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Original Research Article

CLINICAL AND MOLECULAR PROFILING OF BCR-ABL NEGATIVE MYELOPROLIFERATIVE NEOPLASMS IN A TERTIARY CARE CENTRE IN SOUTH INDIA

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ABSTRACT

Background: Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), including Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF), are stem cell disorders defined by abnormal proliferation of myeloid cells. These conditions are linked with genetic alterations, primarily in JAK2, CALR, and MPL genes and present an elevated risk of thrombotic events and transformation to acute leukemia. This study aims to evaluate the clinical presentations and genetic profiles of MPNs in patients from a tertiary care center in South India.

Materials and Methods: This retrospective observational study was conducted at a tertiary medical center in Andhra Pradesh over a four-year period (2019–2023). Twenty-eight treatment-naive adults with confirmed clinical, molecular, and pathological diagnoses were included. Data regarding demographics, clinical signs, laboratory values, bone marrow studies, and genetic mutations were systematically analyzed.

Results: The median age of the patients was 55 years, ranging from 23 to 75, with a slight male predominance (male-to-female ratio 1.1:1). ET emerged as the most frequently diagnosed subtype (46.4%), followed by PV (39.3%) and PMF (14.3%). Common symptoms included abdominal discomfort, poor appetite, and fatigue. Over half of the patients (53.6%) exhibited splenomegaly. Hypertension was the most common associated condition. All patients tested showed JAK2 mutations with no CALR or MPL mutations detected. Thrombotic complications were seen in 39% of the cohort, while none progressed to acute leukemia during the study period.

Conclusion: This single-center analysis highlights JAK2 mutation as the predominant molecular finding in BCR: ABL1-negative MPNs within this South Indian population, with ET being the most common clinical subtype. Although findings are largely consistent with global patterns, regional differences such as earlier onset and lack of CALR/MPL mutations indicate a need for expanded molecular testing and multicenter studies to enhance prognostic tools and therapeutic approaches tailored to the Indian context.

Keywords: Essential thrombocythemia, JAK2 mutation, Molecular diagnostics, Myeloproliferative neoplasms, Polycythemia vera, Primary myelofibrosis.

INTRODUCTION

Myeloproliferative neoplasms are a group of disorders characterized by the overproduction of one or more formed elements of blood without significant dysplasia. In 1951, William Dameshek described these disorders as characterized by an excessive proliferation of hematopoietic precursors in the bone marrow and an excessive production of mature blood cells.

In 2022, the World Health Organization (WHO) revised the classification of myeloid neoplasms to include the following:

1. Chronic myeloid leukemia (CML), BCR: ABL1 positive;
2. Chronic neutrophilic leukemia (CNL)
3. Polycythemia vera (PV);
4. Primary myelofibrosis (PMF);
5. Essential thrombocythemia (ET);
6. Chronic eosinophilic leukemia (CEL) not otherwise specified; and
7. MPN, unclassifiable.

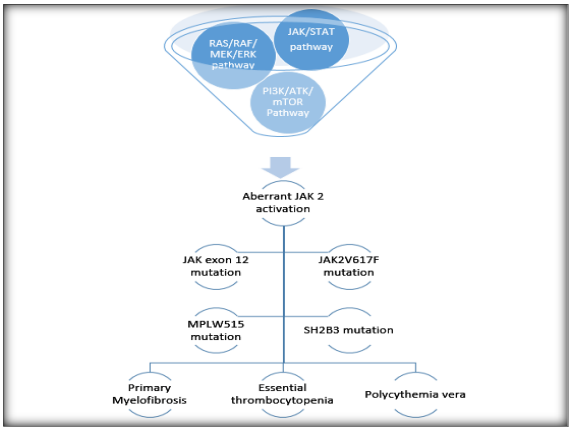
Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs) are clonal disorders of hematopoietic stem cells, encompassing polycythemia vera (PV), essential thrombocytosis (ET), and primary myelofibrosis (PMF). These conditions are characterized by the abnormal proliferation of primarily mature blood cells driven by mutations in the JAK2, CALR, and MPL genes. These mutations result in the constitutive activation of the JAK-STAT signaling pathway, which is a potential target for therapy. MPNs are associated with an increased risk of transforming into acute myeloid leukemia.

In addition to the primary driver mutations, many patients, particularly those with myelofibrosis, also carry mutations in various "myeloid neoplasm-associated" genes. These genes encode proteins involved in processes such as chromatin modification, DNA methylation, RNA splicing, transcription regulation, and oncogenesis. These secondary mutations often occur in the context of clonal hematopoiesis of indeterminate potential (CHIP).

