ORIGINAL ARTICLE

Mortality in Malaria: Intensive Care (MIMIC)

Trupti Trivedi[1*], Poonam Bajaj[2], Nivedita Moulick[3], Namita Padwal[4]

Abstract

Background: While global incidence of malaria has fallen in last decade, it continues to be an important cause of mortality and morbidity in acutely ill febrile patients. Many patients with complicated malaria require ICU care. In past it was believed that vivax is a benign form of malaria, but now all complications of malaria are reported in vivax.

Aims and Objectives:

1. To find out proportion of patients with plasmodium vivax and plasmodium falciparum malaria requiring treatment in Medical ICU.
2. To compare clinical profile and severity of illness in these patients.
3. To study treatment received including organ support requirement in these patients and compare outcome in patients with vivax and falciparum malaria.

Results: During study period total 932 patients were diagnosed as confirmed malaria (601 vivax, 240 falciparum and 91 mixed) and 107 (vivax 74, falciparum 20, mixed 13) required ICU admission. Common symptoms observed apart from fever were, oliguria (48), dyspnea(41), bleeding (29), hemoptysis (15) and petechial rash (13). Mean BUN and creatinine and PT INR of falciparum/mixed malaria patients was significantly higher and HCO3 and pH significantly lower than vivax patients. But PaO2/FiO2 of vivax patient was significantly lower as compared falciparum/ mixed patients. There was no significant difference between two groups with regards to requirement of supportive treatment like inotropes (11/70 vs 5/30, p=0.858), mechanical ventilation (28/70 vs 7/30, p=0.17), platelet transfusion (24/70 vs 9/30, p=0.853) and renal replacement therapy (5/70 vs 3/30 p=0.936). Out of 100 patients, 21 patients expired. Mortality in mixed malaria group (4/12, 33.3%) and vivax group (16/70, 22.9%) was more as compared to falciparum group (1/18, 5.6%, p<0.05).

Conclusions: Incidence of Plasmodium vivax malaria is higher compared to falciparum malaria in hospitalized patients and higher percentage of these need ICU care. Most common complications of malaria are thrombocytopenia followed by renal failure, hepatic dysfunction, ARDS, shock and cerebral dysfunction respectively. Mortality was higher in vivax and mixed malaria compared to falciparum. Higher SOFA score (Sequential organ failure assessment score), lower GCS score (Glasgow coma scale), hypotension, ARDS and metabolic acidosis are predictors of mortality.

Introduction

Malaria is one of the most common causes of deaths from infectious diseases in India and continues to cause significant economical burden. Global incidence of malaria seems to have peaked in 2003 at 232 million cases and has since fallen by about 29% to 165 million new cases in 2013.[1] Plasmodium falciparum is considered to be the main cause of severe and fatal disease, responsible for major complications like cerebral malaria, acute respiratory distress syndrome, hepatic and renal failure, severe acidosis, severe hemolysis and anemia. There were substantial explanations to support the benign nature of vivax malaria till 20th century like low parasite biomass, increased deformability parasitized RBCs and relative paucity of parasite sequestration compared to P. falciparum. There has been remarkable increase in case reports, series and studies describing severe and fatal disease with vivax malaria recently.[2-5] All complications like coma, renal failure, hepatic failure, acute respiratory distress syndrome (ARDS), acidosis, bleeding, shock, multi-organ dysfunction have been recognized in vivax malaria. Now with more sensitive and specific molecular diagnostics and PCR studies, vivax mono-infection is being reliably diagnosed and dilemma of mixed infection causing complications has been removed. A combination of microcirculatory occlusion, cytokine activation, and nitric oxide-mediated changes in vascular tone are believed to cause organ dysfunction that characterizes severe malaria.[6] This can occur in many different organs, a feature that can partly explain the complexity of the clinical manifestations occurring in severe malaria. Another observation made over last few years is that the pattern of complications associated malaria is changing. Hence this study was undertaken to estimate the incidence of severe vivax malaria requiring ICU admission compared to falciparum and mixed malaria and to compare various clinical, and laboratory parameters between vivax and falciparum malaria and determine factors associated with risk of mortality.

Aims and Objectives

1. To find out proportion of patients with plasmodium vivax and plasmodium falciparum malaria requiring treatment in Medical ICU.
2. To compare clinical profile and severity of illness in these patients.

