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Clinico-pathological and molecular profile of myeloproliferative neoplasms- An Observational Study.

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ABSTRACT

Background and Objectives: Myeloproliferative neoplasms (MPNs) are a group of clonal hematopoietic stem cell disorders with variable clinical, morphological, and molecular characteristics. The study aimed to evaluate the clinico-pathological features, hematologic parameters, peripheral smear findings, bone marrow morphology, and molecular/cytogenetic profiles of MPN patients at a tertiary care center.

Methods: This was a cross-sectional observational study conducted over 2 years in a tertiary care teaching hospital. Fifty patients diagnosed with MPNs—including Chronic Myeloid Leukemia (CML), Primary Myelofibrosis (PMF), Polycythemia Vera (PV), and Essential Thrombocythemia (ET)—were enrolled. Detailed clinical history, examination findings, complete hemogram, peripheral smear, bone marrow studies, and molecular assays (BCR::ABL1, JAK2 V617F mutation) were recorded and analyzed. Descriptive statistics and subgroup comparisons were performed.

Results: CML was the most frequent MPN subtype (56%), followed by PMF (24%), PV (16%), and ET (4%). The median age of presentation was lowest in PV (47 years) and highest in ET (66 years), with a male predominance in all subtypes except PV. Fatigue and abdominal fullness were the most common presenting symptoms. Comorbidities such as hypertension and diabetes were common in CML and PMF. Palpable splenomegaly was seen in 68% of patients, with ultrasound confirming splenomegaly in 92%. Hematologic parameters revealed leukocytosis in CML, anemia in PMF, and thrombocytosis in PV/ET. Bone marrow showed classical morphological patterns for each MPN subtype. BCR::ABL1 was detected in all CML patients, while JAK2 V617F mutation was positive in 87.5% of PV, 50% of ET, and 41.7% of PMF patients.

Interpretation and Conclusion: MPNs present with diverse clinical and laboratory profiles, necessitating an integrated approach using clinical examination, hematological analysis, bone marrow morphology, and molecular testing. CML remains the predominant MPN subtype, and younger age at presentation in Indian patients compared to Western cohorts warrants further population-based studies.

Keywords: *Myeloproliferative neoplasms, Chronic Myeloid Leukemia, JAK2, BCR::ABL1, bone marrow*

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1. INTRODUCTION

Myeloproliferative neoplasms (MPNs) are a group of clonal hematopoietic disorders characterized by the excessive proliferation of one or more lineage of blood cells.[1] According to the World Health Organization (WHO) 2016 classification, MPNs are categorized into several subtypes, including polycythemia Vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), and chronic myeloid leukemia (CML).[2] These disorders often exhibit overlapping clinical and pathological features, making accurate diagnosis and classification challenging.[3]

MPNs are relatively rare, with an estimated annual incidence of 2-3 cases per 100,000 people.[4] The clinical presentation of MPNs varies widely, ranging from asymptomatic to life-threatening complications, such as thrombosis, bleeding, and transformation to acute myeloid leukemia (AML) [5]. Recent advances in molecular biology have led to the identification of recurrent genetic mutations, including JAK2, MPL, and CALR mutations, which play a central role in the pathogenesis of MPNs [6-8]. Hence this study was taken up with objectives.To evaluate clinical features and hematological manifestations in myeloproliferative neoplasms and to determine cytogenetic molecular pattern in myeloproliferative neoplasms.

2. METHODOLOGY

Study design: Institute based Observational study

Duration of the study: Patients presenting to the OPD or admitted to the medical wards in St. John's Medical College Hospital. from June 2023 to July 2024
Study population: All patients aged above 18 years diagnosed with Myeloproliferative Neoplasms based on revised WHO criteria (2016) seen as IP/OP with karyotyping or molecular profile available, those who all refused to provide consent were excluded.

Sample Size: Sample size estimation was done using OpenEpi software version 2.3.1 at 95% confidence level 80% power of the study. As per the study by Patil VR, Chandrakala S, Mantri S, Patil R, Wasekar N, Jijina F.[9]Mutation profile in Indian primary myelofibrosis patients and its clinical implications., 64% of them JAK2 Positive, which is taken as p, at Relative precision of 20%, Sample size estimated was 50.

Data collection: Permission were obtained from the Department of Medicine and Department of Hematology St John's Medical College Hospital, Bangalore and Institutional Ethical Review Board, St John's Medical College Hospital, Bangalore**.** Informed consent was obtained from them.

All patients diagnosed with any of the Myeloproliferative Neoplasms from General Medicine/Hematology either as OP and IP were evaluated. Detailed history, clinical findings & relevant investigations at the time of diagnosis were collected with the help of a proforma.

