Original Article

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Pulmonary Manifestations of Dengue Fever at a Tertiary Care Centre in Northern India: A Cross-sectional Study

Internal Medicine Section

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ABSTRACT

Introduction: Dengue Fever (DF) is associated with systemic inflammation, clinically manifesting as involvement of different organ systems, including the pulmonary system. Pulmonary involvement is characterised by pleural effusion, pneumonia, haemoptysis, pulmonary haemorrhage, secondary bacterial infections with Acute Respiratory Distress Syndrome (ARDS), and Dengue Haemorrhagic Shock Syndrome (DHSS), which are the leading causes of mortality and morbidity.

Aim: This study aims to analyse the pleuropulmonary manifestations associated with DF.

Materials and Methods: This cross-sectional study was conducted at a tertiary care centre in northern India from June 2018 to November 2018. A total of 140 patients diagnosed with DF using Non-Structural protein 1 (NS1), Immunoglobulin (Ig)M, (Ig)G rapid card tests and confirmed by Enzyme-Linked Immunosorbent Assay (ELISA) were included. Patients were examined for pleuropulmonary manifestations and other systemic features. Baseline investigations, including Complete Blood Count (CBC), Haematocrit (Hct), Liver Function Test (LFT), Renal Function Test (RFT), chest X-ray (PA view), and High-Resolution Computed Tomography (HRCT) of the chest when required, were performed. Data analysis was carried out by using Statistical Package for Social Sciences (SPSS) version 25.0.

Results: A total of 140 patients (108 males and 32 females) aged between 18 and 35 years were included and analysed. Among them, 113 (81%) were diagnosed with uncomplicated febrile illness, 17 (12%) with Dengue Haemorrhagic Fever (DHF), and 10 (7%) as Dengue Shock Syndrome (DSS). Patients with co-morbidities, particularly respiratory system illnesses, and young patients were found to be at increased risk of morbidity. Pleuropulmonary manifestations observed in the study included pleural effusion, pneumonia, pulmonary haemorrhage, ARDS, and pneumothorax.

Conclusion: DF is associated with the involvement of the pulmonary system, and its incidence is increased in cases of moderate to severe disease. Therefore, pleuropulmonary manifestations can be useful in evaluating the severity of DF cases.

Keywords: Dengue shock syndrome, Haemorrhage, Oedema, Pneumonia, Shock

INTRODUCTION

Dengue Fever (DF) is a self-limiting mosquito-transmitted acute febrile illness caused by an arbovirus (genus flavivirus). It is clinically characterised by a spectrum that varies between asymptomatic and severe disease states with fatal complications. All four serotypes of the dengue virus can cause the disease, which varies from mild self-limiting to severe forms such as DHF or DSS. Dengue viral infections represent a significant healthcare problem in tropical and sub-tropical regions worldwide. The World Health Organisation (WHO) estimates that there are about 50-100 million dengue cases with approximately 22,000 deaths each year [1,2]. The epidemic trend in India is on the rise, and all four serotypes are found in the country. Symptomatic dengue virus infections are grouped into categories: 1) undifferentiated fever; 2) DF; 3) DHF; and 4) expanded dengue syndrome [3].

Most cases are self-limiting and present as non-specific febrile illnesses. Severe forms such as DHF and DSS are associated with systemic manifestations that involve almost every body organ. Severe forms are characterised by immune activation and increased levels of Tumour Necrosis Factor (TNF), Interleukin 8 (IL-8), and other mediators of inflammation, and endothelium being the target of immunopathological mechanisms.

These mechanisms lead to varied systemic manifestations, including those in the pulmonary system. DHF is associated with ARDS, with dengue virus antigen lining the alveolar epithelial cells. Increased vascular permeability is associated with interstitial oedema, leading to pulmonary dysfunction. Pulmonary haemorrhage is found to be associated with or without haemoptysis. Pleural effusion and ascites are attributed to plasma leakage, increased vascular permeability, and haemostatic dysfunction, and they can also be influenced by co-morbid conditions involving the pulmonary system [3-5]. Thus, the aim of the present study was to analyse the pleuro-pulmonary manifestations in patients with DF.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Department of Internal Medicine, Pt. BDS PGIMS Rohtak, Haryana, India, from June 2018 to November 2018, for a duration of six months. A total of 140 patients admitted to the medicine wards with complaints of fever and thrombocytopenia, subsequently diagnosed as cases of DF, were enrolled after obtaining proper consent from the patients and receiving due consideration and approval from the Ethical Committee (IEC/18/623). The sample size was calculated using an online sample size calculator at clincalc.com, with final sample size of 135.

