

## ORIGINAL ARTICLE

## Frequency of Plasma Leak in Patients with Dengue Fever

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## ABSTRACT

**Objective:** To find out the frequency of plasma leak as evident by pleural effusion and ascites in the patients of dengue fever.**Study Design:** Cross-sectional study.**Place and Duration:** Medical unit of Hayatabad Medical Complex, Peshawar Pakistan from April 2021 to September 2021.**Methodology:** Patients diagnosed as having dengue fever based on positive dengue antigen (NS 1) test or antibodies serology on enzyme linked immunosorbent assay (ELISA) were evaluated. Plasma leak was defined as having ascites or pleural effusion evident on ultrasound or X ray chest of the patients with active dengue fever. Hematocrit of >50% in female and 55% in male was considered as indirect indicator of plasma leak.**Results:** In a total of 154 patients, 89 (57.8%) were male and 65 (42.2%) female with age ranging between 14 to 75 years while mean age was 40.6±15.54 years. The over all frequency of plasma leak as evident by ascites or pleural effusion was 44.2% (n=68). The minimum duration in which plasma leak was noted, remained 4 days while the maximum was 8 days after the start of illness. The duration of patient's hospital stay was 5 to 17 days (mean 9.53±3.43 days).**Practical implications:** The frequency of plasma leak was higher in complicated dengue fever patients as compared to patients with less or no complications.**Conclusion:** Plasma leak is an important and frequent feature of dengue fever. X ray chest and ultrasound can detect majority of plasma leak in patients with hemoconcentration.**Keywords:** dengue fever, plasma leak, dengue NS1, dengue shock, dengue hemorrhage

## INTRODUCTION

Dengue fever is one of the most serious illnesses amongst the human viral infections. Worldwide about 128 countries are affected by the dengue virus infection<sup>1</sup> however it is becoming endemic in certain regions of the south Asia like Pakistan and India.<sup>2</sup> Under reporting of dengue cases is possible because of cases with mild symptoms or asymptomatic which do not present to the health facility. This may lead to an underestimate of the overall prevalence of dengue infection. One estimate mentions the overall worldwide burden of dengue fever as 390 million annually out of which 96 million are clinically with complications.<sup>3</sup> About 71650 cases were reported in Pakistan from 2005 till 2016 with 757 deaths. The worst situation was in 2011 when 21685 cases were reported with 350 deaths.<sup>4</sup>

Dengue fever is caused by the bite of female vector *Aedes aegypti* mosquito which breeds in the summer and humid environment. That is why dengue fever surges occur mostly in the summer. The mosquito lays eggs mostly in the clean stagnant water commonly in the houses like washroom utensils, and ground ditches. The dengue fever virus belongs to the family of RNA viruses that is *Flavivirus* genus/*Flaviviridae* family. There are four serotypes of dengue virus named as (DENV-1, DENV-2, DENV-3, and DENV-4).<sup>5</sup>

Dengue fever has many serious complications including plasma leak, severe hemorrhage, shock, hepatitis and vomiting leading to dehydration. Plasma leak with hemoconcentration is one of the most common complications of dengue fever. According WHO dengue fever case classification, plasma leak is one the feature and predictor of severe dengue fever.<sup>6</sup> Plasma leak as evident by ascites or pleural effusion occur in 3 to 6 days after the start of illness and has a significant association with underlying liver involvement.<sup>7</sup> It occurs in about 48% of the adult dengue fever patients.<sup>8</sup> It is usually detected on ultrasound and X-ray of the chest as pleural effusion, ascites or thickening of the gall bladder wall.<sup>9</sup> Plasma leaks occur because of the endothelial dysfunction and increased permeability of the microvasculature leading to transudation of protein rich fluid from the vessels into the sites like many loose tissues, pleural and peritoneal spaces.<sup>10</sup> The main pathogenic mechanism of plasma leak is inflammatory markers rather dengue viremia itself. Some literature mentioned the role of cytokines like tumor necrosis factor alpha in the causation of plasma

leak.<sup>11</sup> The nonstructural (NS-1) protein of dengue virus is also considered to be a contributing factor.<sup>11</sup> The mainstay of management of plasma leak is fluid replacement which may be intravenous or oral in case without shock while IV fluid is preferable in patients with shock.<sup>12</sup>

