Etiological Profile, Morbidity and Mortality In Adult Thrombocytopenia Cases: A Study from Central India

Yadav B S*, Varma A V, Jain S K***,Toppo N A******

*Assistant Professor, Dept. of pathology NSCB, Medical College, Jabalpur-482003 ** Professor And Head, Department of Pathology, SAIMS Indore- 452001, ***Associate Professor, Department of Pathology, NSCB, Medical College, Jabalpur-482003 ****Associate Professor, Dept. of Community Medicine NSCB Medical College, Jabalpur-482003

Abstracts: Background: Thrombocytopenia is known since ages causing major catastrophes to human being. Researchers are always conducted in thrombocytopenic for better diagnosis, treatment and prognosis. Platelet counts in peripheral blood below 1 lac /µL termed as thrombocytopenia. Aims: To explore etiologies of thrombocytopenia in adults and to find incidence of morbidity, pattern of bleeding diathesis and mortality along with its association to severity of thrombocytopenia. Methods: It was a cross-sectional study done over a period of one year among 252 indoor cases of thrombocytopenia. Diagnosis was made with the help of clinical data and investigations performed. Bleeding manifestations and mortality were recorded and correlated with severity of thrombocytopenia. Results: The most common cause of thrombocytopenia was Septicaemia (24.21%) followed by megaloblastic anaemia (13.10%). Other causes included alcoholic liver disease, non-alcoholic liver disease and malignancies. Where 41 (16.27%) cases presented with bleeding manifestations. Incidence of bleeding manifestation was found highest that is 27.27% (P=0.008) in severe and least 9.44% in mild thrombocytopenia. Overall mortality rate was 19.84%, where 29.54%, 22.22% & 14.96% cases died with severe, moderate and mild thrombocytopenia respectively. Septicaemia (40%) was the most common cause of death followed by alcoholic liver disease (14%) and non-alcoholic liver disease (12%). Despite of being second most common etiology of thrombocytopenia, megaloblastic anemia showed only 8% mortality. Conclusion: Septicemia is leading cause of thrombocytopenia followed by megaloblastic anemia in Malwa region of Madhya Pradesh. Commonest bleeding manifestation in these cases is petechial hemorrhages seen more frequent in severe thrombocytopenia. More than half of the deaths in thrombocytopenic patients is attributed to septicemia and chronic liver disease. [Yadav S NJIRM 2017; 8(6):60-65]

Key Words: bleeding manifestation, chronic liver disease, megaloblastic anaemia, mortality, septicaemia, Thrombocytopenia

Author for correspondence: Bhagwan Singh Yadav, F - 04 Doctor's Colony NSCB Medical College Campus, Jabalpur – 482003. M: 9893122118 E- Mail: drbhagwan4@gmail.com

Introduction: Platelets play very important role in haemostatic mechanism. Normal platelet count ranges from 150,000 to 400,000/µL. A count below 100,000/µL is generally considered to constitute thrombocytopenia. However, spontaneous bleeding does not become evident until the count fall below 20,000/µL. Platelet counts in the range of 20,000 to 50,000/µLcan aggravate post- traumatic bleeding[1].

The causes of thrombocytopenia vary and can be associated with bleeding which could be a life threatening like intracranial bleeding. Thrombocytopenia is very common in severely ill patients admitted in intensive care units (ICU). Severe thrombocytopenia leads to risk of bleeding which is further aggravated in ICU patients where additional interfering factors are present that delay haemostatic mechanisms [2] .

Mechanism of thrombocytopenia varies from decreased platelet production e.g. vitamin B12 and folate deficiency, leukemia, sepsis (bacterial or viral infection) to increased destruction e.g. idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome (HUS),disseminated intravascular coagulation (DIC), post-transfusion purpura and sequestration of platelet in hypersplenism. Drugs other than chemotherapeutics which can cause thrombocytopenia are quinine, valproic acid, methotrexate, carboplatin, interferon, isotretinoin and heparin[3].

Early identification and intervention of underlying condition and platelet transfusions are required to prevent fatal outcome. Majority of studies on adult with thrombocytopenia have focused on specific etiology or associated with some symptom like fever. On the other hand, Bhalara et al[4] has taken different etiologies in consideration for one month duration study on adults during rainy season where mosquito transmitted diseases were the commonest cause. But, in India there is lack of extensive researches which

covers wide etiological spectrum of thrombocytopenia.

