

Comparative Study of Immune Cells Among Patients of Dengue Fever and Dengue Haemorrhagic Fever

Aarya Chitransh¹, Vinod Joshi^{1*}, Bennet Angel¹, Annette Angel¹,
Khushbu Kumari¹, Rashmi Chouhan², Reshu Chauhan¹, Monika Dheer¹,
Bhawna Sharma¹, Komal Tomar¹

¹Centre of Excellence in Virology & Immunology, Sharda University, Greater Noida, Uttar Pradesh, India, ²Shri Maneklal M. Patel Institute of Sciences and Research, Kadi Sarva Vishwavidyalaya, Gandhinagar, Gujarat, India. *Corresponding Author's Email: vinodjoshidmrc@gmail.com

Abstract

Dengue virus (DENV) infection represents various clinical forms ranging from mild Dengue Fever (DF) to severe Dengue Haemorrhagic Fever (DHF)/ Dengue Shock Syndrome (DSS). There are four strains of DENV and each of these are serotypically different from one other. The virus enters the host blood stream during bite of *Aedes* mosquito. The virus interacts with the blood components and may trigger variety of response in the form of thrombocytopenia, leukopenia, neutropenia, lymphocytosis etc. The immune response and sensitization in these cases is reflected by leukocyte count variations and blood cell parameters which may serve as indicators of disease severity. To analyse the leukocyte trends in two sets of patients: one group having mild symptomatic infection and the other having severe infection of dengue, the present study was conducted. The blood samples were collected from Dengue positive patients referring to Sharda Hospital, U.P. Blood smear was prepared and stained with Leishman stain and various WBCs were counted and recorded. Of the overall WBC types studied, lymphocytes appeared to be crucial factor in severe patients when compared with simple DF patients. High levels (above the reference) were seen in 32.58% patients of severe dengue, while only 12.64% of simple DF cases had high levels of lymphocyte. The analysis of blood parameters specifically the levels of lymphocytes in dengue infected patients, can prove to be early markers in assessing the disease risk, severity and in improving the clinical management of dengue patients.

Keywords: Adaptive Immunity, Cytokines, Dengue Fever, Dengue Haemorrhagic Fever, Immune Cells, Innate Immunity.

Introduction

Dengue Fever (DF) is widespread in both tropical as well as subtropical regions of the world (1). The disease manifests itself in various clinical forms, ranging from simple fever to life threatening conditions such as Dengue Haemorrhagic Fever (DHF)/ Dengue Shock Syndrome (DSS). Clinical features may vary from mild to severe complications and may even lead to death (2). Dengue is caused by a member of genus *Flavivirus*, i.e., Dengue virus. It has a lipid bilayer envelope and a positive sense, single stranded RNA genome (~11 Kb) (3). It is primarily transmitted by mosquito vectors such as *Aedes aegypti* and *Aedes albopictus* and has four distinct serotypes varying from DENV-1 to 4. In India, there has been an increase in the incidence of Dengue since the last 10 -15 years as surveyed by the National Centre for Vector Borne Disease Control (NCVBDC) (4). India stands third globally in terms of disease burden (5,

6). During the year 2025, there were 1,21,824 cases and 131 deaths reported in India. In the state of Uttar Pradesh, a total of 9206 cases and 3 deaths were recorded last year (2025). The most common clinical symptoms of DF are characterised by High grade fever, severe headache, vomiting, skin rashes, pain behind the eyes (retro-orbital pain), muscle pain and joint pain. Many patients also experience generalised weakness during early phase of infection and some patients are completely recovered with supportive care. Few cases may progress to severe condition DHF/DSS. DHF is characterised by plasma leakage, increased vascular permeability, bleeding complications of the gums, blood in urine and stool, gastrointestinal haemorrhage, pleural haemorrhage, ascites and thrombocytopenia (2). DSS is a condition where such complications arise at once and then lead to multiple organ dysfunction and death (if not

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managed by clinical care properly). The progression from DF to DHF/DSS can be influenced by several factors like virulence, infecting serotype, host genetic background, immune status and previous infection by any dengue serotype. There are few theories which have been put forth by researchers in the past to address the severe forms of disease i.e., DHF and DSS. One is the Antibody Dependant Enhancement (ADE) theory which suggests that a patient infected by any one of the DENV strain will have a serious consequence when infected second time with another strain. This is because the immune system forms an antigen-antibody complex against the first one which is then made known to the Fc receptors on the surface of WBCs specifically macrophages (7, 8). Another theory states that due to selection pressure, some strains have a high epidemic nature (9, 10). Despite the theories, the pathogenesis of severe forms still remains controversial.

When a Dengue virus infected *Aedes* mosquito bites the host, the blood doesn't reach the proboscis immediately. To draw blood, the mosquito first releases saliva containing anticoagulants that help recruiting blood cells at the site of bite, and then the virus is also inoculated in the host (11). The virus along with salivary contents enters the capillaries and tiny venules (small veins). The cells present in skin like Langerhans cell or Dendritic cells are the first to come in contact and get infected. The Dengue virus is an obligatory intracellular parasite, it cannot survive in extracellular environment and it needs the machinery of the host cell for its survival and for successful replication (12).

Before the adaptive system acts against the dengue virus and specific antibody are produced, there is incubation period that ranges from 3 days to 14 days (average 4-8 days) depending on host's immune system (13-15). Firstly, the infected cells of epidermis are targeted for phagocytosis. Then, the adaptive immune cells, i.e., T-Cytotoxic cell recognises and target the viral peptides and present them via MHC-I molecule. The Natural killer cell also can target the infected cells and induce cell death using granzymes and perforin, leading to burst of cells.

Interestingly, the main soldiers of our immune system are targeted by the Dengue virus, such as Dendritic cell, Macrophage-like cells and

monocytes (16). Low immune cell population might be the result of necrosis of these phagocytic cells. These cells also later become reservoir for dengue virus transmission and further evade the immune cells (17).

In the absence of any anti-viral therapeutic molecule and vaccine (vaccine available is of limited utility) (18), the understanding the immunological basis of severe dengue (DHF/DSS) becomes an important researchable issue. Innate and adaptive immune response against dengue varies among cases of DF and DHF and can be measured through the counts of proportional percentage of leukocytes in terms of Eosinophils, Neutrophils, Macrophage-like cells (Activated monocyte like cells), basophils, dendritic cells and lymphocytes. Many earlier researchers have reported studies on immune cells (19-22). To establish immunological indications of probability of DHF/DSS among patients of DF, we have undertaken a comparative study of innate and immune cells among DF and DHF/DSS patients. The paper reports the details.

