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Clinico-Pathological Features and Outcome of Primary Myelofibrosis: Experience from a Developing Country

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Abstract

Objective The objective of the study is to assess clinical and laboratory parameters in PMF patients presenting to our institute.

Methodology: This prospective observational study was carried out at Armed Forces Bone Marrow Transplant Center from October 2022 to March 2025. The sample size was calculated with a 95% confidence level, resulting in a total of 210 patients. All patients, irrespective of gender were included. Patients were diagnosed with MF (pre-fibrotic/Overt fibrotic stage) based on history, clinical examination and WHO diagnostic criteria 2022. All samples were screened for mutations in JAK 2 V617F, JAK 2 Exon12, CALR and, cMPL. Data analysis was done using SPSS version 23.

Results: A total of 210 patients were included in the study, with the mean age of 53.1 ± 16.6 years. There were 70% (n=147) males and 30% (n=63) females. Most the patients i.e. 71.0% (n=149) were diagnosed with overt phase of PMF, while 15.2% of the patients presented in pre-fibrotic phase of PMF. The common symptoms at presentation was weakness and easy fatigability and progressive pallor. On examination around 66.2% patients presented with splenomegaly and 33.8% had hepatomegaly. As per DIPPS scoring system 20% (n=42) were having low risk disease, while 33%, 37% and 9% fell under intermediate 1, intermediate 2 and high risk disease respectively. A total of 25 patients (11.9%) experienced disease transformation during the study period. The overall survival (OS) of patients diagnosed with PMF in our cohort is 65.6%, with a median follow-up of 36 months, and Progression-free survival (PFS) is calculate to be 84.4%.

Conclusion: This study offers real-world data on primary myelofibrosis (PMF) from a developing country and underscores the significant gaps in clinical care. This study also highlights a low risk of transformation in MPNs in our population. Further prospective studies are required to understand the full clinical spectrum of the disease better and to compare the outcomes of different treatment approaches.

Key words: Primary Myelofibrosis, Developing countries, Myeloprolifirative Neoplasms.

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Introduction

According to the WHO classification (2022), Philadelphia negative myeloproliferative neoplasms (MPNs) include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF), as well as less common entities such as chronic neutrophilic leukemia, chronic eosinophilic leukemia, and juvenile myelomonocytic leukemia.[1] PMF is the rarest among all MPNs, with an annual incidence of approximately 0.5 to 1.5 cases per 100,000 individuals, and it occurs more frequently in males.2 PMF is characterized by mutations in *JAK2*, *CALR*, or *MPL*, which activate the JAK-STAT signaling pathway, resulting in clonal myeloproliferation.[3] PMF usually affects older individuals typically fifth or sixth decade of life, with a median survival ranges from 3.5 to 5.5 years.[4]

PMF presents with symptoms including anemia up to transfusion dependency, hepatomegaly, splenomegaly, leukocytosis or leukopenia, thrombocytosis or thrombocytopenia, and other constitutional symptoms.[5] Histopathologically, PMF is characterized by megakaryocytic atypia, bone marrow fibrosis, and extra medullary hematopoiesis.6 Mortality in PMF is often due to leukemic transformation (up to 20%), cardiovascular complications, bleeding, and infections. Introduction of JAK2 inhibitors provide symptomatic relief and reduce splenomegaly. Currently, allogeneic stem cell transplantation is the only curative option avaliable.[7]

Several prognostic scoring systems have been developed till date to estimate survival in PMF. The International Prognostic Scoring System (IPSS), the first prognostic scoring system for PMF, introduced in 1997, is applied at diagnosis and incorporates five risk factors:

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age, haemoglobin, WBC, peripheral blasts, and constitutional symptoms. Based on these, patients are stratified into four risk groups i.e. Low risk, intermediate 1, intermediate 2 and High Risk.[8] The Dynamic International Prognostic Scoring System (DIPSS), an evolution of IPSS, can be applied throughout the disease course. DIPSS-Plus further incorporates platelet count, cytogenetics, and transfusion dependency.[9] More recent models include Mutation-Enhanced International Prognostic Score System (MIPSS-70) and Genetically Inspired Prognostic Scoring System (GIPSS), which integrate genetic and cytogenetic data for refined risk assessment. MIPSS70-Plus adds hemoglobin levels and cytogenetics relative to age and sex, while GIPSS is based solely on genetic mutations and karyotype abnormalities.[10]

Despite the diverse population, epidemiological data on MPNs in Pakistan remain limited and no specific data exist on the demographics or outcomes of myelofibrosis patients in Pakistan. This study aims to provide real-world experience on the clinical profile, management, and outcomes of MF patients in Pakistan. The objective of the study is to assess clinical and laboratory parameters in PMF patients presenting to our institute. By analyzing cases from our center, we seek to better understand disease patterns in our local population.

