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**INTERNATIONAL JOURNAL OF  
 ADVANCED RESEARCH (IJAR)**

Article DOI:10.21474/IJAR01/6792  
 DOI URL: <http://dx.doi.org/10.21474/IJAR01/6792>



### RESEARCH ARTICLE

#### HEMATOLOGICAL PARAMETERS IN DENGUE FEVER.

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#### Manuscript Info

#### Abstract

#### Manuscript History

Received: 20 January 2018  
 Final Accepted: 22 February 2018  
 Published: March 2018

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#### Introduction:-

Arboviruses represent a serious public health problem in tropical and subtropical regions of the world. Dengue virus, the most important arthropod borne diseases is transmitted to humans by mosquitos of the Aedes family. Over the past two decades, there has been global increase in the frequency of DF, DHF and its epidemics, with a concomitant increase in disease incidence. Considering this great burden of disease, vigorous research is being going on to better understand the pathophysiology especially in the field of hematological involvement. Most cases of dengue are self-limited, and the course of the disease is a nonspecific febrile state, general malaise and weakness. Patients feel severe muscle pain and retro-orbital pain, with or without skin rash. Laboratory tests may reveal increased hepatic enzyme levels, leukopenia and thrombocytopenia, which are abnormalities consistent with but nonspecific for dengue fever. The most severe forms of the disease are dengue shock syndrome and dengue hemorrhagic fever. The shock syndrome is due to an important alteration in capillary permeability and significant capillary leakage of plasma into extra-vascular spaces, and is associated with immune activation and high serum levels of tumor necrosis factor- $\alpha$  (TNF) receptor, interleukin (IL)-8, and other factors.

#### Aims And Objective:-

To study hematological parameters in dengue fever.

#### Material And Methods:-

The mentioned study was conducted in patients attending the OPD and patients admitted in IPD King George's Medical University, Lucknow and those referred from nearby hospitals in Lucknow during year 2016-2017. It's a observational study. All the patients with signs and symptoms of dengue fever were investigated for dengue viral serology i.e NS1 Antigen (by RT-PCR), IgM dengue antibody (MAC ELISA) and IgG (MAC ELISA) dengue. The patients who were positive for either NS1 antigen or IgM dengue alone or along with IgG positive were included in the study. The patients were classified according to WHO classification of dengue.

1. Dengue fever (DF)
2. Dengue haemorrhagic fever (DHF)
3. Dengue shock syndrome (DSS)

#### Study Methodology:-

All the patients were admitted and detailed history of clinical symptoms and clinical signs along with detailed investigations were done in all dengue positive patients. All the patients were categorized into three clinical types of dengue fever (DF, DHF, DSS) as per WHO guidelines according to presenting clinical symptoms and signs. All the patients were managed as per WHO guideline as per the category of dengue fever [1].

In our study various hematological parameters were compared between three clinical types of dengue fever.

All the acute viral syndrome patients who were negative for dengue viral serology i.e NS1 Antigen and/or IgM antibody, were excluded from the study. Patients who were having cardiac illness, diabetes mellitus, hypertension and other coinfection were excluded from the study.

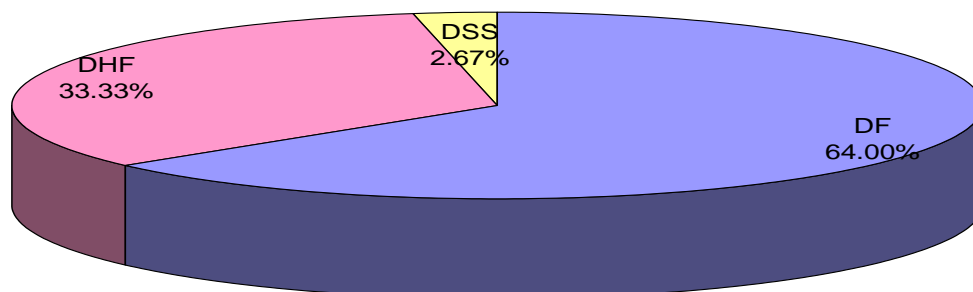
#### Hematological Parameters Evaluated:-

1. Haemoglobin [12-15 gm /dl]
2. Differential leucocyte count [ $N_{40-80}L_{20-40}E_{1-6}M_{1-3}$ ]
3. Total platelet count [1.5-4.5 lac/mm<sup>3</sup>]
4. Hematocrit [36-46 %]

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean $\pm$ SD.

