

4 **Aim of the study:** To observed changes in clinical, hematological and biochemical
5 parameters of dengue and malaria over a period of ten days in patients who presents with low
6 platelet count.

9 **Study design:** Prospective observational study.

Methodology: Patients of acute fever who were diagnosed as malaria or dengue by peripheral smear, rapid antigen testing or serology were included. Complete blood count including platelet count; liver function test and renal function tests were done in all cases on day 2, 4, 6, 8 and day 10 to see progressive changes. Results were analysed subsequently.

Results: The patients of dengue presented earlier (4.11 ± 1.42) around 4th day as compared to malaria. The skin rash, bleeding tendency, tourniquet test positivity and respiratory abnormalities were more frequent in dengue patients, while abdominal pain, diarrhoea, anaemia, jaundice, hepatomegaly and splenomegaly were more frequent in malaria patients.

White blood cells count showed initial rise in malaria and fall in dengue which gradually recovered by 10th day in both diseases. Fall in haemoglobin was seen only in malaria cases. There was continuous fall in platelet count till 6th day of illness in dengue patient while in malaria patient fall appeared early on 2nd day of fever but was inconsistent, which gradually

recovered. Platelet fall was more severe in dengue as compared to malaria, so was bleeding tendencies. Bleeding tendencies were more frequent when the platelet count was below 20,000/ μ L.

Transaminase levels were more severely deranged and manifested early in malaria, while serum creatinine and blood urea were more deranged in dengue. Both these biochemical abnormalities return to normal by 10th day of illness.

Conclusion: We suggest that our observations can be used in remote areas where facilities for specific test are not available or limited by financial constraints or in epidemics.

Key Words: Thrombocytopenia, Liver function tests, Kidney function test, Dengue, Malaria, Bleeding tendencies, Outcomes.

INTRODUCTION:

Many diseases can present with fever and thrombocytopenia such as dengue, malaria, septicaemia, leptospirosis, enteric fever, human immunodeficiency virus(HIV), TTP-HUS, rickettsial infections, viral hepatitis, rodent born viruses such as Hanta and Lassa fever, leukaemia etc.^{1,2,3,4} Dengue and malaria are the two most common arthropod borne diseases in northern India during rainy season and are responsible for large number of morbidity and mortality. Both can present with high grade fever with thrombocytopenia. Their early diagnosis and specific management is of utmost importance⁵. Confirmation of dengue and malaria requires technical expertise which at times may not be available. Differences in certain haematological parameters which include low platelet count, haemoglobin concentration and hematocrit have been reported to be associated with malaria and dengue⁶.⁷ In the present study we have compared the progressive alteration in clinical and routine laboratory parameters to differentiate between dengue and malaria.

48 **MATERIALS AND METHODS:**

49 All cases of acute fever with thrombocytopenia presenting in Lady Harding medical college
 50 were included in this study. **Inclusion criteria:** Patients with (1) age > 18 years and (2)
 51 history of fever (i.e. oral A.M. temperature of >37.2°C (>98.9°F) or a P.M. temperature
 52 >37.7°C (>99.9°F) for 2-7 days and (3) thrombocytopenia (i.e. platelet count less than 1,
 53 50,000/ μ L) (4) Confirmation of Malaria was done by peripheral smear, malarial antigen
 54 testing, and of dengue by NS1 antigen, dengue serology. **Exclusion criteria:** All other causes
 55 of thrombocytopenia with fever. A detailed history and physical examination was done .All
 56 patients were subjected to a battery of laboratory investigations which included routine
 57 blood investigations like complete blood count, liver function tests, kidney function tests etc.
 58 Patients were followed up with clinical features, haematological parameters and biochemical
 59 parameters on 2nd ,4th ,6th ,8th and 10th day of fever, during their stay in the hospital until an
 60 outcome (recovery or discharge in health or expiry) or till ten days from beginning of
 61 illness (i.e. Day 1 of fever) was reached.

62 Results were statically analysed. Sample statistics like mean, median and standard deviation
 63 were calculated for Quantitative data. Tests of significance like Chi-square test and difference
 64 of proportion was applied for categorical data. Mean and standard deviation was compared by
 65 Student T test. Association between two continuous variables was assessed by correlation
 66 analysis and spearman's correlation coefficient. Statistical significance was set up at $p \leq 0.05$

67 **RESULTS:**

68 A total number of 134 cases were included in the study of which, 67% were of Dengue and
 69 33 % were of Malaria. High grade fever with chills and rigors was the main presenting
 70 feature and was present in 100% of patients.

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72 **TABLE 1: Age of patients and duration of fever in study population**

Number	Mean Age $\pm$ SD (in Years)	Duration of fever at Presentation $\pm$ SD (in Days)
Dengue (n = 90)	34.82 $\pm$ 10.76	4.11 $\pm$ 1.42
Malaria (n =44)	34.09 $\pm$ 10.48	4.84 $\pm$ 1.58

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74 The age range of the patient was 18-85 years. Mean age (Table 1) of the sample population
 75 was 34.65 $\pm$ 10.79 years. The dengue patients presented early in the course of illness. The
 76 mean duration of illness (Table 1) at presentation was 4.11 $\pm$ 1.42 days in dengue patients
 77 while it was 4.84 $\pm$ 1.58 days in malaria. There was a male preponderance noticed in our study
 78 population.

