Clinical Manifestations and Predictors of Thrombocytopenia in Hospitalized Adults with Dengue Fever

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Abstract

Background: India is one of the seven identified Southeast Asian countries reporting frequent outbreaks of dengue fever (DF). **Aims:** This study was to analyze clinical and laboratory profile and predictive markers of thrombocytopenia and length of hospital stay in DF. **Materials and Methods:** This record-based retrospective study conducted in a coastal district of Karnataka, South India, included all dengue cases in adults aged >18 years, admitted during period of January 2011 to December 2014. Multivariate logistic regression analysis was carried out to compute odds ratio (OR) and 95% confidence interval (CI) to assess independent associations of variables with low platelet count and longer duration of hospital stay. **Results:** Among 207 dengue immunoglobulin M (IgM) antibody confirmed cases (mean age of 36.94 ± 14.61 years), 143 (69.1%) were males and 64 were females. The mean duration of illness and hospital stay were 4.94 ± 3.58 days and 5.98 ± 2.58 days, respectively. Abdominal symptoms included nausea and vomiting (53.6%), abdominal pain (25.1%), and diarrhea (13.5%). Bleeding manifestations were seen in 24 (11.6%) cases and fluid accumulation was revealed in 18 (8.7%) cases. The mean platelet count was $110,159.42 \pm 68,397.32$ (cells/mm^3). Low platelet count on admission was associated with the presence of rash (OR = 0.43, 95% CI 0.23-0.81), high aspartate aminotransferase (AST) levels (OR = 3.14, 95% CI 1.58-6.23), high alanine aminotransferase (ALT) levels (OR = 2.91, 95% CI 1.55-5.47), and low albumin levels (OR = 4.48, 95% CI 1.02-19.75). The duration of hospital stay was associated with diarrhea (OR = 0.4, 95% CI 0.18-0.9), abdominal pain (OR = 0.52, 95% CI 0.27-1.00), ascites (OR = 0.26, 95% CI 0.09-0.69), and low hemoglobin (OR = 0.46, 95% CI 0.25-0.86) level on admission. **Conclusions:** Though thrombocytopenia on admission was associated with the presence of rash, high AST and ALT levels, and low albumin levels, it was not predictive of length of hospitalization. Duration of hospital stay was longer with the presence of diarrhea, abdominal pain, ascites, and low hemoglobin level on admission.

Keywords: Dengue fever, profile, thrombocytopenia

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Introduction

Dengue is the most rapidly spreading mosquito-borne viral disease with four serotypes. An estimated 50-100 million cases of dengue fever (DF) and about 250,000-500,000 cases of dengue hemorrhagic fever (DHF) occur every year.[1] In Southeast Asia, the average number of cases of DHF per year has increased from 10,000 in the 1950s to over 200,000 in the 1990s. Thus, dengue virus

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remains a major cause of morbidity and mortality in tropical areas.[2] Epidemic DF was common in Asia and Pacific region throughout the twentieth century.[3]

India is one of the seven identified Southeast Asian countries reporting frequent outbreaks of the disease, with case fatality rates as high as 3-5%.[4] There have been several outbreaks from rural areas of Karnataka, Haryana, and Maharashtra. Dengue has a wide spectrum of presentation ranging from fever to life-threatening hemorrhage and shock, often with an unpredictable outcome. The spectrum of clinical presentation is variable in different epidemics and in different age groups.[5-7] Though many previous studies have reported the clinical profile in dengue patients, studies focussing on predictors of thrombocytopenia and length of hospital stay are scarce from India and this region. This is important considering the burden of the disease during epidemics, its impact on hospital admissions, and the requirement of platelet transfusion.

The present study is conducted among confirmed dengue cases in adults aged >18 years to determine demographic, clinical, laboratory profile, and disease outcome at a tertiary center in South India. It also aims to analyze the predictors of thrombocytopenia and the length of hospital stay among admitted cases with DF.

Materials and Methods

This is a retrospective, record-based study conducted at a tertiary care hospital in South India. The institutional ethical clearance was obtained before the study. The demographic, clinical, and laboratory parameters were recorded in a predesigned pro forma. The study included all confirmed dengue cases in adults aged >18 years admitted during the period of January 2011 to December 2014. All standardized dengue enzyme linked immunosorbent assay (ELISA) immunoglobulin M (IgM) antibody positive (Panbio Kit, Australia) cases were included in the study. Those cases with dengue IgG antibody positivity alone were excluded. Cases of leptospirosis, malaria, and acute viral hepatitis were excluded by careful review of case records for history and examination findings suggestive of same or laboratory findings confirming these diagnoses. Those cases with coinfection from viral or other organisms were also excluded. Complete medical record of all such cases that included signs and symptoms, method of diagnosis, management, duration of stay, and clinical outcome were retrieved from the patient's information reports.

