

## Clinical and Etiological Profile of Fever with Thrombocytopenia: A Tertiary Care Hospital Based Study

Kailash Chandra Saini<sup>1</sup>, Shivam Sethi<sup>2\*</sup>, R P Agrawal<sup>3</sup>, P Sirohi<sup>4</sup>, J K Meel<sup>5</sup>, Khetaram Sharma<sup>2</sup>

<sup>1</sup>MBBS, MD (General Medicine), Consultant Physician, Navalgarh, Jhunjhnu, Rajasthan, India.

<sup>2</sup>PG Resident (IIIrd Year), <sup>4</sup>Professor, <sup>5</sup>Medical Officer, Department of Medicine, S P Medical College, Bikaner, Rajasthan, India.

<sup>3</sup>Principal and Controller, Senior Professor (Medicine), S P Medical College, Bikaner, Rajasthan, India.

### ABSTRACT

**Objectives:** Febrile thrombocytopenia is a condition commonly caused by infections. The present study is intended to know the underlying etiology of fever with thrombocytopenia, the various presentations and complications in our community.

**Materials and Methods:** A cross-sectional epidemiological study was conducted including 1217 patients aged more than 14 years with fever and thrombocytopenia admitted in the medical wards from October 2013 to September 2014. Detailed clinical examination and routine investigations were done; specific investigations like blood culture, widal test, antigen test for malaria, IgM ELISA leptospira, IgM ELISA dengue, bone marrow aspiration/biopsy etc. were done as and when indicated. The data are presented as percentage and numbers. Rates and ratios are computed.

**Results:** Infection was the commonest cause of thrombocytopenia and dengue was the commonest of the infections followed by malaria. Bleeding manifestations were seen in 42.7% of patients. 91.40% of patients with bleeding tendencies had petechiae/purpura as the commonest bleeding manifestation, followed by spontaneous bleeding in 57%. Spontaneous bleeding was noted when platelet counts were less than 20,000. Petechiae/Purpura were seen more commonly when platelet count was in the range of less than or equal to 50,000. Good recovery was noted in 95%, while 5% had mortality. Septicemia accounted for 85.24% of deaths followed by malaria (6.55%) and dengue (5%).

**Conclusion:** Fever with thrombocytopenia is an important clinical condition commonly caused by infections, particularly dengue and malaria. In majority of patients thrombocytopenia was transient and asymptomatic, but in significant number of cases there were bleeding manifestations. On treating the specific cause drastic improvement in platelet count was noted. Mortality in febrile thrombocytopenia is not directly associated with degree of thrombocytopenia but with concomitant involvement of other organs leading to multiorgan dysfunction.

**Keywords:** Dengue, Infection, Mortality, Petechiae/Purpura, Spontaneous Bleeding.

### \*Correspondence to:

**Dr. Shivam Sethi,**  
PG Resident (IIIrd Year),  
Department of Medicine,  
S P Medical College, Bikaner, Rajasthan, India.

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### INTRODUCTION

Fever is defined as an elevation of the body temperature above the normal circadian range, as the result of a change in the thermoregulatory center located in the anterior hypothalamus. A morning temperature of more than 37.2°C (98.9 °F) or evening temperature of more than 37.7°C (99.9°F) would define fever.<sup>1</sup> Thrombocytopenia is defined as platelet count less than 150,000 / $\mu$ l. This is due to decreased production, increased destruction (immunogenic and non- immunogenic) and increased sequestration in spleen.<sup>2</sup> At times, the fever course is prolonged and fever with thrombocytopenia narrows the differential diagnosis of the clinical entity. Septicemia, infections like malaria, dengue,

leptospirosis, typhoid, human immunodeficiency virus (HIV) and miliary tuberculosis are some of the common causes of fever with thrombocytopenia.

Therefore, a well-organized systemic approach, carried out with an awareness of causes of fever with thrombocytopenia can shorten the duration of investigations and bring out the diagnosis.

### MATERIALS AND METHODS

A cross-sectional epidemiological study was conducted including 1217 patients (age $\geq$ 14 years) admitted with fever and thrombocytopenia in the medical wards from October 2013 to

September 2014 in the department of medicine, S.P. medical college & associated group of hospitals, Bikaner. We prospectively collected a series of 1217 patients of fever with thrombocytopenia.