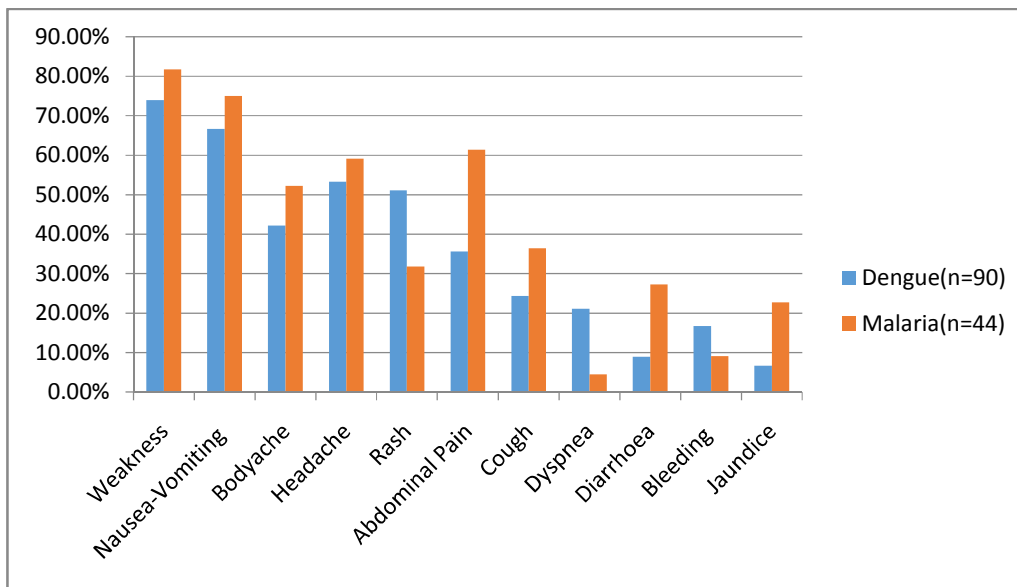
79 **TABLE 2: Clinical features of Dengue and Malaria**

Clinical Symptoms			Clinical Sign		
Symptoms	Dengue	Malaria	Sign	Dengue	Malaria
Weakness	74.0%	81.8%	Pallor	33.3%	47.0%
Nausea/Vomiting	66.7%	75.0%	Torniquet Test	42.2%	27.3%
Bodyache	42.20%	52.30%	Petechie/Purpura	35.6%	22.7%
Headache	53.3%	59.1%	Splenomegaly	10.0%	47.7%
Rash	51.1%	31.8%	Icterus	11.1%	36.4%
Abdominal Pain	35.6%	61.4%	Respiratory abnormality	18.9%	2.3%
Cough	24.4%	36.4%	Hepatomegaly	4.4%	27.3%

Dyspnea	21.1%	4.5%	Ascitis	20.0%	4.5%
Diarrhoea	8.9%	27.3%	Impaired Consciousness	8.9%	2.3%
Bleeding	16.7%	9.1%			
Jaundice	6.7%	22.7%			

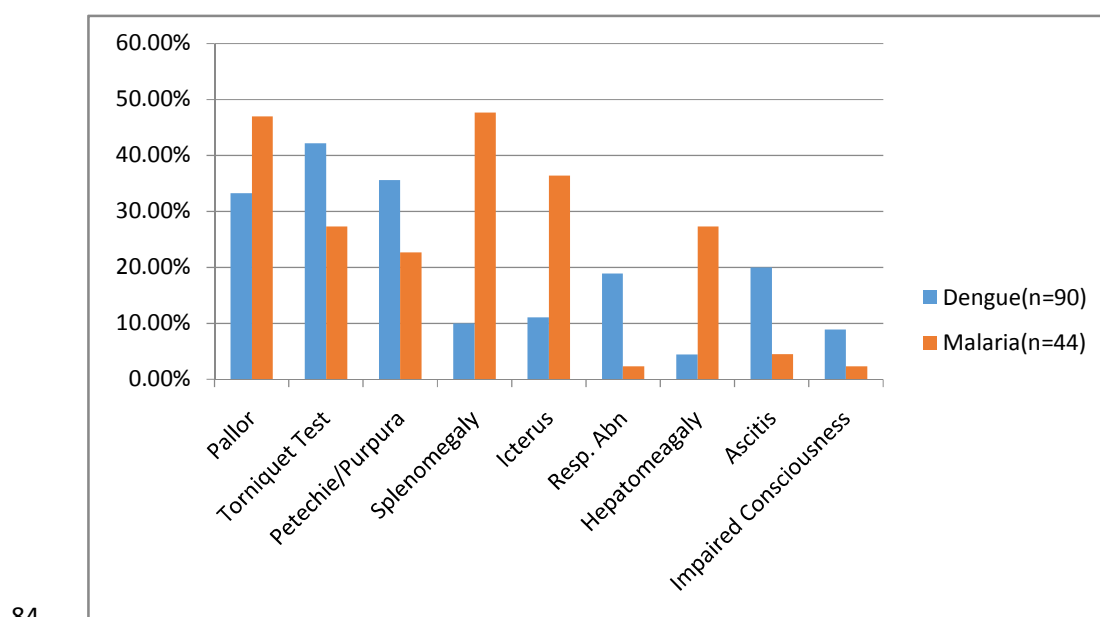
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81 **Image 1: Comparison of clinical symptoms in dengue and malaria**



