

## **Original Research Article**

### **CLINICO-HEMATOLOGICAL STUDY OF THROMBOCYTOPENIA ON THE BASIS OF BONE MARROW EXAMINATION IN A TERTIARY CARE HOSPITAL**

#### **ABSTRACT**

**BACKGROUND:** Thrombocytopenia can occur in a variety of clinical conditions. Bone marrow aspiration is crucial for diagnosis. The purpose of this study was to investigate the causes of thrombocytopenia, its spectrum, and how to interpret the results of bone marrow aspiration.

**AIM & OBJECTIVES:** To study the cases of thrombocytopenia on the basis of bone marrow examination for correlation of bone marrow findings with clinical features, haematological parameters and other investigations in cases of thrombocytopenia. Secondary objective is to investigate the role of morphological examination of bone marrow aspiration and trephine biopsy in diagnosis of various disorders leading to thrombocytopenia.

**RESULTS:** The cross-sectional prospective study lasted two years, from May 2019 to May 2021, at a tertiary care centre where clinico-haematological evaluation of patients with thrombocytopenia was done on the basis of bone marrow examination. A total of 103 cases with thrombocytopenia underwent bone marrow examination of which most patients belonged to the age group of 41-50 with a male preponderance. Majority of the patients presented with generalized weakness and pallor. Megaloblastic anaemia was the most predominant cause followed by acute myeloid leukemia and dimorphic anaemia. More research into the pathogenesis of megakaryocytic alteration and its contribution to thrombocytopenia could lead to a better understanding of the pathogenesis of a variety of hematopoietic disorders and the identification of broader clinical applications.

**KEY WORDS**- Thrombocytopenia, Bone marrow, Clinico-hematological study.

## **INTRODUCTION**

Thrombocytopenia is defined as a reduction in the peripheral blood platelet count below the lower normal limit of 1.5L/cu.mm <sup>(1)</sup>. Despite the diversity of disorders associated etiologically, thrombocytopenia results from four mechanisms: Artefactual thrombocytopenia, deficient platelet production, accelerated platelet destruction and abnormal distribution or pooling of the platelets within the body <sup>(2)</sup>. It is the commonest cause of abnormal bleeding. Thrombocytopenia develops when there is disequilibrium in the balance between platelet production, distribution and destruction. More than one factor may be affected in some disorders <sup>(3)</sup>. Bone marrow examination is a useful and cost-effective diagnostic procedure in haematological practice. Both neoplastic and non-neoplastic haematological diseases are diagnosed with the help of bone marrow examination. This procedure is also employed for the classification of anaemia, various cytopenias under evaluation and pyrexia of unknown origin. The bone marrow examination may either confirm the clinically suspected disease or may provide the previous unsuspected diagnosis <sup>(4)</sup>, <sup>(5)</sup>, <sup>(6)</sup>, <sup>(7)</sup>. Bone marrow biopsy is a more reliable method for detecting marrow infiltrate, the pattern of marrow involvement and the cellularity of marrow. The role of bone marrow aspiration in thrombocytopenic patients is to rule out haematological diseases like leukemia and myelodysplastic syndrome in adults.

The present study has been undertaken to study the causes of thrombocytopenia based on bone marrow examination for correlation of bone marrow findings with clinical features, haematological parameters and other investigations in cases of thrombocytopenia. The secondary objective is to investigate the role of morphological examination of bone marrow aspiration and trephine biopsy in the diagnosis of various disorders leading to thrombocytopenia.

## **MATERIALS AND METHODS**

The study was a 2-year cross-sectional, prospective study of clinico-haematological evaluation of cases of thrombocytopenia based on bone marrow examination in the haematology section of our hospital which is a tertiary care centre. The study was carried out from May 2019 to May 2021. **Patients of all age groups presenting with thrombocytopenia and who have undergone bone marrow examination were included in the study.** Exclusion criteria included patients on aspirin or other anticoagulant therapy, haemophilia,

thrombocytopenia cases where bone marrow examination was unindicated and other coagulation disorders.

