"STUDY OF PATIENTS OF FALCIPARUM MALARIA AND SEVERITY ASSESSMENT WITH RISK PREDICTION USING MALARIA SEVERITY SCORE"

By

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DOCTOR OF MEDICINE

IN

GENERAL MEDICINE

Under the guidance of

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I hereby declare that this dissertation/thesis entitled **"STUDY OF PATIENTS OF FALCIPARUM MALARIA AND SEVERITY ASSESSMENT WITH RISK PREDICTION USING MALARIA SEVERITY SCORE"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. Raveesha A.** MD, Professor, Department of General Medicine, Sri Devaraj Urs Medical College, Tamaka, Kolar.

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A WORD OF GRATITUDE

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ABSTRACT

BACKGROUND:

According to the *World Malaria Report 2010*, there were 225 million cases of malaria and an estimated 781 000 deaths in 2009 [1]. Malaria is one of the major public health problems in Karnataka and contributes about 7-10% of the total cases of malaria in the country.[2] In Kolar, Geographical reconnaissance ,revealed that irrigation tanks, wells and streams are the major breeding grounds for the mosquitoes *Anopheles culicifacies* and *An. Fluviatilis* , known vectors of malaria[2]. Kolar district has always been an endemic area for malaria.[3] A study from Sri Devraj Urs Medical college showed that despite good awareness about malaria, adoption of the mosquito control methods was poor in the area.[3]

It has been observed that no two patients of falciparum malaria are same in severity[4]. Research on objective assessment of disease severity and prediction of mortality risk in malaria is lacking even if it frequently develops multiple organ dysfunction during the course of illness[5-6]. Objective risk assessment have been proved very useful for clinical decision making, in evaluating new therapies, in improving quality of treatment, and for proper utilization of resources in various critical conditions like sepsis, acute myocardial infarction etc.[7-8.]

Even if the diagnostic features of severe malaria have been set out by WHO, there is no objective criteria to quantify the severity of each complication. The aim of the study is to find out the usefulness of malaria severity score to predict to assess severity with risk prediction and design appropriate management measures.

OBJECTIVES:

1. To study the clinical features of Plasmodium. falciparum malaria .

2 . To assess the severity using Malaria severity score based on multiple organ dysfunction.

3. To find out how the malaria severity score is useful in predicting the outcome and designing improved management measures.

METHODS:

All adult patients (>18 years) of malaria presented to Department of Medicine of Sri R.L.JALAPPA Hospital and Research centre, attached to Sri DEVARAJ URS MEDICAL COLLEGE, and S.N.R Hospital for a period of one year. All Proven cases of P.*falciparum* malaria in adults. (Thin and Thick Smear study/ Rapid Card Test for malaria /QBC test) Every patient will be evaluated by history, clinical examination and relevant investigations and stratified as per malaria severity score.

RESULTS:

In our study GCS was impaired in 6.7%, 36.7 % had impaired serum creatinine and 50 % impaired blood urea. Total bilirubin was high in 27.7 %. Systolic blood pressure less than 90 mmHg was seen in 13.3 %, blood glucose was impaired in 3.3%. Haemoglobin was decreased in 46.7%, low platelets was seen in 36.7% and altered total counts in 26.6 %.

In Total Organs involved, 6.66 % patient had five organ system involved that's highest in our study. Highest group was two organ involvements, i.e. 26.66 %. In present study highest level of dysfunction is seen in the form of Renal and Haematological involvement, followed by Hepatic and cardiovascular involvement.

Uncomplicated Malaria accounts for 13.3% in our sudy. One organ dysfunction is 40% is noted in present study. Two organ dysfunction accounts for 17.1% in our study. Similarly three organ dysfunction accounts for 10% , four organ dysfunction accounts for 3.33%, five organ dysfunction accounts for 6.66% ,involvement of six organ dysfunction and seven organ dysfunction was not noted in our study.

In this study it was observed that the majority 40 % had a probability of death 3.1 %. The maximum probability of death was 61.70 % in 3.3 % subjects. Though there were >40% probability of death among 10% of subjects all the patients survived by aggressive management in Medical Intensive Care unit with continuous monitoring, Artesunate based combination therapy and supportive care. Supportive measures like maintenance of hydration, antibiotics for any concurrent infections, blood transfusion, dialysis, ventilator support etc. were given according to individual needs. Patient with more than 40% probability of mortality was allocated resources aggressively with favorable outcome.

CONCLUSION:

Malaria severity score can help physicians to assess severity and stratify the risk and allocated resources as per need in limited resource setting, a common scenario in our country. It`s helpful in predicting outcome as probability of death is given for each score and patient with high probability of mortality can identified , to provide more attention and quality care. Malaria severity score is good indicator of severity due its stratification of every organ dysfunction in different level of severity.

KEY WORDS: Plasmodium Falciparum, Malaria severity score, Organ dysfunction score,

LIST OF ABBREVIATIONS

ACT =	Artesunate Combination Therapy
BW =	Body Weight
CBC =	Complete bloodcount
CNS =	Central Nervous System
DIC =	Disseminated Intravascular Coagulation
ESR =	Erythrocyte sedimentation rate
G6PD =	Glucose 6 Phosphate Dehydrogenase
GIT =	Gastro Intestinal Tract
IM =	Intramuscular
IV =	Intravenous
LDH =	Lactate Dehydrogenase
P.F. =	*P.falciparum*
PF HRP =	Plasmodium Falciparum Histidine Rich Protein
PT =	Prothrombin time
P.V. =	*P. vivax*
TLC: =	Total Leukocyte Count
TPC:=	Total Platelet Count
RBC =	Red Blood Cell
WBC =	White Blood Cell

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INTRODUCTION

Just like the absence of sadness is not joy, the absence of disease is not health. The WHO states this, and all of us instinctively know it. Health is our greatest gift. It is GOD given, but the duty to nurture it is ours alone.

Malaria is a protozoan disease transmitted by the bite of infected Anopheles mosquitoes.[1]Infection is caused by a parasite of genus Plasmodia which is transmitted to human beings by a pre infected female anophelene mosquito. (3) Of the four species of plasmodia causing human malaria, P.falciparum has the potential of developing life threatening complications, which may result in fatality those are Genus Plasmodium has 4 species- *P. vivax*(PV), *P. falciparum* (PF), *P.malariae* and *P. ovale*. In India, *P. Vivax* and *P. falciparum* are the species commonly found. Malaria is one of the major public health problems in Karnataka and contributes about 7-10% of the total cases of malaria in the country.[3].

In spite of worldwide efforts to reduce malaria transmission, it is still the major cause of morbidity and mortality, with overall fatality rate of 10-30 % (4) was seen. According to the *World Malaria Report 2010*, there were 225 million cases of malaria and an estimated 781 000 deaths in 2009 [2.] The main areas where disease predominates are the rural and remote areas, where prompt treatment is not available or not detected in time. (5)

Malaria parasite affects multiple organs of the body like liver, spleen, brain, gastro intestinal tract (G.I.T), gall bladder, pancreas, blood vessels and placenta. So the clinical picture could be wide spectrum ranging from simple malaise to life threatening CNS symptoms like coma.

Different organs get involved in various ways like parasitic sequestration in the internal organs, intravascular and immune mediated destruction of RBCs and platelets and cytokine mediated injury. [6]

As the target of malaria parasite is RBC, peripheral blood smear examination is the major diagnostic tool of the disease. Malaria can cause haemostatic abnormalities that range from asymptomatic thrombocytopenia to fulminant disseminated intravascular coagulation (DIC). [7] Early investigators suggested that the major coagulation abnormality of malaria was DIC, but in recent years clinicians have recognized thrombocytopenia is common and early sign of malaria infection, whereas DIC is rare. [8] It has been estimated that 80% of patients infected with either *P.vivax* or *P.falciparum* malaria develop thrombocytopenia during their infection and although the thrombocytopenia is caused by increased platelet destruction, the mechanism has been unknown. [9]Thrombocytopenia is a common and early sign of malarial infection. [4].

Not surprisingly in fatal cases malaria may be complicated with multiple organ dysfunction, the cumulative effects of which cause fatality[4]. It has been observed that no two patients of falciparum malaria are same in severity[5]. Research on objective assessment of disease severity and prediction of mortality risk in malaria is lacking even if it frequently develops multiple organ dysfunction during the course of illness5[-6]. Objective risk assessment have been proved very useful for clinical decision making, in evaluating new therapies, in improving quality of treatment, and for proper utilization of resources in various critical conditions like sepsis, acute myocardial infarction etc.[7-8]Traditional malariometric indices mostly focus on parasitaemia[9-10].

Inspite of considerable progress in understanding the pathogenesis of the disease, the treatment mortality rate of cerebral malaria is 15-22 % and it can rise above 30% when associated with multiple organ dysfunction.[11, 12, and 13.] In fatal cases malaria may be complicated with multiple organ dysfunctions, the cumulative effect of which causes fatality [13]. Even if the diagnostic features of severe malaria have been set out by WHO, there is no objective criteria to quantify the severity of each complication.

The knowledge regarding the changing spectrum of malaria is very helpful for early diagnosis, because it may become untreatable if the vital time is lost. With malaria severity score one can assess severity with risk prediction and design appropriate management measures. Awareness of relative prevalence of different complications in a particular geographic area could greatly facilitate the approach towards early diagnosis and prompt treatment [14].

OBJECTIVES:

1. To study the clinical features of Plasmodium falciparum malaria.

2. To assess the severity using Malaria severity score based on multiple organ dysfunction.

3. To find out how the malaria severity score is useful in predicting the outcome and designing improved management measures.

REVIEW OF LITERATURE

MALARIA INTRODUCTION:

Malaria is a protozoan disease transmitted by the bite of infected *Anopheles* mosquitoes. It is the most important of the parasitic diseases of humans, with transmission in 107 countries containing 3 billion people and causing 1–3 million deaths each year [10]. Each year, there are more than 225 million cases of malaria, killing around 781,000 people according to the World Health Organization's 2010 World Malaria Report, deaths worldwide [11, 12].

HISTORY OF MALARIA:

Malaria, has been described since antiquity. Hippocrates is usually credited with the first clear description amongst occidental writers: In Epidemics he distinguished different patterns of fever, and in his Aphorisms he describes the regular paroxysms of intermittent fever.

. Malaria was thought by Italian writers to be caused by the offensive vapours emanating from the Tiberianmarsh[15]. The word 'malaria' comes from the Italian, and means literally 'bad air'. Indeed the cause of the seasonal periodic fevers was a continuous source of debate until the late nineteenth century[16].

Malaria in its long career in the history of world has dominated the life of mankind. It has proved to be decisive factor in wars. The history of Malaria probably goes back to history of

mankind because references to the periodic fever suggestive of malaria can be found in the early Chinese and Hindu writing[17].

THE CHRONOLOGY OF MALARIA[17]:

- 1600s: Use of the ''Peruvian bark'' by Jesuits for the treatment of malaria
- 1820: Pelletier and Caventou extract pure quinine alkaloids
- 1880: Laveran identified the causative agent for malaria while working in Algeria
- 1885: P vivax and P malariae are identified by Golgi
- 1889: Sakharov (1889) and Marchiafava and Celli (1890) identify P falciparum
- 1897: Ross demonstrates the transmission of avian malaria by Culex fatigans
- 1898: Grassi, Bignami, and Bastianelli show that malaria is transmitted by the Anopheles mosquito
- 1902: Ronald Ross received Nobel prize for his work on malarial transmission by Culex fatigans.
- 1907: Alphonse Laveran received Nobel prize for his work on role played by protozoa in causing disease. First to notice malarial parasite in blood of patient suffering from malaria
- 1934: Synthesis of chloroquine (Resochin) in Germany by IG Farben
- 1939: Paul Muller discovers the insecticidal properties of DDT.
- 1944: Proguanil is synthesized by Curd, Davey, and Rose in England
- 1948: Paul Hermann Müller received Nobel prize for discovering insecticidal properties of DDT.
- 1950s: Emergence of drug-resistant chloroquine
- 1950: Elderfield synthesized primaquine
- 1980s: Rediscovery of artemisinin derivatives in China.

- 1989: (Halfan) Halofantrine
- 1991: Identification of the Histidine-rich protein 2 by Parra et al thereby leading to the development of rapid diagnostic tests.

GLOBAL BURDEN OF DISEASE:

According to the *World Malaria Report 2010*, there were 225 million cases of malaria and an estimated 781 000 deaths in 2009 [1]. Malaria is one of the major public health problems in Karnataka and contributes about 7-10% of the total cases of malaria in the country[2]. In Kolar, Geographical reconnaissance ,revealed that irrigation tanks, wells and streams are the major breeding grounds for the mosquitoes *Anopheles culicifacies* and *An. Fluviatilis* , known vectors of malaria[2]. Kolar district has always been an endemic area for malaria[3].

EPIDEMIOLOGICAL SITUATION IN INDIA:

Approximately 2.5 million malaria cases are reported annually from South Asia, of which 76% are reported in India[18, 19]. Malaria is endemic throughout India with 95% of the population at risk of infection[20]. Infections caused by Plasmodium falciparum have increased in India in recent years [18, 16, 21]. The major endemic areas in India are in the north-eastern states -Andhra Pradesh, Chhattisgarh, Gujarat, Jharkhand, M.P., Maharashtra, Rajasthan and Orissa, besides a few focal areas in other parts of the country. About 80 per cent of Indian population lives in low endemic zones with malaria prevalence of less than 2 cases per 1000 population per year. The incidence rate (number of cases per 1000 population) is highest in Arunachal Pradesh followed by Orissa, Mizoram, Goa, Meghalaya, Tripura, Jharkhand, West Bengal, Rajasthan and Chhattisgarh[22] .Orissa, followed by West Bengal, Maharashtra,

Rajasthan, Mizoram, Assam, Meghalaya, Gujarat, Karnataka, Madhya Pradesh, Manipur and Jharkhand report the largest number of deaths[23, 21].

ETIOLOGY:

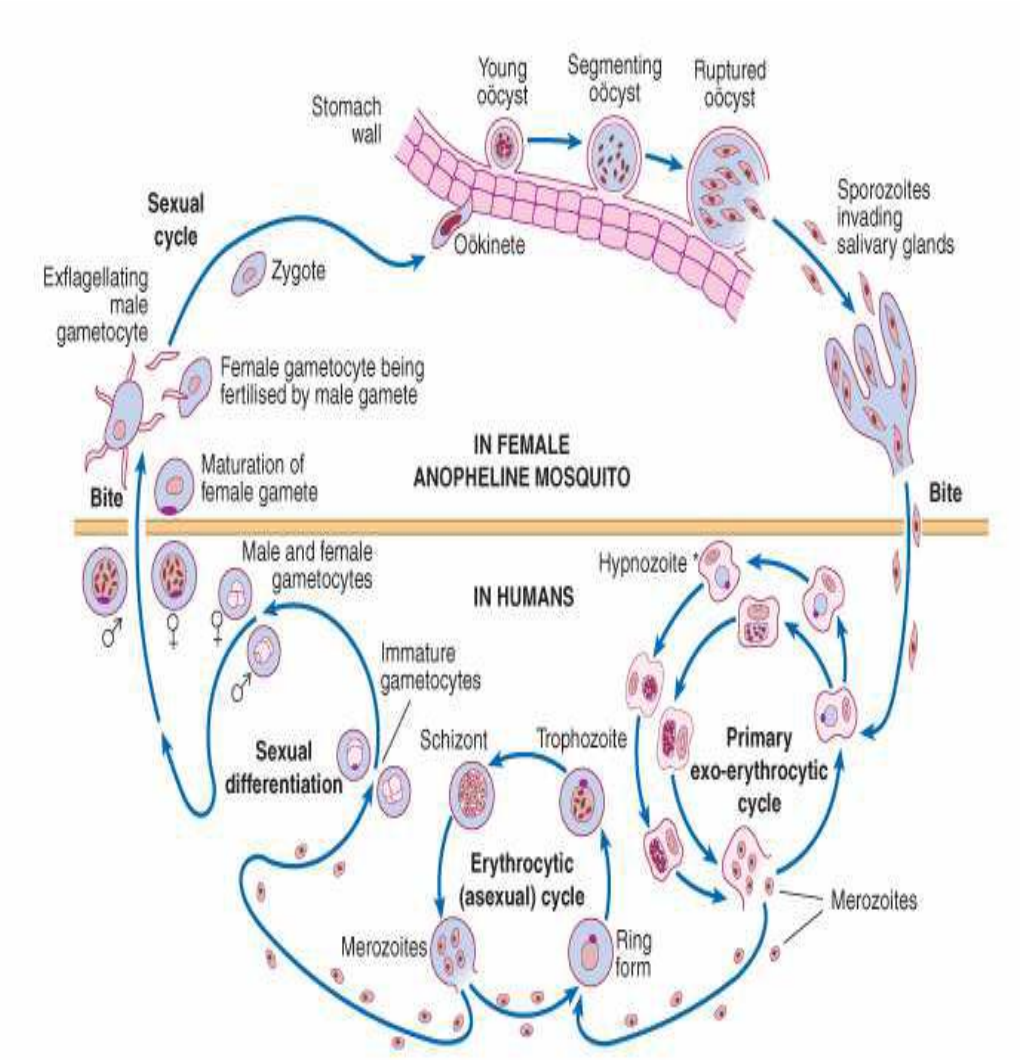
Four species of the genus *Plasmodium* cause nearly all malarial infections in humans (although rare infections involve species normally affecting other primates). These are *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Severe disease is largely caused by *Plasmodium falciparum* while the disease caused by *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae* is generally a milder disease that is rarely fatal[24]. *Plasmodium knowlesi* is a zoonosis that causes malaria in macaques but can also infect human[25,26].