Plasma leak in patients with dengue fever is a predictor or association with severe dengue fever. It is associated with dengue hemorrhage, dengue shock and dengue hepatitis. Therefore, this study was performed to find out the frequency of plasma leak in patients of dengue fever thereby predicting or expecting the underlying serious complications. Ultrasound is probably the most sensitive tool in our setup to find out plasma leak as evident by pleural effusion or ascites.

## METHODOLOGY

This was a cross sectional study performed in the medical unit of Hayatabad Medical Complex Peshawar Pakistan from April 2021 to September 2021. One hundred and fifty four hospitalized patients were enrolled for the study. Patients were hospitalized because of having fever of more than 102°F, unable to take oral medications because of nausea and vomiting, thrombocytopenia of less than 50000/Cmm or evidence of any other complication.

The patients were consecutively collected from the medical wards during the summer of 2021. Patients were diagnosed as dengue fever based on nonstructural antigen (NS-1) and antibodies serology through ELISA. Apart from full clinical examination, patients were subjected to investigations like full blood count, liver functions, X ray chest and ultrasound for abdomen and chest to find out any effusion. Plasma leak was defined as having ascites or pleural effusion that developed within the 2-7 days of illness. Though it was difficult to assess about the baseline hematocrit of the patients, therefore we took hemoconcentration with hematocrit of >50% in female and 55% in male (20% increase from the baseline) as indirect indicator of plasma leak.<sup>13</sup>

Patients who might have ascites or pleural effusion due to other reasons like congestive cardiac failure, renal problems, or chronic liver diseases as evident by their previous medical record or clinical examination, were excluded from the study. All the patient data was collected in a preformed Performa for subsequent evaluation. Data was analyzed using "Statistical Package for

Social Sciences (SPSS)<sup>®</sup>, version 26.0 and descriptive statistics were shown.

**RESULTS**

We consecutively collected 154 patients who were admitted to the medical ward with consistent medical history, examination and diagnosis of dengue fever. The number of female patients was 65 (42.2%) while the male patients were 89 (57.7%) as shown in figure-1. The age range of the patients was from 14 to 75 years with a mean of 40.6±15.54. The overall frequency of plasma leak was 44.2% (n=68). The frequencies of plasma leak as only ascites, only pleural effusion and ascites with pleural effusion both are shown in table-1.

We further stratified the frequency to the age group, associated other complications like hemorrhage from any site as skin, nose, gums etc., hepatitis as evident by elevated liver enzymes and shock (Table-2). There was no difference of plasma leak frequency in different age groups amongst the study patients. The frequency in patients with hemorrhage was 54.83% (n=17/31), in patients with hepatic involvement as evident by elevation of alanine amino transferase by more than twice the upper limit of

normal was 48% (n=38/77) and in patients with shock was 83.33% (n=5/6).

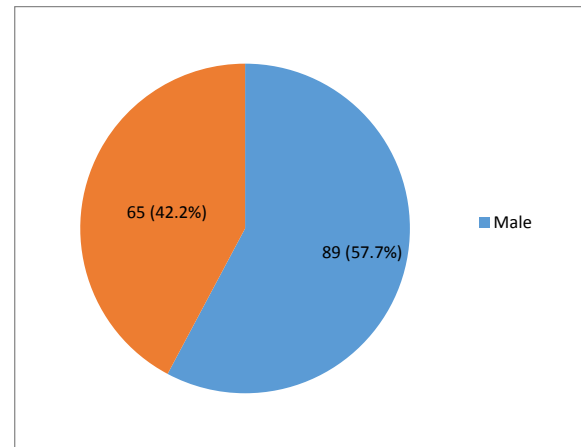


Figure1: Distribution of Gender

Table 1: Frequency of plasma leak in dengue fever

Category of leak	Pleural effusion only	Ascites only	Pleural effusion & ascites both	Total
	21 (13.6%)	18 (11.7%)	29 (18.8%)	68 (44.2%)