Thus, the present study was aimed to explore various causes, bleeding manifestations, mortality, its incidence and correlation with etiology and severity of thrombocytopenia along with presentation of bleeding in adult thrombocytopenia patients of Malwa region (Madhya Pradesh) of central India.

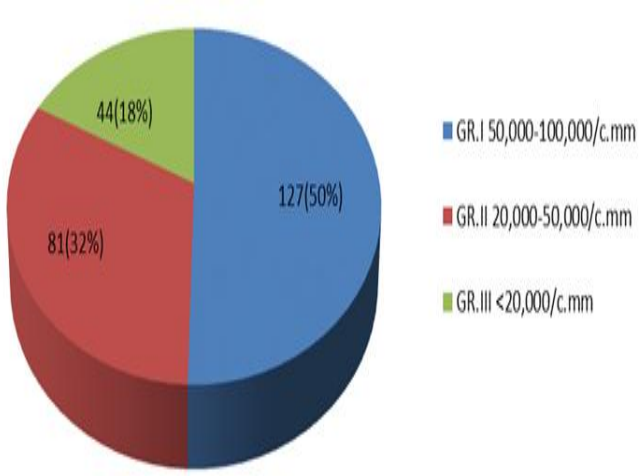
Methods: This cross sectional study was conducted on adults(>18 years of age) presenting with thrombocytopenia (platelets count <100,000/µL on admission) at tertiary healthcare centre, Indore, Madhya Pradesh for one year (January 2012 to December 2012) duration after obtaining approval of ethical committee. An inform consent was taken from the subjects. This was an observational study. Subjects who had undergone chemotherapy for neoplasm or already received platelet transfusion prior to admissions were excluded from study. Clinical case history was followed by haemogram on five part differential hematology analyzer (Mindray BC 3200), peripheral smear and subsequently urine and stool samples analysis for occult blood. Platelet counts obtained from haematology analyser were confirmed by peripheral smear examination.

Subjects presenting with thrombocytopenia were categorized into three groups on the basis of platelets counts. Group I (Plts count -50,000-100,000/µL) was consider as Mild thrombocytopenia, Group II (Plts count 20,000-50,000/µL) as Moderate thrombocytopenia and Group III (Plts count <20,000/µL) as severe thrombocytopenia. Bone marrow aspiration and trephine biopsies were carried out as per the clinical indications. The bone marrow aspiration procedure and staining were carried out by standard methods. All the bone marrow aspirates were stained with May-Grunwald Giemsa and trephine biopsies were stained by haematoxylin and eosin. Special staining of perl's stain, myeloperoxidase, Sudan black B and Periodic acid Schiff were done on aspirate smears as needed. Reticulin stain was done on biopsy where ever indicated.

Statistical analysis was done by chi-square test & unpaired t test. And p value of <0.05 was considered for significant association.

Result: Total 252 adult thrombocytopenia cases with 135(53.57%) males &117(46.43%) females fulfilling the criteria were included in present study, where 50% of cases were found with mild thrombocytopenia followed by moderate 32% and severe thrombocytopenia 18% (figure-1).

Fig 1: Thrombocytopenia cases as per platelet count groups



Etiology of thrombocytopenia: In present study out of 17 different etiologies of thrombocytopenia, the most common etiologies was septicaemia (24.21%)followed by megaloblastic anemia (17.46%), alcoholic liver disease (ALD) (11.11%), non-alcoholic liver disease (NALD) (8.3%), malaria (P. Falciparum & P. Vivax) (8.73%), malignancy (7.1%) and haematological malignancy (6.7%). On the other hand, Leptospirosis (0.79%), ITP (0.79%), TTP (0.40%), and aplastic anaemia (1.19%) were the least common.

B) Morbidity (bleeding diathesis due to thrombocytopenia)

1) Association of bleeding diathesis and severity of thrombocytopenia.

Table 1: Bleeding manifestation incidence in different platelet count groups

Bleeding cases	Case distribution as per platelet count						Total cases N=252	
	GR. I N=127		GR.II N=81		GR. III N=44			
	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
	12	9.44	17	21	12	27.27	41	16.27

As shown in table number 1; 41 patients (16.27%) of total thrombocytopenia cases presented with bleeding manifestations. Incidence of bleeding manifestation was found highest in severe thrombocytopenia group III that is 27.27% (P=0.008) and was least in mild thrombocytopenia group I (9.44 %). 17 cases (21%) of moderate thrombocytopenia were found with bleeding. Thus the percentage of cases with bleeding manifestations increased with the severity of thrombocytopenia (P=0.008).