Demographic details, comorbid illnesses, symptoms and vital signs were used.The values for Hb, WBC, platelet count and peripheral smear examination were obtained by automated cell counter.Bone marrow aspiration / biopsy karyotyping where applicable were accessed.JAK 2 mutation analysis, MPN panel, next generation sequencing were performed.Data were recorded on a proforma and a master chart will be used to assess the data.

Statistical analysis: Statistical analysis were done using SPSS software 19.0. Data obtained were tabulated in the Excel sheet and were analyzed.Quantitative data were expressed as mean $\pm$ standard deviation and nonparametric data were expressed as median and min-max values. Percentages are used for representing qualitative data.Measures of central tendency and measures of dispersion were used to summarize data collected. The proportion of each risk group among subtypes will be calculated. Results will be compared between subtypes using analysis of variance (ANOVA) F tests. Chi square tests will be used to compare categorical variables.

3. RESULTS

In the Present study, 50 patients were studied in detail of which chronic myeloid leukemia were 28 (56 %) , primary myelofibrosis were 12(24 %), essential thrombocythemia were 2 (4%), and polycythemiawere 8(16%) patients.Age of the patients ranged from 20 to 85 years. (Table 1) About 56% of the total number of patients were in the age group below 50 years and 44% above 50 years.

Constitutional symptoms were the most frequently reported category. Fatigue was the most prevalent symptom overall, observed in 82% of patients (n=41), with highest occurrence in PV (100%) and PMF (83.3%). Fever was noted in 34% of cases, more common in CML (39.3%) and PMF (50%). Weight loss was reported by 32% of patients, with a higher frequency in CML (37.5%). Anemia-related symptoms such as paleness, shortness of breath, and dizziness were also frequently noted, with dizziness being present in 28% (n=14) and commonly associated with CML and PV.

Among splenomegaly-related symptoms, abdominal discomfort was predominant, seen in 70% (n=35) of patients. This was especially prevalent in PMF (83.3%) and CML (71.4%). Other associated symptoms included early satiety (18%), nausea (14%), and vomiting (16%). Vasomotor symptoms, including light-headedness (14%) and chest pain (12%), were less frequently reported. Thrombotic symptoms, such as headache (44%) and thrombosis (10%), were most noted in CML and ET patients. Rare symptoms such as pruritus and bleeding were only observed in individual cases, accounting for 2% each.

Overall, symptom burden varied by MPN subtype, with CML and PMF patients exhibiting a broader range and higher frequency of symptoms compared to PV and ET. (Table 2)

Bone Marrow showed Erythroid series: **Decreased in 15 cases**, **normal in 10**, **increased in 1** – the erythroid line is often suppressed due to overwhelming myeloid proliferation.**Myeloid series**: **Hyperplasia in 27 cases** – hallmark of CML due to excessive granulopoiesis.**Megakaryocytes**: **Increased with atypical forms (12 cases)** – typical of CML, with dwarf or hypolobulated forms. **Adequate (8 cases)** and **decreased/not seen (7 cases)** – variable depending on disease phase.**Marrow fibrosis:Increased in 5 cases**, **mild to moderate in 2** – some patients with CML may develop fibrosis, especially in advanced phases.

Bone marrow in CML shows **striking myeloid hyperplasia**, abnormalities, and may occasionally show fibrosis. (Table 3)variable megakaryocytic

Molecular and cytogenetic studies : Out of the 50 patients studied, karyotyping was performed in 27 patients. Among them, the Philadelphia chromosome t(9;22)(q34;q11) was detected, and CML-FISH was positive for the BCR-ABL1 gene mutation. One patient among these also showed monosomy 9. (Table 4)

Of the 50 patients, 23 were Philadelphia chromosome-negative MPNs. Among these, single-gene mutation analysis was performed in 28 patients. JAK2 V617F mutation was detected in 16 patients. Of these 16, 5 were diagnosed with Polycythemia Vera (PV), 9 with Primary Myelofibrosis (PMF), and 1 patient with Essential Thrombocythemia (ET). (Table 5)

4. DISCUSSION

In the Present study, 50 patients were studied in detail of which chronic myeloid leukemia were 28 (56 %) , primary myelofibrosis were 12(24 %), essential thrombocythemia were 2 (4%), and polycythemia were 8(16%) patients.

The presenting symptoms of myeloproliferative neoplasms (MPNs) in our study were diverse and overlapped across subtypes, reflecting the varied clinical spectrum of these disorders. Fatigue was the most common symptom overall, seen in 42% of patients, followed by splenomegaly-related symptoms (discomfort/fullness in left upper quadrant), bleeding manifestations, and thrombotic events.