**Inclusion Criteria**

- Age more than 14 years.
- Fever less than 15 days duration.
- Fever more than 100°F at least once a day.
- Platelet count less than 1, 50,000/ $\mu$ l.

**Exclusion Criteria**

- Known patients of Primary Thrombocytopenia.
- Drug induced thrombocytopenia.
- Diagnosed cases of Thrombocytopenic purpura on treatment.
- Patients with thrombocytopenia already diagnosed to have hematological disorder / malignancy, on treatment with chemotherapy and other immunosuppressant.

The patients fulfilling the selection criterion after excluding 156 patients were selected for the study and consent was obtained. Further, they were subjected to a detailed history and clinical examination according to predesigned and pretested proforma. Routine investigations were done. Specific investigations (complete blood count, erythrocyte sedimentation rate, platelet counts, peripheral smear for malaria parasite, QBC for malaria parasite, bleeding time and clotting time, urine routine and microscopy, blood culture, urine culture, renal function tests, liver function tests, widal test, dengue IgG, IgM, brucella standard agglutination test, leptospira ELISA, bone marrow examination etc.) were done as and when indicated. Once the specific diagnosis was reached, a patient was treated for it specifically and symptomatically (mechanical ventilators, haemodialysis etc.). Platelet transfusions were done for bleeding complications. The patient was followed from the day of admission till their discharge from the hospital. The data are presented as percentage and numbers. Rates and ratios are computed. P value of less than 0.05 was considered as significant.

**Table 1: Etiology of fever with thrombocytopenia**

Etiology	Numbers of patients (n =1217)	Percentage
Dengue	572	47%
Malaria	243	20%
Unexplained	200	16.5%
Septicemia	128	10.5%
Dengue+Malaria	56	4.5%
Enteric fever	12	1%
Leptospirosis	6	0.5%

**Table 2: Etiology and Bleeding tendencies**

Platelet Count	Total Number of Patients (n=1217)	Bleeding tendencies	Percentage	$\chi^2$	p
Dengue + Malaria	56	32	57.14	229.67	<0.001
Dengue	572	314	55.30	9.701	<0.05
Unexplained	200	70	35.00	38.389	<0.001
Malaria	243	66	27.12	6.282	<0.05
Septicemia	128	30	23.80	18.648	<0.001
Enteric Fever	12	0	-	0.119	>0.05
Leptospirosis	6	0	-	0.030	>0.05