[1]Associate Professor, [2]Ex-resident Doctor, [3]Professor and Ex Head of Department of Medicine, [4]Associate professor, Department of Medicine, LTM Medical College and General Hospital, Mumbai, Maharashtra; *Corresponding Author
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Annexure 1: SOFA SCORE FOR assessment of severity of disease

SOFA score	0	1	2	3	4
Respiration PaO_2/FIO_2 (mmHg) SaO_2/FIO_2	>400	<400 221-301	<300 142-220	<200 67-141	<100 <67
Coagulation Platelets x 1000/mm^3	>150	<150	<100	<50	<20
Liver serum bilirubin	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
CNS Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

3. To study treatment received including organ support requirement in these patients and compare outcome in patients with vivax and falciparum malaria.

Material and Methods

It was an observational study in medical ICU (MICU) of a tertiary care centre in Mumbai. All patients admitted to hospital with confirmed malaria (smear and/or rapid test) were screened and those admitted to MICU following were included.

Inclusion Criteria

1. All patients with age>12 years in ICU with confirmed malaria by peripheral smear or rapid antigen test and giving valid consent.
2. Sequential Organ Failure Assessment (SOFA) score of equal to or more than 4 on admission to MICU.

Exclusion Criteria

1. Patients having other concomitant cause for acute febrile illnesses (AFI) like dengue, leptospirosis, enteric fever, scrub typhus or viral hepatitis.
2. Patients with pre-existing severe end stage disease like chronic kidney disease (CKD), advanced AIDS, end stage liver disease and terminal malignancies.

Study Procedure

All indoor patients admitted to hospital over a period of 18 months with acute febrile (AFI) illness were screened for presence of malaria by Peripheral Smear and/or rapid malaria antigen test. Patients requiring Medical ICU care and satisfying inclusion criteria were studied in details. Detailed history was taken which included history of presence, duration and pattern of fever, breathlessness, bleeding, oliguria, altered sensorium, convulsion and any other symptoms. Previous treatment with antimalarials and other supportive treatment were noted. Examination was performed with specific emphasis over blood pressure, respiratory rate, icterus, petechiae, hepatosplenomegaly and organ failure signs. Routine hematological and biochemical investigations were carried out which included complete blood count with peripheral smear, rapid malaria antigen test, liver function tests, renal function test, arterial blood gas analysis, chest X-ray and ECG. Tests to diagnose other causes for AFI like dengue, enteric fever or leptospirosis were done. For dengue, NS1 antigen test was done if patient presented within 5 days of fever onset. Beyond that duration, dengue IgM and IgG antibody test was done. For leptospirosis, PCR (polymerase chain reaction) and leptospira IgM antibody tests were done. For enteric fever blood culture was done. Special tests like USG abdomen, CT, MRI, CSF examination, and 2D-ECHO were carried out when indicated. Patients disease severity index was calculated using SOFA score (annexure 1). Patients were followed up till hospital discharge or death. Primary end point was survival. Secondary end points were duration of hospital stay and requirement of supportive treatment like hemodialysis, ventilator, inotropes and blood component transfusions.

Statistical Analysis: data was analyzed Student's t test for quantitative data. Chi square test and Fishers exact test were applied for qualitative data depending on sample size.

Results

During study period total 932 patients were diagnosed as confirmed malaria (601 vivax, 240 falciparum and 91 mixed) and 107 (vivax 74, falciparum 20, mixed 13) required ICU admission and had SOFA score of 4 or more. Of these 7 patients were excluded from the study as 2 had concomitant dengue (NS1 antigen positive), two had leptospira (PCR test positive). One patient was suffering from terminal malignancy two were having underlying chronic kidney disease. Following this exclusion, remaining 100 patients were studied in detail further. Out of these 100 patients, 32 were malaria positive by smear only, 28 were positive by rapid malaria test and 40 were positive by both.

Their demographic data is shown in Table 1. Age of patients ranged from 15 - 73 years with average a 36.61 years in falciparum group which was comparable with 33.17 and 34.29 years in mixed and vivax group. Out of all 100 patients, 68 patients were male and 32 were female. Three patients were pregnant (2 vivax positive and one falciparum). As there were very few patients in falciparum group and sizable number of patients in mixed group, both are considered together henceforth in analysis for statistical purpose.

