites and schizonts of P. Falciparum.

One or more of the above features in the presence of asexual parasitemia defines severe malaria- Other manifestations of severe malaria which (according to WHO document) do not in themselves define the condition in all geographical areas and age groups include the following –

• Impairment of consciousness less marked than unarousable coma.

• Prostration or weakness, so that the patient cannot sit or walk with no obvious neurological explanation.

• Hyperparasitemia - the relation of parasitemia to severity of illness is different in different populations and age groups. But in general very high parasite densities are associated with increased risk of severe diseases e.g., >5% parasitemia is dangerous in non immunes. Most authorities would regard a parasitemia of > 10% as indicating a potentially dangerous infection irrespective of the other features.

• Jaundice - detected clinically or defined by a serum bilirubin concentration > 50 (imol/L (3 mg%).

• Hyperpyrexia - rectal temperature > 40°C (sustained hyperpyrexia in severe malaria indicates a poor prognosis).

In severe malaria there is often evidence of multiple organ dysfunction and more than one of the above criteria arc fulfilled.

CEREBRAL MALARIA

Defined as unarousable coma i.e. there is non purposeful response or no response to a painful stimulus or altered sensorium- The onset of coma may be sudden often following a generalized seizure or gradual with initial drowsiness, confusion, disorientation, delirium or agitation followed by unconsciousness.

On examination the patient is febrile, unarousable with or without signs of meningitis like neck rigidity. Anemia, Jaundice and hepatosplenomegaly will be there-

The clinical features are usually of symmetrical encephalopathy. Focal signs are unusual. Papilledoema is rare ^1%) but retinal haemorrhages seen in 15% of cases. The haemorrhages are often flame shaped and may have a pale centre

resembling the Roth spots, Bruxism - forced jaw closure with repetitive spontaneous teeth grinding. Brisk Jaw Jerk and a Pout reflex may be present. Other frontal release signs are unusual. Cranial nerves abnormalities are rare. Deep tendon reflexes are brisk and absent abdominal reflexes. Patient may exhibit phasic increase in tone with extensor posturing of the decorticate (arm flexed and legs extended) or decerebrate (arms & legs extended) type rigidity.

Untreated malaria is uniformly fatal, and 20% mortality in treated patients and up to 50% mortality in pregnancy.

Bad prognostic signs are:

- Longer history of coma. and delayed diagnosis.
- Absence of cornea! reflex.
- Decerebrate rigidity,
- Extreme agitation.
- Signs of bleeding (DIC).
- Sustained hyperventilation due to metabolic acidosis : (chest infection or ARDS).
- Generalized or recurrent seizures.

POST MALARIA NEUROLOGICAL SYNDROME

Three percent of adult patients develop late neurological sequelae. It may be due to profound and protracted coma, severe anemia, hypoglycemia and prolonged convulsions. Hemiparesis with variable hemisensory deficit and sometimes hemianopia may be seen. Cortical blindness, diffuse cortical damage, tremor and occasionally cranial nerve patsies seen. There may be residual global encephalopathy like picture due to prolonged hypoglycemia. Psychosis, tremor and cerebellar dysfunction may be seen attributed to treatment with chioroquine or mcHoquine and are usually self limiting. The syndrome of cerebellar ataxia occuring 2-3 weeks after acute uncomplicated malaria has been reported.

Dr. Dhamija's neurological classification of clinical features,

Acute

Asymptomatic

Cerebral Disorders	Acute febrile encephalopathy including coma. cranial nerve palsies. Pyramidal spastic Hemiplegia, Paraplegia
Spinal disorders	Myelitides like - amyotophic lateral sclerosis. Spastic spinal paralysis, Tabes dorsalis like syndrome
Disorders of the peripheral nervous	Neuritis. Polyneuritis, Guillians Barre s syndromes like picture
Acute psychiatric manifestation	Neurasthenic syndrome, Malaria psychosis

Combined syndrome (CerebraL/spinal)	Disseminated encephalomyelitis
Late Sequelae	Epileptic attacks, Extrapyramidal disorders tike dyskinesia. chorea and Parkinson's syndromes. Multiple sclerosis like picture. Cerebellar ataxia and psychatric disorders.

RENAL MANIFESTATION

Acute renal failure

Acute oliguric renal failure associated with vital organ dysfunction may be the presenting feature or evident once the patient recovering from acute illness. Hepatic dysfunction, metabolic acidosis and pulmonary oedema is the usual terminal event. Uraemia with raised creatine and urea level is associated with complications like bleeding, pleural or pericardial effusion and hyperkalaemia requires urgent dialysis. Renal failure may be associated with haemoglobinuria in patients with black water fever.

Black water fever

Associated with high mortality upto 30% in the first half of this century and was described the disease with "Blanch [he check of the bravest". Today the mortality is much low due to early intervention. The passage of black or dark brown red urine (black water or cocacola colour) is often associated with significant renal impairment. It results from massive haemolysis. Patients with black water fever and severe anemia often have a slate grey appearance and their plasma may be red (haemoglobinemia),

RESPIRATORY MANIFESTATION

Hyper ventilation or Kussmaul's breathing is a poor prognostic sign. This may be due to metabolic acidosis resulting from renal failure, aspiration pneumonia in a comatose patient or ARDS. The pulmonary artery occlusion pressure and central venous pressure w.ill be normal (unless patient is over hydrated causing volume overload leading lo pulmonary oedema with decompensate heart) Chest radiograph shows increased interstitial shadow with a normal heart rate,

ALGID MALARIA

In severe falciparum sudden hypotension leads to hypovoluemic shock. It may or may not be associated with septicemia. Orthostatic hypotension i[1]-common in uncomplicated malaria is associated with reflex cardio acceleration and is worsened by the quinine anti malarial Drugs.

HYPOGLYCEMIA

It is either asymptomatic in severely ill patients or presents as a further deterioration in the level of coma. Hypoglycemia occurs in approximately 8% of adults with cerebral malaria in severe malaria the usual signs of sweating and increased sympathetic nervous system activity are commonly absent or indistinguishable from the signs of malaria. The clinical response to glucose is ussally unimpressive. But the hypoglycemia can be prevented by intravenous dextrose infusion.

ANEMIA

The degree of anemia and the rate at which it develops varies enormously. The hemoglobin concentration may fall by upto 2 gm%.

Patients with chronic anemia tolerate well and have adopted to increased oxygen carriage (right shift of oxygen dissociation curve). Acute anemia is fatal as it may precipitate cardiac failure and anoxic encephalopathy.

As patients are vulnerable to bacterial infections of the lungs and urinary tract (Catheterisation) spontaneous gram negative septicemia is an anticipated problem during hospitalization.

LABORATORY DIAGNOSIS

Malaria is diagnosed by microscopic examination of the blood for the evidence of falciparum parasites. Peripheral smear of capillaries or venous blood are usually tested. In difficult to diagnose situation intradermal blood and/or bone marrow smear are useful. Liver or spleenic biopsies or inj. Nor epinephrine subcutaneous and blood smear after half an hour due to spleenic contraction may yield positive results.

For routine peripheral smear thick and thin smears are done, thick, film for parasite identification and thin film for parasite counting and stage identification, the smears arc stained lieshmania or giemsa or field's stain.

Density of parasitemia is measured in thick film by counting number of parasites and number of leucocytes in each filed and using - total leucocytes count to number of parasites per cubic nun.

GRADING

1 - 10-MP	100 fields	+
10-100-MP	100 fields.	++
1-10-MP	One field	++•
10-100-MP	' One field	++•

Intensity of infection is measured in thin films i.e., percentage of RBC. Parasitised / 1000 RBC's (10-100%).

Parasite index (PI): Number of parasites per 1000 RBC's e.g. one field 100 RBC's then 10 fields 1000 RBC's are studied.

For 1000 RBC's number of parasites says for example 40 then the percentage is 4.

The number of paratised Red cells per 100 RBC's / 1000 should be counted. If there are two parasites in one red cell, this is counted as one- At low parasiteinia (<5/1000 on the thin film) the thick film should be counted. The numbers of parasites per 500 white cells are counted. The figures are corrected by the total red cell and white cell counts to give the number of parasites per unit blood volume (fiL).

If parasitemia is high the stage of parasite development should be assessed on the thin Him. The proportion of asexual parasites containing visible pigment ie. mature trophozoites and schizonts should be counted The presence of pigments in neutrophil and monocytcs are also noted. In patients who are already on treatment but the pigment may still be present in leucocytes after clearance of parasilcmia giving an important clue to the diagnosis. Monocytes containing pigment are cleared more slowly than pigment containing in neutrophils.

OTHER TECHNIQUES

- Fluorescent dye acridine orange staining of malaria parasites (which contain DNA and RNA)'and visualizing them under ultraviolet light microscopic after collecting blood in specialized capillary tubes for testing.
- Detection of monoclonal antibody against P. Falciparum histidine rich protein 2 by a rapid and simple stick lest.
- Quantitative buffy coat.

QUANTITATIVE BUFFY COAT

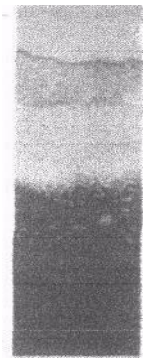
The QBC Test, developed by Becton and Dickenson inc.. is a new method for identifying the malarial parasite in the peripheral blood. It involves staining of the centrifuged and compressed red cell layer with acridine orange and its examination under UV light source. It is fast, easy and claimed to be more sensitive than the traditional thick smear examination.

METHOD

The QBC tube is a high-precision glass hematocrit tube, pre-coated internally with acridinc orange stain and potassium oxalate. It is filled with 55-65 microliters of blood from a finger, ear or heel puncture. A clear plastic closure is then attached. A precisely made cylindrical float, designed to be suspended in the packed red blood cells, is inserted. The tube is centrifuged at i 2,000 rpm for 5 minutes- The components of the buffy coat separate according to their densities, forming discrete bands. Because the float occupies 90% of the internal lumen of the tube, the leukocyte and the thrombocyte cell band widths and the lop-mosi area of red cells are enlarged to 10 limes normal. The QBC tube is placed on the lube holder and examined using a

standard white light microscope equipped with (he UV microscope adapter, an epi-illuminaled microscope objective- Fluorescing parasites are then observed at the red blood cell/while blood ceil interface.

Fig No. II: The QBC Tube



« Platelets

« Lymphocytes/ monocytes

« Granulocytes

« Red Blood Cells

The key feature of the method is centrifugation and thereby concentration of the red blood cells in a predictable area of the QBC tube, making detection easy and fast. Red cells containing Plasmodia are less dense than normal ones and concentrate just below the leckocytes, at the top of the erythrocyte column. The float forces all the surrounding red cells into the 40 micron space between its outside circumference and the inside of the tube. Since the parasites contain DNA which takes up the acridine orange stain, they appear as bright speacks of light among the non-fluorescing red cells. Virtually all of the parasites found in the 60 microliter of blood can be visualized by rotating the tube under the microscope. A negative test can be reported within one minute and positive result within minutes.

COMPARISON BETWEEN PERIPHERAL SMEAR AND QBC TEST FOR DETECTING MALARIA

	Peripheral smear	**QBC**
Method	Combersome	Easy
Time	Longer, 60 – 120 minutes	Faster, 15 0 30 minutes
Sensitivity	5 parasites/ul in thick film and 200/ ul in thin film	Claimed to be more sensitive, at least as good as a thick film
Specificity	Gold standard	? False positives, artifacts may be reported as positive by not-so-well-trained technicians
Species identification	Accurate, gold standard	Difficult to impossible
Cost	Inexpensive	Costly equipment and consumables
Acceptability	100%	Not so
Availability	Everywhere	Limited
Other	- -	Accidentally can detect filarial worms

MORPHOLOGICAL CHARACTERISTIC OF P. FALCIPARUM

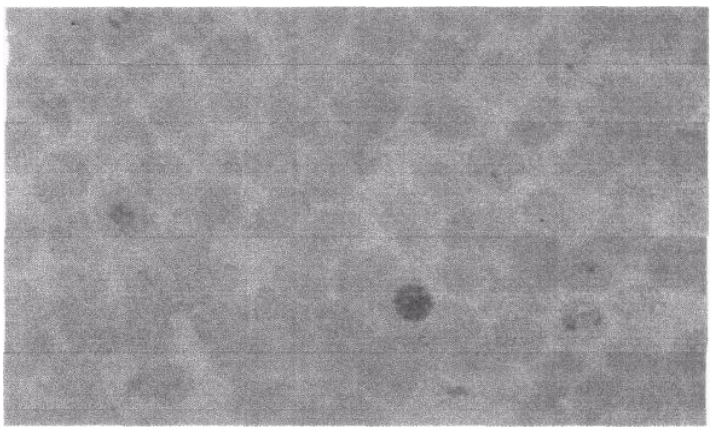


Fig No. DI: Bloodsmear of a P.falciparum culture (Kl strain). Ring stages, Schizont in the lower center, Trophozoite on the left.

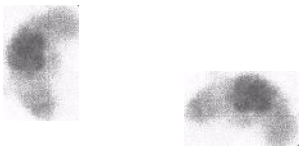


Fig No. IV: Two gametocytes captured from a thick blood smear.