Laboratory investigations include hemoglobin test, total and differential white blood cell (WBC) count, platelet count, liver function tests [aspartate aminotransferase (AST), prothrombin time (PT), alanine aminotransferase (ALT), and serum albumin], serum electrolytes, renal function tests, and ultrasonography (USG) of abdomen. Thrombocytopenia was defined as a platelet count <150,000 cells/mm^3 blood. Similarly, leucopenia was defined as a white cell count <4,000 cells/mm^3. ALT was considered raised if >55 IU/L and >33 IU/L for males and females, respectively. AST was defined as raised if >46 IU/L and >32 IU/L for males and females, respectively. These patients were classified as DF, DHF, and dengue shock syndrome (DSS) as per the World Health Organization (WHO) criteria.[8] The diagnosis of DHF required all four criteria of fever, thrombocytopenia, bleeding, and plasma leakage (hypoproteinemia, 20% change in hematocrit, pleural effusion, or ascites).

Statistical analysis

Collected data were documented using Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corp., Armonk, NY, USA). Statistical analysis was done using descriptive statistics. Results were expressed as percentages, frequencies, and mean ± S.D. Multivariate logistic regression analysis was carried out to compute odds ratio (OR) and 95% confidence interval (CI) to assess the independent associations of the variables with low platelet count and longer duration of hospital stay.

Results

A total of 207 dengue IgM antibody confirmed cases >18 years of age were admitted during the period of January 2011 to December 2014. The mean age of the study group was 36.94 ± 14.61 years with 143 (69.1%) males and 64 (30.9%) females. Eighty-seven patients (42%) were in the age group of 18-30 years. The mean duration of illness was 4.94 ± 3.58 days. The mean duration of hospital stay was 5.98 ± 2.58 days [Table 1].

Bleeding manifestations were seen in 24 (11.6%) patients. The common bleeding manifestations were petechiae (16, 7.7%), gum bleeding (10, 4.8%), ecchymosis (9, 4.3%), malena (4, 1.9%), and subconjunctival hemorrhage (3, 1.4%). One patient expired in the study group. The interventions required included platelet transfusion (16, 7.7%), ventilator support (2, 0.9%), and hemodialysis (1, 0.5%).

Fever was present in all, followed by myalgia (64.7 %) and headache (61.8%). Abdominal symptoms included nausea and vomiting (53.6%), abdominal pain (25.1%), and diarrhea (13.5%). Other symptoms were lethargy (30.9%), retro-orbital pain (28.5%), rash (10.1%), and cough (3.4%) [Figure 1]. Ascites or fluid accumulation was revealed in 18 (8.7%) of cases, 13 (6.3%) had clinical jaundice, 14 (6.8%) had renal failure with serum creatinine level of >1.4 mg/dL and ARDS was seen in 2 (0.9%) cases [Figure 2].

The mean hemoglobin level and white blood cell counts were 13.89 ± 1.91 gm/dL and 4,745.41 ± 3,131.73 cells/mm³, respectively. The mean platelet count was 110,159.42 ± 68,397.32 cells/mm³. The mean AST and ALT values were 178.14 ± 295.04 IU/mL and 109.88 ± 138.13 IU/mL, respectively. Thirteen patients (6.3) were tested positive for IgG antibodies [Table 2].

Table 3 shows the association of low platelet count in DF with various clinical and laboratory parameters. Low platelet count on admission was associated with the presence of rash (OR 0.43, 95% CI: 0.23-0.81), high AST levels (OR 3.14, 95% CI: 1.58-6.23), high ALT levels (OR 2.91, 95% CI: 1.55-5.47), and low albumin levels (OR 4.48, 95% CI: 1.02-19.75). Table 4 shows that the duration of hospital stay was associated with presence of diarrhea (OR 0.4, 95% CI: 0.18-0.9), presence of abdominal pain (OR 0.52, 95% CI: 0.27-1.00), presence of ascites (OR 0.26, 95% CI: 0.09-0.69), and low hemoglobin on admission (OR 0.46, 95% CI: 0.25-0.86).

Discussion

Of 207 cases included in this study who were admitted in the hospital, (mean age 36.94 ± 14.61 years) 143 (69.1%) were males and 64 were females. Eighty-seven patients (42%) were in the age group of 18-30 years. In a study conducted in Lahore, 70% were males (mean age was 36 years) and 30% of the cases were between 20 years and 29 years.[9] In another study conducted at South India, 64.6% were males and 57.5% were in the age group of 15-44 years.[4] Other studies also highlighted that it is more common in males and young individuals.[10,11] Thus, the disease affects the young people, mostly males, which may be because they are more often outdoors and working.

