

## CLINICAL COURSE AND OUTCOME OF PATIENTS WITH DENGUE FEVER, DENGUE HEMORRHAGIC FEVER AND DENGUE SHOCK SYNDROME IN A TERTIARY CARE HOSPITAL IN RECENT ENDEMIC 2022

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### ABSTRACT

**Background:** Dengue fever cases have been increased almost 30-fold over last 50 years and now reaches an estimated 100 million clinically apparent infections annually. This rapid increase in the incidence of dengue fever cases has become a threat not only to public health globally but also economic burden to developing countries like Pakistan and also other countries of South- Asia.

**Objective:** To assess clinical course and outcome in patients with dengue fever, dengue hemorrhagic fever and dengue shock syndrome in patients in a tertiary care hospital.

**Methods:** This cross-sectional study was conducted in the department of Medicine, Fatima Memorial Hospital, Lahore from September to November 2022. Data of all those patients who had dengue fever, dengue hemorrhagic fever and dengue shock syndrome was collected carefully. Laboratory tests were evaluated for the positivity of dengue fever by either NS1 or IgM. All patients who had positive of any of these tests were included in our study. Other laboratory tests (CBC-ESR, serum electrolytes, LFTs, RFTs, Urine analysis, chest x-ray and ultrasound abdomen and chest) were also included to assess the severity of dengue infection. These laboratory tests were repeated at least three times, one day apart to see any improvement or worsening of condition. We divided these patients in three groups according to severity of disease. Data were analyzed by SPSS- version 23. ANOVA was applied for continuous variable and chi-square was applied for categorical variables.

**Results:** The study comprised a total of 207 dengue patients. Distribution of gender, with 58% of the patients were men and 42% were women. The patients were divided into three groups based on their dengue infection severity type: dengue fever, dengue hemorrhagic fever, or dengue shock syndrome. There was no significant difference in blood pressure of dengue fever and dengue hemorrhagic fever, but significant fall of Blood pressure was found in dengue shock syndrome. Similarly respiratory rate change was found in DSS. Temperature changes in these patients were not significant in all types of dengue virus infection. There were significant differences in the oxygen saturation values in dengue fever, dengue hemorrhagic fever and dengue shock syndrome and across the several dengue strains DNV1-4 (p 0.001). The analysis of laboratory data showed that the levels of hemoglobin, hematocrit, platelet count, white blood cell count, alanine transaminase (ALT), and aspartate transaminase (AST) varied considerably across the various dengue severity levels.

**Conclusion:** In our study it was shown that patients had variable level of severity at the time of presentation, and most of patients can be treated but patients who presented late, developed complications and even death in few patients, patients who presented with shock, most of them expired and female to male ratio was different, as most of females expired. There was also significant different oxygen saturation level according to severity of dengue infection. Platelets count was significant but not of predictive value for severity of dengue infection, as patients with very low platelets count recovered.

**Key words;** Dengue fever, dengue hemorrhagic fever, dengue shock syndrome

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### INTRODUCTION

Dengue fever is transmitted by female Aedes-mosquito. It is second most common vector-borne disease in the world after malaria which led to increased morbidity and mortality. Dengue fever cases have been increased almost 30-fold over last 50 years and now reaches an estimated 100 million

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clinically apparent infections annually.<sup>1,2</sup> This rapid increase in the incidence of dengue fever cases has become a threat not only to public health globally but also economic burden to developing countries like Pakistan and also other countries of South- Asia.<sup>3</sup> Dengue infection transmission occurring in 128 countries and almost 4 billion people at risk, of which at least 70% live in Asia-Pacific region. continues to increase globally.<sup>4</sup>