#### Results:-

A total of 75 patients of dengue fever were admitted in the Department during the period of study. Out of these 75 patients, majority were diagnosed as DF (64.00%), only 2 (2.67%) were diagnosed as DSS and rest 25 (33.33%) were diagnosed as DHF.



**Table 1:-** Comparison of Hemoglobin levels in different types of dengue at different follow up.

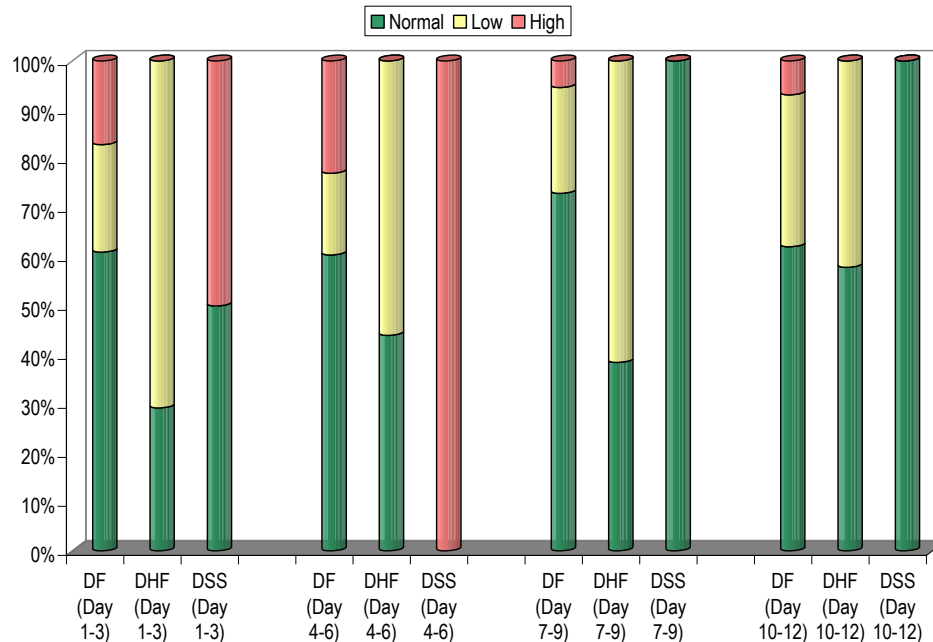
		Total	DF	DHF	DSS
			No.	No.	No.
Day 1-3	Normal ( $\geq 12$ )	43	29	12	2
	Low ( $< 12$ )	24	12	12	0
		67	41	24	2
$\chi^2=3.981$ (df=2); p=0.137					
Day 4-6	Normal ( $\geq 12$ )	38	31	5	2
	Low ( $< 12$ )	34	15	19	0
		72	46	24	2
$\chi^2=15.558$ (df=2); p<0.001					
Day 7-9	Normal ( $\geq 12$ )	24	21	3	0
	Low ( $< 12$ )	18	12	5	1
		42	33	8	1

			$\chi^2=3.162(df=2); p=0.206$		
Day 10-12	Normal ( $\geq 12$ )	30	20	9	1
	Low ( $< 12$ )	20	10	10	0
		50	30	19	1
			$\chi^2=2.485(df=2); p=0.289$		

Hemoglobin levels were found to be lower in maximum population during 4-6 day of fever and was significantly lower in DHF group of diseased population. The reason was hemodilution due to plasma leakage and hemorrhagic tendencies in DHF whose maximum incidence is during 4-6 day of fever. Hemoglobin levels at Day 1-3 were found to be lower in 35.82% population whereas it increased to 47.22% of population on day 4-6. Thereafter the incidence of low haemoglobin level decreased on day 7-10 and day 10-12.

