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Original Research Article

Clinico-Hematological Spectrum of Non-Leukemic Myeloproliferative Disorder

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Abstract: *Myeloproliferative neoplasms (MPNs) are a group of hematological disorders originating from marrow stem cells, characterised by clonal proliferation of hematopoietic components. The three primary non-leukemic MPNs include Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF). These disorders affect the bone marrow, liver, and spleen, leading to various clinical manifestations. Limited data on MPNs in Pakistan necessitates further research to understand their prevalence and demographic distribution.* ***Objective:*** *To assess the spectrum, prevalence, and demographic distribution of non-leukemic MPNs among patients at Benazir Bhutto Hospital, Rawalpindi.* ***Methodology:*** *A retrospective study was conducted over three to four months at Benazir Bhutto Hospital, Rawalpindi. Patient data were analysed using SPSS Version 25, focusing on categorical variables such as age, gender, and MPN type. The diagnosis of MPNs was based on clinical, hematological, and cytogenetic criteria by the 2016 WHO classification.* ***Results:*** *26 patients were diagnosed with non-leukemic MPNs, with a male-to-female ratio of 1.4:1. Among these, 15 males (58%) and 11 females (42%) were affected. Polycythemia Vera was diagnosed in 7 patients (27%), Essential Thrombocythemia in 9 patients (35%), and Primary Myelofibrosis in 7 patients (27%). Three patients (11%) were classified as MPN-Unclassified.* ***Conclusion:*** *The study highlights the demographic distribution and prevalence of non-leukemic MPNs in a tertiary care hospital in Pakistan. These findings emphasise the need for clinical and hematological evaluations and cytogenetic testing for accurate diagnosis. Further genetic and environmental studies are required to explore regional MPN prevalence and pathogenesis variations.*

Keywords: Mean Cell Volume, Lactate Dehydrogenase, Mean Cell Hemoglobin, Myelo-Proliferative Neoplasm

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Introduction

Myeloproliferative neoplasms (MPNs) are a group of hematological disorders that arise from the clonal proliferation of hematopoietic stem cells in the bone marrow. (1) These conditions are characterised by the overproduction of one or more blood cell types and can lead to various complications, including thrombosis, hemorrhage, and transformation into acute leukemia. The three major non-leukemic disorders classified under MPNs are Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF). Understanding these disorders is crucial for accurate diagnosis and effective management. (2)

Polycythemia Vera is primarily characterised by increased red blood cell mass, leading to erythrocytosis. This condition results from a somatic mutation in a single hematopoietic stem cell, which provides a proliferative advantage to its progeny. (3) The JAK2 V617F mutation in approximately 97% of patients indicates an everyday genetic basis for the disease. In addition to elevated red blood cell counts, many patients with PV exhibit increased granulocyte and platelet production. (4)

Diagnosis of PV can be challenging, requiring specific criteria to confirm its presence. Key diagnostic indicators include a high hematocrit level (greater than 0.52 in men and 0.48 in women) or an increased red cell mass, alongside the detection of the JAK2 mutation. In cases where the JAK2 mutation is absent, alternative criteria must be met, including palpable splenomegaly and excluding secondary causes of erythrocytosis. (5)

Clinically, PV often presents with symptoms related to increased blood viscosity, such as headaches, dizziness, and visual disturbances. (6) Patients may also experience pruritus, particularly after hot baths, and exhibit ruddy cyanosis due to increased blood volume. Laboratory findings typically reveal elevated hemoglobin levels, leukocytosis, and thrombocytosis. (7) Management strategies focus on maintaining normal blood counts to reduce the risk of thrombotic events. (8)

Essential Thrombocythemia is characterised by sustained thrombocytosis due to excessive proliferation of megakaryocytes in the bone marrow. (9) Unlike PV, patients with ET typically have normal red blood cell mass and do not exhibit evidence of collagen fibrosis in the bone marrow. The diagnosis relies on a persistent platelet count exceeding 450 × 10^9/L while ruling out other causes of thrombocytosis. (10)

Approximately 50-60% of ET patients harbor the JAK2 V617F mutation; however, those without this mutation often present with mutations in the CALR gene. (11) The clinical manifestations of ET primarily involve thrombotic events due to abnormal platelet function. Symptoms may include erythromelalgia—a burning sensation in the extremities—and an increased risk of arterial and venous thrombosis. (12)

Diagnosis involves confirming elevated platelet counts alongside genetic testing for mutations associated with ET. (13) Treatment strategies aim to mitigate thrombotic risks through low-dose aspirin therapy for all patients. High-risk individuals may require additional interventions such as hydroxycarbamide or anagrelide to lower platelet counts effectively. (14)