The patient was made to lie on one side with his back to the doctor, knees and hips flexed and knees were drawn to their chest. A sterile drape with a central aperture was put over the aspiration site. Aspiration and bone marrow biopsy was done from the posterior iliac spine under local anaesthesia. The bone marrow aspiration needle was inserted and rotated clockwise and anticlockwise. When the marrow was reached, there was a tiny give. The needle was progressed into the marrow for another 1-2 mm before the stylet was removed. Bone marrow aspiration and biopsy procedure- The needle was coupled to a 5-10 ml syringe, and a little amount of marrow was aspirated by quickly pulling the plunger of the syringe. Aspiration was quickly smeared or placed in a petri dish with EDTA <sup>(8,9)</sup>. When necessary, biopsies and aspirations were performed in the same session. The stylet was removed from the needle after aspiration and the cap was then closed. It was then rotated for about 0.5-1 cm to force it deeper into the cavity. The marrow core sample was captured within the needle. After that, the needle was withdrawn in the opposite rotational direction. The material was fixed in 10% formalin overnight and decalcified for 72 hours with 6% EDTA <sup>(10)</sup>. Post-procedure patient care was taken.

In all cases two slides of bone marrow aspiration and one peripheral smear were made on clean glass slides with fresh blood samples, air dried & stained with Jenner's Giemsa and Leishman's stain respectively. Stained glass slides were added two times the quantity of buffered distilled water for next 10 minutes. Slides were then fixed, mounted and viewed under microscope. Images were taken during peripheral smear examination and bone marrow examination which was done systematically under low power, high power and oil immersion.

### **OBSERVATIONS AND RESULTS:**

During the two-year study, a total of 103 cases with thrombocytopenia underwent bone marrow examination in the haematology section in the Department of Pathology. 94 patients had their bone marrow aspirated and 9 had their bone marrow biopsy.

**Table 1: Age and sex distribution in thrombocytopenia.**

Age Group	Male	Female	Total	Percentage
0-10	5	1	6	5.82%

11-20	8	7	15	14.56%
21-30	4	2	6	5.82%
31-40	10	6	16	15.53%
41-50	12	8	20	19.41%
51-60	10	7	17	16.50%
61-70	11	3	14	13.59%
>70	8	1	9	8.77%
Total	68	35	103	100%

The age group of 31-60 years had the highest number of patients (51.45 %), followed by 61-70 years (13.59 %), and the age group of 0-10 years (5.82 %) (Table 1). The sex distribution revealed a male preponderance. 1.94:1 was the male-to-female ratio.

**Table 2: Clinical features of thrombocytopenia cases:**

Sr.No.	Presenting symptoms	No. of Cases	Percentage
1.	Generalized weakness	71	68.93%
2.	Fever	30	29.12%
3.	Dyspnoea	38	36.89%
4.	Bleeding manifestation	5	4.85%
5.	Weight loss	27	26.21%
6.	Pallor	78	75.72%
7.	Lymphadenopathy	8	7.76%
8.	Hepatomegaly	24	23.30%
9.	Splenomegaly	19	18.44%
10.	Bone tenderness	8	7.76%

Pallor (75.72%) was the most common clinical feature in thrombocytopenia patients, followed by generalized weakness (68.93%), dyspnoea (36.89%), fever (29.12%), weight loss (26.21), hepatomegaly (23.30%), splenomegaly (18.44), lymphadenopathy (7.76%), bone tenderness (7.76%), and bleeding manifestations (4.85 %) (Table 2).

**Table 3: Hematological profile of the patients**

Variable	Value
Hb	7.87±0.51
TLC	34,704±14,332
PLT	77,873±6,242
Retic Count	2.34±0.51
RBC Morphology	NN-23.3% MH-12.6% MA-47.6% DA-16.5%

The mean hemoglobin, total leukocyte and platelet values in the study group were 7.87±0.51 g/dl, 34,704±14,332/mm<sup>3</sup> and 77,873±6,242/mm<sup>3</sup> respectively. Megaloblastic anemia (47.6%) was most commonly seen on peripheral smear followed by normocytic normochromic picture which was seen in 23.3% of patients. (Table 3)

**Table 4: Bone marrow cellularity**

Type of cellularity	No. of cases	Percentage
Hypercellular	64	62.13%
Hypocellular	15	14.56%
Normocellular	24	23.30%
Total	103	100%

Hypercellular marrow was most common 64/103 (62.13 %), normocellular marrow was seen in 24/103 (23.30 %) and hypocellular marrow in 15/103 cases (14.56 %) (Table 4).