LIFE CYCLE:[27]

Human infection begins when a female anopheline mosquito inoculates plasmodial *sporozoites* from its salivary gland during a blood meal. These microscopic motile forms of the malarial parasite are carried rapidly via the bloodstream to the liver, where they invade hepatic parenchymal cells and begin a period of asexual reproduction. By this amplification process (known as *intrahepatic* or *pre erythrocytic schizogony* or *merogony*), a single sporozoite eventually may produce from 10,000 to >30,000 daughter merozoites. The swollen infected liver cell eventually bursts, discharging motile *merozoites* into the bloodstream. These then invade the red blood cells (RBCs) and multiply six- to twentyfold every 48–72 hours. When the parasites reach densities of ~50/microliter of blood, the symptomatic stage of the infection begins. In *P. vivax* and *P. ovale* infections, a proportion of

the intrahepatic forms do not divide immediately but remain dormant for a period ranging from 3 weeks to a year or longer before reproduction begins. These dormant forms, or *hypnozoites*, are the cause of the relapses that characterize infection with these two species.

FIGURE 1: THE PLASMODIA LIFE CYCLE .[28,29]



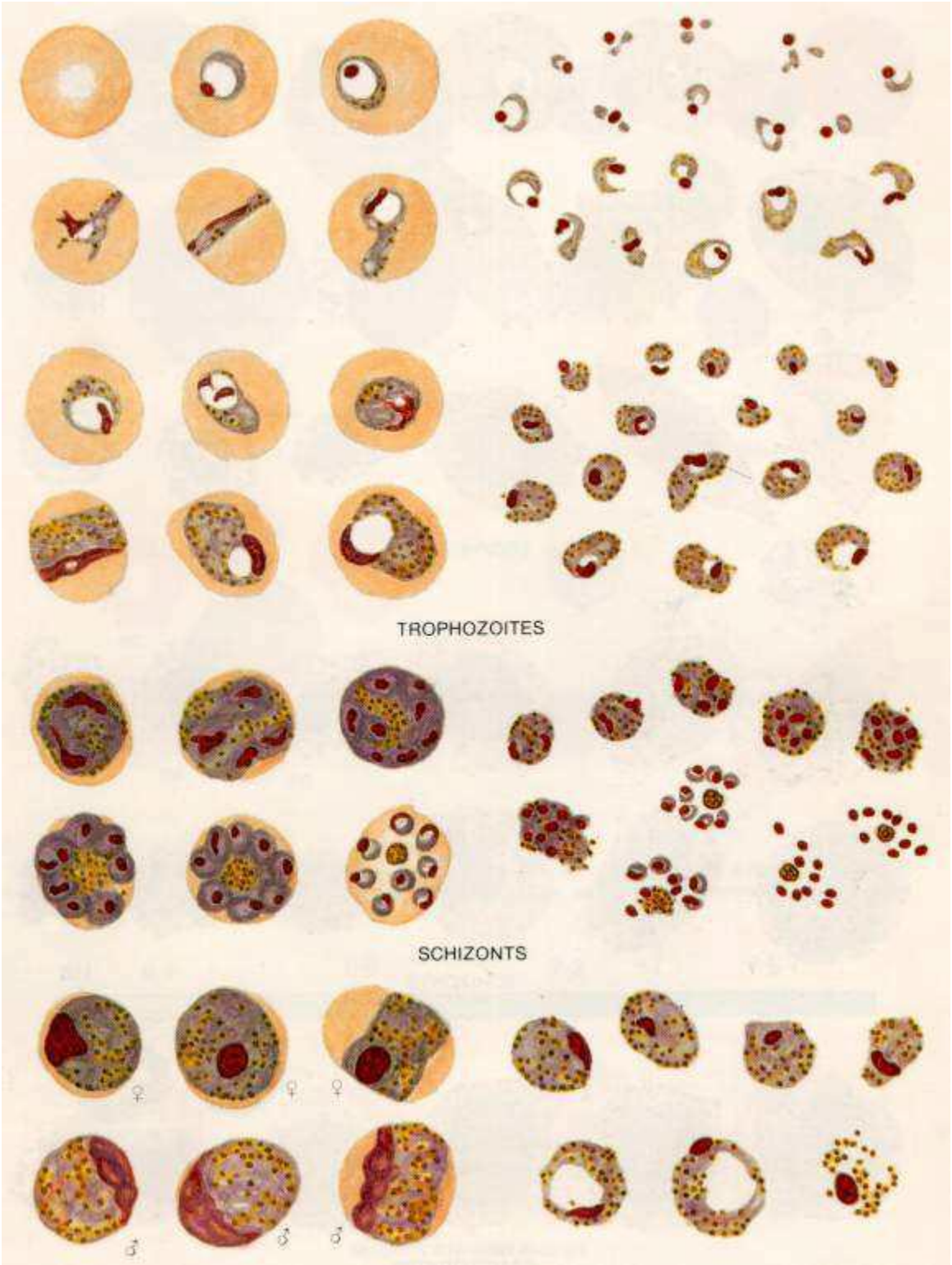


FIGURE 2: MICROSCOPIC VIEW OF VARIOUS FORMS OF PLASMODIUM

The human (asexual) stage of the life cycle begins with the exoerythrocytic phase. When an infected mosquito bites a human, sporozoites in the mosquito's saliva enter the bloodstream [27.] The sporozoites travel to the liver, where they invade hepatocytes [30] over a period of up to 4 weeks, the infected hepatocytes mature into schizonts. In Plasmodium vivax and P. ovale infections only, some schizonts may remain dormant as hypnozoites[31] for weeks to years before causing clinical relapses. With schizont rupture, merozoites are released into the bloodstream [7.] In the erythrocytic phase, merozoites invade erythrocytes and either undergo an asexual cycle of reproduction [32]or develop into non multiplying sexual forms gametocytes[22.] These gametocytes are crucial for perpetuating the life cycle, as they are ingested by a feeding mosquito [33]and undergo sexual reproduction within the mosquito midgut; thousands of infective sporozoites[15]are produced, which then migrate to the salivary glands, ready to initiate another life cycle.[28, 29] With each cycle of schizogony, there is a destruction of [parasitized erythrocytes, releasing cytokines like tumour Necrosis factor (TNF) and interleukins: IL-1, IL-6 and 8. These cytokines are responsible for inducing the characteristic febrile episodes of malaria. Repeated attacks of malaria result in anaemia, which may be out of proportion to the haemolysis caused by the destruction of parasitized erythrocytes. This is explained by the coexisting haemolysis of some of the non-parasitized erythrocytes as well as dyserythropoiesis [28,29].

MOLECULAR INSIGHTS INTO THE PLASMODIAL LIFE CYCLE[34]:

The predominant protein on the sporozoite surface 'circum sporozoite protein' (CSP) is the ligand that binds to the receptors on the hepatocyte surface that is responsible for parasite entry. Also studies have shown that a red cell antigen (Duffy factor) is necessary for invasion by P.vivax parasites and that P.vivax infection is uncommon among black populations because their cells lack the Duffy factor.

TABLE 3: LIGAND AND RECEPTORS IN THE MALARIA PARASITE LIFE CYCLE.[34]

Life cycle event PV 135	**Parasite ligand**	**Host receptor molecule**
Hepatocytic entry by sporozoite	CSP	Unknown
Red cell entry by merozoites P.falciparum	PV 135 Erythrocyte binding antigen 175 (EBA 175)	Duffy factor Glycophorin
Cytodherence of P.falciparum–parasitized RBC'S	Unknown	Thrombospondin CD 36, ICAM – 1, VCAM – 1 (Molecules on endothelial cell surface)

SIGNS AND SYMPTOMS: [27]

Malaria is a very common cause of fever in tropical countries. The first symptoms of malaria are nonspecific; the lack of a sense of well-being, headache, fatigue, abdominal discomfort, and muscle aches followed by fever are all similar to the symptoms of a minor viral illness. Symptoms of malaria include fever, shivering, arthralgia (joint pain), vomiting, anaemia (caused by haemolysis), hemoglobinuria, retinal damage,[35] and convulsions. The classic symptom of malaria is cyclical occurrence of sudden coldness followed by rigor and then fever and sweating lasting four to six hours, occurring every two days in *P. vivax* and *P. ovale* infections, and every three days for *P. malariae*. *P. falciparum* can have recurrent fever every 36–48 hours or a less pronounced and almost continuous fever. For reasons that are poorly understood, but that may be related to high intracranial pressure, children with malaria frequently exhibit abnormal posturing, a sign indicating severe brain damage. [36] Malaria has been found to cause cognitive impairments, especially in children. It causes widespread

anaemia during a period of rapid brain development and also direct brain damage. This neurologic damage results from cerebral malaria to which children are more vulnerable[37]. Cerebral malaria is associated with retinal whitening, [38] which may be a useful clinical sign in distinguishing malaria from other causes of fever. [35]. Severe malaria is almost exclusively caused by *Plasmodium falciparum* infection, and usually arises 6–14 days after infection.[30] Consequences of severe malaria include coma and death if untreated. Young children and pregnant women are especially vulnerable. Severe malaria can progress extremely rapidly and cause death within hours or days. [39]

WHO CRITERIA FOR SEVERE MALARIA:

MANIFESTATION	FEATURES
Initial World Health Organization criteria from 1990 [27]	
Cerebral malaria	Unrousable coma not attributable to any other cause, with a Glasgow Coma scale score ≤ 9. Coma should persist for at least 30 min after a generalized convulsion
Severe anaemia	Hematocrit<15% or haemoglobin< 50 mg/l in the presence of parasite count >10 000/μl
Renal failure	Urine output <400 ml/24 hours in adults (<12 ml/kg/24 hours in children) and a serum creatinine>265 μmol/l (> 3.0 mg/dl) despite adequate volume repletion
Pulmonary edema and Acute respiratory distress syndrome	The acute lung injury score is calculated on the basis of radiographic densities, severity of hypoanaemia, and positive end-expiratory pressure
Hypoglycemia	Whole blood glucose concentration <2.2 mmol/l (<40 mg/dl)
Circulatory collapse (algid malaria)	Systolic blood pressure <70 mmHg in patients > 5 years of age (< 50 mmHg in children aged 1–5 years), with cold

	clammy skin or a core-skin temperature difference >10°C
Abnormal bleeding and/or disseminated intravascular coagulation	Spontaneous bleeding from gums, nose, gastrointestinal tract, or laboratory evidence of disseminated intravascular coagulation
Repeated generalized convulsions	≥ 3 convulsions observed within 24 hours
Academia/acidosis	Arterial pH <7.25 or acidosis (plasma bicarbonate <15 mmol/l)
Macroscopic hemoglobinuria	Haemolysis not secondary to glucose-6-phosphate dehydrogenase deficiency
Added World Health Organization criteria from 2000[10]	
Impaired consciousness	Rousable mental condition
Prostration or weakness	
Hyperparasitemia	> 5% parasitized erythrocytes or > 250 000 parasites/μl (in nonimmune individuals)
Hyperpyrexia	Core body temperature >40°C
Hyperbilirubinemia	Total bilirubin >43 μmol/l (> 2.5 mg/dl)

Many clinical abnormalities have been described in acute malaria, but most patients with uncomplicated infections have few abnormal physical findings other than fever, malaise, mild anaemia, and (in some cases) a palpable spleen. Anaemia is common among young children living in areas with stable transmission, particularly where resistance has compromised the efficacy of antimalarial drugs. In non immune individuals with acute malaria, the spleen takes several days to become palpable, but splenic enlargement is found in a high proportion of otherwise healthy individuals in malaria-endemic areas and reflects repeated infections. Slight enlargement of the liver is also common, particularly among young children. Mild

jaundice is common among adults; it may develop in patients with otherwise uncomplicated falciparum malaria and usually resolves over 1-3 weeks. [27]

DIAGNOSIS: [27]

Table 203-5 Methods for the Diagnosis of Malaria[a]

Method	**Procedure**	**Advantages**	**Disadvantages**
Thick blood film[b]	Blood should be uneven in thickness but sufficiently thin to read watch hands through part of the spot. Stain dried, unfixed blood spot with Giemsa, Field's, or other Romanowsky stain. Count number of asexual parasites per 200 WBCs (or per 500 at low densities). Count gametocytes separately.[c]	Sensitive (0.001% parasitaemia); species specific; inexpensive	Requires experience (artefacts may be misinterpreted as low-level parasitaemia); underestimates true count

Thin blood film[d]	Stain fixed smear with Giemsa, Field's, or other Romanowsky stain. Count number of RBCs containing asexual parasites per 1000 RBCs. In severe malaria, assess stage of parasite development and count neutrophils containing malaria pigment.[e] Count gametocytes separately.[c]	Rapid; species specific; inexpensive; in severe malaria, provides prognostic information[e]	Insensitive (<0.05% parasitaemia); uneven distribution of *P. vivax*, as enlarged infected red cells concentrate at leading edge
PfHRP2 dipstick or card test	A drop of blood is placed on the stick or card, which is then immersed in washing solutions. Monoclonal antibody captures the parasite antigen and reads out as a colored band.	Robust and relatively inexpensive; rapid; sensitivity similar to or slightly lower than that of thick films (~0.001% parasitaemia)	Detects only *Plasmodium falciparum*; remains positive for weeks after infection[f]; does not quantitate *P. Falciparum* parasitaemia

Plasmodium LDH dipstick or card test	A drop of blood is placed on the stick or card, which is then immersed in washing solutions. Monoclonal antibodies capture the parasite antigens and read out as colored bands. One band is genus specific (all malarias), and the other is specific for *P. falciparum.*	Rapid; sensitivity similar to or slightly lower than that of thick films for *P. falciparum* (~0.001% parasitaemia)	Slightly more difficult preparation than PfHRP2 tests; may miss low-level parasitaemia with *P. vivax*, *P. ovale*, and *P. malariae* and does not speciate these organisms; does not quantitate *P. Falciparum* parasitaemia
Microtube concentration methods with acridine orange staining	Blood is collected in a specialized tube containing acridine orange, anticoagulant, and a float. After centrifugation, which concentrates the parasitized cells around the float, fluorescence microscopy is performed.	Sensitivity similar or superior to that of thick films (~0.001% parasitaemia); ideal for processing large numbers of samples rapidly	Does not speciate or quantitate; requires fluorescence microscopy

a.Malaria cannot be diagnosed clinically with accuracy, but treatment should be started on clinical grounds if the laboratory confirmation is likely to be delayed. In areas of the world where malaria is endemic and transmission is high, low-level asymptomatic parasitaemia is common in otherwise-healthy people. Thus malaria may not be the cause of a fever, although

in this context the presence of >10,000 parasites/microliter (–0.2% parasitaemia) does indicate that malaria is the cause. Antibody and polymerase chain reaction tests have no role in the diagnosis of malaria.

b. parasite count/microliter =Asexual parasites/200 WBCs x 40 (assumes a WBC count of 8000/μl).

c.Gametocytemia may persist for days or weeks after clearance of asexual parasites. Gametocytemia without asexual parasitaemia does not indicate active infection.

d. parasite count/microliter = Parasitized RBCs (%) x Hematocrit x 1256

e.The presence of >100,000 parasites/microliter (–2% parasitaemia) is associated with an increased risk of severe malaria, but some patients have severe malaria with lower counts. At any level of parasitaemia, the finding that >50% of parasites are tiny rings (cytoplasm width less than half of nucleus width) carries a relatively good prognosis. The presence of visible pigment in >20% of parasites or of phagocytosed pigment in >5% of polymorph nuclear leukocytes (indicating massive recent schizogony) carries a worse prognosis.

f. Persistence of PfHRP2 is a disadvantage in high-transmission settings, where many asymptomatic people have positive tests, but can be used to diagnostic advantage in low-transmission settings when a sick patient has received previous unknown treatment (which, in endemic areas, often consists of antimalarial drugs). A positive PfHRP2 test indicates that the illness is falciparum malaria, even if the blood smear is negative.

Note: LDH, lactate dehydrogenase; PfHRP2, *P. Falciparum* Histidine-rich protein 2; RBCs, red blood cells; WBCs, white blood cells

TREATMENT:

From Guidelines for diagnosis and treatment of malaria in India 2011, National Institute of Malaria research [40].