2) Pattern (presentation) of bleeding diathesis: In this study the commonest bleeding manifestation was in the form of petechiae (31%).Petechiae was seen in 66% cases with severe thrombocytopenia (p=0.025)(tabale-2**)**

Table 2: distribution of various presentations of bleeding in cases as per platelet counts

No	Presentation of bleeding	Case distribution as per platelet count				
		GR. I N=127	GR. II N=81	GR.III N=44	Total cases	Total cases (%)
	Total cases	12	17	12	41	100%
1	Petechiae	2	3	8	13	31.70
2	Haematemesis	5	6	0	11	26.83
3	Malena	5	3	2	10	24.4
4	Haematuria	4	3	1	8	19.5
5	Menorrhagia	0	2	5	7	17.07
6	Haemoptysis	1	2	0	3	7.32
7	Epistaxis	0	0	1	1	2.44

3) Etiology/causes of bleeding diathesis in thrombocytopenia cases: In present study, Septicemia was the commonest etiology (19.5%) among patients with bleeding manifestations followed by alcoholic (17%) and non-alcoholic (14.6%) liver diseases, haematological malignancy (AML) (9.75%) and megaloblastic anemia (9.71%) respectively .

C) Mortality

1) Association of mortality and severity of thrombocytopenia: In present study total 50 patients (19.84%)died during treatment. Where 29.54% cases with severe thrombocytopenia (Gr. III), 22.22% & 14.96% patients ofGr. II & Gr. I respectively. Thus the rate of death in thrombocytopenia cases was inversely proportional to platelet counts i.e. lower the platelet counts higher was the mortality (table-3).

Table 3: Mortality in patients as per platelet counts

S.no.	Diagnosis	Total death (n=50)	%
1	Septicemia	20	40%
2	Alcoholic liver disease	7	14%
3	Non-Alcoholic liver disease	6	12%
4	Haematological malignacy	4	8%
5	Megaloblastic aneamia	4	8%
6	Cancer	4	8%
7	DIC	3	6%
8	Renal failure	1	2%
9	Aplastic anemia	1	2%
	Total	50	100%

2) Causes/etiologies of thrombocytopenia in mortality cases: According to table-4; in present study most commoncause of death was septicaemia (40%).Megaloblatic anemia showed lower mortality rate i.e. only 8% (table-4) despite of being second most common etiology.

Table 4: Outcome (mortality) of thrombocytopenia cases as per their severity

	Case distribution as per platelet count			
	GR.I N=127	GR.II N=81	GR.III N=44	Total cases
No of deaths	19	18	13	50
Live cases	108	63	31	202
% of death	14.96	22.22	29.54	

Discussion: There are limited literatures in Indian context which has explored causes and clinical presentation of thrombocytopenia and association of its severity to bleeding manifestation and mortality. Most of the studies based on thrombocytopenia are specific to etiology or associated with some condition like fever. In this broad spectrum study, various etiologies & manifestations of thrombocytopenia cases especially in central India have been explored explicitly.

The etiology and its frequency varies in different population groups and it could be attributed to multiple variables like differences in methodology, stringency of diagnostic criteria, geographic area, period of observation, genetic differences, nutritional status and prevalence of infections.

In our study, it was found that males (53.57%) had more preponderance of thrombocytopenia compared to females (46.43%). Similar findings were seen in study by Nair et al[5] in New Delhi of fever associated thrombocytopenia in 107 cases where 69.7% male & 30.3%female cases were affected.

In present study, among 17 different etiologies of thrombocytopenia, septicaemia (24.21%) was found as the most common cause followed by megaloblastic anemia (17.46%), alcoholic liver disease (11.11%) and non-alcoholic liver disease (8.33%).

Nair et al[5] studied thrombocytopenia with fever in New Delhi and showed similar etiologies i.e., Septicaemia (26.6%) as the leading cause of thrombocytopenia followed by Typhoid fever (14.7%), Dengue (13.8%), Megaloblastic anemia (11.9%), Malaria (9.2%) & hematological malignancies (3.7%).

On the other hand, study by Bhalara et al [4] on clinical and etiological profile of thrombocytopenia in adults found dengue (28.6%) and malaria (22.8%) as most common etiologies followed by chronic liver disease (15.2%), hypersplenism (12.3%) and septicemia (6.3%). Dengue and malaria were found to be the commonest causes due to the higher prevalence of these infections during the study period i.e., rainy season, which could be contributing factor for higher variation between different studies.