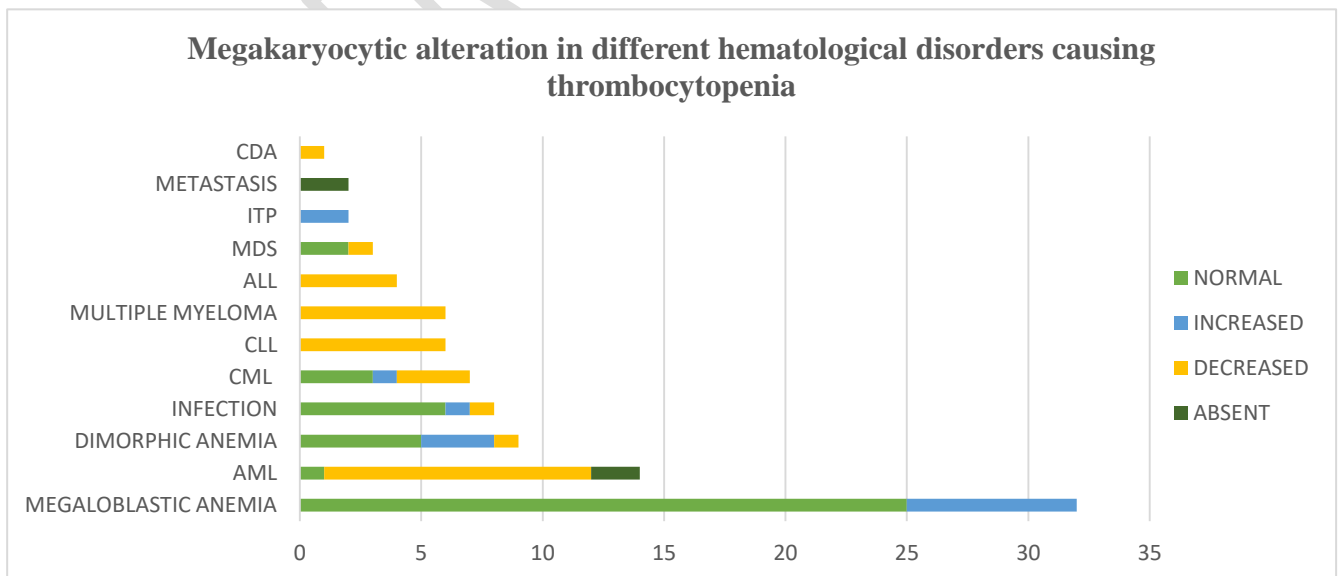
**Table 5: Distribution of cases according to diagnosis of bone marrow aspiration study**

Disorders	Cases	% Of cases
Megaloblastic anaemia	32	31.06%
AML	14	13.59%
Dimorphic anaemia	9	8.73%
Infection	8	7.76%

CML in blast crisis	7	6.79%
CLL	6	5.82%
Multiple myeloma	6	5.82%
ALL	4	3.88%
MDS	3	2.91%
ITP	2	1.94%
Metastasis to bone	2	1.94%
CDA	1	1.06%
Dry tap	9	8.7%

The most common diagnosis on bone marrow aspiration was megaloblastic anaemia 32/103(31.06%) followed by acute myeloid leukemia 14/103(13.59%), dimorphic anaemia 9/103(8.73%), infections were 8/103(7.76%), CML in blast crisis 7/103(6.79%), multiple myeloma and CLL 6/103(6.79%) each, ALL 4/103 (3.88%), MDS 3/103(2.91%), ITP and metastasis to bone 2/103(1.94%) each and 1/103(1.06%) case was congenital dyserythropoietic anaemia. (Fig 2-9) (Table 5).