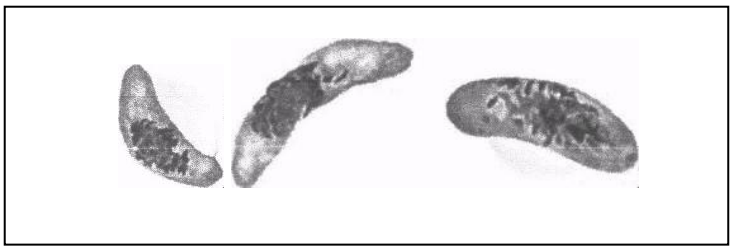


Fig No. V; VI: Mature macrogametocytes (female); Figs. VII; VIII: Mature microgametocytes. (male)

Asexual parasite	Usually ring froms seen. Fine blue cytoplasm ovel, circular, comma shaped with 1-2 chromatin dots. Parasitemia may exceed more than 2%
Merons	Rare in peripheral blood 8-32 merozoites with dark brown – black pigment.
Garmetocytes	Banana shaped male (light blue) female (dark blue) red black mucleus with few scattered blue black pigment granules in cytoplasm.
Red cell changes	Normal size. As parasites matures cytoplasm becomes pale, the cells become created and few small red dots appear over cytoplasm (Maurer' s cleft)

BLOOD PICTURE

Normo choromic normocytic anemia.

Total leucocyte count is normal or increased in servere malaria with occassionally leucoerythroblastic picture.

Monocytosis with eosinopenia with reactive eosinophilia in the weeks following the acute infection.

Thrombocytopenia with fibronogen and fibrin degradation products are increased. A reduction of fibrinogen usally indicate disseminated intravascular coagulation. There is evidence of increased coagulation cascade activity through intrinsic pathway activation with antithrombin III depletion i.e., proportional to disease severity.

- Prothrombin time and partial thromboplastin times arc prolonged.
- Polymorphonuclear leucoelastase levels are elevated in severe infraction suggesting neutrophil activation.
- The C-reactive protein, oroso mucoid (al-acid gtycoprolein) and fibrinogen levels are raised- While albumin level falls immuno globulin and cytokine levels are raised.

Blood urea and serum creatmine may be raised with an increased urea to crcalinmc ratio. Total and conjugated bilirubin, Iransaminases and aikaline phosphatase levels are usually elevated depending upon the severity. Creatinine phosphokmase, myogiobin and plasma urate levels are of raised. Low serum calcium and phosphorous levels arc seen. Hypoglycemia is usually evident and profound in patients with quinine theraphy. In the absence oftheraphy there may be associated elevation of ketones. laceates and alanine levels with hypoinsulinemia. Hyponatremia with normal potassium are seen normally. Bicarbonate levels are reduced and the anion gap widens in proportion to the acidosis. Urine shows hemogiobinuria and traces of albumin.

Cerebrospinal fluid (CSF)

Usually normal but moderately raised proteins and lymphocytes may be seen. The lactate concentration is raised proportional to ihc disease severity.

Features indicating a poor prognosis on admission

Clinical - agitation, hyperventilation, hypothermia (<36.5°C), hypotension (shock) sustained hyperthermia (>39 °C), bleeding, severe anemia (<15%), deep coma, convulsion, Anuria. deep jaundice and signs of hepatocellular failure.

METHODOLOGY

The clinical diagnosis of P. falciparum Malaria is suspected and followed the Manson - Bahr's criteria viz;

TYPE OF STUDY

Cross sectional study. Study Period

october 2009 to September 2011.

Place of study Shri. B.M.Patil Medical

College and Hospital,Bijapur

SOURCE OF DATA

All patients of P. falciparum Malaria with typical presentation with fever, chills, rigors, headache and atypical presentations like altered sensorium, seizure, hepatic encephalopathy, adult respiratory distress syndrome (ARDS), acute renal failure/black water fever, acute abdomen or algid malaria who are proved "Smear positive" either by peripheral blood picture or by quantitative buffy coat (QBC) examination-Sample Size

A total number of 100 (hundred) patients who are proved "Smear positive" for P. falciparum are studied.

SAMPLE SIZE CALCULATION

It is expected to consider a sample of 83 malaria patients for the desired conclusion at 10% allowable error with 0.21% incident rate of p.falciparum malaria in general population(according to API TEXTBOOK OF MEDICINE 8^{TH} EDITION)

INCLUSION CRITERIA

All adults' patients who had a positive blood smear for P. Falciparum Malaria or quantitative buffy coat (qbc) in Shri. B.M.Patil Medical College and Hospital,Bijapur are included.

EXCLUSION CRITERIA

- Pediatric patients
- Patients who are peripheral smear negative but treated with anti malarial drugs (so called clinical Malaria).
- Other malarias (plasmodium vivax, plasmodium ovale, plasmodium malariae) Diabetes mellitus, CRF, chronic liver disease, RHD, coronary artery disease, infections like pneumonia, UTI, viral hepatitis, pregnancy.

STATISTICAL ANALYSIS:

Data will be analyzed using following statistical methods

1. Diagrammatic presentation
2. Mean $\pm$ SD percentage
3. Proper Statistical tests
    a) T test
    b) X^2 test (If necessary)

METHODS OF COLLECTION OF DATA

A prospective study has been undertaken in general ward of shri B.M.Patil medical college Hospital and this includes all the consecutive adult patients. A smear positive uncomplicated, complicated and severe falciparum malaria admitted to dept of medicine from October 2009-september 2011.the method of severity score will be done according to following scoring system.

Criteria for diagnosis of organ dysfunction in malaria

Criteria	Parameters
a) General	1) Fever>101 F
	2) Presence of asexual form of P. falciparum
b) Specific organ system	parameters for defining dysfunction
1. Neurogenic	a) Glasgowcoma scale>13
2. Renal (one or more)	a) Urine output <750ml/24hr
	b) Serum creatinine 1.2mg/dl
	c) Blood urea>36.0mg/dl
3 Hepatic	a) Serum bilirubin>2.0mg/dl
4. Respiratory	a) Respiratory rate>30/min
5. Cardiac (one or more)	a) Systolic blood pressure<90mm hg
	b) Heart rate>120beats/mm
6. Metabolic	a) Blood glucose<60mg/min
7. Heamatological (one or more)	a) Heamoglobin<10gm/dl
	b) Platelet count<80000/microlit
	c) Total leucocyte count<4000 or >12000/microlit

RANGE OF VARIABLES TO ASSESS THE LEVEL SEVERITY OF ORGAN DYSFUNCTION IN MALARIA

Parameters of organ dysfunction	level-0	level-I	level-II	level-III
1. Neurologic GCS score	14-15	10-13	7-9	0--6
2. Renal Blood. urea Serum. creatinine Urine output	10-36mg/dl 0.6-1.2 mg/dl 750-3900 ml/24hrs	37-59mg/dl 1.3-1.9mg/dl 500-750 ml/24hrs	60-119mg/dl 2.0-4.9mg/dl 400--500 ml/24hrs	>120mg/dl >5.0mg/dl <500ml/24hrs
3 Cardiovascular heart rate/min systolic blood pressure	51-119/min 90-160mmhg	120-139/min 70-90mmhg	>140or<51/min 1-70 mmhg	
4. Respiratory respiratory rate	20-30/min	31-40/mi	>41/min	
5. Hematologic Hb TLC Platelet	10-13.9gm/dl 4001-16000/microlit 80000-250000/microlit	7-9.9gm/dl 2001-400/microlit <80000/microlit	<7 gm/dl <2000/microlit	
6 Hepatic Serum. bilirubin	<2.0mg/dl	> 2.0mg/dl		
7 Metabolic Blood glucose	60-110mg/min	< 60mg/min		

MALARIA SEVERITY SCORES OF EACH ORGAN DYSFUNCTION WITH DIFFERENT LEVEL OF SEVERITY.

Organ dysfunction	Level of Severity			
and score	0	I	II	III
Neurologic	Score – 0	Score – 1	Score – 3	Score – 5
Renal	Score – 0	Score – 1	Score – 3	Score – 5
Cardiovascular	Score – 0	Score – 1	Score – 3	Score – X
Respiratory	Score – 0	Score – 1	Score – 3	Score – X
Hematologic	Score – 0	Score – 1	Score – 3	Score - X
Hepatic	Score – 0	Score – 1	X	X
Metabolic	Score – 0	Score – 1	X	X

MALARIA SEVERITY SCORE AND PROBABILITY OF MORTALITY

Severity of Malaria Score	Probability of Mortality
0	1.2
1	3.1
2	4.8
3	7.5
4	10.5
5	12
6	21.1
7	31.1
8	40.1

9	51.8
10	61.7
11	70.8
12	81.8
13	88.8
14	92
15	94.6
16	96.1
17	97.2
18	98.5
19	99.2
20	99.5
21	99.7

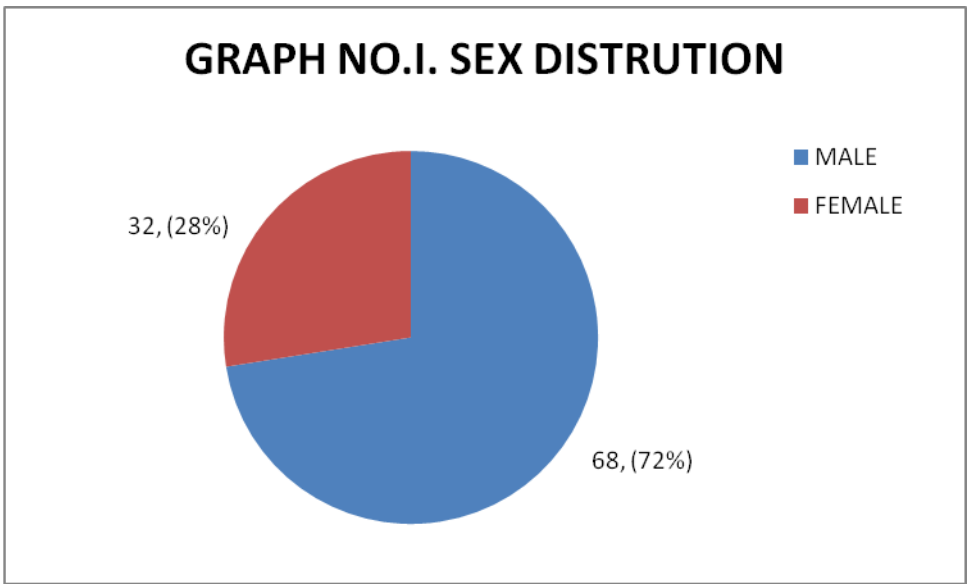
RESULTS

BLDE University's Shri B.M.Patil Medical College, Bijapur. During the prospective study period. Between October 2009 to September 2011, 100 patients who are proved parasitiologically positive for P Falciparum were studied and following observation were made.

TABLE NO.I: SEX DISTRUBUTION

Male	**Female**	**Total**
68	32	100

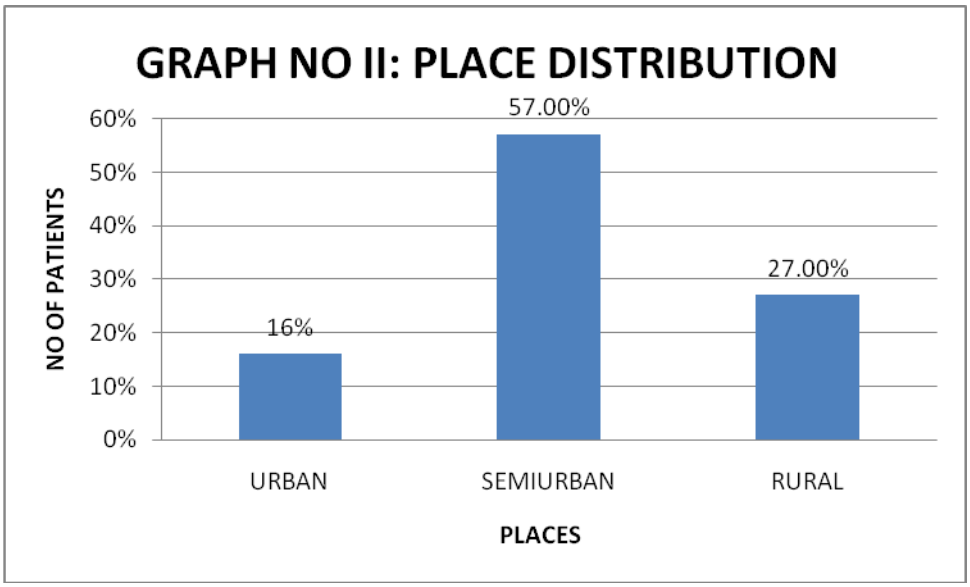
M: F = 2.7.:1



Incidence is 2.7 times more in male population than females in this study.

TABLE NO. II: PLACE DISTRIBUTION

Urban	Semi urban	Rural	Total
16	57	27	100
16%	57%	27%	100%



Of the 100 patients more than half came from semi urben background and the least from the urban background.