**Table 2:-** Comparison of HCT in different types of dengue at different follow up.

		Total	DF	DHF	DSS
			No.	No.	No.
Day 1-3	Normal (36-46)	33	25	7	1
	Low ( $< 36$ )	26	9	17	0
	High ( $> 46$ )	8	7	0	1
		67	41	24	2
			$\chi^2=19.428(df=4); p=0.001$		
Day 4-6	Normal (36-46)	40	29	11	0
	Low ( $< 36$ )	22	8	14	0
	High ( $> 46$ )	13	11	0	2
		75	48	25	2
			$\chi^2=24.281(df=4); p<0.001$		
Day 7-9	Normal (36-46)	34	27	5	2
	Low ( $< 36$ )	16	8	8	0
	High ( $> 46$ )	2	2	0	0
		52	37	13	2
			$\chi^2=8.566(df=4); p=0.073$		
Day 10-12	Normal (36-46)	30	18	11	1
	Low ( $< 36$ )	17	9	8	0
	High ( $> 46$ )	2	2	0	0
		49	29	19	1
			$\chi^2=2.422(df=4); p=0.659$		



On day 1-3, HCT levels of majority of DF (60.98%) were normal, of DHF (70.83%) were low. Out of 2 DSS patients, 1 had normal HCT levels and 1 had high HCT levels. Difference in HCT levels of patients of different types of dengue was found to be statistically significant.

On day 4-6, HCT levels of majority of DF (60.42%) were normal and 11 patients i.e. (22.9%) of dengue fever had high hematocrit. In DHF (56.00%) were low and both patient of DSS were raised. Difference in HCT levels of patients of different types of dengue was found to be statistically significant.

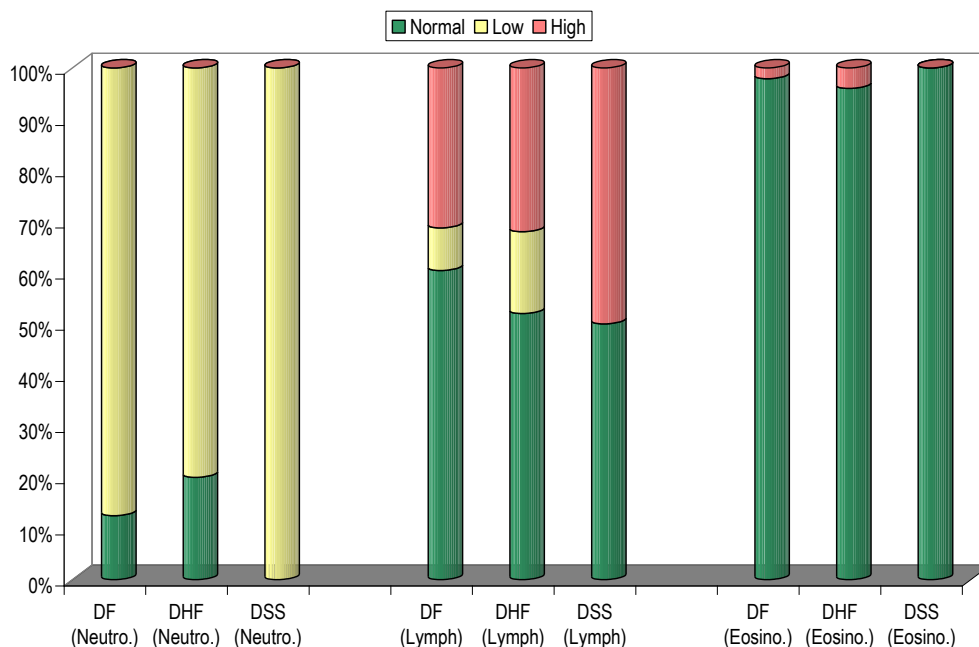
On Day 7-9, HCT levels were normal among majority of DF (72.97%) and both patient of DSS has high hematocrit. Low HCT levels were observed in majority of DHF (61.54%) and 21.62% of DF patients. Difference in HCT levels of patients in different types of dengue was not found to be statistically significant.