Along with fever, myalgia and headache, abdominal symptoms dominated in the study group. They included nausea and vomiting (53.6%), abdominal pain (25.1%), and diarrhea (13.5%). This is because of liver involvement and fluid accumulation in the peritoneal cavity. Hepatomegaly was present in 25 cases (12.1%) and splenomegaly in 16 (7.7%) cases. Similarly, fever, headache, bleeding, abdominal symptoms, and rash were common symptoms seen in earlier studies.[4,7,9,12] Fever with gastrointestinal symptoms is seen in tropical countries with infections such as typhoid, leptospirosis, enteroviral infections, and may often lead to a delay in the diagnosis of dengue. Presence of rash, petechiae, and bleeding tendency along with headache or retro-
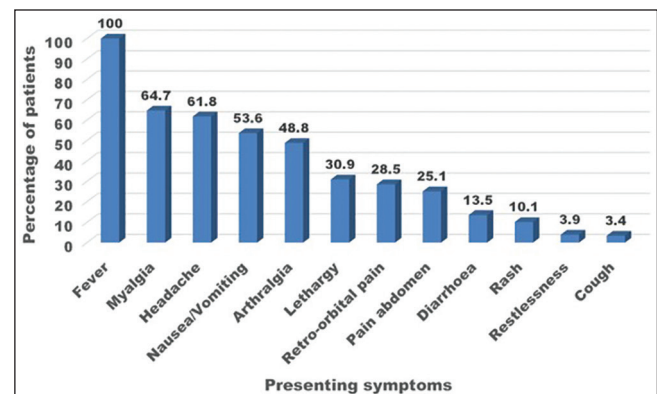
Table 1: Characteristics of study group (*N* = 207)	
Variables	**Numbers (%)**
Gender	
Male	143 (69.1)
Female	64 (30.9)
Age (in years)	
18-30	87 (42)
31-40	49 (23.7)
41-50	31 (15)
51-60	22 (10.6)
61-70	16 (7.7)
71-80	2 (1)
Rural	107 (51.7)
Duration of illness in days	
1-3	70 (33.8)
4-6	91 (44)
7-10	40 (19.3)
>10	6 (3)
Duration of hospital stay in days	
1-3	15 (7.2)
4-6	127 (61.4)
7-10	55 (26.6)
10	10 (4.8)
Outcome	
Improved	206 (99.5)
Expired	1 (0.5)

Table 2: Laboratory investigations	
Laboratory investigations	**Mean ± SD**
Hemoglobin (gm/dL)	13.89±1.91
Total white cell count (cells/mm³)	4,745.41±3,131.73
Neutrophil count (%)	64.42±12.24
Lymphocyte count (%)	30.76±11.38
Platelet count (/mm³)	110,159.42±68,397.32
Serum creatinine (mg/dL)	0.95±0.5
Total bilirubin (mg/dL)	1.01±2.12
Indirect bilirubin (mg/dL)	0.52±0.67
Albumin (gm/dL)	4.00±0.58
Aspartate transaminase (IU/mL)	178.14±295.04
Alanine transaminase (IU/mL)	109.88±138.13
Alkaline phosphatase (IU/mL)	104.74±71.87
Presence of IgG antibodies ELISA [*N* (%)]	13 (6.3)

Figure 1: Presenting symptoms (*N* = 207)

Table 3: Multivariate logistic regression model with low platelet count on admission as the dependent variable

Independent variables	P*	Odds ratio	95% CI	% variance (Nagelkerke pseudo R-square)
Place of residence (Rural)	0.001*	0.43	0.23-0.81	0.048
Presence of rash	0.04*	8.62	1.11-65.77	0.055
High direct bilirubin levels	0.05*	2.34	0.98-5.6	0.028
Low albumin levels	0.04*	4.48	1.02-19.75	0.039
High AST levels	0.001*	3.14	1.58-6.23	0.072
High ALT levels	0.001*	2.91	1.55-5.47	0.078
High ALP levels	0.001*	3.68	1.56-8.7	0.073
Prolonged PT	0.02*	0.47	0.25-0.88	0.04

AST = aspartate transaminase, ALT = alanine transaminase, ALP = alkaline phosphatase, PT = prothrombin time, IgG = immunoglobulin G, *Statistical significance was considered at $P \leq 0.05$

Table 4: Multivariate logistic regression model with longer duration of hospital stay as the dependent variable