Dengue virus has four types from dengue 1 to dengue 4. Any one type can infect a person at a time but subsequent infection with distinctive serotype of Dengue virus (DENVs) has been associated with increase the risk of severe complications. After the development of dengue fever, it results in varying degrees of symptoms, ranging from asymptomatic to dengue hemorrhagic fever and more serious condition dengue shock syndrome, which may lead to fatal outcome.<sup>5, 6</sup> When any person gets infected with dengue virus for first time it is labeled as primary dengue fever. When someone gets re-infected with some of other type of dengue virus, it may lead to serious infection.<sup>7,8</sup> 23 % patients develop dengue hemorrhagic fever or progress to dengue shock syndrome and death.<sup>9</sup>

Various serological tests are available to early identify dengue virus infection, immunoglobulin IgM, NS1 and viral RNA detection by PCR. After the development of primary infection with dengue virus, immunoglobulin IgM appears with raised titers in serum.<sup>10</sup> Non-structural protein (NS1) is a glycoprotein secreted by dengue virus infected human cells, as this protein is essential for viral replication and survival of virus. This NS1 appears as early as within first day of illness and remain in serum for up to 9-10 days. So, this is very important serological test and ideal biomarker to identify virus in early phase of infection. Immunoglobulin IgM start rising from 3-4 days and remain in serum for 10 days.<sup>11,12</sup> PCR to detect viral RNA is not freely available and also costly test. For these reasons NS1 is considered preferable and earlier choice for diagnosing dengue virus infection

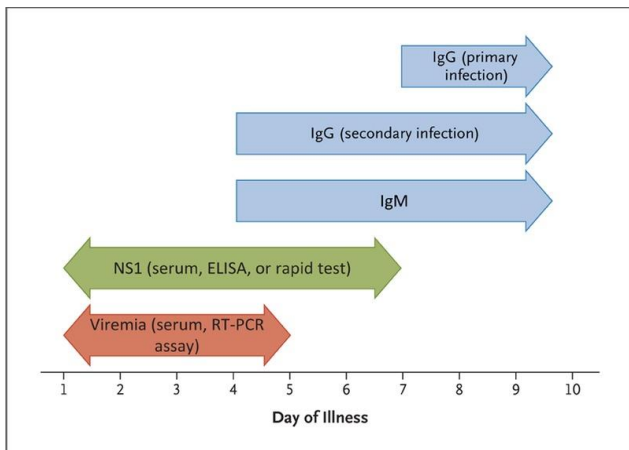


Figure 1: Laboratory Diagnostic Options in a Patient with Suspected Dengue Infection. (13, 14)

As dengue virus infection involves other organs also, so other serological test and imaging are required to establish the level of severity of illness.<sup>15,16</sup> This study provides a comprehensive description of course of illness of dengue patients admitted to a tertiary hospital in Lahore, to provide insights into disease course, treatment and outcome prediction.

## METHOD

This cross-sectional study was conducted in medicine department of a tertiary care hospital through total population sampling. All patients presented either in OPD or ER with symptoms of dengue fever was enrolled in our study. Proper detailed clinical examination was carried out of affected patients after asking detailed history of illness. Positive clinical findings were clerked out on history sheet for record and then relevant laboratory tests were done. Patients with positive serological test i-e Dengue-NS1 and/or Dengue-IgM, were included in our study. PCR was not done in any patient due to non-availability in our setting and cost of test also.