Methodology

Study Design

This study was designed as a descriptive observational study among two sets of patients one suffering from DF and another with DHF and all laboratory-confirmed cases available during the study period were included. A total of 118 patients were enrolled comprising of 87 patients with Dengue Fever (DF) and 31 patients with Dengue Haemorrhagic Fever (DHF).

Classification Criteria

The patients were classified according to W.H.O. 1997 dengue case classification guidelines as Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF). DF is an acute Febrile illness with at least two of following manifestations: headache, retro-orbital pain, rash or leukopenia. Along with this, laboratory confirmation of Dengue infection whether done by Dengue Ag & Ab Duo rapid diagnostic test, which detects dengue NS1 antigen as well as dengue specific IgM and IgG antibodies respectively is also seen. Positive cases were further confirmed by ELISA in the Sharda hospital, Greater Noida (approximate GPS coordinates 28.474172°N, 77.482026°E) and blood was drawn by hospital staff after taking informed consent.

DHF was diagnosed when all four WHO criteria were fulfilled:

- (a) Fever (2-7 days)
- (b) Hemorrhagic manifestation including positive tourniquet test, petechiae, gum bleeding, ecchymosis, gum bleeding, hematemesis or melana
- (c) Thrombocytopenia (Platelet count $<1,00,000$ cell/mm³) and
- (d) evidence of plasma leakage manifested by a $\geq$ 20% rise in hematocrit, pleural effusion, ascites or hypoproteinaemia.

Sample Transportation and Smear

Preparation

The blood samples of Dengue positive cases collected from Sharda Hospital, were then transported to Centre of Excellence in Virology and Immunology, Sharda University, Greater Noida which is an upgraded BSL-2 facility (approximate GPS coordinates 28.472802°N, 77.483716°E) under appropriate biosafety conditions. For smear preparation, small drop (~2.5 to 3 microliter) of blood was taken on a clean glass slide and a thin even smear created. The smear was then stained using Leishman stain as per standard protocol.

Microscopic Observation

The structure of all leukocytes was observed under the phase contrast microscope (m/s Zeiss, Germany). The leukocyte count, including total white blood cells (WBCs), lymphocytes, neutrophils, eosinophils, basophils, monocytes and macrophages like cells were counted per field (10-20 fields) and accordingly calculated using standard calculation method. Cells described as macrophage-like cells were identified based on their morphological features, including relatively

large cell size, abundant cytoplasm, occasional cytoplasmic vacuolation, and phagocyte-like appearance. (We have not used any kind of immunophenotypic or molecular markers for definitive distinction between activated monocytes and macrophages). Therefore, these cells were recorded as macrophage-like mononuclear phagocytic cells based on their morphological characteristics.

Statistical Test and Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (m/s IBM corp., Armonk, NY, USA) including manual calculation also. Further graphs and numerical values were done using Microsoft Excel 2016 (m/s Microsoft corporation, Redmond, WA, USA) and GraphPad Prism (m/s GraphPad Software, San Diego, CA, USA). Descriptive statistical measures, including mean, median, standard deviation, minimum value, maximum value, range and coefficient of variation, were calculated to summarize demographic and haematological parameters of dengue patients. The results were presented using tables and graphs to describe variations in leukocyte and platelet profiles among the study population.

Results

Observed Number of Leukocyte Cells

A total of 118 patients were confirmed with dengue virus infection during the study period. Of these, 69 (58.47%) were male and 49 (41.53%) were female patients. A total of 31 patients were categorized as severe DF cases, while 87 patients were categorized as simple DF cases based upon their clinical and recovery time shown in Tables 1 and 2.

Table 1: Details of Haematological Parameters of DENV Infected Patients (Severe DF Cases)

Patient Code	Age (in Yrs)	Gender (F/M)	Total Leucocyte Count (in cells/cmm)	Differential Leukocytes Count (DLC in %)						Platelet Count
				Innate Immune Cells					Adaptive Immune Cells	
CEVI/DENV/16	54	F	4500	26.6	28.8	2.22	20.0	0.00	22.2	16
CEVI/DENV/25	16	F	4200	7.10	40.4	7.14	14.28	4.70	26.1	28
CEVI/DENV/26	20	M	2800	21.4	28.5	7.10	10.71	7.14	25.0	66
CEVI/DENV/27	24	M	3300	21.2	24.2	9.09	12.12	6.06	27.2	55
CEVI/DENV/28	20	M	6200	12.9	43.5	3.22	19.35	3.22	17.7	94
CEVI/DENV/32	28	M	2600	3.84	57.6	3.84	7.69	3.84	23.0	11

CEVI/DENV/39	35	M	2300	13.0	34.7	4.34	8.69	13.04	26.0	14
CEVI/DENV/45	24	M	5000	12.0	28.0	4.00	12.0	0.00	44.0	8
CEVI/DENV/47	11	M	6000	23.3	23.3	3.30	3.33	10.0	36.6	38
CEVI/DENV/50	19	M	2600	15.3	23.0	0.00	7.69	7.69	46.1	22
CEVI/DENV/55	36	M	4500	15.5	48.8	0.00	8.88	2.22	24.4	111
CEVI/DENV/73	9	F	3100	9.67	29.0	6.40	6.45	3.22	45.1	150
CEVI/DENV/75	30	M	5400	14.8	37.0	3.70	7.40	14.81	22.2	20
CEVI/DENV/79	21	F	3400	8.82	47.0	0.00	14.7	0.00	29.4	150
CEVI/DENV/86	27	M	5200	0.00	15.3	0.00	3.84	3.84	76.9	141
CEVI/DENV/87	25	F	3800	10.5	34.2	7.80	7.89	7.89	31.5	163
CEVI/DENV/103	39	M	12000	15.0	37.5	8.30	12.5	5.83	20.8	60
CEVI/DENV/117	52	M	4200	4.76	0.00	0.00	0.00	4.76	90.4	14
CEVI/DENV/127	20	M	1800	0.00	22.2	11.1	11.1	11.1	44.4	18
CEVI/DENV/134	44	F	6000	20.0	23.3	6.60	6.66	10.0	33.3	67
CEVI/DENV/145	16	M	5500	5.45	45.4	3.63	7.27	1.81	36.3	20
CEVI/DENV/155	32	F	4900	14.2	44.8	4.08	10.20	6.12	20.4	26
CEVI/DENV/162	44	M	9300	21.5	40.8	2.15	2.15	4.30	29.0	80
CEVI/DENV/163	29	F	6800	4.41	47.0	0.00	1.47	0.00	47.0	120
CEVI/DENV/166	30	F	3500	2.85	20.0	0.00	5.71	8.57	62.8	17
CEVI/DENV/167	45	M	4500	8.88	35.5	2.22	2.22	4.44	46.6	23
CEVI/DENV/168	60	M	5800	6.89	41.3	3.44	6.89	20.68	20.6	60
CEVI/DENV/169	36	F	6900	8.69	60.8	5.79	4.34	2.89	17.3	68
CEVI/DENV/171	18	M	6800	8.82	44.1	5.88	8.82	8.82	23.5	64
CEVI/DENV/174	27	F	4000	5.00	65.0	0.00	7.50	0.00	22.5	37
CEVI/DENV/178	19	F	4400	0.00	27.2	9.09	4.54	13.64	45.4	80

