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A Study on Differential Alteration Trend of Monocyte Count and Other Blood Parameters Among Dengue Patients During Hospitalisation in a Tertiary Care Centre of North India - A Prospective Cohort Study

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ABSTRACT

Introduction: Dengue fever is a viral infection that spreads through mosquito bites. It is a serious public health concern in many tropical and subtropical regions around the world.
This study aimed to investigate and analyze differential alteration in various blood parameters specially monocyte count and its trend during the course of hospitalisation among individuals diagnosed with Dengue, providing valuable insights into the hematological alterations associated with the disease. Assessment of Severity of Dengue patients was also done by Dengue scoring.
The dengue score is a model for predicting severity of dengue as ascites and / or pleural effusion. This is calculated by using four parameters: Hct > 15.1%, Serum Albumin < 3.49 mg/dl, platelet count < 49,500/ µl and AST ratio > 2.51. 1 score each is given if present and 0 if absent.
The study analyzed several key parameters such as complete blood count (CBC), platelet count, monocyte count, hematocrit levels, and serum biochemical markers. The main objective was to identify patterns and trends in these parameters during various stages of Dengue infection, starting from the early febrile phase to the critical phase, and finally to the recovery phase.
The study found that Dengue patients experience significant changes in their blood parameters, indicating that the disease has a dynamic impact on the hematological system. During the febrile phase, patients with Dengue exhibited a noticeable decrease in platelet count and hematocrit levels, which are typical symptoms of Dengue-induced thrombocytopenia and plasma leakage. Additionally, the study revealed variations in CBC parameters, such as monocytosis, leukopenia and changes in differential leukocyte counts, which offer further insights into the immune response against the Dengue virus.
Materials and Methods: Study population consisted of 100 adults with Dengue fever and Severe dengue (including those with warning signs and shock). Patients were taken from the wards, and OPD of Dr. Ram Manohar Lohia Institute of Medical sciences, Lucknow, UP. Patients were selected after excluding other causes of acute febrile illness and other causes of severe disease. They were included after ELISA confirmed NS1 and IgM positive cases. Blood sampling was done for other hematological parameters. Clinical and demographic profile were noted after taking proper consent.
Results: Analysis of hematological profile of dengue patients showed Lymphocytosis (67%) and Monocytosis (82%) besides thrombocytopenia. 32((96.9%) had monocytosis in severe dengue and 52(77.6%) in dengue fever patients without warning signs. Though results were not statistically significant for the two groups but were important markers for deciding in-patient management SGOT

was statistically significant with P-value of 0.008. Bleeding manifestations were significant with P-value <0.00001.

Conclusions: Thrombocytopenia is important parameter to diagnose Dengue fever from other febrile illness but monocytosis and its trend over days is an important marker for the prognosis of the severity of dengue patients besides leucopenia.

KEYWORDS: Dengue fever, monocytosis, Thrombocytopenia, severe dengue,

1. INTRODUCTION

A study was conducted in a teaching hospital in Pakistan among patients with dengue infection who had fever. The study was cross-sectional in nature. Out of the total 130 patients with confirmed dengue infection, 23 experienced severe dengue while 107 had non-severe dengue. Patients with severe dengue had several symptoms such as mucosal bleeding (71.4%), fluid accumulation (57.1%), shock (35.7%), and gastrointestinal bleeding (28.6%). The study found that the most significant hematological findings among both severe and non-severe patients with dengue infection were thrombocytopenia, leukopenia, and a raised hematocrit level ($P < 0.001$). Patients suffering from severe dengue infection usually display a significant reduction in their platelet count, with an average of 49.96 × 109 platelets/L. The clinical symptoms of dengue, along with hematological markers, are the most crucial indicators for the diagnosis, prognosis, and treatment of dengue infection. Thrombocytopenia, leukopenia, and elevated hematocrit levels are the most significant hematological parameters that help assess the severity of dengue infection.[1]

Identifying plasma leakages in patients with dengue, also known as dengue hemorrhagic fever (DHF), is crucial in determining which patients are at a high risk of severe dengue.[1]. Plasma leakage is characterized by an increase in hematocrit of at least 20%, hypoalbuminemia, and the presence of pleural effusion or ascites, according to the World Health Organization's criteria. [3]. Platelets are known to be the primary carrier of VEGF [4]. Endothelial activation is believed to cause plasma leakage and shock [5]. D-dimer, which is the product of the breakdown of cross-linked fibrin, indicates hyperfibrinolysis in response to clotting activation and fibrin formation [6]. It is also a marker for hypercoagulability and has been utilized to determine thrombosis in myeloproliferative disease [7], [8].