Other laboratory tests which done were CBC-ESR, liver function tests, renal function test, serum electrolytes, blood sugar level, coagulation profile (PT, APTT). Along with these tests imaging (chest x-ray and ultrasound abdomen and chest) done to identify the signs of severity of dengue fever. We divided patients in three groups. Group-1(DF) was labelled as conscious patient, pulse <100 bpm, Bp= >110/80mmHg, Hb% > 12.0 in male & 10.0 in female patients, TLC count > 3.5 cm/dL, platelets 40-100 cc/dL, ALT/AST upto 2 times raised, no bleeding from any site and imaging showed no fluid in third space (Pleura or Peritoneum), hepatomegaly and gallbladder edema. Group 2 (DHF) was labelled as conscious and responsive with pulse rate=100 Bpm, Bp= >100/70mmhg, Hb% <12.0 in male & <10.0 in females, TLC= <3.5 cc/dL, Platelets <20/ccm/dL, LFTs raised >2 times, petechiae on skin or gum bleed, normal RFTs with imaging showed pleural fluid and peritoneal fluid collection, hepatomegaly and edematous gall bladder. Group 3 (DSS) was labelled as conscious/altered sensorium, Pulse rate= >100bpm, Bp= <90/70 mmHg, Hb%= <10.0 in males and < 9.0 in females, TLC= < 2.5 cm/dL, Platelets= <20/cm/dL, LFTs > 2times, RFTs=deranged, bleeding from different sites, pleural and peritoneal fluid collection on imaging, marked hepatomegaly with edema of gall bladder. By dividing these patients in above groups showed the severity of disease as mild, moderate and severe disease, and monitoring of these patients for severity of disease process was done by doing clinical examination and laboratory work up. Patients with dengue fever were admitted in respective wards and patients having dengue hemorrhagic fever were admitted in high dependency units and patients with dengue shock syndrome were monitored in intensive care units. In patients with DHF and DSS standard IV fluid management was done, two

patients were also given colloids solution (Dextran), while patients with DF, oral rehydration was done. Patients having marked abnormalities in clinical parameters, repeated laboratory tests were carried out on alternate day basis, platelets < 20,000/cmm were monitored two times and coagulation profile was also repeated accordingly. Data were analyzed by SPSS- version 23. ANOVA was applied for continuous variable and chi-square was applied for categorical variables.

**RESULTS**

The study comprised of a total of 207 dengue patients. The patients were divided into three groups based on their dengue infection severity type: dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. Their demographic and clinical data were examined. Out of total, 58% of the patients were male and 42% were females. Males and females did not vary significantly in the distribution of dengue types (p = 0.58).

The patients' average age was 33.97 years, with a standard deviation of 17.74 ± years. The mean age of patients with dengue shock syndrome was the greatest (46.43 years), followed by those with dengue hemorrhagic fever (36.43 years), and dengue fever (30.91 years). Age differences across the various dengue types were statistically significant (p = 0.014).

Patients with dengue fever had the highest mean systolic blood pressure (113.30 mmHg) and diastolic blood pressure (73.24 mmHg), whereas those with dengue hemorrhagic fever had the second-highest and lowest blood pressure readings, respectively. Patients with dengue shock syndrome had the lowest blood pressure (shock) readings. Systolic and diastolic blood pressure among the several dengue types were significantly varied (p 0.001).

Pulse and respiratory rate indicating a more serious clinical appearance, patients with dengue shock syndrome had the greatest mean respiratory rate (23.43 breaths per minute) and pulse rate (106.00 beats per minute). There were significant variations in respiratory and pulse rates (p 0.001) and dengue types (p = 0.004). In dengue hemorrhagic fever, the mean temperature was 100.05°F, while in dengue fever, it was 100.10°F. Despite the fact that the mean temperatures varied depending on the kind of dengue, the differences were not statistically significant (p = 0.096).

Patients with dengue shock syndrome had the lowest mean oxygen saturation (85.57%), which suggests a greater risk of respiratory distress when compared to other dengue types. There were significant differences in the oxygen saturation values across the several dengue strains (p 0.001). (Table 1)

The analysis of laboratory data showed that the levels of hemoglobin, hematocrit, platelet count, white blood cell count, alanine transaminase (ALT), and aspartate transaminase (AST) varied considerably across the various dengue severity levels. The levels of hemoglobin and hematocrit in patients with dengue hemorrhagic fever were higher than those in individuals with dengue fever or dengue shock syndrome. Along with having higher ALT and white blood cell counts than the other two groups, patients with dengue shock syndrome also showed these characteristics. Lower platelet counts than those of patients with dengue fever were seen in individuals with dengue hemorrhagic fever or dengue shock syndrome. Patients who had dengue shock syndrome showed higher AST levels than those who fell into the other two groups.