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83 **Image 2: Comparison of clinical signs of dengue and malaria**



85 Generalized weakness, body ache, headache and nausea-vomiting were the common clinical
 86 features in both dengue and malaria groups. In dengue group rash, dyspnea, bleeding
 87 tendencies, tourniquet test positivity, ascitis and respiratory abnormalities were most frequent
 88 while in malaria patients abdominal pain, jaundice, diarrhoea, pallor, icterus, hepatomegaly
 89 and splenomegaly were more frequently as shown in table 2, image 1 and image 2.

90 **TABLE 3: Haematological parameters during observation period in dengue.**

Dengue	DAY-2 (n=13)	DAY-4 (n=56)	DAY-6 (n=84)	DAY-8 (n=81)	DAY-10 (n=55)
Mean WBC*	4369.2	4201.8	3871.4	4835.3	5720
±SD (/μL)	±1842.7	±2214.2	±1682.1	±1588.4	±1451.9
Mean neutrophils ±SD (%)	66.4±9.2	58.5±12.7	47.3±10.9	53.8±15.7	54.9±14.9
Mean lymphocytes ±SD (%)	24.6±9.2	29.6±9.9	40.0±9.4	33.7±12.7	31.3±10.7

Mean haemoglobin	12.9±2.3	11.6±2.3	11.3±2.0	11.3±2.0	11.5±1.4
±SD (g/dl)					
Mean hematocrit	39.8±6.2	35.6±7.4	35.3±7.1	34.2±6.6	35.2±5.4
±SD (%)					
Mean platelet	59.0±49.8	42.9±31.7	39.5±29.3	56.3±28.9	84.7±21.3
Count					
±SD (X10 ³ /μL)					

91 *WBC-White blood cell

92 In dengue, mean total WBC count on day 2 was 4369.2/μL following which, there was a
 93 significant dip in mean total WBC count on Day 6 and then it significantly increased on Day
 94 10 (p<0.001). The mean neutrophils percentage on day 2 was 66.4 % that decreased till day 6
 95 and then significantly increased till day 10 (p<0.05) opposite trend was noted in lymphocytes,
 96 which increased till day 6 and fell after day 10 (p<0.05).

97 The mean hematocrit and haemoglobin, both were within normal limits, but gradually
 98 decreased from day 2 to day 8 (<0.05). These stabilized thereafter on day 10. The mean
 99 platelet count on day 2 of the illness was 59.0 x 10³/μL, and showed a decrease till day 6 and
 100 increased significantly thereafter (p<0.01). The lowest platelet counts were noticed on day 6.

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107 **TABLE 4-Haematological parameters of malaria during observation period.**

Malaria	DAY-2	DAY-4	DAY-6	DAY-8	DAY-10
	(n=3)	(n=24)	(n=33)	(n=44)	(n=36)
Mean WBC	9133.0	5304.1	3966.6	5400.0	5325.0
±SD (/ μ L)	±8544.7	±2835.7	±1824.7	±2971.5	±2211.3
Mean neutrophils	77.6±13.2	66.2±10.5	62.4±15.5	61.6±19.0	63.2±9.7
±SD (%)					
Mean lymphocytes	18.3±11.5	25.8±8.4	28.1±12.4	26.8±15.7	24.5±9.4
±SD (%)					
Mean haemoglobin	9.4±1.0	9.5±1.6	10.3±2.4	9.7±1.8	9.5±1.5
±SD (g/dl)					
Mean hematocrit	26.6±4.8	28.2±5.4	29.2±7.0	29.1±6.9	28.3±6.6
±SD (%)					
Mean platelet	21.3±8.0	59.6±40.0	43.1±28.3	56.8±37.3	72.6±35.
count					0
±SD ($\times 10^3$ / μ L)					

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109 In malaria, the mean WBC count on day 2 was 9133/ μ L, that decreased till day 6 of fever and
110 significantly increased thereafter till day 10 ($p < 0.05$). The mean neutrophilic percentage
111 followed a significantly decreasing trend from day 2 to day 8 i.e. from 77.6 % to 61.6%.
112 ($p < 0.05$) Similarly lymphocytic percentage significantly increased in the same time period
113 i.e. from 18.3% to 26.8% ($p < 0.05$).
114 The mean hematocrit and haemoglobin, both were low at presentation on day 2 (9.4 g/dl and
115 26.6 % respectively), and remained low throughout the study.

