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GENDER-BASED HEMATOLOGICAL VARIATIONS IN DENGUE FEVER: EVIDENCE FROM A TERTIARY HEALTHCARE SETTING IN PESHAWAR, PAKISTAN

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ABSTRACT

Background: Dengue Fever, a prevalent mosquito-borne disease, particularly impacts tropical and subtropical regions, posing significant public health challenges. Despite its prevalence, gender-specific hematological changes in dengue fever remain understudied, particularly within specific healthcare settings such as Peshawar, Pakistan.

Objective: The study aims to assess the hematological parameters, their gender-based variations, and the prevalence of serological markers among dengue fever patients presenting at a tertiary care setting in Hayatabad, Peshawar, Pakistan.

Materials and Methods: A single-center, descriptive, observational study utilized retrospective data from a private tertiary care hospital in Peshawar, Pakistan. A convenience sample of 101 patients meeting WHO criteria for suspected dengue fever between September and November 2022 was included. Data extraction from electronic health records covered demographics, serology, and hematological parameters. Statistical analysis involved means, standard deviations, frequencies, and percentages using SPSS 26.0.

Results: Predominantly, young males constituted the dengue patient cohort, with NS1 antigen positivity (94.06%) and thrombocytopenia (40.59%) as common serological markers. Male and female hematological profiles exhibited notable variations, including reductions in red blood cell count (11%), hematocrit (26%), hemoglobin levels (13%), and mean corpuscular volume (43%). Thrombocytopenia was prevalent (93%), with lymphocytopenia (20%) and neutrophilia (13%) observed in some cases.

Conclusion: The investigation highlights the predominant occurrence of dengue fever among young males, with NS1 antigen positivity serving as a prevalent serological indicator. Furthermore,

thrombocytopenia emerges as the foremost hematological aberration observed in the studied population.

Keywords (MeSH): Dengue Fever, Hematological Parameters, Thrombocytopenia, NS1 Antigen.

INTRODUCTION:

Dengue Fever is the second most common mosquito derived disease after malaria. (1) An arbovirus belonging to the flavivirus family carries the virus that causes dengue, the carrier to which is the female aedes aegypti and albopictus mosquito. (2) Dengue is endemic in about one-third of the world's population; tropical and subtropical regions—mostly developing nations—carry a disproportionately high burden of the disease. (3) The region thought to have the highest frequency of this disease is Southeast Asia. (4,5) Dengue infection cases are categorized by the World Health Organization (WHO) as severe dengue, dengue with warning signs (abdominal pain, vomiting, mucosal bleeding, hepatomegaly>2cm, fluid accumulation, increased hematocrit), and dengue without warning signs. Fever, body aches, bone discomfort, muscular soreness, retro-orbital pain and generalized weakness are the usual initial symptoms. (2,6,7) Its symptoms can range from none at all to severe consequences including dengue shock syndrome and dengue hemorrhagic fever. (2,8) The known serotypes of dengue virus are DENV1, DENV2, DENV3 and DENV4, recovery from one specific serotype provides complete immunity along with partial immunity to the other types. (3, 6, 8) Stamped water, excessive rainfall, inadequate sanitation, and ineffective mosquito control are among of the reasons that have made dengue a significant public health concern. (6) Some of the dengue infections are associated with neurological manifestations like encephalitis, meningitis myelitis, GBS and myositis, the risk factors to which are high body temperature, elevated hematocrit, thrombocytopenia, skin rash, and liver dysfunction (7) The diagnosis for dengue fever is based on clinical symptoms and abnormal laboratory findings. Some of the hematological findings reported by a study in Ethiopia are thrombocytopenia, anemia, leucopenia and increased hematocrit. (9) Studies have shown that the hematological parameters of dengue fever changes on a daily basis. According to Yousaf and colleagues' dengue fever is endemic in different districts of Pakistan. (10)

Understanding gender-specific hematological changes in dengue fever patients is crucial for tailored treatments and improved outcomes. However, there is a notable scarcity of studies on this topic, especially within Peshawar's tertiary healthcare settings. Bridging these knowledge gaps can significantly enhance our understanding of the disease, facilitating more effective diagnosis and treatment strategies. Moreover, knowledge of gender-associated inequities may help in channelizing public health efforts toward intervened actions, loaning a hand in gap reduction of disease burden at large. Therefore, the current study shall estimate gender-based hematological parameters and their differences among patients with dengue fever in a tertiary care setting in Hayatabad, Peshawar, Pakistan.