On Day 10-12, HCT levels of majority of overall (61.22%) as well as DF (62.07%), DHF (57.89%) and both patients of DSS were in normal range. None of the DHF and DSS patients and only 6.90% DF patients had raised HCT, rest of the DF (31.03% and DHF (42.11%) patients had below normal HCT. Difference in HCT levels of patients in different types of dengue was not found to be statistically significant.

**Table 3:-** Comparison of Baseline differential leucocyte count in different types of dengue.

		Total	DF	DHF	DSS
			No.	No.	No.
Neutrophil	Normal (80-100)	11	6	5	0
	Low (<80)	64	42	20	2
	High (>100)	0	0	0	0
		75	48	25	2
			$\chi^2=1.092(df=2); p=0.579$		
Lympho.	Normal (20-40)	43	29	13	1
	Low (<20)	8	4	4	0
	High (>40)	24	15	8	1
		75	48	25	2
			$\chi^2=1.558(df=4); p=0.816$		
	Monocytes		1.25+0.79 (n=48)	1.36+-0.49 (n=25)	1.00+0.00 (n=2)
			F=0.373; p=0.690		

Eosino.	Normal (1-6)	73	47	24	2
	Low (<1)	0	0	0	0
	High (>6)	2	1	1	0
		75	48	25	2
			$\chi^2=0.289(df=2); p=0.865$		
	Basophils		0.27±0.54 (n=48)	0.44±0.58 (n=25)	0.50±0.71 (n=2)
			F=0.858; p=0.428		



Neutrophil counts of majority of overall patients (85.33%) as well as DF (87.50%), DHF (80.0%) and both patients of DSS were below normal and rest of them had normal neutrophil levels. None of them had raised neutrophil levels. Difference in Neutrophil counts of DF, DHF and DSS patients was not found to be statistically significant.

Lymphocyte counts of majority of overall patients (57.33%) as well as DF (60.42%), DHF (52.0%) and one of the patients of DSS were normal, 15 DF and 8 DHF and one of the patient of DSS had high lymphocyte counts and rest of the DF (8.33%, DHF (16%) and one of the patient of DSS had low lymphocyte counts. Difference in Lymphocyte counts of DF, DHF and DSS patients was not found to be statistically significant.

Eosinophil counts of majority of overall patients (97.33%) as well as DF (97.92%), DHF (96.00%) and both patient of DSS were within normal range and rest of them had raised eosinophil counts. None of them had low eosinophil counts. Difference in Eosinophil counts of DF, DHF and DSS patients was not found to be statistically significant.

Mean monocyte counts among DHF (1.36±0.49) were found to be higher than that among DF (1.25±0.79) and DSS (1.00±0.00) but this difference was not found to be statistically significant (p=0.690).

Difference in mean basophil count of DF (0.27±0.54), DHF (0.44±0.58) and DSS (0.50±0.71) patients was not found to be statistically significant.