The platelet counts also showed a significant dip at day 6 and then increased gradually till day 10 ($p < 0.05$).

Dengue versus Malaria- Hematological profile

Image 3: Comparasion of WBC in dengue and malaria

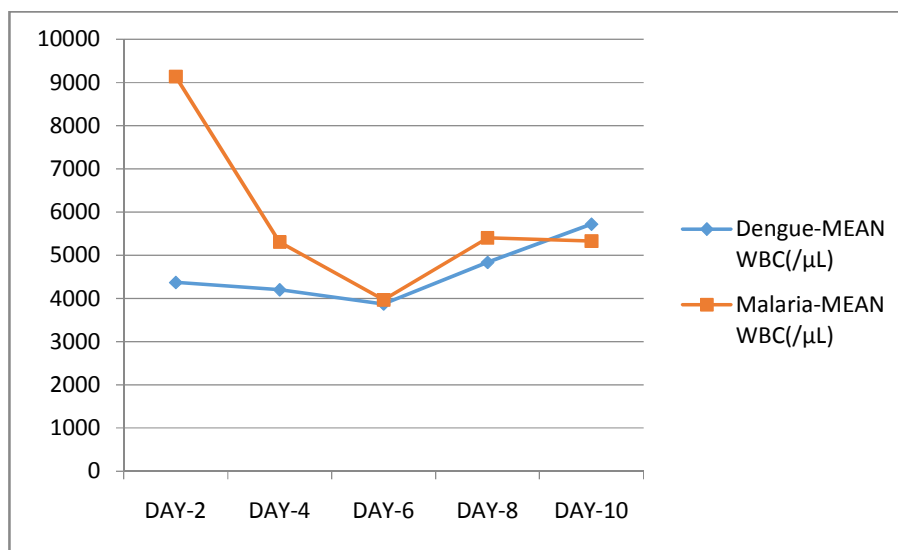
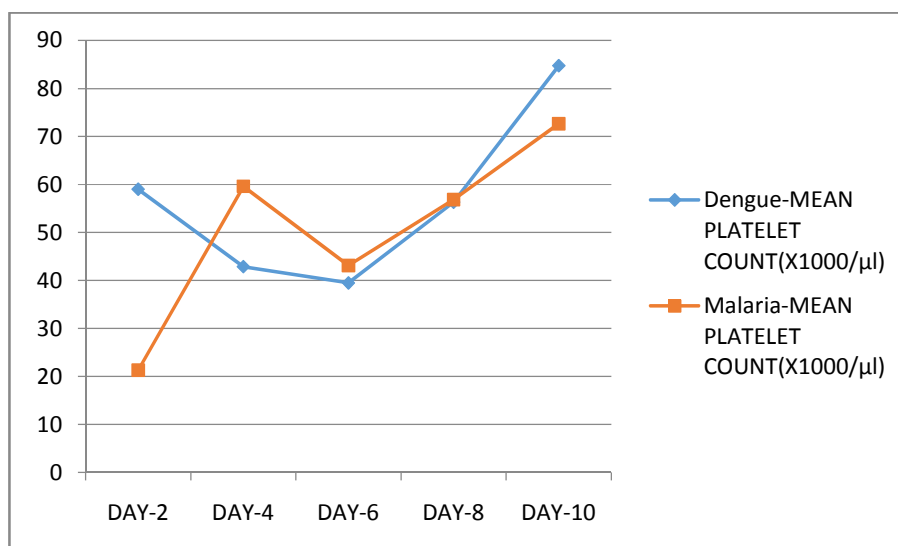


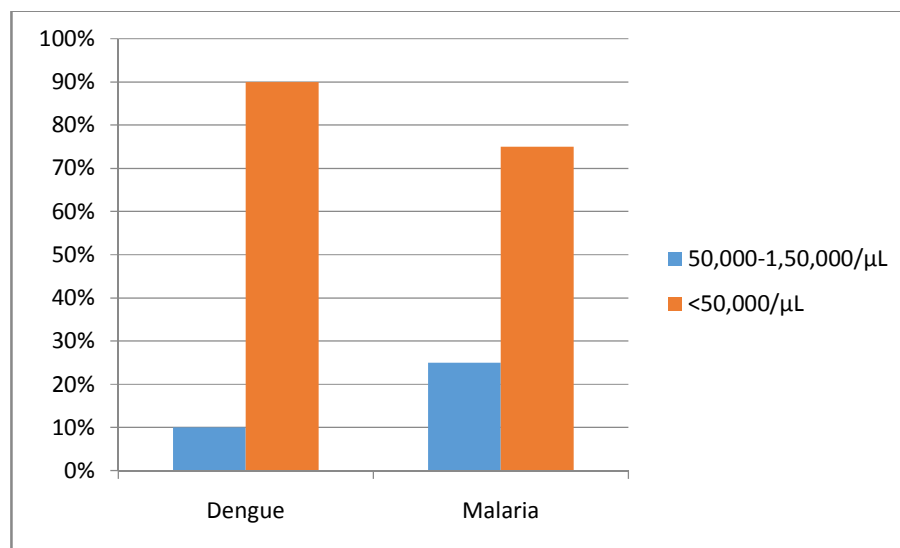
Image 4: Comparasion of platelet in dengue and malaria



Patients presenting with dengue had slightly lower mean WBC as compared to malaria patients but this difference was not significant ($p>0.05$) except on day 2 when malaria patients had higher mean WBC values. Patients with malaria had a significantly higher percentage of neutrophils in blood as compared to their dengue counterparts ($p<0.05$) with a slightly decreasing trend in both groups. Patients in dengue group had a sharp dip on day 6 which was not seen in malaria patients.

