Frequency of Capillary leak syndrome in Dengue fever Patients
Safina Hameed Qureshi¹, Sania Hameed Qureshi², Syed Fahd Shah³, Farid Ullah Shah⁴, Syed Hussain Shah⁵, Syed Zubair Shah⁶

¹² Senior Registrar, Department of Medicine, Federal Government Poly Clinic Hospital, Islamabad. ³ Associate Professor, Department of Surgery, Federal General Hospital, Islamabad. ⁴ Consultant Physician, Federal Government Poly Clinic Hospital, Islamabad. ⁵ Assistant Professor, Department of Rehabilitation Medicine, Combined Military Hospital, Lahore. ⁶ Professor, Department of Paediatrics, Combined Military Hospital, Lahore.

Author’s Contribution
1 Conception of study 2.4 Experimentation/Study conduction 2 Analysis/Interpretation/Discussion 3 Manuscript Writing 5.6 Critical Review 4 Facilitation and Material analysis

Corresponding Author
Dr. Sania Hameed Qureshi, Senior Registrar, Department of Medicine, Federal Government Poly Clinic Hospital, Islamabad. Email: drsaniaqureshi@gmail.com

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Abstract

Introduction: Dengue is a viral disease and it is spread to the world by mosquitos. It is now common in many parts of the world. The severe form of dengue fever with bleeding manifestations is called dengue hemorrhagic fever. Some of the Dengue fever patients developed a capillary leak during a critical period of illness. This study aims at determining the frequency of capillary leaks in admitted dengue fever patients in tertiary care hospitals.

Materials and Methods: The study was conducted over a period of one month from 1st October to 30th October 2019 at the department of Medicine Federal Government Polyclinic Post Graduate Medical Institute, Islamabad. This cross-sectional study comprised of 200 consecutive hospitalized (≥14 years of both gender) dengue fever patients.

Results: Capillary leak syndrome was found in 75 patients with Dengue fever. All of them were Primary Dengue Patients. Both ascites and effusion were present in 31 patients. Ascites were only found in 25 patients, Pleural effusion bilateral in 7, Right-sided pleural effusion in 11, and Left-sided in 1 patient.

Conclusion: It is concluded that capillary leak syndrome is common in dengue patients and its early diagnosis helps us in better management during a critical phase of illness with a better outcome.

Keywords: Dengue Fever, Capillary Leak Syndrome, Dengue Shock.
Introduction

Dengue is a vector-borne viral human disease across the tropical and sub-tropical regions of the world. Dengue virus is transmitted from one person to another person by the bite of female Aedes aegypti and Aedes albopictus.¹ Dengue is present worldwide with almost 128 countries are known to have dengue outbreaks. About 390 million cases occur per year.² Pakistan is a subtropical country having all four serotypes. Dengue can be throughout the year but an outbreak occurs between the summer to autumn season especially after the monsoon.³ Dengue epidemic is a major public threat since 2005 following millions of people at risk. During the current year, 2019 over 25,000 dengue cases have been confirmed from across the country.⁴ There are three phases of dengue fever illness phase I is the phase of febrile illness followed by the critical phase and then there is a recovery. Patients who don’t develop increased capillary permeability in transition from febrile to afebrile phase usually get better and do not enter into the critical phase.⁵ The severity of capillary leak may be different in different patients and severe permeability to plasma and fluids may cause dengue shock or pleural effusion. An increase in pleural effusion may cause increased respiratory distress which is a sign of severe dengue.⁶ This study is only confined to those dengue patients who had capillary leak syndrome in the critical phase of dengue.

Capillary leak syndrome is one of the big problems of severe dengue. The main features of the capillary syndrome are hemoconcentration, hypoalbuminemia, pleural effusion, ascites, and pericardial effusion. Anasarca is not a characteristic of capillary leak syndrome. Capillary leak syndrome is the main pathological factor resulting in dengue shock syndrome and dengue haemorrhagic fever. The Hematocrit in this condition is usually >40% but maybe as high as 55-60%.⁷ This increase in hematocrit is because of increased leakiness to plasma in the late stage of the febrile phase and after the setting of pyrexia may remain for 24 hours to 48 hours.

