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Original Article

Haemorrhagic Tendencies in Patients Presenting with Fever and Thrombocytopenia in a hospital setting - A Cross Sectional Study

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Abstract
Background: *Fever with thrombocytopenia has become the commonest presenting problem in the medical wards. Infection is a common cause of thrombocytopenia. Fever with thrombocytopenia is a common condition that is associated with an increased risk of morbidity and mortality. Infections like Malaria, Dengue, Typhoid and septicaemia are some of the common causes of fever with thrombocytopenia.*
Aims and Objectives: *To study the clinical profile of febrile thrombocytopenia's and to determine the etiology of these febrile illnesses. Also to observe the different bleeding manifestations in order of their incidence in fever with thrombocytopenia and their relation with platelet count.*
Methods: *During the period between 1 January 2015and 31 December 2015 a cross-sectional study was carried out at Govt. Medical College, Ernakulam, Kerala. Patients with febrile thrombocytopenia and age more than 13 years were followed up, diagnosis were made, and bleeding manifestations and requirement of platelet transfusion were recorded.*
Results: *Among the 123 patients studied, common etiology of febrile thrombocytopenia found was dengue (n=51, 41.4%), followed by malaria (n= 8, 6.5%), and Leptospira (n=7, 5.6%).Among the study group, 35.77% had mild platelet count (platelet count below 1 lakh to 50,000), 39.6 % had platelet count in the range of 50,000 -20,000 and 25.2 % had platelet count less than 20,000. 11 cases (8.94%) were presented with bleeding manifestations. Out of this; 4 (3.25%) showed nose/gum bleed, 3 (2.44%) had melena, 2 (1.63%) cases presented with vaginal bleed, 1 (0.81%) sub-conjunctival haemorrhage and 1 (0.81%) presented with haematuria. Rash was observed in 5.6 % of the cases. Good recovery was noted in 93% cases while 3% had mortality and remaining 3 % were referred for better treatment.*
Conclusions: *In our set up infections like Dengue fever was the common cause of fever with thrombocytopenia followed by malaria and Leptospirosis. Thrombocytopenia due to infectious agents shows seasonal variation with peak of incidence in soon after monsoon and early winter season. All cases of thrombocytopenia may not have a bleeding manifestation and may be asymptomatic at initial presentation.*
Keywords: *Fever, Thrombocytopenia, Malaria, Dengue, Spontaneous bleeding, Leptospirosis.*

Introduction

Fever is the most ancient hallmark of any disease. Patients with history fever in a tropical country like India usually have an infectious etiology and many of them have associated thrombocytopenia. Infections like dengue, typhoid, malaria, and leptospirosis are some of the common causes of febrile thrombocytopenia in India[(1)]. Patients with platelet count less than 10,000/micro-liter have increased the risk of spontaneous bleeding, petechiae and bruising[(2)] Dengue fever (DF) is the most common cause of mosquito-borne Arboviral infections. Many undifferentiated febrile illnesses are very common in tropical countries like India which may mimic like dengue, salmonella typhoid, malaria, Leptospirosis, influenza etc. According to WHO, annually 50 million cases of DF occur worldwide with a mortality rate of 2.5%[(3)]. Reduced platelet count might also be due to pseudo thrombocytopenia, which may be caused by EDTA is a common laboratory phenomenon[(4)]. Sometimes infectious causes such as primary hematological disorders may also present with febrile thrombocytopenia[(5)].

There is an increase in the incidence of fever with thrombocytopenia. Routinely we come across many cases, both as inpatients and outpatients presenting as fever with thrombocytopenia. Thrombocytopenia in fever being a prognostic factor can predict the cause and thus helps in early diagnosis and treatment of the same, preventing further fatal outcome associated with it such as intra-cerebral bleed, hemorrhage into vital organs, shock .Though patients can initially present with simple fever, in due course it can lead to unpredictable outcomes including death at times.

In this study, clinical profile of fever with thrombocytopenia, with special emphasis on clinical profile of Febrile thrombocytopenia's and to determine the etiology of these febrile illnesses, different bleeding manifestations in order to find their incidence in fever with thrombocytopenia and their relation with platelet count, and to look into the seasonal variations and to document various complications in thus clinical settings. Patients having thrombocytopenia with fever many times do not have bleeding manifestations. Hence study of correlation between platelet counts and hemorrhagic manifestations will help us to know the correct time for infusion of platelets, thus avoiding unnecessary platelet transfusion.