TABLE NO. III: AGE DUSTRIBUTION

Age	No.of patients	Percentage
12-20	22	22%
21-30	20	20%
31-40	20	20%
41-50	20	20%
51-60	12	12%
61-70	3	3%
71-80	3	3%
Total	100	100%

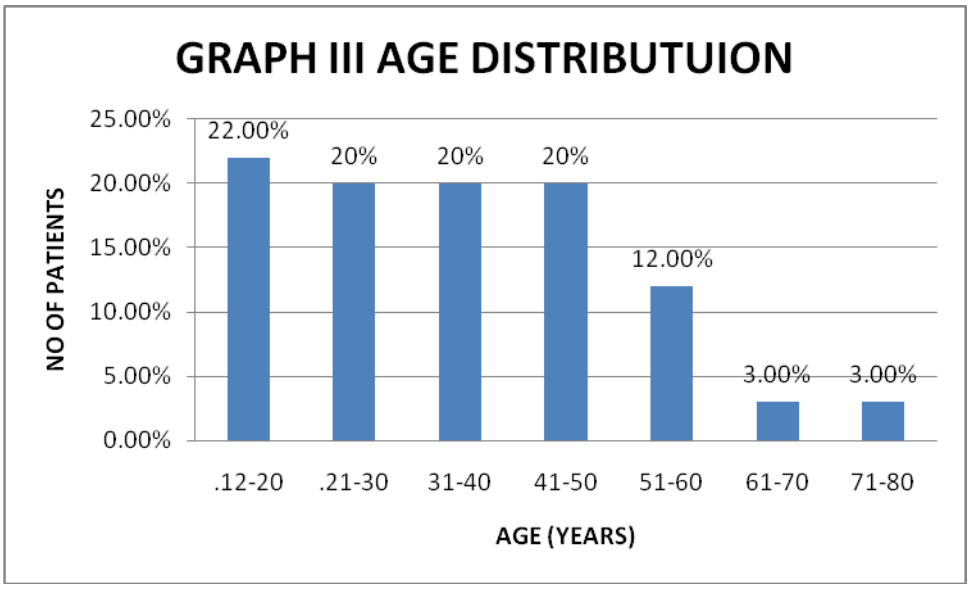
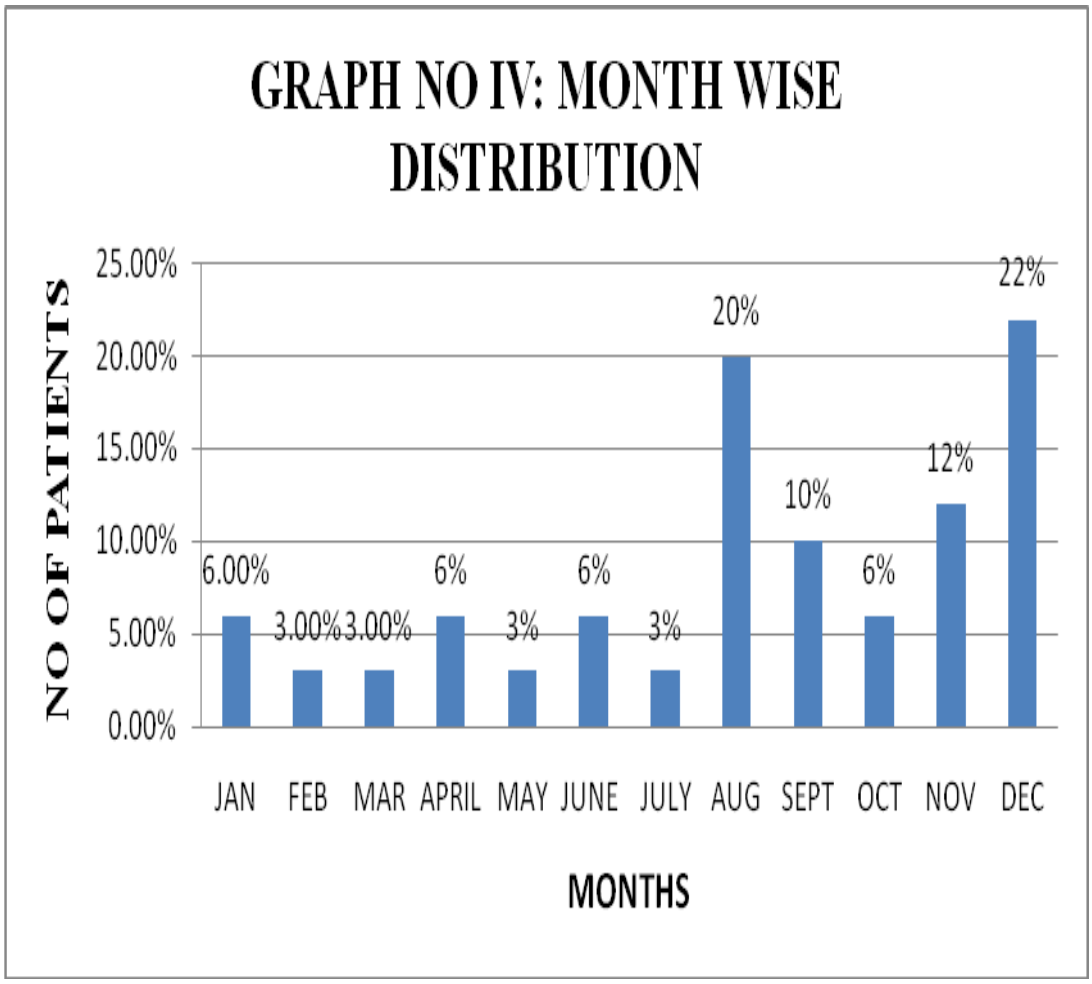


TABLE NO. IV: MONTH – WISE DISTRIBUTION

Month	**No of Patients**	**Percentage**
Jan	6	6%
Feb	3	3%
Mar	3	3%
April	6	6%
May	3	3%
June	6	6%
July	3	3%
Aug	20	20%
Sept	10	10%
Oct	6	6%
Nov	12	12%
Dec	22	22%
Total	100	100%



As is evident from the chart most of the cases are seen in the period between August to December, the humid, warn monsoon months of the year.

TABLE NO. V: OCCUPATIONAL DISTRIBUTION

Occupation	**No. of Patients**	**Percentage**
House wife	20	20.0%
Businessman	7	7%
Professionals	6	6%
Students	6	6%
Politicians	2	2%
Farmers	32	32%
Manual labourers	27	27%
Total	100	100%

Economic Status

24 patients belonged to lower socio economic strata (60%) while 16 patients belonged to higher socio economic strata (40%)

P. Falciparum malaria is seen in all class of population. The incidence is slightly higher (60%) in lower social economic status.

TABLE NO.VI: PERCENTAGE OF BLOOD GROUP DISTRIBUTION

Group	Number of Patients	Percentage
A positive	37	37%
B positive	25	25%
AB Positive	12	12%
O positive	20	20%
B Negative	3	3%
O Negative	3	3%
A Negative	00	00.0%
Total	100	100%

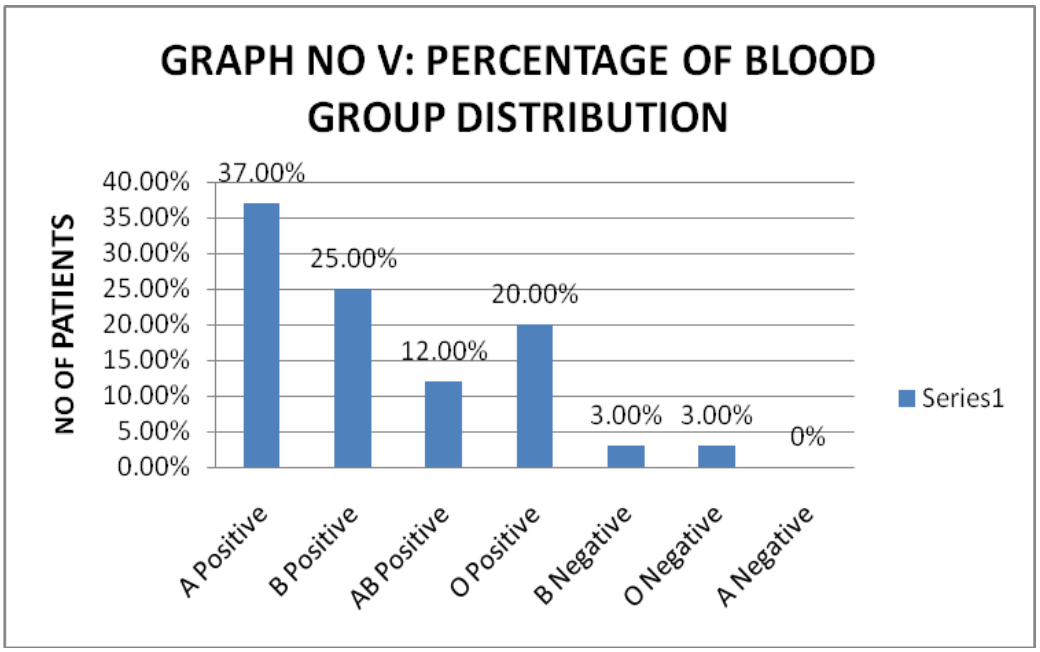
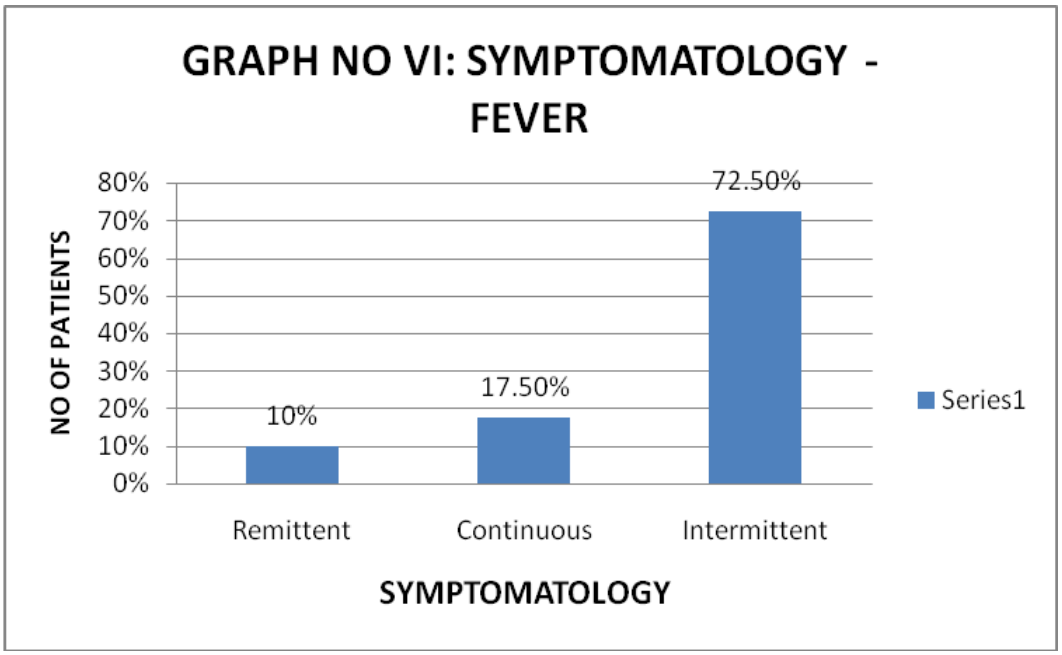


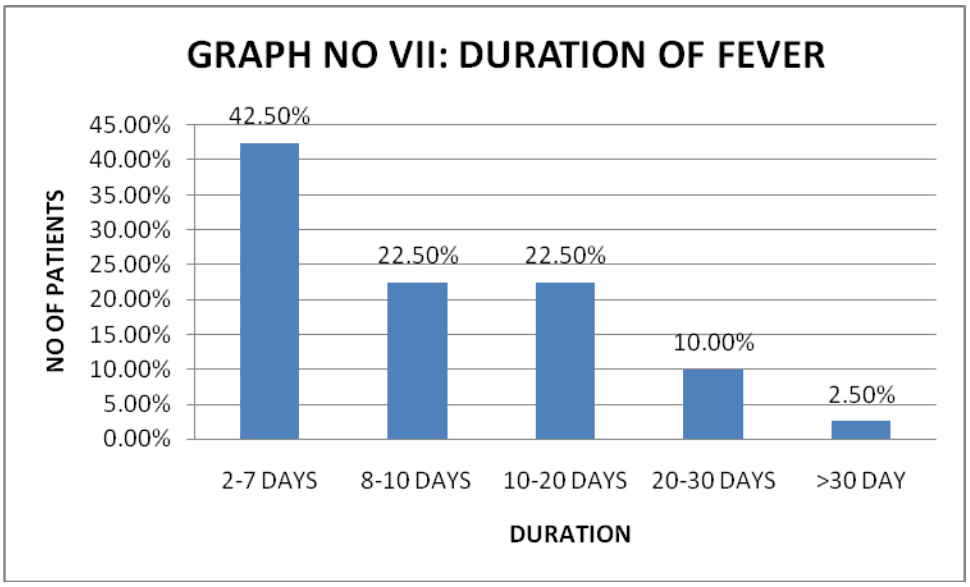
TABLE NO. VII: SYMPTOMATOLOGY

Fever		
Remittent	**Continuous**	**Intermittent**
4 (10%)	7 (17.5%)	29 (72.5%)
Fever duration	**No.of Patients**	**Percentage**
2-7 days	17	42.5%
8-10 days	9	22.5%
10-20 days	9	22.5%
20-30 days	4	10.0%
>30 days	1	2.5%
Headache	**No. of Patients**	**Percentage**
Continuous	3	7.5%
No Headache	7	17.5%
Intermittent	30	75%
Constitutional Symptoms	**No. of patients**	**Percentage**
Generalized weakness and nausea	39	97.5%
Anorexia	38	95%

Nausea/ vomiting	36	90%
Mental status		
Normal	16	40%
Delirium	21	52.5%
Unconscious	3	7.5%

Other associated symptoms – on admission		
Symptoms	**No. of patients**	**Percentage**
Oliguria	18	45%
Cough	15	37.5%
Diarrhoca	11	27.5%
Jaundice	05	12.5%
Acute abdomen	4	10.0%
Dyspnoca	3	7.5%
Bleeding tendency	3	7.5%





Fever was intermittent in 72.5% of the cases, continuous in 17.5% of the cases and remittent in the remaining 10% intermittent fever is the commonest. 72.5% patients had chills and rigors. 27.5% patients had only chills and no rigors. Most of the patients (65%) had presented with acute illness of 2 – 10 day duration of fever. Shortest duration was 2 days and the longest duration was 90 days in this study. 75%

of patients had presented with history of bifrontal dull aching to throbbing headache associated with fever. Three (7.5%) patients complained of continuous headache while 17.5% patients presented without H/o headache. Most of the patients complained of generalized weakness, malaise and anorexia. In one patient history was not available because he was brought in a state of unconsciousness. History of nausea and vomiting was evident in 90% cases. 60% of patients are presented with altered sensorium of which, in 52.5% patients the presenting feature was delirium and 7.5% patients presented with unconsciousness. Generalized convulsions were seen in 2 patients (5%) – as the presenting symptom associated with altered sensorium. Cough was initial manifestation associated with fever in 37.5% and and was associated with dyspnoea in 7.5 patients on admission. 10% of patients were admitted under surgery with H/o acute abdomen and later transferred to medical side once the diagnosis of P. falciparum was made after ruling out all other surgical conditions. Diarrhea of moderate quantity, 6-8 times per day, associated with diffuse pain abdomen was the presenting symptom in 27.5% of the patients. Jaundice was the presenting feature of 12.5% patients, while bleeding tendency was seen in 7.5%, (2.5%) patients. Of these patient ha malaena, (2.5%) patient had haematemesis and one patient had purpura (2.5%) H/o high colored urine with oliguria was noted in 45% of patients while 55% patients had normal urine on presentation.