Timely identification of capillary leak syndrome is important for prompt fluid replacement and indicated progression to dengue shock syndrome. The present study conducted on dengue fever patients is an attempt to describe capillary leak syndrome who were admitted.

Materials and Methods

The study was conducted at Department of Medicine, Government Polyclinic Post Graduate Medical Institute, Islamabad for the period of one month from 1st October to 30th October 2019 during an epidemic outbreak of Dengue fever in Pakistan. It included 200 consecutive confirmed dengue patients (≥14 years of both genders) who were hospitalized for management for dengue fever. Out of the total of 200 patients with Dengue fever, capillary leak syndrome was found in 75 patients. We included these 75 patients with capillary leak syndrome in this study. All these patients had a critical phase of dengue fever. Demographic data, primary or secondary dengue, dengue test report, hematocrit, platelet counts, serum albumin, chest X-ray, ultrasonography chest and abdomen data were collected and recorded on specially designed proforma.

Laboratory diagnosis methods for dengue fever include detection of dengue NS1 antigen and antibodies (IgM/IgG) or both. Primary dengue fever was diagnosed in cases that had either positive NS1 antigen or IgM antibodies or both. Secondary dengue fever was diagnosed if the patient had a positive NS1 antigen or IgM antibodies along with IgG antibodies or the presence of all three (NS1 antigen, IgM, and IgG antibodies). All patients with Dengue fever were followed for capillary leakage and other complications by physical examination and laboratory tests (including complete blood count, biochemistry, and ultrasonography of abdomen and pleural cavities.

All data were entered on a structured proforma and data was analyzed on SPSS version 21.

Results

Out of 200 patients with Dengue fever, 75(37.5%) had capillary leak syndrome. Males were 47(62.6%) and 28(37.3%) were females. The median age, age range, and male to female ratio are shown in Figure 1. The tests results for NS1, IgM, and IgG antibodies are shown in Table 2. All 75 patients (100%) were presented with dengue fever for the first time and no patient presented with dengue fever the second time. Hematocrit > 37.5% in 49(65.3%) patients and >50% in 7(9.3%) patients. Hypoalbuminemia was seen in 64(85.3%) patients. Mild thrombocytopenia in 6(8%), moderate in 13(17.3%), and severe in 56(74.6%) patients. Detail of Plasma leaks in different sites and polyserositis (31 (41.3%) are detailed in Table-3.
Ascites were present in 25 (33.3%) patients and pleural effusion was present in 19 (25.3%) patients with 11 (14.6%) cases having right-sided, 7 (9.3%) cases having bilateral and only 1 (1.3%) cases had isolated left-sided pleural effusion. There was no mortality in our study.

As hypoalbuminemia is generally not present and plasma leak is difficult to recognize that’s why it is difficult to predict that those with dengue fever may have severe complications. In our study Hematocrit level of more than 37.5 was seen in 49 (65.3%) cases. Hypoalbuminemia is moderate to severe in 46 (61.3%) patients. Ultrasound can be used to see even a little amount of pleural effusion and ascites thus helping in detecting a capillary leak. It is 100% accurate and 2009 WHO Guidelines recommend Ultrasound as a good tool for capillary leak syndrome assessment. Thus Ultrasound is better than hematocrit and hypoalbuminemia to assess the presence of capillary leak syndrome early in adult dengue patients. In our study 75 patients were reported to have capillary leak syndrome.

According to WHO Guidelines 2009 describes severe dengue is a shock, severe bleeding, organ failure, or respiratory failure due to leakage of plasma. Many studies had demonstrated the prevalence of capillary leakage on ultrasound from 34% to 100%. In our study 75 cases (37.5%) out of 200 dengue hemorrhagic fever patients had a capillary leak on ultrasound. In this study of 75 cases of capillary leak syndrome, all of them had primary dengue fever (100%). Capillary leak syndrome is as frequently seen in primary as well as in secondary dengue fever. The underlying mechanism of capillary leakage syndrome in dengue fever is not fully understood yet.