Independent variables	P*	Odds ratio	95% CI	% variance (Nagelkerke pseudo R-square)
Presence of diarrhea	0.03*	0.4	0.18-0.9	0.033
Presence of nausea/vomiting	0.80	1.08	0.6-1.95	<0.001
Presence of abdominal pain	0.05*	0.52	0.27-1.00	0.03
Presence of ascites	<0.01*	0.26	0.09-0.69	0.049
Presence of bleeding manifestations	0.87	0.93	0.37-2.29	<0.001
Presence of shock	0.44	2.34	0.27-20.41	0.005
Low hemoglobin percent	0.02*	0.46	0.25-0.86	0.039
Low platelet count at admission	0.71	1.13	0.59-2.17	0.001
Low albumin levels	0.92	1.05	0.41-2.7	<0.001
High serum creatinine levels	0.81	1.16	0.35-3.83	<0.001

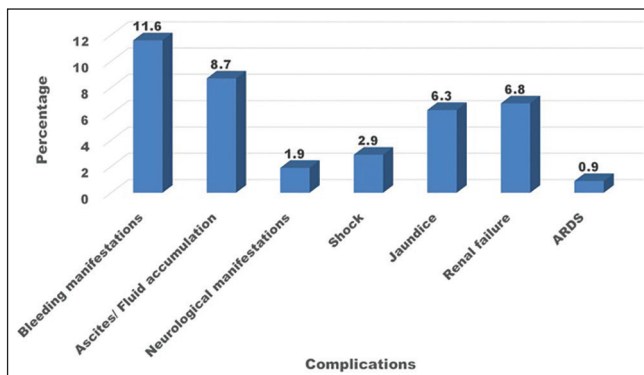*Statistical significance was considered at $P \leq 0.05$

Figure 2: Complications (*N* = 207)

orbital pain in a patient with fever and gastrointestinal manifestations should raise the suspicion of DF.

Hepatomegaly, thrombocytopenia, raised liver enzymes, deranged PT and PTT, hypoalbuminemia, and third-space fluid loss (ascites and pleural effusion) were other clinical and laboratory findings seen in this study. Similar reports were observed in previous studies.[13-15] Four cases (1.9%) had altered sensorium in this study. Neurological manifestations possibly secondary to cerebral hypoperfusion, due to shock, encephalitis/encephalopathy, hepatic dysfunction, metabolic

derangements, such as hyponatremia and hypoglycemia, are reported earlier by other studies as well.[16-18]

In this study, low platelet count on admission was associated with the presence of rash, high AST and ALT levels, and low albumin levels. The duration of hospital stay was longer with presence of diarrhea, abdominal pain, ascites, and low hemoglobin on admission, but it did not correlate with the platelet count on admission. Clinical features including abdominal pain, hepatomegaly, and pleural effusion were more commonly associated with DHF and major bleeding outcome in another study.[19] Such raised levels of liver enzymes were commonly seen in DHF and DSS patients in earlier studies, which are the more severe forms of this viral illness.[14,16,20]

The mean duration of illness in this study was 4.94 ± 3.58 days and the mean duration of hospital stay was 5.98 ± 2.58 days. Among 24 cases (11.6%) with bleeding manifestations, 4 cases (1.9%) had major bleeding in the form of upper gastrointestinal bleeding. Platelet transfusion was given to 16 patients (7.7%), 2 cases required ventilator support, and 1 case required hemodialysis. One patient (0.5%) expired in this study group. The median duration of symptoms and

hospitalization was 8 days (range 3-18) and 4 days (range 1-10), respectively, in a study from Saudi Arabia.[21] In another study from Singapore, the mean length of hospital stay was 4 days in adults admitted with the diagnosis of dengue. In terms of treatment and outcome, older patients were more likely to be given a platelet transfusion compared with younger patients, they were no more likely to require intravenous fluids and have prolonged hospitalization, or die of acute dengue (0% vs. 0.1%, $P = 1.00$).[22] In a report from Pakistan, the mortality rate was 0.6% in admitted cases of dengue, conducted at five tertiary care hospitals.[23] Total number of deaths was 110 all over India in 2010 (mortality 0.4% of 28,066 cases), with 8 reported from Delhi (mortality 0.13% of 6,259 cases).[22] Though the mortality rate was comparable to these two reports,[23,24] the length of hospitalization was much longer in the present study compared to the study from Singapore.[22]

There were few potential limitations of this study. This was a retrospective analysis of available records, therefore many important information were incomplete. The study did not include patients aged <18 years. The study was conducted at a tertiary care hospital, which reported only hospitalized patients aged >18 years; thus, the findings cannot be generalized to the community.

Conclusions

Dengue fever most commonly affects young adults, mostly males. Though thrombocytopenia on admission was associated with the presence of rash, high AST and ALT levels, and low albumin levels, it was not predictive of length of hospitalization. The duration of hospital stay was longer with the presence of diarrhea, abdominal pain, ascites, and low hemoglobin level on admission.

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Conflicts of interest

There are no conflicts of interest.

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