**Fig 1 : Megakaryocytic alteration in various haematological disorders causing thrombocytopenia in BMA**



The numbers of megakaryocytes were seen differently for different diseases. Numbers per low power fields ranged from normal, increased, decreased to absent megakaryocytes (Fig 1). Megakaryocytic morphological changes seen included immature forms, dysplastic forms, bare forms, emperipolesis, budding platelets, cyto-vacuolar forms, micro-megakaryocytes and hypofoms. Lobular changes were also seen ranging from normal, hyperlobated to hypolobated (Table 6).

**Table 6: Morphological alterations of megakaryocytes in various haematological disorders causing thrombocytopenia in bone marrow aspiration**

Conditions	If	Df	Bare Form	Emp	Bud	Cyto-vacuo	Micro-megakaryocyte	Hypo Form
Megaloblastic anaemia	13	18	15	11	0	11	5	0
AML	2	7	8	4	0	0	5	0
Dimorphic anaemia	4	5	4	3	0	3	0	0
Infection	0	0	0	2	0	2	1	3
CML in blast crisis	1	1	0	0	0	0	4	3
CLL	0	0	0	0	0	0	0	0
Multiple myeloma	0	0	0	0	0	0	0	5
ALL	0	0	0	1	0	0	0	4
MDS	1	2	1	0	0	0	2	2
ITP	2	2	2	2	1	2	0	1

### **DISCUSSION:**

The most common age group in this study was 41–60 years old (19 percent), with a male preponderance of 1.94:1. Several other studies found that the most common age groups were 21-30 years old, 15 years old and 51–60 years old with a male preponderance in all studies (11,12,13). There were 103 cases of thrombocytopenia in this research. The most prevalent cause of anaemia was megaloblastic anaemia in 32/103 (31.06 percent) followed by acute myeloid

leukemia in 14/103. (13.59 percent). Anita Javalgi and Subuh Parvez Khan observed similar findings<sup>(14) (16)</sup>. Megaloblastic anaemia was found in 13 percent and 18 percent of patients followed by immune thrombocytopenic purpura in 9.2 percent and 11.5 percent of patients in investigations conducted by Shilpa Patel et al and Mayuri Gohil respectively.<sup>(12) (15)</sup>. There were 9 cases of dry tap during bone marrow aspiration in this research. **Another author reported similar results after performing a biopsy on 12 patients with dry tap on bone marrow aspiration.** There were 32 cases of megaloblastic anaemia in this research, with a male-to-female ratio of 1.6:1. The most impacted age group was 41-50 years (28.12 percent), followed by 31-40 years (21.87 percent). **A broad age range with a male majority was seen in other studies too**<sup>(14) (15) (17)</sup>. The majority of the patients had generalised weakness and a fever. Pallor was present in all of the patients. Hepatosplenomegaly was detected in 18% of individuals which is similar with Tariq M et al. and Chandra J<sup>(18) (19)</sup>. For a definite diagnosis, a bone marrow aspiration was performed. It agreed with research conducted by Manas Muhury et al<sup>(20)</sup>.

In this investigation, nine cases of dimorphic anaemia were discovered with a female preponderance of 1.25:1. The age range 11-20 years had the highest frequency at 55.56 percent. **Dimorphic anaemia was identified in 18.58 percent and 67.74 percent of patients in two similar studies with a male preponderance in both.**<sup>(12)(21)</sup>.

A total of 14 cases of AML were found in this investigation, with a male preponderance (1.3:1). With 28.6 percent, the age range 11-20 years had the highest frequency. **Similar results with a male preponderance were observed in other studies**<sup>(21)(22)(23)</sup>.

In the research, 50 percent of the AML fell into the M3 subtype of the FAB classification, whereas Kulshrestha R discovered 53.57 percent in the M2 subtype<sup>(23)</sup>. In this investigation, four cases of ALL were found, with a male preponderance (3:1). All of the patients were under the age of 20, with 75% of them being under ten years old. Jha et al. and Kulshrestha R found a similar result with a median age of 13 years and 45.83 percent in those aged 20 years<sup>(23)(25)</sup>.