Materials and Methods

A prospective , cross –sectional study was conducted in all fever patients (IP/OP), with platelet count below 1 lakh and age above 13 yrs. visited to Government Medical College , Ernakulam during the period January 2015 to December 2015. The study was approved by the Ethical and Research Committee of Govt. Medical College, Ernakulam and informed consent was obtained from all participants. Patients with underlying medical conditions were excluded from the study.

A careful history was recorded and detailed examination of various systems, including vitals, general examination, respiratory system, gastrointestinal system, CNS, CVS examination. Routine investigation(CXR, blood routine, Random blood sugar, liver function test, renal function test, ECG, serum electrolytes). Specific/special investigations was done as and when indicated.

Diagnosis tests for specific infectious agents also carried out for Dengue virus (Dengue NS1 Ag, Dengue IgM & Dengue IgG ELISA s), Leptospira (Leptospira IgM ELISA), Malaria (peripheral smear examination and Malaria rapid card test-ICT), Salmonella typhi (Blood culture and salmonella typhi IgM) and infectious hepatitis (HBV-HBsAg ELISA, HCV-Anti HCV IgM ELISA , HEV- Anti-HEV IgM ELISA and HAV-Anti-HAV IgM ELISA). Other common infectious causes for febrile thrombocytopenia in our community such as Chikungunya, Scrub typhus, and KFD were not actively looked up on owing to financial and technical constraints.

Data Entry and Statistical Analysis was done by using: CDC- Epi Info™ (Version 7.2). The categorical variables were summarized as frequencies and percentage. Descriptive Statistics were reported using mean ± SD (Standard Deviation) and mean with inter-quartile range

Result

During the period of 1st January 2015 to 31st December 2015, a total of 123 patients (n=123) with febrile thrombocytopenia met the inclusion criteria of the study. The mean fever duration was 4 days (±1). Out of the total subjects 54.47 % (N=67) were male and rest 45.53 % (N=56) were females. The mean age group of febrile thrombocytopenia cases was 41(±16).

In this study, 11 cases (8.94%) were presented with bleeding manifestations. Out of this; 4 (3.25%) showed nose/gum bleed, 3 (2.44%) had melena, 2 (1.63%) cases presented with vaginal bleed, 1 (0.81%) sub-conjunctival hemorrhage and 1 (0.81%) presented with haematuria. Other clinical symptoms observed were arthralgia (78, 63.41%), Myalgia (121, 98.37%), abdominal pain (45, 36.59%), Vomiting (30, 24.39%), rash (7, 5.69%) and jaundice (3, 2.4%). Descriptive analysis of febrile thrombocytopenia cases were included in Table 1.Age group wise analysis showed that 40- 49 year age group were mostly affected (21.95%), followed by 20-29 year age group (21.14 %)

Table 1 Descriptive analysis of febrile thrombocytopenia cases

Variables		Febrile thrombocytopenia cases, N (%)
Age (n=123)	Mean(SD)	41 (±16)
	Median(IQR)	43(26-53)
Sex (n=123)	Male	67(54.47%)
	Female	56(45.53%)
Clinical features (n=123)	Fever	123(100%)
	Myalgia	121(98.37%)
	Arthralgia	78(63.41%)
	Abdominal pain	45 (36.51%)
	Vomiting	30 (24.39%)
	Jaundice	3 (2.4%)
	Rash	7(5.69%)
	Bleeding Manifestations	11 (8.94%)
Fever duration (n=123)	Mean(SD)	4(±1)
Bleeding manifestations (n=11)	Nose/ Gum bleeding	4(3.25%)
	Melena	3 (2.44%)
	Vaginal bleeding	2(1.63%)
	Subconjunctival hemorrhage	1(0.81%)
	Hematuria	1(0.81%)
Rash (n=7)	Petechiae	4(57.14%)
	Erythema	3(42.85%)

In the current study common etiology of febrile thrombocytopenia was dengue (n=51, 41.4%), followed by malaria (n= 8, 6.5%), and Leptospira (n=7, 5.6%) (Table 2). Rest were unknown. Males outnumbered females in all etiologies of febrile thrombocytopenia. Dengue fever mostly affected the age group of 30 -55 (23, 45.1%-of all dengue cases). Malaria and Leptospira were commonly found in the group of 13-30. Age group wise incidence of various etiological agents of febrile thrombocytopenia is shown in Table 3