Inclusion criteria: Patients above 18 years of age, diagnosed with DF based on NS1, IgG/IgM (rapid card test), and confirmed by ELISA (IgG and IgM).

Exclusion criteria: Patients below 18 years of age, febrile thrombocytopenia, and bleeding manifestations due to other causes were excluded from the study.

A total of 163 patients were initially enrolled, out of which 23 patients were excluded for not meeting the inclusion criteria. Finally, 140 patients were included in this study.

Procedure

Patients admitted to the hospital, after fulfilling the mentioned criteria, were enrolled in the study. A detailed history was recorded, including the patient's demographic profile, any previous co-morbidities, duration of febrile illness, headache, retro-orbital pain, backache, abdominal pain, nausea, cough with haemoptysis, myalgia, and rashes. A complete physical and systemic examination was done to evaluate systemic involvement. Blood samples were taken for Complete Haemogram (CH), Total Leukocyte Count (TLC)/Differential Leukocyte Count (DLC), Haematocrit (Hct), Absolute Platelet Count (APC), Bleeding Time (BT), Clotting Time (CT), Prothrombin Time (PT) (to rule out any bleeding disorders), LFT, RFT, serum electrolytes, and complete urine examination. Imaging studies included a chest X-ray for every patient, abdominal Ultrasonography (USG), and High-Resolution Computed Tomography (HRCT) of the chest as and when required. Serology included NS1, IgG, and IgM by rapid card test, with confirmation by ELISA. The collected data were evaluated using appropriate statistical tests.

STATISTICAL ANALYSIS

Data analysis was carried out using SPSS (IBM version 25.0). Clinical and laboratory parameter data were expressed in numbers and percentages.

RESULTS

This study included 140 patients, with 108 males and 32 females, resulting in an M:F ratio of 2.86 [Table/Fig-1]. According to the Traditional WHO classification (1997), there were 121 cases of DF, 15 cases of DHF, and four cases of DSS. The highest number of cases was observed in the 18-35 years age group for both males and females. The lowest number of cases was found in the age group >55 years (25%). The study included 93 (66.43%) patients from rural areas and 47 (33.57%) from urban areas [Table/Fig-1]. Out of the 140 patients, 113 (80.72%) were diagnosed with DF, 17 (12.14%) presented with haemorrhagic manifestations, and 10 (7.14%) presented with DSS [Table/Fig-2]. The most common presenting features included fever (100%), body aches (79.28%), abdominal pain (65%), arthralgia (64.28%), vomiting and nausea (59.28%), retro-orbital pain (49.28%), rashes (40.71%), bleeding (20.71%), and jaundice (13.57%) [Table/Fig-3]. Among the 140 patients, 40 (28.57%) had hypertension, five had diabetes mellitus, six patients with chronic kidney disease, five had chronic liver disease, four had chronic pulmonary diseases, and three had chronic cardiac diseases [Table/Fig-4].

S. No.	Demographic details of all participants	Frequency (n)	Percentages (%)
1.	**Gender**		
	Male	108	77.14
	Female	32	22.86
2.	**Age group (years)**		
	18-35	68	48.60
	36-55	37	26.40
	>55	35	25.00
3.	**Locality**		
	Rural	93	66.43
	Urban	47	33.57

[Table/Fig-1]: Demographic Details of all study participants (Total N=140).

S. No.	Clinical presentation	N (140)	%
1	Dengue Fever (DF)	113	81%
2	Dengue Haemorrhagic Fever (DHF)	17	12%
3	Dengue Shock Syndrome (DSS)	10	7%

[Table/Fig-2]: Clinical presentation of all study participants.

S. No.	Clinical symptoms	N (140)	%
1	Fever	140	100
2	Body ache	111	79.28
3	Arthralgia	90	64.28
4	Pain abdomen	91	65
5	Nausea/Vomiting	83	59.28
6	Retro orbital pain	69	49.28
7	Rashes	57	40.71
8	Jaundice	19	13.57
9	Cough	55	39.28
10	Haemoptysis	41	29.28
11	Hypotension	27	19.28
12	Bleeding manifestations	29	20.71

[Table/Fig-3]: Clinical symptoms as observed in all study participants.