Polycythemia vera (PV) is primarily characterized by an increased red cell mass; essential thrombocytosis (ET) is defined by an isolated rise in platelet counts; and primary myelofibrosis (PMF) involves the gradual replacement of the hematopoietic compartment with collagen fibers, leading to bone marrow failure and extramedullary hematopoiesis, often accompanied by constitutional symptoms.

ET and PV can also progress to result in a secondary MF, with a 10-year risk of post-ET MF and post-PV MF being <4% and 10%, respectively.[1]

Molecular Alterations



Signaling in MPN patients. Shows the different MPN and aberrant JAK2 activation and a spectrum of downstream pathways11

In BCR-ABL1 negative MPNs, the common driver mutations are Janus kinase (JAK2), JAK2 point mutations, myeloproliferative leukemia virus proto-oncogene (MPL), and Calreticulin gene mutation (CALR).

The molecular subtype which is triple-negative MPN is that which does not exhibit mutations in JAK2, CALR, or MPL genes but possesses histological and phenotypic features consistent with MPNs. Triple-negative cases of ET and PMF account for approximately 20% and 5 to 10% of cases, respectively.2,3

The less common driver mutations include granulocyte colony stimulating factor 3 receptor CSF3R, KIT and other rearrangements involving platelet-derived or fibroblast-growth-factor receptors (PDGFRA, PDGFRB, FGFR1).

The non-driver mutations are not specific to the diagnosis of MPN but prognosticate the risk of disease progression and shortened survival. They also predict transformation to acute leukemia. These include genes influencing:

- Epigenetic regulation like EZH2, ASXL1, TET2, DNMT3A and IDH1/2.
- RNA spliceosome mutations machinery components like SRSR2, SRSF2, SF3B1 and U2AF1.
- Transcription factors and signal transduction genes, including FLT3, NF1, TP53, NRAS, RUNX1, SH2B3 and CBL.

Clinical presentation

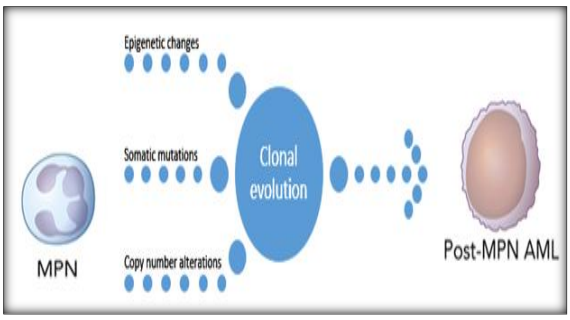
MPN patients are at variable risk of vascular complications, including arterial or venous thrombosis at unusual sites, including the portal vein, hepatic vein, and bleeding. In addition, patients may have fatigue, constitutional symptoms like fever, weight loss, night sweats, microvascular symptoms like headaches, erythromelalgia, itchiness, bone pain, thrombosis, symptoms of early satiety, and abdominal discomfort. Some patients present with a thrombotic event or have a history of thrombosis.

On physical examination, palpable splenomegaly and/or hepatomegaly and evidence of extra-medullary hematopoiesis at other sites may be found. Peripheral blood studies are notable for blood counts that exceed the upper limit of normal and changes consistent with hyper metabolism, such as elevated serum levels of lactate dehydrogenase and uric acid. Leucoerythroblastic changes on peripheral blood smear are characteristic of myelofibrosis or primary myelofibrosis. Secondary erythrocytosis and thrombocytosis must be ruled out.

A portion of patients with ET and especially those with PV may develop secondary myelofibrosis, whereas all MPN patients may progress to a blast phase that is indistinguishable from AML, sometimes preceded by a myelodysplastic phase.

The presence of two or more somatic mutations was associated with reduced overall survival and increased risk of transformation to acute myeloid leukemia.[10]

Various routes to leukemic transformation in MPNs



Mutations in epigenetic modifiers, such as TET2 and ASXL1, can occur either before or after the JAK2V617F mutation. Over time, additional somatic genetic and epigenetic remodeling events, influenced by various intrinsic or extrinsic cellular factors, enhance the proliferative and self-renewal capabilities of the expanding cell population, ultimately leading to blast-phase transformation.

In many cases, leukemic clones can develop from populations of JAK2V617F wild-type cells, suggesting that a separate, coexisting clonal process is evolving.

