Dr. Raman Sharma
Professor, Department of
Medicine, GMC, Amritsar,
Punjab, India

Dr. Ghritachi Sandal
Senior Resident, Department
of Medicine, GMC, Amritsar,
Punjab, India

Dr. Ajay Chhabra
Professor, Department of
Medicine, GMC, Amritsar,
Punjab, India

Clinico-etiological profile in patients of thrombocytopenia

Dr. Raman Sharma, Dr. Ghritachi Sandal and Dr. Ajay Chhabra

Abstract
Introduction: Thrombocytopenic patients in the hospital suffer a twofold greater mortality rate than those who are not. The etiologies of thrombocytopenia are diverse. Various studies on thrombocytopenia are done in the past have related to specific etiologies. But, in India there is lack of extensive researches which covers wide etiological spectrum of thrombocytopenia.
Aim: To study the clinico-etiological profile in patients of thrombocytopenia prevalent in our region.
Methods: This Cross Sectional study was conducted on 100 patients with thrombocytopenia attending outdoor department or admitted in Medicine Department of Guru Nanak Dev Hospital, attached to Government Medical College Amritsar. The study required these routine investigations. Baseline platelet counts were done on the day of admission repeated on alternate days until normal or near normal platelet count reached. On the basis of platelet count, mild thrombocytopenia was considered if platelet counts[4] were $>70 \times 10^3/\mu L$, moderate if platelet counts were between $20\text{-}70 \times 10^3/\mu L$ and severe if platelet counts were $<20 \times 10^3/\mu L$.
Results: Based on platelet count, among 100 study cases mild thrombocytopenia was observed in 52 (52%) cases, moderate thrombocytopenia in 44 (44%) cases and severe thrombocytopenia in 4 (4%) cases. Fever was the most common clinical symptoms in patients with thrombocytopenia and splenomegaly was the most common signs. 36% of total thrombocytopenia cases presented with bleeding manifestations. The common etiologies of thrombocytopenia in our study were dengue fever, megaloblastic anemia, cirrhosis and enteric fever. Mild thrombocytopenia was more prevalent in 41-50 year males and moderate thrombocytopenia in 31-40 year males while 41-50 years females presented more with severe thrombocytopenia. Presenting complaints were splenomegaly and petechiae in mild to moderate thrombocytopenia groups. While, hepatomegaly and gross bleed in the form of hematuria were the presentations in the severe thrombocytopenia group.
Conclusion: The etiology of thrombocytopenia is seen to vary geographically and seasonally which contribute to significant morbidity and mortality. Prompt diagnosis and immediate specific treatment of underlying etiology causing thrombocytopenia, with maintenance of platelet count and haemostatic function gives good recovery.

Keywords: thrombocytopenia, Clinico-etiological, patients

Introduction
Thrombocytopenia is defined as a platelet count below the 2.5th lower percentile of the normal platelet count distribution. Results of the third US National Health and Nutrition Examination Survey (NHANES III) support the traditional value of $150 \times 10^9/L$ as the lower limit of normal [1, 2]. However, platelet count between 100 and $150 \times 10^9/L$ do not necessarily indicate disease if they have been stable for more than 6 months [3] and the adoption of a cut-off value of $100 \times 10^9/L$ may be more appropriate to identify a pathologic condition [4].
Three major pathophysiological mechanisms in thrombocytopenia are decreased platelet production, increased platelet destruction or consumption, or increased splenic sequestration (capturing of circulating platelets in the spleen). On the basis of platelet count, mild thrombocytopenia is considered if platelet counts are $>70 \times 10^3/\mu L$, moderate if platelet counts are between $20\text{-}70 \times 10^3/\mu L$ and severe if platelet counts are $<20 \times 10^3/\mu L$ [5].
Bleeding manifestations in the form of petechiae, purpura, epistaxis and gingival bleeding are more common; hematuria and gastrointestinal bleeding are rare. With platelet count of more than 1 lakh/cumm is usually normal and bleeding time remains normal [6]. Platelet count of 50,000-1,00,000/μL cause mild prolongation of the bleeding time, bleeding occurs only after severe trauma. Platelet count of <50,000/μL have early bruising, manifested by skin purpura after minor trauma.

Corresponding Author:
Dr. Ghritachi Sandal
Senior Resident, Department
of Medicine, GMC, Amritsar,
Punjab, India

Platelet count of <20,000/µL have spontaneous bleeding, they usually have petechiae and may have intracranial or spontaneous internal bleeding.