Table 2: Details of Haematological Parameters of DENV Infected Patients (Simple or Mild DF Cases)

Patient code	Age (in Yrs)	Gender	Total Leucocyte Count (in cells/ μ l) (4-11 x 10 ³ /cmm)	Differential Leukocytes Count (DLC in %)						Platelet Count
				Innate Immune Cells					Adaptive Immune Cells	
				Eosinophils (0.00 – 6.00 %)	Neutrophils (40.00 – 70.00 %)	Basophils (0.00 – 2.00 %)	Monocytes (0.00 – 10.00 %)	Macrophage like Cells (0-1%)	Lymphocytes (20.00 – 45.00 %)	
CEVI/DENV/17	20	M	3100	9.60	12.9	19.35	19.35	12.90	25.8	163
CEVI/DENV/20	61	F	6200	14.5	37.0	12.90	16.12	1.61	17.4	100
CEVI/DENV/21	42	F	4700	14.8	25.5	6.38	21.27	2.12	29.7	90
CEVI/DENV/22	23	F	3300	12.1	51.5	3.03	12.12	0.00	21.2	109
CEVI/DENV/23	32	F	4600	30.4	26.0	8.60	4.34	13.04	17.3	157
CEVI/DENV/24	53	M	21000	14.2	60.0	4.70	6.66	1.90	12.3	194
CEVI/DENV/29	16	M	4700	19.1	25.5	2.12	6.38	6.38	40.4	100
CEVI/DENV/30	35	M	2800	7.14	17.8	7.14	14.28	10.71	42.8	12
CEVI/DENV/31	80	F	7100	30.9	56.3	2.81	2.81	1.40	5.63	157
CEVI/DENV/33	50	F	5500	23.6	34.5	9.09	5.45	3.63	23.6	166
CEVI/DENV/38	27	M	10000	23.0	27.0	2.00	17.0	4.00	27.0	121
CEVI/DENV/46	7	F	5600	25.0	28.5	3.51	10.71	7.14	25.0	176
CEVI/DENV/48	25	F	4600	21.7	43.4	4.34	13.04	0.00	17.3	130

CEVI/DENV/49	19	M	4600	17.3	34.7	8.69	4.34	8.69	26.0	19
CEVI/DENV/54	28	M	2400	0.00	16.6	0.00	16.66	33.33	33.3	90
CEVI/DENV/56	13	M	12900	17.0	44.9	1.55	17.82	0.70	17.8	175
CEVI/DENV/57	11	M	7400	8.10	24.3	2.70	10.81	0.00	54.0	45
CEVI/DENV/58	33	M	7400	32.4	37.8	2.70	5.40	2.70	18.9	251
CEVI/DENV/59	21	M	5000	14.0	34.0	4.00	6.00	8.00	34.0	30
CEVI/DENV/60	19	M	6200	19.3	22.5	6.45	6.45	9.67	35.4	38
CEVI/DENV/61	26	M	6000	10.0	46.6	0.00	3.33	3.33	36.6	144
CEVI/DENV/62	29	M	5600	17.8	28.5	3.57	17.85	7.14	25.0	133
CEVI/DENV/63	42	F	2600	11.5	30.7	3.84	3.84	15.38	34.6	40
CEVI/DENV/64	16	M	4000	15.0	35.0	7.50	7.50	5.00	30.0	229
CEVI/DENV/74	36	F	5600	21.4	32.1	7.14	3.50	7.14	28.5	288
CEVI/DENV/76	20	M	7600	5.26	23.6	10.52	5.26	5.26	50.0	150
CEVI/DENV/77	25	F	4200	4.76	42.8	0.00	14.28	0.00	38.0	105
CEVI/DENV/80	40	M	3000	6.66	26.6	6.66	6.66	13.33	40.0	130
CEVI/DENV/88	27	F	3900	7.69	28.2	0.00	7.69	5.12	51.2	244
CEVI/DENV/89	21	F	5500	7.27	41.8	0.00	14.28	0.00	38.1	80
CEVI/DENV/102	18	M	16100	12.4	24.8	14.28	12.42	11.18	24.8	33
CEVI/DENV/104	26	M	5900	27.1	28.8	3.38	10.16	5.08	25.4	62
CEVI/DENV/105	20	F	8400	26.1	35.7	3.71	9.52	3.57	21.4	184
CEVI/DENV/106	11	F	2600	7.69	61.5	0.00	0.00	15.38	15.38	188
CEVI/DENV/107	21	M	2100	14.2	33.3	9.52	0.00	9.52	33.3	75
CEVI/DENV/108	25	F	1800	0.0	55.5	0.00	0.00	11.11	33.3	170
CEVI/DENV/109	23	F	2000	0.0	40.0	10.0	0.00	11.11	40.0	100
CEVI/DENV/116	24	F	3300	12.1	36.3	6.06	0.00	3.03	24.2	57
CEVI/DENV/118	32	M	3500	17.1	25.7	8.57	5.71	8.57	34.2	38
CEVI/DENV/119	26	M	2400	8.33	41.6	0.00	12.5	0.00	37.5	150
CEVI/DENV/120	21	F	3500	8.57	48.5	5.71	5.71	5.71	25.7	148
CEVI/DENV/121	20	F	6400	12.5	42.1	3.12	4.68	1.56	35.9	103
CEVI/DENV/122	21	M	6600	0.00	45.4	3.03	3.03	0.00	48.4	301
CEVI/DENV/123	23	F	1600	0.00	62.5	12.5	0.00	0.00	25.0	89
CEVI/DENV/124	75	F	3000	0.00	33.0	0.00	0.00	6.66	60.0	262
CEVI/DENV/125	17	M	2000	5.00	40.0	5.00	5.00	10.0	35.0	20
CEVI/DENV/126	53	F	5200	11.5	42.3	3.84	3.84	11.53	26.9	225
CEVI/DENV/128	40	M	6200	9.67	58.0	0.00	6.45	6.45	19.3	80
CEVI/DENV/129	74	F	3600	16.6	44.4	0.00	11.11	2.77	25.0	20
CEVI/DENV/130	18	M	6200	0.00	41.9	3.22	3.22	12.90	38.7	60
CEVI/DENV/131	31	F	5400	14.8	48.1	3.70	3.70	11.11	18.5	189
CEVI/DENV/132	27	M	8600	15.1	26.7	6.97	6.97	8.13	36.0	124
CEVI/DENV/133	51	F	6200	3.12	43.7	6.25	6.25	9.37	31.2	25
CEVI/DENV/135	22	F	3200	25.0	31.2	0.00	12.5	6.25	25.0	65
CEVI/DENV/136	31	M	4600	26.0	17.3	4.34	8.69	8.69	34.7	50
CEVI/DENV/137	34	M	5600	28.5	17.8	7.14	14.28	7.14	25.0	17
CEVI/DENV/138	16	M	4000	5.00	40.0	0.00	15.0	5.00	35.0	70
CEVI/DENV/139	30	M	3800	5.26	15.7	0.00	44.7	0.00	34.2	15
CEVI/DENV/140	30	M	3500	17.1	42.8	5.71	14.28	5.71	14.2	12
CEVI/DENV/141	18	M	4700	17.0	36.1	4.25	12.76	6.38	23.4	16
CEVI/DENV/142	31	M	5600	21.4	44.6	1.78	7.14	3.57	17.8	329
CEVI/DENV/143	18	F	5700	5.26	54.3	3.50	3.50	1.75	31.5	131
CEVI/DENV/144	15	F	5200	1.92	26.9	1.92	7.69	7.69	53.8	23
CEVI/DENV/146	49	M	3100	16.1	35.4	6.45	12.90	6.45	22.5	35