MATERIALS AND METHODS:

This was a single-center, descriptive, observational study using retrospective data from a private tertiary care hospital in Peshawar, Khyber Pakhtunkhwa, Pakistan. The sample comprises 101 patients who visited the hospital from September to November 2022. The inclusion criteria for the study adhered to the 2009 WHO guidelines for suspected dengue fever, having a duration of fever more than 2 days (axillary temperature $\geq 38^{o}$ C) and two or more of the following symptoms: headache, retroorbital pain, myalgia, rash, and bleeding manifestations. In addition, any patient having a positive NS1-Ag (Nonstructural protein-1 antigen) test, thrombocytopenia, which is a platelet count of less than 150,000/mm3, or positive dengue antibody serology with IgM or IgG or both, was included. The study excluded those patients who had negative dengue tests, either NS1 & IgM, or their blood count reports were not available, or the patients were suffering from some other concurrent illness like typhoid, Kala-azar, or malaria even if their dengue serology was positive. The study further excluded patients whose bacterial infections were confirmed, those with chronic conditions like bone marrow

disease and liver cirrhosis, or those who had a history of blood transfusions. Also excluded were those with only the presence of IgG antibodies (indicating past exposure) and an absence of symptoms. The informed consent was waived because of the retrospective nature of the study. The affiliated institutional review board and the ethics committee approved the study design to ensure proper ethical conduct. Data was extracted from electronic health records (EHRs) covering a wide array of variables. The covariates included the demographics like age, gender, serology status of the patients and also, the hematological parameters in the blood samples of patients—Hb (Hemoglobin) levels, RBC (Red Blood Cell) count, TLC (Total Leukocyte Count), HCT (Hematocrit), platelet count, MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin Concentration), MPV (Mean Platelet Volume), neutrophils, lymphocytes, and mixed cell population. The cut-off values for each test result considered were based on the reference range used by the laboratory. The data was recorded using MS Excel spreadsheets, and all the analysis was done on SPSS 26.0. Calculations of the means included the lowest, highest, and overall, while standard deviations and frequencies and percentages were used to summarize central tendencies, variability, and distribution of categories for the two variables under study.

RESULTS

Among the 101 dengue patients, the median age was 41.43 years with a standard deviation of ±20.03 years. Predominantly, patients were young males, with the 13-26 age group comprising 43.56% (44/101) of the cohort and males representing 67.33% (68/101) of all cases. The 83-96 age group was least affected, accounting for merely 1% of the patient population. *(Table 1)*

Table 1: Age and Gender Distribution of Patients.

Age Groups (years)	Male (%)	Female (%)	Total (%)
13-26 Years	32 (47.06%)	12 (36.36%)	*44 (43.56%)*
27-40 Years	9 (13.23%)	9 (27.27%)	*18 (17.82%)*
41-54 Years	17 (25.00%)	8 (24.24%)	*25 (24.75%)*
55-68 Years	7 (10.29%)	3 (9.09%)	*10 (9.90%)*
69-82 Years	2 (2.94%)	1(3.03%)	*3 (2.97%)*
83-96 Years	1 (1.47%)	0 (0.00%)	*1 (1.00%)*
Total	*68 (100.00%)*	*33 (100.00%)*	*101 (100.00%)*

In the study, 94.06% (95/101) of patients showed acute dengue infection with positive NS1 antigen tests. Thrombocytopenia was observed in 40.59% (41/101) of cases, more prevalent in males (29.70%) (30/101) than females (10.89%) (11/101). IgM and IgG antibodies were detected in 8.91% (9/101) and 4.95% (5/101) of the patients, respectively. *(Table 2)*

Table 2: Distribution of Serological Markers and Thrombocytopenia in Patients.