Thrombocytopenic patients in the hospital suffer a twofold greater mortality rate than those who are not. In various studies, thrombocytopenia was found to be an important risk factor of mortality and morbidity. It is a marker of organ dysfunction and has been associated with poor prognosis [7]. Thus history, physical examination, complete blood count and peripheral blood smear are all critical components in the initial evaluation of thrombocytopenic patients. Early identification and intervention of underlying condition and platelet transfusions are required to prevent fatal outcome. Majority of studies on adults with thrombocytopenia have focused on specific etiology or associated with some symptom like fever. But, in India there is lack of extensive researches which covers wide etiological spectrum of thrombocytopenia.

Therefore the present study is aimed to study the clinico-etiological profile in patients of thrombocytopenia prevalent in our region. With the help of this study we intend to correlate the clinical features and laboratory findings and derive a conclusion regarding the possible etiology for thrombocytopenia and thus its diagnosis and management.

Material and Methods
This Cross Sectional study was conducted on 100 patients with thrombocytopenia attending outdoor department or admitted in Medicine Department of Guru Nanak Dev Hospital, attached to Government Medical College Amritsar. It was carried out after seeking permission from Institutional Ethics Committee, Government Medical College, Amritsar. Written informed consent was obtained from the patients. All new patients aged more than 18 years with thrombocytopenia (Platelet count less than 1,50,000/mm^3) and confirmed on peripheral blood smear were included in the study. Patients with age less than 18 years, patients not giving informed consent, patients with platelet count more than 1,50,000/µL, cases of pseudo thrombocytopenia and patients with no clinical details available were excluded from the study.

The study required these routine investigations: complete haemogram, peripheral blood picture, platelet count, urine routine test, liver function test, blood urea, serum creatinine, chest X-ray, ultrasound, E.C.G. Special Investigations like dengue antibodies, malarial parasite test, HBsAg, HCV antibodies, HIV antibodies, Widal test, ESR, RA factor, blood culture (if needed), ANA profile (if needed), bone marrow (if needed) as and when required.

On the basis of platelet count, mild thrombocytopenia was considered if platelet counts[4] were >70 × 10^3/µL, moderate if platelet counts were between 20-70 × 10^3/µL and severe if platelet counts were <20 × 10^3/µL.

Baseline platelet counts were done on the day of admission repeated on alternate days until normal or near normal platelet count reached. In patients with bleeding manifestations or with platelet count <50000/µL, repeat platelet count was done daily till rising trends of platelet achieved. All patients were given supportive treatment and specific treatment after definitive diagnosis. Patients with platelet count less than 20000/µL or with bleeding manifestations were treated with platelet concentrate, if indicated. Patients were followed till the duration of their stay in the hospital.

The classification of platelet transfusion into either therapeutic, to treat bleeding or prophylactic, to prevent bleeding, was based on the modified world health (WHO) bleeding score.

Prophylactic transfusion was given to patients with bleeding scores 0 or 1 and therapeutic transfusion to patients with bleeding scores of 2 or higher.

Statistical analysis
The collected data was analyzed using SPSS statistics software 21. Version. To describe the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables and the mean & S.D were used for continuous variables.

Results
In the present study, mean age of the study population came out to be 41.35±16.34 years. 21-30 years and 31-40 years were the most common age group presenting with thrombocytopenia with 23% cases each, while least common cases belonged to 71-80 years and >80 years of age with 3% cases each. Male predominance was observed with a Male: Female ratio of 1.04:1.

We observed that an average platelet count at admission of patients under study was 80670 cells/µL with minimum of 9000 cells/µL. Based on platelet count, among 100 study cases mild thrombocytopenia was observed in 52 (52%) cases, moderate thrombocytopenia in 44 (44%) cases and severe thrombocytopenia in 4 (4%) cases.