As shown in Table 2 common symptoms observed were fever (100) followed by oliguria (48), dyspnea (41), bleeding (29), hemoptysis (15) and petechial rash (13). There was no significant difference between symptoms of vivax and Falciparum/ mixed malaria. As shown in Table 3, respiratory rate of patients in vivax group at presentation was significantly more as compared to falci/ mixed group. Mean BP was lower in vivax group than in Falci/mixed group but the difference was statistically not significant. SOFA score was similar between the two groups (vivax 9.6, falciparum/ mixed 9.87 p=0.729). As shown in Table 4 complications noted were thrombocytopenia followed by renal involvement, hepatic involvement, ARDS, hypotension, anemia and cerebral malaria respectively. There was no significant difference between two groups with regards to these complications. As shown in Table 5, Mean BUN and creatinine and PT

Table 1: Demographical data

Parameters	Falciparum n=18	Mixed n=12	Vivax n=70	Total n=10
Age (yrs)				
Mean±SD	36.61±9.34	33.17±13.84	34.29±13.95	
Range	23 – 56	17 – 57	15 – 73	
# Sex (%)				
Male	12 (66.7)	09 (75.0)	47 (68.1)	68
Female	06 (33.3)	03 (25.0)	23 (31.9)	32

@ By Student 't' Test; P Not Significant; # by Chi-square Test; P Not Significant

Table 2: Comparison of symptoms in Vivax and Falciparum/mixed Malaria in ICU

Symptoms	Vivax (n=70)	Falci/Mixed (n=30)	Total (n=100)	p value
Fever	70(100%)	30(100%)	100(100%)	-
Dyspnea	32(45%)	9(30%)	41(41%)	0.214
Hemoptysis	12(17%)	3(10%)	15(15%)	0.541
Bleeding	20(28%)	9(30%)	29(29%)	0.923
Rash	9(12%)	4(13%)	13(13%)	0.795
Oliguria	30(42%)	18(60%)	48(48%)	0.176

Table 3: Comparison of examination findings in Vivax and Falciparum/mixed Malaria in ICU

	Vivax Mean±SD	Falci/Mixed Mean±SD	p value*
Pulse	88.45±13.36	84.43±10.95	0.15
Mean BP	71.75±14.57	77.36±20.75	0.126
Respiratory rate	26.21±9.72	22±7.09	0.035
GCS	13.95±1.91	14.03±2.24	0.856
SOFA	9.6±3.69	9.87±3.23	0.729

*By Student t test

Table 4: Comparison of complications Vivax and Falciparum/mixed Malaria in ICU

	Vivax (n=70)	Falci/Mixed (n=30)	Total (n=100)	p value
Hypotension (mean BP<70 mmhg)	25(35.7%)	7(23.3%)	32(32%)	0.326
Tachypnea (Respi. rate>20)	37(52.8%)	9(30%)	46(46%)	0.06
Cerebral malaria (GCS<10)	4(5.7%)	3(10%)	07(07%)	0.732
Anaemia (Hb<12 for males and <11 for females)	18(25.7%)	8(26.6)	26(26%)	0.881
Thrombocytopenia (platelet<1.5 L)	70(100)	29(96.6)	99(99%)	0.661
Renal involvement (creat >1.5mg%)	50(71.4%)	26(86.66)	76(76%)	0.168
Hepatic involvement (total bilirubin >2mg %)	43(61.4%)	24(80%)	67(67%)	0.115
ARDS (PaO_2/FiO_2<300)	32(45.7%)	7(23.3%)	39(39%)	0.06

(Chi square test)

INR of falciparum/mixed malaria patients was significantly higher and HCO3 and pH significantly lower than vivax patients. But PaO2/FiO2 of vivax patient was significantly lower as compared falciparum/mixed patients. There was no significant difference between two groups with regards to mean Hemoglobin, platelet count, liver function test (SGOT, SGPT, total bilirubin) and random blood glucose value on admission. There was no significant difference between two groups with regards to requirement of supportive treatment like inotropes (11/70 vs 5/30, p=0.858), mechanical ventilation (28/70 vs 7/30, p=0.17), platelet transfusion (24/70 vs 9/30, p=0.853) and renal replacement therapy (5/70 vs 3/30 p=0.936).