**Figure 1: Thrombocytopenia and bleeding tendencies**

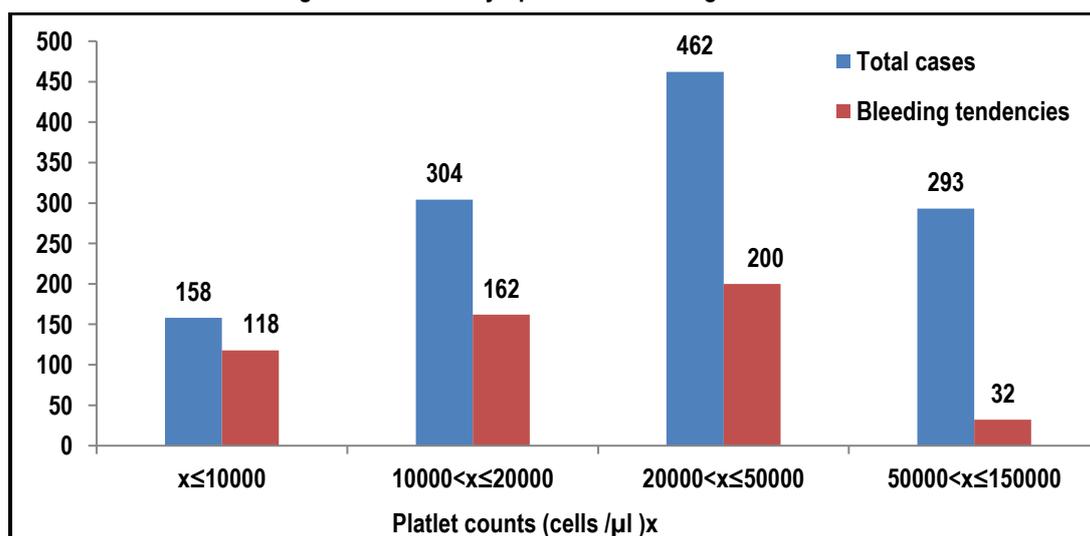


Figure 2: Correlation of petechiae/purpura with thrombocytopenia

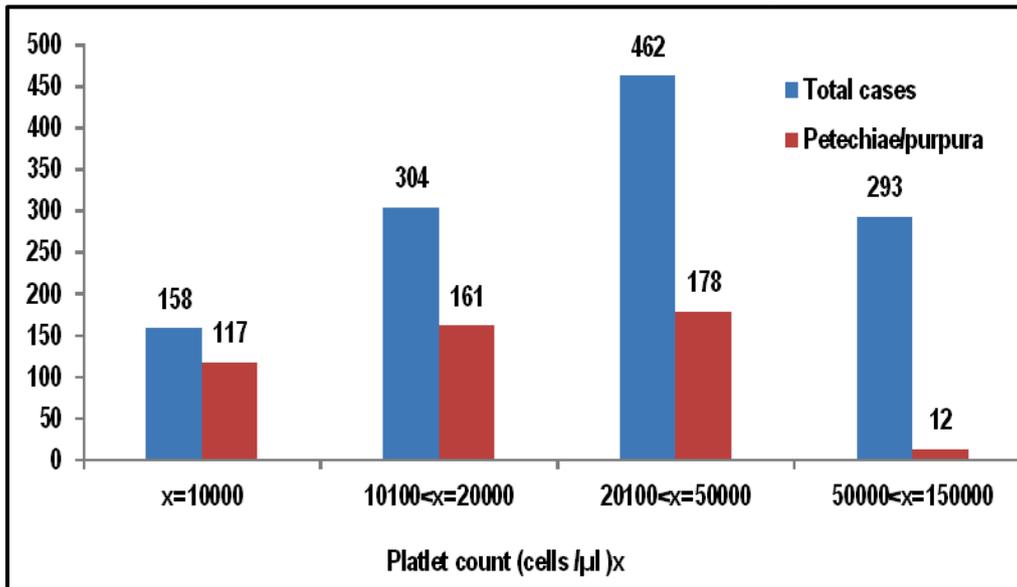


Figure 3: Thrombocytopenia and bleeding symptoms

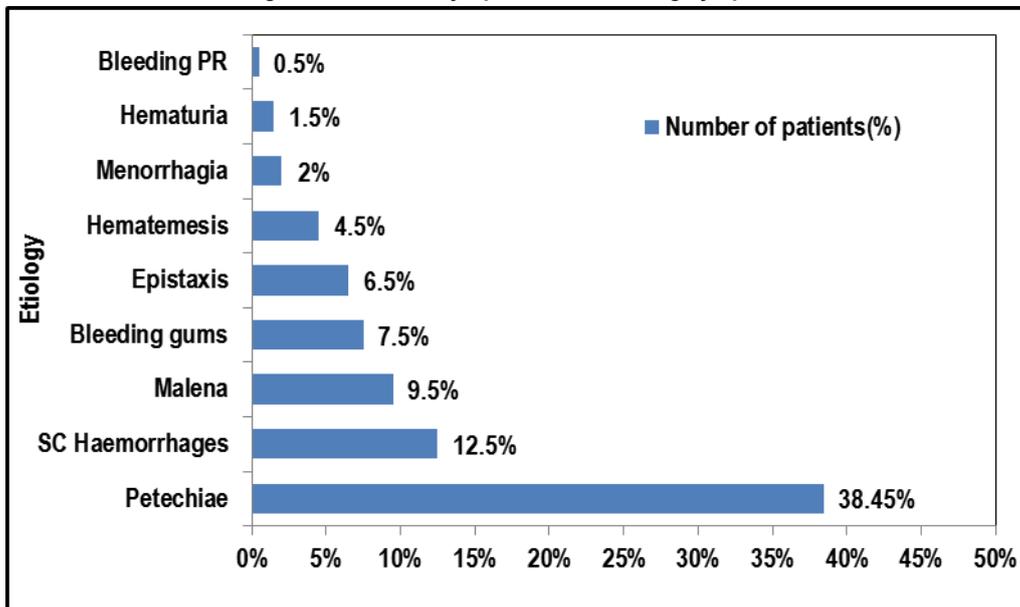
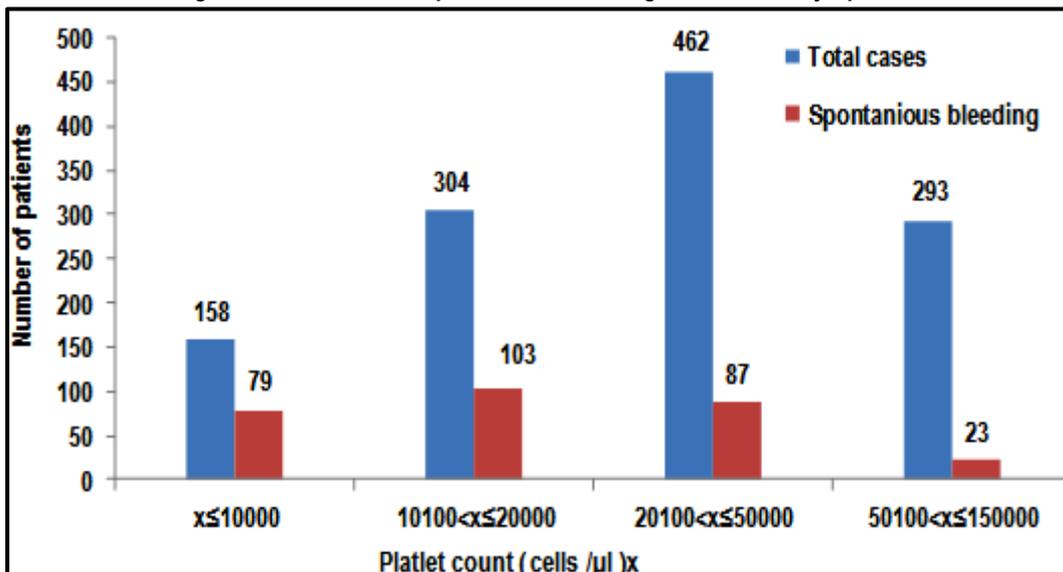