**Patients developed pancytopenia in 75% of cases and bicytopenia in 100% of cases. Similar discoveries were obtained by other researchers**<sup>(23) (24)</sup>. The current study revealed that 58.96 percent of patients had L2 type ALL, while Kulshrestha R's study revealed that 75 percent of patients had L2 type ALL<sup>(23)</sup>.

In this investigation, six cases of multiple myeloma were discovered, with a 5:1 male to female ratio. With a frequency of 66.67 percent, the age group 51-60 had the greatest

incidence of cases. In their study, Greipp P R and Cavo M discovered a comparable prevalence <sup>(27)(28)</sup>. Pallor, generalised weakness, and bone tenderness were seen in the majority of the patients in this research. Singhal and Bartl found that the majority of patients (66.66 percent) had moderate thrombocytopenia <sup>(29)(30)</sup>. According to Chadbrun et al., a peripheral blood smear indicated normocytic normochromic RBCs with rouleaux development <sup>(31)</sup>.

This study found seven incidences of CML in blast crisis, with a 6:1 male to female ratio. With 28.60 percent of cases, the age group 41-50 had the highest prevalence. In their study, Shweta Joshi and Rao S discovered a similar incidence. Bicytopenia and leucocytosis were seen in all of the individuals <sup>(24)(32)</sup>.

This investigation found five cases of chronic lymphocytic leukemia, with a 2:1 male-to-female ratio. The age group 41-50 years old had the highest prevalence, accounting for 83.33 percent of all cases which was comparable to other studies <sup>(23)(24)(33)</sup>. According to research done by Kulshrestha R, the majority of patients in this study reported generalised weakness and lymphadenopathy <sup>(23)</sup>. CLL did not show any other morphological abnormalities in megakaryocytes. Tejinder Singh et al. also found hypolobated megakaryocytes in their study <sup>(26)</sup>.

In this investigation, eight cases of infection were found, with a male-to-female ratio of 1.6:1. Fifty percent of the patients were between the ages of 31 and 40. Septicaemia struck four people, dengue fever afflicted three and a post-covid infection affected one. Findings reported by Anjan Kumar and Mayuri Gohil revealed 25% of patients having sepsis and 6% having leishmaniasis, respectively <sup>(12)(34)</sup>. This research included three patients of myelodysplastic syndrome. A peripheral smear revealed pancytopenia with dyserythropoietic cells. For confirmation, a bone marrow aspiration was performed which showed findings similar to that of another study <sup>(26)</sup>.

Two incidences of bone marrow metastases were discovered. One had metastatic adenocarcinoma, while the other had a spillover mantle cell lymphoma. Muhury et al. described two examples of metastasis in which the number of megakaryocytes was reduced but there was no morphological change in the megakaryocytes <sup>(20)</sup>.

## **CONCLUSION**

Thrombocytopenia is the commonest clinical presentation of various life-threatening diseases. The pattern of disorders leading to thrombocytopenia differs in age group, clinical presentation and aetiology. Megaloblastic anaemia is the commonest cause of

thrombocytopenia followed by haematological malignancies. So, the leading cause of thrombocytopenia's, which is megaloblastic anaemia is treatable and also preventable by improving lifestyle. The diagnosis and severity of thrombocytopenia and underlying pathology help in the management and prognosis of these disorders. Bone marrow biopsy is helpful in cases of thrombocytopenias where a dry tap is obtained. It is helpful in the diagnosis of bone marrow infiltration i.e., metastatic malignancies and also in aplastic anaemia and myelofibrosis. The study of bone marrow forms the mainstay in the diagnosis of thrombocytopenia cases. Bone marrow examination is a simple, safe outpatient procedure and yields an impressive amount of diagnostically valuable data in a wide variety of disorders of thrombocytopenia. Additional studies examining megakaryocytic alteration and its contribution to thrombocytopenia can add to our growing understanding of the pathogenesis of a variety of hematopoietic disorders and may potentially identify wider scope clinical applications for the newer strategies for platelet count and function regulation. Bone marrow examination certainly helps in early management and better outcome of the patient illness.

