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Original Research Article

Epistaxis in Dengue Haemorrhagic Fever: A Clinical Study

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Conflict of interest: Nil

Abstract:

Background: Dengue fever is caused by dengue virus of Flaviviridae family which is transmitted by Aedes aegypti mosquito. Dengue haemorrhagic fever (DHF) clinically presenting as epistaxis, oral/gum bleeding. Thrombocytopenia may be linked to DHF illnesses, with risks that can vary from severe bleeding or blood clotting to no risk at all. Thrombocytopenia is characterised by a platelet count that falls below the lower threshold of the normal range. The present study was carried out on 17 DHF with Epistaxis patients to established clinical profiling/ management of epistaxis in dengue haemorrhagic fever.

Materials and Methods: This prospective study was conducted at Tertiary Care Centre (HIMS), Ataria, Sitapur, UP from June 2021 - August 2021.Complete blood count including differential blood count, packed cell volume (PCV) and absolute platelet count (APC), PT/INR with NS1 card test were done. PCV and APC were monitored serially, at least once a day and if necessary more frequent intervals. Renal functions and liver enzymes were done routinely for all patients by using an auto-analyser. Ultrasonography of abdomen and radiograph chest was done by an experienced sonologist and radiograph chest were done for all patients. Fluid management of patient was according to WHO guidelines.

Results: A total of 17 dengue haemorrhagic fever (NS1 positive) with epistaxis cases were studied. Out of 17 cases, 14 cases were male (82.35%) and 3 cases were female (17.65%). Male: female was 4.67, aged 18-70 years, and mean age was 40 years. The mean and median patient ages were 40 and 35 years, respectively (95% confidence interval [95% CI]: 35.3-41.2 years). Platelet count range 12k to 150k with mean of 30.76k. Mean platelet count among patients with epistaxis those were not required nasal packing (9 Cases) was 44k and subsequently mean platelet count of those were required nasal packing (8 cases) was 22.25k. It was Observed, Hb range from 8.6 gm/dl to 14.7 gm/dl with mean of 11.24 gm/dl. Pt/INR was also observed, range from 13.67 Sec to 14.13 Sec with mean of 13.81 Seconds. Transfusion was required in 6 cases (35.3%) and subsequently non required cases were 11 (64.7%).The mean platelet count upon hospital discharge was 111.2 × 109/L (95% CI: 97.8-124.7 × 109/L). The mean lowest leukocyte count was 4.6 × 109/L (95% CI: 3.8-5.3 × 109/L), with a minimum value of 0.7 x 109/L and a maximum value of 57.0 × 109/L. Plasma leakage was observed in 100% of the cases (95% CI: 99.9) and hypotension and hemodynamic instability occurred in 89.9.0% and 99.87% of these cases respectively. Regarding the CBC, anemia was observed in 68.0% of the cases (95% CI: 77.8-89.4), and the mean lowest hemoglobin level of all patients who received any type of transfusion during hospitalization was 8.6 g/dL.

Conclusion: The present study was carried out in 17 patients with DHF-Epistaxis, so far it was done in a large samples as compared to reported case studies on DHF-Epistaxis. Hence, our results, on thrombocytopenia, platelet counts, Haematocrit levels, HB values, transaminase levels Lymphocyte counts, transfusions, and Nasal Packing etc could be considered as a land mark cut-off for the treatment and management of Dengue Hemorrhagic Fever with Epistaxis.

Keywords: Dengue Fever (DF), Dengue Haemorrhagic Fever (DHF), Dengue Fever with Bleed (DFB), Epistaxis, Thrombocytopenia. Nasal Packing.

Introduction

Dengue fever is caused by dengue virus of Flaviviridae family which is transmitted by Aedes aegypti mosquito. There are known four serotypes of dengue viruses (DENV1 to DENV4) found worldwide. The Dengue virus is an RNA virus with a positive strand that is enclosed in a protective capsule. It consists of three genes that encode the structural proteins: the nucleocapsid or core protein, the membrane-associated (M) protein, and the enveloped glycoprotein.

Additionally, it has seven non-structural proteins. There is a temporary cross protection across the four kinds, which diminishes and vanishes over the course of many months after infection [1]. Dengue fever is generally a self-limiting illness, with symptoms typically appearing after an incubation period of 8-10 days and lasting for around 2-7 days. The condition might be asymptomatic or exhibit a wide array of clinical signs, ranging from moderate fever to a potentially fatal shock syndrome [2].

It is one of the major public health concerns in about 100 tropical and sub-tropical countries of the world which includes Southeast Asia, South and Central America and Western Pacific. More than 2.5 billion people are affected by this disease. Around 50-100 million cases occur yearly and nearly 500,000 cases developing into fatal dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [3]. The mortality rate for individuals with treated dengue hemorrhagic fever or dengue shock syndrome is 1%, but it rises to 20% if left untreated [4]. The dengue virus infection has been classified by WHO & others in their guidelines which is delineated below in figure-1.

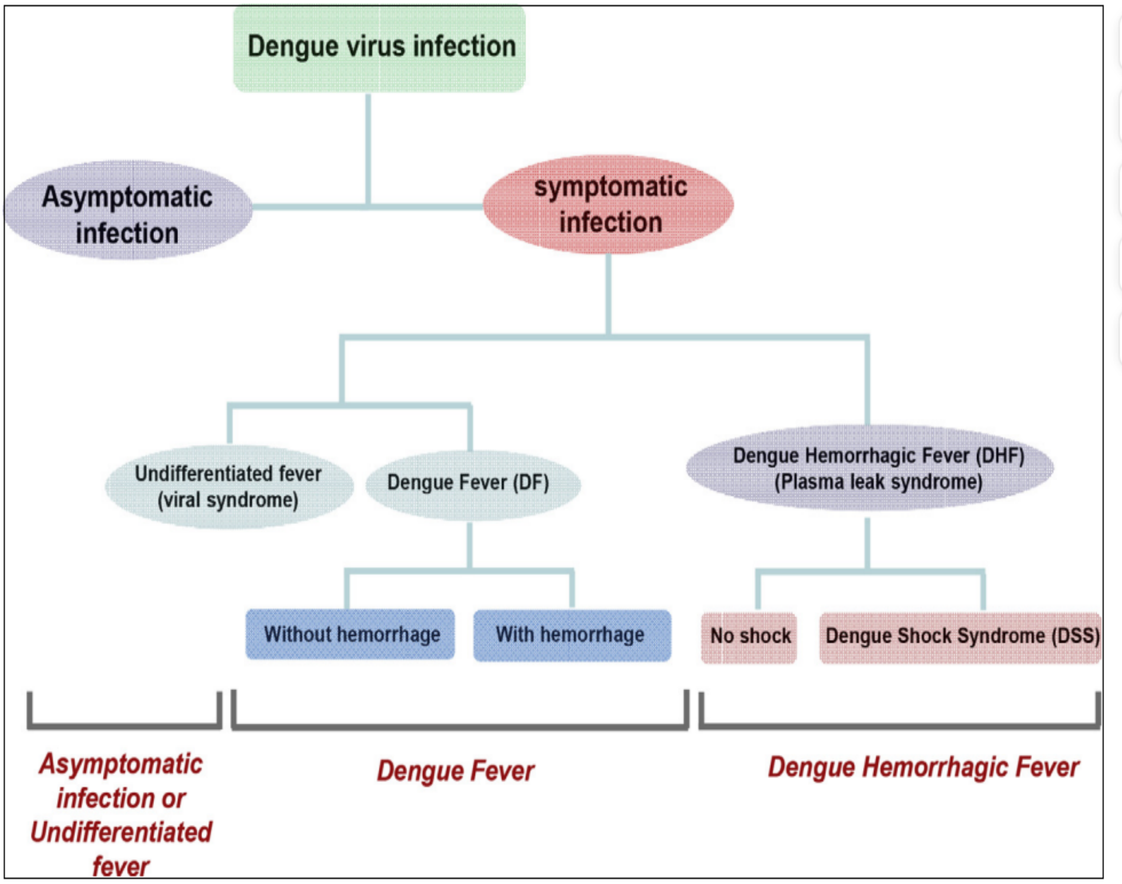

Figure 1: Flow chart of the classification of dengue infection [1].