CEVI/DENV/147	24	F	4200	4.76	47.6	0.00	4.76	4.76	38.0	30
CEVI/DENV/148	46	F	10600	7.54	58.4	0.00	13.2	0.00	20.7	110
CEVI/DENV/149	31	M	4600	10.8	43.4	6.52	4.34	13.04	21.7	25
CEVI/DENV/150	37	F	3000	6.60	50.0	10.0	6.66	6.66	20.0	102
CEVI/DENV/151	19	M	4000	7.50	45.0	5.00	12.5	5.00	25.0	61
CEVI/DENV/152	27	M	5100	5.88	39.2	1.96	23.52	3.92	25.4	45
CEVI/DENV/153	35	M	3200	3.12	15.6	9.37	12.50	9.37	50.0	35
CEVI/DENV/154	30	M	4900	6.12	61.2	4.08	6.12	6.12	16.3	28
CEVI/DENV/156	25	F	11800	11.8	42.3	3.38	16.94	3.38	22.0	60
CEVI/DENV/157	42	F	5900	11.0	33.8	2.54	19.49	3.38	29.6	30
CEVI/DENV/158	50	M	3100	3.22	25.8	3.22	0.00	19.31	48.3	37
CEVI/DENV/159	32	M	2500	4.00	12.0	4.00	4.00	12.0	64.0	45
CEVI/DENV/160	39	F	15500	4.51	56.7	1.93	5.16	7.74	23.87	45
CEVI/DENV/161	22	M	5700	3.50	28.0	0.00	3.50	12.28	52.63	101
CEVI/DENV/165	65	F	7000	1.42	24.4	2.85	4.28	2.85	64.28	13
CEVI/DENV/170	28	M	2500	0.00	68.0	0.00	4.00	0.00	28.0	96
CEVI/DENV/172	31	M	21200	11.7	75.4	0.94	1.88	1.88	8.00	11
CEVI/DENV/173	17	M	5300	5.66	41.5	1.88	13.20	3.77	33.96	150
CEVI/DENV/175	35	M	8200	3.65	48.7	1.21	3.65	2.43	40.24	86
CEVI/DENV/176	38	M	6200	1.61	35.4	1.61	1.61	3.22	56.40	28
CEVI/DENV/177	55	F	3600	5.55	55.5	0.00	0.00	11.11	27.77	41
CEVI/DENV/179	26	M	6800	5.88	20.5	0.00	5.88	8.82	58.82	40
CEVI/DENV/180	16	F	4000	2.50	27.5	0.00	1.00	10.0	45.00	25

The descriptive statistical analysis of all study participants was performed for each haematological parameter, including the mean, median, standard deviation, minimum and maximum values, range, and coefficient of variation (CV), as presented in Table 3. The average age of the patients was approximately 29.7 years, with a median age of 27 years. The youngest patient was 9 months old, while the oldest was 80 years, indicating that dengue affected individuals across a wide age range. The mean total leukocyte count (TLC) was approximately 5,393 cells/cmm, with a median value of 4,700 cells/cmm. TLC values ranged from 420 to 21,200 cells/cmm, demonstrating considerable variation among patients. The lower end of this range suggests the presence of leukocytopenia in a substantial proportion of cases, a common haematological finding in dengue infection. The mean platelet count was approximately 88,383/cmm, while the median platelet count was 66,603/cmm. Platelet counts varied widely, ranging from 8,103/cmm to 329,103/cmm. Both the mean and median values were considerably below the normal clinical

reference range of 150,000-450,000/cmm, indicating that thrombocytopenia was a prominent feature in the study population. Among the haematological parameters, we also analysed that TLC and platelet count exhibited large standard deviations and broad ranges, reflecting substantial clinical heterogeneity among patients. The coefficient of variation for platelet count was 80.5% which is indicating marked variability in platelet levels across the cohort. In contrast, neutrophil percentage showed a relatively lower coefficient of variation (approximately 38%), suggesting comparatively stable values among patients. Macrophage like cells and basophils displayed very low mean values along with high coefficients of variation. This pattern likely reflects their low abundance in peripheral blood and the greater impact of small numerical changes on variability estimates. Overall, the observed variability in several blood parameters highlights the diverse haematological manifestations of dengue infection and differences in disease severity among patients.

Table 3: Descriptive Statistical Analysis of Haematological Parameters in all DENV Infected Patients

	Age (in Years)	Total Leucocyte Count (Absolute)	Eosinophil (%)	Neutrophil (%)	Lymphocyte (%)	Basophil (%)	Monocyte (%)	Macrophage like cells (%)	Platelet Count
Mean	29.61	5393.39	11.17	36.58	32.39	4.23	8.41	6.25	88382.66
Median	27	4700	9.64	35.94	28.8	3.6	6.93	5.71	66603
SD	13.71	3300.78	8.04	13.91	14.07	3.93	6.33	5.16	71121.41
Min	9	420	0	0	5.63	0	0	0	8103
	months								
Max	80	21200	32.43	75.47	90.47	19.6	44.73	33.33	329103
Range	79.25	20780	32.43	75.47	84.84	19.6	44.73	33.33	321000
CV	46.32	61.2	71.98	38.01	43.43	92.79	75.2	82.64	8.47

Note: Data are presented as descriptive statistics for all 118 patients. Count = number of observations, Mean is average value, SD = Standard Deviation, Min = Minimum Value, 25% = First Quartile (Q1), Median = 50th Percentile, 75% = Third Quartile (Q3), Max = Maximum Value, % = Percentage.