Table 2: Frequency of plasma leak with & without complications of dengue fever

Category of complication	Without complications	Hemorrhage	Hepatitis ALT>2ULN	Shock
Frequency of plasma leak	1 (1.6%)	17 (54.8%)	38 (48.1%)	5 (83.3%)
Number of patients	61	31	79	6

ALT-Alanine aminotransferase, ULN-upper limit of normal

Eighty-six (55.9%) of the patients were having hemoconcentration according to the mentioned criteria. The frequency of plasma leak which could be detected through ultrasound and X ray chest in these patients was 73.3% (n=63/86).

**DISCUSSION**

Though small number of patients with dengue fever may become complicated like dengue hemorrhage and dengue shock but may be responsible for significant number of morbidities and mortalities. The exact frequency of dengue complications may be difficult to find out because of many patients with mild symptoms who may not present to the hospitals at all. Since this study was performed in the hospitalized patients therefore the actual frequency of plasma leak in all dengue fever patients may be lower than the frequency in hospitalized patients. Ultrasound can detect the plasma leakage as ascites and pleural effusion in earlier phase with positive likelihood ratio 2.14 (95% CI 1.12 – 4.12).<sup>14</sup> We also used ultrasound as the main investigation for detecting plasma leak in the form of pleural effusion or ascites.

Since plasma leak may be an important clinical sign which is associated with these complications and can be easily detected through clinical examination or ultrasound of the chest and abdomen, therefore this study aimed at finding out the frequency of plasma leak in the hospitalized patients with dengue fever. Some studies included gall bladder thickening in addition to ascites and pleural effusion as evidence of plasma leak.<sup>15</sup> Suwanto et al in 2016 used ascites and pleural effusion as indicators of plasma leak in dengue patients.<sup>16</sup> In our study, we also included ascites and pleural effusion detected on ultrasound and X ray chest as evidences for plasma leak.

The systemic review of 15 studies recruiting 15794 patients reported the frequency of plasma leak as 36.8% and is one of the important clinical predictor or indicator of underlying serious dengue fever complications.<sup>17</sup> The same study reports the frequency of plasma leak in dengue hemorrhagic fever as 45.7%. Our study reports the frequency of plasma leak as evident by ascites or pleural effusion in the hospitalized patients with dengue

fever as 44.2% (n=68) while the frequency in the patients with hemorrhage was 51.6% (n=16/31). A study from Thailand on 667 dengue patients reported a plasma leak of 47.7% in the dengue fever patients.<sup>8</sup> Similar results were found by other study.<sup>18-21</sup>

There are many studies on frequency of plasma leak in symptomatic and hospitalized patients.<sup>18-22</sup> Unfortunately, many patients might be either asymptomatic or with minor symptoms who might not have presented to the hospital and so the actual percentage of plasma leak may be even lower than mentioned in the literature. In our study we found that 55.9% (n=86) of the patients were fulfilling the criteria of hemoconcentration. Out of these patients 73.3% (n=63) were having ultrasonic evidence of plasma leak as either pleural effusion, ascites or both. If we consider hemoconcentration as an indicator of plasma leak,<sup>13</sup> then ultrasound and X-ray chest can detect 73.3% of the overall plasma leak. But some other reasons may be responsible for hemoconcentration in some patients like dehydration due to persistent vomiting.

Being a single center study conducted on a relatively small sample size, our findings need further verification. Further prospective trials should be conducted to report outcomes among patients of dengue fever with plasma leakage.

**CONCLUSION**

Plasma leak is an important clinical and ultrasonographic sign which can be easily detected in low cost health facilities. The frequency of plasma leak was higher in complicated dengue fever patients as compared to patients with less or no complications. Ultrasonography and X ray chest can detect plasma leak as pleural effusion or ascites in 73.3% of the patients with hemoconcentration.

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