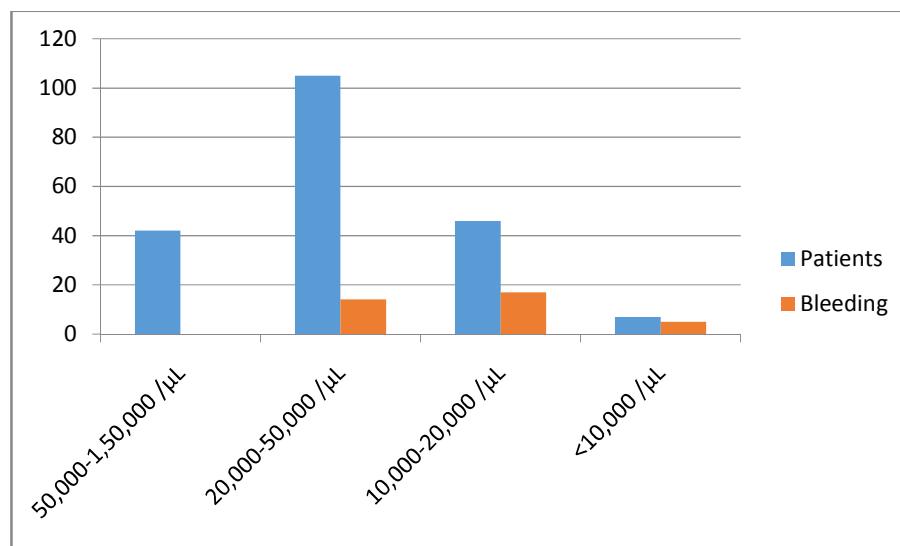
Patients with malaria had lower haemoglobin level as compared to dengue patients ($p<0.01$). A similar trend was seen in hematocrit values too ($p<0.01$). Patients in dengue group had significant and consistent fall in the platelet count till day 6 with a rising trend thereafter as compared to patients of malaria who had a fluctuating trend till day 6 and significant rise on day 10 ($p<0.05$).

Image 5: Severity of thrombocytopenia in dengue and malaria



The finding of severe thrombocytopenia was more marked among the dengue patients ($p<0.05$) of which 81(i.e. 90%) out of 90, presented with a platelet count $\leq 50,000/\mu\text{L}$ as compared to only 33(i.e. 75%) patients out of 44 in malaria group.

141 **Image 6: Relationship between bleeding tendencies and platelet count**



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143 None of the patient having platelet count above 50,000/μL developed any sign of bleeding
 144 (for eg. petechie-purpura, melena, per-rectal bleed, gum bleed, menorrhagia, hematuria,
 145 epistaxis or subconjunctival haemorrhage), while 13.3% of the patients having platelet count
 146 between 50,000/μL to 20,000/μL developed bleeding tendencies and 37% of those having
 147 platelet count between 20,000/μL to 10,000/μL while 71.4% of those having platelet count
 148 below 10,000/μL developed one or more signs of bleeding.

149 **TABLE 5: Biochemical parameters during observation period in dengue.**

Dengue	DAY-2	DAY-4	DAY-6	DAY-8	DAY-10
	(n=13)	(n=56)	(n=84)	(n=81)	(n=55)
Mean blood urea ±SD (mg/dl)	52.0±14.5	42.2±22.3	36.4±19.6	34.3±15.9	30.9±14.6
Mean serum creatinine (mg/dl)	1.6±0.5	1.2±0.5	1.1±0.5	1.1±0.2	0.9±0.1
Mean total serum	1.5±0.8	1.7±1.2	1.6±1.5	1.6±1.9	1.1±0.3

bilirubin					
±SD (mg/dl)					
Mean serum alanine	168.0±165.	106.1±125.	86.9±124.	70.4±66.2	64.8±35.3
transaminase	5	0	3		
±SD (U/L)					
Mean serum aspartate	187.6±196.	86.8±99.2	68.3±81.6	64.5±80.9	45.8±23.5
transaminase	5				
±SD (U/L)					
Mean serum alkaline	246.4±147.	133.0±84.8	137.3±86.	145.6±102.	163.2±118.
phosphatase	5		4	5	6
±SD (U/L)					

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151 Dengue patients initially presented with relatively high mean blood urea and serum creatinine
 152 levels of illness but there was a significant improvement towards normal from day 4 onwards
 153 ($p<0.05$). The mean total serum bilirubin levels was initially deranged on day 2 (1.5 mg/dl)
 154 followed by normalization on day 10 ($p<0.05$). Liver enzymes also showed similar trend.