Fever was the most common clinical symptoms in patients with thrombocytopenia with 75(75%) cases followed by myalgia in 22 (22%) cases, chills in 16 (16%) cases, abdominal pain in 13 (13%) cases, vomiting in 10(10%) and cough in 5 (5%) cases. Least common symptoms were headache, loose stools and hematuria in 3 (3%) cases each. (Figure 1). Table 1 shows distribution of clinical symptoms among grades of thrombocytopenia.
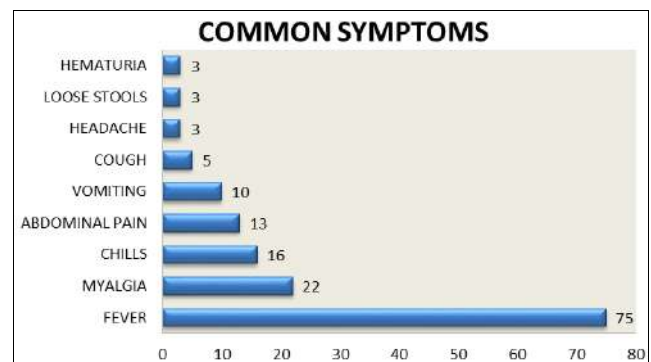

Fig 1: Distribution of cases based on common clinical symptoms

Table 1: Distribution of clinical symptoms among grades of thrombocytopenia

Symptoms	Mild (n=52)	Moderate (n=44)	Severe (4)
Fever	37 (71.5%)	34 (77.2%)	4 (100%)
Myalgia	7 (15.9%)	12 (23.1%)	3 (75%)
Chills	10(19.2%)	5 (9.1%)	1(25%)
Headache	2(3.8%)	1(2.3%)	0
Abdominal pain	9(17.3%)	3(6.8%)	1(25%)
Vomiting	6(11.5%)	4(9.1%)	0
Loose stools	2(3.8%)	1(2.3%)	0
Cough	3(5.8%)	1(2.3%)	1(25%)
Hematuria	0	1(2.3%)	2 (50%)

In the present study, most common signs were splenomegaly in 28 (28%) cases, hepatomegaly in 18(18%) cases, pleural effusion in 11(11%) cases, lymphadenopathy in 9(9%) cases, hypotension in 8(8%) cases and least common symptom was jaundice in 1 (1%) case. (Figure 2)
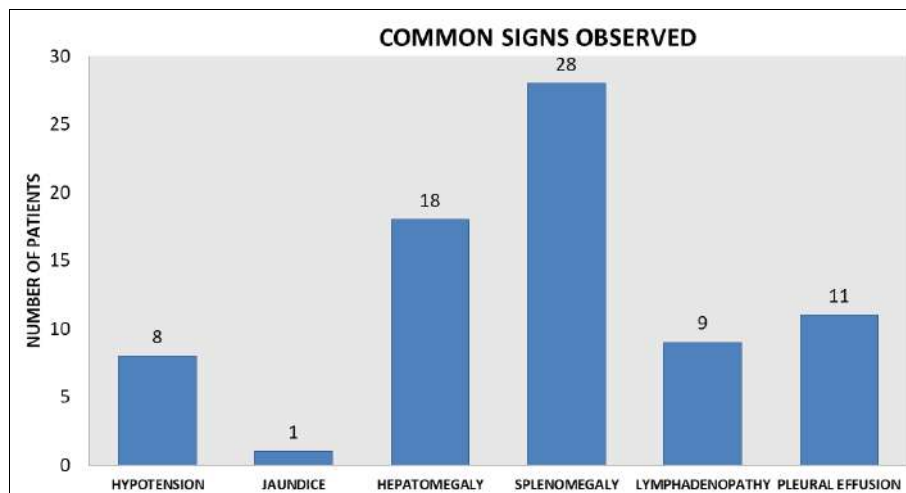

Fig 2: Common signs observed

Further, when clinical signs observed were compared among all the three grades of thrombocytopenia, we observed that splenomegaly was observed 50% cases of severe thrombocytopenia, Hepatomegaly was observed in 75% cases of severe thrombocytopenia, lymphadenopathy was observed to be associated with 50% case of severe thrombocytopenia. Overall severe thrombocytopenia was observed to be associated with increased incidence of clinical signs in comparison to mild and moderate thrombocytopenia.

Bleeding symptoms
In the present study 36 (36%) of total thrombocytopenia cases presented with bleeding manifestations. Most common type of bleeding symptoms observed were petechiae in 22 (22%) cases, purpura in 11(11%) cases and hematuria in 3 (3%) cases. (Figure 3)
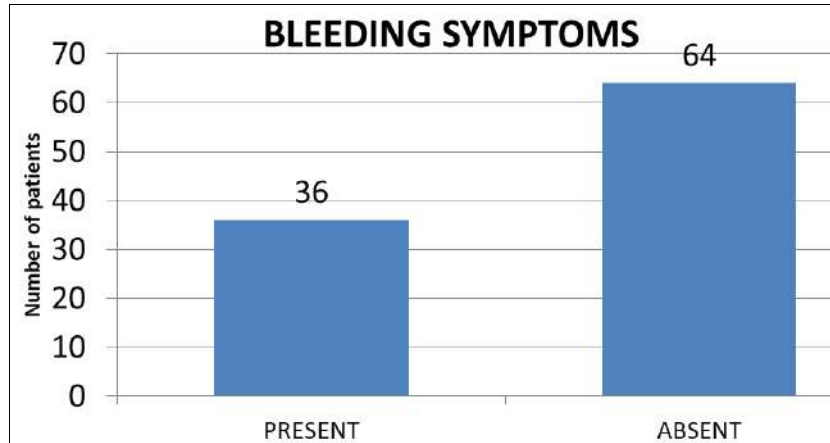