S. No.	Co-morbidities	N (140)	%
1	Diabetes	5	3.57
2	Hypertension	40	28.57
3	Chronic kidney diseases	6	4.28
4	Chronic liver diseases	5	3.57
5	Chronic pulmonary diseases	4	2.85
6	Chronic cardiac diseases	3	2.14

[Table/Fig-4]: Co-morbidities details of the study participants.

A total of 113 cases were diagnosed as dengue cases with mild systemic involvement, 17 with DHF, and 10 with DSS. The most common pleuropulmonary manifestation was pleural effusion (28.57%), followed by pneumonia (11.42%), ARDS (8.57%), and DSS with lung involvement in 7.14 cases. Pleural effusion was the most common complication among pleuropulmonary complications, observed in 40 (28.57%) patients, followed by pneumonia in 16 (11.42%) patients, ARDS in 12 (8.57%) patients, and pneumothorax in one patient [Table/Fig-5].

S. No.	Pleuro-pulmonary complication	N (140)	%
1	Pleural Effusion (PE)	40	28.56
	Unilateral PE	27	19.28
	Bilateral PE	13	9.28
2	Pneumonia	16	11.42
	Atypical Pneumonia	9	6.42
	Secondary pneumonia	7	5
3	ARDS	12	8.57
4	Pneumothorax	1	0.71

[Table/Fig-5]: Pleuropulmonary complication detected amongst all study participants.

Regarding haematological findings, 85% of patients had a platelet count below 150,000, with 30 patients requiring platelet transfusion. 53 patients had leukopenia, and 44% showed an increase in Hct [Table/Fig-6]. Out of the total patients, 99 (71.71%) were having positive for NS1Ag, 25 (17.85%) showed IgM positivity, and 16 (11.42%) were positive for both antigen and antibody [Table/Fig-7].

S. No.	Haematological feature (platelets/cumm)	N (140)	%
1	<20000	19	13.51
2	20000-50000	22	15.71
3	50000-100000	65	46.42
4	100000-150000	15	10.71
5	>150000	19	13.57

[Table/Fig-6]: Haematological features.

Among the patients, 40 (28.57%) patients were having pleural effusion, 16 (11.42%) had pneumonia, 12 (8.57%) were having

S. No.	Serology (Positivity)	N (140)	%
1	Ns1Ag	99	71.71
2	IgM	25	17.85
3	IgM/IgG and Ns1Ag	16	11.42

[Table/Fig-7]: Serology.

ARDS pattern on X-ray, and only one patient had pneumothorax [Table/Fig-8]. HRCT was performed on 30 patients, which showed pleural effusion in all 30 patients, pneumonia in 16 (53.33%) patients, an ARDS pattern in 12 (40%) patients, pneumothorax in two patients, and pulmonary haemorrhage in one patient [Table/Fig-9].

S. No.	Chest X-ray (N=140)	N (140)	%
1	Pleural effusion	40	28.57
2	Pneumonia	16	11.42
3	ARDS	12	8.57
4	Pneumothorax	1	0.71

[Table/Fig-8]: Chest X-ray.

S. No.	HRCT chest	N (=30)	%
1	Pleural effusion	30	100
2	Pneumonia	16	53.33
3	ARDS	12	40
4	Pneumothorax	2	6.66
5	Pulmonary haemorrhage	1	3.33

[Table/Fig-9]: HRCT chest.

The clinical features of DF, including fever, body ache, arthralgia, abdominal pain, nausea, and vomiting, were observed in patients with pleuropulmonary complications. Patients with respiratory symptoms such as cough, haemoptysis, and shortness of breath were treated with supplementary oxygen, ventilator support, and conservative medical management.

DISCUSSION

Dengue, an acute febrile illness caused by the flavivirus and primarily occurring in tropical and subtropical regions, is a significant health problem. It is now endemic in more than 100 countries worldwide [5]. In recent years, there has been an emerging trend of the disease, resulting in a major health issue in South-East Asia, including India. The WHO guidelines from 2009 categorise patients with DF into non-severe and severe forms. The non-severe form is further divided into two groups based on the presence or absence of warning signs [1,2]. The non-severe form without warning signs includes patients who live in endemic areas or have a travel history to endemic areas and present with fever and at least two of the following clinical features: vomiting, nausea, body aches, rash, leukopenia, and a positive tourniquet test [2]. The non-severe form with warning signs includes patients with the aforementioned features plus persistent vomiting, abdominal pain, tiredness, third space fluid collection (pleural effusion and ascites), bleeding (mucosal), restlessness, lethargy, hepatomegaly (>2 cm), and increased hematocrit with a rapid decrease in platelet count. The severe form of the disease is described as having one of the following clinical features: shock due to severe plasma leak, with or without fluid accumulation, respiratory distress, severe bleeding, or systemic organ involvement [1-3].