Out of 100 patients, 21 patients expired. Mortality in mixed malaria group (4/12, 33.3%) and vivax group (16/70, 22.9%) was more as compared to falciparum group (1/18, 5.6%, p<0.05). As shown in Table 6 Mean pulse, respiratory

Table 5: Comparison of biochemical parameters in Vivax and Falciparum/mixed Malaria in ICU

	Vivax Mean±SD	Falci/mixed Mean±SD	p value*
Hb	12.37±2.31	12.16±2.37	0.68
Platelet	39685±31674	42433±42401	0.721
BUN	55.47±39.73	85.7±52.07	0.002
Creatinine	3.25±2.06	4.87±2.65	0.001
SGOT	71.16±101	86.27±89.72	0.481
SGPT	116.46±132	176.6±164.43	0.056
Bilirubin	4.33±3.71	5.85±3.12	0.052
INR	1.34±0.42	1.7±0.75	0.003
pH	7.34±0.1	7.29±0.12	0.034
HCO_3	20.13±4.32	16.83±5.32	0.002
PaO_2/FiO_2	319.07±131.71	393.67±95.86	0.006
RBS	121.67±57.89	131.97±71.11	0.449

*By Student t test

Table 6: Comparison of clinical and biochemical profile between survived and expired group

	Survived Mean±SD	Expired Mean±SD	p value
Age	35.34±13.06	31.67±13.03	0.255
Days of fever	4.58±3.57	3.86±3	0.399
Pulse	83.46±10.49	101.52±10.36	<0.001
MBP	75.37±15.92	66.83±18.39	0.037
RR	21.89±6.86	36.52±7.47	<0.001
GCS	14.23±2.01	13.05±1.72	0.016
Hb	12.32±2.12	12.28±3.03	0.945
Platelet	40848±34540	39238±37701	0.853
BUN	61.38±41.71	76.43±58.02	0.181
Creatinine	3.5±2.16	4.6±2.9	0.57
SGOT	64.18±63.35	119±170.37	0.021
SGPT	121.72±118.53	182.57±214.47	0.087
Total bilirubin	4.69±3.26	5.16±4.71	0.596
INR	1.36±0.42	1.78±0.87	0.002
HCO_3	19.84±4.44	16.52±5.55	0.005
PaO_2/FiO_2	384.81±92.42	178.05±101.83	<0.001
SOFA	8.62±2.63	13.67±3.78	<0.001

Student t test

Table 7: Comparison of presenting symptoms and complications between survived and expired group

	Survived (n=79)	Expired (n=21)	p value
Dyspnoea	22(27.84%)	19(90.47%)	<0.001
Haemoptysis	3(3.79%)	12(57.14%)	<0.001
Bleeding	14(17.72%)	15(71.42%)	<0.001
Oliguria	36(45.57%)	12(57.14%)	0.462
Hypotension (mean BP<70mmHg)	20(25.31%)	12(57.14%)	0.008
Tachypnea (Respi rate > 20)	26(32.91%)	20(95.23%)	<0.001
Anaemia (Hb<12 in males & < 11 in females)	21(26.58%)	5(23.81%)	0.892
Thrombocytopenia (platelets <1.5 lacs)	78(98.73%)	21(100%)	1
Renal involvement (creatinine >1.5)	59(74.68%)	17(80.95%)	0.775
Hepatic involvement (Total bilirubin> 2)	55(69.62%)	12(57.14%)	0.415
X-ray infiltration	11(13.92%)	13(61.90%)	<0.001
ARDS	21(26.58%)	18(85.71%)	<0.001

(Chi square test)

rate, PT-INR and SOFA score was significantly higher and mean BP, GCS, HCO3 andPao2/Fio2 was significantly lower in patients who expired. As shown in Table 7 dyspnea, hemoptysis, bleeding, hypotension, tachypnea and X-ray infiltration of ARDS were significantly more in patients who

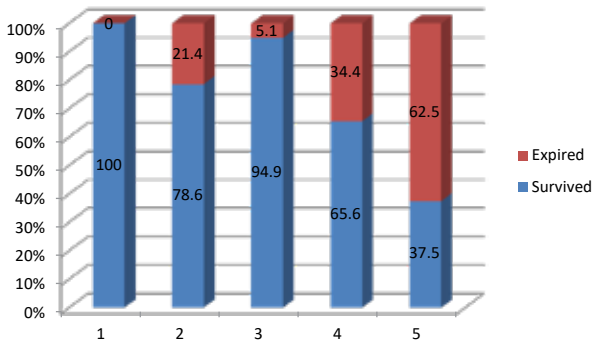

Fig. 1: Impact of number of organ dysfunction on survival (p<0.0001)