**Table 4:-** Comparison of Total Platelet Count (TPC) in different types of dengue at different follow up.

		Total	DF	DHF	DSS
			No.	No.	No.
DF	Normal (1.5-4.5 lakh)	2	0	2	0

	Below normal (<1.5 lakh)	65	41	22	2
		67	41	24	2
			$\chi^2=3.694(df=2); p=0.158$		
Day 4-6	Normal (1.5-4.5 lakh)	2	2	0	0
	Below normal (<1.5 lakh)	73	46	25	2
		75	48	25	2
			$\chi^2=1.156(df=2); p=0.561$		
Day 7-9	Normal (1.5-4.5 lakh)	0	0	0	0
	Below normal (<1.5 lakh)	49	32	15	2
		49	32	15	2
			$\chi^2=-; p=-$		
Day 10-12	Normal (1.5-4.5 lakh)	6	5	1	0
	Below normal (<1.5 lakh)	45	27	18	0
		73	32	19	0
			$\chi^2=1.233(df=1); p=0.267$		

At day 1-3, all the patients except 2 (8.33%) DHF patients had TPC counts below normal levels (<1.5 lakh) and rest had normal TPC count. Association of TPC count and type of dengue was not found to be statistically significant.

At day 4-6, all the patients except 2 (4.17%) DF patients had TPC counts below normal levels (<1.5 lakh) and rest had normal TPC count. Association of TPC count and type of dengue was not found to be statistically significant.

At day 7-9, all the patients had TPC counts below normal levels (<1.5 lakh).

At day 10-12, all the patients except 5 (15.63%) DF and 1 (5.26%) DHF patients had TPC counts below normal levels (<1.5 lakh) and rest had normal TPC count. Association of TPC count and type of dengue was not found to be statistically significant.

### Discussion:-

Out of the total 75 patients studied during study period various hematological parameters were studied like haemoglobin, hematocrit, total leucocyte count, lymphocyte count, differential leucocyte count, total platelet count, and mean corpuscular volume during 1 to 3, 4 to 6, 7 to 9 and 10 to 12 days after the days of onset of fever or constitutional symptoms. These parameters also compared between three types of dengue fever, DF, DHF and DSS.

It is important to know the mechanism of thrombocytopenia in dengue in order to design appropriate intervention. While hemophagocytosis or bone marrow suppression are possible explanations, we propose that endothelial sequestration of platelets could be the dominant mechanism of thrombocytopenia in patients with severe dengue. Endothelial sequestration is caused by platelet adherence to von Willebrand factor (vWF), expressed on vascular endothelial cells. Increased vWF expression, if associated with a significant reduction in its rate of cleavage, may result in increased expression on endothelial surfaces of ultra-large (uncleaved) vWF multimers, which avidly entrap platelets. This sequence would lead to two downstream effects: platelet plugs in the microcirculation and low platelet counts in peripheral blood. Microcirculatory platelet plugs within an organ can lead to organ failure. In the current study thrombocytopenia was mainly seen on day 4-6 of fever when fever starts subsiding. At day 4-6, 95.8% of DF patients and 100% of both DHF and DSS had thrombocytopenia, although association of TPC count and type of dengue was not found to be statistically significant. Similarly at day 7-9, all the patients had TPC counts below normal levels (<1.5 lakh). But at day 10-12 this proportion fall down to 84.3% in DF and 94.7% in DHF. Similar incidence of thrombocytopenia was noticed in other studies like 83% in Shasta et al, 78% in Trupti dongle et al, 75% in Munde et al, 69.5% in Ragini et al where further fall in platelet count was noticed during hospital stay.

In cases of dengue fever, a high hematocrit is a danger sign of an increased risk of dengue shock syndrome. Hemoconcentration can be detected by an escalation of over 20% in hematocrit levels that will come before shock. It