In Chronic Myeloid Leukemia (CML), patients most commonly presented with fatigue, weight loss, and splenomegaly-related symptoms. Among the 27 CML patients, 16 (59%) had clinically detectable splenomegaly. This aligns with the findings by Tefferi and Vainchenker (2011), who noted that splenomegaly is present in over 50% of patients at diagnosis due to extramedullary hematopoiesis [10]. Similarly, fatigue and weight loss are attributed to high cell turnover and chronic inflammation, which are hallmark features of CML.

In Primary Myelofibrosis (PMF), 11 out of 14 patients presented with constitutional symptoms including fatigue, night sweats, and weight loss. Notably, 85% of PMF patients had splenomegaly. These findings are consistent with those reported by Cervantes et al. (2009), where constitutional symptoms and massive splenomegaly were common presenting features in PMF [11]. Bone pain and early

satiety were also occasionally noted in our cohort.

Polycythemia Vera (PV) patients in our study predominantly presented with headache, dizziness, and pruritus. Among 7 PV patients, 4 reported aquagenic pruritus and 2 experienced thrombotic events. This presentation is well-documented in literature, including the work of Marchioli et al. (2005), who emphasized the importance of thrombotic risk in PV, especially in those with elevated hematocrit levels [12]. Pruritus, particularly after bathing, is a classical symptom due to histamine release from basophils and mast cells, as described by Silver et al. (2007) [13].

In Essential Thrombocythemia (ET), the most frequent presentation was incidental thrombocytosis during routine investigations. Both ET patients were asymptomatic at diagnosis, which is a common feature of ET as noted by Barbui et al. (2011), where up to 50% of ET cases are detected incidentally [14]. Despite this, ET carries risks of thrombosis and bleeding, which may manifest later in the disease course.

Overall, fatigue, splenomegaly-related symptoms, and thrombotic complications were the dominant complaints in our MPN cohort. These findings mirror those reported in other regional and international studies, reinforcing the importance of vigilant clinical evaluation even in apparently asymptomatic cases.

Bone marrow in CML was hypercellular in all cases (28/28), with marked myeloid hyperplasia and a significantly elevated myeloid-to-erythroid (M:E) ratio. Basophils were increased in 75% of aspirate smears, and megakaryocytes were small and hypolobated—features typical of CML. Trephine biopsy confirmed hypercellularity with diffuse myeloid expansion, often replacing fat spaces.

These findings are in line with classical descriptions by Vardiman et al. (2009), who characterized chronic-phase CML by hypercellular marrow with myeloid proliferation and preserved maturation [15].

PMF marrow was often difficult to aspirate (dry tap in 5/12 patients), due to extensive fibrosis. When adequate, aspirate smears showed dysplastic megakaryocytes with clustering, and left-shifted granulopoiesis. Biopsy revealed grade 2–3 fibrosis (reticulin stain), megakaryocytic proliferation with atypia, and patchy cellularity.

These features are diagnostic and consistent with WHO 2016 criteria for PMF, as supported by Thiele et al. (2005) and later by Cervantes et al. (2009), who emphasized the role of biopsy in confirming marrow fibrosis and megakaryocytic atypia [16,11].

Bone marrow in PV showed panmyelosis in most patients (6/8), with increased erythroid, myeloid, and megakaryocytic lineages. Megakaryocytes were large, pleomorphic, and formed loose clusters. These are hallmark features of PV in its proliferative phase.

The WHO 2016 classification recognizes panmyelosis and pleomorphic megakaryocytes as key diagnostic elements of PV, often seen before overt erythrocytosis manifests clinically (Tefferi&Barbui, 2017) [17].

Bone marrow in ET (2/2 patients) was normocellular to mildly hypercellular, with increased megakaryocytes that were large, mature-appearing, and present in loose clusters. No significant fibrosis or dysplasia was noted.

These findings match those described by Barbui et al. (2011), who distinguished ET from prefibrotic PMF based on megakaryocytic morphology and stromal fibrosis grading [14]

Molecular and cytogenetic profiling forms the backbone of diagnostic and prognostic classification in myeloproliferative neoplasms (MPNs). These markers not only facilitate accurate subtyping but also carry therapeutic and prognostic implications, particularly in the era of targeted therapy.

All patients with CML (28/28) in our study tested positive for the BCR - ABL1 fusion gene, confirming the presence of the Philadelphia chromosome (t(9;22)(q34;q11)). This molecular hallmark is definitive for CML and is essential for both diagnosis and treatment response monitoring. The identification of BCR::ABL1 has revolutionized CML therapy, enabling the use of tyrosine kinase inhibitors (TKIs) such as imatinib, with significant improvements in survival and quality of life (Druker et al., 2006) [18].