Primary Myelofibrosis is distinguished by progressive fibrosis of the bone marrow and extramedullary hematopoiesis in organs such as the spleen and liver. (15) This condition often leads to severe anemia and massive splenomegaly due to ineffective hematopoiesis. The pathophysiology involves hyperplasia of abnormal megakaryocytes that stimulate fibroblast proliferation through cytokine secretion. (16)

Clinically, PMF typically presents insidiously in older adults with symptoms such as fatigue, weight loss, night sweats, and abdominal discomfort due to splenomegaly. (17) A notable laboratory finding is a leukoerythroblastic blood film characterised by tear-drop shaped red blood cells. (18) The diagnosis is supported by bone marrow biopsy showing fibrosis and hypercellularity.

Genetic mutations also play a significant role in PMF; approximately 55% of patients have JAK2 mutations, while CALR mutations are found in about 25% of cases. (19) PMF treatment focuses on alleviating anaemia and splenomegaly symptoms. Ruxolitinib, an oral JAK2 inhibitor, has shown efficacy in reducing spleen size and improving quality of life for patients with PMF. (20)

Feature Polycythemia Vera (PV) Essential Thrombocythemia (ET) Primary Myelofibrosis

Myeloproliferative neoplasms encompass a spectrum of disorders that share common genetic underpinnings but manifest distinct clinical features and treatment challenges. (21) Polycythemia Vera is primarily characterised by erythrocytosis, Essential Thrombocythemia by thrombocytosis without significant red cell mass changes, and Primary Myelofibrosis by bone marrow fibrosis leading to extramedullary hematopoiesis. (22) Understanding these differences is critical for clinicians in diagnosing and managing these complex disorders effectively. Ongoing research into their pathophysiology will further enhance our understanding and treatment options for patients affected by these neoplasms. (23)

Methodology

The study was conducted as a retrospective analysis focusing on patients diagnosed with non-leukemic myeloproliferative neoplasms. A retrospective design allowed for a comprehensive clinical and laboratory data evaluation over a defined period using existing patient records. The research was carried out at the Pathology Department of Benazir Bhutto Hospital, Rawalpindi, Pakistan, a tertiary care facility equipped with advanced diagnostic tools and staffed by experienced hematologists, making it an ideal setting for studying hematological disorders. The study duration spanned three to four months following ethical approval, ensuring an adequate sample size for statistical validity.

All patients diagnosed with non-leukemic myeloproliferative neoplasms between 2018 and 2021 were included in the study. The patient selection criteria encompassed individuals of all ages and genders diagnosed with Polycythemia Vera, Essential Thrombocythemia, or Primary Myelofibrosis. Exclusion criteria included patients diagnosed with chronic myeloid leukemia, chronic eosinophilic leukemia, or chronic neutrophilic leukemia. Institutional consent was obtained before initiating the study, ensuring compliance with ethical standards and maintaining patient confidentiality.

Data analysis was performed using SPSS version 25. Descriptive statistics, including frequencies and percentages, were used for categorical variables to summarise demographic and clinical characteristics. The diagnosis of myeloproliferative neoplasms was established based on clinical presentation, hematological parameters, and cytogenetic findings by the 2016 World Health Organization (WHO) classification criteria.

Hematological evaluation included a complete blood count (CBC) on venous blood samples collected using standard phlebotomy techniques. Approximately 2 mL of whole blood was drawn into ethylenediaminetetraacetic acid (EDTA) vials for analysis using an automated hematology analyser. The measured parameters included total leukocyte count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and platelet count.

A peripheral blood smear was prepared to assess morphological abnormalities. A drop of blood was placed approximately one centimeter from one end of a clean glass slide, and a spreader was used at a 45-degree angle to create a thin film. The smear was air-dried before microscopic examination to evaluate red cell morphology, platelet distribution, and white blood cell differentiation.

Bone marrow aspiration was performed at multiple anatomical sites, including the posterior superior iliac spine, anterior superior iliac spine, sternum, vertebral spinous processes, and tibia. The aspiration procedure was carried out using Salah, Klima, or Islam needles. Local anesthesia with 2% lignocaine was administered before the procedure. After antiseptic preparation and appropriate patient positioning, a small skin incision was made, and the aspiration needle was advanced into the bone marrow cavity using a gentle dull motion. Approximately 0.5 mL of bone marrow was aspirated, and smears were prepared immediately to prevent clotting. Any residual sample was preserved in an EDTA vial for further examination.