DF is characterised by systemic inflammation, manifesting as systemic involvement that affects almost every organ system. While DF can occur in all age groups, there is an increased incidence in the younger age group (18-30 years), with a higher prevalence in males. Clinical manifestations of systemic involvement include fever, body aches, myalgias (with varying incidence), headache, arthralgias, retro-orbital pain, nausea with abdominal pain, jaundice, and haemorrhagic manifestations include petechiae, epistaxis, hematuria, melena, and internal bleeding. Organ dysfunction may also occur depending on the extent of involvement [6]. Dyspnoea may be attributed to pleural effusion (commonly), ARDS, pulmonary haemorrhage, pneumonia, and shock. The present study aimed to evaluate the pleuropulmonary manifestations, as well as associated systemic involvement.

In the present study, DF was found to be more prevalent in the younger and productive age group, with a higher incidence in males, as they are more commonly exposed to the vector. The clinical presentation of DF correlated with laboratory parameters such as TLC, platelet count, leukopenia, Hct, and serology, which were consistent with various studies reported in the literature [4,5,7].

The severity of Pleural Effusion (PE) varied from unilateral to bilateral, ranging from mild and asymptomatic to massive bilateral effusion requiring therapeutic tap and diuretics. The severity of pleural effusion correlated with capillary leak, decrease in platelet count, increased vascular permeability, hypoalbuminemia, and associated complications as ARDS/DHSS [8]. Pleural effusion is usually mild and considered a transudate, but when significant, it is considered a sign of severe disease and impending complications, including ARDS, DHF, and DHSS. In severe cases, hemothorax has also been reported. Diagnostic modalities for detecting and evaluating pleural effusion include chest X-ray, Ultrasonography (USG), HRCT of the chest, and biochemical and cytological analysis of pleural fluid, with predominantly transudate on biochemical analysis [7-9].

Pleuropulmonary manifestations of DF include pleural effusion, pneumonia (including primary viral pneumonitis and secondary bacterial infections), pulmonary haemorrhage (with or without haemoptysis), non-cardiogenic pulmonary oedema, and ARDS in severe cases [10,11]. Pleural effusion was the most common pleuropulmonary complication observed in the present study.

Pneumonia was the second most common respiratory complication observed, with clinical presentation and chest X-ray and HRCT findings consistent with secondary bacterial infection [12]. Dengue is not known to cause primary pneumonia, but inflammation of the lung parenchyma leads to plasma leakage and leukopenia, which predisposes to secondary bacterial infections and complicates

the natural course of the disease, particularly in patients with severe disease and comorbid conditions [6]. Secondary infections can manifest as pneumonia, bacteremia, and bacteriuria, with Staphylococcus aureus and mycoplasma, along with influenza viral infections, complicating the course of DF [9,13]. In the present study, pneumonia was observed in 11% of the cohort, with varying incidence reported in the literature. Secondary infections, including pneumonia, should be suspected when prolonged fever, suppressed Total Leukocyte Count (TLC), and progression of the disease to a severe form are observed.

Prompt evaluation for secondary infections, including pneumonia, should be done through sputum examination and culture, as well as blood and urine culture, along with imaging studies. Prompt antibiotic therapy should be instituted. Cough, haemoptysis, and dyspnoea were also observed as significant respiratory manifestations and precursors of severe life-threatening complications such as ARDS and DHSS. Patients with ARDS were found to have associated complications such as Gastrointestinal Tract (GIT) bleeding, petechiae, epistaxis, and secondary bacterial infections, as low platelet count and sepsis are reported as precursors of ARDS in patients with DF. ARDS was observed in 12 (8.57%) cases in the present study [5,9,13].

In dengue-endemic areas, Dengue Haemorrhagic Shock Syndrome (DHSS) is reported as the leading cause of ARDS. The main cause of pleuropulmonary manifestations has been attributed to thrombocytopenia and capillary leak syndrome. Atypical presentations, such as cholecystitis and ARDS, sometimes complicate management, as ARDS can develop rapidly and increase mortality and morbidity. Prognostic factors described in the literature include age, co-morbid conditions, coagulopathy, and transaminitis [9,12,14]. Dengue virus is detected in pulmonary endothelial cells and macrophages, and histopathological findings in fatal cases show haemorrhage and interstitial pneumonitis [9].