The statistical analysis of hematological parameters in severe dengue patients provides valuable understanding of the patterns of immune dysregulation associated with severe manifestations of the disease shown in Table 4. The mean age of patients was 29.35 years, with an extensive age range from 9 years to 60 years, indicating a predominantly young adult cohort with notable pediatric involvement. The mean

total leukocyte count was 4,758.71/cmm, at the lower end of the normal range, suggesting immune suppression or a dysregulated immune response typical of severe viral infections. Notably, the leukocyte counts varied widely, ranging from as low as 420/cmm to as high as 12,000/cmm, highlighting the heterogeneous nature of immune responses in severe dengue patients.

Table 4: Descriptive Statistics for Severe Dengue Patients

Parameter	Count	Mean	SD	Min	25%	Median	75%	Max
Age (Years)	31	29.35	12.68	9	20	27	36	60
Total Leucocyte Count (Absolute)	31	4758.71	2241.14	420	3350	4500	5900	12000
Eosinophils	31	565.16	503.61	0	300	400	700	2000
Neutrophils	31	1793.54	1116.22	0	850	1500	2450	4500
Lymphocytes	31	1521.93	829.84	380	1000	1200	2050	4000
Basophils	31	196.77	199.13	0	50	200	250	1000
Monocytes	31	393.54	317.21	0	200	300	450	1500
Macrophages like cells	31	287.74	280.69	0	100	200	350	1200
Platelet Count	31	59387.1	46832.1	8000	20000	55000	80000	163000

Note: Data are presented as descriptive statistics for 31 severe dengue patients. Count = number of observations, Mean is average value, SD=Standard Deviation, Min = Minimum Value, 25% = First Quartile (Q1), Median = 50th Percentile, 75% = Third Quartile (Q3), Max = Maximum Value, % = Percentage.

Platelet counts were markedly reduced, with a mean of 59,387.10/cmm, consistent with the thrombocytopenia, a hallmark of severe dengue. The broad range (8,000/cmm to 163,000/cmm) underscores the severity of platelet consumption and the diverse clinical presentations among patients. The eosinophil count demonstrated a low mean value of 565.16/ μ L, indicating suppressed

eosinophilic activity in most patients, although some cases showed higher levels, reflecting variability in immune activation. Neutrophil counts were moderately elevated with a mean of 1,793.55/ μ L, signifying ongoing systemic inflammation commonly observed in severe dengue infections in form of rashes and itching.

The lymphocyte count averaged 1,521.94/ μL , suggesting relative lymphocyte depletion as compared to healthy individuals, likely due to low immune response. Basophil counts were generally high (mean of 196.77/ μL), consistent with an acute phase immune response leading to more basophilic activation. Monocyte (mean of 393.55/ μL) and macrophage like cells (mean of 287.74/ μL) counts were modest, reflecting compromised immune response observed in all cases where no significant rise in Total leukocyte count was seen.

The analysis of 87 mild dengue patients was also seen. The mean age of the patients was 29.70 years,

with an age range including 9 months to 80 years, reflecting a broad age distribution in the cohort. The mean total leukocyte count was 5604.60/cmm, which is within the normal range, but the high variability (standard deviation of 3599.99/cmm) suggests fluctuating immune responses among patients. The platelet counts in these patients had a mean of 98,574.71/cmm, which is low as compared to healthy, but with a wide range (from 11,000/cmm to 329,000/cmm), indicating mild thrombocytopenia in almost cases as most common feature in dengue infections shown in Table 5 and Figures 1A-1D respectively.

Table 5: Descriptive Statistics for Mild Cases of Dengue

Parameter	Count	Mean	SD	Min	25%	Median	75%	Max
Age (Years)	87	29.69	14.13	0.75	20	27	35	80
Total Leucocyte Count (Absolute)	87	5604.59	3599.99	1600	3400	4900	6200	21200
Eosinophils	87	680.95	679.41	0	200	400	900	3000
Neutrophils	87	2246.11	2296.62	300	1100	1700	2400	16000
Lymphocytes	87	1650.43	956.52	400	900	1400	2050	4500
Basophils	87	222.27	294.41	0	100	200	250	2300
Monocytes	87	488.94	477.08	0	200	400	600	2300
Macrophage like Cells	87	313.57	271.36	0	200	200	400	1800
Platelet Count	87	98574.71	75553.71	11000	36000	86000	149000	329000

Note: Data are presented as descriptive statistics for 87 dengue patients. Count = Number of Observations, Mean is average value, SD = Standard Deviation, Min = Minimum Value, 25% = First Quartile (Q1), Median = 50th Percentile, 75% = Third Quartile (Q3), Max = Maximum Value, % = Percentage.

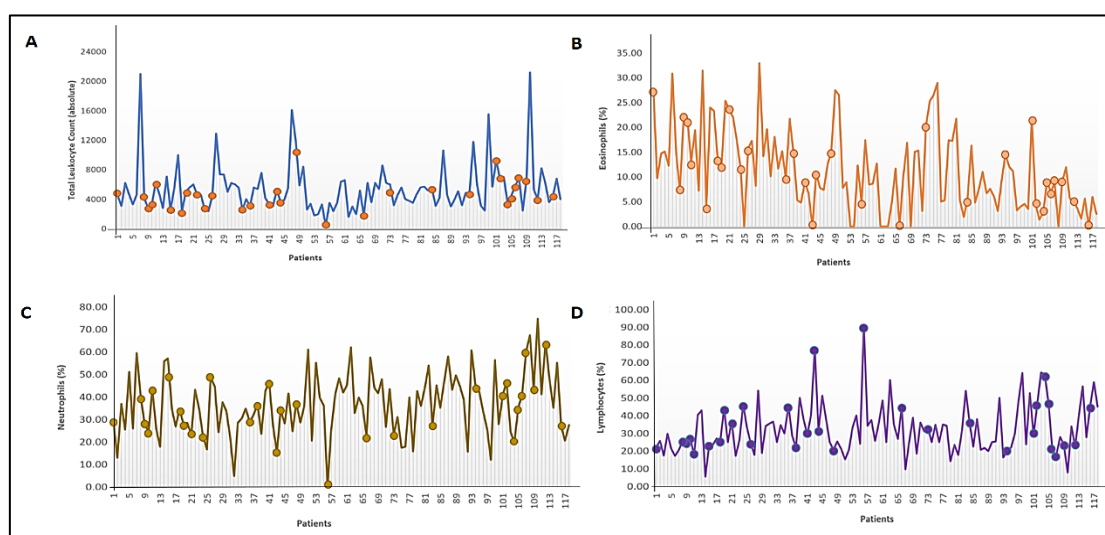


Figure 1: (A) Graph of Total Leukocyte with Respect to Number of Patients, (B) Graph of % Eosinophils with Respect to Number of Patients, (C) Graph of % Neutrophils with Respect to Number of Patients, (D) Graph of % Lymphocytes with Respect to Number of Patients