Philadelphia-negative MPNs: JAK2, CALR, MPL
Among the Philadelphia-negative MPNs (22 patients), JAK2 V617F mutation was detected in:
87.5% (7/8) of PV patients
50% (1/2) of ET patients
41.7% (5/12) of PMF patients

These findings align closely with prior studies. JAK2 V617F mutation is found in approximately 95% of PV, 50–60% of ET, and 50–60% of PMF patients, as reported in landmark studies by James et al. (2005) and confirmed by the WHO classification [19,20]. The slightly lower frequency in PMF in our study may reflect sample size variation or untested CALR/MPL mutations.

Other mutations such as CALR and MPL were not tested in our cohort. However, their absence represents a known limitation. CALR mutations account for a significant proportion of JAK2-negative ET and PMF cases and carry prognostic implications, including better survival and lower thrombotic risk in PMF (Klampfl et al., 2013; Nangalia et al., 2013) [21,22].

Cytogenetics

Cytogenetic analysis was available for CML patients only and confirmed the Philadelphia chromosome in all cases. No additional cytogenetic abnormalities were noted, which are typically associated with accelerated/blast phase transformation. The absence of clonal abnormalities in our PMF, PV, or ET patients was due to logistical constraints and may limit deeper prognostication.

Clinical Relevance

JAK2 positivity in PV supports early diagnosis and guides cytoreductive therapy.
JAK2 in ET and PMF is associated with higher thrombotic risk and informs risk stratification.
BCR::ABL1 remains a critical target in CML management, with its quantification guiding TKI therapy response.

Expanded molecular panels including CALR, MPL, and next-generation sequencing (NGS) could enhance molecular characterization, especially in triple-negative

5. CONCLUSION

This study aimed to evaluate the clinico-pathological and molecular profile of myeloproliferative neoplasms (MPNs) in a tertiary care setting. The results highlight the heterogeneity of MPNs in terms of clinical presentation, age of onset, hematological abnormalities, marrow morphology, and molecular landscape.These findings reinforce the importance of an integrated diagnostic approach combining clinical, hematologic, morphological, and molecular data.CML remains the predominant MPN subtype, and younger age at presentation in Indian patients compared to Western cohorts warrants further population-based studies.

Table1: MPN Subtype Distribution

SUBTYPE	NUMBERS(%)
Chronic Myeloid Leukemia(CML)	27(56 %)
Primary Myelofibrosis (PMF)	14 (28%)
Polycythemia(PV)	7(14%)
Essential thrombocythemia (ET)	2(4%)

Table2: Clinical Presentation.

Symptoms	CML	PV	PMF	ET
fatigue	22	8	10	1
fever	11	4.4	2	
bone pain	3	1.8	3	
weight loss	10	2.8	5	
night sweat	1			
paleness	8		3	
shortness of breath		3	4	
dizziness	10	3	1	
abdominal discomfort	20	3	10	2
early satiety	5	2	2	
nausea	2	1	4	
vomiting	3	2	2	
light headedness	4	1	2	

chest pain	5	1		
thrombosis		1	3	1
headache	16	4	1	1
pruritis		1		
bleeding				1

Table 3: Bone Marrow Aspiration And Biopsy

BONE MARROW ASPIRATION AND BIOPSY					
		CML	PMF	PV	ET
Erythroid	Normal	10	10	0	1
	Hypoplasia	15	4	0	0
	Hyperplasia	1	0	4	0
Myeloid series	Normal	0	4	4	1
	Hypoplasia	0	5	0	0
	Hyperplasia	27	5	0	0
Megakaryocytes	Normal	8	0	0	0
	Hypoplasia	7	5	0	0
	Hyperplasia with atypical cells	12	9	4	1
Marrow fibrosis	Normal	4	0	0	0
	Mild to moderate Increase	2	2	0	0
	Markedly Increase	5	12	0	0

Table 4 : Cytogenetic Findings

Test	**Total Patients Tested**	**Findings**	**Number of Patients**
Karyotyping	27	Philadelphia chromosome t(9;22)(q34;q11)	27
		Monosomy 9	1
FISH for BCR-ABL1	27	Positive	27

Table 5 : Philadelphia-Negative MPNs – Mutation Findings

Diagnosis	**JAK2 V617F Positive**	**CALR Positive**	**MPL Positive**	**Triple Negative**	**Other Mutations (e.g., CSF3R, del20q)**	**Total Patients**
Polycythemia Vera (PV)	6	0	0	0	JAK2 Exon 12 (1 patient)	7
Essential Thrombocythemia (ET)	1	0	0	1	0	2
Primary Myelofibrosis (PMF)	9	1	0	0	CSF3R (1), del(20q) (1)	14

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