Clinical Presentation: (Table-1) [1].

Dengue presents clinically as fever, headache, retro orbital pain and back ache. There are also bleeding episodes in more severe form, dengue haemorrhagic fever clinically presenting as epistaxis, oral/gum bleeding, petechiaes, ecchymosis and gingival bleeding [1,2,3]. The clinical symptoms, signs and duration of dengue infection is delineated below in table-1.

Table 1: The clinical symptoms of dengue infection [1]

Category	Symptoms	Duration
Dengue fever (DF)	"Flu-like" syndrome	2-7 Days
	Retro-orbital pain	
	Fever	
	Rash	
	Intense headache	
	Intense joint and muscle pain	
	Nausea	
Dengue Hemorrhagic Fever (DHF)	Plasma leakage	After 3-5 days of fever
	Pleural effusion, bleeding	
	Thrombocytopenia with <100,000 platelets/mL	
	Raise in hematocrit levels	
	Restlessness	
	Abdominal pain	
	Vomiting	
	Sudden drop in temperature	
Dengue Shock Syndrome (DSS)	Temperature reaches 37.5° C-38° C	After 3-5 days of fever
	Hypotension	
	Decrease in platelet count leads to leakage of	
	plasma subsequent shock	
	Fluid accumulation with respiratory distress	
	Critical bleeding	
	Organ impairment	
	Cardiorespiratory failure and cardiac arrest	

These symptoms may be attributed to a reduction in platelet count during dengue fever. The dengue virus has been extracted from many types of white blood cells, including polymorphonuclear leukocytes, monocyte/macrophages, and dendritic cells. Furthermore, it has been identified in megakaryocyte progenitors and platelets that are present in the bloodstream. These results indicate that the dengue virus may cause a decrease in platelet count by directly interacting with megakaryocytes and platelets. These Studies have shown that the dengue virus may decrease the number of platelets in the bloodstream, regardless of whether the virus attaches to or enters platelets or their early forms. Therefore, it is likely that two processes contribute to the development of thrombocytopenia in dengue: hindered production of platelets and destruction of platelets in the peripheral regions [5,6].

The diagnosis of dengue virus infection may be confirmed via laboratory testing, either by directly detecting viral components in the patient's serum or indirectly through serology. The detection of viral nucleic acid or viral antigen has a high level of specificity, but it is labour-intensive and expensive. On the other hand, serology has a lower level of specificity, but it is less expensive and more readily available. Thrombocytopenia may be linked to several illnesses, with risks that can vary from severe bleeding or blood clotting to no risk at all. Thrombocytopenia is characterised by a platelet count that falls below the lower threshold of the normal range, namely less than 150,000 platelets per microliter (μl) [7].

Megakaryocytes are the specific kind of blood cell responsible for the production of platelets. James Homer Wright originally established this link in 1906. He discovered that circulating platelets and a large bone marrow cell, today referred to as a megakaryocyte, had similar staining qualities when exposed to a modified Romanowsky stain. A single megakaryocyte generates a range of 1000 to 3000 platelets [8,9]. Thrombopoietin has significant influence on almost every stage of megakaryocyte development and maturation, and it is synthesised by the Liver. An inverse correlation exists between the standard platelet count and the average platelet volume, leading to a rather consistent amount of platelets in circulation. The body safeguards the overall mass of platelets, rather than the count of individual platelets. Roughly 33% of the overall platelet mass is typically stored in a splenic pool that may be readily exchanged. Platelets have a typical lifespan of 7-10 days as they move through the bloodstream. Hemostasis relies on a sufficient quantity of operational platelets, together with an intact coagulation (clotting factor) system. [10]

Degree of Thrombocytopenia:

Mild: platelet count of 100,000 to 150,000/µl, Moderate: platelet count of 50,000 to <1,00,000/µl and Severe: platelet count of <50,000/µl. Patients who are actively bleeding and have thrombocytopenia should get an urgent platelet transfusion to maintain platelet counts over 50,000/µl in most bleeding conditions, including disseminated intravascular coagulation (DIC). If there is bleeding in the central nervous system, the platelet counts should be kept above 1,00,000/µl. Transfusion used as a prophylactic measure against uncontrolled bleeding. Prophylactic platelet transfusion is used to avoid spontaneous bleeding in a majority of patients who have platelet counts below 10,000/µl owing to bone marrow suppression. However, for patients who are feverish or septic, higher thresholds (specifically, 20,000 to 30,000/µl) are used.[11,12]. Risk Factors for dengue haemorrhagic fever: (figure-2) [1,5]. The figure-2, described the risk factors which may be correlated with DHF as mentioned below.

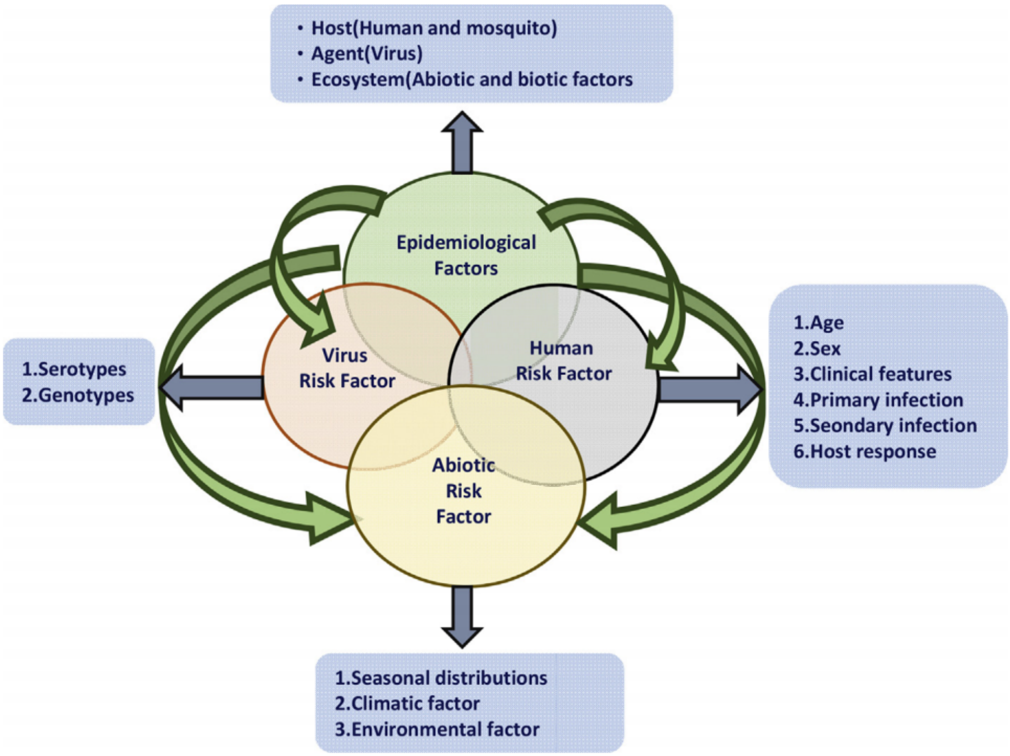

Figure 2: The risk factors correlate with dengue haemorrhagic fever [1].