Treatment of uncomplicated malaria

All fever cases diagnosed as malaria by RDT or microscopy should promptly be given effective treatment.

TREATMENT OF P. VIVAX MALARIA:

- Confirmed P. vivax cases should be treated with chloroquine in full therapeutic dose of 25 mg/kg divided over three days.

- In some patients, P. vivax may cause relapse (form of P. vivax or P. ovale parasites called as hypnozoites remain dormant in the liver cells. These hypnozoites can later cause a relapse).

- For its prevention, primaquine should be given at a dose of 0.25 mg/kg body weight daily for 14 days under supervision.

- Primaquine is contraindicated in known G6PD deficient patients, infants and pregnant women.

- Caution should be exercised before administering primaquine in areas known to have high prevalence of G6PD efficiency; therefore, it should be tested if facilities are available.
- Primaquine can lead to haemolysis in G6PD deficiency defect.

- Patient should be advised to stop primaquine immediately if he/she develops symptoms like dark coloured urine, yellow conjunctiva, bluish discolouration of lips, abdominal pain, nausea, vomiting etc. and should report to the doctor immediately.

TREATMENT OF P. FALCIPARUM MALARIA: -

- Artemisinin Combination Therapy (ACT) should be given to all confirmed P. falciparum cases found positive by microscopy or RDT.

- This is to be accompanied by single dose primaquine (0.75 mg/kg body weight) on Day 2.

- ACT consists of an artemisinin derivative combined with a long acting antimalarial (amodiaquine, lumefantrine, mefloquine or sulfadoxine-pyrimethamine).

- The ACT recommended in the National Programme of India is Artesunate (4 mg/kg body weight) daily for 3 days and sulfadoxine (25 mg/kg body weight) - pyrimethamine (1.25 mg/kg body weight) on Day 0.

- Presently, fixed dose combinations of artemether+ lumefantrine, artesunate + amodiaquine and blister pack of artesunate + mefloquine are registered for marketing in India and are available for use.

- Artemisinin and its derivatives should not be used as monotherapy.

- Second-line antimalarial treatment:

- alternative ACT known to be effective in the region;
- artesunate plus tetracycline or doxycycline or clindamycin, any of these combinations should be given for 7 days;
- quinine plus tetracycline or doxycycline or clindamycin, any of these combinations should be given for 7 days.

TREATMENT OF MALARIA IN PREGNANCY: -

- ACT should be given for treatment of P. falciparum malaria in second and third trimesters of pregnancy, while quinine is recommended in the first trimester. P. vivax malaria can be treated with chloroquine[40].

TREATMENT OF SEVERE FALCIPARUM MALARIA:

- Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with any effective antimalarial first available.

- For adults, artesunate 2.4 mg/kg BW IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended treatment. Artemether, or quinine, is an acceptable alternative if parenteral artesunate is not available: artemether 3.2 mg/kg BW IM given on admission then 1.6 mg/kg BW per day; or quinine 20 mg salt/kg BW on admission (IV infusion or divided IM injection), then 10 mg/kg BW every 8 h; infusion rate should not exceed 5 mg salt/kg BW per hour.

- Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier), and, thereafter, complete treatment by giving a complete course of:
  – artemether plus lumefantrine,
  – artesunate plus amodiaquine,
  – dihydroartemisinin plus piperaquine,
  – artesunate plus sulfadoxine-pyrimethamine,
  – artesunate plus clindamycin or doxycycline,
  – quinine plus clindamycin or doxycycline.

ORAL ARTEMISININ MONOTHERAPY IS BANNED IN INDIA:

Artemisinin derivatives must never be administered as monotherapy for uncomplicated malaria. These rapidly acting drugs, if used alone, can lead to development of drug resistance.

TREATMENT OF MIXED INFECTIONS:

Mixed infections with P. falciparum should be treated as falciparum malaria. However, antirelapse treatment with primaquine can be given for 14 days, if indicated.

TREATMENT BASED ON CLINICAL CRITERIA WITHOUT LABORATORY CONFIRMATION:

- All efforts should be made to diagnose malaria either by microscopy or RDT. However, special circumstances should be addressed as mentioned below:

- If RDT for only P. falciparum is used, negative cases showing signs and symptoms of malaria without any other obvious cause for fever should be considered as ‘clinical malaria and treated with chloroquine in full therapeutic dose of25 mg/kg body weight over three days.

- If a slide result is obtained later, the treatment should be completed according to species.

- Suspected malaria cases not confirmed by RDT or microscopy should be treated with chloroquine in full therapeutic dose.

TREATMENT FAILURE/DRUG RESISTANCE:

After treatment patient is considered cured if he/she does not have fever or parasitaemia till Day 28. Some patients may not respond to treatment which may be due to drug resistance or treatment failure, especially in falciparum malaria. If patient does not respond and presents with following, he/she should be given alternative treatment [40].

EARLY TREATMENT FAILURE (ETF):

Development of danger signs or severe malaria on Day 1, 2 or 3, in the presence of parasitaemia; parasitaemia on Day 2 higher than on Day 0, irrespective of axillary temperature; parasitaemia on Day 3 with axillary temperature >37.5°C; and parasitaemia on Day 3, >25% of count on Day 0 [40] .

LATE CLINICAL FAILURE (LCF):

Development of danger signs or severe malaria in the presence of parasitaemia on any day between Day 4 and Day 28 (Day 42) in patients who did not previously meet any of the criteria of early treatment failure; and presence of parasitaemia on any day between Day 4 and Day 28 (Day 42) with axillary temperature >37.5°C in patients who did not previously meet any of the criteria of early treatment failure[40].

LATE PARASITOLOGICAL FAILURE (LPF):

Presence of parasitaemia on any day between Day 7 and Day 28, with axillary temperature <37.5°C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure [40].

Such cases of falciparum malaria should be given alternative ACT or quinine with Doxycycline. Doxycycline is contraindicated in pregnancy, lactation and in children up to 8 years. Treatment failure with chloroquine in P. vivax malaria is rare in India[40].

CHEMOPROPHYLAXIS:

Chemoprophylaxis is recommended for travellers, migrant labourers and military personnel exposed to malaria in highly endemic areas. Use of personal protection measures like insecticide-treated, bednets should be encouraged for pregnant women and other vulnerable populations.

SHORT-TERM CHEMOPROPHYLAXIS (LESS THAN 6 WEEKS)

- Doxycycline: 100 mg daily in adults and 1.5 mg/kg body weight for children more than 8 years old.
- The drug should be started 2 days before travel and continued for 4 weeks after leaving the malarious area.
- Doxycycline is contraindicated in pregnant and lactating women and children less than 8 years.

LONG-TERM CHEMOPROPHYLAXIS (MORE THAN 6 WEEKS)

- Mefloquine: 5 mg/kg body weight (up to 250 mg) weekly and should be administered two weeks before, during and four weeks after leaving the area.

- Mefloquine is contraindicated in cases with history of convulsions, neuropsychiatric problems and cardiac conditions.

From Guidelines for diagnosis and treatment of malaria in India 2011, National Institute of Malaria research [40].

HEMATOLOGICAL COMPLICATIONS IN MALARIA:

Malaria affects almost all blood components and is a true haematological infectious disease. Anaemia and thrombocytopenia are the most frequent malaria-associated haematological complications and have received more attention in the scientific literature due to their associated mortality [41]. The presence of thrombocytopenia in acute febrile travellers returning from tropical areas has become a highly sensitive clinical marker for malaria diagnosis [42]. One study has reported 60% sensitivity and 88% specificity of thrombocytopenia for malaria diagnosis in acute febrile patients [43]. The sensitivity of thrombocytopenia together with the acute febrile syndrome was 100% for malaria diagnosis, with a specificity of 70%, a positive predictive value of 86% and a negative predictive value of 100% [44]. Since the beginning of the 1970s, there have been reports proposing that malaria-associated thrombocytopenia is quite similar in *P. Vivax* and *Plasmodium falciparum* infections [45]. However, more recent data in India has shown how thrombocytopenia exhibited a heightened frequency and severity among patients with *P. Vivax* infection[46].

BLOOD COUNT AND BLOOD FILM:

Anaemia is found in many cases. It is often mild but may be moderate or severe [47, 48]. The red cells are usually normochromic and normocytic. The absolute reticulocyte count is not increased, even in severely anaemic patients. As in P. falciparum malaria, neutropenia, thrombocytopenia, lymphopenia and monocytosis may occur[48,49,50] . The gd T-cells are transiently increased during the paroxysms of fever[51]. Pre-existing eosinophilia is suppressed during P. vivax infection and recurs after therapy[52] .The blood film usually shows atypical lymphocytes[48], increased numbers of band cells and occasional neutrophil metamyelocytes.[47] Studies of neutrophil kinetics show decreased marrow granulocytes, a markedly increased marginated granulocyte pool, a reduced circulating granulocyte pool and a prolongation of

the $T_{1/2}$ of circulating neutrophils. Thus, there appears to be a rapid release of marrow granulocytes into the blood coupled with a shift of neutrophils from the circulating to the marginated cell pools. [47]

PATHOPHYSIOLOGY OF ANAEMIA

The pathophysiological processes causing the haematological changes in malaria are complex, multiple, and incompletely understood. In acute malaria, the anaemia is caused mainly by a combination of peripheral haemolysis and suppression of erythropoiesis. By contrast, in chronic malaria it is caused mainly by dyserythropoiesis and ineffective erythropoiesis. In acute malaria, macrophages are activated probably by several mechanisms. These are: (a) cytokines (e.g. IFN-g and TNF-a) released by activated T-lymphocytes, (b) parasite products, including haemozoin, and (c) the phagocytosis of parasitized red cells. Suppression of erythropoiesis and alterations in other haemopoietic lineages may result from the high levels of IFN-g and TNF-a generated over a short period and by direct effects of parasite products. In chronic malaria, the pathophysiology of severe anaemia may be somewhat different. Here, the high erythropoietin levels have time to cause marked erythroid hyperplasia. The considerable ineffectiveness of erythropoiesis may be the consequence of (a) modest increases in TNF acting on erythropoiesis over a prolonged period, (b) cytokine imbalance with the underproduction relative to TNF of IL-10 and possibly IL-12 or other cytokines, and (c) macrophage dysfunction affecting stimulatory and inhibitory haemopoietic growth factors [41].

Mechanisms considered , being involved in the pathogenesis of the anaemia of malaria.

Shortened red cell survival

A. Of parasitized red cells[41]

During schizogony

Secondary to membrane damage due to deparasitization by pitting in the spleen Related to antimalarial therapy [a]

B. Of non-parasitized red cells[41]

Immune mechanisms

Through macrophage activation and hyperplasia

Splenic pooling and hypersplenism[b]

Impaired erythropoiesis

A. Direct effect of parasite products

B. Indirect effects[41]

(a) Effects of parasite products on T-lymphocytes, macrophages and other stromal cells leading to cytokine imbalance

(b) Activation and hyperplasia of macrophages by lymphokines and parasite products leading to:

(i) Production of monokines, including TNF and other cytotoxic molecules (nitric oxide)

(ii) Haemophagocytosis

(c) Inhibition of erythroid progenitor cells secondary to cytokine imbalance

(d) Blunted erythropoietin response (acute malaria)

C. Packing of marrow sinusoids by parasitized red cells [41]

a. In blackwater fever.

b.Related to changes in macrophages.

PATHOGENESIS OF MALARIAL THROMBOCYTOPENIA:

Coagulation disturbances-

A study based on 31 American soldiers in Vietnam with chloroquine-resistant falciparum malaria noted the following changes in the acute phase of the disease using the same patients as their own controls during convalescence: decrease in the platelet count and prothrombim activation time, increase in the activated thromboplastin time, and reduction in factors V, VII and VIII with normal fibrinogen [53]. This report suggested that thrombocytopenia was simply a consequence of the coagulation disorders presented by these patients, an idea that persisted for many decades in the literature. In Manaus, 2004, a study with falciparum and vivax patients demonstrated a negative correlation between platelet counts, thrombin-anti-thrombin complex and D-dimers, suggesting that the activation of coagulation could be partially responsible for thrombocytopenia [54].

Splenomegaly –

The spleen in malaria has played a crucial role in the immune response against the parasite, as well as controlling parasitaemia due to the phagocytosis of parasitized red blood cells (RBCs) [55]. In the experimental model with *Plasmodium chabaudi*, thrombocytopenia was absent in splenectomised mice, showing that the spleen was essential for thrombocytopenia. [56] In patients with malaria, the increase in the macrophage-colony stimulating factor is associated to thrombocytopenia, suggesting that macrophages play a role in the destruction of

these particles [57]. In the comparison of spleens from patients with severe falciparum malaria vs. those of control and septic patients, it was shown that splenic dendritic cells are increased in malaria and there is a reduction in B lymphocytes and macrophages in the splenic cords [58]. *P. vivax* passing through the spleen would activate the transcription of polymorphic Vir proteins to escape from macrophage destruction in this organ. On the other hand, these same proteins would permit the binding of parasitized RBCs to barrier cells, creating an isolated microenvironment in the spleen that would be rich in reticulocytes [59]. More recent studies with the murine model of *Plasmodium yoelii* evidenced that there was higher parasite accumulation, reduced motility, loss of directionality, increased residence time and altered magnetic resonance only in the spleens of mice infected with the non-lethal 17X strain [60]. This same model has never been used to study the role of the spleen in thrombocytopenia, but opens new avenues for functional and structural studies of this lymphoid organ.

Bone marrow alterations-

The finding of a *P. vivax* trophozoite inside a human platelet suggested that thrombocytopenia could be the result of invasion of these particles by the parasites themselves, similar to what was classically proposed for RBCs. As these same authors did not find parasites inside megakaryocytes, they proposed that the penetration took place in the peripheral circulation [61]. However, this observation was never seen again in the literature. Likewise, a "dysmegakaryopoiesis" was proposed, similar to what happened in the human malarial anaemia model, where dyserythropoiesis was triggered by cytokines. In the few studies that examined the bone marrow for this purpose, megakaryocytic lineage was apparently preserved. Thrombopoietin indeed seems to rise during the acute disease even in the presence of liver compromise, suggesting that no bone marrow inhibition is seen [62]. Additional data from FBC samples in vivax patients showed that there is a significant

negative correlation between platelet count and mean platelet volume [63], suggesting that megakaryocytes are able to release mega platelets in the circulation to compensate for the low absolute number of platelets in the periphery. Similar results were shown in children with falciparum malaria [64]. These mega platelets are probably able to sustain a good primary haemostasis that could explain the low frequency of severe bleeding in malaria patients.

Antibody-mediated platelet destruction-

There is evidence that platelet-associated IgG (PAIgG) is increased in malaria and is associated with thrombocytopenia. However, this is a generic definition for all types of IgGs that may be found on the platelet surface, including antibodies stored inside platelet α-granules. Therefore, increased PAIgG could also be interpreted as platelet activation and exposition of IgGs on the surface, and not necessarily auto-immunity, as suggested in anecdotal case reports where antibodies against glycoproteins were detected in malaria [65, 66]. During acute malaria, thrombocytopenia is most probably associated with the binding of parasite antigens to the surface of platelets to which antimalarial antibodies also bind, leading to the *in situ* formation of immune complexes (ICs) [67]. Because the generation of IC's is proportional to the amount of available antigen, the negative correlation between platelet count and peripheral parasitaemia reported in many studies [68,69] corroborates ICs as a potential mechanism of platelet destruction. The presence of amino acid residues tyrosine 193 [9Y(193)] and serine 210 [S(210)] on apical membrane antigen-1 (AMA-1) was significantly associated with normal platelet counts in *P. Vivax* malaria independent of the level of parasitaemia that also provides supporting evidence for this [70].

Oxidative stress-

In a study of 103 patients with acute falciparum malaria, there was a negative correlation between platelet count and nitrogen reactive intermediates [71]. There is also a strong association between platelet count and intra-platelet glutathione peroxidase, suggesting that a compensatory mechanism is presented by platelets to face the oxidative burst found in malaria[72].

Platelet aggregation –

P. falciparum induces systemic acute endothelial cell activation and the release of activated von Willerbrand factor (vWF) immediately after the onset of the blood-stage infection [73]. Even without consumptive coagulopathy, the increase in soluble glycoprotein-1b (GP1b) concentrations results from vWF-mediated GP1b shedding, a process that may prevent excessive adhesion of platelets and parasitized erythrocytes [74]. Antimalarial drugs have also been shown as potential inhibitors of platelet aggregation in vivo and in vitro, what precludes careful inclusion and exclusion criteria of patients to be used in clinical research [75].