Figure 4: Correlation of spontaneous bleeding with thrombocytopenia



**OBSERVATIONS**

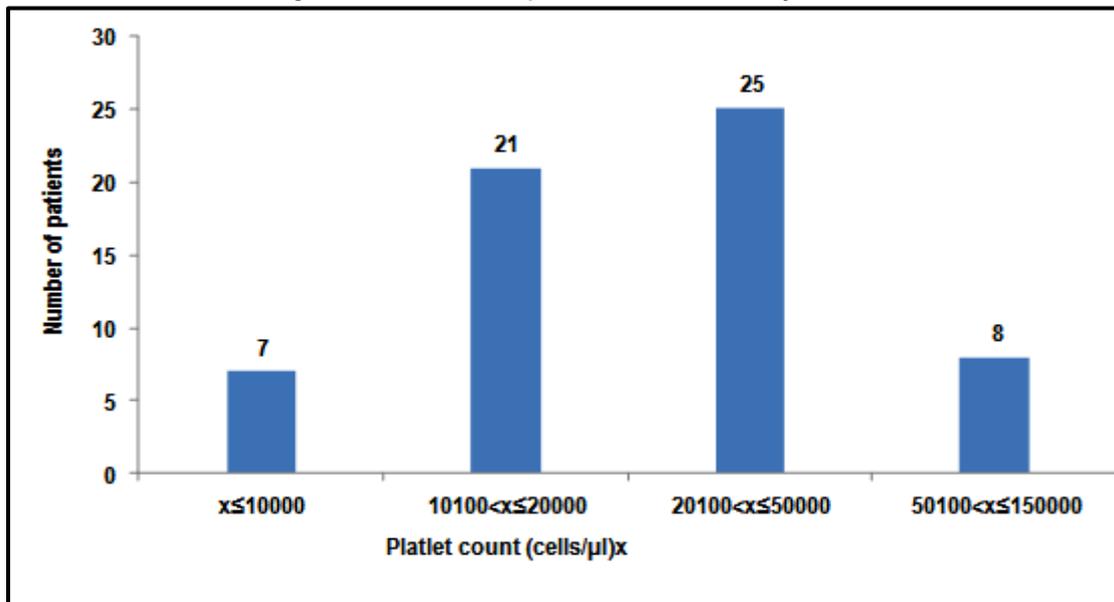
Out of 1217 cases of fever with thrombocytopenia, 858 were males and 359 were females. In this study 24% of the patients were in the range of  $50,000 < \text{platelet count} \leq 1,50,000$ , followed by 38%, 25% and 13% of the patients in the range of  $20,000 < \text{platelet count} \leq 50,000$ ;  $10000 < \text{platelet count} \leq 20,000$  and up to 10000 respectively. Out of 1217 cases, a definitive diagnosis could be made in 1017 cases. Among them dengue was the major cause accounting for 572 (47%) of the total cases. Second major cause was malaria in 243 (20%) cases followed by unexplained causes in 200 (16.5%) cases, septicemia in 128(10.5%), enteric fever in 12(1%) and leptospirosis in 6 (.5%) (table 1).