The eosinophil count had a mean of 680.95/ μL , but with considerable variability (standard deviation

of 679.41/ μL), reflecting the variability immune response seen in dengue infections. Eosinophil

levels were elevated in some patients, which may indicate immune activation or an allergic response. The mean neutrophil count was 2246.11/ μ L, with a wide range from 300/ μ L to 16,000/ μ L, showing immune activation in some patients, with neutrophils being a key player in the inflammatory response during dengue shown in Figures 2A-2D. The mean lymphocyte count was 1650.44/ μ L, suggesting that most patients had normal or slightly reduced lymphocyte levels, with some patients exhibiting low counts (down to 400/ μ L),

possibly indicating immune suppression in certain individuals. Basophils had a mean count of 222.28/ μ L, but the range of 0 to 2300/ μ L suggests that basophils are not heavily involved in the immune response during non-severe dengue. Monocyte counts had a mean of 488.94/ μ L, and basophils, macrophages like cells were also found to have low counts on average (mean of 313.57/ μ L), indicating potential immune suppression or redistribution of immune cells.

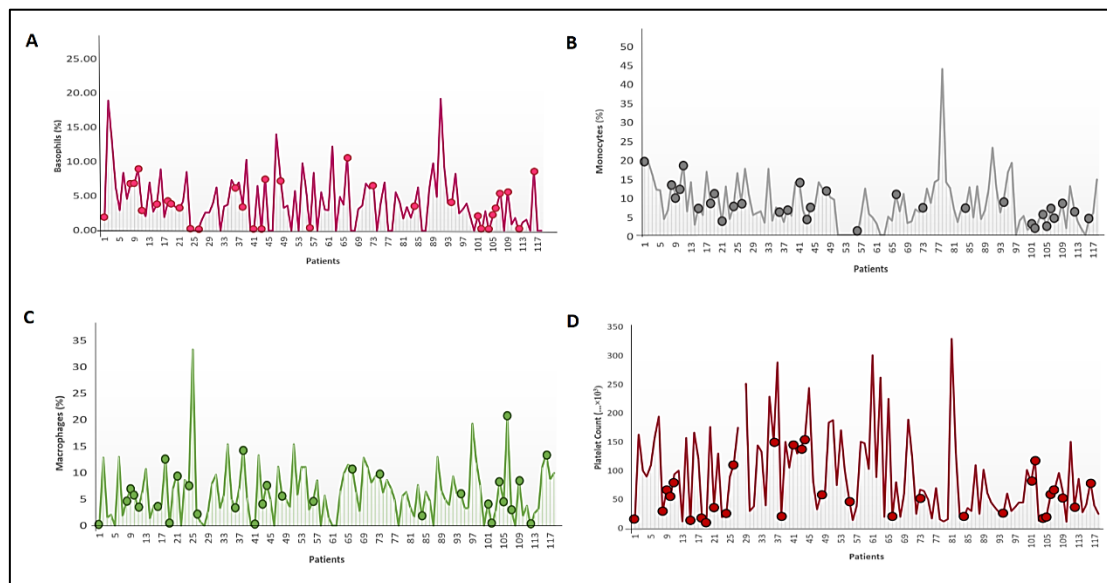


Figure 2: (A) Graph of Total % Basophils with Respect to Number of Patients, (B) Graph of % Monocytes with Respect to Number of Patients, (C) Graph Of % Macrophage Like Cells with Respect to Number of Patients, (D) Graph of Platelet Count with Respect to Number of Patients

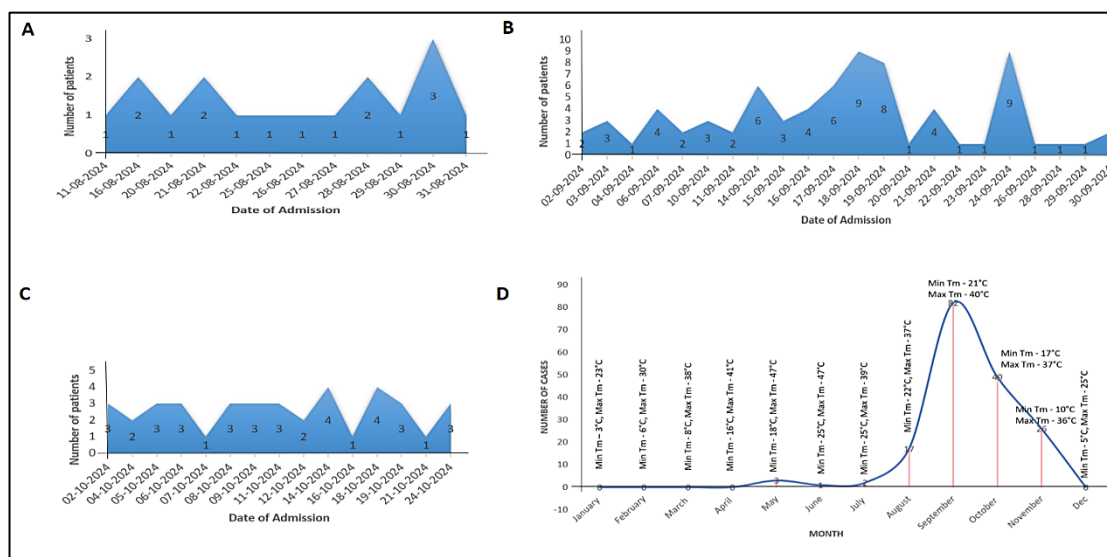


Figure 3: (A) Graphical Representation of Number of Patients Admitted with Respect to Date in Month of August-2024, (B) Graphical Representation of Number of Patients Admitted in with Respect to Date in Month of September-2024, (C) Graphical Representation of Number of Patients Admitted with Respect to Date in Month of October-2024, (D) Number of Patients Admitted in Hospital

Analysis of reported cases with respect to month and temperature were done as depicted in Figures 3A-3D. Out of total Dengue positive patients analysed for infection month wise (in year 2024), 74 patients were hospitalized in month of September, followed by 39 patients in October, 26

patients in November, 17 in August, 3 in May, 2 in July and only 1 positive case in June. The data presented in graph as shown in Figures 4A and 4B also distribution of patient with month in relation to the minimum and maximum temperature reported.