Studies conducted on thrombocytopenia with fever among adult by Gandhi et al [6], Patil et al[7], Dash et al[8] and Kumar et al[3] also found malaria and dengue as the most common etiologies followed by septicemia, enteric fever. As these studies included only thrombocytopenia with fever cases, percentage of infective etiologies were higher, while in our study, incidence of dengue was low (1.59%) compared to these studies due to inclusion of cases having variable etiologies of thrombocytopenia unspecific to fever and Malwa region of Madhya Pradesh is also not endemic for dengue. The cases of megaloblastic anemia with thrombocytopenia were higher in our study. The fact behind could be the incidence of megaloblastic anemia in adults is higher in Malwa region of Madhya Pradesh which may be related to dietary factors as explained in study by Joshi et al [9].

We found chronic liver disease (alcoholic liver disease (11.11%) and non-alcoholic liver disease (8.33%)) etiology contributed 19.44% cases of thrombocytopenia which was quite comparable with a study conducted by Bhalara et al[4] having 15.2% cases.

The development of thrombocytopenia in patients with chronic liver disease is complex and multifactorial. Pathogenesis includes hypersplenism, secondary to portal hypertension, aberrations of the immune system resulting in the formation of antiplatelet antibodies and/or immune-complexes that bind to platelets and facilitate their premature clearance and thrombopoietin deficiency secondary to liver dysfunction [10,11].

In our study malignancy contributed 7.1% cases of thrombocytopenia. Cancer as etiology was not reported in other studies probably they had carried at the centres not having facilities for cancer therapy.

We found 50.45% (127) cases of mild thrombocytopenia, 32.14 %(81) cases of moderate thrombocytopenia&17.46 %(44) cases severe thrombocytopenia. Where cases of mild thrombocytopenia were significantly higher than moderate & severe thrombocytopenia cases (0.000) These findings are in accordance with Gandhi et al[6], Nair et al[5], Bhalara et al[4], and Kumar et al[3] studies, where they found 57.17%, 56.8%, 59.8% and 50% incidence of platelet count >50000/µL respectively.

In our study 16.27% (41 patients) of total thrombocytopenia cases presented with bleeding manifestations. Incidence of bleeding manifestation was found highest in severe thrombocytopenia (group III)[27.27%] and least in mild thrombocytopenia (group I) [9.44 %] whereas in moderate thrombocytopenia (group II), only 17 cases [21%] presented with bleeding. Thus the percentage of cases with bleeding manifestations increased with severity of thrombocytopenia (P=0.008).

In present study among total cases with bleeding manifestation, the commonest type of bleeding presentation was petechiae (31%) followed by hematemesis (26.83%) and malena (24.4%). Petechiae was seen in 66% cases with severe thrombocytopenia (P=0.025).

Nair et al[5] reported in study of thrombocytopenia with fever found bleeding manifestations in 41.3 % cases. Our study showed bleeding manifestation in 16.47%

cases as we have included all cases of thrombocytopenia irrespective of febrile status. Nair et al[5] also got petechiae/purpura & gastrointestinal bleed as commonest manifestations in thrombocytopenic patients which is similar to present study.

Patil et al[7] study showed 23% cases presenting with bleeding manifestation, out of this 73.9% presented with petechiae followed by spontaneous bleedings in 26.9% while in a similar study by Lohitashwa et al[12] purpura (63%) was the commonest bleeding manifestations followed by spontaneous bleeding (37%).

Dash et al[8]study on thrombocytopenia with fever found that 53% cases presented with bleeding manifestation, out of which 66% and 34% cases presented with petechiae/purpura and spontaneous bleeding respectively.

In present study septicemia was the commonest etiology (19.5%) among patients with bleeding manifestations followed by Alcoholic (17%) and Non Alcoholic (14.6%) liver diseases, haematological malignancy (9.75%) and Megaloblastic anemia (9.71%) respectively. While Nair et al[5]also got septicemia as the commonest cause of bleeding manifestation, while typhoid fever & dengue were next common causes in contrast to liver diseases in present study. Bhalara et al[4] found bleeding secondary to thrombocytopenia in 46 patients with dengue (60.8%), as the most common etiology followed by chronic liver disease, sepsis, haematological malignancy, and ITP. Dengue was found as the most common etiology probably due to rainy season in which study was conducted.

In our study total 50 patients (19.84%) died during treatment. Among which 29.54% 22.22% & 14.96% cases were with severe (Gr. III), moderate (Gr. II) & mild (Gr. I) thrombocytopenia respectively. Thus the rate of death in thrombocytopenia cases was inversely proportional to platelet counts i.e. lower the platelet counts higher was the mortality.