Figure-2, illustrating the risks factors including viral factors, epidemiological factors, human factors and abiotic factors correlated with DHF development were presented.

Clinical Presentation

Dengue haemorrhagic fever (DHF) and Dengue shock syndrome (DSS): Dengue haemorrhagic fever (DHF) is a severe form of dengue fever which is manifested with haemorrhagic tendencies and can potentially develop into fatal dengue shock syndrome (DSS).The pathophysiological characteristics of DHF which demarcates it from dengue fever are plasma leakage, increased vascular permeability and abnormal haemostasis. The underlying mechanism causing DHF and DSS are still unknown but evidence points towards intensity of immunological response to dengue virus leading to pathophysiological cascade which ultimately causes plasma leakage [13,14]. Several previous studies also advocated that the Plasma leakage is the hallmark in the pathogenesis of bleeding manifestations in DHF [13,15]. Several studies have proposed autoimmunity of viral infection against human cells resulting from excessive production of cytokines and chemokines, including C3a, C5a, tumor necrosis factor (TNF)-α, interleukin (IL)-2, IL-4, IL-6, IL-8, IL-10, interferon (INF)-γ, monocytechemotactic protein (MCP)-1, and histamine. Activation of these inflammatory mediators disrupted endothelium leading to increased vascular permeability, leucopenia, thrombocytopenia, activation of the coagulation cascade, and fibrinolysis. Activation of all these cascades caused the hemorrhagic manifestations of DHF and more significantly DSS [10-17].

Many researchers have worked on DF/DHF/ DSS in India as well as abroad. A few studies on DHF/DSS are delineated below.

A study advocated that the hemorrhagic diathesis was a common complication of dengue fever. Such complications typically occurred toward the end of the febrile period, when the symptoms of classic dengue fever resolve. Clinically, bleeding was usually mild and manifests itself as epistaxis, gum bleeding, hematuria, and menorrhagia. Only occasional cases of severe gastrointestinal or retroperitoneal bleeding were reported. It was also advocated that the average platelet count on the day of onset of symptoms was 36× 109/L (range 33–44). The lowest platelet count was recorded 1 day before the onset of symptoms in 1 patient, on the day of onset of symptoms in 2 patients, and 1 day after the onset of symptoms in 1 patient. The average platelet count at the nadir of thrombocytopenia was 33 × 109/L (range 26–40), the study concluded as the retinal hemorrhages were exceedingly rare as acomplication of dengue fever [18].

A case study of a 38-year-old male with dengue fever along with its hemorrhagic manifestation of multiple purpura and petechiae [12]. In this study it was also observed that the patient continued to have reddish-coloured urine and had one more episode of gums bleed on his third day of admission with a platelet count of 6,000 x 10^9/L. Infectious diseases department was consulted who recommended transfusion six units of platelets. Platelet count continued to deteriorate further with a count of 2,000 x 10^9/L on his sixth day of admission but with clinical improvement in his fever and bleeding manifestations [19].

A case study also documented the inferior epigastric hemorrhage and rectus sheath hematoma as a consequence of dengue in a 49-year-old female presented with complaints of intermittent high-grade fever for the past 4 days, lower abdominal pain and altered sensorium for 1 day. [20].

A case of imported dengue hemorrhagic fever (DHF) in a 10-year-old Philippine boy has also been reported. The patient was admitted to the hospital with a 4-day history of high fever, headache, and malaise, and a 2-day history of epistaxis and hematemesis. Blood test revealed a white blood cell count of 2500/μL, a platelet cell count of 32 000/μL, and hematocrit levels of 45.2%. Ultrasonography revealed ascites surrounding the liver [21]. To the best of our knowledge, only case studies on DHF with gum/ rectus/ epistaxis/oral bleeding may not be established the clinical profiling, treatment and management strategies for DHF with epistaxis/oral bleeding. Therefore, the present study was carried out on 17 DHF with Epistaxis patients to established clinical profiling/ management of epistaxis in dengue haemorrhagic fever.

Aim and Objectives:

Aim: A clinical study of epistaxis in dengue haemorrhagic fever, in tertiary care centre, Ataria, Sitapur, UP. India

Objectives:

Primary Objective:

To identify all confirmed cases of dengue haemorrhagic fever (NS1+) with epistaxis followed by treatment.

Secondary Objectives:

1. To take detailed history and examine the patients
2. To investigate and treatment
3. To analyze all the data using SPSS software

Material and Methods:

This prospective study was conducted at Tertiary Care Centre, Ataria, Sitapur, UP from June 2021 - August 2021.

The study included 17 adults (aged 18 to 70 years) that were admitted with acute febrile illness with 2 or more of the following manifestations: headache, retro orbital pain, myalgia, arthralgia, rash, and hemorrhagic manifestations (DHF) with epistaxis. All these patients were evaluated with dengue serology using microwell ELISA method. Serology was considered positive if antibody titer is ≥1:400 on a late acute or convalescent phase serum specimen for either IgG or IgM antibodies.

A detailed history of each case was recorded in pre-structured case record forms including symptoms, signs and laboratory investigations. Detailed clinical examination was done at the time of admission and close follow up of the patient was done to watch for progression of disease. Blood pressure was measured by using an appropriate age matched cuff. Complete blood count including differential blood count, packed cell volume (PCV) and absolute platelet count (APC), PT/INR with NS1 card test were done. PCV and APC were monitored serially, at least once a day and if necessary more frequent intervals. Renal functions and liver enzymes were done routinely for all patients by using an auto-analyser. Ultrasonography of abdomen and radiograph chest was done by an experienced sonologist and radiograph chest were done for all patients. [1,8]. Fluid management of patient was according to WHO guidelines. [figures -3 and 4).

Inclusion Criteria

Inclusion Criteria: All diagnosed case of dengue haemorrhagic fever (NS1 positive) with epistaxis irrespective of age and sex.

Exclusion Criteria

- Patient not giving consent for study
- Study Design
- Prospective observational study.

Study Period

- 3 months (June-2021- August 2021)
- Study Design
- Prospective observational study.