Thrombocytopenia is commonly seen in all types of dengue and is associated with variable clinical outcome [9], [10], [11]. This is due to bone marrow depression, destruction and lengthening of the platelet life cycle [12], [13]. Severity of DHF is related to the level of platelet count and DSS is related to high Hematocrit and platelet count.[2].

This may be due to bone marrow suppression, destruction and lengthening of the platelet life cycle [12], [13]. The level of platelet count correlates with severity of DHF, and high haematocrit with marked thrombocytopenia support the diagnosis of dengue shock syndrome (DSS) [2]. It has been considered as an important factor responsible for bleeding events in DHF [14]. Platelet activation is significantly increased in dengue-patients, especially with thrombocytopenia, which exhibited signs of apoptosis pathway activation [15].

The normal range for absolute monocyte counts in adults is between 0.2-0.8× 10. However, this value can vary significantly depending on the age and sex. In males, the monocyte count is usually higher under normal physiological conditions. However, the total white blood count, as well as other WBC types such as lymphocytes and granulocytes, do not differ significantly.[20]

It has been observed that monocyte, a type of white blood cell, are more sensitive to inflammatory stimuli in men than women. This difference is likely due to the variation in sex harmones, between the two genders.

[20, 21] Regarding racial differences, some studies have shown no significant differences, [22], while others have indicated that blacks and Asians have slightly lower absolute monocyte counts compared to Caucasians. [23,24].

WHO has defined monocytosis as an absolute monocyte count > 1×10^9 /L with monocytes is > 10% of leucocytes persisting for >3 months.[25]

There are multiple causes of monocytosis. basically, divided into clonal and reactive.

Reactive – 1. Transient- Bone marrow recovery, Exercise-induced, Acute infections, Splenectomy, Stress-induced	2. Persistent - Chronic infections, Rheumatologic conditions, Medication-induced
Clonal – 1. Acute neoplasms- Acute monocytic / myelomonocytic leukemia, chronic neoplasms, Myelomonocytic (chronic/ juvenile), dendritic cell leukemia, , myeloid neoplasms with PDGFRB rearrangement etc.	Chronic – Chronic myeloid leukemia , Myeloproliferative neoplasms with monocytosis- Essential thrombocythemia b. Polycythemia vera c. Primary myelofibrosis

2. METHODS

a. Inclusion and exclusion criteria

Inclusion criteria:

Participants were selected from the OPD and Wards in Medicine department of Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, who were positive for Dengue confirmed by NS1 and IgM reports. Around 100 patients were included for the study.

Exclusion criteria:

Study populations with negative profile tests and IgG positive patients were excluded. Acute febrile illness patients were excluded due to any other infections or causes.

b. STATISTICAL ANALYSIS

The data analysis was performed using the SPSS 24 statistical program. Qualitative variables were presented as frequencies, percentages, and charts, and were tested using One-Way ANOVA. To observe trends in monocyte, count among dengue patients, descriptive statistics such as mean and standard deviation were used. Quantitative variables were presented as mean and standard deviation. The normally distributed continuous variables were compared between non-severe and severe groups using the two independent sample t test and chi^2test. Logistic regression models were applied to assess the associations of age group, sex and their combinations with leukocytosis and monocytosis. Additionally, creating a line graph over time can visually represent the trends in monocyte counts. The statistical analysis was conducted with 95% confidence limits, and a P-value of less than 0.05 was considered statistically significant.