TABLE NO. VIII

Sign	No. of Patients	Percentage
Nutritional status		
Poorly nourished	11	27.5%
Well nourished	29	72.5%
Severe anemia	23	57.5%
Icterus	17	42.5%
Central cyanosis	1	2.5%
CNS Manifestation		
Delirium (Disoriented, incoherent)	21	52.5%
Deep tendon jerks sluggish & plantars extensor	18	45%
Meningeal signs positive	16	40%
Unconsciousness	3	7.5%
Flapping tremor	1	2.5%
ARDS	6	15%
Hepatomegaly	26	65%
Splenomegaly	27	67.5%
Acute abdomen	4	10%
Bleeding tendencies		
Epistaxis	1	2.5%
Purpura	1	2.5%

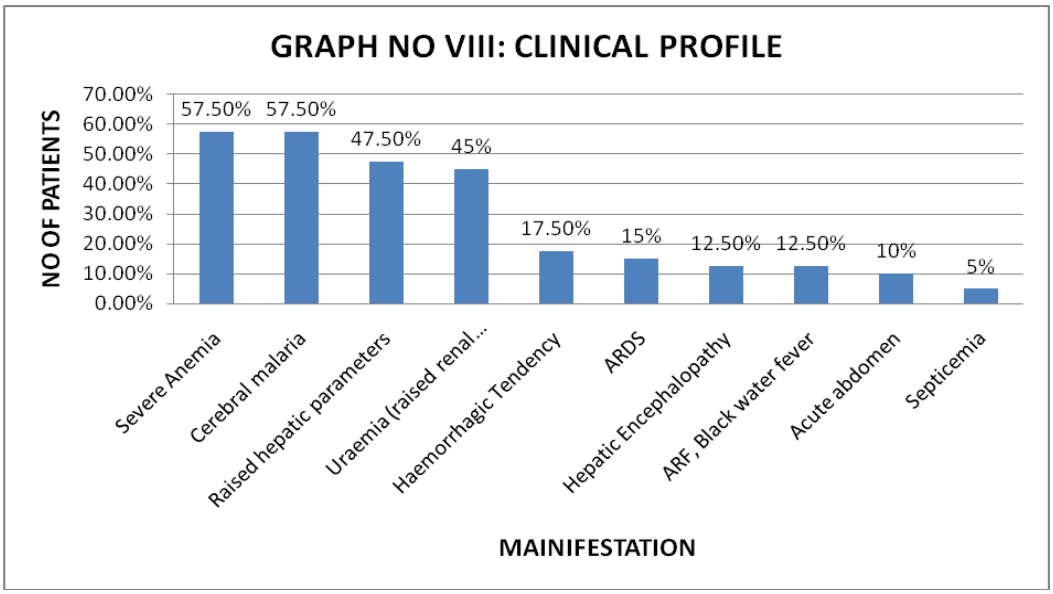
General nourishment was moderate to good in 72.5% of patients where as 27.5% of patients were poorly nourished. 57.5% patients presented with moderate to severe anemia. 42.5% patients had clinically recognizable jaundice as presenting symptom. Central cyanosis was noticed in one patient who presented with dyspnoea associated with fever on admission. Out of 24 patients (60%) who presented with altered sensorium 2! (92.5%) patients were in delirium while 3 (7.5%) patients were deeply unconscious on admission. Out of 24 patients who presented with altered sensorium 16 patients had signs of meningeal irritation, Plantars were extensors in 18 cases with absent or sluggish tendon jerks. Flapping tremor was noticed in one patient (2.5%) on admission. One more peculiar observation in cerebral malaria patients was absence of palpable spleen. 1/3"[1] oi (he patients did not have it.

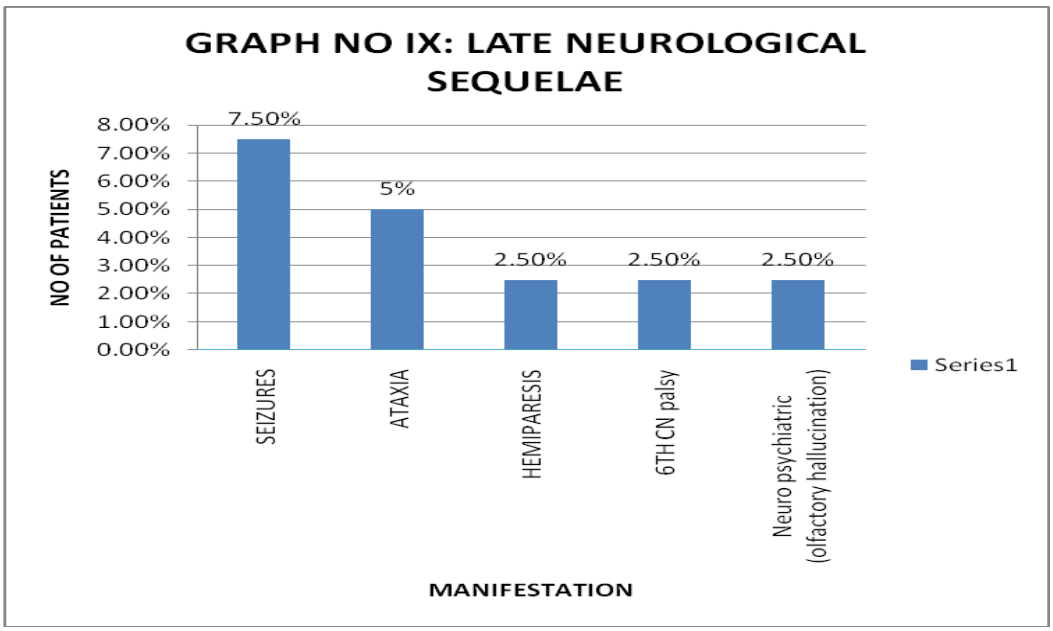
Chest manifestation - 6 patients (15%) were having tachypnoea and shallow breathing on admission. They were dyspnea. with bilateral crepitations and occasional rhonchi. All these patients were never associated with any chronic respiratory illness in the past. Probably these patients were having an cariy ARDS picture. Cardiovascular system - was unremarkable except sinus tachycardia m aii patients on admission and benign haemic murmur in severely anemic patients.

Abdomen - Liver was palpable in 26 patients (65%) (2 cm to 8 cm). Spleen was palpable in 27 patients (67.5%) (Just palpable to 14 cm). Acute surgical abdomen like presentation with nausea, vomiting abdominal guarding and rigidity were seen in 4(10%) patients and were admitted under surgery.

TABE NO. IX: CLINICAL PROFILE

Manifestation	No. of cases	Percentage
Severe Anemia	23	57.5%
Cerebral Malaria	23	57.5%
Raised hepatic parameters	19	47.5%
Uraemia (raised renal parameters)	18	45%
Haemorrhagic Tendeny	07	17.5%
ARDS	06	15%
Hepatic Encephalopathy	05	12.5%
ARF, Black water fever	05	12.5%
Acute abdomen	4	10%
Septicemia	2	5%
Late neurological sequelae		
Seizures	3	7.5%
Ataxia	2	5%
Hemiparesis	1	2.5%
6th CN palsy	1	2.5%
Neuro psychiatric (olfactory hallucination)	1	2.5%
Ocular manifestations		
Papilloedema	3	7.5%
Retinal Haemorrhage	2	5%
Retinitis	1	2.5%


GRAPH NO VIII: CLINICAL PROFILE
NO OF PATIENTS
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
57.50%
57.50%
47.50%
45%
17.50%
15%
12.50%
12.50%
10%
5%
Severe Anemia
Cerebral malaria
Raised hepatic parameters
Uraemia (raised renal...
Haemorrhagic Tendency
ARDS
Hepatic Encephalopathy
ARF, Black water fever
Acute abdomen
Septicemia
MAINIFESTATION


GRAPH NO IX: LATE NEUROLOGICAL SEQUELAE
NO OF PATIENTS
8.00%
7.00%
6.00%
5.00%
4.00%
3.00%
2.00%
1.00%
0.00%
7.50%
5%
2.50%
2.50%
2.50%
SEIZURES
ATAXIA
HEMIPARESIS
6TH CN palsy
Neuro psychiatric (olfactory hallucination)
Series1
MANIFESTATION

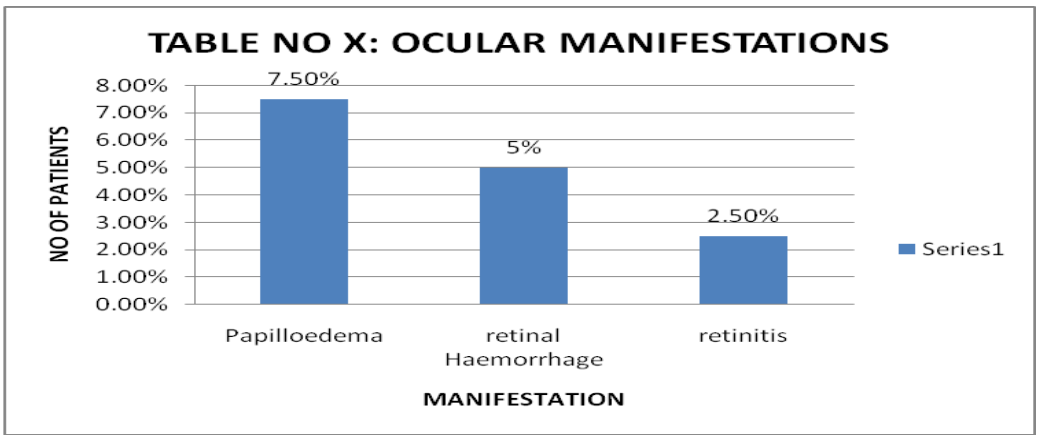


TABLE NO X: OCULAR MANIFESTATIONS
NO OF PATIENTS
8.00%
7.00%
6.00%
5.00%
4.00%
3.00%
2.00%
1.00%
0.00%
7.50%
5%
2.50%
Papilloedema
retinal Haemorrhage
retinitis
Series1
MANIFESTATION

Cerebral malaria was diagnosed in 23 (57.5%) of the patients. Moderate to severe anemia was noticed in all these patients. Raised hepatitic and renai parameters were observed in 47.5% and 45% patients respectively. Haemorrhagic tendency like upper GI bleeding, malena and epistaxis were noted in 7 patients on admission. 6(15%) patients presented with progressive respiratory failure (ARDS). 5 patients presented with acute renal failure/blade water fever, while hepatic encephalopathy was observed in 5 (12.5%) patients. Only prolonged pyrexia was seen in 12.5% patients. 10% of patients had acute abdomen.

Amongst cerebral malaria patients 10 (43.5%) of them had no other organ involvement except a moderate to severe anemia, 13 (56.5%) patients had other organ involvement like hepatic failure in 4 (30.70%) patients, renal failure / black water fever in 5 (38,40%) patients. ARDS in 2 (15.45%) patients and Bleeding tendency in 2 (15.45%) patients.

While improving on antimalarial therapy, late neurological manifestations were observed in some of the patients from 7^{th} day onwards. In that 3 (7.5%) patients had generalized seizure and 2 (5%) patients had cerebellar ataxia, where as 1 patient (2.5%) each developed $6^{"1}$ CN palsy (on the left side) and right hemiparesis. One patient had transient olfactory hallucination.

3 (7.5%) patients had papilloedema 2 (5%) had retinal haemorrhage and 1 (2.5%) patient had retinitis.

TABLE NO. X: LABORATORY INVESTIGATIONS

Blood	**No. of Patients**
Haemoglobin	
2-5 gm %	5(12.5%)
5-10 gm %	22 (55.0%)
> 10 gm %	13 (32.5%)
Anemia	
Dimorphic anaemia	27 (67.5%)
Normocyctic hypochromic	06 (15%)
Normal blood picture	07 (17.5%)
Reticulocyte count	
0.2-2%	20 (50%)
2-4 %	16 (40%)
4-10%	04(10%)
Leucocyte count	
Leucocytosis	07 (17.5%)
Leucopenia	05 (12.5%)
Normal range	28 (70%)

Anemia was seen 83% of P. falciparum infected patients. Five patients had severe anemia and 22 patients had moderate anemia. The blood picture was normal in seven patients, 6 patients had nonnocytic hypochromic anemia while 27 patients had dimorphic anemia. 70% of the patients had normal leucocytes count though with monocytosis. 17.5% of patients had leucocytosis indicating associated bacterial infection or recent massive bleeding and 12.5% of the patients had leucopenia on admission.