The relationship between thrombocytopenia and severe malaria –

Severe thrombocytopenia (platelet count under 50,000/mm3), despite not being considered severe malaria according to World Health Organization criteria (WHO 2010) due to the inability to cause death *per se*, has been occasionally associated with severity [76,77] or not [78]. On the other hand, considering that many studies point to a clear negative correlation between platelet count and parasitaemia[79], it should be investigated if thrombocytopenia could be used in the surveillance of drug resistance, where higher parasitaemia for prolonged periods are usually found. Interestingly, in areas where thrombocytopenia and other types of

clinical severity are frequently reported, resistant parasites are also being simultaneously detected [80, 81], possibly explaining why the prevalence of thrombocytopenia worldwide is not homogeneous.

Avoiding the consensual understanding that platelets are particles devoted to the maintenance of primary haemostasis, it has been shown that platelets participate in the pathogenesis of micro vascular malaria, adhering to the endothelium when it is previously stimulated with tumour necrosis factor (TNF) (Lou et al. 1997). Even in the non-stimulated cerebral endothelium, platelets may adhere and facilitate the adhesion of *P. falciparum*-parasitized RBCs, through CD36 is ubiquitous in endothelial cells and, coincidentally, platelets [82]. More severe patients presented more severe thrombocytopenia and higher TNF levels [83].

Clinical management of malarial thrombocytopenia –

To date, there is no robust evidence on how to manage patients with malaria and thrombocytopenia. Platelet transfusion has been widely followed, but with no confirmed efficacy. The indication of prophylactic platelet transfusion when platelet counts are under 10,000/mm3 probably applies only when the bone marrow is compromised and is not able to release efficacious platelets [84]. This does not seem to be the case in malaria.

The use of corticoids has never been followed, probably due to the fact that the recovery of thrombocytopenia following antimalarial treatment is seen in almost all cases, with good prognosis for all species that infect humans [68] and with the lack of robust evidence of immune-mediated destruction of platelets as a major mechanism. It was also found that in patients with cerebral falciparum malaria, dexamethasone exacerbated the neurological

symptoms and increased the frequency of gastrointestinal bleeding [85, 86]. However, in none of these studies was platelet recovery analysed as a secondary endpoint.

Immune modulators are also candidates in the adjuvant antimalarial therapy [87], based on the drug-induced inhibition of adhesion molecules in RBCs and platelets [88]. The exploration of drugs known by their anti-inflammatory effect, modulating TNF, e.g., pentoxyfylline and thalidomide, upon severe malaria, could not only contribute to the understanding of the mechanisms of severity but also clarify the association between platelets and severe disease.

UM Jadhav et al [89]. (2004) at Mumbai studied 1565 subjects. Normal platelet count was noted in 21.6% cases. The mean platelet count in falciparum malaria (n=590) was 100,900/µl as against vivax malaria (n=973) where the mean platelet count 1,15,390/µl. Platelet count < 20,000/µl was noted in only 1.5% cases in vivax malaria as against 8.5% cases of falciparum malaria

A study by Kochar DK et al[46] (2010) included 1,064 patients admitted with malaria to study thrombocytopenia (platelet count < 150,000 /cumm) in Plasmodium falciparum (Pf) and Plasmodium vivax (Pv) mono infection and mixed infection (Pf + Pv). The breakup of patients was 525 (49.34%) Pf, 460 (43.23%) Pv and 79 (7.42%) mixed malaria (Pf + Pv). Thrombocytopenia was observed in 24.6% (262/1064) patients. The risk was greatest in the mixed infections in comparison to monoinfection individually (43.04% [34/79]. Pv monoinfection (31.09% [143/460]) had greater risk compared to Pf monoinfection (16.19% [85/525]. The occurrence of severe thrombocytopenia (platelet count <20,000 /cumm) was also higher in Pv monoinfection (18.18% [26/143]) in comparison to either Pf monoinfection (10.59% [9/85], but this association was statistically not significant. Six patients (3 Pv, 2 Pf and 1 mixed) developed severe epistaxis requiring platelet transfusion. There was no relation

between parasite density and platelet count as many patients with severe thrombocytopenia had parasite density similar to patients without thrombocytopenia.

MATERIAL AND METHODS

SOURCE OF DATA:

All adult patients (>18 years) of malaria presented to Department of Medicine of Sri R.L.JALAPPA Hospital and Research centre, attached to Sri DEVARAJ URS MEDICAL COLLEGE, and S.N.R Hospital for a period of one year.

INCLUSION CRITERIA:

All Proven cases of P.*falciparum* malaria in adults.

(Thin and Thick Smear study/ Rapid Card Test for malaria /QBC test)

EXCLUSION CRITERIA:

- Diabetes mellitus,
- Chronic renal failure,
- Chronic liver disease,
- Coronary artery disease,

Study Design:

Prospective study

Study Duration:

One year time bound study

Sampling and Sample Size:

All the confirmed cases of Plasmodium Falciparum reported to RLJH and SNR during the time duration was taken into study.

METHOD OF COLLECTION OF DATA:

Data will be collected by using pre-tested Proforma meeting the objectives of the study. The purpose of the study will be carefully explained to the patients and informed consent will be taken.

Blood will be drawn for Peripheral smear for malaria parasite and other investigations as mentioned below will be sent for examination.

Patients will be examined and assessed on admission .Full recovery or death will be only two outcomes considered in the study.

Study will be done in following steps:

1. Enrolment of patients as per above criteria.
2. Defining Organ dysfunction as mentioned below.
3. Defining 3 levels of severity of organ dysfunction as mentioned below.
4. Severity score as mentioned below. Lowest score being 0 and Highest is 21.

Estimation of probability using appropriate statistical method under guidance of the Bio-Statistician as below.

Criteria for diagnosis of organ dysfunction in malaria [4]:

a) General :

1) Fever ≥ 101^0F.

2) Presence of parasitic form of P. falciparum in peripheral smear or positive rapid card test.

b) Organ Specific Organ System Parameters for defining dysfunction

1. Neurologic	a) Glasgow Coma Scale ≤ 13
2. Renal (one or more)	a) S-creatinine ≥ 1.2 mg/dL
	b) B. Urea ≥ 36.0 mg/ dL
3. Hepatic	a) S. bilirubin ≥ 2.0 mg/dL
4. Respiratory	a) Respiratory rate ≥ 30/ minute
5. Cardiac (one or more)	a) Systolic blood pressure ≤ 90 mm Hg.
	b) Heart rate ≥ 120 beats / minute < 51 beats/min
6. Metabolic	a) Blood. Glucose ≤ 60 mg/dL
	b) Arterial pH <7.3 14
	c) Serum HCO_3 > 15 mmol/L 14
7. Haematological (one or more)	a) Haemoglobin< 10.0 gm/dL

b) Platelet count < 80,000/µl

c) Total leukocyte count <4000/µl or > 12,000

Each parameter will be further sub divided and score will be allotted according the table below and analysed for severity assessment and outcome i.e. full recovery or death will assed according to the severity.

Parameters of Range of variables for different Level of Severity Organ Dysfunction[4] (modified).

	Level-0	Level- I	Level-II	Level-III
1) *Neurologic :* GCS Score	14-15	10-13	7-9	0-6
2) *Renal:* B. Urea(mg/dl)	10.0-36.0	37.0-59.0	60.0-119.0	>120.0
S.Creatinine(mg/dl)	0.6-1.2	1.3-1.9	2.0-4.9	>5.0
3) *Cardiovascular*: Heart rate/min	51-119	120 -139	>140or<51	
Systolic Blood Pressure mmHg	90-160	70-89	41-69	
4) Respiratory : Respiratory Rate/min	20-30	31-40	>41	
5)*Haematologic :* Heamoglobin (gm/dl)	10.0-13.9	7.0-9.9	<7.0	
Total Leucocyte Count (/cumm)	4001-16,000	2001-4000	<2000 or 10-20000	
Platelet (/cumm)	80,000-2,50,000	<80,000		
6) *Hepatic:* Serum Bilirubin (mg/dl)	<2.0	≥ 2.0		
7) *Metabolic:* Blood Glucose (mg/dl)	60.0-110.0	<60.0		
Blood [14]: arterial pH serum HCO_3	>7.4 > 15 mmol/L	< 7.3 <15 mmol/L		

Severity Score of each organ dysfunction with different level of severity[4]

Organ Dysfunction and Score	0	I	lI	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	
Respiratory	Score -0	Score -1	Score -3	
Hematologic	Score -0	Score -1	Score -3	
Hepatic	Score -0	Score -1		
Metabolic	Score -0	Score -1		

Investigations:

1. Peripheral Smear (Both thick and thin smear) / Rapid card test for Malarial Parasite/QBC Test
2. Complete haemogram
3. Chest X-ray.
4. Urine routine.
5. Blood urea, Serum creatinine,
6. Serum electrolytes- Sodium, potassium.
7. Blood glucose.
8. Serum Bilirubin.
9. Arterial blood gas analysis

STATISTICAL ANALYSIS

Data was entered into Microsoft excel data sheet and analysis is done by using EPI INFO 7 Version. Descriptive statistics like frequencies and proportions are computed. Pearson Correlation was computed for continuous variables. Total severity score and probability of death is calculated using the reference values.

RESULTS AND OBSERVATIONS

Table 1: Showing Age Distribution of the Subjects

Age Distribution	Frequency	Percent
<30years	11	36.7
30 to 50 years	15	50.0
> 50 years	4	13.3
Total	30	100.0

In our study it was observed that majority of the patients were in the age group of 30 to 50 years i.e. (50%).

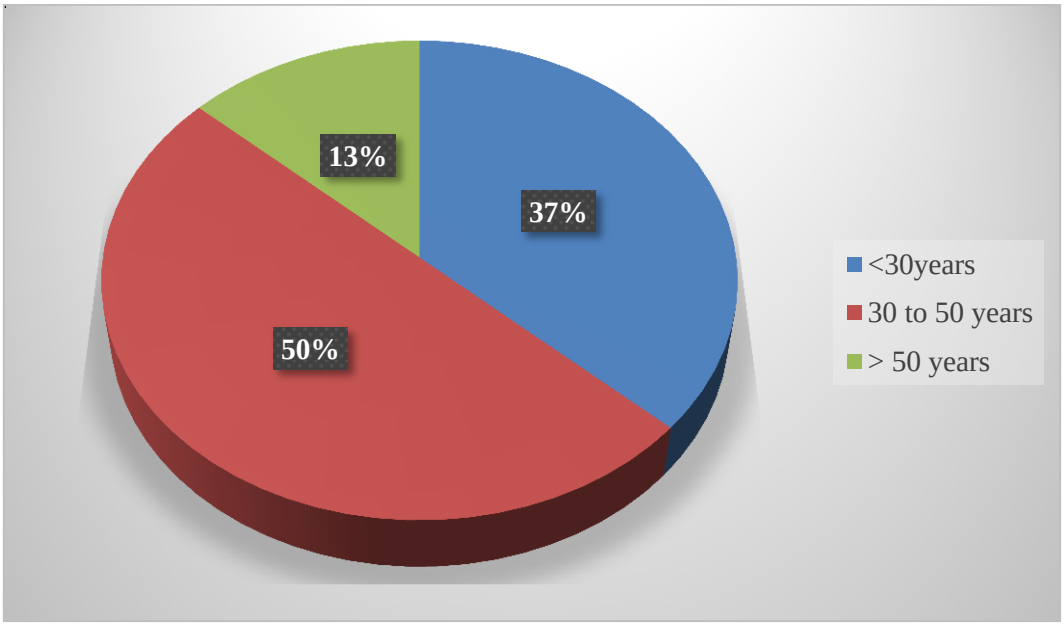


Figure 1: Pie Diagram Showing Age Distribution of the Subjects

Table 2: Showing sex distribution of the subjects

Sex	Frequency	Percent
Male	18	60.0
Female	12	40.0
Total	30	100.0

In the study it was observed that majority of the case were males i.e. 60% and 40% were females.

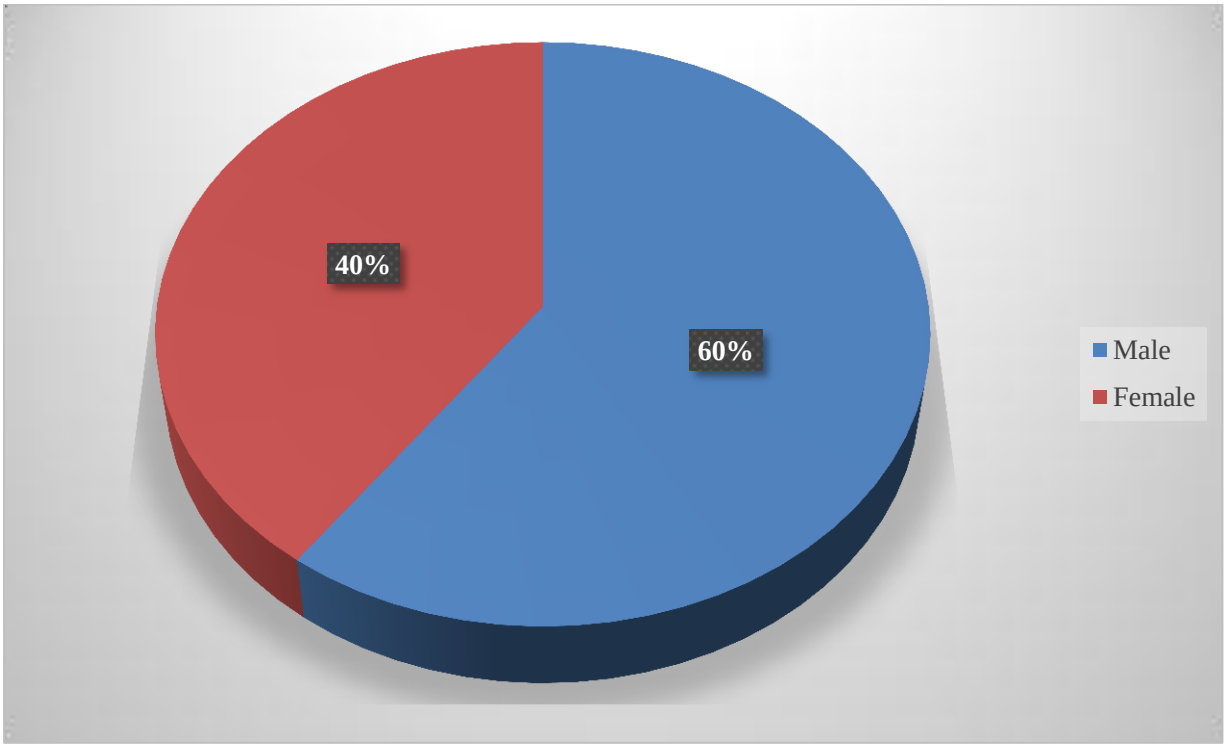


Figure 2: Pie Diagram showing sex distribution of the subjects

Table 3: Showing Distribution of Subjects based on Glasgow Coma Scale Score

GCS Score	Frequency	Percent
<13	2	6.7
>13	28	93.3
Total	30	100.0

In our study it was observed that majority of the patients had a GCS score of >13 i.e. 93.3%.

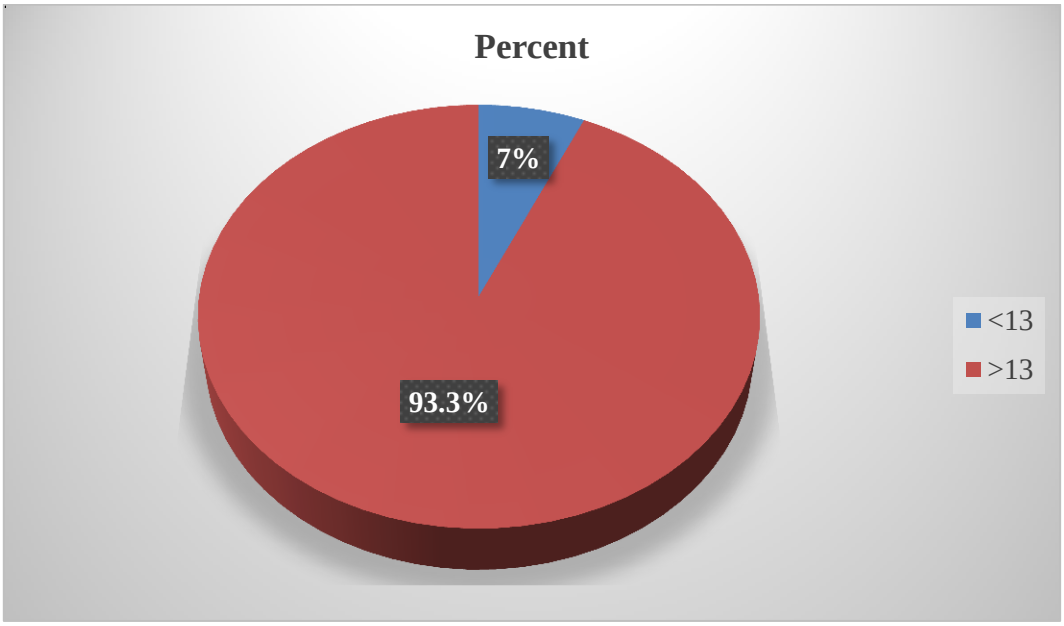


Figure 3: Pie Diagram ShowingDistribution of Subjects based on Glasgow Coma Scale Score

Table 4: Showing Distribution of Subjects based on Serum Creatinine Levels

Serum Creatinine	Frequency	Percent
>1.2	11	36.7
<1.2	19	63.3
Total	30	100.0

In the study it was observed that majority of the subjects had serum creatinine < 1.2 mg/dl i.e. 63.3%.