155 **TABLE 6- Biochemical parameters of malaria during observation period.**

Malaria	DAY-2	DAY-4	DAY-6	DAY-8	DAY-10
	(n=3)	(n=24)	(n=33)	(n=44)	(n=36)
Mean blood urea	74±1.7	34.3±12.6	32.1±8.1	40.8±23.1	39.7±21.2
±SD (mg/dl)					
Mean serum	1.4±0.4	1.1±0.2	1.0±0.2	1.3±0.6	1.2±0.5
creatinine					
±SD (mg/dl)					

Mean total serum bilirubin ±SD (mg/dl)	10.4±1.0	2.9±1.7	2.9±2.2	2.0±2.0	1.7±1.5
Mean serum alanine transaminase ±SD (U/L)	500.6±725.1	114.4±163.1	99.3±93.9	135.9±120.8	135.3±125.2
Mean serum aspartate transaminase ±SD (U/L)	349.0±476.3	88.5±126.5	83.5±53.0	102.3±91.0	108±82.3
Mean serum alkaline phosphatase ±SD (U/L)	552.0±19.2	191.1±134.3	159.3±114.9	172.7±102.5	163.2±118.6

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157 Mean blood urea and serum creatinine levels were significantly high on day 2 of the illness
 158 i.e. 74 mg/dl and 1.2 mg/dl but normalized later with appropriate treatment. Mean serum total
 159 bilirubin was significantly higher on initial days and decreased from day 4 onward in malaria
 160 patients ($p<0.05$). Liver enzymes were deranged on 2nd day but rapidly improved on
 161 following days.

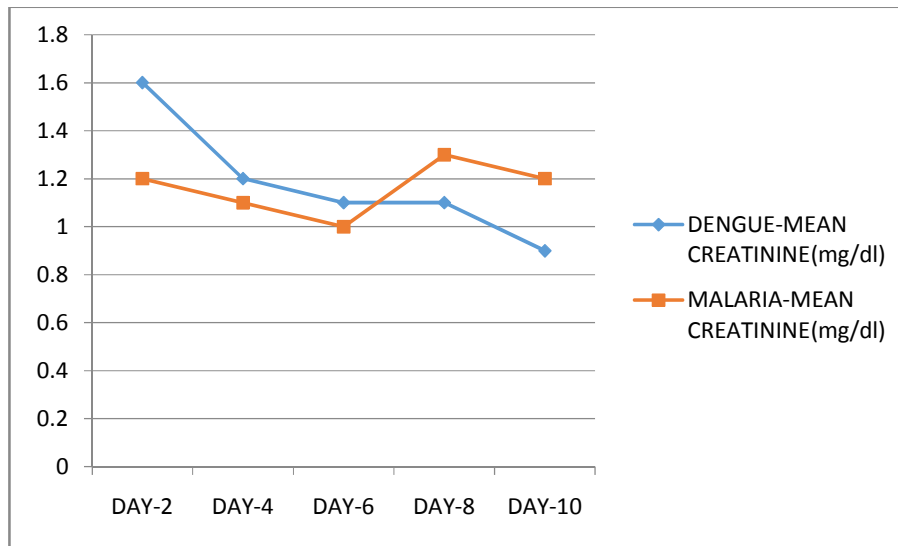
162 **Dengue versus Malaria- Biochemical profile**