Table 2: Etiological profile of febrile thrombocytopenia

Etiology	Number, n=123, N (%)
Dengue fever	51 (41.4%)
Malaria	8(6.5%)
	Plasmodium vivax – 5(62.5%)
	Plasmodium falciparum -2 (25%)
	Mixed infection (P. vivax+ P. falciparum)-1(12.5%)
Leptospirosis	7(5.6%)

Table 3: Age incidence of various etiological agents of febrile thrombocytopenia

Age group	Dengue fever N (%)	Malaria N (%)	Leptospira N (%)
13-30	17(33.3)	7(87.5)	3(42.9)
30-55	23(45.1)	1(12.5)	2(28.6)
55-80	10(19.6)	0	2(28.6)
>80	1(2)	0	0

Study regarding degree of thrombocytopenia showed that, 35.77% had mild platelet count (platelet count below 1 lakh to 50,000), 39.6 % had platelet count in the range of 50,000 -20,000 and 25.2 % had platelet count less than 20,000 . In Patients with dengue virus infection, 30 cases (58.8%) showed moderate thrombocytopenia (platelet count less than 50,000) and 11 cases (21.6%) presented with mild thrombocytopenia (platelet count less than 1 lakh) and only 10 cases (19.6%) had severe thrombocytopenia (platelet count less than 20,000). In the case of malaria 5 cases (62.5%) showed moderate thrombocy-topenia (platelet count less than 50,000) and 3 cases (37.5%) had severe thrombocytopenia (platelet count less than 20,000). 3 cases (42.9%) of Leptospira diagnosed cases showed moderate thrombocytopenia, 2 cases(28.6%) showed severe

thrombocytopenia, and remaining two (28.6%) had mild thrombocytopenia. Degree of thrombocytopenia in various diseases are shown in Figure 1

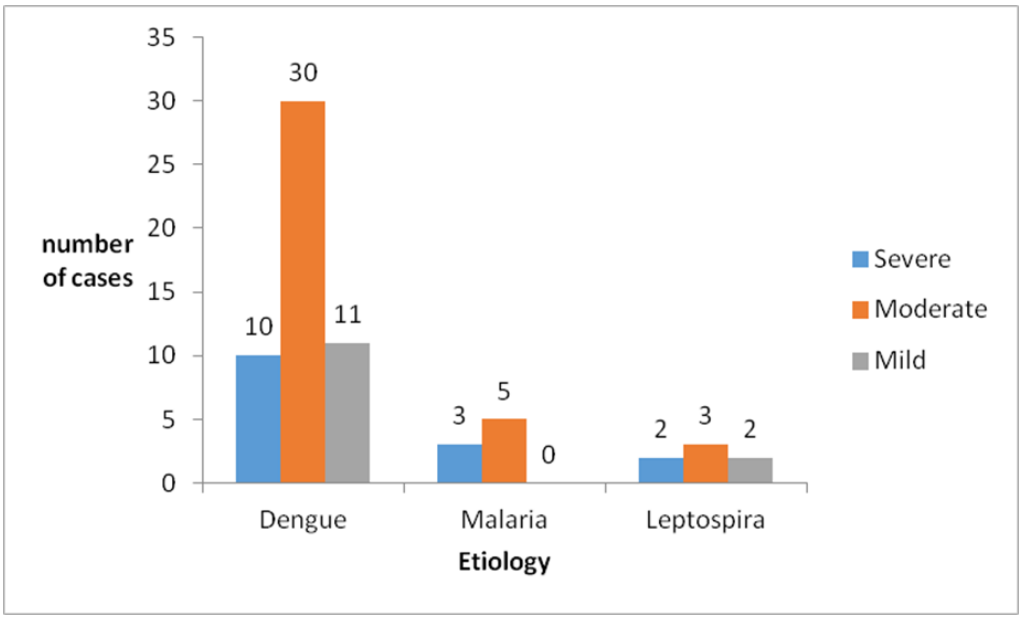

Figure 1: Etiology of Febrile thrombocytopenia in different platelet count range

In our study, maximum number of dengue and malaria cases with thrombocytopenia are seen soon after monsoon season (August – October). Detailed description of the seasonality is shown in Figure 2