Study Period: 3 months (June-2021- August 2021)

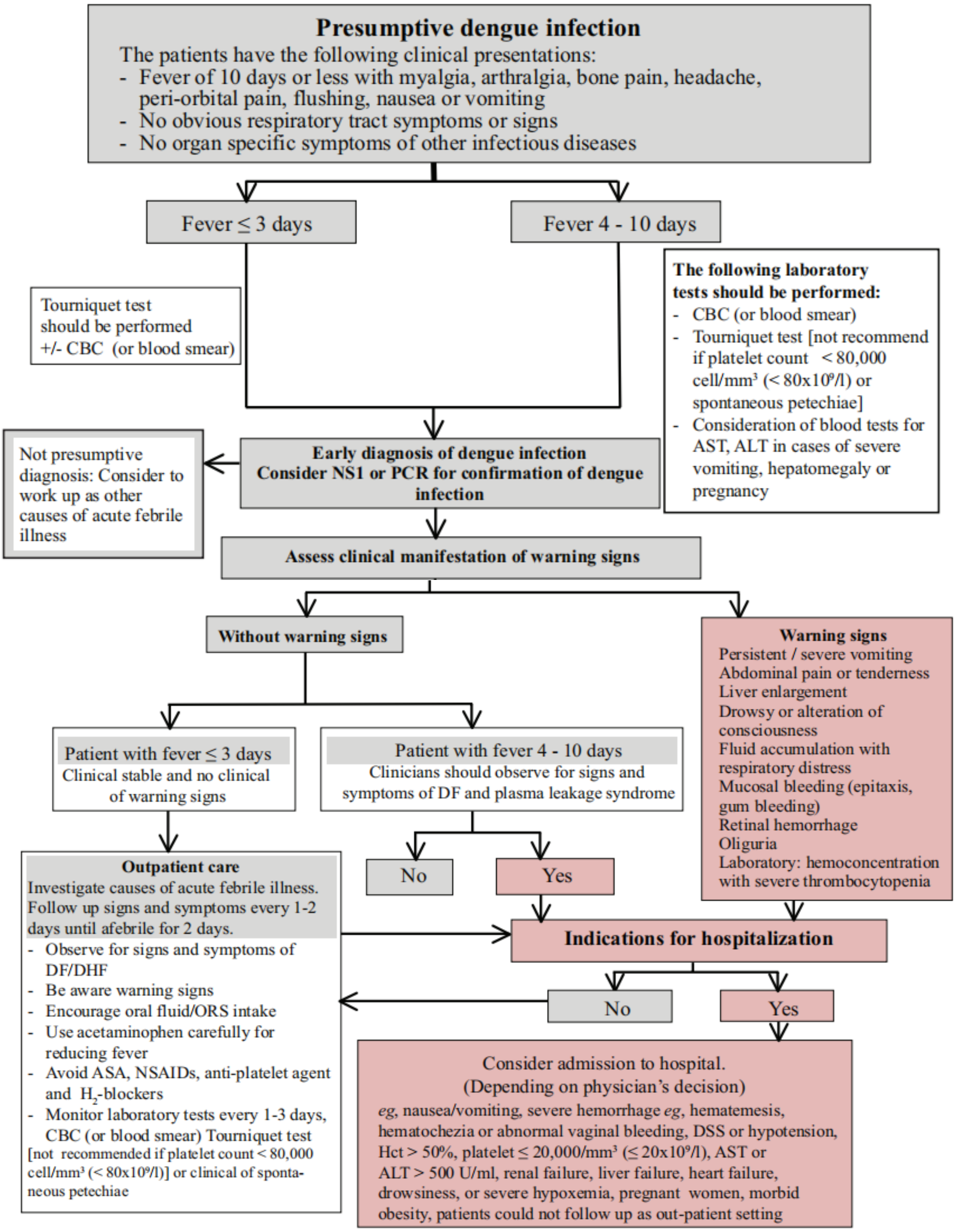

Figure 3: Guidelines for management of Dengue outpatients. [8]

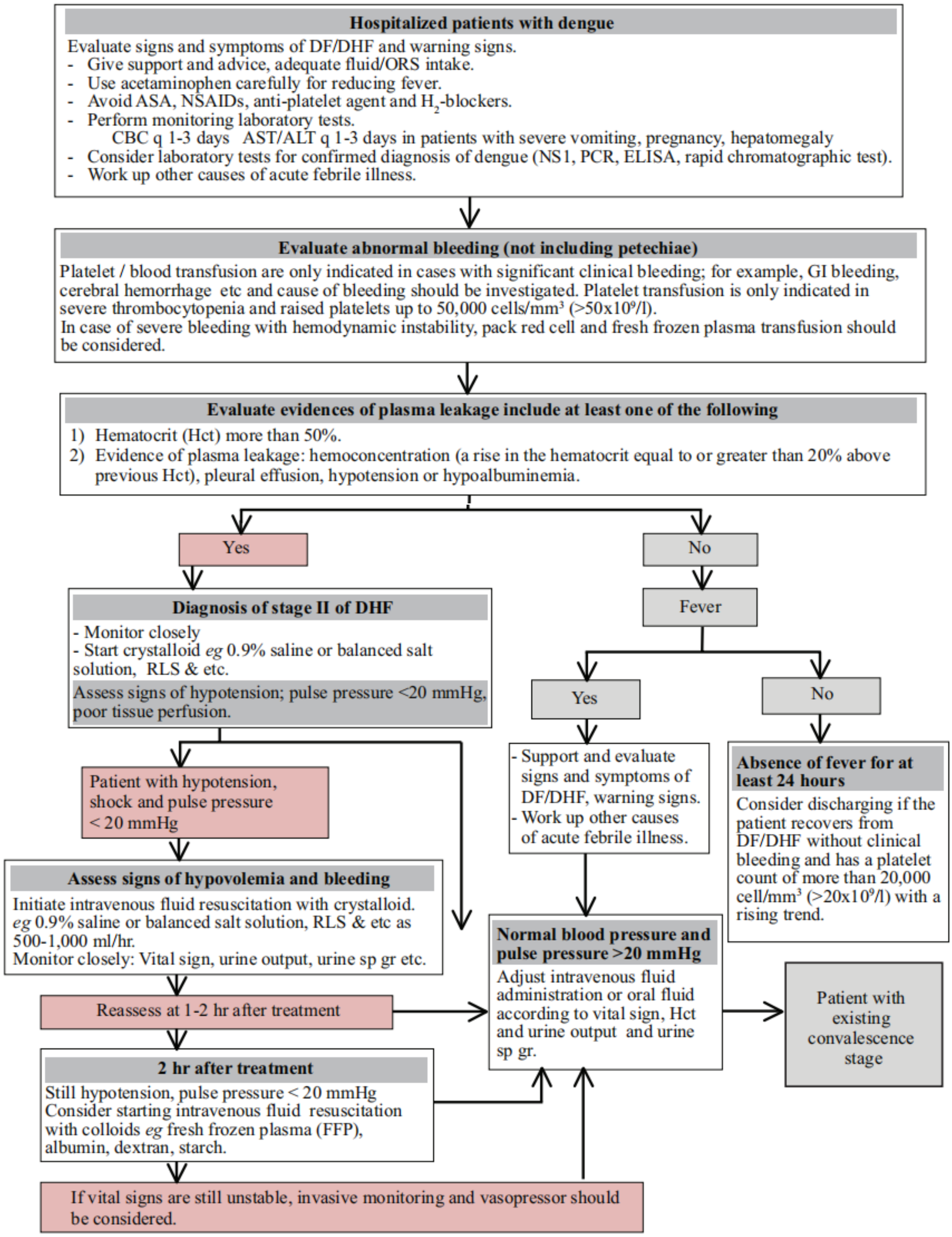

Figure 4: Guidelines for management of DF/DHF In patients

Statistical Analysis: Statistical analysis was done by using SPSS software version 26.3. Different groups were compared with chi-square test. Correlations were calculated using Pearson's correlation coefficient.