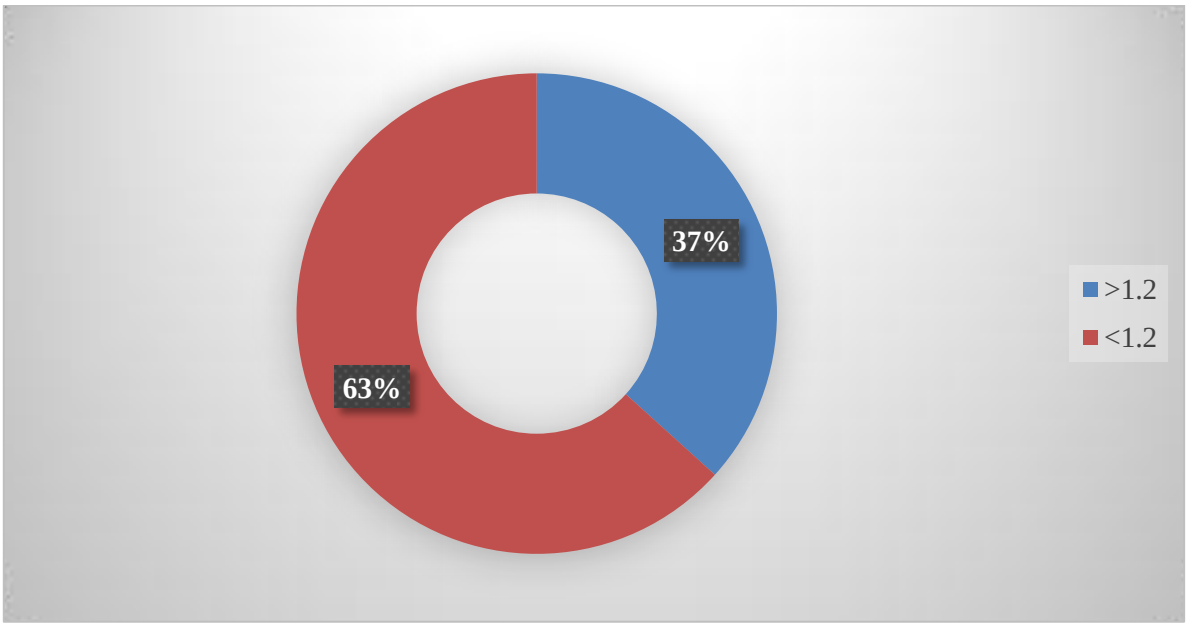


Figure 4: Pie Diagram Showing Distribution of Subjects based on Serum Creatinine Levels.

Table 5: Showing Distribution of Subjects based on Serum Urea Levels

Serum Urea	Frequency	Percent
>36	15	50.0
<36	15	50.0
Total	30	100.0

In present study it was observed that 50% of the subjects had serum urea >36 mg/dl and 50% had serum urea >36 mg/dl.

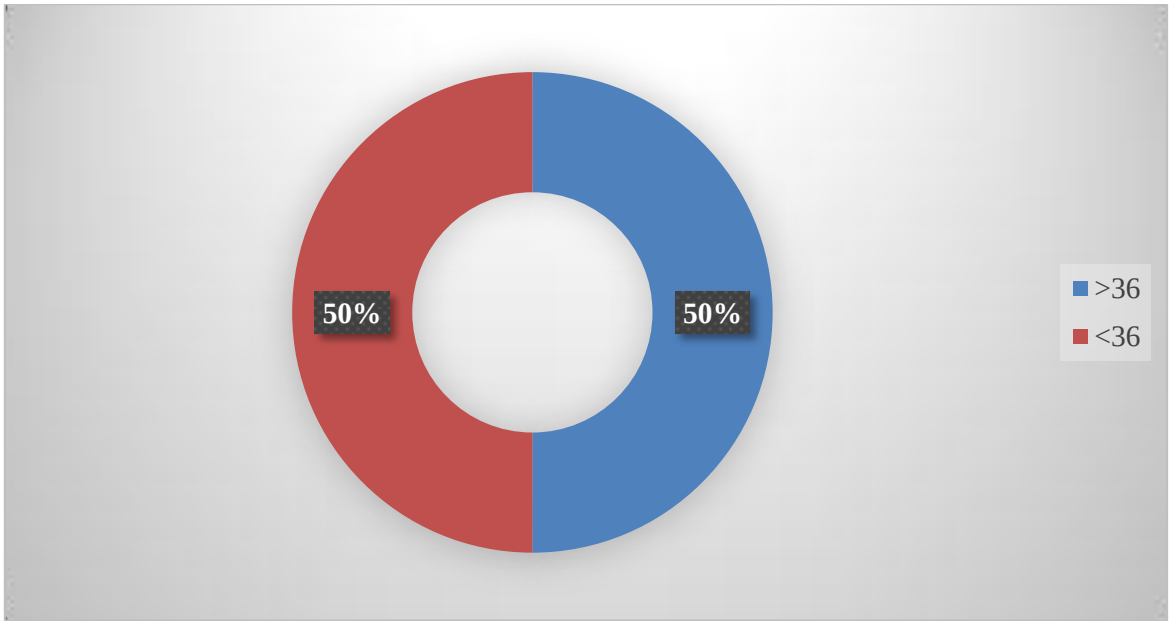


Figure 5: Pie Diagram Showing Distribution of Subjects based on Serum Urea Levels.

Table 6: Showing Distribution of Subjects based on Serum Bilirubin Levels

Serum Bilirubin	Frequency	Percent
>2	8	26.7
<2	22	73.3
Total	30	100.0

In the study it was observed that majority of the subjects had serum bilirubin levels < 2 mg/dl i.e. 73.3%.

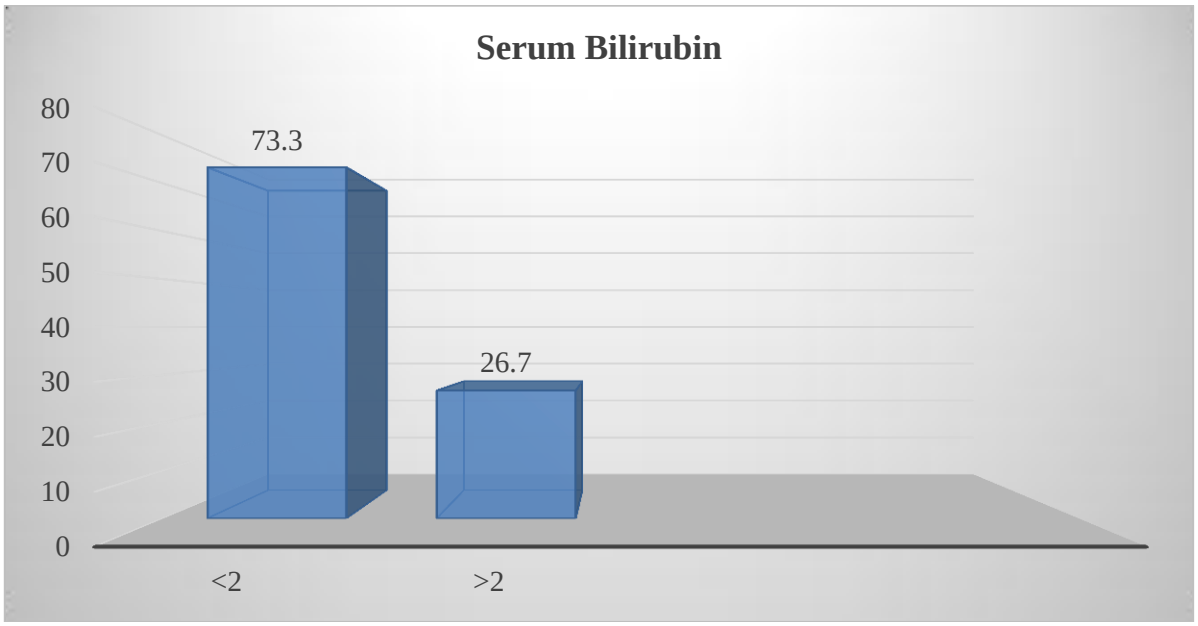


Figure 6: Bar Diagram Showing Distribution of Subjects based on Serum Bilirubin Levels.

Table 7: Showing Distribution of Subjects based on Respiratory Rate

Respiratory Rata	Frequency	Percent
<30	30	100.0

In the study it was observed that all the subjects had Respiratory rate <30 cycles per minute with

Table 8: Showing Distribution of Subjects based on Systolic Blood Pressure

SBP	Frequency	Percent
<90	4	13.3
>90	26	86.7
Total	30	100.0

In the study it was observed that majority of the subjects had Systolic Blood pressure > 90 i.e. 86.7% and below 90mmHg systolic were 13.3%.

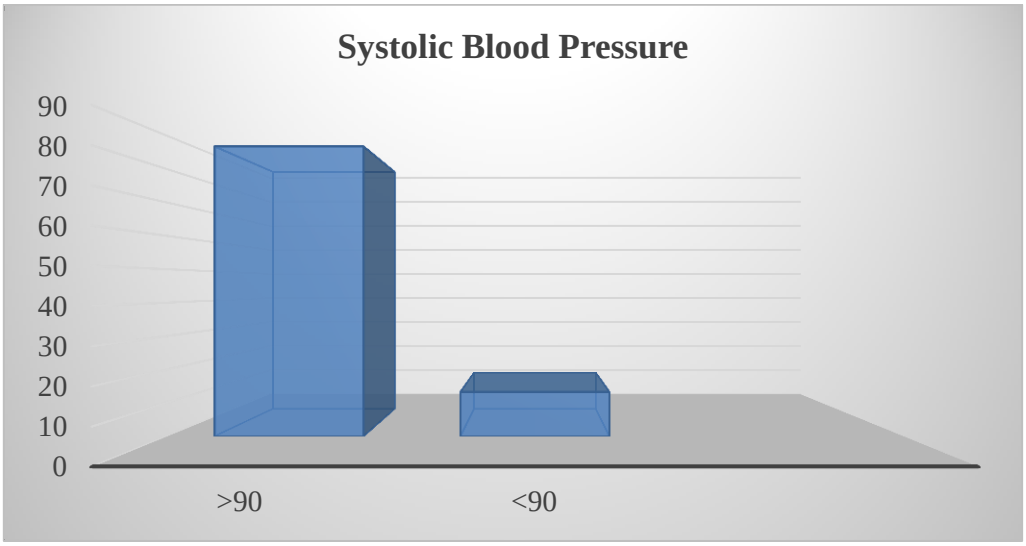


Figure 7: Bar Diagram Showing Distribution of Subjects based on Systolic Blood Pressure.

Table 9: Showing Distribution of Subjects based on Heart Rate

Heart Rate	Frequency	Percent
>120	1	3.3
<120	29	96.7
Total	30	100

In the study it was observed that majority of the subjects had Heart rate <120 beats per minute i.e. in 96.7%.

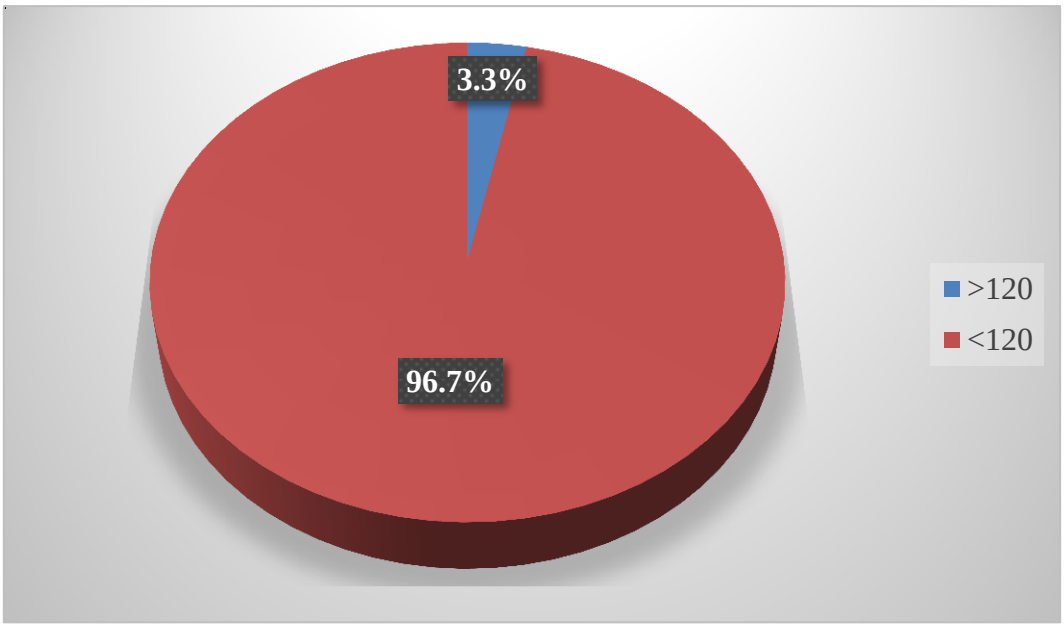


Figure 8: Pie Diagram Showing Distribution of Subjects based on Heart Rate

Table 10: Showing Distribution of Subjects based on Serum Glucose Levels

Serum Glucose Levels	Frequency	Percent
<60	1	3.3
>60	29	96.7
Total	30	100.0

In our study it was observed that majority of the subjects had Serum Glucose Level >60 mg/dl i.e. in 96.7%.

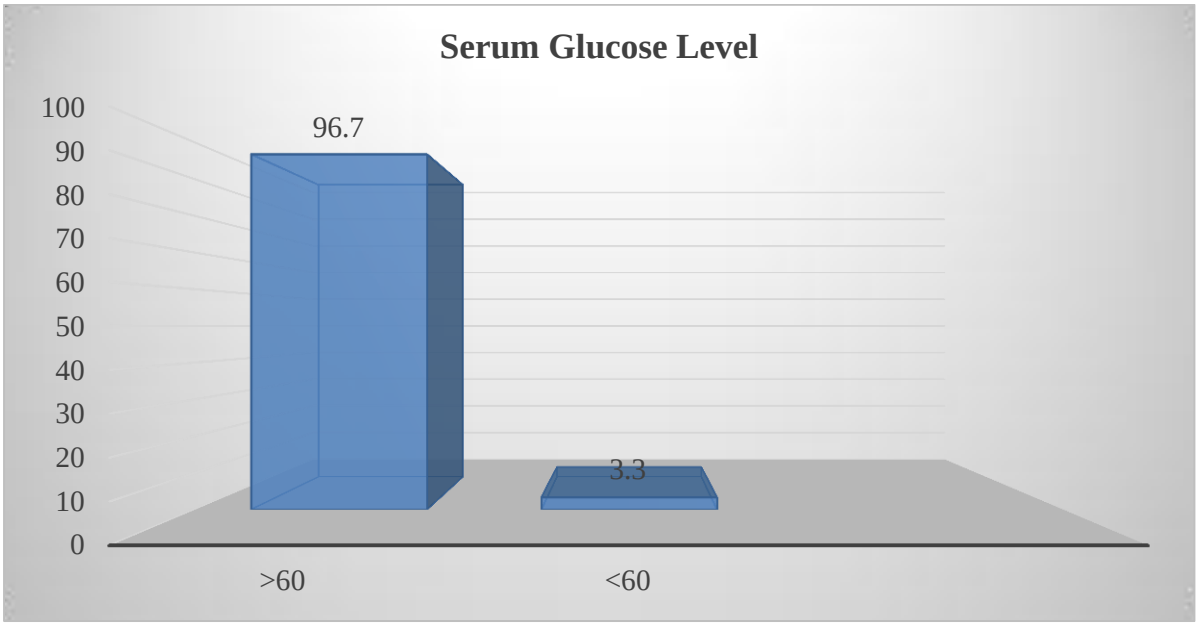


Figure 9: Bar Diagram Showing Distribution of Subjects based on Serum Glucose Levels

Table 11: Showing Distribution of Subjects based on pH levels

PH Levels	Frequency	Percent
<7.3	3	10.0
>7.3	27	90.0
Total	30	100.0

In present study it was observed that majority of the subjects had Blood pH > 7.3 mg/dl i.e 90%. 10% of patients had pH < 7.3