TABLE NO. XI: HAEMORRHAGIC PROFILE

Hemorrihagic profile	**Normal**	**Abnormal**
Bleeding time	28 (70%)	12 (30%)
Clotting time	19 (47.5%)	21 (52.5%)
Prothrombin time	18 (45%)	22 (55%)
Platelet count	33 (82.5%)	07 (17.5%)
1. Liver function test	**Normal**	**Increased**
Bilirubin	19 (47.5%)	21 (52.5%)
SGOT	19 (47.5%)	21 (52.5%)
SGPT	19 (47.5%)	21 (52.5%)
2. RBS (67 to 275 mg%)	**No of patients**	**Percentage**
< 40 mg%	00	00

60 to 100mg %	18	45%
100 to 126 mg%	10	25%
126 to 180 mg%	09	22.5%
> 180 mg%	3	7.5%
3. Urea (BUN) (28mg% to 440mg%	No. of patients	Percentage
< 30 mg%	13	32.5%
30 to 50 mg%	10	25%
50 to 100mg%	10	25%
100 to 200 mg%	4	10%
> 200 mg%	3	7.5%
4. Creatinine (0.8 mg% to 12 mg %)	No. of Patients	Percentage
< 1.70 mg%	25	62.5%
1.72 to 3 mg %	10	25%
3 to 6 mg %	1	2.5%
6 to 10 mg %	2	5%
> 10 mg %	2	5%

Twenty two (55%) patients had a prolonged prothrombin time where as severe thrombocytopenia was observed in 7 (17-5%) patients which arc significant in the complication of hemorrhage in falciparum malaria indicating the severity of disease.

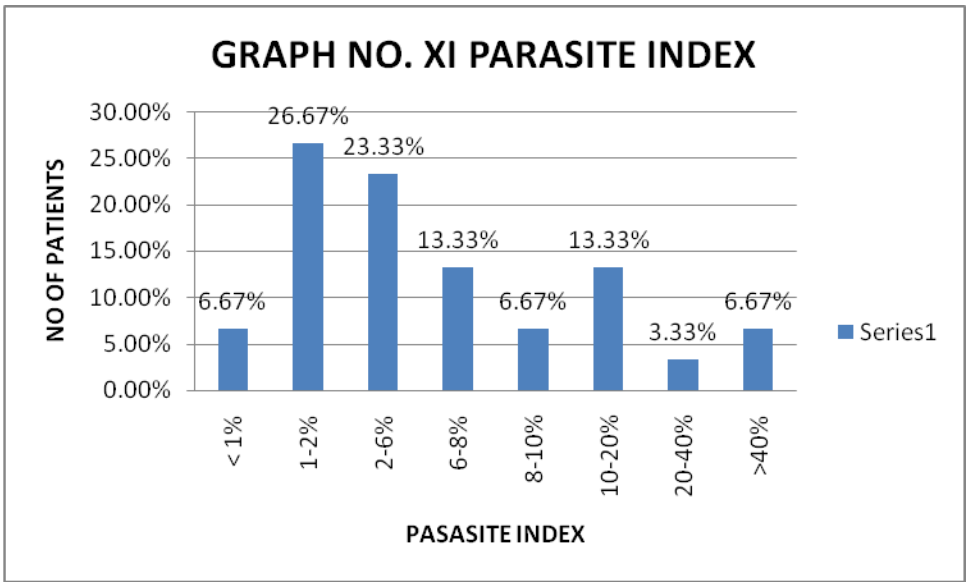
Twenty one (52.5%) of the patients had abnormal Liver function tests. A raised serum creatinine was seen in only in 15 (37,5%) patients while 27 (67.5%) patients had increased blood urea. Contrary to popular belief hypogiycemia was not observed in this study during admission. During follow up 4 (!0%) patients developed hypogiycemia. Also 3. (7.5%) patients were detected to be hyperglycemic (who were not known diabetics), probably due to over cautious management of anticipated hypogiycemia.

Other tests: H1V test was positive in 2 (5%) patients, who had normal recovery. Perhaps HIV infection does not come in the way of recovery of malaria. Blood cultures were negative in all 13 cases tested. CSF was normal in all 14 cases tested. Serum electrolytes were normal in 24 patients (60%) Hyperkelmia was seen in 5 (12.5%) patients.

CT scan of the brain was required in 3 patients on admission due to delay in diagnosis- It was a normal study in 2 patients and one patient had cerebral oedema. All of them were proved smear positive for P, Falciparum.

Table No. XII: Parasite Index

Parasite Index	< 1%	1-2%	2-6%	6-8%
No, of patients	2 (6.67%)	8 (26.67%)	7 (23.33%)	4 (13.33%)
Parasite Index	8-10%	10-20%	20-40%	> 40%
No. of patients	2 (6.67%)	4 (13.33%)	1 (3.33%)	2 (6.67%)



Range of parasite index 0.01-70%

Most of the patients (60%) had a parasitic index of 1-8%, 2 patients had parasitic index of more than 40%. 70% of the patients has both ring form and gametocytes, while 15% of the patients had only ring stage in peripheral smear and 10% had ring, gametocytes and schizonts in the peripheral blood. In 5% only gametocytes were seen. Only 75% of the patients were diagnosed exclusively on peripheral smear examination alone. While 25% patients required Qbc examination for the diagnosis.

DISCUSSION

Malaria is an important parasitic infection with considerable morbidity and mortality. This disease was almost eradicated in 1960's and has re-emerged is a major public health problem in the last few decades. Although exact statistic are not available, about 110 million cases are reported.

The present study was conducted in the Department of Medicine, BLDE'S shri B.M.PATILMedical college Hospital during the period of sept 2009 to aug 2010 among 100 patients of P. Falciparum Malaria with typical presentation with fever, chilss, rigors, headache and atypical presentations like altered sensorium, seizure, hepatic encephalopathy, adult repiratory distress syndrome (ARDS), acute renal failure/black water fever, acute abdomen or algid malaria who are proved "Smear positive" either by peripheral blood picture or by quantitative buffy coat (QBC) examination.

The results of the present study revealed that, incidence in males is slightly higher (2.7:1) than females is maximum between August to December. Incidence is qually common in adults up to age of 50 years and as the age advances it falls rapidly. Parasite index did not correlate with the morbidity and mortality of P. falcipaurm malaris, probably mature stage schizont in peripheral smear indicate worst prognosis. Hepatic encephalopathy was observed in 5(12.5%) patients. ARF/black water fever in 5(12.5%) of the patients, ARDS was observed in 10 (25%) of the patients. Combinatio therapy is alternative to overcome drug resistant falciparum malaria. Mortality was 20% Seven of these18 patients had no splenomegaly. Thus absence of splenomegly in cerebral malaria infer grave prognosis. Some of the patients were

coming from the area of river project near Gokak (40% of patients). This is explained probably because of stagnation of water and hence mosquito breeding.

Age, Sex and Occupation

The male sex group showed a slight increase in incidence (2.7:1) than female sex group probably due to their occupation and hence proximity to vector contract.

Of the 40 patients, 80% cases were between 12 to 50 years of age group, with a peak of 22.5% patients in 2^{nd} decade of life though it is equally distributed in all age groups. The younger population is affected mainly because of no or partial immunity to P. falcipaurm.

Hence, sex and age do not affect the incidence or severity of P. calcipaurm malaria infection except that they relate to the frequency of exposure and the development of immunity.

Falciparum malaria is equally distributed in all classes of socio economic status as it is blood parasite disease spread by vector female anopheles mosquito in non or partially immune patients.

Season

In our study August to December recorded a higher of 80% incidence of P. falciparum malaria. Malaria transmission is profoundly influenced by climate. Optical conditions for transmission occur between 20-30 ^{0}C temperature and a mean relative humidity of at least 60% Sporongony does not occur <60 ^{0}C or above 33 ^{0}C. High humidity in this season favours mosquito longevity. The slight drop in July may be explaned by excessive rain, washing out the breeding sites of mosquito thus less transmission in this part of the country. The study correlate with Rajastan study where 85% cases were reported during rainy season.

Gupta R et al 1994[111]	Present Study
August to December	August to December
Reproted cases of falciparum malaria	Reproted cases of falciparum malaria
85% of the patients	85% of the patients

Blood group and p. falciparum malaria.

It is evident that the commonest blood group is O positive in Bijapur comprising 46% of the population, While A and B groups compares 27% and 23% respectively and AB positive the lowest 4% only. It is observed that the incidence of P. falciparum is less in O positive patients compared to A and B groups and even if it occurs, its morbidity and mortality were comparatively less. Carlson J. has the credit of first original research in 1993 regarding ABO blood group importance in P. falciparum malaria. However the study group figures were not available hence could not be correlated in this study. Erythrocytes resetting in P. falciparum has major role in the pathogenesis of cerebral malaria and other organ dysfunction. Rosette formation of uninfected RBC to infected RBC is influenced by a variety of host factors such as host immunity, ABO blood group and Hb phenotype. In cerebral malaria molecules involved in resetting are deferent than those involved in cytoadherence. Difference in resetting ability were also seen between red cell of different ABO blood group with a diminished.

Rosetting potential in blood group 0 red cells impaired rosette formation ma. Thus contribute to the innate resistance to sc severe. P. falciparum malaria that is known to exist in certain red cell disorders like sickle cell trait, α and β thalessemia, HbE haemoglobinopathics and microcystosis and in individuals of blood group 0.

Rosette formation 1% flit main contributing factor in the pathogenesis of complicated malaria was fouund to be governed by strong adhesive forces with lectin like bindings between parasite derived protenin exposed on the P. falciparum infected RBC surface – rosettings and various carbohydrate receptors seem to be contained within blood group A or B antigen. Thus it is evident that A and B blood group have increased incidence of severe P. falciparum malaria.

SYMPTOMATOLOGY

Fever and constitutional symptoms

In this study all patients had h/o fever. Fever with chills and rigor was intermittent in 72.5% of the cases while 17.5% cases had continuous fever and 10% had remittent fever. The fever was irregular at first, before the classical 48 hours periodicity became established. The classical cold, hot and sweating stages were not frequent perhaps because of early intervention and or associated complications.

History of headache was observed in 82.5% of the patients. of these 75% had intermittent bifrontal throbbing headache, 7.5% had continuos headache, while 17.5% patients never c/o headache.

As in any other febrile illness, the fever was associated with generalized weakness and malaise in most of the patients (97.5%) Anorexia in 38 (95%) patients and nausea/vomiting was observed in 90% of patients.

In this study all patients had fever (100%) where as in one study conducted in Agra (UP) military Hospital 5.4% of the patients were afebrile through out the illness and presented with only vague constitutional symptoms and later as the complications.

Mental Status:

Altered sensorium was present in 60% of the cases and H/o seizures in 5% patients. It is attributed to various factors viz : Hyperpyrexia, Lactic acidosis, hypoglycemia etc. The sequestration of parasite in the microvasculature of brain and other vital organs leads to altered sensorium and generalized convulsions.

Cerebral Malaria

Bijapur is endemic for P. falciparum malaria. The incidence of cerebral malaria in this study is 57.5% with variable involvement of other systems. This hospital being tertiary referral centres, the high incidence of cerebral malaria is expected. The reported incidence of cerebral malaria is between 2 – 55%. The reported incidence in endemic area is 3.05%. All the patients had fever, headache and latered sensorium of variable intensity during presentation. This correlate well with the study by Bajja et al. Rajasthan. Where fever, was seen in 100% of cases but altered sensorium was noted in 64.8% cases but headache in 72% cases.

	Gopinath (North East (1986)[74]	Mehta (Agra) (1989) [74]	Dhamija (North East (1989)	Bajiya (Rajasthan) (1996)[113]	Present Study
Incidence	7.45%	3.05%	25.7%	55%	57.5%
Delirium	66%	3.05%	39.5%	64.80%	52.5%
Coma	5%	0.8%	3.2%	6.48%	7.5%
Headache	80%	100%	100%	72%	82.5%
Meningeal Sign	25%	15%	20%	18.91%	40%
Neurological sequelae	30%	17%	26%	23.5%	20%
Ocular manifestations	0.8%	--	17%	21.3%	15%

Meningeal sings were positive in 40% of the cases compared to 18.91% of the cases in Rajasthan study and 25% in North East study. Involvement of meninges and symmetrical encephalopathy is attributed to resetting in the microvasculature. 70.83% of cerebral malaria patients were in delirium, disoriented and incoherent state, while 12.5% were comatose and rest 16.47% patients showed only mild to moderate confusion. In Rajasthan study 6.48% were comatose.

Sings only in cerebral malaria	Gopinath (North East) (1986)	Mehta (Agra) (1989) [14]	Bajiya (Rajasthan) (1996)[113]	Present study
Hepatomegaly	50%	75%	9.10%	65%
Splenomegaly	68%	70%	63%	67.5%

Spleen was palpable in 67.5% of cases of cerebral malaria and in 32.5% cases there was no palpable spleen. This is in correlation with Rajasthan epidemic study where 63% patients had palpable spleen. Hepatomegaly was noticed in 65% of cases in our study. Same findings were correlated with a similar study, while only 9.10 patients had clinically palpable liver in another study. Two patients had decorticate rigidity (5%), while tendon reflexes were sluggish and plantars were extensor in 45% of the patients. In the rest normal tendon reflexes were clicited. While in Rajastan study only 2.6% patients had loss of deep tendon reflex and 8% had in fact exaggerated reflexes.

CT scan of the brain was done in 3 patients because of the delay in diagnosis. It was unremarkable in two patients while one patient showed diffuse cerebral oedema attributed to an increase in intra cerebral blood volume.

Abdomen

Liver was palpable (2 to 8cm) in 65% of the patients while spleen was palpable clinically (Just palpable to 14cm) in 67.5% Elven (27.5%) patients had diarrhea at the onset and 10% of patients were admitted under surgery with H/o acute abdomen. It is because of sequestration of parasites in the gut microcirculation causing visceral ischemia mimicking acute surgical abdomen with guarding, rigidity

and shock associated with constitutional symptoms, which might have lead to these incidence. Jaundce was the intital manifestation in 42.5% of the patients. It is due to prehepatic (due to haemolysis), hepatic (microvascular sequestration in the liver during sporogony) and cholestatic component due to obstruction in the microvascular blood flow to the liver. It is due to vascular changes causing congestion and dilatation of sinusoidal vassels, perivascular haemorrhage resulting form capillary endothelium damage.