Results: A total of 17 dengue haemorrhagic fever (NS1 positive) with epistaxis cases were studied in Tertiary Care Centre, Ataria, Sitapur, Up India during the study period. Hemorrhagic manifestations with epistaxis were identified as hemorrhagic dengue according to criteria set by this study. In our study, 14 cases were male (82.35%) and 3 cases were female (17.65%). Male: female was 4.67, aged 18-70 years, and mean age was 40 years. The mean and median patient ages were 40 and 35 years, respectively (95% confidence interval [95% CI]: 35.3-41.2 years).

Table 2: Distribution of Age and Gender in dengue haemorrhagic fever- epistaxis patients.

Sl. No	Age (years)	Number & Percent-age%	Gender		P Value
			Male	Female	0.05
1	18-20	4, 23.52%	4	0	
2	21-30	2, 11.76%	2	0	
3	31-40	2, 11.76%	2	0	
4	41-50	4,23.52%	2	2	
5	51-60	3,17.64%	3		
6	61-70	2, 11.76%	1	1	
Total	18-70 years	17,	14	3	0.01

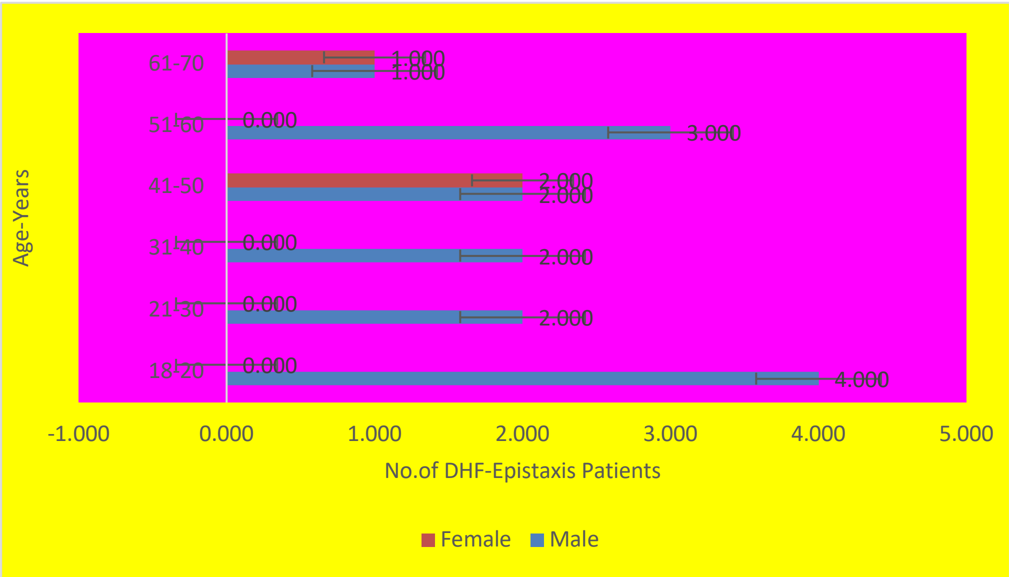

Figure 5: Distribution of Age and Gender in dengue haemorrhagic fever- epistaxis patients.

Platelet count range 12k to 150k with mean of 30.76k.

Mean platelet count among patients with epistaxis those were not required nasal packing was 44k and subsequently mean platelet count of those were required nasal packing was 22.25k. It was Observed, Hb range from 8.6 gm/dl to 14.7 gm/dl with mean of 11.24 gm/dl. Pt/INR was also observed, range from 13.67 Sec to 14.13 Sec with mean of 13.81 Seconds. Transfusion was required in 6 cases (35.3%) and subsequently non required cases were 11 (64.7%) [Figure-6].

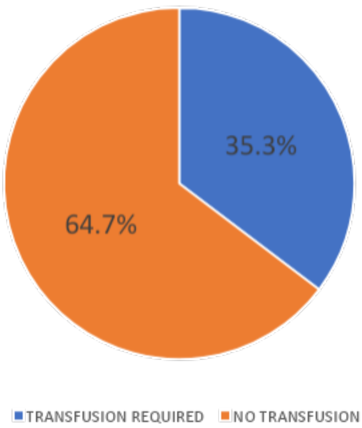

Figure 6: illustrating the % of Patients of DHF-Epistaxis, required/non required of Transfusion.

Packing was required in 8 cases (47.05%) and 9 cases (52.95%) were under non required [Figure-7].

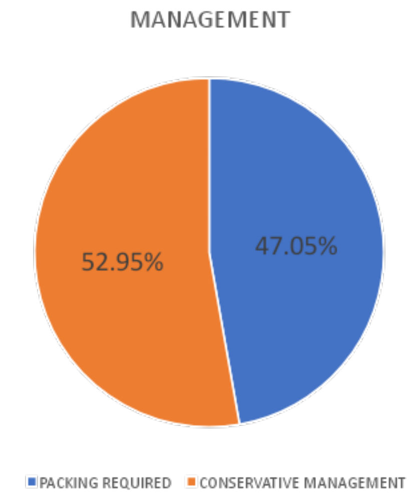

Figure 7: illustrating the % of Patients of DHF-Epistaxis, required/non required of Packing as a treatment-management.

Among 17 cases, 7 cases (41.17%) were having blood group AB, 5 cases (29.41%) were having blood group O, 3 cases (17.64%) were having blood group A, and only 2 cases(11.76%) were under blood group B [Figure-8]

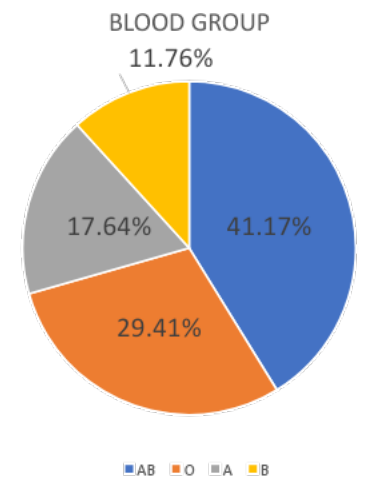

Figure 8: illustrating the % of Patients of DHF-Epistaxis, as per blood group.

The most frequently reported signs and symptoms, listed in order of incidence, were fever, headache and myalgia (Table 2). Bleeding occurred in 100% of the cases (95% CI: 99.9) and was mainly distributed as epistaxis (100%).

Plasma leakage was observed in 100% of the cases (95% CI: 99.9) and hypotension and hemodynamic instability occurred in 89.9.0% and 99.87% of these cases respectively. Regarding the CBC, anemia was observed in 68.0% of the cases (95% CI: 77.8-89.4), and the mean lowest hemoglobin level of all patients who received any type of transfusion during hospitalization was 8.6 g/dL. Eosinophilia was observed in 98.6% of the cases (95% CI: 88.6-93.9). Several platelet counts were performed for each patient during hospitalization. A mean platelet count of 30.76k x 109/L (95% CI: 22.25k-24.1 × 109/L), with a minimum value < 1 × 109/L of blood was observed when the lowest values for each patient were considered.

The mean platelet count upon hospital discharge was 111.2 × 109/L (95% CI: 97.8-124.7 × 109/L). The mean lowest leukocyte count was 4.6 × 109/L (95% CI: 3.8-5.3 × 109/L), with a minimum value of 0.7 x 109/L and a maximum value of 57.0 × 109/L (Table 3).