In the case of TP53-mutant post-myeloproliferative neoplasm (MPN) acute myeloid leukemia (AML), there is a distinct pathway to leukemic transformation. This occurs when the "second-hit" loss of heterozygosity (LOH) of TP53 in an existing JAK2V617F/TP53 heterozygous-mutant clone leads to rapid clonal expansion, chromosomal instability, and blast-phase transformation.[12]

Treatment modalities:

The primary goal of treatment for polycythemia vera (PV) is the prevention of thrombosis. Low-risk patients are typically treated with low-dose aspirin and phlebotomy, while high-risk patients receive cytoreductive treatment in addition to these therapies. For all patients, the objective is to lower the hematocrit to below 45%. This target significantly reduces the rate of cardiovascular deaths and major thrombosis compared to higher hematocrit levels. Unless there is a history of major bleeding, an allergy to the drug, severe asthma, or gastric intolerance, low-dose aspirin (100 mg daily) is recommended for all patients. The ultimate aim of this treatment regimen is to limit the availability of iron for erythropoiesis. However, this often leads to severe and prolonged iron deficiency, with fatigue being a significant burden affecting the quality of life in patients with PV.

Hydroxyurea (HU), an antimetabolite that prevents DNA synthesis, is an approved treatment for PV. It is also used for sickle cell anemia due to its ability to reactivate the synthesis of hemoglobin F, leading to a significant reduction in occlusive and hemolytic events.

****Non-Cytotoxic Drugs for PV and Essential Thrombocythemia (ET)****

Interferon-alpha (IFN-α) is a non-leukemogenic agent with multiple potential activities against hematopoietic progenitor cell proliferation and differentiation. It effectively reduces hematocrit or platelet count to target levels in the majority of cases, without causing thrombo-hemorrhagic events. This makes it a suitable treatment option for the youngest patients with PV and ET. However, tolerance can be poor due to acute and chronic side effects, leading to discontinuation in about one-third of patients. IFN-α is not teratogenic and does not cross the placenta, making it recommended for cytoreduction during pregnancy according to current guidelines.

Nagrelide is commonly used to control platelet counts in patients with ET and is effective in managing thrombocytosis. However, cardiovascular side effects, such as palpitations and headache (and less frequently congestive heart failure), may necessitate early discontinuation of treatment. Anagrelide is considered free of leukemogenic potential but should not be prescribed during pregnancy. It may also be beneficial for patients with PV or ET who are refractory or resistant to other treatments, or who experience side effects from hydroxyurea.

In primary myelofibrosis (PMF), treatment aims to alleviate anemia, reduce splenomegaly, and improve systemic symptoms. Therapies such as androgens, prednisone, erythropoiesis-stimulating agents, and danazol have shown variable effectiveness in some patients. Low-dose thalidomide combined with prednisone improves anemia or thrombocytopenia in 30% to 50% of cases.

Lenalidomide, a thalidomide analogue, has demonstrated excellent and durable responses in PMF patients with the del(5q) abnormality, and it is recommended as the first-line therapy for this subset of patients. When controlling excessive myeloproliferative conditions, such as leukocytosis, thrombocytosis, or progressive splenomegaly, hydroxyurea is the preferred drug. Additionally, in patients who relapse after hematopoietic stem cell transplantation (HSCT), a graft-versus-myelofibrosis effect may be observed following donor lymphocyte infusion, resulting in a notable reduction of bone marrow fibrosis.

Diagnosis

2022 WHO criteria for diagnosis of MPNs[4]

Diagnostic Criteria for Polycythemia Vera

Diagnosis of PV necessitates the presence of either all three major criteria or the first two major criteria and one minor criterion.

Major criteria

1. Hemoglobin greater than 16.5 g/dL in males and hemoglobin greater than 16.0 g/dL in females or Hematocrit greater than 49% in males and hematocrit greater than 48% in females or

Increased red cell mass greater than 25% above the mean normal predicted value
2. Presence of JAK2 V617F or JAK exon 12 mutation
3. Bone marrow biopsy with trilineage myeloproliferation (panmyelosis) and hypercellularity for age

Minor criterion

4. Serum erythropoietin is below normal

Patients with PV who fulfill the diagnostic criteria should also be evaluated for secondary causes of polycythemia.

Diagnostic Criteria for Essential Thrombocythemia

Diagnosis of ET requires either the presence of all four major criteria or the first three major criteria and the minor criterion.

Major criteria

1. Platelet count greater than or equal to 450 X 10^9/L.
2. Bone marrow biopsy with a proliferation of megakaryocyte lineage with increased numbers of large, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters. No increase in neutrophil granulopoiesis or erythropoiesis. No relevant bone marrow fibrosis.
3. Not meeting WHO criteria for BCR-ABL1 positive CML, PMF, PV, or other myeloid neoplasms.
4. Detection of JAK2, CALR, or MPL mutation

Minor criterion

5. Presence of clonal marker or absence of evidence for reactive thrombocytosis

Diagnostic Criteria for Primary Myelofibrosis

The diagnosis of PMF requires the presence of all three major criteria and at least one of the minor criteria.