A trephine biopsy was performed primarily from the posterior or anterior superior iliac spine using Jamshidi or Islam needles. The biopsy was obtained in the same setting as the bone marrow aspiration but was taken from a slightly different insertion site to prevent contamination. Once the needle was secured within the cortical bone, rotational movements were used to advance it to a depth of approximately 1.5 to 2 cm. The biopsy sample was gently extracted to avoid crush artefacts after detaching the core specimen through clockwise and counterclockwise rotations. Impression smears were prepared, and the cylindrical biopsy specimen was immediately fixed in a preservative solution for histopathological examination.

All procedures were performed under strict aseptic conditions, and hemostasis was ensured post-procedure by applying firm pressure at the puncture site. Any residual bleeding was controlled with additional compression or suturing if necessary. Data from hematological, cytogenetic, and morphological analyses were compiled to confirm the diagnosis of myeloproliferative neoplasms.

Results

A total of 26 patients were diagnosed as PV, ET or Myelofibrosis during the study period. The male-to-female ratio was 1.4:1, with 15 males (58%) and 11 females (42%). Out of 26 patients, there are 7 (27%) patients of PV, 9 (35%) patients of ET, 7 (27%) patients of Myelofibrosis and 3 (11%) patients of MPN-Unclassified. The seven patients of PV include five males and two females with male to female ratio of 2.5:1. The nine patients of ET include five males and four females with male to female ratio of 1.25:1. The seven patients of Myelofibrosis include four males and three females with male to female ratio of 1.3:1. The three patients of MPN-Unclassified include one male and two females with male to female ratio of 1:1.2. (Table 1-4)

Table 1 shows the count and percentage of diagnoses.

Diagnosis	Count	Percentage
Polycythemia Vera	7	27%
Essential Thrombocythemia	9	35%
Myelofibrosis	7	27%
MPN-Unclassified	3	11%
Total	26	100%

Table 2: Age-wise distribution of diagnosis.

Age Group	Polycythemia Vera	Essential Thrombocythemia	Myelofibrosis	MPN-Unclassified	Percentage
15 – 29	2 (29%)	1 (11%)	0 (0%)	0 (0%)	12%
30 – 44	1 (14%)	1 (11%)	0 (0%)	1 (33.3%)	12%
45 – 59	0 (0%)	3 (33%)	4 (57%)	1 (33.3%)	31%
60 – 74	4 (57%)	4 (45%)	2 (29%)	1 (33.3%)	42%
75 – 89	0 (0%)	0 (0%)	1 (14%)	0 (0%)	5%
Total	7	9	7	3	26 (100%)

Table 3 shows the count and percentage of diagnoses I genders.

Gender	Count	Percentage
Male	15	58%
Female	11	42%
Total	26	100%

Table 4: Showing age-wise distribution of gender.

Age Group	Male	Female	Percentage
15 – 29	1 (7%)	2 (18%)	12%
30 – 44	2 (13%)	1 (9%)	12%
45 – 59	3 (20%)	5 (46%)	31%
60 – 74	8 (53%)	3 (27%)	42%
75 - 89	1 (7%)	0 (0%)	3%
Total	15	11	26 (100%)

Discussion

This study ascertained several vital facts in Pakistani patients with PV, ET and Myelofibrosis. Sex ratios for PV, ET and IMF in this study are quite different from international data. Male to Female ratio in PV was 2.5:1, which is almost double. Female preponderance in ET (female to male ratio of 2:1) has been reported in several studies, however, the female to male ratio was found to be 1:1.25 in this study. The seven patients of Myelofibrosis include four males and three females with a male to female ratio of 1.3:1. Although PV and ET are identified by chance in a proportion of patients, almost half of the patients with these conditions in this study came to medical attention due to incidental abnormal laboratory findings. For PV and ET, the most common reason for consultation was abnormal complete blood count (CBC) findings carried out as routine testing.

This study shows that most patients had been diagnosed with ET, i.e. 9 out of 26 patients (35%). PV and myelofibrosis have exact incidences, i.e., 7 out of 26 patients (27%) (Table 1). Patients with PV mostly had an age between 60-74 years (57%) and no patient had been reported in age groups 45- 59 and 75-89 (Table 2). Patients with ET mostly had an age between 60-74 years (45%) and no patient had been reported in the age group 75-89 (Table 2). Patients with Myelofibrosis mostly had an age between 45-59 years (57%) and no patient had been reported in age groups 15-29 and 30-44 (Table 2). The incidence of male patients is mainly between age 60 and 74 (53%) (Table 4). The incidence of female patients is primarily seen between the ages of 45 and 59 (46%), and no females have been reported between the ages of 75 and 89 (Table 4).