Table 3: Clinical characteristics in patients with dengue haemorrhagic fever with epistaxis admitted to Tertiary Care Centre

Signs and symptoms	n %	95% CI
Fever	17 ,100%	89.4-99.2
Headache	15, 88.32%	74.7-83.1

Myalgia		8, 47.05%	48.7-63.1
Abdominal pain		9, 52.94%	53.9-68.2
Arthralgia		6 , 35.29%	38.5-47.4
Vomiting		13, 76.47%	72.7-86.0
Retro-orbital pain		6, 35.29%	31.2-42.0
Skin rash		11, 64.70%	69.4-79.7
Lethargy		13, 76.47%	73.9-80.2
Itching		14, 82.35%	78.2-83.7
Respiratory distress		12,70.58%	69.3-78.6
Painful hepatomegaly		2, 11.76%	9.78-17.7
Grade	I	0	0
	II	14, 82.85%	78.5-83.8
	III	2, 11.76%	9.79- 18.1
	IV	1, 5.88%	4.97- 6.19
Epistaxis		17,100%	98.1-99.9

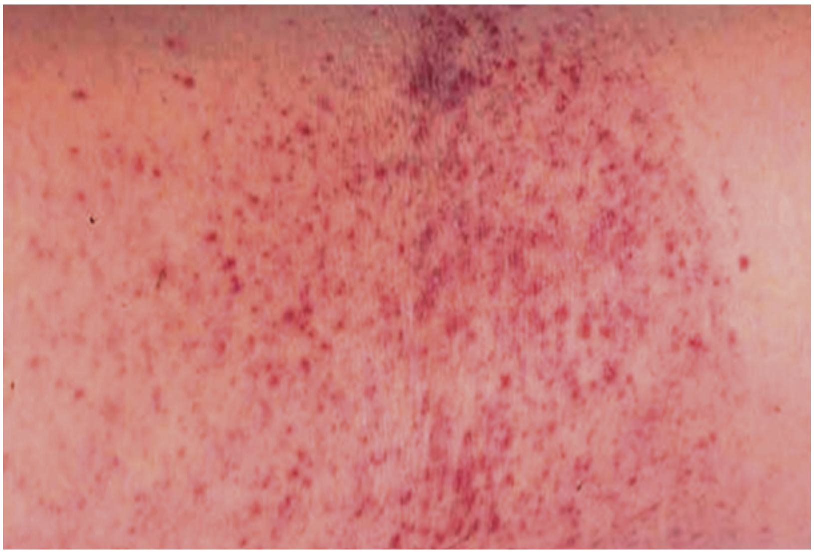

Figure 9: Skin Rash:

Table 4: Blood component transfusion characteristics of patients with dengue hemorrhagic fever with epistaxis

Variables		**n %**	**95% CI**	**P Value**
Transfusions by patient	YES	6, 35.29	31.2-42.0	0.05
	NO	11, 64.70	69.4-79.7	
Blood component transfused	Platelet concentrate	2, 11.76	9.79- 18.1	0.05
	FFP	3, 23.52	27.2-32.0	
	Platelet concentrate and FFP	1, 11.76	9.79- 18.1	
Transfusions by blood component	Platelet concentrate	2, 11.76	9.79- 18.1	0.05
	FFP	3, 23.52	27.2-32.0	
	Packed red blood cells	1, 11.76	9.79- 18.1	

Table 5: Description of hematic characteristics of patients with dengue hemorrhagic fever with epistaxis.

Variables		**n %**	**95% CI**	**P Value**
Hematological observations	Anemia	11, 64.70	69.4-79.7	0.05
	Leucopenia	16, 84.32	84.7-88.1	
	Thrombocytopenia	14, 82.35	78.2-83.7	
Eosinophilia		13, 76.47	73.9-80.2	
Platelets (×109/L) At discharge		17 ,100%	89.4-92.2	0.05
Platelets-Lowest		16, 84.32	84.7-88.1	
Total leukocyte count (per mm3)	- < 4000	11, 64.70	69.4-79.7	0.001
	- 4000-11,000	4, 23.52	27.2-32.0	
	- > 11,000	2, 11.76	9.79- 18.1	

Liver function tests	Serum asparate trans-aminase (> 40 IU/L)	16, 84.32	84.7-88.1	0.01
	Serum alanine transaminase (> 40 IU/L)	16, 84.32	84.7-88.1	
	- Serum bilirubin (> 1 mg/dl)	15, 88.32	74.7-83.1	
IgM hemagglutination" antibody titres (> 1:160)		16, 84.32	84.7-88.1	
Hematocrit (%)	>40	1, 5.88	4.97- 6.19	0.05
	30-40	2, 11.76	9.79- 18.1	
	<30	14, 82.35	78.2-83.7	

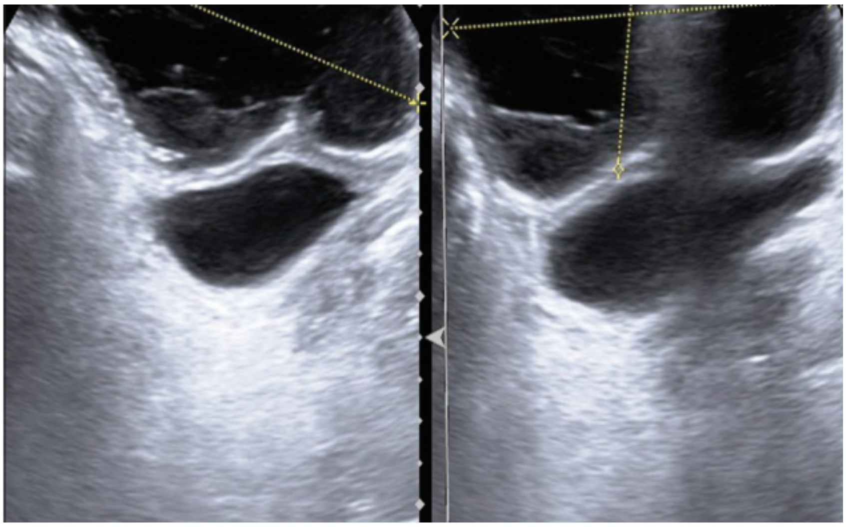

Figure 10: Ultrasound abdomen shows hematoma in the intra-muscular plane on the right lower abdomen.

Discussion

The wide spectrum of symptoms associated with dengue poses a challenge for physicians in accurately diagnosing the disease. Some folks are asymptomatic. Infants and toddlers who are infected often exhibit mild skin rashes and have fever, without any other symptoms. Older children and adults may also experience these mild symptoms, or they may exhibit typical dengue symptoms such as prolonged high fever lasting 2-7 days, intense muscle and bone pain, discomfort in the eyes, fatigue, headaches, minor bleeding, skin rashes, and feelings of nausea and vomiting. Dengue sickness has a bimodal fever response. During the first phase of the sickness, the patient has an elevated body temperature, which later decreases and then increases once again. Additional indications of dengue fever include reduced leukocyte count and thrombocytopenia [22,23]. In individuals with dengue fever, skin haemorrhages may manifest as red or purple regions on the body. The recuperation period for dengue fever may last for several weeks, during which patients may have symptoms of weariness and depression.[11-13]. Dengue is a prevalent illness that occurs often throughout the monsoon and winter seasons. Additionally, it is a prevalent factor in fever cases linked to thrombocytopenia. Thrombocytopenia is commonly found in varying degrees and often manifests with a severe form (platelet count < 50,000/µl). This severe form is associated with bleeding symptoms and may require platelet transfusion, either as a treatment or as a preventive measure. Platelets may be transfused for therapeutic purposes, such as treating acute bleeding or preparing for an invasive operation that may induce bleeding, or for preventive purposes, to avoid spontaneous bleeding.[6,14,23].