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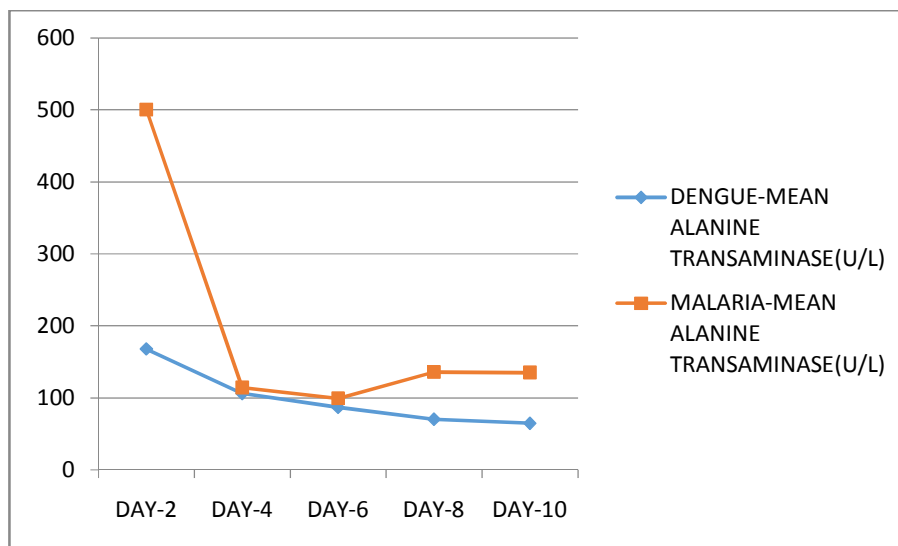
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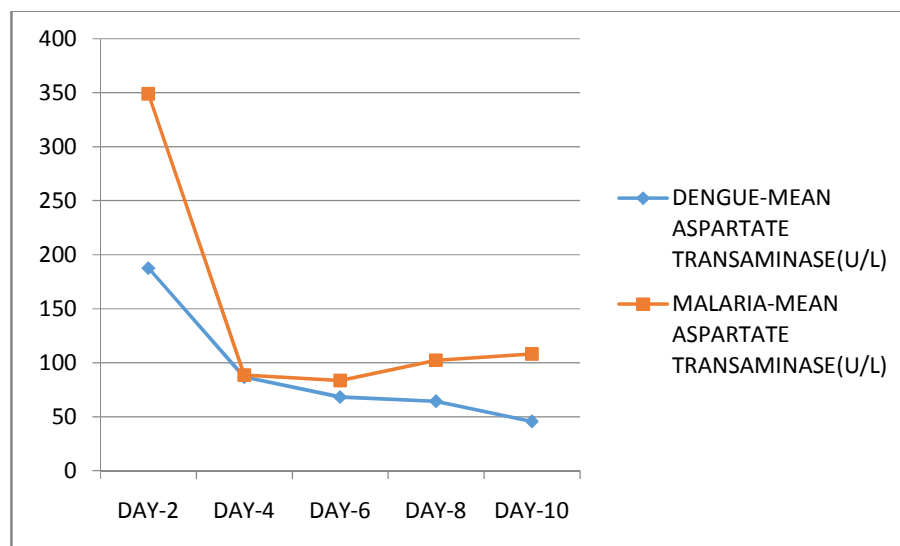
166 **Image7: Comparison of creatinine in dengue and malaria**



168 **Image 8: Comparison of Alanine transaminase in dengue and malaria**



174 **Image 9: Comparison of Aspartate transaminase in dengue and malaria**



176 Patients of dengue had a continuously decreasing trend in the mean blood urea and serum

177 creatinine levels while malaria patients had a fluctuating course of the same with a

178 significantly higher values on day 10 ($p < 0.05$).

179 Patients with malaria had significantly higher values of mean serum total bilirubin and liver

180 enzyme levels when compared to dengue from day 4 to 10 ($p < 0.05$).

181 **Table 7: Clinical outcome**

Disease Outcomes	Duration of illness (in days) of discharged patients				Expired
Days	4-5	6-7	8-9	≥ 10	
Dengue(n=90)	0	12	21	55	2
Malaria(n=44)	0	0	8	36	0

183 Of the 134 patients, 2 patients of dengue expired, one of whom was due to dengue shock

184 syndrome and other was due to dengue hemorrhagic fever.

185 **DISCUSSION:**

186 During rainy season dengue and malaria are the two most common mosquito born diseases in
187 north India and frequently associated with thrombocytopenia and other complications. Our
188 study showed a higher number of dengue patents (90) than malaria (44) with
189 thrombocytopenia.

190 Male predominance was noticed in both groups but more in malaria group which was similar
191 to study done by Epelboin et al⁸, who also noticed a male predominance among malaria
192 group i.e. 77.9% as compared to 57.2% in dengue group. This might be due to outdoor
193 profession of males, and are exposed to more risks of mosquito bites and females are mostly
194 housewives in our country.

195 Patients with dengue presented earlier as compared to malaria group ($p < 0.05$). The mean
196 duration of presentation in dengue patients was 4.11 ± 1.42 days while it was 4.84 ± 1.58 day
197 in malaria group. This may be explained by early onset of severe constitutional symptoms in
198 dengue patients.

199 Most common clinical symptom among the patients in our study was generalized weakness
200 (78%) followed by nausea-vomiting (63.5%), bodyache (51.5%), headache (49%), rash
201 (42%) and abdominal pain (40%). These finding correlated well with the Malaysian study by
202 Tong et al⁹ while it contradicts the Indian study by Kumar and Chandra¹⁰ in Uttar Pradesh,
203 India (Table 8).

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Table 8: Comparison of symptoms with other study.

Symptoms	Present study (%)	Kumar and Chandra (%)	Tong Seng Fah (%)
Headache	49.0	8.42	66.7
Nausea/Vomiting	63.5	18.9	69.7
Body pain	51.5	4.2	69.7
Rash	42.0	3.6	24.2
Abdominal Pain	40.0	16.3	
Cough	34.5	7.8	
Jaundice	16.5	-	-

The patients in dengue group frequently had rash, dyspnoea, bleeding tendencies, tourniquet test positivity, ascitis and respiratory abnormalities while malaria patients presented frequently with abdominal pain, jaundice, diarrhoea, pallor. Icterus (20.5%), hepatomegaly (17%) and splenomegaly (26.5%). Our study contradicts the study done by Handargal et al¹¹ in their malaria cases who noted icterus (2%), splenomegaly (6%) and hepatomegaly (3%) in their patients. Prevalence of petechie/purpura was noted in 29% of the patients in our study which correlates with the study by Dash et al¹² who noted the same in 35% of the patients.