The patients with a history of transfusion in PV were 1 out of 7 (14%), in ET 2 out of 9 (23%) and in Myelofibrosis 2 out of 7 (29%). The patients with a history of splenomegaly in PV were 3 out of 7 (43%), in ET 5 out of 9 (56%), in Myelofibrosis 7 out of 7 (100%) and MPN- Unclassified 3 out of 3 (100%). The patients with a history of liver enlargement in PV were 2 out of 7 (29%), in ET 2 out of 9 (22%), in Myelofibrosis 2 out of 7 (29%) and MPN- Unclassified 2 out of 3 (67%). The patients with a history of lymph node enlargement in PV were 0 out of 7 (0%), in ET 0 out of 9 (0%), in Myelofibrosis 1 out of 7 (14%) and in MPN-Unclassified 1 out of 3 (33%). The patients with history of pallor in PV were 1 out of 7 (14%), in ET 4 out of 9 (45%), in Myelofibrosis 6 out of 7 (86%) and MPN-Unclassified 2 out of 3 (67%). The patients with a history of bleeding in PV were 2 out of 7 (29%), in ET 0 out of 9 (0%), in Myelofibrosis 1 out of 7 (14%) and MPN-Unclassified 1 out of 3 (33%). The patients with a history of bruising in PV were 0 out of 7 (0%), in ET 1 out of 9 (11%), in Myelofibrosis 1 out of 7 (14%) and MPN-Unclassified 0 out of 3 (0%). The patients with a history of thrombotic complication (i.e. abdominal pain) in PV were 1 out of 7 (14%), in ET 1 out of 9 (11%), in Myelofibrosis 1 out of 7 (14%) and MPN-Unclassified 0 out of 3 (0%).

A research conducted at the Agha Khan University concluded that 58 patients were diagnosed as PV, ET or IMF during their study. Male to female ratio was 1.1:1 with mean±SD age of 57.3±13.3 for males and 56.3±16.6 for females. Male to Female ratio in PV was 2.1:1. Female to male ratio in ET was found to be 3.8:1 in their study. All six patients with IMF were males. Only three (10.7%) patients with PV had pruritus, whereas it has been reported in as high as 68% of the patients with PV. Thrombotic events were present in four (14.3%) patients with PV (cerebrovascular event in 2, Budd-Chiari syndrome in 1 and gangrene in 1). These data are comparable to international data. In ET, however, only one (4.2%) patient presented with cerebrovascular thrombosis. Incidence rates of thrombosis in ET varying from 9 to 22 percent have been described in various studies31. Another study from India, carried out by Sonal Gupta and Sujata R. Kanetkar, concluded that a total of 41 cases diagnosed as MPN on complete blood count, peripheral smear examination, bone marrow aspirate, bone marrow biopsy with cytogenetic JAK2 V617F mutations; and BCR-ABL1 mutation in cases of CML with molecular response data were studied. The study included 41 cases of MPNs, with 37 cases diagnosed as CML and one case each of PMF, CNL, PV and MPN-Unclassifiable. The cases of PMF, PV and MPN-U were seen in male patients. PMF, CNL, PV and MPN-U were observed in patients above 60 years of age. (31)

Conclusion

Clinical and hematological findings and characteristic cytogenetic mutation according to 2016 WHO classification of Myeloproliferative neoplasms, can help arrive at the correct diagnosis of MPNs. BCR-ABL1 and JAK2 mutation studies help diagnose and initiate appropriate treatment strategies for these patients. In the new era of ‘tailor-made

treatment' and 'targeted therapy' the use of cytogenetic mutations to characterise the disease prognosis and outcome, justifies the approach of the revised 2016 WHO classification. These mutation analyses give us a complete insight into the biology of the disease, thus defining the actual disease entity. Though these are relatively high-cost tests, they have the advantage of being accurate, reproducible and adding valuable information to morphology in classifying diseases. The possible influence of genetic and environmental factors on milder phenotype of these conditions in the Pakistani population needs further exploration.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRBEC-MMS-033-24)

Consent for publication

Approved

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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

AA

Manuscript drafting, Study Design, Conception of Study, Development of Research Methodology Design

RAMD

Review of Literature, Data entry, Data analysis, and drafting articles.

MA

Conception of Study, Development of Research Methodology Design

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Study Design, manuscript review, critical input, Manuscript drafting, Study Design

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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