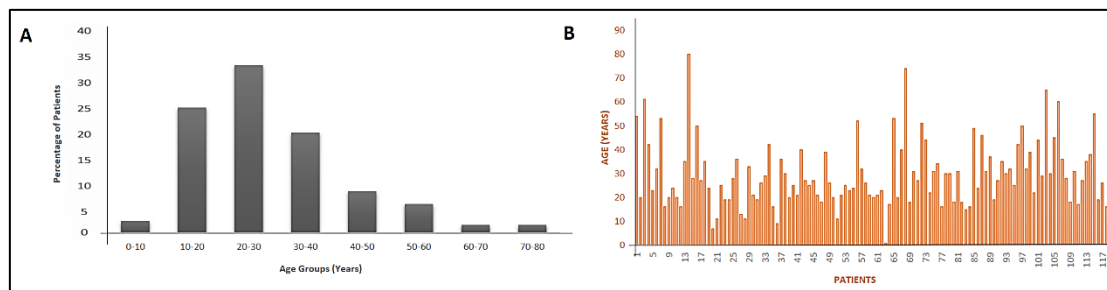


Figure 4: (A) Graphical Representation of Percentage of Patients According to Age Group, (B) Age of Individual Patients

Table 6: Age Group and Number of Dengue Infected Patients

Age Group (Years)	Number of Patients	Percentage
0-10	3	2.54
10-20	30	25.42
20-30	40	33.89
30-40	24	20.33
40-50	10	8.47
50-60	7	5.93
60-70	2	1.69
70-80	2	1.69

Age wise distribution of the 118 patients showed 40 patients in the category of 20-30 years, 30 patients in the category of 10-20 years, 24 patients in the category of 30-40 years. as shown in Table 6. Maximum patients were in the category of 20-30 years in age.

The analysis revealed significant differences in leukocyte count between mild and severe cases of Dengue. Patients with mild infection exhibited a moderate decrease in total leukocyte count whereas, patients with severe infection showed

more pronounced leukopenia and low number of phagocytic and lymphocytic cell, suggesting low immune sensitization. Lymphocyte counts were markedly reduced in severe cases compared to mild cases, indicating a compromised innate and adaptive immune response. Neutrophil levels were relatively stable in mild cases but showed a decline in severely infected individuals which may contribute to increased susceptibility to secondary infections.

Table 7: Age Group Analysis of Dengue in Three Major Group

Age Group	Dengue Fever (N= 87)		Severe Dengue (N=31)	
	Number of patients (n)	Mean Age (Years)	Number of patients (n)	Mean Age (Years)
Pediatric (<18)	12	12.98	4	13.00
Adult (18-59)	71	30.25	26	30.69
Old age (≥60)	4	70.00	1	60.00
Total	87	29.69	31	28.97

Among the 87 patients diagnosed with dengue fever (DF), the majority were adults aged 18-59 years (71 cases, 81.6%). Pediatric patients

younger than 18 years were 12 (13.8%) whereas 4 patients (4.6%) were aged 60 years or older as shown in Table 7. A similar age distribution was

observed in the dengue haemorrhagic fever (DHF) group. Out of 31 DHF patients, 26 (83.9%) belonged to the adult age category which were high in both sets making it the most represented group. Pediatric patients constituted 12.9% (4/31) of the cases, whereas only one patient (3.2%) was

in the elderly age group. This analysis indicate that adults represented the largest proportion of dengue cases in both DF and DHF groups, while pediatric and elderly patients accounted for a relatively smaller share of the study population.

Table 8: Age Wise Comparison of Haematological Among Three Major Groups

Parameter	DHF patients		
	Pediatric (<18 years) n=4	Adult (18–59 years) n=26	Old Age (≥60 years) n=1
Total Leucocyte Count (cells/cmm)	4700.00	4873.08	5800.00
Neutrophils (%)	34.52	35.34	41.30
Eosinophils (%)	11.38	11.15	6.89
Basophils (%)	2.69	3.33	6.89
Monocytes (%)	7.83	8.39	6.89
Lymphocytes (%)	36.02	35.35	20.60
Platelet Count ($\times 10^3$ /cmm)	59.00	59.42	60.00

Parameter	DF patients		
	Pediatric (<18 years) n=12	Adult (18–59 years) n=71	Old Age (≥60 years) n=4
Total Leucocyte Count (cells/cmm)	5058.33	5676.06	5975.00
Neutrophils (%)	35.72	37.80	40.52
Eosinophils (%)	9.33	11.34	15.86
Basophils (%)	2.33	3.39	3.74
Monocytes (%)	7.93	8.50	8.58
Lymphocytes (%)	37.11	30.86	28.08
Platelet Count ($\times 10^3$ /cmm)	121.92	96.10	72.50

In DF patients, the mean total leucocyte count increased with age, rising from 5058.33 cells/cmm in pediatric patients to 5676.06 cells/cmm in adults and 5975.00 cells/cmm in the elderly as shown in Table 8. Neutrophil percentages also increased with age (35.72%, 37.80%, and 40.52%, respectively), while lymphocyte percentages decreased from 37.11% in pediatric patients to 30.86% in adults and 28.08% in elderly individuals. Platelet counts were highest among pediatric patients (121.92×10^3 /cmm) and progressively declined in adults (96.10×10^3 /cmm) and the elderly (72.50×10^3 /cmm). A similar trend was observed in DHF patients. The

mean total leucocyte count increased from 4700.00 cells/cmm in pediatric patients to 4873.08 cells/cmm in adults and 5800.00 cells/cmm in the elderly as shown in Table 8. Neutrophil percentages were highest in elderly patients (41.30%), whereas lymphocyte percentages were lowest (20.60%). Platelet counts remained markedly reduced across all age groups, with mean values of 59.00, 59.42, and 60.00 $\times 10^3$ /cmm in pediatric, adult, and elderly patients, respectively. These findings indicate age-related variations in haematological parameters with more severe thrombocytopenia observed in DHF than in DF.

Table 9: Gender-wise Comparative Analysis in DF and DHF Patient

Parameter	Dengue Fever	
	Female (n = 38)	Male (n = 49)
Total Leucocyte Count (cells/cmm)	5160.53	5948.98
Neutrophils (%)	41.59	34.57
Eosinophils (%)	11.22	11.30
Basophils (%)	2.89	3.88
Monocytes (%)	7.09	9.46

Lymphocytes (%)	29.78	33.01
Platelet Count ($\times 10^3$ /cmm)	112.55	87.73
Dengue Haemorrhagic Fever		
Parameter	Female (n = 12)	Male (n = 19)
Total Leucocyte Count (cells/cmm)	4625.00	5042.11
Neutrophils (%)	38.96	33.19
Eosinophils (%)	9.82	11.82
Basophils (%)	3.47	3.10
Monocytes (%)	8.64	8.03
Lymphocytes (%)	33.58	35.83
Platelet Count ($\times 10^3$ /cmm)	76.83	48.37

Among the DF patients, males (n = 49) were more numerous than females (n = 38). The mean total leucocyte count was higher in males (5948.98 cells/cmm) than in females (5160.53 cells/cmm). Females had a higher neutrophil percentage (41.59% vs. 34.57%), whereas males had higher monocyte (9.46% vs. 7.09%) and lymphocyte percentages (33.01% vs. 29.78%). The mean platelet count was 87.73×10^3 /cmm in males and 112.55×10^3 /cmm in females.