RESULTS

1. DENGUE SCORE

	N	SEVERE DENGUE	DENGUE FEVER
Fever n= 100% ≤ 3 days ≥ 3 days	 17 83	 5 (14.2%) 23(65.7%)	 12(18.56%) 49(75.38%)
Hemoconcentration ≥ 15.1%, n (%) ≤15.1%, n (%)	 1 99	 32(91.4%) 0	 65 (100%) 0
Serum Albumin ≥3.49 mg/dl n (%) ≤3.49 mg/dl n (%)	 61 39	 26(74.2%) 6(17.14%)	 47(72.3%) 34(52.3%)
Platelet count ≥ 49,500/cmm n (%) ≤49,500/cmm n (%)	 34 66	 15(42.85%) 22(62.8%)	 21(32.30%) 41(63 %)
AST Ratio ≥2.51 n (%) ≤2.51 n(%)	 77 23	 30 (85.7%) 24(68.57%)	 48(73.84%) 17(26.15%)

The Dengue scoring has been developed to diagnose severe cases as earliest as possible. Though SOFA scoring is applicable in all sick patients but it cannot be applied to Dengue like viral illness as thrombocytopenia is an important predictor in the severity of dengue, which is not included in SOFA score. Sofa score lacks hematocrit and APTT also.

Therefore, above scoring was used to create two groups as Dengue fever (Asymptomatic / without warning signs) and severe dengue (dengue with warning signs).

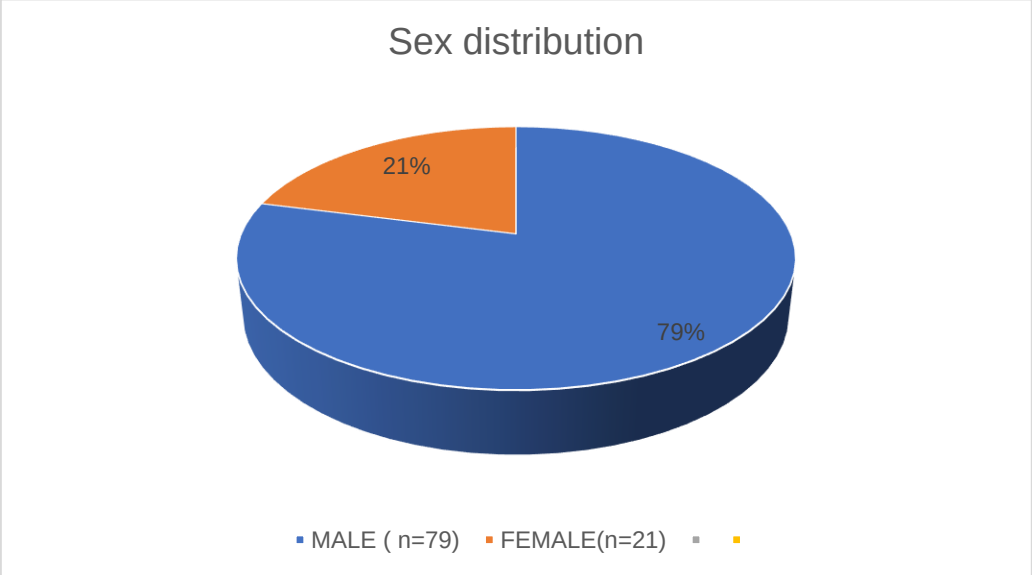
100 patients were included after laboratory confirmation for Dengue. Fever was reported in all the patients (100%). Those less than 3 days of fever were total 17%, out of which 5 (14.2%) in severe dengue and 12 (18.56%) in dengue fever. Those with more than 3 days of fever were 83, Out of which Severe dengue were 23 (65.7%) and 49 (75.3%) were in dengue fever. Almost all patients 99% had Hematocrit ≥15.1% in both the groups. Serum Albumin ≤3.49 mg/dl was more in dengue fever 34 (52.3%). Thrombocytopenia was almost similar in both the groups 22(62.8%) ~41(63 %).

30 (85.7%) and 48(73.84%) Of Severe Dengue had AST RATIO ≥ 2.51.