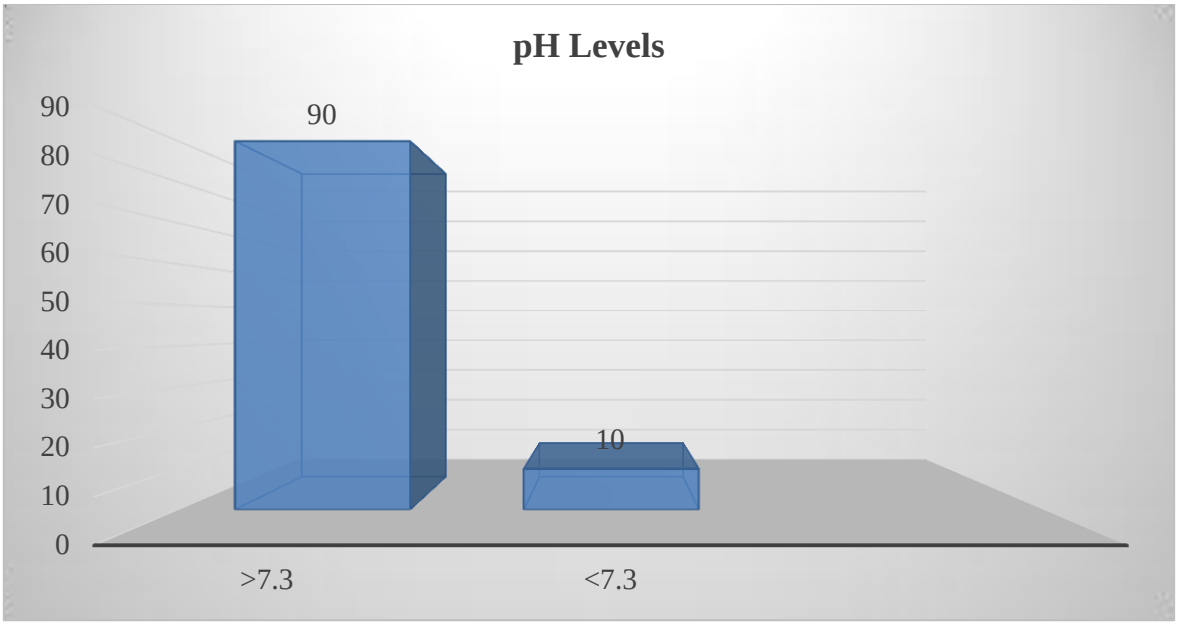


Figure 10: Bar Diagram Showing Distribution of Subjects based on pH Levels

Table 12: Showing Distribution of Subjects based on Serum Bicarbonate Levels

HCO3	Frequency	Percent
>15	29	96.7
<15	1	3.3
Total	30	100.0

In the study it was observed that majority of the subjects had Serum Bicarbonate Level >15 mg/dl i.e. in 96.7%.

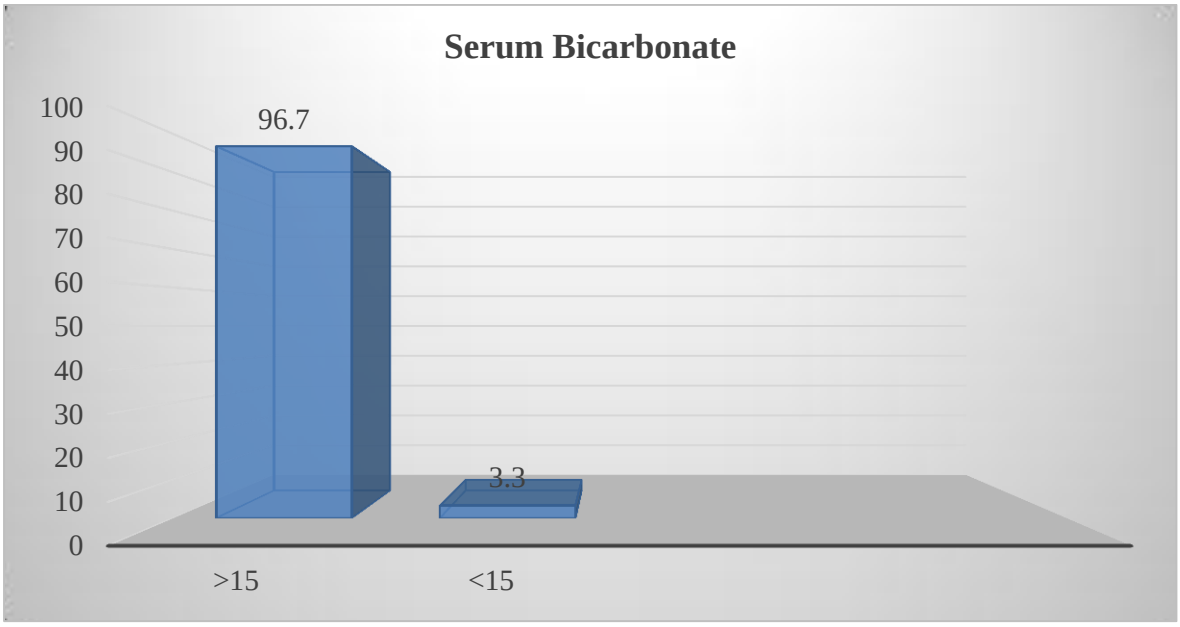


Figure 11: Bar Diagram Showing Distribution of Subjects based on Serum Bicarbonate Levels

Table 13: Showing Distribution of Subjects based on Hemoglobin levels

Hb%	Frequency	Percent
<10	14	46.7
>10	16	53.3
Total	30	100.0

In our study it was observed that majority of the subjects had Hb% >10 i.e. in 53.3%. Hb < 10 was seen in 46.7%.

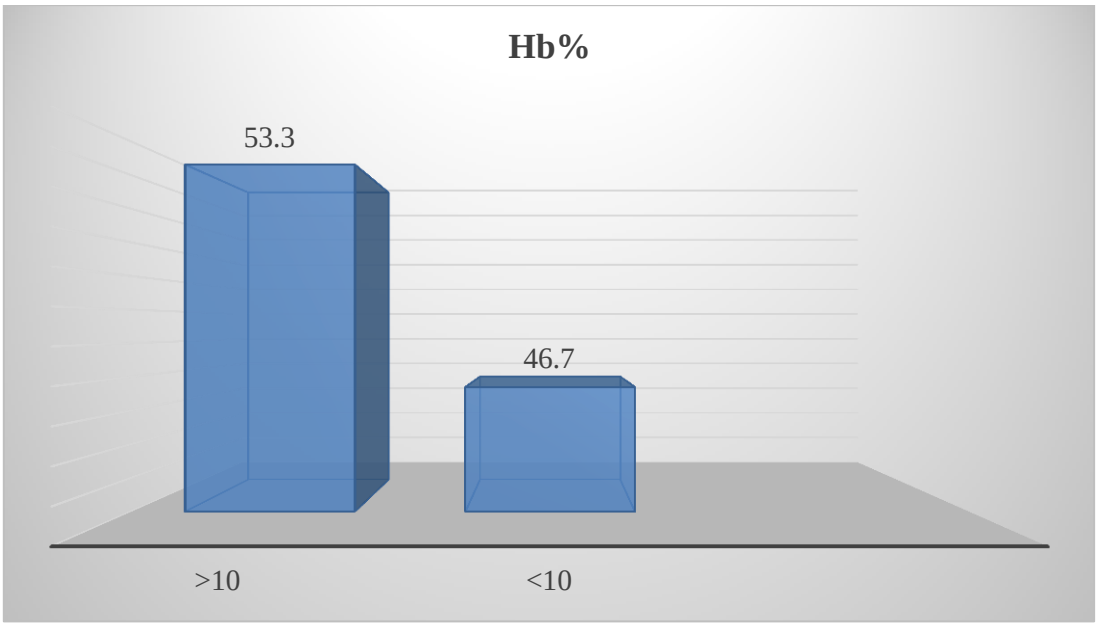


Figure 12: Bar Diagram Showing Distribution of Subjects based on Hb%

Table 14: Showing Distribution of Subjects based on Platelet count

Platelet Count	Frequency	Percent
<80000	11	36.7
>80000	19	63.3
Total	30	100.0

In the study it was observed that majority of the subjects had platelet count >80000 i.e. in 63.3%.

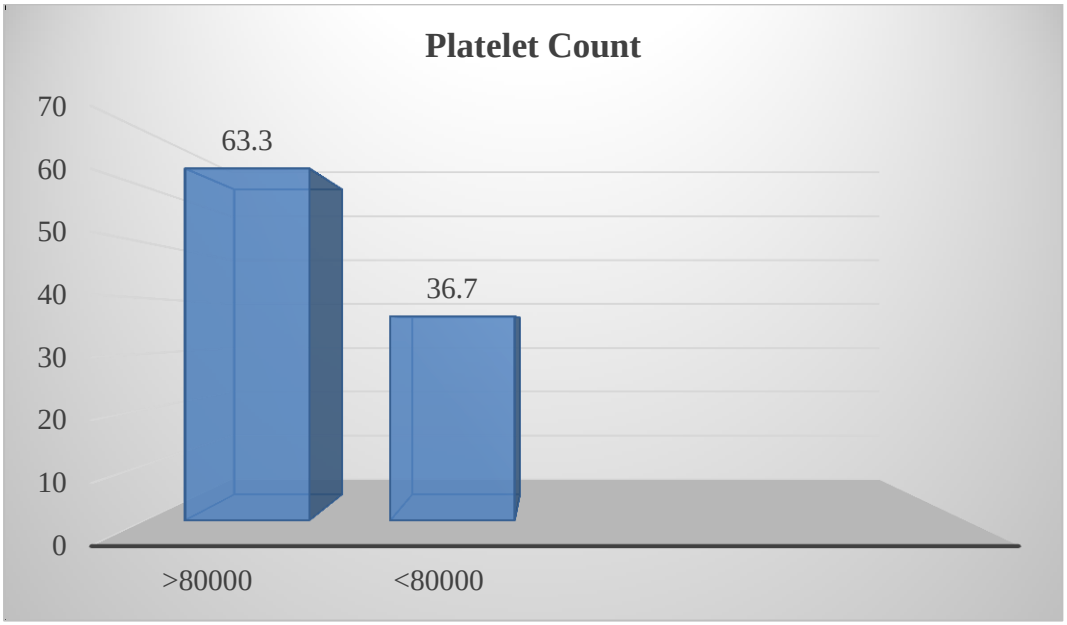


Figure 13: Bar Diagram Showing Distribution of Subjects based on Platelet Count

Table 15: Showing Distribution of Subjects based on Total Count

Total Leukocyte Count	Frequency	Percent
>12000	7	23.3
4000 to 12000	22	73.3
<4000	1	3.3
Total	30	100.0

In the study it was observed that majority of the subjects had TLC in the range 4000 – 12000 i.e. in 73.3%.

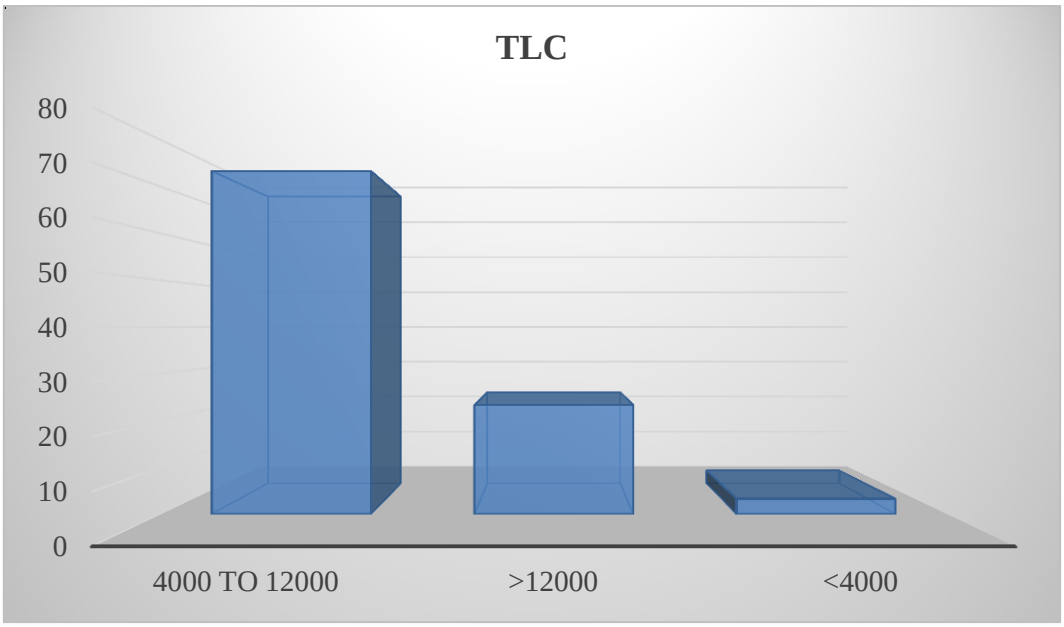


Figure 14: Bar Diagram Showing Distribution of Subjects based on Platelet Count

Table 16: Criteria for Diagnosis of Organ Dysfunction in Malaria:

	Criteria	**n= 30**
General	Fever ≥ 101^0F.	9 (30%)
	P. falciparum in peripheral smear or positive rapid card test.	30 (100%)
Organ Specific		
Neurologic	Glasgow Coma Scale ≤ 13	2 (6.7%)
Renal (one or more)	a) S-creatinine ≥ 1.2 mg/dL	11 (36.7%)
	b) B. Urea ≥ 36.0 mg/ dL	15 (50%)
Hepatic	S. bilirubin ≥ 2.0 mg/dL	8 (26.7%)
Respiratory	Respiratory rate ≥ 30/ minute	None
Cardiac (one or more)	a) Systolic blood pressure ≤ 90 mm Hg	4 (13.3%)
	b) Heart rate ≥ 120 beats / minute or < 51 beats/min	1 (3.3%)
Metabolic	a) Blood. Glucose ≤ 60 mg/dL	1 (3.3%)
	b) arterial pH <7.3	3 (10%)
	c) serum HCO_3 > 15 mmol/L	29 (96.7)
Haematological (one or more)	a) Haemoglobin < 10.0 gm/dL	14 (46.7%)
	b) Platelet count < 80,000/μL	11 (36.7%)
	c) Total leukocyte count <4000/μL or > 12,000	8 (26.6%)

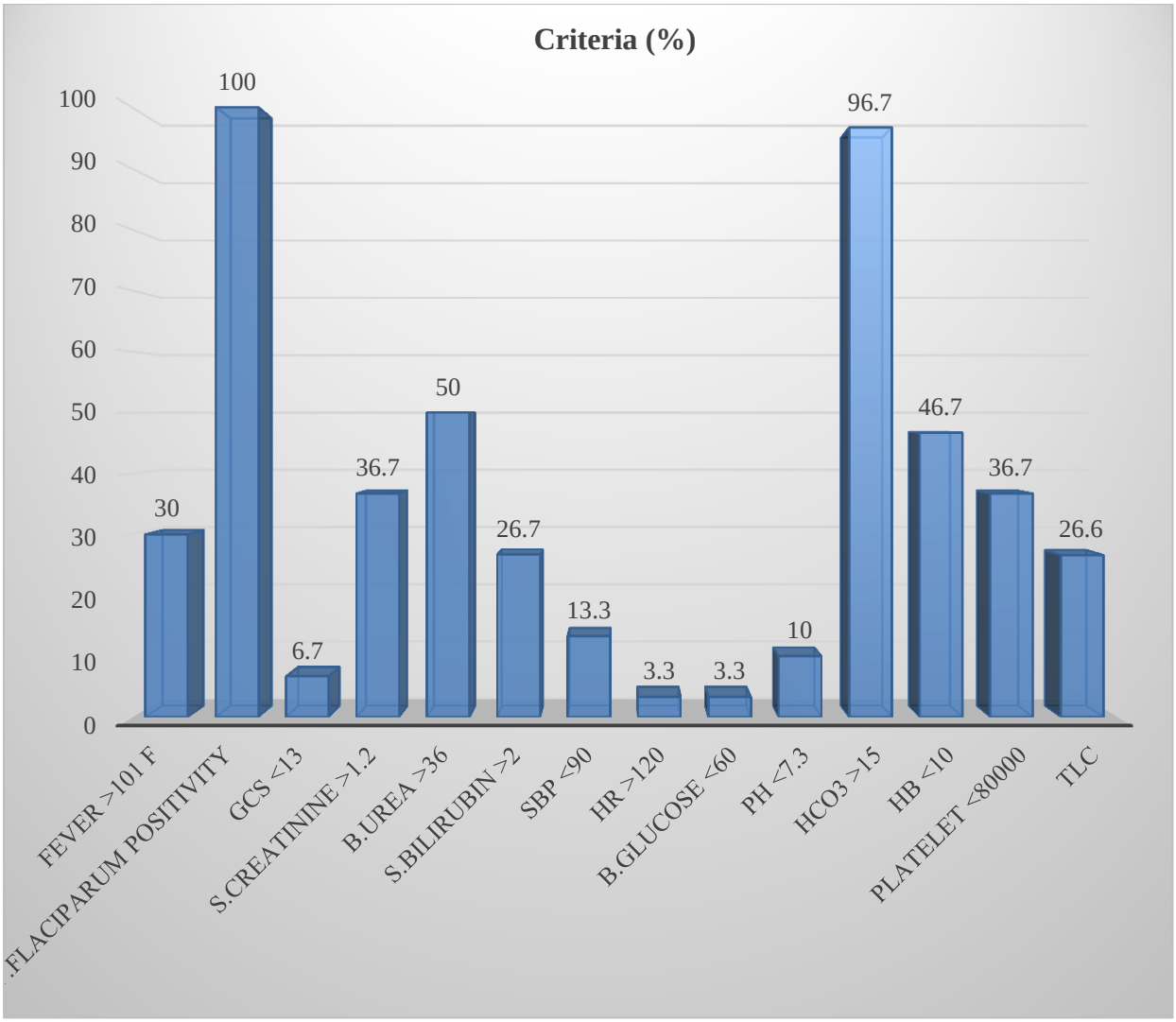


Figure 15: Bar Diagram showing Criteria wise distribution in percentage for Diagnosis of Organ Dysfunction in Malaria

Table 17: Correlation between Total organ Dysfunction score and GCS

		Total Organ Dysfunction Score	GCS
Total Organ Dysfunction Score	Pearson Correlation	1	-0.643**
	p value		0.0001
	N	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

In the study it was observed that there was negative correlation between total organ dysfunction score and GCS to evaluate Neurological dysfunction.

r = -0.643 and was statistically significant. I.e. as the Total organ dysfunction score increases there is decrease in GCS at a significant level and Vice versa.