It is revealed that among all the causes of thrombocytopenia, septicaemia cases showed maximum mortality (32.78%) along with Aplastic anemia & ALL (33.33%) while Megaloblastic anemia which was second commonest cause of thrombocytopenia, had least mortality (6.06%).

Similar to our study Dash et al[8] found 22% mortality in there study on fever with thrombocytopenia, out of which 68.18% mortality occurred in severe thrombocytopenia cases. Major cause of mortality was septicemia (77%) followed by malaria (18%) and dengue (5%).

Study by Nair et al[5]of thrombocytopenia with fever also showed highest mortality in septicemia cases, while study of Malik et al [13] showed Aplastic anemia as more prevalent cause among younger age groups & had very high mortality. Patil et al[7] in their study noticed mortality in 5% of patients with major etiology i.e. septicemia in 60% patients followed by malaria and viral fever. In the study by Lohitashwa et al[12]septicemia accounted for 78% and dengue for 22% of mortality. Kumar et al[2] study on fever with thrombocytopenia found 9.47% mortality where 83.33% were due to septicemia with multiorgan dysfunction and 16.67% were due to complicated malaria.

Conclusion: It has been concluded that Thrombocytopenia is a feature of many transient illnesses or serious life-threatening diseases. Its etiology, severity and mortality rates are associated with each other.

In terms of etiology, septicemia was found as the most common cause and TTP as least common cause. Apart from etiology, septicemia also showed highest mortality rate in contrast of megaloblastic anemia which showed lower mortality rate despite of being second most common etiology.

Septicemia was also most evident and prominent etiology among the subjects, who presented with bleeding manifestation followed by alcoholic and non-alcoholic liver disease. Petechial hemorrhage was the most common bleeding manifestation followed by hematemesis and malena.

References:

1. Frank F, Colin C, David P, Bryan R. De gruchy's clinical Hematology in Medical practice. 5th ed .New Delhi: Blackwell sci. ltd;2010. Chapter 14, The Hemorrhagic disorders; Capillary and platelet defects;p.360-405.

2. Greinacher A, Selleng K. Thrombocytopenia in the Intensive Care Unit Patient. Hematology. 2010;1:135-143.
3. Kumar P, Chandra K. A Clinical study of febrile thrombocytopenia: A hospital-based retrospective study. Indian Journal of Clinical Practice. 2014; 24(10):952-957.
4. 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;4:7-10.
5. Nair PS, Jain A, Khanduri U, Kumar V. A Study of Fever-associated Thrombocytopenias. JAPI.2003;(51): 1173.
6. Gandhi AA, Akholkar PJ. Clinical and laboratory evaluation of patients with febrile thrombocytopenia. National J of Medical Research. 2015; 5(1):43-46.
7. Patil P, Solanke P, Harshe G. To study clinical evaluation and outcome of patients with febrile thrombocytopenia. Int J of Scentific and Research Publications. 2014;4(10):1-3.
8. Dash HS, Ravikiran P, Swarnalatha G. A study of clinical and laboratory profile of fever with thrombocytopenia and its outcome during hospital stay. International J Scientific Research. 2013 Nov; 2 (11): 445-447.
9. Joshi P, Joseph D, Bajpai P, Manoria P, Joshi P, Yadav V, Dagore H, Jha R.K. Prevalence of anemia among the general population of malwa (m.p), India. J Evaluation of Med and Dental Sciences. 2013;2(1):46-51.
10. Weksler BB. Review article: the pathophysiology of thrombocytopenia in hepatitis C virus infection and chronic liver disease. Aliment Pharmacol Ther 2007;3(2):217-25.
11. Poordad F. Review article: thrombocytopenia in chronic liver disease. Alimentary Pharmacology & Therapeutics. 2007;26(1):5–11.
12. Lohitashwa SB, Vishwanath BM, Srinivas G. Clinical and Lab Profile of Fever with Thrombocytopenia. Abstract Free Paper Oral Presentation - APICON, 2008. Available at: http://www.japi.org/march_2009/oral_presentation.
13. Malik S, Sarwar I, Mehmood T, Naz F. Aetiological considerations of acquired aplastic anaemia. J Ayub Med Coll Abbottabad. 2009;21(3):127-130.

Conflict of interest: None

Funding: None

Cite this Article as: Yadav S, Varma V,Jain K,Toppo A. Etiological Profile, Morbidity and Mortality In Adult Thrombocytopenia Cases: A Study from Central India. Natl J Integr Res Med 2017; 8(6):60-65