In the DHF group, males (n = 19) also outnumbered females (n = 12). The mean total leucocyte count was higher in males (5042.11 cells/cmm) than in females (4625.00 cells/cmm). Females had higher neutrophil (38.96% vs. 33.19%) and monocyte percentages (8.64% vs. 8.03%), while males had higher eosinophil (11.82% vs. 9.82%) and lymphocyte percentages (35.83% vs. 33.58%). The mean platelet count was lower in males (48.37×10^3 /cmm) than in females (76.83×10^3 /cmm) as shown in Table 9.

Discussion

Our results indicate a significant reduction in total leukocyte count in severe cases of Dengue compared to mild ones suggesting a more profound immunosuppressive effect in severe dengue cases. Previous studies have reported similar trends, where leukopenia is a hallmark of DENV infection due to bone marrow suppression and peripheral destruction of leukocytes (22).

Differential leukocyte analysis showed a marked reduction in neutrophil count in severe cases of dengue, which was consistent with previous findings (23), who reported that severe dengue is associated with increased vascular permeability and immune dysregulation leading to neutropenia. Conversely, lymphocytosis was observed in both mild and severe dengue patients, but the degree was more pronounced in severely infected. This is

in agreement with the findings of Green and co-workers (24), who suggested that increased lymphocyte activity is linked to an exaggerated immune response, leading to severe disease manifestations.

The observed leukocyte trends in our study support the hypothesis that severe dengue cases are linked to immune dysregulation (25-27). The depletion of lymphocytes in severely infected patients suggests T-cell exhaustion due to insufficient immune activation. Additionally, the inverse relationship between lymphocytes and neutrophils in these patients worsen immune vulnerability. Therefore, careful evaluation of blood cell and their ratios may assist clinicians in identifying patients at greater risk of severe disease and support timely clinical decision-making.

Notably, some severely ill patients exhibited depleted leukocyte counts indicating severe immune suppression and impaired leukocyte regeneration, further compromising the ability to prevent DENV infections.

There are dengue vaccines available, but their use is limited to specific age groups and conditions. Dengvaxia is approved for individuals aged 9-16 years who have had a previous dengue infection confirmed by laboratory and live-in areas where dengue is common. This restriction is due to safety concerns; administering the vaccine to those without prior dengue exposure may increase the risk of severe dengue upon subsequent infection (28).

Our study observed that 79.66% of infected patients belonged to the age group of 10-40 years. This highlights the need for targeted vaccination strategies that focus on the most affected age groups. If existing vaccines fail to provide sufficient protection, prioritizing vaccine development and distribution for this highly susceptible population

could be a crucial step in reducing disease burden and improving public health outcomes.

Overall, the hematological profile of severely infected patients highlights serious immune dysregulation, characterized by thrombocytopenia, inflammatory neutrophilia, lymphocytic suppression, and heterogeneous leukocyte responses. These results expand the understanding of the complex immune mechanisms underlying severe dengue and support the importance of hematological parameters as prognostic markers in clinical practice.

The hematological profile of mild DENV cases shows thrombocytopenia, neutrophil activation and variable lymphocyte responses. Despite the presence of immune activation in some individuals, there is significant immune variability which may influence the clinical course of the disease. This analysis provides a clearer understanding of the immune dysregulation that occurs even in non-severe dengue cases offering valuable insights into immune biomarkers for disease severity and potential targets for therapy. Almost severe dengue patients have reported with low level of platelet count below minimum range. Basophils and mast cell contain histamine in their granules that can be released into the surrounding tissues following cellular activation or cellular damage (29). Histamine increases vascular permeability by causing blood vessels to become more permeable which can contribute to plasma leakage which is a key feature of severe dengue. Platelets also contribute to the inflammatory response by releasing vasoactive and pro-inflammatory mediators upon activation (30). These mechanisms may collectively promote the increased vascular permeability and plasma leakage observed in severe dengue cases and that can be detected by hematocrit level, high hematocrit might severe leakage of blood contents to surrounding tissue and can be important predictor for DHF patients (31).

The elevated basophil counts observed in the present study may reflect an enhanced inflammatory response and increased mediator release during dengue infection (32). This finding suggests a possible role of basophils in the immunopathogenesis of dengue particularly in the progression from normal dengue fever to dengue haemorrhagic fever.

Conclusion

Dengue and its severe forms Dengue Haemorrhagic Fever and Dengue Shock Syndrome are reported every year which adds to the disease burden worldwide. Vaccines are at the various stages of development. While the diagnostic tools can detect presence and absence of dengue antibodies and antigen, diagnosing the blood of the infected patient can also predict the risk towards severity as well as immune response of the infected patient. Present paper highlights need of additional diagnostic measures to understand the difference between simple DF and severe forms of Dengue. Early detection via blood cell count pattern, may help clinicians adopt proactive treatment strategies to prevent DHF/DSS complications.

The study was conducted at single centre which may limit the generalizability of the results with respect to other population and geographic regions. The elderly age contained very few patients especially in DHF group which might be restricting the age-based comparison.

Further investigations involving histamine quantification and assessment of basophil activation markers would help clarify the exact contribution of these cells to dengue-associated vascular leakage and disease severity.

Abbreviations

CV: Coefficient of Variation, DF: Dengue Fever, DHF: Dengue Haemorrhage Fever, DSS: Dengue Shock Syndrome, Min: Minimum, Max: Maximum, SD: Standard Deviation, TLC: Total Leucocyte Count.

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Author Contributions

All the authors contributed equally to conceptualization, data analysis, and manuscript writing for this study.

Conflict of Interest

The authors have no competing interests (financial or otherwise) to declare.

Data Availability

The demographic data were taken from patients/guardians along with clinical data were taken from

hospital with proper consent from Head of Department as well as patients. However, the processed data can be made available from the corresponding author on a reasonable request.

Declaration of Artificial Intelligence (AI) Assistance

The authors declare no use of artificial intelligence (AI) for the write-up of the manuscript. The authors take full responsibility for the content's originality, interpretation and accuracy.

Ethics approval

The study has been approved by the Institutional Ethical Committee, Sharda University, India (SU/SMS&R/76-A/2024/69).

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