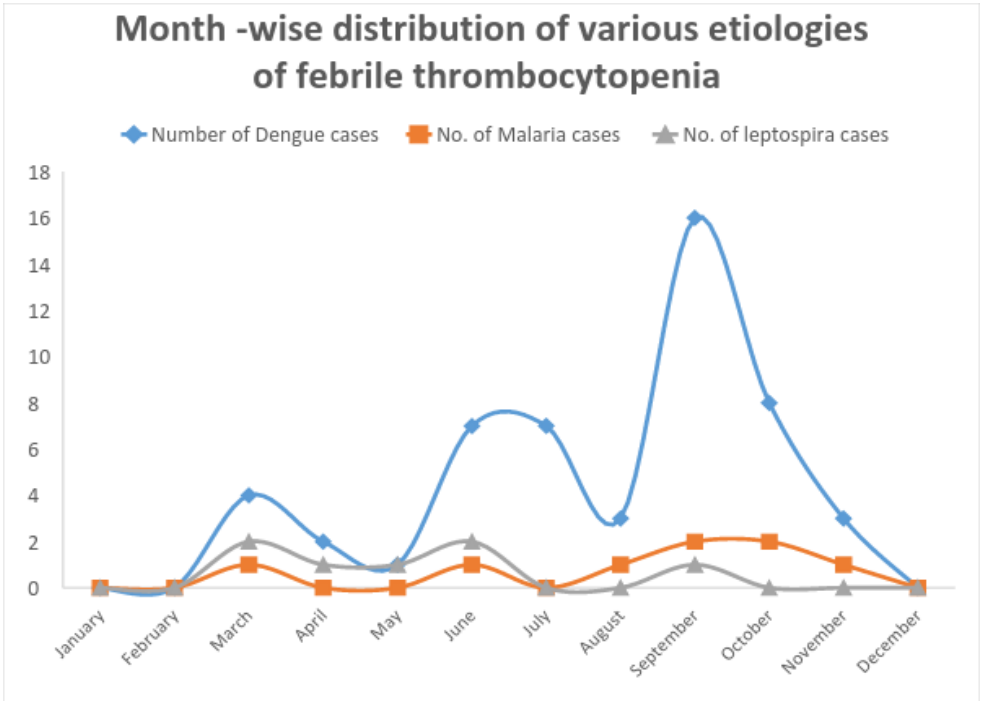

Figure 2: Month wise distribution of various aetiologies of febrile thrombocytopenia

Regarding the complications associated with febrile thrombocytopenia, out of 123 cases, 86 % of the febrile thrombocytopenia cases didn't experience any kind of complication. Major complication found among these cases were renal failure (6.5%), Jaundice (2.4%), DHF (2.4%), myocarditis (1.63%) and ARDS (0.81%). Among 123 cases with febrile thrombocytopenia, 114 cases (92.67%) cases were better at the time of discharge, 4 (3.25%) were died and 5 (4.07%)

were referred to another hospitals. Out of 4 mortality cases, 3 cases diagnose as dengue and 1 diagnosed as Leptospirosis case. Complications associated with these cases were 2 renal failure (50%), 1 Jaundice (25%) and 1 DHF (25%). Among death cases 50 % cases experienced severe thrombocytopenia and 50 % cases had moderate thrombocytopenia.

Discussion

In the present study, spontaneous bleeding was the major heaemorrhagic manifestation accounting for 5.7%. In the study most common bleeding manifestation was purpura, followed by gum bleed and epistaxis. Bhalara et al at Civil Hospital, Ahmadabad, observed that among febrile thrombocytopenic patient observed 11% cases had Bleeding manifestations[2]. Study done by Nair et al at St. Stephen's Hospital, New Delhi, for period of one and half years showed that spontaneous bleeding was the common bleeding manifestation with 31 cases(68%) followed by petechiae / purpura accounting for 10 cases (22.22%), others 4 cases (9.88%)[5]. In Srinivas study petechiae /purpura was the common bleeding manifestation with 31 cases (63%) followed by spontaneous bleeding accounting for 18 cases (37%)[1]. In Gandhi et al from Department of Medicine, Rural Medical College, Loni, study petechiae / purpura was the common bleeding manifestation with 14 cases (14%) followed by spontaneous bleeding accounting for 10 cases(10%) [6]. In study done by Patil petechiae was the major manifestation73.9% followed by spontaneous bleeding (26.9%)[7].