Gender	NS1	IgM	IgG	Thrombocytopenia	Total (%)
Male	65 (64.36%)	5 (4.95%)	3 (2.97%)	30 (29.70%)	*68 (67.33%)*
Female	30 (29.70%)	4 (3.96%)	2 (1.98%)	11 (10.89%)	*33 (32.67%)*
Total	*95 (94.06%)*	*9 (8.91%)*	*5 (4.95%)*	*41 (40.59%)*	*101 (100.00%)*

Analyzing CBC parameters across genders reveals notable variations and consistencies. In males, parameters such as RBC count exhibit wider ranges, with mean values of 5.91 million cells/µL. Conversely, in females, ranges are narrower, yielding a mean of 4.81 million cells/µL. The White Blood Cell (WBC) count averages at 9.39 thousand cells/µL for both genders. Hematocrit

demonstrates a mean of 37.30% for males and 32.11% for females. Similarly, hemoglobin levels follow a comparable trend, with males showing a broader range (mean of 13.07 g/dL) compared to females (mean of 12.60 g/dL). Platelet count maintains a mean of 37.36 thousand cells/µL for both genders. However, the Mean Platelet Volume (MPV), reflecting platelet size, exhibits a mean of 8.25 femtoliters for males and 11.68 femtoliters for females. Nevertheless, parameters like MCH and MCHC demonstrate consistent ranges between both genders, with overall mean values of 25.02 picograms and 34.21 g/dL, respectively. (Table 3)

Table 3: Haematological Parameters among the studied Dengue Fever Patients.

Hematological Parameters (Normal Range)	**Units**	**Gender**	**lowest value**	**Highest value**	**lowest mean**	**highest mean**	**Mean**	**Overall Mean**
Red Blood Cell (RBC) Count (4-6)	×10.e6/ µl *(1,000,000 per microliter)*	Male	1.29	9.60	3.04	8.79	*5.91*	*5.36*
		Female	3.15	6.25	3.47	6.16	*4.81*	
White Blood Cells count (4-11)	×10.e3/ µl *(1,000 per microliter)*	Male	1.10	20.20	3.20	15.57	*9.38*	*9.39*
		Female	1.65	17.75	2.74	16.06	*9.40*	
Hemoglobin Level (11.5-17.5)	g/ dL *(grams per deciliter)*	Male	3.35	19.60	7.81	18.33	*13.07*	*12.83*
		Female	8.50	16.53	9.71	15.50	*12.60*	
Hematocrit (36-54)	% *(percent)*	Male	8.50	56.50	29.15	55.85	*42.50*	*37.30*
		Female	23.50	31.04	30.05	34.18	*32.11*	
Mean Corpuscular Volume (76-96)	f L *(femtoliters)*	Male	60.20	97.00	72.00	97.00	*84.50*	*82.15*
		Female	60.20	99.42	70.45	89.17	*79.81*	
Mean Corpuscular Hemoglobin (27-33)	p g *(picograms)*	Male	17.80	32.36	24.68	25.48	*25.08*	*25.02*
		Female	20.60	29.56	24.68	25.24	*24.96*	
Mean Corpuscular Hemoglobin Concentration (33-35)	g/ dL *(grams per deciliter)*	Male	29.50	39.50	32.06	36.50	*34.28*	*34.21*
		Female	33.06	37.40	32.20	36.08	*34.14*	
Platelet Count (150-450)	×10.e3/ µl *(1,000 per microliter)*	Male	9.00	65.72	29.70	45.02	*37.36*	*37.36*
		Female	11.30	63.42	45.03	29.69	*37.36*	
Mean Platelet Volume (7.2-11)	f L *(femtoliters)*	Male	5.00	11.80	5.00	11.50	*8.25*	*9.96*
		Female	22.97	35.90	5.67	17.70	*11.68*	
Neutrophils (40-75)	% *(percent)*	Male	20.80	86.30	30.24	78.50	*54.37*	*56.71*