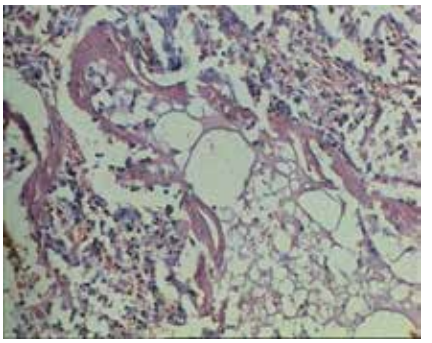

Fig. 2: Histopathology of lung from autopsy of patient with ARDS and multiorgan failure due to malaria

succumbed. However presence of oliguria, anemia, thrombocytopenia, renal and hepatic involvement did not have significant impact on survival. As shown in Figure 1, mortality of patients increased with increase in number of organ dysfunction (p< 0.0001). Duration of ICU stay in survived patients varied from 2 to 23 days. Hypotension(13/39 vs 7/40), renal involvement (32/39 vs 27/40) and hepatic involvement (30/39 vs 25/40) was more in survived patients whose ICU stay was of more than 4 days. But this difference was statistically not significant. Initial SOFA score was more in survived patients whose stay in ICU was more than 4 days (9.28 vs 7.98, p=0.026).

Out of 35 patients who required mechanical ventilation, 4 patients suffered from VAP (Ventilator Associated Pneumonia). Five patients out of 100 patients developed catheter associated urinary tract infection. These patients were treated with appropriate antibiotics. There was no long term morbidity in any the form of permanent neurological, hepatic or renal sequel in any of the survived patients. One of the expired patients underwent autopsy. His lung showed remarkable changes of ARDS like thick hyaline membrane, inflammatory cells and destruction of alveolar spaces as shown in Figure 2.

Discussion

P. vivax malaria is now increasingly associated with severe disease and high case fatality.The exact cause of changes in the clinical profile of vivax malaria is uncertain. Genetic alterations of the parasite or vector or chloroquine resistance may be responsible.[5] It was previously believed that the severe disease with vivax malaria is actually caused by co-infection of vivax and falciparum and while schizonts of P. vivax are detected in venous blood in contrast those of P. falciparum remain undetected as they are found in the capillaries of internal organs. However with availability of the recently developed tests of malarial antigen and the nucleic acid amplification technique it has become evident that vivax monoinfection can be a cause of severe malaria and death.[7] In present study mixed infections were identified by peripheral smear and rapid malaria test. In 2009 Kochar et al reported series of 11 cases of severe vivax malaria from Bikaner. They used antigen and PCR test to exclude falciparum co-infection.[8] In present study there were more hospital admissions with vivax as compared to falciparum malaria. This is concordant with the fact that in India and other Southeast Asian countries, incidence of vivax malaria is on rise. In Africa also where falciparum is much more common, vivax is emerging as a major type of malaria with complications.[9] A similar study of clinical profile of malaria in 314 patents, done in a tertiary referral centre in South Canara,[10] plasmodium vivax was the major parasite type (52.54%), followed by P. falciparum (33.75%), and followed by mixed malarial infection (13.69%) which matches with the pattern observed in present study. Study from a tertiary care hospital in Mumbai also showed higher incidence of severe vivax malaria than falciparum and mixed malarias.[11] Most of the patients were in the age group of 21- 30 years. This finding matches observations in a study done in South Canara (Karnataka) aimed at studying the demographic profile of malaria. Majority of their patients were males between the age group of 15 and 40 years.[10] The factors responsible for this pattern include outdoor work and outdoor sleeping habits in young males and other socioeconomic and cultural factors. There was no significant difference between symptoms of vivax and Falciparum/ mixed malaria in this study. It is difficult to differentiate various types of acute undifferentiated fevers in tropics based on clinical presentation alone- an enlarged liver and spleen could be found in malaria, dengue, typhoid fever and leptospirosis. Similarly, headache, neck stiffness and other signs of meningeal inflammation-traditionally associated with meningitis, lack accuracy for ruling in or ruling out meningitis.[12] Thrombocytopenia, renal failure and liver dysfunction were common complications. Only one third of patients with thrombocytopenia required platelet transfusions as they were administered only in case of clinical bleeding or severe thrombocytopenia with platelet count <10000/cmm. Only 7.14% patients with renal failure required renal replacement therapy. Mean BUN and creatinine value was significantly more in falci/ mixed patients as compared to vivax patients which was similar to what has been observed in another study from Mumbai.[13] Hepatic involvement was not significantly different in vivax and falci/mixed malaria. Cerebral malaria was found in 7% of patients with higher incidence in falci/ mixed malaria (10%), but the difference was not statistically significant. Cerebral malaria was much less as compared to 40% incidence in a similar study done in an ICU at tertiary care hospital in Mumbai in 2002.[14] A study by Tjitra in Southeast Asia showed severe anaemia as the most common complication[15] but there were no such patients in present study. The prevalence of ARDS was comparable in both the groups but the mean