Table 18: Correlation between Total organ Dysfunction score, Blood urea and Serum Creatinine

		Total Organ Dysfunction Score	Blood Urea mg/dl	Serum Creatinine mg/dl
Total Organ Dysfunction Score	Pearson Correlation	1	0.570**	0.326
	p value		0.001	0.079
	N	30	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

In the study it was observed that there was positive correlation between total organ dysfunction score, Blood urea and Serum Creatinine to evaluate renal dysfunction. r = + 0.57 for Blood urea and r = 0.326 for Serum Creatinine and was statistically significant for blood urea. I.e. as the Total organ dysfunction score increases there is increase in Blood urea at a significant level and Vice Versa. Though there was positive correlation for Serum creatinine it was not statistically significant.

Table 19: Correlation between Total organ Dysfunction score, Heart Rate and Systolic Blood Pressure

		Total Organ Dysfunction Score	Heart Rate	Systolic BP
Total Organ Dysfunction Score	Pearson Correlation	1	-0.372*	-0.168
	p value		0.043	0.375
	N	30	30	30

*. Correlation is significant at the 0.05 level (2-tailed).

In the study it was observed that there was negative correlation between total organ dysfunction score, Heart rate and Systolic Blood pressure to evaluate cardiac dysfunction. r = -0.372 for Heart rate and r = -0.168 for SBP and was statistically significant for heart rate. I.e. as the Total organ dysfunction score increases there is decrease in Heart rate at a significant level and Vice Versa. Though there was negative correlation for SBP it was not statistically significant.

Table 20: Correlation between Total organ Dysfunction score, Heart Rate and Systolic Blood Pressure

		Total Organ Dysfunction Score	Resp. Rate
Total Organ Dysfunction Score	Pearson Correlation	1	0.432*
	p value		0.017
	N	30	30

*. Correlation is significant at the 0.05 level (2-tailed).

In the study it was observed that there was positive correlation between total organ dysfunction score and Respiratory rate to evaluate Respiratory dysfunction in malaria.

r = +0.432 and was statistically significant. I.e. as the Total organ dysfunction score increases there is increase in respiratory rate at a significant level and Vice Versa.

Table 21: Correlation between Total organ Dysfunction score, Hb%, TLC and Platelet count

		Total Organ Dysfunction Score	Hb gm/dl	TLC	Platelets
Total Organ Dysfunction Score	Pearson Correlation	1	0.507**	-0.098	-0.546**
	p value		0.004	0.605	0.002
	N	30	30	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

In the study it was observed that there was positive correlation between Total organ dysfunction score and Hb% i.e. r = 0.507, which implies as the Score increases there is increase in Hb% at a significant level. And there was negative correlation between total organ dysfunction score, TLC and platelet count i.e. r = -0.098for TLC and r = -0.546 for platelet count. I.e. as the Total organ dysfunction score increases there is decrease in platelet count at a significant level and Vice Versa. Though there was negative correlation for TLC it was not statistically significant.

Table 22: Correlation between Total organ Dysfunction score and Serum Bilirubin

		Total Organ Dysfunction Score	Sr. Bilirubin mg/dl
Total Organ Dysfunction Score	Pearson Correlation	1	0.414*
	p value		0.023
	N	30	30

*. Correlation is significant at the 0.05 level (2-tailed).

In the study it was observed that there was positive correlation between total organ dysfunction score and Serum Bilirubin to evaluate Liver dysfunction in malaria.

r = +0.414 and was statistically significant. I.e. as the Total organ dysfunction score increases there is increase in serum bilirubin at a significant level and Vice Versa.

Table 23: Correlation between Total organ Dysfunction score, Blood Glucose, Blood PH and Blood HCO3

		Total Organ Dysfunction Score	Blood Glucose	Blood pH	Blood HCO3
Total Organ Dysfunction Score	Pearson Correlation	1	-0.312	0.095	-0.431*
	p value		0.093	0.617	0.017
	N	30	30	30	30

*. Correlation is significant at the 0.05 level (2-tailed).

In the study it was observed that there was negative correlation between Total organ dysfunction score, Blood HCO3 and Blood Glucose i.e. r = -0.431 and -0.312 respectively, which implies as the Score increases there is decrease in HCO_3% and Blood Glucose. Correlation was statistically significant for Blood HCO_3.

Table 24: Showing Total Severity Score for Neurological Dysfunction

Neurological Dysfunction	**Level-0**	**Level- I**	**Level-II**	**Level-III**
GCS Score	14-15	10-13	7-9	0-6
Percentage	28 (93.3%)	2 (6.7%)	-	-
Total Severity Score	0	2	-	-

In the study it was observed that majority of subjects had GCS score between 14 to 15 corresponding to Level- 0 of severity score i.e. in 93.3%. There were no subjects in level II and level III. No severe neurological deterioration was observed in 93.3% of patients.

Table 25: Showing Total Severity Score for Renal Dysfunction

Renal Dysfunction	Level-0	Level- I	Level-II	Level-III
B. Urea(mg/dl)	**10.0-36.0**	**37.0-59.0**	**60.0-119.0**	**>120.0**
Percentage	17 (56.7%)	8 (26.7 %)	4 (13.3%)	1 (3.3%)
Total Severity Score	0	8	12	5
Creatinine	**0.6-1.2**	**1.3-1.9**	**2.0-4.9**	**>5.0**
Percentage	20 (66.7%)	8 (26.7 %)	2 (6.6%)	-
Total Severity Score	0	8	6	-

In the study it was observed that majority of subjects were in Level – 0 of severity with respect to Blood urea i.e. 56.7%. 26.7%, 13.3% and 3.3% were in Level I, Level II and Level III score. Similarly for Serum Creatinine majority 66.7% were at level – 0. 26.7% and 6.6% were at level I and level II respectively. There were no subjects at level III.

66.7 % of the patients had normal renal function test at presentation.

Table 26: Showing Total Severity Score for Cardiovascular Dysfunction

Cardiovascular Dysfunction	Level-0	Level- I	Level-II	Level-III
Heart rate/min	**51-119**	**120 -139**	**>140or<51**	-
Percentage	28 (93.3%)	1 (3.3%)	1 (3.3%)	
Total severity Score	0	1	3	
Systolic Blood Pressure	**90-160**	**70-89**	**41-69**	
Percentage	28 (93.3%)	2 (6.7%)	-	
Total Severity Score	0	2	-	

In the study it was observed that majority of subjects 93.3 % were in Level – 0 of severity i.e within normal limits with respect to Heart Rate i.e. 93.3%. 3.3% and 3.3% in Level I and Level II Score.

Similarly for Systolic Blood Pressure majority 93.3% were at level – 0 within normal limits and 6.7% were at level I.

Table 27: Showing Total Severity Score for Respiratory Dysfunction

Respiratory Dysfunction	**Level-0**	**Level- I**	**Level-II**	**Level-III**
Respiration Rate	20-30	31-40	>41	-
Percentage	30 (100%)			
Total Severity Score	**0**			

In the study it was observed that all the subjects had Respiratory rate of 20 to 30 corresponding to Level- 0 of severity score i.e. in 100% i.e within normal limtis.

Table 28: Showing Total Severity Score for Hematologic Dysfunction

Hematologic Dysfunction	**Level-0**	**Level- I**	**Level-II**
Hb (gm/dl)	**10.0-13.9**	**7.0-9.9**	**<7.0**
Percentage	17 (56.6%)	8 (26.8%)	5 (16.6%)
Total Severity Score	0	8	15
TLC (/cmm)	**4001-16,000**	**2001-4000**	**<2000 or** **10-20000**
Percentage	27 (90%)	2 (6.7%)	1 (3.3%)
Total Severity Score	0	2	3
Platelet (/cmm)	**80,000-2,50,000**	**<80,000**	
Percentage	19 (63.3%)	11 (36.7%)	
Total Severity Score	0	11	

In our study it was observed that majority of subjects were in Level – 0 of severity i.e within normal limits , with respect to Hb% i.e. 56.6%. 26.8% and 16.6% were in Level I and Level II Score. Similarly for Total Leukocyte count majority 90% were at level – 0 and 6.7% were at level I and 3.3% at Level II. Similarly for Platelet count majority 63.3% were at level – 0 i.e within normal limits and 36.7% were at level I.

Table 29: Showing Total Severity Score for Hepatic Dysfunction

Hepatic Dysfunction	**Level-0**	**Level- I**
S. Bilirubin (mg/dl)	**<2.0**	**≥ 2.0**
Percentage Score	22 (73.3%)	8 (26.7%)
Total Severity Score	0	8

In present study it was observed that the subjects had total bilirubin in level I of severity score i.e. in 26.7% and 73.3 % were within normal limits.

Table 30: Showing Total Severity Score for Metabolic Dysfunction

Metabolic Dysfunction	**Level-0**	**Level- I**
B. Glucose (mg/dl)	**60.0-110.0**	**<60.0**
Percentage	29 (96.7%)	1 (3.3%)
Total Severity Score	0	1
Arterial pH	**>7.4**	**< 7.3**
Percentage	27 (90%)	3 (10%)
Total Severity Score	0	3
Serum HCO_3	**> 15 mmol/L**	**<15 mmol/L**
Percentage	29 (96.7%)	1 (3.3%)
Total Severity Score	0	1

In our study it was observed that majority of subjects were in Level – 0 of severity with respect to Blood Glucose i.e. 96.7% and 3.3% were in Level I Score.

Similarly for Arterial PH majority 90% were at level – 0 and 10% were at level I.

Similarly for Serum HCO3 majority 96.7% were at level – 0 and 3.3% were at level I.

Table 31: Showing Severity Score and Probability of death for Malaria Severity Score[4]

Severity Score (Criteria B)	Probability of death (%)	Frequency	Percent
0	1.20	3	10
1	3.10	12	40
2	4.80	4	13.3
3	7.50	4	13.3
4	10.50	2	6.66
6	21.1	2	6.66
8	40.10	1	3.3
9	51.8	1	3.3
11	61.70	1	3.3
Total		30	100.0

In the study it was observed that the majority 40 % had a probability of death 3.1 %. The maximum probability of death was 61.70 % in 3.3 % subjects. Though there were >40% probability of death among 10% of subjects all the patients survived by aggressive management in Medical Intensive Care unit with continuous monitoring, artesunate based combination therapy and supportive care.

DISCUSSION

Malaria Severity Score for organ dysfunction used in our study is adapted from Malaria severity score by Mohapatra et. al. And this score is modified with extra component of pH and Bicarbonate from arterial blood gas analysis. In study by Mohapatra et al[4] it was noted that severe malaria is a variable disease causing dysfunction of various organs in different combinations and with variable grades of severity, which was evident in our study too.

In our study GCS was impaired in 6.7%, 36.7 % had impaired serum creatinine and 50 % impaired blood urea. Total bilirubin was high in 27.7 %. Systolic blood pressure less than 90 mmHg was seen in 13.3 %, blood glucose was impaired in 3.3%. Haemoglobin was decreased in 46.7%, low platelets was seen in 36.7% and altered total counts in 26.6 %.

In Total Organs involved, 6.66 % patient had five organ system involved that's highest in our study. Highest group was two organ involvements, i.e. 26.66 %. In similar study by Mohapatra et al.[4], highest, 20.8 % patients had only organ dysfunction. In present study highest level of dysfunction is seen in the form of Renal and Haematological involvement, followed by Hepatic and cardiovascular involvement. A patient with highest number of organs involvement, does not necessary translates in high severity as level of severity can be low in each organ dysfunction. Similarly a patient with few organ system involvements can have high severity due highest levels of severity in each organ dysfunction level.

Uncomplicated Malaria accounts for 13.3% in our study whereas comparison 12.4% by Mohapatra et al[4] . In study by Mohapatra et al[4] One organ dysfunction was 20.8 % were as

40% is noted in present study. Two organ dysfunction accounts for 17.1% in our study in contrast with 26.66 % by Mohapatra et al[4]. Similarly three organ dysfunction accounts for 10% , four organ dysfunction accounts for 3.33%, five organ dysfunction accounts for 6.66% ,involvement of six organ dysfunction and seven organ dysfunction was not noted in our study. In contrast in study by Mohapatra et al[4], three organ dysfunction accounts for 18.2 % , four organ dysfunction accounts for 17.1%, five organ dysfunction accounts for 4.5% ,involvement of six organ dysfunction and seven organ dysfunction was not noted. It can be due to the early treatment with chlroquine at primary health centre where patient presents first, hence prevented from reaching six or seven organ dysfunction.

Either a patient has involvement of several organs with low (level-I) to moderate (level-II) level of dysfunction or few organs with severe level (level-III) of dysfunction. In any such clinical situation the mortality risk is very high.

Each score has been further translated into probability of mortality[4]. In this study it was observed that the majority 40 % had a probability of death 3.1 %. The maximum probability of death was 61.70 % in 3.3 % subjects. Though there were >40% probability of death among 10% of subjects all the patients survived by aggressive management in Medical Intensive Care unit with continuous monitoring, Artesunate based combination therapy and supportive care. Supportive measures like maintenance of hydration, antibiotics for any concurrent infections, blood transfusion, dialysis, ventilator support etc. were given according to individual needs. Patient with more than 40% probability of mortality was allocated resources aggressively with favorable outcome.

Ruel Teaño *et al*[92] from Philippines proposed a clinical scoring index for predicting outcome in cerebral malaria. Scoring protocol was formulated and the 5 variables incorporated into the

system, with a possible score of 0-14. Five factors were found to be significantly associated with an unfavourable outcome. Patients with impaired consciousness, multiple convulsions, laboured respiration, circulatory collapse and abnormal bleeding were all found to be highly associated with a poor prognosis.

Saroj K Mishra *et al* [93] from Ispat General Hospital, Rourkela, Orissa developed a scoring system (Malaria prognostic score) to predict outcome of adults suffering from severe P. falciparum malaria. The malaria score for adults was (MSA) = 1(severe anaemia) + 2 (acute renal failure) + 3(Respiratory distress) + 4 (cerebral malaria). The MSA ranges from 0 to 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 study results had shown that severe anemia, acute renal failure, respiratory distress and cerebral malaria were the major factors influencing to the mortality rate of disease

Prof. M K Mohapatra and Prof. S P Das[4] from Orissa have developed the Malaria Severity Score: a method for severity assessment and risk prediction of hospital mortality for falciparum malaria in adults. In a one more study by Mohapatra et al[30], it was found that seven major organ dysfunction occurred commonly in malaria, basis for Malaria severity score based on organ dysfunction. For the assessment of the degree of severity, 12 different variables were extracted from the data base and grouped according to systems .Depending on the range of abnormal finding of the variables 3 levels of severity (I, II, and III) were determined . The level of severity was not equal for all types of Organ dysfunction (OD). Neurologic and renal dysfunctions were with all the 3 levels of severity and received the

maximum of 5 points for the most severe level of dysfunction, hence considered as most severe form of organ dysfunction.