There is infiltration of the lung parenchyma with mononuclear cells and hyperplasia of alveolar macrophages, with hyaline membrane formation and hypertrophy of type II pneumocytes. Clinically, ARDS does not differ from the classical presentation, with symptoms including hypoxia, respiratory distress, suppression of Total Leukocyte Count (TLC), and an altered alveolar-arterial oxygen gradient. Progression to the severe form characterises the clinical picture [10,13].

Dengue Haemorrhagic Fever (DHF) is clinically characterised by increased capillary permeability resulting in fluid extravasation, haemostatic abnormalities with decreased platelet count, and haemorrhagic manifestations. Major haemorrhage in severe cases is associated with shock, sometimes refractory, leading to DSS, in present study, DHF was observed in 21 (15%) patients. The development of DHF involves a complex interplay of the virus, immune response, and intrinsic host factors. Clinically, DHF is characterised by dyspnoea, haemoptysis, and hypotension. Imaging studies, especially HRCT of the chest, reveal thickening of interlobar septa, Ground-glass Opacities (GGO), poorly defined small nodules, and features of Diffuse Alveolar Haemorrhage (DAH) in severe cases. Although DAH is infrequently reported as a complication of DF, it is a known complication. The incidence of DAH reported in the literature is 1.4%, and two patients (1.42%) in this study were observed to have DAH [9].

Alveolar haemorrhage is attributed to multiple factors, including low platelet count with platelet dysfunction, coagulation abnormalities, capillary dysfunction, and Disseminated Intravascular Coagulation (DIC). The classical triad described in Diffuse Alveolar Haemorrhage (DAH) includes haemoptysis, a rapid fall in hemoglobin levels over a period of 24-48 hours, and the appearance of new pulmonary infiltrates on imaging. DSS usually develops when patients have prolonged hypotension and severe plasma leakage, with a higher incidence of ARDS than in patients with DHF alone. Pneumothorax is rare in dengue fever, with only a few case reports described. Pneumothorax can be due to the exacerbation of underlying chronic pulmonary disease or complications associated with mechanical ventilation [13]. Cough, with or without expectoration, and haemoptysis are important clinical manifestations in patients with respiratory system involvement. These symptoms are attributed to interstitial oedema, haemostatic dysfunction, and secondary infections. Dyspnea is due to pulmonary parenchymal inflammation, oedema, exacerbation of underlying comorbid conditions, and complications including ARDS, pulmonary haemorrhage, and congestive heart failure. At times, ascites can also contribute to dyspnoea. In patients with undifferentiated fever and unexplained dyspnoea, along with haemoptysis and pulmonary infiltrates on imaging, dengue fever should be considered as a differential diagnosis.

Imaging studies, such as chest X-ray, usually reveal pleural effusion with or without pneumonitis as a common finding. Areas of consolidation can be patchy and bilateral, with features of ARDS in severe cases. HRCT of the chest is being used to assess the severity and complications, which include pleural effusion and lung parenchymal involvement, such as consolidation with air bronchograms, multifocal Ground-glass Opacities (GGO), pleural effusion with interlobar septal thickening and a crazy-paving pattern, and findings of alveolar haemorrhage in severe cases [12,14]. Complications associated with dengue fever significantly correlate with a fall in platelet count as a marker of disease progression and impending respiratory system complications [10-13].

Pleuropulmonary complications, though less common in non-severe cases of dengue fever, commonly complicate moderate to severe cases and pose challenges in management [8]. A high degree of clinical suspicion and early diagnosis are of utmost importance in order to decrease morbidity and mortality. Patients diagnosed with dengue fever, particularly moderate to severe cases, should be evaluated daily for systemic involvement, especially in the pulmonary system. While there is no specific treatment available for dengue fever, early detection of systemic complications and introduction of supportive treatment, including correction of abnormalities and proper monitoring, can significantly improve clinical outcomes [10,14].

Limitation(s)

Firstly, this study was conducted at a single centre, so a smaller number of patients were enrolled. Secondly, other systemic manifestations were not included in this study.

CONCLUSION(S)

Dengue Fever (DF) is associated with involvement of the pulmonary system, with pleural effusion being the most common manifestation. Other complications are also seen in the more severe forms of dengue, such as DSS and DHF, which can have a complicated course and can be fatal if not managed properly and in a timely manner. Additionally, pulmonary manifestations can serve as a useful clinical tool for assessing the severity of DF. Pleuropulmonary manifestations are a valuable clinical tool that correlates well with the severity of dengue.

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