Table 1: Demographics and clinical characteristics among different dengue type

Demographic & Clinical characteristics	Dengue Type			Total	p-Value
	Dengue fever	Dengue Hemorrhagic Fever	Dengue Shock Syndrome		
male	62(59.0)	57(60)	1(14.3)	120(58)	0.58
female	43(41.0)	38(40.0)	6(85.7)	87(42)	
Age	30.91(17.72)	36.43(16.80)	46.43(22.13)	33.97(17.74)	.014**
BP Systolic	113.30(15.71)	111.58(12.40)	82.86(13.80)	111.48(13.16)	.000**
BP Diastolic	73.24(10.24)	72.95(11.10)	53.57(9.45)	72.44(11.15)	.000**
Pulse	90.89(12.54)	87.12(11.45)	106.00(22.48)	89.67(12.91)	.000**
RR	19.44(3.44)	19.11(2.61)	23.43(7.25)	19.42(3.34)	.004**
Temp	100.08(1.16)	100.05(1.09)	101.00(1.00)	100.10(1.13)	.096
O2	97.42(1.17)	96.67(1.81)	85.57(5.97)	96.6763(2.77)	.000**

\*\* Highly significant \*significant

For continuous variables ANOVA was applied, For categorical variable chi square test was applied

Table 2; showing 1, 3, 5, means that all these lab tests were done on day 1, day 3 and day 5

Table 2: Distribution of labs according to the severity of dengue

Labs	Severity of Dengue			Total	P-value
	Dengue fever	DHF	DSS		
Hb1	13.18±1.98	14.08±2.47	13.47±2.74	13.61±2.28	.019
HB3	13.41±1.94	13.66±2.11	12.79±2.25	13.51±2.02	.432
Hb5	13.16±1.90	13.21±1.86	11.96±1.94	13.14±1.89	.239
P-value	0.0001	0.0001	0.180		
HCT1	39.50±5.41	41.68±6.69	41.27±8.36	40.56±6.20	.043*
HCT3	40.34±5.25	40.22±5.75	39.50±7.92	40.26±5.55	.924
HCT5	39.45±5.25	39.32±5.15	37.34±6.99	39.32±5.25	.591
P-value	0.0001	0.0001	0.034		
WBC1	4.83±1.93	5.62±3.62	9.66±4.32	5.35±3.04	.000**
WBC3	4.64±2.21	5.90±3.18	8.87±4.54	5.36±2.92	.000**
WBC5	4.87±2.61	6.45±2.96	9.11±5.14	5.74±3.04	.000**
P-value	0.187	0.001	0.368		
PLT1	151.08±91.08	52.24±52.53	58.57±41.80	102.59±89.06	.000**
PLT3	124.23±74.65	43.05±38.13	31.43±19.63	83.84±71.97	.000**
PLT5	125.67±72.27	70.62±45.61	41.43±32.92	97.56±66.80	.000**
P-value	0.0001	0.0001	0.156		
ALT	99.82±99.15	142.94±190.99	435.00±408.30	130.94±173.68	.000**
AST	141.54±159.51	262.69±437.45	1545.56±1415.67	244.61±470.76	.000**

\*\* Highly significant HB1-done on day 1, Hb3 day 3 and day 5, Hb5, DHF=dengue hemorrhagic fever, DSS= dengue shock syndrome Hb- hemoglobin, HCT –hematocrit, WBC= white blood cells, PLT= platelets, ALT= alanine transaminase, AST= aspartate transaminase. \*significant

For continuous variables ANOVA was applied. For categorical variable chi square test was applied