2. Patient characteristics and clinical parameters

Characteristics	Number of patients (n)
Age	(14-76)
Sex	79 Male (79%) 21 Female (21%)

FIGURE 1



3. Patients with severe dengue

Severe thrombocytopenia (%)	
≥10000/ µL	7(7%)
<10,000/ µL	93(93%)
Severe dengue	
AST> 1000	3(%)
DSS	4(%)
RESPIRATORY DISTRESS	10(%)
SEVERE BLEEDING	17(%)
ORGAN FAILURE	5(5%)
Length of stay	
Days< 5days	74(%)
Days>5days	26(%)
Abdominal usg	
Absence of pleural Effusion /ascites n (%)	79(%)
Presence of pleural Effusion/Ascitis n (%)	21(%)

Further, Severity of Dengue was observed in following parameters as warning signs. Severe Dengue had AST> 1000 in 3% (n=3), DSS in 4%(n=4), respiratory distress in 10% (10), severe bleeding in form of epistaxis >Malena > gum bleeding > hematemesis. Occasional patients reported Bleeding per vagina in females also 17% (n=17). Multiple organ failure was present in 5%(n=5) of patients.

Prolonged duration of stay was related to severity of dengue. In the present study stay was more than 5 days in 26 %(n=26) cases. Clinical fluid accumulation was defined as ascites [24,32] and /or pleural effusion.

4. Various Biochemical parameters among studied dengue patients.

Parameters	SGOT	SGPT	NLR	LMR	AST RATIO
Range	3-40 u/l	3-30 u/l	(1-2)	2.05	>2.51
Normal	3	19	1-2 (35)	>2.05	
Increased	97 ↑↑	81 ↑↑	≥2 (19)	82 ↑↑	79 ↑↑
Decreased	0	0	≤1 (46)	12	20

LFT was increased in all case of dengue regardless of severity. However, increase of SGOT was more than SGPT. This elevation was more seen in patients with shock in severe dengue (dengue with warning signs). AST ratio ≥ 2.51 was seen in 79% (n= 79) cases which is though high but non-significant in the two groups.

5. Characteristics and demographics of the participants

Parameters	Severe dengue (n= 35)	Dengue fever (n= 65)
Leucopenia	13 (39.3%)	24(35.8%)
Neutropenia	25 (75.7%)	50(74.6%)
Monocytosis	32((96.9%)	52(77.6%)
Thrombocytopenia	35(100%)	60(89.5%)
Lymphocytopenia	2(5.7%)	14(21.5%)
Lymphocytosis	24(68.5%)	48(73.8%)
LMR >2.05	29(82.8%)	57(87.6%)
LMR<2.05	6(17.14%)	8(12.3%)

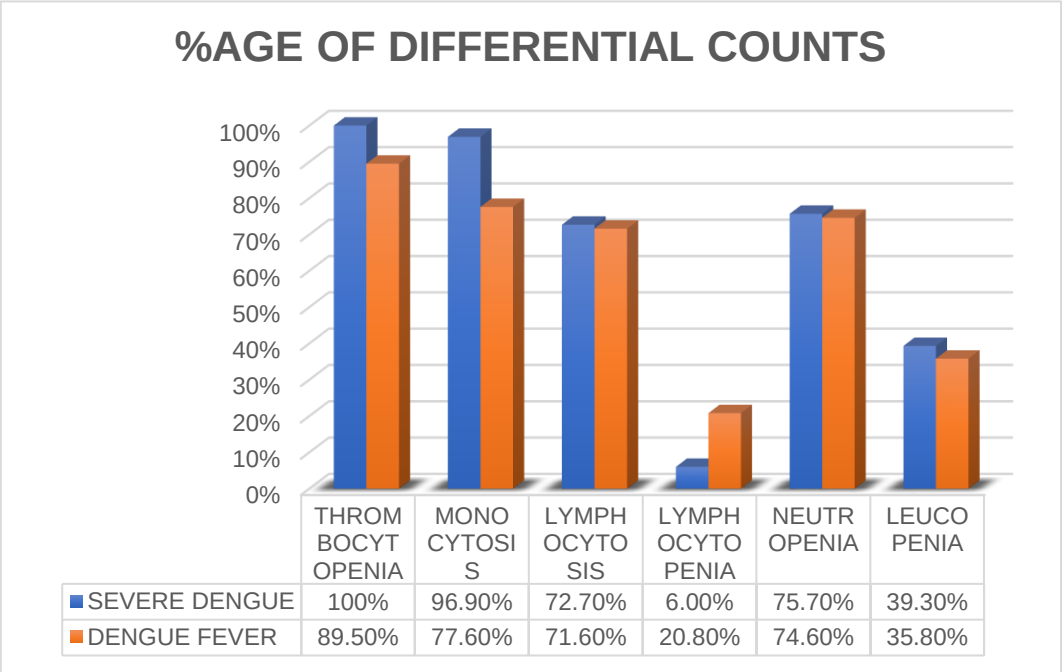
In present study, monocytosis was seen in more in severe dengue cases 96.9%(n=32) than in dengue fever patients 77.6% (52). Thrombocytopenia was the most reported in severe dengue 100% than in dengue fever cases 89.5% (60). Among severe dengue, lymphocytopenia 5.7%(n=2) and lymphocytosis 68.5%(n=24) was less seen than in dengue fever patients. Lymphocytic monocytic ratio almost similar in either group.