Major criteria

1. Bone marrow findings of megakaryocyte proliferation with atypia, bone marrow fibrosis <grade 2, increased age-adjusted cellularity, granulocytic proliferation, and reduced erythropoiesis
2. Detection of JAK2, CALR, or MPL mutation or presence of clonal marker or no reactive bone marrow reticulin fibrosis
3. Not meeting the WHO criteria for BCR-ABL1 positive CML, ET, PV, MDS, or other myeloid neoplasms.

Minor criteria

4. Anemia not attributed to another comorbid condition.
5. Leukocytosis greater than or equal to 11 X 10^9/L
6. Palpable splenomegaly
7. Elevated LDH

Diagnostic criteria for Chronic Neutrophilic Leukemia

1. Peripheral blood with WBC greater than or equal to 13 X 10^9/L, segmented neutrophils plus band forms greater than or equal to 80% of WBCs, neutrophil precursors less than 10%, rare myeloblasts, monocyte count less than 10%, and no dysgranulopoiesis. Circulating blasts, rarely observed.
2. Bone marrow hypercellularity with elevated neutrophil granulocytes in percentage and absolute number, normal neutrophil maturation.
3. Detection of *CSF3R* ^{T618I} or other activating *CSF3R* mutation or in the absence of a *CSF3R* mutation sustained neutrophilia for at least 3 months, splenomegaly and no identifiable cause of reactive neutrophilia including an absence of a plasma cell neoplasm. Or if a plasma cell neoplasm is present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies.
4. Not meeting WHO criteria for *BCR-ABL1* positive CML, ET, PV, or PMF or an MPN with eosinophilia or tyrosine kinase gene fusions.

MATERIALS AND METHODS

Study Design and Data Source

This is an institution-based observational study that included all the patients diagnosed as MPN who visited the OPD in the department of Medical Oncology at GSL General Hospital. Data was extracted from the medical records department for a period of four years. We analysed the data of patients who presented between 2019 and 2023. The data was entered prospectively into the Institute's database.

Patient Population

The study population consisted of 28 patients who were diagnosed with BCR: ABL1 negative myeloproliferative neoplasm were included. All of whom were ≥18 years old, with clinical pictures and/or lab parameters and molecular work-up suggestive of a diagnosis of MPN and were previously untreated. Patients who were evaluated with molecular work-up suggestive of Chronic myeloid leukemia were excluded.

Clinico-pathological characteristics

The demographics and baseline characteristics included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, onset of illness, clinical presentation, any co-morbidities, baseline hemogram, peripheral smear, bone marrow aspiration and biopsy, and if affordable, molecular genetics.

Statistical Analysis

To answer the objectives of this observational study, data were collected with no formal sample size calculation. The inclusion period was from 2019 to 2023.

Descriptive statistics were used to represent summary and dispersion measures of demographic, clinical, and disease characteristics of the cohort of patients.

RESULTS

Over a period of four years, a total of 28 cases were observed.

The median age at diagnosis for MPN is 55 years. In this study, 23 patients (82%) were above the age of 50. Median age is 55 years (23- 75 years). No significant gender preponderance was observed. 15 patients were males (54%) and 13 (46%) were females (1.1:1). (Table 1).

Table 1: Age and Gender distribution

		Frequency (n)	Percent (%)
Age	**<50**	5	17.9
	>50	23	82.1
	Total	28	100
Gender	**Male**	15	53.6
	Female	13	46.4
	Total	28	100

The most recognized symptoms of MPN disorders include fatigue, early satiety, and abdominal discomfort.

The presenting complaints represented in this data include weakness in 6 patients (21.4 %), fever in 5 (17.9%), abdominal pain in 10 (35.7%), reduced appetite in 9 (32.2%), dyspnea in 1 (3. 6%), orthopnea in 1 (3.6%), melena in 1 (3. 6%), hematemesis in 1 (3. 6%) and weight loss in 3 patients (10.7 %) (Table 2).

Table 2: Distribution of symptoms

		Frequency (n)	Percent (%)
Symptoms	Weakness	6	21.4
	Fever	5	17.9
	Abdominal pain	10	35.7
	Reduced appetite	9	32.2
	Dyspnea	1	3.6
	Orthopnea	1	3.6
	Melena	1	3.6
	Hematemesis	1	3.6
	Weight loss	3	10.7

Table 3: Splenomegaly and hepatomegaly

		Frequency (n)	Percent (%)
Splenomegaly	Present	15	53.6
	Absent	13	46.4
	Total	28	100
Hepatomegaly	Present	4	14.3
	Absent	24	85.7
	Total	28	100

The most common comorbidities seen in MPN are hypertension, diabetes, and dyslipidemia. In our study, the most common comorbidity was hypertension, seen in 9 patients (32.1%), 3 (10.7) were diabetic, and 1 patient (3.6) had COPD. 54% of the patients had no known comorbidities (Table 4).