In this study, of 123 cases (67 male and 56 female patients), the maximum prevalence of fever with thrombocytopenia was in the age group of 40-49 years of about 22%. Among these 123 cases, 48(39.6%) had platelet count between 50,000 and 20,000, followed by 44 (35.7%) who had count between 100,000 to 50,000, and 31 (25.2%) had severe thrombocytopenia (Platelet count <20,000). These findings correlate with Nair et al study [5], Modi et al study [8] and Bhalara et al study [2].

The most common aetiology responsible for febrile thrombocytopenia in the current study was found to be Dengue fever (41.4%). The main mechanisms probably involved in dengue-induced thrombocytopenia are impaired thrombopoiesis and peripheral platelet destruction[9]. Malaria (6.5%) was the second common cause responsible for febrile thrombocytopenia which includes P. vivax (62.5%), P.falciparum (25%), and Combined P.falciparum-P.vivax malaria (12.5%). Thrombocytopenia in malaria is probably due to increased splenic sequestration, immune-mediated destruction, and a shortened platelet survival and consumption by DIC [10]. Leptospirosis (5.6%) was the third common cause of febrile thrombocytopenia in this study.

In Nair study septicaemia was the leading cause of fever associated with thrombocytopenia. Second common cause was enteric fever, followed by dengue Megaloblastic anaemia, malaria and haematological malignancy. In Srinivas study malaria was the leading cause of fever associated with thrombocytopenia. Second common cause was enteric fever followed by septicaemia, dengue, and leptospirosis. In the Gandhi et alstudy Dengue was leading cause of fever associated with thrombocytopenia. Second common cause was septicaemia followed by Malaria, HIV, viral hepatitis, and enteric fever cases. Raikar s found that dengue, was the most common cause of thrombocytopenia then malaria, enteric fever. According to Anand et al common cause of febrile thrombocytopenia was dengue fever, followed by malaria then by mixed infection with dengue and malaria[11].

Dengue fever cases usually rise during and just after the rainy season, or June through October in India, because the virus needs time to grow and complete its life cycle. The Aedes aegypti vector mosquito which breeds during the rains continues to reproduce and add to its numbers usually till the winter months[12]. Same pattern of activity was observed in the current study. More dengue cases was observed during early winter and soon after monsoon (August to October).

In the mortality group (4 cases) platelet count in 2 cases were below 20,000 and 2 cases showed moderate thrombocytopenia (50,000 to 20,000). However all patient received platelet transfusion till the time death. Among death cases, 3 died due to Dengue fever and associated renal failure in 2 patients and DHF in one patient. Remaining mortality was due to leptospirosis. Our study shows mortality of 5.8 % among dengue fever cases (N=51), which correlates with studies done by Anand et al[115] (2014) , Anuradha et al (1998), Kabra et al(1999) Gomber et al (2001), Narayanan et al (2002) demonstrated mortality in 4.8% 6.6%,7.5%, 4.8%, 3.4% respectively[(13–16)].

Limitation of the study

Since this is a hospital based study, it has limitations. The actual picture of febrile thrombocytopenia cases and those with bleeding manifestations were underestimated because only patients referred to the GMC, Ernakulam for a particular study period were included in the study. Serological or molecular diagnosis of other aetiological agents for febrile thrombocytopenia are expensive and hence could not be done and the final diagnosis of fever could not be arrived at in majority of cases.

Conclusion

Thrombocytopenia, a common observation in hemograms needs a systematic evaluation to find out the underlying cause which can be of infective or no infective etiology. All cases of thrombocytopenia may not have a bleeding manifestation and may be asymptomatic at initial presentation. However in few cases it may lead to severe bleeding which may be life threatening for the patient. Hence the prompt diagnosis and immediate specific treatment of underlying etiology of febrile thrombocytopenia with maintenance of platelet count and haemostatic function gives good recovery. In our set up infections like dengue fever, malaria Leptospirosis are usually associated with febrile thrombocy-topenia. Thrombocytopenia due to infectious agents shows seasonal variation with peak of incidence in soon after monsoon and early winter season.