Tourniquet test positivity in dengue group was 42.2 % in our study, which is similar to study by Mourao et al¹³ from Brazil, while Gomber et al¹⁴ from India found tourniquet test positivity in lesser number of patients. Tourniquet test was positive in 27.3% of the malaria patients also which suggests that tourniquet test is neither specific nor sensitive for diagnosis of the dengue.

In dengue patients there was a gradual fall in the mean WBC count and platelet count till day 6 and started rising thereafter, while in malaria initially WBC count was high on 2nd day which gradually settles to normal by 10th day. Malaria patients had significantly low haemoglobin and hematocrit values as compared to their dengue counterparts that can be explained by direct parasitisation of erythrocytes by plasmodium resulting in lysis of infected cells¹⁵. After invading the RBC, the growing malarial parasite consumes and degrades intracellular proteins principally haemoglobin. The parasite also alters the RBC membrane by changing its transport properties, exposing cryptic surface antigens and inserting new parasite-derived proteins. The RBC becomes more irregular in shape, more antigenic, and less deformable¹⁶ and become more prone to haemolysis.

Table 9: Severity of thrombocytopenia in dengue patients

Platelet counts among dengue patients	Present study	Irfan Arshad et al	Palange et al
1,50,000-50,000/ μ L	10%	22%	28%
<50,000/ μ L	90%	78%	72%

Sever thrombocytopenia (platelet count $\leq$ 50,000/ μ L) was present in 90% of dengue patients while 75% of malaria patients. This was in consensus with the findings by Irfan Arshad et al¹⁷ from Pakistan and Palange et al¹⁸ from Maharashtra, India. Thrombocytopenia was the most marked finding in both dengue and malaria but there was a continuous fall in platelet count till day 6 in dengue patients and rise thereafter while in malaria platelet fall was noticed early on 2nd day of fever which gradually recovered, Both nonimmunological destruction, splenic sequestration, shortened platelet survival and immune mechanism involving specific

241 platelet-associated IgG antibodies that bind directly to malarial antigen in the platelets have
242 been suggested to play a role in the lysis of platelets.^{19,20}

243 The thrombocytopenia in dengue is caused due to IgM antiplatelet antibodies which induce
244 platelet lysis via complement activation²¹ and by bone marrow suppression leading to
245 decreased platelet synthesis²². Bleeding manifestations like Petechie-purpura, melena,
246 bleeding per rectum, gum bleeding, hematuria, menorrhagia or epistaxis were more
247 frequently seen among patients having platelet count $\leq 20,000/\mu\text{L}$.

248 Kidney function tests were more commonly affected in dengue patients while liver function
249 tests were more frequently and severely deranged in malaria patients, which gradually
250 recovered, both had a tendency to normalize towards the end of the study with appropriate
251 treatment.

252 Duration of illness and stay in hospital, both were higher among malaria group as compared
253 to dengue. Out of the 90 patients of dengue, 33 were discharged before 10th day of illness
254 while rest of 55 were discharged on or after 10th day of illness, 2 patients succumbed to
255 illness. Patient with malaria had a late recovery with 36 out of 44 patients being discharged
256 on or after day 10 of illness.

257 **CONCLUSIONS AND RECOMMENDATIONS:**

258 Dengue and malaria are the most common febrile illness in northan India during rainy session
259 (May to September).

260 Both can present with acute febrile illness with derangement of hematological, parameters,
261 liver function tests and renal function tests.

262 Specific diagnosis may not be possible in all cases due to lack of expertise, laboratory and
263 financial constrains.

The course of both diseases were observed for ten days in our study and found that dengue patients presented earlier due to sever constructional symptoms than malaria. Generalized weakness, body ache, headache, nausea and vomiting were the common features in both diseases.

The patients of dengue frequently had rash, dyspnea, bleeding tendencies, ascitis and respiratory abnormalities while malaria patients presented more frequently with abdominal pain, jaundice, diarrhoea, pallor, icterus, hepatomegaly and splenomegaly.

White blood cells count showed initial rise in malaria and fall in dengue. Platelet fall was more sever in dengue as compared to malaria, so was bleeding tendencies. Bleeding tendencies were more frequent when the platelet count was below 20,000/ μ L.

Transaminase levels were more severely deranged and manifested early in malaria, while serum creatinine and blood urea were more deranged in dengue. Both these biochemical abnormalities return to normal by 10th day of illness.

We conclude that changes in these clinical, hematological and biochemical parameters can suggest some differentiation between malaria and dengue which may be very useful in remote areas or when facilities for specific diagnosis are limited or not available.

CONSENT: Consent of all patients taken prior to enrolment into the study.

ETHICAL APPROVAL was taken from ethical committee of Lady Harding medical college.

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