mainly occurs during critical phase of illness. So in this study serial observations of hematocrit was done and the results were ; on day 1-3, HCT levels of majority of DF (60.98%) were normal, of DHF (70.83%) were low. Out of 2 DSS patients, 1 had normal HCT levels and 1 had high HCT levels. Difference in HCT levels of patients of different types of dengue was found to be statistically significant. On day 4-6, HCT levels of majority of DF (60.42%) were normal, of DHF (56.00%) were low and of both of DSS were raised. Difference in HCT levels of patients of different types of dengue was found to be statistically significant. On Day 7-9, HCT levels were normal among majority of DF (72.97%) and 38.46% of DHF patients. Low HCT levels were observed in majority of DHF (61.54%) and 21.62% of DF patients. Only 5.41% had raised HCT levels. Difference in HCT levels of patients in different types of dengue was not found to be statistically significant. On Day 10-12, HCT levels of majority of overall (61.22%) as well as DF (62.07%) and DHF (57.89%) were in normal range. The same pattern of haematocrit has been observed in similar studies. In a study by Dhooria *et al*, (2008) rise of haematocrit (>40%) was found in 35.5% patients [2]. In the study by Maimoona M. Ahmed *et al* showed that haematocrit of >40% was seen in 41.25%, 30-40% in 53.75 % patients. In Rajesh deshwal *et al* raised hematocrit (>45%) was noted in 20.77% of patients at presentation[3]. This difference in observation for incidence of high haematocrit can be due to early administration of intravenous fluids so that haematocrit levels do not follow the natural course instead there is low haematocrit due to hemodilution with fluid administration.

Haemoglobin levels in dengue fever corresponds to hematocrit level and hemoconcentration. There was fall in hb in patients with bleeding manifestation. In this study we have observed the pattern of hb level over the whole duration of illness and in the three clinical types. Hemoglobin levels at Day 1-3 were found to be within normal limits among 43 of 67 (64.18%) patients and rest had lower hemoglobin levels, difference in proportion of patients having normal hemoglobin among DF (70.73%) and DHF (50.00%) was not found to be statistically significant ( $p=0.137$ ). Hemoglobin levels at Day 4-6 were found to be within normal limits among 38 of 72 (52.78%) patients and rest had lower hemoglobin levels, proportion of patients having normal hemoglobin was higher among DF as compared to DHF (67.39% vs. 20.83%). Hemoglobin levels at Day 7-9 were found to be within normal limits among 24 of 42 (57.14%) patients and rest had lower hemoglobin levels, difference in proportion of patients having normal hemoglobin among DF (63.64%) and DHF (37.50%) was not found to be statistically significant ( $p=0.206$ ). Hemoglobin levels at Day 10-12 were found to be within normal limits among 30 of 50 (60.00%) patients and rest had lower hemoglobin levels, difference in proportion of patients having normal hemoglobin among DF (66.67%), DHF (47.37%) and DSS (100.0%) was not found to be statistically significant ( $p=0.289$ ).

32.84% were found to have lymphocytosis (Lymphocyte count >40). In this study it was clear that dengue causes leucopenia with lymphocytosis and thrombocytopenia. Difference in proportion of DF, DHF and DSS patients having different lymphocyte count was not found to be statistically significant. In a study by Munde *et al* in Pune, leukopenia in 50% patients [4]. Similar results were seen in the study done by Pratyusha *et al* reported leucopenia in 66.2% [5]. In the study by Maimoona M. Ahmed *et al* showed that Leucopenia ( $< 4.3 - 10.8 \times 10^9$  cells/L) was also common 68.93% of patients had a WBC of  $< 4.0 \times 10^9$  /L in 2005-2008.

### Conclusion:-

1. Anemia ( $<12\text{gm/dl}$ ) was found to be more common in DHF group than DF but there was no change in proportion of anaemic patients with disease progression.
2. Absolute lymphocyte count was seen to be raised during initial phase of illness (4-6days) but came down to normal limit with disease progression.
3. Hematocrit value gradually became low during follow-up from the day of onset of symptoms to 12 th day after the onset of symptoms. The reason behind this was mostly due to administration of intravenous fluid during hospitalization. Amongst the various clinical types, incidence of low haematocrit was significantly higher in DHF and was due to bleeding manifestations.
4. Thrombocytopenia ( $<1.5$  lakhs/cumm) was found as a constant finding, seen in 96% patients and it was present in all the three clinical types of dengue patients.

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