Table 4: Comorbidities

		Frequency (n)	Percent (%)
Comorbidity	T2DM	3	10.7
	HTN	9	32.1
	COPD	1	3.6

Table 5: Distribution of Myeloproliferative Neoplasms

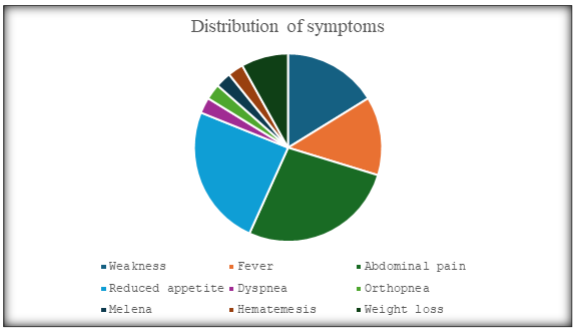
	Frequency (n)	Percent (%)
Essential thrombocytosis	13	46.4
Polycythemia vera	11	39.3
Primary myelofibrosis	4	14.3
Total	28	100.0

Molecular analyses were conducted in 96.4% of our cases. All were positive for JAK2 mutations, which is inclusive of JAK2 V617F mutation and JAK2 exon 12-15 mutation (Table 6).

None of the patients tested positive for the MPL mutation or for CALR.

Table 6: JAK2 V617F

		Frequency	Percent
JAK2 V617F	Negative	13	46.4
	Positive	15	53.6
	Total	28	100.0



Clinical examination findings revealed splenomegaly at presentation in 15 patients (53.6%), and 4 patients (14.3%) had hepatomegaly (Table 3).

The most frequently identified MPN in our study group was essential thrombocytosis, 46.3% (13), closely followed by polycythemia vera, 39.3% (11), and a less common subset of patients were diagnosed with primary myelofibrosis, i.e., 14.3% (4). (Figure 1; Table 5).

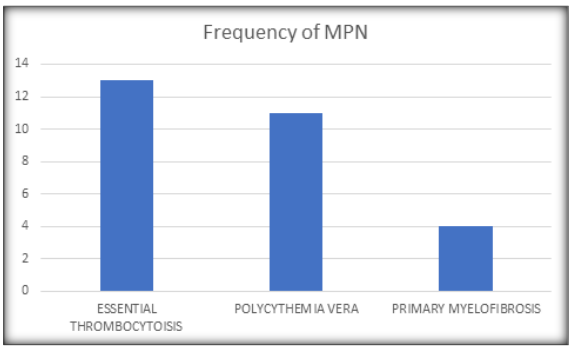


Figure 1: Distribution of Myeloproliferative Neoplasms

The incidence of arterial and venous thrombosis in PMF is about the same as in ET and is significantly lower than in polycythemia vera.7 In this study, 11 patients (39%) had a history of vascular events, including infarction, causing CVA and arterial or venous thrombosis.

The most common causes of death in myelofibrosis include the progression of leukemia in about 20% of patients. None of the patients in this study transformed to acute leukemia.

Sub-group analysis:

Essential Thrombocytosis

Most of the patients in the subgroup were over 50 years (77%). Peripheral smear findings were conclusive in 9 patients (69.2%). Bone marrow aspiration and biopsy confirmed the diagnosis in 9 patients (69.2%). All except one patient were molecularly subtyped and were positive for JAK2 mutations with JAK2 V617 F mutation being exclusively positive in 8 of the 13 patients. Most common presenting symptom was abdominal discomfort. 10 of 13 patients were hypertensive. 6 of 13 patients had splenomegaly. 7 patients of ET had vascular events, both arterial and venous thrombosis were observed. Hydroxyurea was advised as the major cytoreductive therapy with administration of antiplatelet drugs as required.

Polycythemia Vera

Most of the patients in the subgroup were over 50 years (81%). Peripheral smear findings alone were inconclusive in most. Bone marrow aspiration and biopsy confirmed the diagnosis in 6 patients (66.6%). All the patients were molecularly subtyped and were positive for JAK2 mutations with JAK2 V617 F mutation being exclusively positive in 6 patients. 3 patients had vascular events. 2 patients needed regular phlebotomy and all others were managed with cytoreductive therapy with hydroxyurea.

Primary Myelofibrosis

All the patients in the subgroup were over 50 years (100%). Peripheral smear findings were inconclusive. Bone marrow aspiration and biopsy confirmed the diagnosis in all 4 patients (100%). All the patients were molecularly subtyped and were positive for JAK2 mutations. Of the 4 patients, only one patient developed a vascular event with superior mesenteric vein thrombosis.