6. Association of Dengue infection with Monocyte count and other lab findings

Parameters	TLC	Neutrophils	Lymphocytes	Eosinophils	monocytes	basophils	Platelet count
Range							
Normal (n)	57	0	13	85	18	100	0
Increased (n)	8	21	67 ↑↑	15	82 ↑↑	0	0
Decreased(n)	35	79	20	0	0	0	100

When monocytosis and lymphocytosis was compared in all the total patients, monocytosis was seen in 82% of cases which is greater seen than the lymphocytosis 67%. Neutropenia was the major observation in both the patient's group but could not help in differentiating the severity of disease. It was seen in 75.7% (n=25) in severe dengue and 74.6%(n=50) in dengue fever patients. Eosinophilia was seen as non-significant in only 15 % patients.

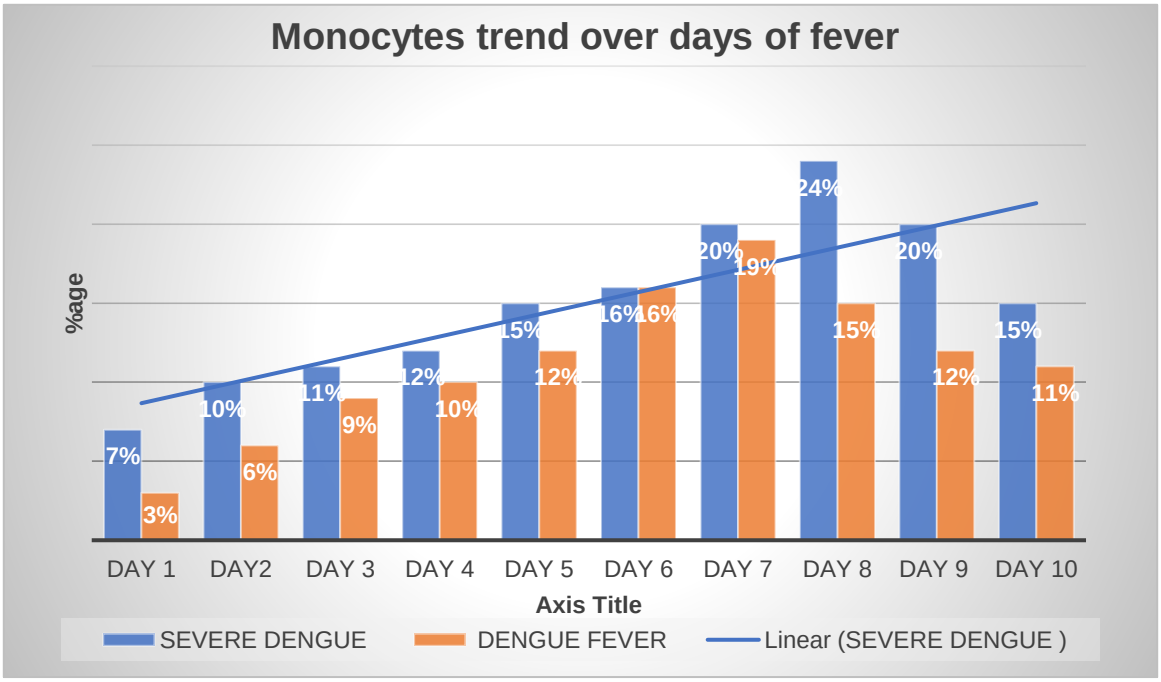
FIGURE 2



	THROMBOCYTOPENIA	MONOCYTOSIS	LYMPHOCYTOSIS	LYMPHOCYTOPENIA	NEUTROPENIA	LEUCOPENIA
SEVERE DENGUE	100%	96.90%	72.70%	6.00%	75.70%	39.30%
DENGUE FEVER	89.50%	77.60%	71.60%	20.80%	74.60%	35.80%