Fig 3: Presentation of bleeding symptoms

Incidence of bleeding manifestation was found highest in severe thrombocytopenia followed by moderate thrombocytopenia and least in cases of mild thrombocytopenia. Petechiae were seen in all 100% cases of severe thrombocytopenia, while purpura and hematuria were seen in 50% cases each. (Table 2)

Table 2: Distribution of bleeding symptoms within grades of thrombocytopenia

	Mild thrombocytopenia (n=52)	Moderate thrombocytopenia (n=44)	Severe thrombocytopenia (n=4)
Petechiae	8 (15.3%)	10 (22.7%)	4 (100%)
Purpura	4 (7.7%)	5 (11.4%)	2 (50%)
Hematuria	0	1 (2.3%)	2 (50%)

In present study, out of 19 different etiologies of thrombocytopenia, the most common etiologies was dengue fever (35%), followed by megaloblastic anemia (13%), cirrhosis (12%),enteric fever (10%), leukemia (10%), septicemia (7%) malaria (P. *falciparum* & P. *vivax*) (4%),ulcerative colitis and chronic kidney disease (2% each). On the other hand, leptospirosis (1%), idiopathic thrombocytopenic purpura (1%), lymphoma (1%),

hypocellular bone marrow (1%), rheumatoid arthritis (1%), haemolytic anemia (1%)and myelodysplastic syndrome 1(1%), were the least common.

Among cirrhosis patients, bleeding manifestations were seen in 7 (58.3%) cases, which presented as petechiae in 5 (71.4%) cases, purpura in 1(14.2%) cases and hematuria in 1 (14.2%) case. In dengue patients, bleeding manifestations were seen to be maximum with 16 (64%) cases, which presented as petechiae in 8 (50%) cases, purpura in

6(37.5%) cases and hematuria in 2 (12.5%) cases. In enteric fever patients, HIV patients and sepsis bleeding manifestations were seen 1 (10%), 1 (25%) and 1 (14.2%) case respectively and all presented as petechiae (100%). In megaloblastic anemia patients, bleeding manifestations were seen 2 (15.4%) cases and 1 case each as petechiae and purpura. In malaria patients, bleeding manifestations were seen 1 (25%) case and it presented as purpura (100%). (Table 3)

Table 3: Distribution of bleeding symptoms within common etiologies in patients of thrombocytopenia

Common Etiology	N	Petechiae	Purpura	Hematuria	Total bleeding manifestations present
Cirrhosis	12	5 (71.4%)	1(14.2%)	1 (14.2%)	7 (58.3%)
Dengue	35	8 (50%)	6(37.5%)	2 (12.5%)	16 (64%)
Enteric fever	10	1(100%)	0	0	1 (10%)
Hiv	4	0	1 (100%)	0	1 (25%)
Megaloblastic anemia	13	1 (50%)	1 (50%)	0	2 (15.4%)
Malaria	4	0	1(100%)	0	1 (25%)
Sepsis	7	1 (100%)	0	0	1 (14.2%)

Discussion

Thrombocytopenia is the commonest platelet abnormality encountered in the clinical practice. In the present study of 100 cases with thrombocytopenia, we observed that 21-30 years and 31-40 years were the most common age group.

In similarity to our observations, Yasmeen Khatib et al. [8], Shah et al. [9] and Kakanale et al. [10] also reported 21-30 years to be the most common age group in their studies as well. In contrast to our findings authors like Kumar et al. [11], Unnikrishanan et al. [12] and Lye et al. [13] reported 60 to 65 years as the most common age group in patients presenting with thrombocytopenia. This variation in age groups in different studies may be attributed to difference in the population studied, geographical and seasonal variations and also the etiological factors causing thrombocytopenia in their studies.