DISCUSSION

We present a study illustrating an assorted view of clinical and molecular characteristics of patients with BCR::ABL1 negative MPNs from southern part of India in coastal Andhra. The findings present a fascinating juxtaposition with both national and international reports, revealing patterns that converge in some areas, while diverging in others. A thorough comparative analysis with global studies is integral to enriching the understanding of the distribution and clinical presentation of these diseases, enabling insights that could inform better diagnostic and therapeutic approaches. This comparative framework is particularly crucial in highlighting the potential influence of genetic, environmental, and diagnostic factors on disease patterns across different populations.

Prevalence and Subtypes of MPNs

In our cohort, Essential Thrombocythemia (ET) emerged as the most commonly diagnosed subtype of MPNs. This observation aligns with the results reported by Tefferi et al,[1] who documented that ET accounted for 45.1% of MPN cases in the Mayo Clinic registry, underscoring the predominance of ET in global epidemiological data.

Age Distribution and Demographic Patterns

Our findings on age distribution revealed a peak incidence of MPNs in patients aged 50 to 60 years,

consistent with earlier studies by Bose et al,[10] and Shah et al,[14] who reported similar. In a similar large study published by VA Guntiboina el al,[25] the clinic pathological profile was comparable with an earlier median age of presentation which was 51 years and a male preponderance of 2.1:1. In another study by Roopa Dixit et al,[26] the results were indistinguishable with a median age at presentation of 56 years of graphic trends in their respective cohorts, particularly for Polycythemia Vera (PV) and ET.

These studies also noted that the mean age for these two subtypes was concentrated in the sixth decade of life. However, in our cohort, we observed that the age of onset for ET appeared slightly younger than in some other cohorts, which mirrors the results reported by Yonal-Hindilerden et al,[15] in a Turkish study. This divergence in age distribution may suggest the influence of geographic, environmental, or genetic factors that could potentially affect the age of disease onset.

It is important to consider that the distribution of MPNs across age groups may also be shaped by advances in diagnostic techniques. Improved awareness and earlier detection in populations with access to better healthcare could lead to an apparent shift in the average age at diagnosis. The younger onset observed in our ET cohort may be a result of such factors or could point to different underlying genetic or environmental risk factors prevalent in this region.

Sex Distribution and Disease Susceptibility

The sex distribution of MPNs in our study demonstrated a male predominance in the cases of PV and Primary Myelofibrosis (PMF), a finding that is well-documented in the global literature. Barbui et al,[16] have emphasized the male sex as a significant risk factor for disease progression in PV and MF, suggesting that males may be more susceptible to the hematological alterations that characterize these disorders. This gender disparity in disease progression is crucial for the development of gender-specific monitoring strategies and treatment plans in clinical practice.

Understanding the biological underpinnings of these gender differences could open up new avenues for targeted therapies. Hormonal influences or genetic factors may contribute to the increased risk observed in males, warranting further investigation into sex-specific molecular markers for MPNs.

Hematological and Clinical Findings

The hematological findings in our study were largely consistent with previous Indian studies, such as the work by Pathak et al,[17] who reported significantly elevated levels of hemoglobin and hematocrit in patients with PV, as well as increased platelet counts in ET cases. These findings align with the pathophysiological nature of MPNs, where excessive proliferation of blood cells often results in abnormal hematologic parameters. However, a point of discrepancy emerged when comparing our data with the European Leukemia Net (ELN) registry. In our study, patients with PMF exhibited relatively lower leukocyte counts compared to their counterparts in the ELN registry. This difference may reflect variations in regional hematologic norms or differences in disease stage at the time of presentation.

The understanding of these regional variations is crucial for improving the diagnostic accuracy and treatment outcomes in different populations. For instance, lower leukocyte counts in PMF patients in our cohort might suggest that the disease is diagnosed at a later stage or that other regional factors, such as nutritional status or access to healthcare, are influencing disease presentation.

Splenomegaly as a Clinical Feature

Our study also found splenomegaly to be a prominent feature in both PMF and PV patients, with 80% of PMF patients and 60% of PV patients showing signs of splenic enlargement. These findings are in line with those of Passamonti et al,[18] who demonstrated that splenomegaly is a defining clinical feature in nearly 90% of PMF cases. The frequent presence of splenomegaly in our study suggests that the clinical presentation of these diseases in our cohort may be more advanced at the time of diagnosis. This aligns with the notion that late diagnosis, which is often observed in regions with limited access to specialized healthcare, may contribute to more pronounced clinical features such as splenomegaly.

The significant presence of splenomegaly in our study underscores the importance of early detection and timely intervention. Clinical markers like splenomegaly can be used to assess disease progression and guide treatment decisions, making them essential elements in the routine management of MPNs.