Both the group had high hematocrit and normal hemoglobin levels except in those who history of anemia. Higher hematocrit was present in all patients, in vitro study has revealed cross reaction of proinflammatory mediators like tumour necrosis factor alfa and NS1 Antibodies with surface proteins on endothelial cells leading to apoptosis of these cells, thus causing plasma leakage.[29]

FIGURE 3

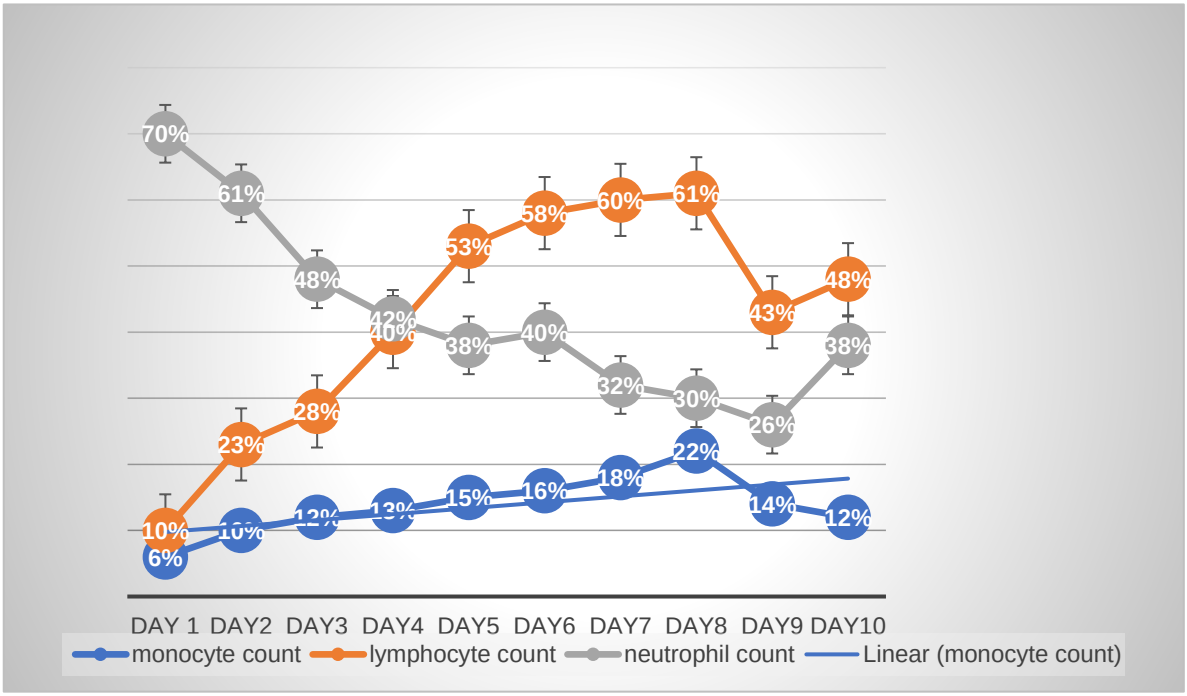


Monocytosis was seen in increasing trend over 7-8 days in a similar fashion in both the groups. There was significant neutropenia over these days. While thrombocytopenia was variably present in individual patients.

Not much specific inter-relation was seen among various differential counts.

Following graph was interpreted after comparing the differential counts.

FIGURE 4



Leukopenia was defined as total WBC count less than 4000 per cubic mm, less than 1,00,000 per cubic mm was taken as thrombocytopenia. Monocytosis was defined as more than 8% and eosinophilia was defined as above 6% while basophilia was taken as more than 2%.

Above chart was observed after taking mean of daily differential counts of severe dengue and dengue fever patients. Similar observation was seen in the either group. There was progressive decrease in leucocyte counts over 7 to 8 days of admission while monocyte counts were increased. Lymphocytopenis was seen in early days before 4th day thereafter there was small increase in counts.