For within comparison Kruskal Wallis H test was applied

Complications	Gender		Total	P-value
	Male	Female		
Bleeding	36.0 (30.0%)	32 (36.8%)	68	.369
Organ dysfunction	3 (2.5%)	6 (6.9%)	9	.170
Ascites	21 (17.5%)	20 (23.0%)	41	.378
Pleural	27 (22.5%)	22 (25.3%)	49	.741
PLT mega	32 (26.3%)	28 (32.2%)	60	.439
PCV	2 (1.7%)	13 (14.9%)	15	.001
FFP	1 (0.8%)	7 (8.00%)	8	.010
Dengue shock	1 (0.8%)	6 (6.9%)	7	.058
Dengue fever	62 (51.7%)	43 (49.4%)	105	
DHF	57 (47.5%)	38 (43.7%)	95	

PCV= Pack cell volume, FFP= Fresh frozen plasma,

There were no significant gender differences in the frequency of bleeding, ascites, pleural effusion, or thrombocytopenia, according to the examination of male and female patients. However, it was not statistically significant; females had a greater incidence of organ dysfunction than males. PCV was significantly different across the two sexes, with females experiencing it more frequently than male patients. Additionally, there were

substantial differences in the administration of FFP across the sexes, with more women getting it. Overall, the study points to some gender-related differences but greater associations may call for more research.

## DISCUSSION

Dengue fever is rising globally but more affected population is still in developing countries like Pakistan. Most of infected patients had mild disease and even do not seek medical advice but patients with moderate to severe disease, present in OPD or ER. Dengue admissions showed a clear seasonal pattern during the high epidemic weather from July to November. Patients who were admitted 105 (50.72%) had mild dengue fever, 95 (45.89%) with dengue hemorrhagic fever and 7 (3.38%) with dengue shock syndrome. Most of our patient admitted either they have uncontrolled symptoms especially fever and severe myalgias and some patients had laboratory reports with low platelets counts. Clinical deterioration developed in most of our patients from day 5 to 7, which is quite similar to study done by Yacoub S, Wills B. Predicting outcome from dengue.<sup>17</sup>

Thrombocytopenia and leukopenia was noted more commonly in these patients, but there was poor correlation of thrombocytopenia and bleeding, which was quite similar with study done by Wills B.<sup>18</sup> Liver function tests were deranged in all patients of dengue virus infection, results were comparable with a study done by Nguyen TL, which predicted that progressive worsening of liver functions is a sign of disease severity and progression to serious outcome.<sup>19,20</sup> Ascites and pleural effusion was present in all patients with dengue shock syndrome, and also in patients with dengue hemorrhagic fever.

No particular symptoms or signs can predict which patient will progress to dengue shock syndrome, these results were comparable with study was also same result in another study done in Indonesia.<sup>21</sup> But patients with high grade fever, markedly low platelets, palpable and tender liver and signs of plasma leak were signs which lead to progression of disease in these patients. At admission, lethargy, abdominal distension, pleural effusion and presence of hypoalbuminemia, low Bp, were found to predict such serious outcomes.

Another important point in our study that not all patients who present with DSS have mortality, as in our study out of 7 patients who presented with DSS two recovered and 5 died due to refractory shock, female patients with DSS all died. Male patients are often overrepresented in dengue epidemics, but female sex has been associated with more severe disease.<sup>22,23</sup>

## CONCLUSION

In our study it was shown that patients had variable severity of infection at the time of presentation, and most of patients can be treated but patients who presented late developed complications and even death in few patients, patients who presented with shock, most of them expired and female to male ratio was significant, as most of females expired. There was also significant difference in oxygen saturation level according to severity of dengue infection. Platelets count difference was significant but have not predictive value for severity of dengue infection, as patients with very low platelets count recovered. Early presentation to medical care or timely intervention with crystalloids can save more lives. Patients who present late develop serious outcome like dengue shock syndrome and death

Awareness of health care professionals and public regarding preventive strategies is essential to fight against this disease and if dengue infection develops, seek medical consultation as soon as possible.

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**Conflict of Interest:** Authors declare no conflict of interest.

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