Molecular Findings and Mutation Analysis

Molecular analysis in our study revealed a high prevalence of JAK2 mutations across the MPN subtypes, particularly in PV, where nearly 100% of patients were found to harbour this mutation. This finding corroborates the work of Vannucchi et al,[19] who documented the near-complete association of JAK2 mutations with PV. The absence of CALR or MPL mutations in our cohort is noteworthy and may be due to under-testing or a true lower prevalence of these mutations in this population, as similarly observed by Ghosh et al.[20] in an Indian cohort.

Interestingly, no cases of triple-negative MPNs (lacking JAK2, CALR, and MPL mutations) were observed in our cohort, which is consistent with the general understanding that JAK2 mutations are a strong diagnostic marker in our region. The absence of these triple-negative cases further strengthens the notion that JAK2 mutations are the hallmark of MPNs in our patient population.

Symptomatology and Disease Burden

In terms of symptomatology, fatigue and pruritus were reported as the most common symptoms in PV patients, which echoes the symptom burden outlined in the MPN Landmark Survey by Mesa et al.[21] The severity of symptoms, particularly in PMF patients,

underscores the need for effective symptom management strategies. Our findings emphasize the importance of incorporating patient-reported outcomes into clinical assessments, as this approach can help in understanding the true extent of disease burden from the patient's perspective. Given that the symptoms associated with MPNs can significantly impact quality of life, adopting a holistic approach to care is vital in improving patient outcomes.

Treatment Patterns and Future Directions

Regarding treatment, hydroxyurea was the most commonly prescribed agent, particularly for patients with PV and ET, which aligns with the treatment protocols observed in the REVEAL study in the United States. However, the use of newer therapies, such as ruxolitinib, was limited in our cohort. This underutilization of novel therapies is likely due to barriers related to cost and availability, a concern that has been noted by Gangat et al.[24] These disparities highlight the challenge of aligning local practices with international treatment guidelines, especially in low- and middle-income regions where access to newer medications may be restricted.

Our findings suggest that while the clinical and hematological landscape of MPNs in our region largely aligns with global patterns, unique variations exist that warrant further investigation. These variations could be due to differences in ethnicity, environmental exposures, and access to diagnostic and therapeutic resources. Furthermore, the limited availability of next-generation sequencing and molecular diagnostics in our setting hampers the ability to fully profile MPNs at the molecular level, which is now considered standard practice in Western healthcare systems.

Strengths and Limitations

A major strength of our study lies in the inclusion of a well-categorized cohort of MPN patients, allowing for robust clinical-laboratory correlations. Additionally, the comparative tables provided a comprehensive understanding of intra-group variations and were valuable in aligning our findings with global literature. However, several limitations need to be acknowledged. First, the retrospective design of the study and the relatively small sample size constrain the generalizability of our results. Second, molecular studies were performed on a limited basis, which restricted our ability to stratify patients according to specific genetic mutations. These limitations suggest the need for future studies with larger, more diverse cohorts and a focus on molecular profiling.

CONCLUSION

Future Directions

Looking ahead, it is crucial to conduct multicenter prospective studies that incorporate comprehensive molecular data and patient-reported outcomes to deepen our understanding of MPN biology, particularly in Indian and Southeast Asian populations. Developing region-specific prognostic models could improve risk stratification and help tailor therapies to individual patients. Additionally, advocating for wider access to mutation testing and newer therapeutic agents is essential to aligning local practices with international standards, ultimately improving patient care and outcomes.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study.

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1. Tefferi A. Essential thrombocythemia, polycythemia vera, and myelofibrosis: Current management and the prospect of targeted therapy. American Journal of Hematology. 2008 Jun;83(6):491–7.
2. Milosevic Feenstra JD, Nivarthi H, Gisslinger H, Leroy E, Rumi E, Chachoua I, et al. Whole-exome sequencing identifies novel MPL and JAK2 mutations in triple-negative myeloproliferative neoplasms. Blood. 2016 Jan 21;127(3):325–32.
3. Xénia Cabagnols, Favale F, Pasquier F, Kahia Messaoudi, Defour JP, Jean-Christophe Ianotto, et al. Presence of atypical thrombopoietin receptor (MPL) mutations in triple-negative essential thrombocythemia patients. Blood. 2016 Jan 21;127(3):333–42.
4. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022 Jun 22;36(7):1703–19.
5. Mesa R, Miller CB, Thyne M, Mangan J, Goldberger S, Fazal S, et al. Myeloproliferative neoplasms (MPNs) have a significant impact on patients' overall health and productivity: the MPN Landmark survey. BMC Cancer. 2016 Feb 27;16(1).
6. Geyer H, Mesa RA. Approach to MPN Symptom Assessment. Current Hematologic Malignancy Reports. 2017 Sep 23;12(5):381–8.
7. Barbui T, Carobbio A, Cervantes F, Vannucchi AM, Guglielmelli P, Antonioli E, et al. Thrombosis in primary myelofibrosis: incidence and risk factors. Blood. 2010 Jan 28;115(4):778–82.
8. Vinay Anand Guntiboina, Nag A, Kumar J, Sushant Sonu Vinarkar, Rath A, Bhave S, et al. PB2223: Clinicopathological, cytogenetic and molecular characteristics of patients with non-cml myeloproliferative neoplasms: a single center study. HemaSphere [Internet]. 2023 Aug 1 [cited 2024 Jul 16];7(S3):e8162334–4.
9. Paul T, Dixith R, Sara A, Vangala N, Uppin S, Uppin M, et al. Clinicopathological spectrum of BCR-ABL-Negative myeloproliferative neoplasms with correlation with Janus-