We observed male predominance with Male: Female ratio came of 1.04:1. The reason for this increased incidence in males in our study may be due to prolonged outdoor activities in males in comparison to females.

Fever was the most common clinical symptom reported in patients with thrombocytopenia with 75% cases, followed by myalgia in 22% cases. Severe thrombocytopenia was associated maximum cases presenting with symptoms like fever (100%), myalgia (75%), chills (25%), abdominal pain (25%), cough (25%) and hematuria (50%). While in comparison, both moderate thrombocytopenia patients and mild thrombocytopenia presented with less incidence and severity of clinical symptoms.

Modi T et al. [14] also reported that fever was the most common presenting clinical symptom in patients with thrombocytopenia, followed by headache, body ache, vomiting, retro orbital pain, nausea, joint pain, abdominal pain, and respiratory symptoms. In yet another study by Ahmed S et al. [15] most common clinical feature included fever, followed by vomiting, abdominal pain and rashes.

Splenomegaly was the most common signs observed in 28% cases followed by hepatomegaly in 18% cases. In similarity with our results Badvi et al. [16] also reported similar finding sin their study as well.

In the present study, 36% of total thrombocytopenia cases presented with bleeding manifestations. Most common type of bleeding symptoms observed were petechiae in 22% cases, purpura in 11% cases and hematuria in 3% cases. On

comparison of bleeding manifestations with the age groups, we also observed that 71-80 years of age group presented with 66.6% cases of bleeding manifestations, whereas, both 31-40 years and 21-30 years of age groups presented with 30.4% cases of bleeding manifestations. Hence, our findings suggest that with increasing age bleeding tendency also increased.

Incidence of bleeding manifestation was found highest in severe thrombocytopenia followed by moderate thrombocytopenia and least in cases of mild thrombocytopenia. Petechiae were seen in all 100% cases of severe thrombocytopenia, while purpura and hematuria were seen in 50% cases each. Therefore, our findings suggest that the percentage of cases with bleeding manifestations increased with severity of thrombocytopenia.

In similarity to our results, Yadav B S et al. [17] also reported that 16.27% cases in their study presented with bleeding manifestations and incidence of bleeding manifestation were found highest in severe thrombocytopenia and least in mild thrombocytopenia.

Patil et al. [18] in their study showed 23% cases presenting with bleeding manifestation, out of this 73.9% presented with petechiae followed by spontaneous bleeding in 26.9%. Saini et al. [19] also reported that 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%.

Out of 19 different etiologies of thrombocytopenia observed in our study, dengu fever was the most common etiology, which could be attributed to higher prevalence of such infections during the study period i.e. rainy season, which could be contributing factor for higher variation between different studies.Kakanale et al. [10] also reported that the most common cause for febrile thrombocytopenia in their study was dengue fever. In some other studies by Tejas M et al. [14], and Gandhi et al. [20], malaria was the commonest followed by dengue.

Further when we compared specific etiologies with the bleeding manifestations in our study, we observed that in dengue patients, which was our most common etiological factor for thrombocytopenia, 75% of patients had severe thrombocytopenia, 38.6% had moderate thrombocytopenia and 28.8% had mild thrombocytopenia. Further, bleeding

manifestations in these patients were observed in 64% cases, which presented as petechiae in 50% cases, purpura in 37.5% cases and hematuria in 12.5% cases.

In the present study, mild thrombocytopenia was more prevalent in 41-50 years old male patients with dengue, who presented with splenomegaly and bleeding manifestations in the form of petechiae and purpura. Moderate thrombocytopenia, was seen to be most common in males aged 31-40 years and the most common cause was dengue. Dengue remained the most common cause in severe thrombocytopenia seen in 41-50 years old females, whose presentation was hepatomegaly and petechiae and hematuria were the presenting bleeding manifestations.

Conclusion

The common etiologies of thrombocytopenia in our study were dengue fever, megaloblastic anemia, cirrhosis and enteric fever. Mild thrombocytopenia was more prevalent in 41-50 year males and moderate thrombocytopenia in 31-40 year males while 41-50 years females presented more with severe thrombocytopenia. Presenting complaints were splenomegaly and petechiae in mild to moderate thrombocytopenia groups. While, hepatomegaly and gross bleed in the form of hematuria were the presentations in the severe thrombocytopenia group. Thus, prompt diagnosis and immediate specific treatment of underlying etiology causing thrombocytopenia, with maintenance of platelet count and haemostatic function gives good recovery.

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