Noppadon Tangpukedee et al[94]. developed Malaria Severity Prognostic Score = 4.38 (schizontemia)+ 1.62 (gametocytemia) + 1.17 (dehydration) + 0.14 (overweight by body mass index; BMI) + 0.05 (initial pulse rate) +0.04 (duration of fever before admission) – 0.50 (past history of malaria in last 1 year) – 0.48 (initial serum albumin) –5.66. The results of the study had agreed with those studies that presence of schizontemia and gametocytemia in malaria patients affecting to the severity of disease.

In an earlier study, the APACHE II scoring for predictive outcome in cerebral malaria had been conducted by Wilairatana and Looareesuwan[95]. There were many variables used in the score system e.g., vital signs, serum electrolytes, serum creatinine, hematocrit, etc. However, the results of the study suggested that the APACHE II system was useful for stratifying the prognosis of group outcome in cerebral malaria patients with the accuracy of 95.8%[95].

The coma and malaria (CAM) score[96], was developed using the multinational SEAQUAMAT trial conducted in Asia and was validated in 2 additional, large prospectively gathered datasets from Vietnam and Bangladesh. The 5-point CAM score uses only a patient's GCS and the plasma base deficit and has strong predictive value for mortality. Results showed Acidosis (base deficit) and cerebral malaria (measured as Glasgow Coma Score) were the main independent predictors of outcome. The 5-point Coma Acidosis Malaria (CAM) score was simply derived from these 2 variables. Mortality increased steadily with increasing score. A CAM score <2 predicted survival with a positive predictive value and concluded that patients with a CAM score <2 at hospital admission may be safely treated in a general ward,

provided that renal function can be monitored. The CAM score should not be used in isolation from clinical evaluation of the patient[96].

In an another study by Lurdes C Santos[97], severe cases of malaria in patients admitted to an ICU were reviewed retrospectively and identification of variables associated with in-ICU mortality performed. Malaria prediction score (MPS), malaria score for adults (MSA), simplified acute physiology score (SAPSII) and a score based on WHO's malaria severe criteria were applied. Two prognostic scores of malaria were applied:

(1) Malaria Prediction Score (MPS) determined by: 2.13 + 0.02 × (age) + 0.25 × (creatinine) - 0.24 × (hemoglobin) + 3.05 (malaria cerebral criteria) + 0.8 (presence of pregnancy) + 0.8 (ventilated) (where age = age in years; creatinine is in mg/dl, hemoglobin in g/dl; presence of pregnancy, cerebral malaria or ventilatory support, when present = 1, when absent = 0);

(2) Malaria Score for Adults (MSA) was applied to all but three children and the score was determined by: 1 (severe anemia) + 2 (acute renal failure) + 3 (respiratory distress) + 4 (cerebral malaria). The MSA ranges from 0 to 10

Fifty nine patients were included in the study, all but three were adults; 47 (79,6%) were male; parasitaemia on admission, quantified in 48/59 (81.3%) patients, was equal or greater than 2% in 47 of them (97.9%);the most common complications were thrombocytopenia in 54 (91.5%) patients, associated with disseminated intravascular coagulation (DIC) in seven (11.8%), renal failure in 31 (52.5%) patients, 18 of which (30.5%) oliguric, shock in 29 (49.1%) patients, liver dysfunction in 27 (45.7%) patients, acidaemia in 23 (38.9%) patients, cerebral dysfunction in 22 (37.2%) patients, 11 of whom with unrousable coma, pulmonary edema/ARDS in 22 (37.2%) patients, hypoglycemia in 18 (30.5%) patients; 29 (49.1%) patients presented five or more dysfunctions. Comparing the four scores, the SAPS II and the

WHO score were the most sensitive to death prediction. As per study severe malaria cases should be continued monitored in the ICUs. SAPS II and the WHO score are good predictors of mortality in malaria patients[97].

In a by Justin F Doherty et al.[98] retrospective study of patients with WHO severe falciparum malaria admitted to ICU at the Hospital for Tropical Diseases, London, UK. The relationship between clinical variables and risk of death or a prolonged ICU stay were examined with logistic regression. The predictive value of the MSA and CAM score were calculated. 124 patients were included. Cerebral malaria and acute kidney injury occurred earlier (median day 1) than acute respiratory distress syndrome (median day 3). Six patients had community acquired bacterial co-infection. Eight patients were co-infected with HIV, five of whom were newly diagnosed. The positive predictive value of a CAM score <2 or an MSA <5 for death were 12% and 22% respectively. The study showed that both a CAM score <2 and an MSA <5 identified patients who would survive. However, these scores had limited ability to predict mortality and it remains unclear what role, if any, they may play in clinical practice in areas of the world where malaria is not endemic. No clinical factor was associated with a poor outcome but given the low case fatality rate,as the study was under-powered to detect such a difference

Some of the limitation in our study was that arterial blood gas analysis, may not readily available everywhere. And one of the major strength of study by Mohapatra at el was high number of patient and long duration of study, whereas in comparison our sample size may not be large enough. Being a tertiary care hospital many patient referred are already on treatment rendering them smear or rapid card test negative. Another factor responsible may be for changing prevalence of P.*Falciparum to* P.*Vivax.*

Malaria severity score can help physicians to assess severity and stratify the risk and allocated resources as per need in limited resource setting, a common scenario in our country. It`s helpful in predicting outcome as probability of death is given for each score and patient with high probability of mortality can identified , to provide more attention and quality care. Malaria severity score is good indicator of severity due its stratification of every organ dysfunction in different level of severity.

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CONCLUSION

In the study it was observed that majority of the patients were in the age group of 30 to 50 years i.e. (50%).

In the study it was observed that majority of the case were males i.e. 60% and 40% were females

In the study it was observed that majority of the patients had a GCS score of >13 i.e. 93.3%.

In the study it was observed that majority of the subjects had serum creatinine >1.2 mg/dl i.e. 63.3%. Serum Creatinine in majority 66.7% were at level – 0. 26.7% and 6.6% were at level I and level II respectively. There was no subjects at level III

In the study it was observed that 50% of the subjects had serum urea >36 mg/dl. Majority of subjects were in Level – 0 of severity with respect to Blood urea i.e. 56.7%. 26.7%, 13.3% and 3.3% were in Level I, Level II and Level III score.

In the study it was observed that majority of the subjects had serum bilirubin levels <2 mg/dl i.e. 73.3%.

In the study it was observed that majority of the subjects had Heart rate <120 beats per minute i.e. in 96.7%. It was observed that majority of subjects were in Level – 0 of

severity with respect to Heart Rate i.e. 93.3%. 3.3% and 3.3% in Level I and Level II Score.

For Systolic Blood Pressure majority 93.3% were at level – 0 and 6.7% were at level I.

In our study it was observed that majority of the subjects had Serum Glucose Level >60 mg/dl i.e. in 96.7%. Majority of subjects were in Level – 0 of severity with respect to Blood Glucose i.e. 96.7% and 3.3% were in Level I Score.

In present study it was observed that majority of the subjects had pH Level >7.3 i.e. in 90%. Similarly for Arterial pH majority 90% were at level – 0 and 10% were at level I. Similarly for Serum HCO_3 majority 96.7% were at level – 0 and 3.3% were at level I.

In the study it was observed that majority of the subjects had Hb% <10 i.e. in 46.7%.

In our study it was observed that majority of the subjects had platelet count >80000 i.e. in 63.3%.

In present study it was observed that majority of subjects were in Level – 0 of severity with respect to Hb% i.e. 56.6%. 26.8% and 16.6% were in Level I and Level II Score. Similarly for Total Leukocyte count majority 90% were at level – 0 and 6.7% were at

level I and 3.3% at Level II. Similarly for Platelet count in majority 63.3% were at level – 0 and Low platelet was observed in 36.7% were at level I.

In the study it was observed that the majority 36.7% had a probability of death 3.1%. The maximum probability of death was 88.8% in 6.7% subjects.

Though there were >40% probability of death among 10% of subjects all the patients survived by aggressive management in Medical Intensive Care unit with continuous monitoring, Artesunate based combination therapy and supportive care. Patient was observed and monitored 24 hours in Medical Intensive Unit and treated.

Malaria severity score helps to assess severity and risk stratification and to allot better resources.

Some of the limitation in study was that arterial blood gas analysis which may not readily available everywhere.

Our sample size is small it can due to being a tertiary care hospital many patient referred are already on treatment rendering them smear or rapid card test negative. Further application in large sample size is required.

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APPENDIX 1:

PROFORMA:

Sl. No-

"STUDY OF PATIENTS OF FALCIPARUM MALARIA AND SEVERITY ASSESSMENT WITH RISK PREDICTION USING MALARIA SEVERITY SCORE."

STUDENT: **Dr. Ashish Kumar Agrawal GUIDE**: **Dr. Raveesha A.**

I. IDENTIFICATION DATA:

Name: Age:

Address:

Sex: M / F HOSP./I.P NO:

DOA: DOD:

Diagnosis at admission:

II. PRESENTING COMPLAINTS:

1. Fever

a) Duration- days

b) Nature: Intermittent

Remittent

Continuous

c) Degree: Mild / Mod /Sev

d) Shaking chills: Yes / No.

7. Abdominal pain Yes / No.

8. Abdominal mass Yes / No.

9. Diarrhoea Yes / No.

10. Breathlessness: Yes / No.

11. Altered sensorium Yes / No.

2. Headache: Yes / No.

3. Myalgia: Yes / No.

4. Jaundice: Yes / No.

5. Nausea: Yes / No.

6. Vomiting: Yes / No.

12. Convulsions Yes / No.

13. Cough Yes / No.

14. Bleeding tenderncies Yes / No.

15. Dark colored urine Yes / No.

16. Decreased urine output Yes / No.

17. Others :

Other complaints if any:

III. Past History:

History of malaria Yes / No

History of blood transfusion Yes / No

Treatment history: Received antimalarials Yes / No.

Details:

IV. Family history:

V.PERSONAL HISTORY:

Addictions: Alcohol:
Tobacco:
Betel Nut:

VIII. GENERAL PHYSICAL EXAMINATION:

1. Appearance Well / ill / toxic

2. Dehydration: None / Some / Severe.

3. Temperature: 4. Pulse:

5. Respiration: 6. Blood pressure:

7. Pallor: Yes / No, 8. Icterus: Yes / No.

9. Cyanosis: Yes/ No 10. Clubbing:

11. Pedal edema: 12. Lymphedenopathy:

14. Purpuric spots: 15.Upper GI Bleeding

16. Wasting 17. Acidotic Breathing:

18. Fundus examination

IX. **SYSTEMIC EXAMINATION:**

CARDIO – VASCULAR SYSTEM:

RESPIRATORY SYSTEM:

ABDOMINAL EXAMINATION:

Distension: Yes/ No

Hepatomegaly Present / Absent.

Size Tenderness- Present / Absent

Surface Margin Consistency

Splenomegaly Present / Absent.

Size Tenderness- Present / Absent.

Surface Margin Consistency

Other details:

CENTRAL NERVOUS SYSTEM

Higher motor function:

Cranial Nerves:

Motor Examination:

Co – Ordination and Gait:

Involuntary Movements:

Sensory Examination:

Cerebellar signs:

Signs of Meningeal Irritation:

OUTCOME:

Duration of hospital stay:

Complications:

Status at end of hospital stay: Recovered / Death

Investigations : WORK UP.

1. Peripheral Smear / rapid card test for Malaria Parasite:
2. Complete Haemogram

Hb% 2) TC 3) DC 4) PLT

3 . Chest X-ray:

4. Urine routine:
5. Blood urea: Serum creatinine:
6. Serum electrolytes- Sodium: Potassium:
7. Blood glucose:
8. Serum Bilirubin:
9. Arterial blood gas analysis:

Severity Score of each organ dysfunction with different level of severity[4]

Organ Dysfunction	Organ Dysfunction and Score
Neurologic	
Renal	
Cardiovascular	
Respiratory	
Hematologic	
Hepatic	
Metabolic	

Total Organ Dysfunction Score:

Appendix 2- MASTERCHART

"STUDY OF PATIENTS OF FALCIPARUM MALARIA AND SEVERITY ASSESSMENT WITH RISK PREDICTION USING MALARIA SEVERITY SCORE."

Student: Dr. Ashish Kumar Agrawal

Serial No.	Name/ID	Sex	Age	GCS	Bl Urea	Sr. Creatinine	Heart Rate	Systolic BP	Resp. Rate	Hb	TLC	Platlets	Sr. Bilirubin	Blood	Blood pH	Blood HCO3	Criteria A	Criteria A	Criteria B	Total Oragn
			Years		mg/dl	mg/dl	b/min	mmHg	cycle/min	g/dl	cells	cells	mg/dl	Glucose			Temp>101F	Malaria Positive	Score	Dysunction Score
1	Chandramma 684405	F	35	15	61	1.1	40	80	25	6.5	13,800	10000	10.6	66	7.3	24	1	1	8	10
2	Buddanna B 686756	M	27	15	24	0.7	100	100	20	10.6	4400	15000	1.2	200	7.4	24	0	1	1	2
3	Puspavati 686878	F	25	15	27	1.6	101	118	20	8.6	6400	180000	0.4	114	7.42	24	0	1	2	3
4	Munegowda 4681 SNRH	M	60	15	26	0.6	89	90	20	6.2	10000	130000	0.8	100	7.4	24	0	1	3	4
5	Narssama 687553	F	50	15	40	1.1	100	130	21	7	6000	82000	1.2	90	7.38	24	0	1	4	5
6	Muneamma 687821	F	60	11	61	0.7	80	130	22	5.5	9500	90000	4.2	111	7.1	10.3	1	1	9	11
7	Kantamma 4782 SNRH	F	52	15	28	0.4	80	100	20	10.9	5200	98000	0.8	88	7.4	24	0	1	1	2
8	Badhara Reddy 692918	M	42	15	61	1.8	80	110	24	14.3	8400	150000	1	85	7.38	24	0	1	4	5
9	Venkatesh 693483	M	45	15	36	1	90	110	22	9	3200	90000	2.2	92	7.4	24	0	1	1	2
10	Venkateshan 4996 SNRH	M	25	15	33	1.8	90	110	16	14.7	4700	98000	0.8	103	7.4	24	0	1	2	3
11	Kailash 697285	M	48	15	32	0.2	90	100	22	8	6400	1.2	0.6	98	1.41	24	0	1	1	2
12	Dasalu 712722	M	26	15	46	1.6	82	110	22	13	4400	1.2	1	59	7.38	24	1	1	1	3
13	Lakshamma 5668 SNRh	F	50	15	30	1	110	110	26	11	13000	60000	0.8	110	7.36	24	1	1	1	3
14	Sumithra 716061	F	42	13	60	2.1	60	80	28	6	14000	70000	2.1	90	7.32	24	1	1	11	13
15	Ibrahim Khan 727286	M	60	15	50	1.4	70	110	20	11.1	6400	32000	11.2	93	7.4	24	0	1	3	4
16	Narayan Swamy 727653	M	50	15	30	1	80	100	20	12.7	5500	17000	6.2	72	7.41	24	1	1	2	4
17	Hemalatha 6677 SNRH	F	37	15	48	1.6	92	90	20	9	4400	100000	0.8	110	7.38	24	0	1	1	2
18	Manjunath 772644	M	28	15	30	1	100	126	25	9	14400	145000	1	92	7.39	24	1	1	3	4
19	Vinod Kumar 773998	M	30	15	50	1.8	120	130	28	9	4400	98000	0.7	101	7.4	24	1	1	2	3
20	Girish 794136	M	25	15	135	2.3	106	130	22	11.4	5400	21000	1.2	73	7.39	24	0	1	6	7
21	Karthik 6829 SNRH	M	20	15	42	1.3	100	110	25	8	13500	90000	2.4	90	7.38	24	0	1	3	4
22	S.V Manjunath 796064	M	32	15	32	1	112	110	20	13	6300	60000	0.9	72	7.4	24	1	1	1	3
23	Hankanashi 819663	F	30	15	31	0.9	78	120	22	10.2	6400	27000	1.2	122	7.39	24	0	1	1	2
24	Kadiramma 810662	F	42	15	11	0.51	80	110	22	11.8	6700	297000	3.8	97	7.4	24	0	1	1	2
25	Salam 821147	M	26	15	32	0.8	80	110	21	11.7	5000	20000	1	122	7.38	24	0	1	1	2
26	Rathnamma 822680	F	35	15	43	0.8	100	100	20	6.1	20600	2.57	1.9	92	7.4	24	0	1	6	7
27	Naveen 834437	M	27	15	36	1.2	80	120	20	13.8	4000	150000	1.5	96	7.38	24	0	1	0	1
28	Syed Rafiq 841848	M	50	15	30	1	86	110	20	12.8	8000	100000	0.5	155	7.4	24	0	1	0	0
29	Suma 817768	F	38	15	30	0.6	82	100	20	10	13600	110000	1	100	7.36	24	0	1	0	1
30	Raghavendra 947738	M	35	15	40	1.1	80	110	23	11	6000	120000	0.5	100	7.4	24	0	1	1	2