While eosinophils and basophils remain unchanged throughout the hospitalisation time. This was not shown in the graph.

STATISTICAL ANALYSIS

1. SEX

	FREQUENCY	PERCENT	VALID PERCENT	CUMULATIVE PERCENT
VALID Female	21	21	21	21
Male	79	79	79	79
Total	100	100.0	100	

2. AGE

	FREQUENCY	PERCENT	VALID PERCENT	CUMULATIVE PERCENT
VALID 11-20	19	19	19	19
21-30	22	22	22	22
31-40	24	24	24	24
41-50	16	16	16	16
51-60	15	15	15	15
61-70	2	2	2	2
71-80	2	2	2	2
81-90	0	0	0	0
Total	100	100.0	100.0	

AGE (Class interval)	*f*	Cumulative frequency (c.f)	Mid-point (x_i)	fX_I
11-20	19	19	15.5	294
21-30	22	41	25.5	561
31-40	24	65	35.5	852
41-50	16	81	45.5	728
51-60	15	96	55.5	832.5
61-70	2	98	65.5	131
71-80	2	100	75.5	151
	Σf=100			ΣfX_I=3550

$$\text{Mean} = \frac{\Sigma f X_I}{\Sigma f} = \frac{3550}{100} = 35.50 \quad SD = 17.11$$

	Mean (n=	SD	Mean (n=	SD	p -value
LYMPHOCYTOSIS	52.95	9.35	52.34	7.23	0.381

The calculated value is smaller than critical value (0.3033<1.667) so the means are not significantly different.

	Mean (n=4)	SD	Mean(n=16)	SD	p -value
LYMPHOCYTOPENIA	14.75	2.94	14.68	4.25	0.489

The calculated value is smaller than critical value (0.0275< 1.734), so the means are not significantly different.

	Mean(n=33)	SD	Mean(n=91)	SD	p-value
SGOT	590.96	1340.63	237.7	263.47	0.008849

The calculated exceeds the critical value (2.4045 > 1.658) so the means are significantly different.

LMR	Mean(n=20)	SD	Mean (n=29	SD	p
≥2.05	7.377	9.3382	4.6717	5.5367	0.443

The absolute value of the calculated "t" is smaller than critical value (1.273<1.679) so the means are not significantly different.

	Mean (n=34)	SD	Mean(n=60)	SD	p -value
MONOCYTOSIS	14	4.4524	13.2	6.083	0.049

The calculated value is smaller than critical value (0.6012<1.662), so the means are not significantly different

3. Clinical parameters

			Chi ^{2} test	P -value
PAIN ABDOMEN	SEVERE DENGUE	DENGUE FEVER	0.638	0.424
Yes	17(18.90) [0.19]	37(35.10) [0.10]		
No	18(16.10) [0.22]	28(29.90) [0.12]		
Bleeding manifestations			48.28	<0.00001
Yes	26 (10.88) [21]	5 (20.12) [11.36]		
No	7 (22.12) [10.33]	56(40.55) [5.59]		
Headache /myalgia			0.438	0.507
Yes	17(15.85) [0.15]	28 (29.52) [0.08]		
No	15 (16.52) [0.14]	33 (31.48) [0.07]		

4. Hematological and demographical parameters

Variables	SEVERE DENGUE	N= 35	DENGUE FEVER	N=65	T test p-value
Age	MEAN	35.80	M	33.54	
	SD	14.79	SD	13.23	0.223
TLC	M	2.123	M	1.944	
	SD	0.66	SD	0.722	0.110
HCT (%)	M	39.79	M	40.10	
	SD	9.69	SD	6.48	0.435
SGPT U/L	M	267.38	M	144.78	
	SD	552.60	SD	190.19	0.108
ALP U/L	M	126.49	M	130.53	
	SD	70.67	SD	79.80	0.395
MCV (fl)	M	93.94	M	93.51.	
	SD	11.71	SD	9.51.	0.427
MCH (pg)	M	31.01	M	30.98	
	SD	3.99	SD	3.60	0.487
NLR	M	1.74	M	1.32	
	SD	1.50	SD	0.97	0.077
AST/ALT RATIO	M	2.123	M	1.944	
	SD	0.66	SD	0.722	0.110
	M	3.472	M	3.707	
SERUM ALBUMIN	SD	0.37	SD	0.610	.0876