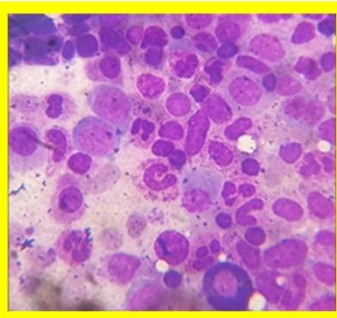


Fig. 2 : Bone marrow aspiration showing Megaloblastic Anemia with Erythroblast with seive-like chromatin and Giant metamyelocyte; Giemsa stain (1000X)

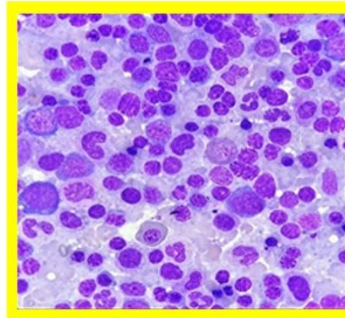


Fig. 3 : Bone marrow aspiration showing Dimorphic Anemia with micronormoblast and megaloblast erythropoiesis; Giemsa stain (100X)

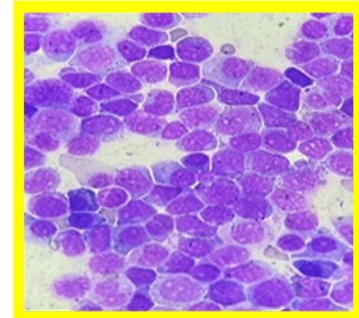


Fig. 4 : Bone marrow aspiration showing Acute Myeloid Leukaemia with blast crisis; Giemsa stain (1000X)

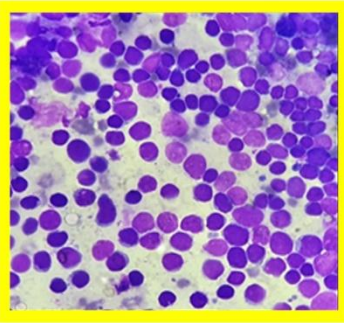


Fig. 5 : Bone marrow aspiration showing Acute Lymphocytic Leukaemia ; Giemsa stain(1000X)

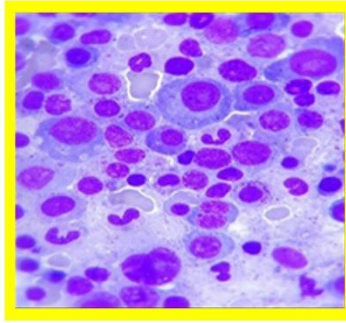


Fig. 6 : Bone marrow aspiration showing Multiple Myeloma ; Giemsa stain(1000X)

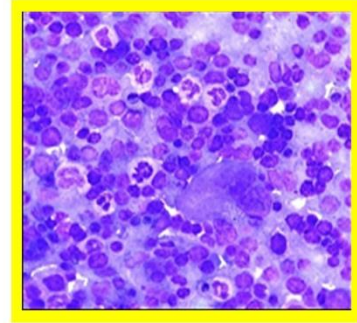


Fig. 7 : Bone marrow aspiration showing Myelodysplastic Syndrome ; Giemsa stain (1000X)

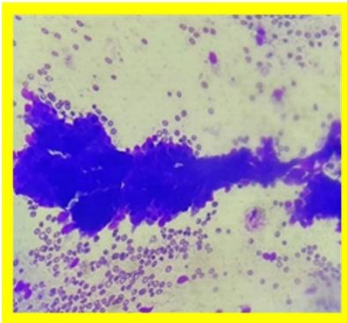


Fig. 8 : Bone marrow aspiration showing Metastatic Adenocarcinoma ; Giemsa stain (100x)

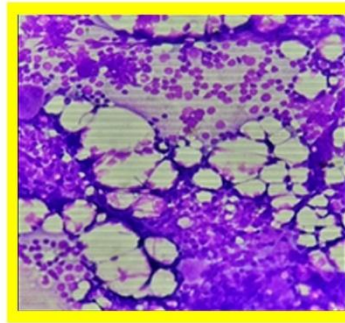


Fig. 9 : Bone marrow aspiration showing Mantle cell lymphoma ; Giemsa stain (100X)

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