To date, the main risks which trigger DHF were still controversial owing to the complexity of disease progression caused by DENV-host interaction. Currently, DF and DHF remain to be viewed as a global issue. Understanding the pathogenesis and validating efficient prevention and control strategy are demanded against dengue invasions to humans. Factors from both host and pathogen that may correlate or enhance directly or indirectly DHF are still needed further investigations. DHF usually appeared following secondary dengue infections, but may sometimes appear following primary infections, especially in infants. In clinical, these patients display a higher level of DENV viral load and a slower rate of clearance of DENVs and viruse immune complexes than patients with classic DF syndromes [24,25].

Table 6: The risk factors correlate with DHF development.

Risks	Description
Antibody Dependent Enhancement (ADE)	*This theory was first described in 1964. *The antibodies from primary DENV infection lack the ability to neutralize secondary heterotypic DENV infection. *Cross-reactive antibodies form infectious virus-antibody complexes that enter cells, enhancing viral production.
Cytokine dysregulation	*DENV antibodies promote the entrance of a second serotype of DENV, activating a rapid production of cytokine (especially pro-inflammatory type 1 cytokines) *Induced cytokines affect vascular endothelial cells leading plasma leakage. *Cytokines as prognostic markers for disease severity (IFN-g, TNF-a, IL-6, IL-8,VEGF-A, IL-2 and RANTES L-1RA, MCP-1, TGF-b, HGF, IP-10, and sTNFRp75)
Changes of lipid profile	*Changes of lipid profiles correlated with DHF *Cholesterol and lipid rafts promoted DENV entry *LDL and HDL induce an imbalance in the inflammatory response correlated with the severity of dengue. *The increase TG, VLDL and HDL, and decrease of TC and LDL triggered DHF. *The lowest cholesterol and VLDL levels associated with severe bleeding and hepatic dysfunction. *LDL-C and LPS levels associated with risk of developing DHF and severity of plasma leakage

Clinically, DHF usually begins with a sudden rise in temperature and others symptoms similar to those of DF. The body temperature of DHF patients remains high for 2-7 days. Hepatomegaly and splenomegaly were sometimes observed. Hemorrhagic tendency may apparent in many ways such as positive tourniquet test, petechiae, ecchymoses or purpura; mucosal bleeding, and hematemesis. The most common hemorrhagic features are petechiae, where the Epistaxis and gingival bleeding are uncommon and gastrointestinal bleeding may be observed in severe cases. In DHF, bleeding may not correlate with the platelet counts and usually occurs once the fever has developed, resulting in the difficulty for diagnosis and prediction of DHF development. Presently, several hypotheses regarding DHF pathogenesis were proposed. Most of these hypotheses are not mutually exclusive, and together they harbour multiple elements that collectively may explain most of the phenomena observed in the various presentations of DENV infection. The pathogenesis of DHF grades I/II is complicated and multifactorial, involving both viral and host factors [26,27].

A previous study found that the dengue was the main cause of thrombocytopenia in patients with fever [17]. Our study also showed a higher number of male patients, which aligned with the findings of above study. The manifestation was most prevalent among individuals aged 25-35, with the highest incidence occurring between the ages of 18 and 50. This finding also aligned with a previous study [17] which reported that the majority of patients (92.5%) fell within the 18-50 age group. In contrast, a study found that the 40-49 age group was most affected (21.95%), followed by the 20-29 age group (21.14%). Our investigation revealed that the majority of patients had a moderate degree of thrombocytopenia, which aligned with the findings of previous studies [18,19]. Out of the 17 patients included in our research, all of them, accounting for 100% of the total, had epistaxis bleeding symptoms. Our investigation also revealed that a significant proportion of patients had cutaneous bleeding, namely in the form of rash or petechiae. This finding aligned with the previous researches [4,19].

Females were predominant in this study, accounting for 17.64% cases in comparison to the 48% reported in previous study [20]. The mean patient age in our study was 40 years (95% CI: 36.3-44.2 years), It was higher than that reported in other studies [21,22] These differences in age groups can be attributed to the case selection criteria and the types of existing coverage in the hospitals where the studies were conducted.

On assessing the distributions of observed clinical manifestations, fever and headache were the most frequent, results that were in agreement with several studies in the literature [4,5,6,22,23].

A study advocated that the hemorrhagic skin manifestation such as maculo popular rashes were in 41%, purpura in 34%, Petechiae in 19% and ecchymoses in 13% of the cases. It was reported that, among 100 cases, 56 patients showed only hepatomegaly and 46 splenomegaly and 30 patients showed hepatosplenomegaly, pleural effusion and 4 with signs of ARDS among them 3 patients were died despite of all possible treatment. Out of 100 patients, 99 showed leucopenia and 10 were anemic and 25 showed platelet count less than 1,50,000 cells/cumm [28].Our study results were almost similar with the above study.

In this study, bleeding occurred in 100% of cases with epistaxis. The occurrence of hemorrhagic manifestations was reported in 50.2% of 175 pediatric patients, and these cases included hematemesis in addition to petechiae and epistaxis.[16]. The bleeding occurred in 6% of the cases with gastrointestinal sites has been reported in a previous study and it was the most common factor.[13]. Another study from India reported that 15.1% of patients exhibited bleeding, with petechiae (9.3%) and epistaxis (2.7%).[11] Despite the concern of hemorrhagic manifestations, a previous study concluded that there was no correlation between hemorrhagic manifestations and serum platelet counts.[24] These data from the literature hinder a better comparison of results, mainly due to differences in the patient selection criteria. In contrast in our study the serum platelet counts and thrombocytopenia was directly correlated with hemorrhagic manifestations-DHF-Epistaxis.

The occurrence of hematocrit changes in this study also differed from those reported in the literature. In the present study, 64.7% of patients had anemia at some point during hospitalization. A study reported a mean hematocrit of 35.4%.[26]. Collection of the mean erythrocyte parameters only upon admission was insufficient since hematocrit variations can occur as a result of the hydro electrolytic status during patient hospitalization or because of bleeding that can lead to a reduced hematocrit.

The changes in transaminases have been described in more than 80% of the cases,[14,27] it was similar to that observed in our study, in which 95% of the cases had AST levels ranging from 140.7-478.7 IU/L and ALT levels ranging from 105.6-229.7 IU/L. These results demonstrated the importance of laboratory assessment upon admission and during hospitalization.

It has been reported in a study that, a total of 10.6% patients with dengue hemorrhagic fever received some form of transfusion, and 6.9% of these received platelet concentrate, 5% received FFP and 3.1% received packed red blood cells [28]. In India, a group of patients received platelet concentrate; among these cases, 31.8% were considered inappropriate transfusions and 26.9% received FFP.[15]

It has also been reported in a study that, a total of 12.6% patients received platelet transfusions.[26] In India, 42.6% of patients received platelet concentrates, 5% received plasma and 2.2% received packed red blood cells.[11]. The platelet concentrate transfusions were performed in 12% of cases, with no significant difference in the incidence of hemorrhagic manifestations when compared with the group that did not receive platelet transfusions, even in patients with platelet counts < 25.0 × 109/L.[13]. However, this study also showed that 46.5% of patients who received platelet concentrate transfusions had platelet counts higher than 88.0 × 109/L and 1.2% presented some type of bleeding.