In the BDS Post graduate institute of medical sciences Rohtak study Jaundice was seen in 100% of the patients and hepatomegaly in 75% of the cases compared to 42.5% ad 65% of patients respectively in this study. while in a study of complicated falciparum malaria in S.P. Medical College Bikaner Rajasthan (North West India) study the incidence of jaundice was 30% and hepatomegaly in 50% cases. Which is close to the present stuy and both prehapatic, hepatitis and post heapatitic type of hyperbilirubinemia noted. Hepatic encephalopathy like picture with altered sensorium and flapping tremor were seen in 5% patients.

	S.P. Medical College, Bikaner study	**BDS Medical Sciences, Rohtak**	**Present study.**
Jaundice	30%	100%	42.5%
Hepatomegaly	50%	75%	65%

High colured urine with reduced out put was seen in 45% of the patients while 55% patients had normal urine. While uraemia was seen (raised renal parameter) in 42.5% of the patients only 15% had sings of ARF Black water fever. Malarial ARF was reported 1.08% incidence in Behrampur study.

	Mahakur et. al Behrampur (Orissa) 1983	Bajiya et al. Rajasthan 1996	Present study
ARF/Black water fever	1.08%	5.40%	12.5%
Uraemia (Only raised renal parameters)	24.70%	21.70%	45%

The incidence and our findings in renal profile is correlated with the findings in Rohtak and Rajasthan study. In our study 3 patients required dialysis (7.5%) out of which 2 underwent peritoneal dialysis and one hemodialysis. The patient who underwent hemodialysis later expired due to multi-organ failure. Rest all improved progressively on therapy.

Chest :

Cough was found in 37.5% of the patients, while 15% of the patients had early signs of respiratory insufficiency with tachypnoea, dysponea, shallow breathihg, acidosis and bilateral chest sings like decreased air entry, crepitatioins and rohonchi. ARDS was the end result in 10 (25%) patients of which 3 (7.5%) were put on ventilator. In the Bikaner study the incidence of ARDS was 7.02% compared to 5% in the present study. One patient (2.5%) had central cyanosis on admission, with ARDS like picture was admitted under a cardiologist with a diagnosis of pulmonary embolism was later transferred to medicine once peripheral smear was positive for P. falciparum. The patient improved remarkably with only antimalarial therapy.

Heamotological manifestation:

	Gupta A. et al. 1987 Rajasthan	**Mehta S.R. 1989 Agra**	**Bajiya et. al Rajasthan**	**Present Study**
Anemia	54%	83%	86.48%	57.5%
Haemorrhagic tendencies	21.8%	5.08%	18.6%	17.5%

Severe anemia was noticed in 57.5% of the patients while 62.5% patients required blood transfusion. Two patients (5%) required emergency blood transfusion due to acute blood loss (one patient due to disseminated intravascular coagulation and other due to massive upeer GI bleeding).

In 50% patients the reticulocyte count was increased. The pathogenesis of anemia is multi factorial – Immune mediated (Haemolytic) destruction of and non parasitized RBC's and natural lysis of infected RBC's. Splenic clearance and bone marrow dysfunction also contributed to anemia. Anemia was 86.4% in Bikaner study and 54% in another study. Haemorrhagic tendencies were noticed in 17.5% of the cases in this study correlates with the Bikaner study.

Laboratory diagnosis of P. flaciparum:

Peripheral smear and parasite index were the usual mode of diagnosis of P. falciparum. but it is known that in difficult, undiagnosed cases a bone marrow study or intradermal smear may be examine for the parasites. Twenty five percent of our cases were peripheral smear negative persistently, but the bone marrow smear was positive for falciparum malarial parasites. This it is evident that bone marrow study can be conducted in difficult undiagnosed cases. When there is a strong suspicion of falciparum malaria clinically.

Gametocytes in P. falciparum malaria appear in the peripheral smear after several broods have undergone schizogony (sporogony). It takes usually abot 10 day for gametocytes to appear in the peripheral blood, after the initial invasion. So gemetocytes can be seen at 16-17 days of infection in the peripheral blood. It has almost happened so almost happened so in this study initially, in those who were peripheral smear negative.

Erythrocyte schizogony occur inside the capillaries on internal organs such as spleen, liver and bone marrow. Hence only the ring forms and not the growing trophozoites and schizonts are found in the peripheral smear.

The appearance of parasite depends upon the density of the parasite in the peripheral smear. The microscopic density is in the neighborhood of 10 parasites/mm3 blood. during the 10^{th} day of infection parasites generally appear in thick smear.

The parasite index ranges from 0.01 – 70%. It does not correlate with the severity of the disease and depends on:

1. Timing at which the blood was drawn and smear examined.
2. Expert microscopy examination.
3. Previous anti malarial medications if any,
4. The stage and maturity of the parasite and
5. The immune status of the host.

In this study a parasite index of 2% had severe morbifity and mortality and a patient of 70% parasite index (mostly ring stage) had walked out of the hospital with full improvement on anti malarial therapy alone. 82% had a range of 0.01 to 10% with varying severity of illness, While in 12.5% had a parasite index of 10 to 40%. Five percent of patients had parasite index of more than 40% parasitemia has traditionally been used as a measure of severity. But the sensitivity and specificity of parasitemia alone as prognostic indicator is limited but depends on :

- The mature parasites in the peripheral blood (schizonts) indicating a poor prognosis that the mere number of parasite in the peripheral blood.
- Number of polymorphic neuclear neutrophil leucocytes which contain malarial pigments>5% indicates poor prognosis, and
- If>50% parasites contain visible pigments that carries worst prognosis. The prognosis is better if>50% of parasite are at the tiny ring stage.

Normally a parasite index of 10% increase the risk of morbidity and mortality, while 50% parasite index is usually associated with 50% mortality in immune adults and up to 20% parasite index may not have severe disease compared to non immune.

Hypoglycemia :

Hypoglycemia was not seen during admission in our study. However during follow up in the hospital four (10%) patients who were on quinine therapy had sever hypoglycemia, a correlation with an earlier study. Where severe hypoglycemia was seen in 4.32% of cases. Three *7.5%) patients were detected to be hyperglycemic (who were not known diabetic). Probably due to overcautions management of anticipated hypoglycemia.

Late neurological sequelae :

The reported incidence of late Neurological sequelae is 0.12% - 10.5% (post malaria neurological syndrome). In our study the incidence of late neurological sequelae was 20% (8 patients). In all of them it occurred during recovery phase of the illness and all of them were either on quinine or artesunate therapy and none of them were on mefloquine which is more commonly associated with later neurological sequelae like psychosis and transient encephalopathy.

	Bajiya et al.	**Our study**
Seizures	21.62%	7.5%
Ataxia	4.87%	5%
Hemiparesis	2.43%	2.5%
Cranial nerve palsy	0.54%	2.5%
Neuropsychiatric	8.94	2.5%

Mortality

The mortality was 20% male to female ration was 1 : 1

In all, 8 patients died in the present study comprising 20% of the sample size. In this group spleenomegaly was remarkably absent in 7 of them. In the last patient who died the spleen was just palpable. In this group the fever ranged from 2 to 20 days and none of them had received chloroquine before admission. All these 8 patients had cerebral malaria with various other complications like ARDS in 3 patients, hepatic encephalopathy in one patient, and multi organ failure in one patient, cardiac arrhythmia with failure in one patient, Hepatorenal syndrome and disseminated intravascular coagulation in one patient each. The parasite index did not correlate with the mortality as discussed earlier. The present study has less mortality compared to 33.5% in a larger study done in Bikaner Rajasthan. Early diagnosis, anticipation of complications, close monitoring of vital parameters and combination therapy to overcome drug resistance perhaps helped to contain the extent of mortality in this study.

SUMMARY

Incidence and place of distribution:

It is evident from the available data, that the incidence of complicated P. falciparum malaria has shown a threefold increase in BLDE"S shri.B.M.PATIL Mdical college Hospital commensurate with the rising incidence of P. falciuparum malaria.

Rapid urbanization, an increase in floating population due to better mode of transportation and the highway connecting the major cities which are natural reservoirs of infection, ideal weather for vector multiplication contribute to the rising incidence.

The reported incidence of only 15% in urban area is probably due to awareness about malaria, early detection and treatment, easy availability of medical facilities.

Most of the reported cases were imported i.e. the patients had returned from a recent trip to other major cities with known edemicity. Many also were from hot arid neighboring districts like Bagalkot and few cases from Goa.

A total of 50% gave H/o visit to endemic malarial zone.

Semi urban population recorded 27.5% incidence it is probably because of increasing population with poor basic health facilities, poor sanitation and closeness to vector transmission due to their occupation (Agricultural worker or manual laborers or truck hailing from villages).

CONCLUSION

Bijapur is an endemic zone for P. falciparum, there is alarming rise in incidence of falcipaurm malaria-The incidence of P. falcipurm malaria is maximum between August to December (80%) in concurrence with the Bikaner study. Incidence in males is slightly higher (2.7:l) than females. Incidence is equally common in adults' upto age of 50 years and as the age advances it falls rapidly.

The severity of illness and mortality was significantly higher in AB blood group individuals. Parasite index did not correlate with the morbidity and mortality of p.falcipaurm malaria, probably mature stage schizont in peripheral smear indicate worst prognosis,The incidence of cerebral malaria is 57.5% slightly higher than the national available data as explained earlier-

Severe anemia was observed in 23 (57.5%)of patients, while 25 (62.5%) of the patients required blood transfusion. haemorrhagic tendencies were noticed in 17.5% of the cases. Hepatic encephalopathy was observed in 12(12.5%) patients. ARF/black water fever in 5(1.2.5%) of the patients, ARDS was observed in 6 (15%) of the patients.Acute abdomen like presentation was seen in 4 (I0%) of the patients while 2 (5%)of the patients had septicemia.

Though severe hypoglycemia was not observed at the time of admission, in 4 patients (10%) severe hypoglycemia was observed during quinine therapy in this study.Combination therapy is a suitable alternative to overcome drug resistant falciparum malaria.Mortality was 20%. Seven of these 16 patients had no splenomegaly. Thus absence of splenomegaly in cerebral malaria infer grave prognosis.

AB positive, A positive, B positive and B negative blood groups had the higher mortality. Mixed malaria was seen in one (2.5%) patient. Quantitative, buffy coat method is more sensitive in identifying the parasite than by peripheral smear.

Assessment of severity of organ dysfunction is required for risk stratification, prognostication and planning of treatment and to arrest in progression of disease and hence mortality on 1 day of admission.

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ANNEXURE – V

Investigations or interventions required in this study are :

1. Complete blood count.
2. Peripheral smear.
3. QBC
4. Random blood sugar.
5. Urine routine.
6. Bleeding time and Clotting time.
7. Serum creatinine.
8. Blood urea.
9. Serum electrolytes.
10. Liver function tests *
11. Chest X-ray.*
12. CT scan.*

- Wherever required.

There is no animal experiment involved in this study.

PROFORMA

Name:	IP. No:
Age:	Address:
Sex:	Date of Admission:
Occupation:	Date of Discharge:
Religion:	Status at Discharge:

PRESENTING COMPLAINTS:

HISTORY OF PRESENTING ILLNESS:

PAST HISTORY:

History of malaria in the past:

PERSONAL HISTORY:

FAMILY HISTORY:

GENERAL PHYSICAL EXAMINATION:

Pallor:

Icterus:

Cyanosis:

Clubbing:

Pedal edema:

Lymphadenopathy:

Vital Signs:

Plus rate:

Blood pressure:

Temperature:

Respiratory rate:

GASTROINTESTINAL SYSTEM

Inspection

Plapation :

Splenomegaly:

Hepatomegaly:

Percussion

Auscultation:

CARDIOVASCULAR SYSTEM:

GENTRAL NERVOUS SYSTEM:

COMPLICATIONS OF MALARIA :

Impaired consciousness :

Prostration :

Jaundice:

Cerebral malaria:

Generalised convusions :

Severe anemia:

Renal failure:

Hypoglycemia:

Fluid electrolyte, acid base disturbances:

{ulmonary oedema :

Alagid malaria:

DIC:

Hyperpyrexia:

PROVISIONAL DIAGNOSIS:

FOLLOW UPS:

OUTCOME:

CONCLUSION:

INVESTIGATIONIS

HAEMATOLOGY

Heamoglobin	gm/dl
TC	Cells/mm^3
DC	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Basophils	%
Monocytes	%
ESR	Mm/1 hr
Blood group	
Peripheral smear study for malarial parasite	
QBC test	
Follow up peripheral smear study for malarial parasite	

RENAL FUNCTION TESTS

Urea	mg/dl
Creatinine	mg/dl
Unconjugated bilirubin	mg/dl
Total protein	mg/dl
Total protein	mg/dl
Albumin	
SGOT	IU/L
SGPT	IU/L
ALP	IU/L

DIAGNOSIS

ANNUXURE – IV

KEY TO MASTER CHART

AS	:	Artisunate
ARDS	:	Adult respiratory distress syndrome
ATX	:	Ataxia
B	:	Businessman
C	:	Continuous
CQ	:	Chloroquine
CM	:	Cerebral malaria
CNP	:	Cranial nerve plasy
D	:	Delirium
DC	:	Doxycycline
DIC	:	Disseminated intravascular coagulation
DMC	:	Dimorphic
E	:	Expired
F	:	Female
G	:	Gametocytes
GI	:	Gastrointestinal tract
H	:	Hypochromic
HC	:	High coloured
HD	:	Hemodialysis
HW	:	House wife
I	:	Intermittent

i	:	Improved
JUGR	:	Intra uterine growth retardation
K	:	Potassium
M	:	Male
N	:	Normal
NC	:	Normocytic
MOF	:	Multi organ failure
PD	:	Peritoneal dialysis
PT	:	Plantar
QN	:	Quinine
R	:	Ring
Re	:	Remittent
ST	:	Student
T	:	Trophoblasts
UC	:	Unconscous
+	:	Present
-	:	Absent

ANNEXURES

B. L. D. E. U's

SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL &

RESEARCH CENTRE, BIJAPUR

RESEARCH INFORMED CONSENT FORM

TITLE OF THE PROJECT:

"THE MALARIA SEVERITY SCORE: A METHOD FOR SEVERITY ASSESMENT AND RISK PREDICTION OF HOSPITAL MORTALITY FOR FALCIPARUM MALARIA IN ADULTS"

GUIDE : DR. M. S. MULIMANI M.D.