DISCUSSION

Monocytes and their mature counterparts, macrophages, are essential components of the mononuclear phagocyte system. They play a crucial role in ingesting microorganisms and foreign material in various tissues. Additionally, they regulate inflammatory and immune responses by interacting with lymphocytes, and differentiate into dendritic cells to serve as antigen presenting cells [1]. When activated by signals like chemokines and cytokines, monocytes adhere and migrate to sites of infection or inflammation through diapedesis. Furthermore, monocytes have an ambiguous interaction with the coagulation cascade.

Of the total (n=100), 21% were female, and 79% male. Majority were in 31-40 age groups 24%(n=24) followed by 22% (n=22) in 21-30 age groups.

The demographic data like age and gender was not very significant (p- value 0.223). Pleural effusion and abdominal distension were present in both the groups 79%(n=79), but not significant in deciding the severity of disease. History of bleeding (epistaxis, gingival or gastrointestinal bleeding) and severe hemorrhage (pulmonary or gastrointestinal bleeding) in physical examination were more frequent in serious dengue disease (p<0.00001). Serum albumin similar in both severe dengue and dengue fever patient (p<0.087). Platelets count, hematocrit, and hemoglobin parameters were same in both the patients. Thrombocytopenia was the common finding in all patients but severity depends on its duration of prolongation [26]. The rate of thrombopoiesis has got a new parameter, immature platelet fraction (IPF). This helps in predicting platelet recovery in dengue patients. [17]. Several review studies were done in dengue patients on bone marrow which has shown the transient suppression of haematopoiesis for 3-4 days after infection. This might be the protective mechanism to limit injury to marrow stem cells [26].

There was pathogenesis and studies which has shown no interaction of dengue infected endothelial cells with monocytes, basophils and eosinophils [22] but in present study trend in monocytosis has been observed both in severe dengue and dengue fever patients

The CBC count in dengue patients changes daily during fever, especially on days 3 to 8. It begins with progressive leukopenia followed by thrombocytopenia and hemoconcentration caused by plasma leakage.

In our study, monocytosis was seen in around 96% patients of severe dengue, though non-significant (p-value 0.049) between the two groups. This was similar to the earlier studies done where the it was 84.6% [26]. The proportion of monocytosis was more in

severe dengue than dengue fever patients simulating the study where same observation was seen in dengue hemorrhagic patients [28]. This was the significant finding which will help in differentiating severity of the disease. Lymphocytosis and lymphocytopenia were both more in dengue fever patients.

Earlier studies done in India has shown Basophilia (>2%) in 52.9% of Dengue patients [16] but in the present study basophils remain normal throughout the admission time. The main cause of basophilia can be due to recovery from bone marrow suppression during convalescent phase. [26]

LFT derangements were severe in few patients where it was > 5000-6000 U/L. Some patients also reported MODS. But the overall elevation of SGOT (p -value 0.0088) was significant than SGPT (p-value 0.108) and Alkaline phosphatase (p- value 0.395).

Other parameters like MCV (p- value-0.427) and MCH (p- value 0.487) were not significant. Several inflammatory parameters were also compared like LMR (p-value 0/443) and NLR (p-value 0.077). They were though elevated than their reference range but non- significant.

CONCLUSIONS

Bodyache, abdominal distension, pleural effusion, and hypoalbuminemia were the best clinical and laboratorial markers of serious dengue disease in hospitalized patients while bleeding, severe hemorrhage, hemoconcentration and thrombocytopenia though were unable to differentiate statistically between the severe dengue and dengue fever but important parameters to decide whether to manage the patient in outpatient basis or in-patient basis. Monocytosis and its trend was an important finding observed in Dengue patients but further studies were needed to look for specific relation to its various stages. The study was limited due to its small sample size and single-centered.

Author contribution

Conceptualisation: Jyoti Verma, Methodology: Jyoti Verma and Abhishek Kumar, Data collection and Analysis: Anil Upadhyay and Jyoti Verma, Review and editing: Jyoti Verma.

All authors contributed to the article equally.

Declaration by Authors

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