Clinical manifestations of thrombocytopenia were there in 512 patients. Bleeding tendencies are more commonly seen in patients with platelet count less than 20,000 (figure 1). Out of 512 patients, 468 (91.40%) patients had petechiae/purpura. Petechiae/purpura are more commonly seen in patients with platelet count less than 20,000 and usually seen up to platelet counts of 50,000 (figure 2). Spontaneous bleeding was seen in 292 (57%) patients. Out of the 292 cases having spontaneous bleeding, 152 (52%) cases had Sub-conjunctival hemorrhages, 116 (39.8%) cases had malena, 91(31.16%) cases had bleeding gums, 67(23%) cases had epistaxis, 55 (18.8%) cases had hematemesis, 24 (8.2%) cases had menorrhagia, 18(6%) cases

had hematuria and 6 (2%) case had bleeding per rectum (figure 3). Mixed infections with both dengue and malaria had highest bleeding tendency (57.14%). Among other causes, 55.3% cases of dengue, 35% cases of unexplained causes, 23.8% cases of septicemia, 27.12% cases of malaria had bleeding tendencies. (table 2). Generally, spontaneous bleeding was noted in platelet count  $< 20,000$  but in some may be due to qualitative defects, it was seen in platelet count in the range of  $> 50,000/\mu\text{l}$  also. Some patients with platelet count of 10,000 did not have spontaneous bleeding (figure 4).

Out of 1217 cases, 1156 cases had good recovery and 61 cases expired. Out of 61 cases of mortality, 52(85.24%) were due to septicemia and was the common cause followed by malaria 4(6.55%) cases, dengue 3(5%) cases, leptospirosis 1 case and 1 case due to mixed infection with malaria and dengue (table 3). In 61 mortality cases, majority of platelet count was in the range of  $10000-50000/\mu\text{l}$  (Figure 5). Patients having spontaneous bleeding and having platelet count  $< 10,000$  were transfused platelets. Supportive treatment including IV fluids, analgesics, and proton pump inhibitors were given to all patients having requirement of these. Out of 243 cases having malaria, 4 patients required hemodialysis; of them 2 were expired and 2 were discharged. All 1156 cases, who had good recovery were followed up and their platelet count was repeated at the time of discharge.

**Figure 5: Distribution of platelet count in mortality cases**



**Figure 6: Petechial rash on the leg of patient with Falciparum malaria**



**Table 3: Diseases that accounted to mortality**

Etiology	Total Number of Patients (n=1217)	Mortality	Percentage	$\chi^2$	p
Septicemia	128	52	85.24	90.567	<0.001
Malaria	243	4	6.50	48.372	<0.001
Dengue	512	3	5.00	293.44	<0.001
Leptospirosis	6	1	1.63	27.444	<0.001
Dengue + Malaria	56	1	1.63	0.992	>0.05

**Table 4: Comparison of cause of fever with thrombocytopenia**

Diagnosis	Nair study (%)	Srinivas study (%)	Prithviraj study (%)	Present study (%)
Dengue	14	14	15	47
Malaria	09	41	54	20
Septicemia	27	19	4	10.5
Enteric fever	15	24	6	1
Leptospirosis	00	00	00	.5
Others	18	2	21	16.5

## DISCUSSION

In this study infection was the established diagnosis in 83.50% of the cases. Dengue (47%) was the commonest cause of fever with thrombocytopenia followed by malaria (20%), unexplained cause (16.5%), septicemia (10.5%), dengue+malaria (4.5%), enteric fever (1%) and leptospirosis (.5%).

In a study by Srinivas et al<sup>3</sup> infections were also the most common cause but here malaria (41%) was the most common cause of fever with thrombocytopenia followed by enteric fever (24%), septicemia (19%), dengue (14%). In another study by Prithviraj patil et al<sup>4</sup> malaria (54%) remained the most common cause followed by dengue (15%), other causes (21%), enteric fever (6%), septicemia (4%) (table4). This may be due to seasonal and geographical variation. Incidence and prevalence of various infections vary seasonally and geographically. Some infectious diseases occur cyclically. A Study conducted during epidemic of a disease shows high incidence of the same. Therefore, duration and time period of study conducted also affect the study results. Available resources also affect the diagnosis of a disease.