INVESTIGATOR : DR. VINAYAK. S. INGALAGI

PURPOSE OF RESEARCH:

I have been informed that the purpose of this study is to study the malaria severity score: a method for severity assessment and risk prediction of hospital mortality for falciparum malaria in adults.

PROCEDURE:

I understand that I will undergo detailed history and clinical examination, laboratory investigations.

RISKS AND DISCOMFORTS:

I understand that there is no risk involved and I may experience mild pain during the above-mentioned procedures.

BENEFITS:

I understand that my participation in this study will help to understand the importance of studying the malaria severity score: a method for severity assessment and risk prediction of hospital mortality for falciparum malaria in adults will provide a rationale for early management.

CONFIDENTIALITY:

I understand that the medical information produced by the study will become a part of hospital record & will be subjected to confidentiality and privacy regulations of hospital. If the data is used for publications, the identity of the patient will not be revealed.

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or withdraw for study at any time.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me during the study I will get medical treatment but no further compensations.

(Signature of Guardian) **(Signature of Patient)**

MASTER CHART

S.No	ESR (MM/hr)	PS/Parasite Stage	Bone Marrow	parasite index (%)	RTC (%)	BT (Min/Sec)	T	C	Albumin	Sugar	Micro (WBC/Cast/HPF	Protein gm%	SGOT-U/L	SGPT /IU/L	AP	T	D	RBS mg%	BUN mg%	Creatinine mg%	CSF	Electrolytes	Others	Shock	Haemorrhage	Hypoglyemia	Acute GE	Cerebral malaria	ARF/BW Fever	HE	ARDS	Acute abdomen	Severe anemia	Pregnancy	Late complications	Diagnosis	Treatment	Blood transfusion	Outcome
1	140	DM	-	2.0	4.6	3.0	16	14	-	-	-	5.6	82	51	-	0.7	-	67	30	0.8	N	N	CTN	+	GI	+	-	+	-	-	-	-	+++	+	S	CM	Q+TC	+	i
2	28	DM	-	2.0	4.0	2.0	26	13	-	-	-	4.7	27	18	10.0	1.0	-	192	29	1.1	N	N	CTBE	+	DIC	-	+	+	-	-	+	-	++	-	DIC	CM	Q+DC	+	E
3	180	DM	RG+	-	3.0	3.0	14	14	-	-	-	5.0	40	36	-	1.7	0.6	115	36	1.1	-	N	-	-	-	-	-	-	-	-	-	-	++	-	-	-	CQ	+	i
4	100	DM	-	70.0	4.0	2.0	15	13	-	-	-	5.5	108	125	-	5.4	3.8	215	288	5.6	N	N	-	-	-	-	-	+	+	+	-	-	++	-	MOD	CM	Q+DC	-	i
5	75	DM	RG+	1.5	1.0	2.3	15	13	+	-	-	6.1	24	25	-	0.9	-	92	30	1.1	-	N	-	-	GI	-	-	-	-	-	-	-	++	-	DIC	-	Q+DC	+	i
6	106	DM	-	3.0	3.0	4.3	14	14	-	-	-	6.0	52	48	-	0.9	-	84	50	1.7	N	-	-	-	-	-	-	+	-	-	-	-	-	-	S	CM	Q+DC	-	i
7	98	DM	RG+	0.0	4.0	5.0	13	13	-	-	-	5.8	52	48	-	0.8	-	86	29	1.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DT	-	Q+DC	-	i
8	70	DM	-	2.0	2.0	3.3	14	14	-	-	-	4.1	65	45	-	0.8	-	75	71	1.7	-	N	-	-	-	-	+	-	-	-	-	-	-	-	-	-	Q+DC	-	i
9	100	DM	-	2.0	4.0	7.0	26	14	++	-	+	5.1	26	20	-	0.7	-	183	418	10.9	N	K+	RA	+	-	-	+	+	+	-	+	-	-	-	ARDS	-	Q	+	E
10	120	H	-	12.0	3.0	7.0	16	13	+	-	+	5.0	217	100	-	17.7	11.5	100	310	7.9	-	N	-	+	GI	-	-	+	+++	+++	-	+	-	-	GIB	-	Q	+	E
11	10	H	-	4.0	2.0	7.0	14	14	+	-	+	6.0	105	145	-	0.8	-	92	29	1.1	-	N	-	-	-	-	-	-	-	+	-	-	-	-	-	-	Q	-	i
12	120	DM	-	50.0	2.0	3.0	14	14	+	-	-	5.6	115	60	-	1.1	-	125	102	1.9	N	N	-	+	-	+	-	+	+	-	-	+	-	-	GIB	CM	Q+TC	+	i
13	156	DM	RG+	0.0	0.8	3.0	18	14	-	-	-	5.6	96	112	11.0	1.4	-	92	33	1.1	-	-	-	+	-	+	-	+	-	+	-	-	+++	-	-	CM	Q+DC	+	i
14	88	DM	-	0.0	5.0	4.3	16	14	+	-	-	6.0	38	44	-	0.7	-	100	36	1.1	N	N	-	-	-	+	-	+	-	-	-	-	-	-	HG	CM	Q+DC	+	i
15	31	DM	-	10.0	1.0	5.0	14	14	+	-	-	6.5	42	36	-	0.8	-	275	36	1.1	N	N	-	+	-	-	-	+	-	-	+	-	-	-	S,ARDS	CM	Q+DC	-	E
16	70	NC	RG+	0.0	1.2	3.3	16	14	+	-	+	6.0	215	180	-	2.6	1.0	108	69	3.0	-	N	-	+	GI	-	-	-	+++	+	+	-	++	-	NP	-	AS+D	+	i
17	66	DM	-	5.0	3.5	5.0	14	14	-	-	-	4.6	70	55	6.7	2.6	1.0	83	60	2.0	-	N	-	-	-	-	-	+	+	+	-	-	++	-	HG	CM	AS+D	+	i
18	26	DM	-	5.0	0.2	3.0	14	14	+	-	+	5.8	64	46	-	0.8	-	92	30	1.1	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	CM	Q	-	i
19	175	NC	RG+	0.0	6.5	4.5	16	14	-	-	-	6.3	59	63	6.3	2.0	-	83	40	1.1	-	-	RA	-	-	-	+	+	-	+	-	-	+++	-	-	CM	Q	+	i
20	16	DM	-	8.0	4.0	3.3	18	14	+	-	-	5.0	36	42	8.7	1.1	-	150	113	1.9	-	-	-	+	-	-	-	-	+	-	+++	-	-	-	ARDS	-	Q	-	i
21	117	NC	-	8.0	0.5	5.0	16	14	+	+	-	7.0	48	23	-	2.3	0.8	100	95	1.1	N	N	-	-	-	+	-	+	+	+	+	-	-	-	HG	CM	CQ	+	E
22	16	NH	-	2.0	2.0	3.0	14	13	-	-	-	5.8	40	32	-	0.8	-	117	38	1.1	-	N	-	-	-	-	-	-	-	-	-	-	-	-	-	-	AS	-	i
23	130	NC	RG+	0.0	2.0	3.0	16	14	-	+	-	5.8	42	36	-	0.8	-	275	88	1.9	N	N	-	+	GI	-	-	+	+	-	-	-	-	-	-	CM	Q+DC	-	i
24	18	DM	-	40.0	1.0	11.0	33	13	+	-	-	6.0	950	750	32.0	31.0	19.0	82	32	1.5	-	K+	-	+	GI	-	-	+	-	+++	-	-	-	-	COMA	CM	Q	+	E
25	152	NC	-	3.0	3.5	3.3	18	14	-	-	-	6.5	300	250	15.0	6.3	3.7	83	342	9.0	-	K+	-	+	-	-	-	-	+	+++	-	-	+++	+	ARDS	-	AS+D	+	E
26	120	H	-	2.5	2.0	4.3	17	13	+	+	+	4.4	125	137	9.3	11.4	7.4	150	136	3.0	N	N	-	-	-	-	-	+	+++	+++	-	-	++	-	COMA	CM	Q+DC	+	i
27	62	DM	RG+	0.0	7.4	4.0	16	13	+	-	-	5.2	144	132	8.0	2.0	-	70	22	1.0	-	-	-	+	-	-	-	-	-	+	-	-	+++	-	-	-	Q+DC	-	i
28	75	DM	-	5.0	2.0	9.0	17	13	+	-	+	6.0	92	70	-	2.0	-	217	236	1.7	N	N	-	-	NB	-	-	+	+++	+	-	-	+++	-	NB	CM	Q+DC	+	i
29	75	DM	RG+	0.0	2.0	5.0	14	14	++	-	+	5.8	46	38	-	0.8	-	80	28	1.1	-	-	-	-	-	-	-	-	-	-	-	-	+++		-	-	Q+DC	-	i
30	90	NH	-	5.0	1.5	3.0	14	14	+	-	+	5.8	48	40	-	1.0	-	158	25	0.8	-	N	CTN	+	-	-	-	+	-	-	-	-	+++		6CNP	CM	Q+DC	+	i
31	151	DM	-	2.8	2.5	5.0	14	13	+	-	+	5.0	48	35	10.0	1.7	0.9	75	94	2.3	-	N	-	+	-	-	-	-	+	-	+	-	++	+	DF	-	AS+D	+	i
32	130	DM	-	11.0	4.9	4.3	14	14	+	-	-	4.8	225	110	8.7	7.1	4.9	133	84	2.6	N	K+	-	+	-	-	-	+	-	+	+	-	++	-	ARDS	CM	Q	+	E
33	74	NH	-	12.0	5.0	7.3	14	14	+	-	+	4.8	43	57	14.0	2.9	1.7	125	178	10.9	-	K+	-	+	-	-	+	+	+++	+	+	-	++	-	-	CM	Q	+	i
34	120	NH	-	20.0	4.0	5.0	20	14	+	-	-	4.6	180	300	15.0	25.1	16.6	192	150	3.8	-	N	-	+	GI	+	+	+	+	+++	-	-	++	-	HE	CM	Q+DC	-	i
35	5	NC	-	0.0	1.0	4.0	14	14	+	-	-	6.0	82	56	-	1.1	0.3	100	28	1.1	N	-	-	+	-	-	-	+	-	-	-	+	-	-	-	CM	Q+DC	+	i
36	114	DM	-	6.0	4.0	3.3	17	14	+	-	-	5.8	86	74	8.0	1.7	1.1	100	88	1.5	-	N	-	+	-	-	-	-	+	-	-	+	++	-	-	-	Q+DC	-	i
37	72	DM	-	0.5	3.0	3.3	17	13	++	-	+	6.3	65	60	10.0	6.3	5.1	83	65	1.9	-	N	-	-	-	-	+	-	+	+	-	-	++	-	-	-	Q+DC	+	i
38	105	DM	-	5.0	3.0	3.3	18	14	-	-	-	5.7	88	60	10.0	2.3	0.9	83	26	1.1	-	-	-	-	-	-	-	+	-	+	-	-	++	-	-	CM	Q+DC	+	i