Conflict of interest statement

The authors have no conflict of interest

References

1. To study clinical evaluation and outcome of patients with febrile thrombocytopenia. - Google Search [Internet]. [cited 2016 Nov 17]. Available from: https://www.google.co.in/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=To+study+clinical+evaluation+and+outcome+of+patients+with+febrile+thrombocytopenia.
2. Bhalara SK, Shah S, Goswami H, Gonsai RN. Clinical and etiological profile of thrombocytopenia in adults: A tertiary-care hospital-based cross-sectional study. Int J Med Sci Public Health. 2015;4(1):7–10.
3. WHO, World Health Organization (2000). Scientific working group on dengue. Meeting report, Geneva, Switzerland, 3-5 April 2000. WHO: Geneva. - Google Search [Internet]. [cited 2016 Nov 23]. Available from: https://www.google.co.in/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=%5D+WHO%2C+World+Health+Organization+(2000).+Scientific+working+group+on+dengue.+Meeting+report%2C+Geneva%2C+Switzerland%2C+3-5+April+2000.+WHO%3A+Geneva.
4. Nagler M, Keller P, Siegrist D, Alberio L. A case of EDTA-dependent pseudo-thrombo-cytopenia: simple recognition of an under-diagnosed and misleading phenomenon. BMC Clin Pathol. 2014;14:19.
5. Nair PS, Jain A, Khanduri U, Kumar V. A study of fever associated thrombocytopenia. JAPI 2003;51:1173. - Google Search [Internet]. [cited 2016 Nov 17]. Available from: https://www.google.co.in/search
6. Clinical assessment of fever with thrombocytopenia – A prospective study |

IJMRHS [Internet]. [cited 2016 Nov 17]. Available from: http://ijmrhs.com/clinical-assessment-of-fever-with-thrombocytopenia-a-prospective-study/

7. Patil P, Solanke P, Harshe G. To study clinical evaluation and outcome of patients with febrile thrombocytopenia. Intl Jr of Sci and Research Publications. 2014; 4(10):01-03. - Google Search [Internet]. [cited 2016 Nov 22]. Available from: https://www.google.co.in/search
8. Modi TN, Mehta AD, Sriram AS. Clinical Profile of Febrile Thrombocytopenia: A Hospital-Based Cross-Sectional Study. J Res Med Dent Sci. 2016;4(2):115–20.
9. Azeredo EL de, Monteiro RQ, de-Oliveira Pinto LM. Thrombocytopenia in Dengue: Interrelationship between Virus and the Imbalance between Coagulation and Fibrinolysis and Inflammatory Mediators. Mediators Inflamm. 2015 Apr 27;2015:e313842.
10. Lacerda MVG, Mourão MPG, Coelho HCC, Santos JB. Thrombocytopenia in malaria: who cares? Mem Inst Oswaldo Cruz. 2011 Aug;106 Suppl 1:52–63.
11. Clinical Outcomes of Patients Presenting As Fever with Thrombocytopenia in Marathwada Region Nikalje Anand1 , Talib S.H.2 , Pagar Bhushan3 , Patil Sumit4 , Patil Piyush5 , Kurhade Aniket6 - Google Search [Internet]. [cited 2016 Nov 17]. Available from: https://www.google.co.in
12. Sharma RS, Kaul SM, Sokhay J. Seasonal fluctuations of dengue fever vector, Aedes aegypti (Diptera: Culicidae) in Delhi, India. Southeast Asian J Trop Med Public Health. 2005 Jan;36(1):186–90.
13. Anuradha S, Singh NP, Rizvi SN, Agarwal SK, Gur R, Mathur MD. The 1996 outbreak of dengue hemorrhagic fever in Delhi, India. Southeast Asian J Trop Med Public Health. 1998 Sep;29(3):503–6.
14. Kabra SK, Jain Y, Pandey RM, Madhulika null, Singhal T, Tripathi P, et al. Dengue haemorrhagic fever in children in the 1996 Delhi epidemic. Trans R Soc Trop Med Hyg. 1999 Jun;93(3):294–8.
15. Gomber S, Ramachandran VG, Kumar S, Agarwal KN, Gupta P, Gupta P, et al. Hematological observations as diagnostic markers in dengue hemorrhagic fever--a reappraisal. Indian Pediatr. 2001 May;38(5):477–81.
16. Narayanan M, Aravind MA, Thilothammal N, Prema R, Sargunam CSR, Ramamurty N. Dengue fever epidemic in Chennai--a study of clinical profile and outcome. Indian Pediatr. 2002 Nov;39(11):1027–33.