value of PaO2/FiO2 was significantly less in P. vivax compared to falci/ mixed and 35% of patients required mechanical ventilation. This was in contrast to results found in a study done by Nadkar et al where ARDS was more in falciparum malaria as compared to vivax malaria.[11] All these complication patterns clearly shows that over a decade, cerebral malaria and severe anaemia have remarkably decreased while ARDS and renal, hepatic dysfunction are increasing in severe malaria. Reasons for this changing pattern of complications can be change in virulence or genetics of the parasite or early use of faster acting anti-malarial drugs[16] or a combination of multiple factors. Recent analysis suggests that severe malarial anemia, severe thrombocytopenia, pulmonary distress, cerebral syndromes (ranging from seizures to coma), and hepatic and renal dysfunction dominated reported syndromes in patients with a diagnosis of *P. vivax* infection and classified as having severe disease. Severely ill patients with a diagnosis of P. falciparum infection have the same syndromes but are more likely to present with two or more of these.[17] A recent retrospective study concluded that anemia, hepato-renal dysfunctions were equally frequent in vivax malaria and it can no longer be considered as benign infection.[18]

In our study the overall mortality was 21% and P. vivax and mixed malaria had higher mortality than falciparum malaria, which was in contrast to an observational study done at another tertiary care hospital in Mumbai[13] where mortality was significantly lower in vivax malaria (1.77%) than in falciparum (9.71%) and mixed malaria (10.29%) . However that study was on all hospitalized patients and present study was in ICU patients. A study from Orissa found that there were 4 independent risk factors for a patient of developing complicated malaria-no fever on presentation, high parasite count, mono infection with falciparum, and longer fever to treatment interval.[19] Predictors of mortality in our study were higher SOFA, lower GCS, hypotension, metabolic acidosis and ARDS irrespective of species of malaria. A study by V.B. Kute in Ahmedabad concluded that Mortality in malaria was associated with higher APACHE II, SOFA, MODS, GCS scores and requirement of inotrope, and ventilator support.[20]

There are important limitations of present study. As during monsoon season there is a surge of admission of patients with acute febrile illness and there are large number of patient needing ICU care. But there are constraints due to limited number of ICU beds, hence all cases of severe malaria needing ICU care cannot be shifted to ICU and many of them are continued to be managed in the general wards. Those who require mechanical ventilation and inotropic support are given preference over patients with other organ involvement for ICU care. Due to this reason, pattern of organ involvement and mortality of severe malaria patients in our ICU cohort cannot be directly extrapolated to pattern of complications in overall severe malaria cases admitted to the hospital.

Conclusions

Incidence of Plasmodium vivax malaria is higher compared to falciparum malaria in hospitalized patients and higher percentage of these need ICU care.

Young males are most vulnerable in suffering from complicated malaria. Oliguria, dyspnea, bleeding and hemoptysis are common presenting symptoms in both vivax and falciparum malaria in ICU.

Most common complications of malaria are thrombocytopenia followed by renal failure, hepatic dysfunction, ARDS, shock and cerebral dysfunction respectively. Falciparum/mixed patients had more mean BUN and creatinine value and more metabolic acidosis as compared to vivax group. Mean PaO2/FiO2 was less in vivax malaria as compared to falciparum/ mixed malaria. Organ support requirements like mechanical ventilation, platelet transfusion, renal replacement therapy and inotropic support were similar between plasmodium vivax and falciparum/ mixed patients.

Overall mortality in our study was 21% in ICU patients with complicated malaria. Mortality was higher in vivax and mixed malaria compared to falciparum. Higher SOFA score (Sequential organ failure assessment score), lower GCS score (Glasgow coma scale), hypotension, ARDS and metabolic acidosis are predictors of mortality.

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