In most of the studies infections represented the most important cause of fever with thrombocytopenia with a relative frequency ranging from 68% - 100%. However, in a study by Nair PS, Jain A, Khanduri U, Kumar V<sup>5</sup> (2003) at St.Stephen's hospital, New Delhi, for period of one and half years, a total of 109 cases (76 male, 33 female patients) were studied with the same criteria as in our study. Septicemia with 29 cases was the leading cause of fever associated with thrombocytopenia. Second common cause was enteric fever followed by dengue and malaria with 16, 15 and 10 cases respectively. In our study clinical manifestations of thrombocytopenia were there in 512 (42.7%) patients and petechiae/ purpura (91.40%) was the commonest bleeding manifestation followed by spontaneous bleeding (57%). In some other similar study by Srinivas<sup>3</sup> et al, Prithviraj patil<sup>4</sup> et al, petechiae/ purpura was also the commonest bleeding manifestation (73.9%) ,(63%) respectively followed by spontaneous bleeding (26.9%), (37%) respectively.

In a study conducted by Nair PS et al<sup>5</sup>, out of 109 patients 45 patients had thrombocytopenic signs accounting for 41.3%. Out

of 45 patients spontaneous bleeding was seen in 31 patients accounting for 69%, the commonest bleeding manifestation followed by petechiae / purpura accounting for (22.22%), because septicemia was the most common cause in their study which causes spontaneous bleeding more commonly than petechiae / purpura.<sup>6</sup>

In septicemia there may be a striking propensity toward intravascular fibrin deposition, thrombosis (consumption coagulopathy) which causes increased spontaneous bleeding. Infectious disease causes thrombocytopenia by impaired platelet production and increased destruction and Petechiae / purpura is the earliest manifestations of thrombocytopenia. A platelet count of approximately 5000–10,000 is required to maintain vascular integrity in the microcirculation. When the count is markedly decreased, petechiae first appear in areas of increased venous pressure, the ankles and feet in an ambulatory **patient (figure 6)**. **Wet** purpuras, blood blisters are thought to denote an increased risk of life-threatening hemorrhage in the thrombocytopenic patient. Excessive bruising is seen in disorders of both platelet number and function.<sup>6</sup>

In our setup 95 % of cases showed increasing trends in platelet count both at the time of discharge and in future follow up. While in Nair PS et al<sup>5</sup> study during the course of follow up platelet count showed increasing trends accounting for 63.3% and continuously falling counts in 7.3% in their study, because septicemia was the most common cause of fever with thrombocytopenia in their study which has very high mortality, while infections were the most common cause in our study in which platelet count improved rapidly on treatment. Srinivas<sup>3</sup> et al, Prithviraj patil<sup>4</sup> et al, also found results consistent with our study.

In our study septicemia was the most common cause (85.24%) of death followed by malaria (6.55%) and dengue (5%). In the study of Prithviraj patil<sup>4</sup> et al septicemia accounted for 60%, dengue accounted for 20% and other causes accounted for 20% of mortality. In the study of Srinivas<sup>3</sup> et al septicemia accounted for 78% and dengue accounted for 22% of mortality. In conclusion septicemia was the major cause of mortality. The findings were consistent with existing literature. A study done on mortality in

sepsis by Finfer S et al<sup>7</sup> shows 37.5% mortality. Another study by Kirsi-Maija et al<sup>8</sup> shows 18.4% mortality by sepsis. Variations in the definition of severe sepsis can explain differences in mortality rates among septic patients.<sup>9</sup>

Mortality depends on severity of disease, diagnosis made, available treatment and care, time of initiation of treatment and associated other medical illness. Mortality can be reduced by early and right diagnosis, timely and effective treatment and care. In future various pathological and microbiological imaging modalities should be needed for research and diagnosis of many viral hemorrhagic fevers.

#### LIMITATIONS

There were a few limitations to our study. This was a single centre study. In our study in 200 out of 1217 patients, cause of thrombocytopenia remained undiagnosed, because we could not take follow up of such large number of patients and some required investigations were not available at our centre.

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