Previously the concept was that the most severe features of dengue develop in individuals who had the previous infection of dengue with any of the strains. Second-time infection with another strain results in a low level of antibodies, these antibodies instead of removing the virus form an antigen-antibody complex. This causes an increase in virus entry into white cells and results in enormous replication of virus which activates many folds in cytokine synthesis and activation of complement factors. The vasoactive factors produced by the macrophages lead to many fold rise in vascular permeability causing leakage of plasma, decrease in circulating volume, and shock. Meltzer et al noted that secondary infection is not mandatory to develop capillary leak syndrome and the

### Table 1: Laboratory Result

<table>
<thead>
<tr>
<th>Dengue Serology</th>
<th>NS1</th>
<th>IgM</th>
<th>IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>37.5-40.0</td>
<td>50.1-60.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>07</td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>3.5-3.0</td>
<td>2.9-2.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>08</td>
<td></td>
</tr>
<tr>
<td>Platelet count (x10^3/cm mm)</td>
<td>&lt;20</td>
<td>20-50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Site of Capillary Leak

<table>
<thead>
<tr>
<th>Type of capillary leak</th>
<th>No. of cases (%) (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites + Pleural effusion</td>
<td>31 (41.3%)</td>
</tr>
<tr>
<td>Ascites only</td>
<td>25 (33.3%)</td>
</tr>
<tr>
<td>Isolated right sided pleural effusion</td>
<td>11 (14.6%)</td>
</tr>
<tr>
<td>Isolated left sided pleural effusion</td>
<td>01 (1.33%)</td>
</tr>
<tr>
<td>Bilateral pleural effusion</td>
<td>07 (9.33%)</td>
</tr>
</tbody>
</table>

### Discussion

Dengue fever varies in severity and it can present just as febrile illness or with severe dengue fever disease. Plasma leak which starts at the end stage of febrile illness and it may lead to dengue shock is characteristic of severe disease. Capillary leak syndrome is a more common severe complication of dengue fever as compared to other feared complications which cause a lot of panic and distress such as severe bleeding and organ impairment. Hematocrit ≥20%, hematocrit≤20% after fluid replacement and features such as pleural effusion, ascites, and hypoproteinemia are the hallmark of capillary leak syndrome. As hypoalbuminemia is generally not present and plasma leak is difficult to recognize that’s why it is difficult to predict that those with dengue fever may have severe complications.

In our study Hematocrit level of more than 37.5 was seen in 49 (65.3%) cases. Hypoalbuminemia is moderate to severe in 46 (61.3%) patients. Ultrasound can be used to see even a little amount of pleural effusion and ascites thus helping in detecting a capillary leak. It is 100% accurate and 2009 WHO Guidelines recommend Ultrasound as a good tool for capillary leak syndrome assessment. Thus Ultrasound is better than hematocrit and hypoalbuminemia to assess the presence of capillary leak syndrome early in adult dengue patients. In our study 75 patients were reported to have capillary leak syndrome.

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### Figure 1: Age Wise Presentation (n=75)
risk of severe disease may not be increased by secondary infection. In our study we have noted that it is not necessary that patients must have secondary dengue infection to develop the capillary leak syndrome or severe dengue infection. The idea that secondary infection leads to an enhanced immune response which in turn causes capillary leakage in dengue fever needs further evaluation. In the capillary leak, syndrome fluid was collected at multiple sites. In this study, Polyserositis was present in 31(41.3%) patients, followed by ascites in 25(33.3%), pleural effusion in 19(25.3%) patients. The accumulated fluid was mild to moderate in present cases are referred for management this may cause selection bias. Secondly, a further study is needed on a larger sample conducted at multiple centers to validate our result.

We had some limitations in our study. As this study was conducted in a tertiary care hospital where severe cases are referred for management this may cause selection bias. Secondly, a further study is needed on a larger sample conducted at multiple centers to validate our result.

## Conclusion

One of the most important things for the clinician is to recognize those patients who may progress to severe disease, so time management and hydration stop the progression of dengue fever to severe dengue fever and its complications. Early ultrasonography for capillary leak syndrome is suggested in severe dengue patients. Capillary leakage in primary dengue is as common as in secondary dengue fever.

## References