In the present study, (6), 35.29% of patients received some form of transfusion (2), 11.76% of those patients received platelet concentrate, (3) 23.52 received FFP and only (1), 11.76% received packed red blood cells.

In an observational study of dengue patients in Martinique, several received platelet concentrate transfusions. Of the 350 evaluated cases, 9 (2.6%) received platelet transfusions, with a mean of 3.66 IU per patient (range: 2.8-13.2 IU), 3 (8.6%) received packed red blood cells and 2 (0.6%) received FFP.[17]

A study reported that the 3.4 IU of platelet concentrate were infused per patient,[15] a substantially smaller volume than that documented in our study (2.5 IU per patient).The reported mortality in a study from Thailand was 1.14%,[16] while mortality rates in Martinique and India were less than 1% [17] and 2%, respectively [14] but there was no mortality was observed in this study. The presence of bleeding or clinical severity increases the indication for transfusions, and the indicators of plasma leakage and elevated transaminase levels might be related to severity and subsequently increased mortality. More Research works with large sample size are required to establish accurate data for treatment & management of DHF-Epistaxis.

Conclusion

The present study was carried out in 17 patients with DHF-Epistaxis, so far it was done in a large samples as compared to reported case studies on DHF-Epistaxis. Hence, our results, on thrombocytopenia, platelet counts, Haematocrit levels, HB values, transaminase levels Lymphocyte counts, transfusions, and Nasal Packing etc could be considered as a land mark cut-off for the treatment and management of Dengue Hemorrhagic Fever with Epistaxis.

References

1. World Health Organization. Dengue hemorrhagic fever: diagnosis, treatment, prevention, and control. 2nd ed. 1997.

2. Khan S, and Rahman SZ, Oral bleeding in dengue fever - Our perspective, Bangladesh Journal of Medical Science, 2021; 20 (1): 11-16
3. Chlebicki MP, Ang B, Barkham T, and Laude A. Retinal Hemorrhages in 4 Patients with Dengue Fever. Emerging Infectious Diseases, 2005; 11(5):
4. Rao SV, Jacob GG, Raju NA, Ancheri SA. Spontaneous arterial hemorrhage as a complication of dengue. Indian J Crit Care Med 2016; 20:302-4.
5. Kusama Y, Ito K, Tajima S and Kutsuna S.A pediatric case of imported dengue hemorrhagic fever in Japan. J Gen Fam Med, 2017; 18:414–417.
6. Sreenivasulu T, Jahnavi K. A study of clinical profile of patients with Dengue fever at a tertiary care hospital. International Journal of Advances in Medicine,2018; | 5(1):202-206
7. Rai JK, Mehrotra N, and Adivasi R. Evaluating the Bleeding Tendencies of Dengue Fever Patients Hospitalized to the Indian Medical Centre. Journal of Cardiovascular Disease Research, 2023; 14 (12): 1460-66
8. World Health Organization Dengue: Guidelines for diagnosis, treatment, prevention, and control. Geneva: WHO; 2009.
9. Goel A, Patel DN, Lakhani KK, Agarwal SB, Agarwal A et al. Dengue Fever- A Dangerous foe. JIACM 2004; 5(3):247-58
10. Waidab W, Suphapeetiporn K and Thisyakorn U. Pathogenesis of dengue hemorrhagic fever: From immune to genetics, Journal of Pediatric Infectious Diseases, 2008; 3: 221–227
11. Adane T, Getawa S. Coagulation abnormalities in dengue fever infection: A systematic review and meta-analysis. PLOS Negl Trop Dis. 2021; 15(8): e0009666.
12. Lee IK, Liu JW, Yang KD. Fatal dengue hemorrhagic fever in adults: emphasizing the evolutionary pre-fatal clinical and laboratory manifestations. PLOS Negl Trop Dis. 2012; 6(2): e1532.
13. Lee VJ, Lye DCB, Sun Y, Fernandez G, Ong A, Leo YS. Predictive value of simple clinical and laboratory variables for dengue hemorrhagic fever in adults. J Clin Virol. 2008; 42(1):34-9.
14. Shastri PS, Taneja S. Dengue and other viral hemorrhagic fevers. Indian J Crit Care Med. 2021; 25; Suppl 2: S130-3. doi: 10.5005
15. Pawar A, Chafekar N. Clinical study of diagnosed cases of dengue fever in tertiary Care Hospital in North Maharashtra. MVP J Med Sci. 2018; 5(1):58-63. doi: 10.18311/mvpjms/2018/v5/i1/11018.
16. Khan KU, Khan MI, Uddin A, Imran M, Khan MS, Khalid R et al. Frequency of Bleeding Diathesis amongst patients presenting with dengue fever in Tertiary Care Hospital. PJMHS, 2021; 15(12):3915-7.
17. Raza MA, Khan MA, Ejaz K, Haider MA, Rasheed F. A case of dengue fever with hemorrhagic manifestations. Cureus. 2020; 12(6): e8581.
18. Rajapakse S, Rodrigo C, Maduranga S, Rajapakse AC: Corticosteroids in the treatment of dengue shock syndrome. Infect Drug Resist. 2014, 7:137-143
19. Chuansumrit A, Chaiyaratana W: Hemostatic derangement in dengue hemorrhagic fever. Thromb Res. 2014, 133:10-16.
20. Jeewandara C, Gomes L, Wickramasinghe N, et al.: Platelet activating factor contributes to vascular leak in acute dengue infection. PLoS Negl Trop Dis. 2015, 9:e0003459.
21. Logia P, Selvam V, Parasuraman V, Renuka MK, Rajagopalan RE. Predictors of clinically significant bleeding in thrombocytopenic dengue patients admitted to Intensive Care Unit: A retrospective Study. Indian J Crit Care Med. 2023; 27(12):888-94.
22. Suresh VK, Vijayan D, Kunhu S, Mohamed Z, Thomas S, Raman M. Thromboelastographic analysis of hemostatic abnormalities in dengue patients admitted in a multidisciplinary intensive care unit: A cross-sectional study. Indian J Crit Care Med. 2018; 22(4):238-42.
23. Radhika BV, Sooraj CS, Kamath V. A study of febrile thrombocytopenia International Journal of Contemporary Medical Research. 2019; 6(9):1.
24. Wang WH, Urbina AN, Chang MR, Assavalapsakul W, Lu PL, Chen YH and Wang SF, Dengue hemorrhagic fever e A systemic literature review of current perspectives on pathogenesis, prevention and control. Journal of Microbiology, Immunology and Infection, 2020; 53: 963-978.
25. Tantawichien T, Dengue fever and dengue haemorrhagic fever in adults Southeast Asian J Trop Med Public Health, 2015; 46 (Sup.1): 79-98.
26. Fujimotoa DE, Koifmanb S, Clinical and laboratory characteristics of patients with dengue hemorrhagic fever manifestations and their transfusion profile. Brazilian Journal of Hematology and Hemotherapy, 2014;36(2):115-120
27. Tantawichien T, Dengue fever and dengue haemorrhagic fever adolescents and adults. Paediatrics and International Child Health, 2012; 32 (S1): 22-27.
28. Kalayanarooj S, Clinical Manifestations and Management of Dengue/DHF/DSS. Tropical Medicine and Health, 2011; 39 (4): 83-87.