		Female	27.42	92.80	37.50	80.62	*59.06*	
Lymphocytes (20-45)	% *(percent)*	Male	10.30	69.80	15.62	54.20	*34.91*	*33.54*
		Female	5.00	54.20	12.77	51.60	*32.18*	
Mixed Cell Population (5-20)	% *(percent)*	Male	3.40	26.90	3.75	23.40	*13.57*	*13.76*
		Female	2.20	22.43	3.60	24.30	*13.95*	

Exploring condition wise of dengue fever on blood profiles revealed a fascinating array of patterns in complete blood count (CBC) parameters. Within the cohort, a distinct 11% experienced a reduction in red blood cell (RBC) count, accompanied by leukopenia in 22% of cases. Moreover, 26% displayed decreased hematocrit (HCT), while 13% exhibited lowered hemoglobin (Hb) levels. Notably, a significant 43% demonstrated diminished mean corpuscular volume (MCV), with a rare 1% presenting elevated MCV. The investigation also highlighted the prevalence of abnormalities in mean corpuscular hemoglobin concentration (MCHC), affecting 69% of individuals. Furthermore, thrombocytopenia was widespread, afflicting 93% of the cohort. Interestingly, lymphocytosis and neutrophilia were observed in 9% and 13% of patients, respectively. (Table 4)

Table 4: Haematological variations among studied Dengue cases.

CBC Parameters	**Variations *(Probable Description)***	**Gender**		**Total**	**Percentage**	**Total Percentage**
		Male	**Female**			
Red Blood Cell count	High *(erythrocytosis)*	7	2	9/ 101	*9%*	*20%*
	Low *(anemia)*	7	4	11/ 101	*11%*	
White Blood Cells count	High *(leukocytosis)*	4	5	9/ 101	*9%*	*31%*
	Low *(leukopenia)*	15	7	22/ 101	*22%*	
Hematocrit	High *(erythrocytosis)*	2	0	2/ 101	*2%*	*28%*
	Low *(anemia)*	14	12	26/ 101	*26%*	
Hemoglobin	High *(erythrocytosis)*	3	0	3/ 101	*3%*	*16%*
	Low *(anemia)*	6	7	13/ 101	*13%*	
Mean Corpuscular Volume	High *(macrocytic anemia)*	1	0	1/ 101	*1%*	*45%*
	Low *(microcytic anemia)*	27	16	43/ 101	*43%*	
Mean Corpuscular Hemoglobin Concentration	High *(Hemoconcentration)*	47	23	70/ 101	*69%*	*82%*
	Low *(Hemodilution)*	12	1	13/ 101	*13%*	
Mean Corpuscular Hemoglobin	High *(macrocytic anemia)*	0	0	0/ 101	*0%*	*35%*
	Low *(microcytic anemia)*	22	13	35/ 101	*35%*	
Platelets	High *(thrombocythemia)*	0	0	0/ 101	*0%*	*93%*
	Low *(thrombocytopenia)*	65	29	94/ 101	*93%*	
Lymphocytes	High *(lymphocytosis)*	7	2	9/ 101	*9%*	

	Low *(lymphocytopenia)*	11	9	20/ 101	*20%*	*29%*
Neutrophils	High *(neutrophilia)*	4	9	13/ 101	*13%*	
	Low *(neutropenia)*	5	1	6/ 101	*6%*	*19%*

DISCUSSION:

The global prevalence of dengue has surged significantly in recent years, as evidenced by a substantial rise in reported cases to the World Health Organization (WHO). The figures have escalated from 505,430 cases in the year 2000 to a staggering 5.2 million cases in 2019. It is important to note that a significant majority of dengue cases either exhibit no symptoms or manifest mild symptoms that individuals manage on their own. Consequently, the true incidence of dengue is likely underestimated due to underreporting. Moreover, a considerable number of cases are often misdiagnosed as other febrile illnesses, further contributing to the challenge of accurately assessing the magnitude of the disease. (11) In addition to the global trend, dengue fever is also endemic in Pakistan, according to data from the National Institute of Health (NIH) in Islamabad. The reported cases in Pakistan for the years 2017, 2018, 2019, and 2020 were 22,938, over 3,200, 24,547, and 3,442, respectively. As of November 2021, the reported cases for that year had reached 48,906, indicating a rising trend in the prevalence of dengue fever in the country. (12) The study was conducted to explore specific factors, and based on our investigation, out of the 101 participants, 94.06% tested positive for NS1, 8.91% for IgM, and 4.95% for IgG. In contrast, a separate study carried out in Thailand by Manas Kotepui (13) revealed distinct results, with 20.7% of their participants testing positive for NS1, 12.4% for IgM, and 17.6% for IgG. When comparing our current study with another conducted in 2020 (14), it was found that approximately 9% of patients in our study exhibited leukocytosis, while 22% showed leukopenia. In contrast, the earlier study reported that 16% of patients had leukocytosis and 22% had leukopenia. Furthermore, the same study observed that all patients presented with thrombocytopenia, with 83% having lab values below 50,000. In our study, however, 93% of the patients demonstrated thrombocytopenia, and none exhibited thrombocytosis. A study by Dylan Kain (15) showed that 42% of the patients had lymphopenia, 30% had thrombocytopenia and neutropenia was noted in about 19% of the patients. In this study, 13% of the patients had neutrophilia and only 6% of the patient's showed neutropenia. Likewise, research conducted in India (16) revealed that 82.85% of the patients experienced leukopenia, while 1.14% exhibited leukocytosis. Additionally, 43.42% of the patients showed a reduction in hematocrit (<40%), and 26.28% displayed an elevation in hematocrit (>45%). In our study, 2% of the patients demonstrated an increased hematocrit, and 26% exhibited a decreased hematocrit with a mean value of 37.30%. This aligns with the findings of the Indian study, where the mean hematocrit value was 39.15%. Hematocrit results from another study showed that 16.6% of the patients presented with it. (17) Our study aligns with another research conducted in India, where the findings revealed a concordance. In both studies, a high percentage of cases were observed to have thrombocytopenia, with 99.07% of cases in the Indian study exhibiting this condition, mirroring the pattern observed in our research. (18) The hematological parameters analyzed in this study for dengue fever were consistent with findings from a concurrent local study (19). In that particular study, the mean hemoglobin was documented at 12.7g/dl, closely resembling our study's mean hemoglobin of 12.83g/dl. Additionally, the local study reported a mean hematocrit of 42.2%, contrasting with our study where the mean hematocrit was 37.30%. This was further supported by the previous study done by Bano et al. and Ferede et al., which showed thrombocytopenia in most of their patients studied (20), thus coinciding with our findings that there is a persistent presentation of thrombocytopenia in dengue fever cases.

The limitations of the study may be in the introduction of biases through convenience sampling and also from the fact that the exclusion criteria used could be rather restrictive to allow for the generalization of findings. Another key limitation could be relying solely on retrospective data from a single-center tertiary care hospital in Peshawar, Pakistan. This may restrict the applicability of the conclusions drawn in this study to broader populations. However, the strengths lie in adhering to

WHO guidelines for diagnosing dengue fever and comprehensive data extraction from electronic health records.

CONCLUSION:

Study findings confirmed that most of the cases were in young males; common serological markers identified were NS1 antigens and thrombocytopenia. CBC parameters showed a decrease in the count of red blood cells, hematocrit, hemoglobin levels, and MCV; there was thrombocytopenia, and some patients had lymphocytopenia with neutrophilia. These findings further reiterate the importance of awareness regarding hematological profile for this endemic infection in the geographical location under study to be diagnosed and managed properly.

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