associated kinase 2 mutation. Indian Journal of Medical and Paediatric Oncology. 2019;40(1):35.
10. Bose P, Hochster H, et al. Clinical characteristics of essential thrombocythemia: a comparison between large cohort studies and our own experience. *Blood. 2019;133(5):408-15.
11. Lundberg, P., Karow, A., Nienhold, R., Looser, R., Hao-Shen, H., Nissen, I., Girsberger, S., Lehmann, T., Passweg, J., Stern, M., Beisel, C., Kralovics, R., & Skoda, R. C. (n.d.). Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. Blood, 123(14), 2220–2228.
12. Kleppe, M., & Levine, R. L. (2012). New pieces of a puzzle: The current biological picture of MPN. Biochimica Et Biophysica Acta (BBA) - Reviews on Cancer, 1826(2), 415–422.
13. Dunbar, A. J., Rampal, R. K., & Levine, R. (2020). Leukemia secondary to myeloproliferative neoplasms. Blood, 136(1), 61–70.
14. Shah S, Soni P, et al. An analysis of the epidemiology and treatment of polycythemia vera in India. Indian J Hematol Blood Transfus. 2021;37(3):330-8.
15. Yonal-Hindilerden I, Akcay T, et al. Clinical features and treatment outcomes in patients with essential thrombocythemia in a Turkish cohort. Leukemia Research. 2016;43(6):745-50.
16. Barbui T, Thiele J, et al. Risk factors for thrombosis in polycythemia vera and essential thrombocythemia. J Clin Oncol. 2018;36(30):3166-75.
17. Pathak S, Gupta M, et al. Hematological and clinical characteristics of polycythemia vera in India: a single-center experience. Indian J Hematol Blood Transfus. 2017;33(2):214-9.
18. Passamonti F, Santeufemia DA, et al. Clinical, hematologic, and molecular features of primary myelofibrosis: a retrospective study of 207 patients. J Clin Oncol. 2010;28(23):4390-5.
19. Vannucchi AM, Lasho TL, et al. Mutational profile of myeloproliferative neoplasms: JAK2, CALR, and MPL mutations. Blood. 2011;118(2):118-25.
20. Ghosh K, Nandy A, et al. Prevalence of CALR and MPL mutations in Indian patients with essential thrombocythemia and myelofibrosis. Leukemia Research. 2020;91:106313.
21. Mesa RA, Miller CB, et al. Symptom burden in myeloproliferative neoplasms: results from the MPN Landmark Survey. Blood. 2016;128(3):446-55.
22. Tan J, Tan A, et al. Clinical and hematological features of myeloproliferative neoplasms in Southeast Asia. Leukemia Research. 2018;74:55-61.
23. Kiladjian JJ, Passamonti F, et al. Hydroxyurea for polycythemia vera and essential thrombocythemia: a long-term cohort study. Blood. 2017;130(12):1407-15.
24. Gangat N, Vannucchi AM, et al. Ruxolitinib in patients with myelofibrosis: updated results from a phase 3 trial. Blood. 2019;134(10):899-907.
25. Guntiboina VA, Gurram MK, Kotha VK, Maddileti K, Damera SR. Clinical, hematological, and molecular profile of Philadelphia-negative myeloproliferative neoplasms: an institutional experience. Asian J Transfus Sci. 2023;17(1):37–42
26. Dixith R, Sara A, Vangala N, Uppin SG, Uppin MS, Narendra AMVR, Paul TR. Clinicopathological spectrum of BCR-ABL-negative myeloproliferative neoplasms with correlation with Janus-associated kinase 2 mutation. Indian J Med Paediatr Oncol. 2019;40(1):35–40.