S.No	ESR (MM/hr)	PS/Parasite Stage	Bone Marrow	parasite index (%)	RTC (%)	BT (Min/Sec)	T	C	Albumin	Sugar	Micro (WBC/Cast/HPF)	Protein gm%	SGOT-U/L	SGPT /IU/L	AP	T	D	RBS mg%	BUN mg%	Creatinine mg%	CSF	Electrolytes	Others	Shock	Haemorrhage	Hypoglyemia	Acute GE	Cerebral malaria	ARF/BW Fever	HE	ARDS	Acute abdomen	Severe anemia	Pregnancy	Late complications	Diagnosis	Treatment	Blood transfusion	Outcome
39	10	NC	-	2.0	1.0	3.3	14	14	-	-	-	6.8	38	30	8.0	0.8	-	83	28	0.9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	MM	-	Q+DC	-	i
40	65	R	-	15.0	10.0	4.3	18	14	+	-	+	6.2	200	162	6.0	3.1	2.0	108	43	1.5	N	N	-	-	-	-	-	+	+	+	-	-	++	-	-	CM	Q+DC	+	i
41	140	DM	-	2.0	4.6	3.0	16	14	-	-	-	5.6	82	51	-	0.7	-	67	30	0.8	N	N	CTN	+	GI	+	-	+	-	-	-	-	+++	+	S	CM	Q+TC	+	i
42	28	DM	-	2.0	4.0	2.0	26	13	-	-	-	4.7	27	18	10.0	1.0	-	192	29	1.1	N	N	CTBE	+	DIC	-	+	+	-	-	+	-	++	-	DIC	CM	Q+DC	+	E
43	180	DM	RG+	-	3.0	3.0	14	14	-	-	-	5.0	40	36	-	1.7	0.6	115	36	1.1	-	N	-	-	-	-	-	-	-	-	-	-	++	-	-	-	CQ	+	i
44	100	DM	-	70.0	4.0	2.0	15	13	-	-	-	5.5	108	125	-	5.4	3.8	215	288	5.6	N	N	-	-	-	-	-	+	+	+	-	-	++	-	MOD	CM	Q+DC	-	i
45	75	DM	RG+	1.5	1.0	2.3	15	13	+	-	-	6.1	24	25	-	0.9	-	92	30	1.1	-	N	-	-	GI	-	-	-	-	-	-	-	++	-	DIC	-	Q+DC	+	i
46	106	DM	-	3.0	3.0	4.3	14	14	-	-	-	6.0	52	48	-	0.9	-	84	50	1.7	N	-	-	-	-	-	-	+	-	-	-	-	-	-	S	CM	Q+DC	-	i
47	98	DM	RG+	0.0	4.0	5.0	13	13	-	-	-	5.8	52	48	-	0.8	-	86	29	1.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DT	-	Q+DC	-	i
48	70	DM	-	2.0	2.0	3.3	14	14	-	-	-	4.1	65	45	-	0.8	-	75	71	1.7	-	N	-	-	-	-	+	-	-	-	-	-	-	-	-	-	Q+DC	-	i
49	100	DM	-	2.0	4.0	7.0	26	14	++	-	+	5.1	26	20	-	0.7	-	183	418	10.9	N	K+	RA	+	-	-	+	+	+	-	+	-	-	-	ARDS	-	Q	+	E
50	120	H	-	12.0	3.0	7.0	16	13	+	-	+	5.0	217	100	-	17.7	11.5	100	310	7.9	-	N	-	+	GI	-	-	+	+++	+++	-	+	-	-	GIB	-	Q	+	E
51	10	H	-	4.0	2.0	7.0	14	14	+	-	+	6.0	105	145	-	0.8	-	92	29	1.1	-	N	-	-	-	-	-	-	-	+	-	-	-	-	-	-	Q	-	i
52	120	DM	-	50.0	2.0	3.0	14	14	+	-	-	5.6	115	60	-	1.1	-	125	102	1.9	N	N	-	+	-	+	-	+	+	-	-	+	-	-	GIB	CM	Q+TC	+	i
53	156	DM	RG+	0.0	0.8	3.0	18	14	-	-	-	5.6	96	112	11.0	1.4	-	92	33	1.1	-	-	-	+	-	+	-	+	-	+	-	-	+++	-	-	CM	Q+DC	+	i
54	88	DM	-	0.0	5.0	4.3	16	14	+	-	-	6.0	38	44	-	0.7	-	100	36	1.1	N	N	-	-	-	+	-	+	-	-	-	-	-	-	HG	CM	Q+DC	+	i
55	31	DM	-	10.0	1.0	5.0	14	14	+	-	-	6.5	42	36	-	0.8	-	275	36	1.1	N	N	-	+	-	-	-	+	-	-	+	-	-	-	S,ARDS	CM	Q+DC	-	E
56	70	NC	RG+	0.0	1.2	3.3	16	14	+	-	+	6.0	215	180	-	2.6	1.0	108	69	3.0	-	N	-	+	GI	-	-	-	+++	+	+	-	++	-	NP	-	AS+D	+	i
57	66	DM	-	5.0	3.5	5.0	14	14	-	-	-	4.6	70	55	6.7	2.6	1.0	83	60	2.0	-	N	-	-	-	-	-	+	+	+	-	-	++	-	HG	CM	AS+D	+	i
58	26	DM	-	5.0	0.2	3.0	14	14	+	-	+	5.8	64	46	-	0.8	-	92	30	1.1	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	CM	Q	-	i
59	175	NC	RG+	0.0	6.5	4.5	16	14	-	-	-	6.3	59	63	6.3	2.0	-	83	40	1.1	-	-	RA	-	-	-	+	+	-	+	-	-	+++	-	-	CM	Q	+	i
60	16	DM	-	8.0	4.0	3.3	18	14	+	-	-	5.0	36	42	8.7	1.1	-	150	113	1.9	-	-	-	+	-	-	-	-	+	-	+++	-	-	-	ARDS	-	Q	-	i
61	117	NC	-	8.0	0.5	5.0	16	14	+	+	-	7.0	48	23	-	2.3	0.8	100	95	1.1	N	N	-	-	-	+	-	+	+	+	+	-	-	-	HG	CM	CQ	+	E
62	16	NH	-	2.0	2.0	3.0	14	13	-	-	-	5.8	40	32	-	0.8	-	117	38	1.1	-	N	-	-	-	-	-	-	-	-	-	-	-	-	-	-	AS	-	i
63	130	NC	RG+	0.0	2.0	3.0	16	14	-	+	-	5.8	42	36	-	0.8	-	275	88	1.9	N	N	-	+	GI	-	-	+	+	-	-	-	-	-	-	CM	Q+DC	-	i
64	18	DM	-	40.0	1.0	11.0	33	13	+	-	-	6.0	950	750	32.0	31.0	19.0	82	32	1.5	-	K+	-	+	GI	-	-	+	-	+++	-	-	-	-	COMA	CM	Q	+	E
65	152	NC	-	3.0	3.5	3.3	18	14	-	-	-	6.5	300	250	15.0	6.3	3.7	83	342	9.0	-	K+	-	+	-	-	-	-	+	+++	-	-	+++	+	ARDS	-	AS+D	+	E
66	120	H	-	2.5	2.0	4.3	17	13	+	+	+	4.4	125	137	9.3	11.4	7.4	150	136	3.0	N	N	-	-	-	-	-	+	+++	+++	-	-	++	-	COMA	CM	Q+DC	+	i
67	62	DM	RG+	0.0	7.4	4.0	16	13	+	-	-	5.2	144	132	8.0	2.0	-	70	22	1.0	-	-	-	+	-	-	-	-	-	+	-	-	+++	-	-	-	Q+DC	-	i
68	75	DM	-	5.0	2.0	9.0	17	13	+	-	+	6.0	92	70	-	2.0	-	217	236	1.7	N	N	-	-	NB	-	-	+	+++	+	-	-	+++	-	NB	CM	Q+DC	+	i
69	75	DM	RG+	0.0	2.0	5.0	14	14	++	-	+	5.8	46	38	-	0.8	-	80	28	1.1	-	-	-	-	-	-	-	-	-	-	-	-	+++		-	-	Q+DC	-	i
70	90	NH	-	5.0	1.5	3.0	14	14	+	-	+	5.8	48	40	-	1.0	-	158	25	0.8	-	N	CTN	+	-	-	-	+	-	-	-	-	+++		6CNP	CM	Q+DC	+	i
71	151	DM	-	2.8	2.5	5.0	14	13	+	-	+	5.0	48	35	10.0	1.7	0.9	75	94	2.3	-	N	-	+	-	-	-	-	+	-	+	-	++	+	DF	-	AS+D	+	i
72	130	DM	-	11.0	4.9	4.3	14	14	+	-	-	4.8	225	110	8.7	7.1	4.9	133	84	2.6	N	K+	-	+	-	-	-	+	-	+	+	-	++	-	ARDS	CM	Q	+	E
73	74	NH	-	12.0	5.0	7.3	14	14	+	-	+	4.8	43	57	14.0	2.9	1.7	125	178	10.9	-	K+	-	+	-	-	+	+	+++	+	+	-	++	-	-	CM	Q	+	i
74	120	NH	-	20.0	4.0	5.0	20	14	+	-	-	4.6	180	300	15.0	25.1	16.6	192	150	3.8	-	N	-	+	GI	+	+	+	+	+++	-	-	++	-	HE	CM	Q+DC	-	i
75	5	NC	-	0.0	1.0	4.0	14	14	+	-	-	6.0	82	56	-	1.1	0.3	100	28	1.1	N	-	-	+	-	-	-	+	-	-	-	+	-	-	-	CM	Q+DC	+	i
76	114	DM	-	6.0	4.0	3.3	17	14	+	-	-	5.8	86	74	8.0	1.7	1.1	100	88	1.5	-	N	-	+	-	-	-	-	+	-	-	+	++	-	-	-	Q+DC	-	i
77	72	DM	-	0.5	3.0	3.3	17	13	++	-	+	6.3	65	60	10.0	6.3	5.1	83	65	1.9	-	N	-	-	-	-	-	+	-	+	+	-	-	++	-	-	-	Q+DC	+	i

	ESR (MM/hr)	PS/Parasite Stage	Bone Marrow	parasite index (%)	RTC (%)	BT (Min/Sec)	T	C	Albumin	Sugar	Micro (WBC/Cast/HPF)	Protein gm%	SGOT-U/L	SGPT /IU/L	AP	T	D	RBS mg%	BUN mg%	Creatinine mg%	CSF	Electrolytes	Others	Shock	Haemorrhage	Hypoglyemia	Acute GE	Cerebral malaria	ARF/BW Fever	HE	ARDS	Acute abdomen	Severe anemia	Pregnancy	Late complications	Diagnosis	Treatment	Blood transfusion	Outcome
78	105	DM	-	5.0	3.0	3.3	18	14	-	-	-	5.7	88	60	10.0	2.3	0.9	83	26	1.1	-	-	-	-	-	-	-	+	-	+	-	-	++	-	-	CM	Q+DC	+	i
79	10	NC	-	2.0	1.0	3.3	14	14	-	-	-	6.8	38	30	8.0	0.8	-	83	28	0.9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	MM	-	Q+DC	-	i
80	65	R	-	15.0	10.0	4.3	18	14	+	-	+	6.2	200	162	6.0	3.1	2.0	108	43	1.5	N	N	-	-	-	-	-	+	+	+	-	-	++	-	-	CM	Q+DC	+	i
81	140	DM	-	2.0	4.6	3.0	16	14	-	-	-	5.6	82	51	-	0.7	-	67	30	0.8	N	N	CTN	+	GI	+	-	+	-	-	-	-	+++	+	S	CM	Q+TC	+	i
82	28	DM	-	2.0	4.0	2.0	26	13	-	-	-	4.7	27	18	10.0	1.0	-	192	29	1.1	N	N	CTBE	+	DIC	-	+	+	-	-	+	-	++	-	DIC	CM	Q+DC	+	E
83	180	DM	RG+	-	3.0	3.0	14	14	-	-	-	5.0	40	36	-	1.7	0.6	115	36	1.1	-	N	-	-	-	-	-	-	-	-	-	-	++	-	-	-	CQ	+	i
84	100	DM	-	70.0	4.0	2.0	15	13	-	-	-	5.5	108	125	-	5.4	3.8	215	288	5.6	N	N	-	-	-	-	-	+	+	+	-	-	++	-	MOD	CM	Q+DC	-	i
85	75	DM	RG+	1.5	1.0	2.3	15	13	+	-	-	6.1	24	25	-	0.9	-	92	30	1.1	-	N	-	-	GI	-	-	-	-	-	-	-	++	-	DIC	-	Q+DC	+	i
86	106	DM	-	3.0	3.0	4.3	14	14	-	-	-	6.0	52	48	-	0.9	-	84	50	1.7	N	-	-	-	-	-	-	+	-	-	-	-	-	-	S	CM	Q+DC	-	i
87	98	DM	RG+	0.0	4.0	5.0	13	13	-	-	-	5.8	52	48	-	0.8	-	86	29	1.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DT	-	Q+DC	-	i
88	70	DM	-	2.0	2.0	3.3	14	14	-	-	-	4.1	65	45	-	0.8	-	75	71	1.7	-	N	-	-	-	-	+	-	-	-	-	-	-	-	-	-	Q+DC	-	i
89	100	DM	-	2.0	4.0	7.0	26	14	++	-	+	5.1	26	20	-	0.7	-	183	418	10.9	N	K+	RA	+	-	-	+	+	+	-	+	-	-	-	ARDS	-	Q	+	E
90	120	H	-	12.0	3.0	7.0	16	13	+	-	+	5.0	217	100	-	17.7	11.5	100	310	7.9	-	N	-	+	GI	-	-	+	+++	+++	-	+	-	-	GIB	-	Q	+	E
91	10	H	-	4.0	2.0	7.0	14	14	+	-	+	6.0	105	145	-	0.8	-	92	29	1.1	-	N	-	-	-	-	-	-	-	+	-	-	-	-	-	-	Q	-	i
92	120	DM	-	50.0	2.0	3.0	14	14	+	-	-	5.6	115	60	-	1.1	-	125	102	1.9	N	N	-	+	-	+	-	+	+	-	-	+	-	-	GIB	CM	Q+TC	+	i
93	156	DM	RG+	0.0	0.8	3.0	18	14	-	-	-	5.6	96	112	11.0	1.4	-	92	33	1.1	-	-	-	+	-	+	-	+	-	+	-	-	+++	-	-	CM	Q+DC	+	i
94	88	DM	-	0.0	5.0	4.3	16	14	+	-	-	6.0	38	44	-	0.7	-	100	36	1.1	N	N	-	-	-	+	-	+	-	-	-	-	-	-	HG	CM	Q+DC	+	i
95	31	DM	-	10.0	1.0	5.0	14	14	+	-	-	6.5	42	36	-	0.8	-	275	36	1.1	N	N	-	+	-	-	-	+	-	-	+	-	-	-	S,ARDS	CM	Q+DC	-	E
96	70	NC	RG+	0.0	1.2	3.3	16	14	+	-	+	6.0	215	180	-	2.6	1.0	108	69	3.0	-	N	-	+	GI	-	-	-	+++	+	+	-	++	-	NP	-	AS+D	+	i
97	66	DM	-	5.0	3.5	5.0	14	14	-	-	-	4.6	70	55	6.7	2.6	1.0	83	60	2.0	-	N	-	-	-	-	-	+	+	+	-	-	++	-	HG	CM	AS+D	+	i
98	26	DM	-	5.0	0.2	3.0	14	14	+	-	+	5.8	64	46	-	0.8	-	92	30	1.1	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	CM	Q	-	i
99	175	NC	RG+	0.0	6.5	4.5	16	14	-	-	-	6.3	59	63	6.3	2.0	-	83	40	1.1	-	-	RA	-	-	-	+	+	-	+	-	-	+++	-	-	CM	Q	+	i
100	16	DM	-	8.0	4.0	3.3	18	14	+	-	-	5.0	36	42	8.7	1.1	-	150	113	1.9	-	-	-	+	-	-	-	-	+	-	+++	-	-	-	ARDS	-	Q	-	i