Methodology

This prospective observational study was carried out at Armed Forces Bone Marrow Transplant Center from October 2022 to March 2025. The sample size was calculated with a 95% confidence level, resulting in a total of 210 patients.

Inclusion Criteria: All patients, irrespective of gender, who reported to the hospital during the course of the study with a confirmed diagnosis of PMF based on clinical, hematologic, cytogenetic, or molecular evidence (e.g., absence of the Philadelphia chromosome or BCR-ABL fusion gene) as per WHO 2022 diagnostic criteria and Complete clinical records, including diagnostic work-up, treatment response and follow-up data were included.

Exclusion Criteria: Patients with missing or insufficient data regarding diagnosis, treatment course, or follow-up outcomes or with a history of other hematological or solid organ malignancies or who discontinued follow-up before 6 months or whose treatment and outcome status could not be ascertained were excluded from the study. Also Patients presented with secondary myelofibrosis were excluded from the study.

Ethical clearance was approved by the Institutional Ethics Committee of the Armed Forces Bone Marrow Transplant Center to ensure maintaining ethical standards. Patients were diagnosed with MF (pre-fibrotic/Overt fibotic stage) based on history, clinical examination and WHO diagnostic criteria 2022. Samples for complete blood counts (CBC) were taken in EDTA tube and run on automated hematology analyzer. Trephine biopsy samples, each measuring a minimum of 2 cm, were collected from the posterior superior iliac spine of every patient in accordance with the International Council for Standardization in Hematology (ICSH) guidelines. The core biopsies were then sent to the histopathology department for standard processing and were stained using hematoxylin (Bio Optica), eosin (SHURStain), and reticulin (prepared in-house with Merck reagents). Samples for molecular analysis were taken in EDTA tube and sent to the molecular department of the hospital. All samples were screened for mutations in JAK 2 V617F, JAK 2 Exon12, CALR and, cMPL. Patients with PMF were risk stratified DIPSS criteria. Response assessment was done as per IWG-MRT criteria[11] and physician discretion.

SPSS software (IBM SPSS Statistics, version 23.0) was used to calculate the frequency of qualitative variable and mean, median and standard deviation of quantitative variables. Overall survival (OS) was defined as the time from diagnosis or presentation to date of death or last visit. Progression free survival (PFS) was calculated from the date of diagnosis to transformation into leukemia. OS and PFS were analyzed using Kaplan-Meier survival curves, with comparisons made using the log-rank test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 210 patients were included in the study, the median age of the patients was 53.1 ± 16.6 years with majority i.e. 62.9% of the patient falling in >50 years' age group category. There were 70% (n=147) males and 30% (n=63) females. Most the patients i.e. 71.0% (n=149) were diagnosed to have overt phase of PMF at their first presentation to AFBMTC, while 15.2% of the patients

presented in pre-fibrotic phase of PMF. 8.1% and 3.8% of the patients presented as over phase of PMF while being previously diagnosed and treated for PV and ET respectively (i.e. Post PV- myelofibrosis and Post ET-myelofibrosis). Around 1.9% (n=4) patients, previously labeled as MPN presented with severe cytopenia and significant weight loss, were diagnosed to have Acute Myeloid Leukemia. The common symptoms at presentation were weakness, easy fatigability, progressive pallor with transfusion dependency along with abdominal distension. On examination 66.2% patients presented with splenomegaly and 33.8% had hepatomegaly, when measured by abdominal palpation below the costal margin (BCM), the mean estimated size was 10.6 ± 6.5 cm BCM of spleen and 6.1 ± 4.6 cm BCM of liver. As per DIPPS scoring system 20% (n=42) were having low risk disease, while 33%, 37% and 9% fell under intermediate 1, intermediate 2 and high risk disease respectively. The frequency of JAK2 V617F, cMPL, CALR mutation in PMF patients was 54.8%, 3.3%, 14.8% respectively and around 26.7% (n=56) patients found to be Triple Negative. Frequencies of different parameters are given below is given in Table I.

Different therapeutic options were tried for the patients diagnosed with PMF to treat and response assessment was done as per IWG-MRT criteria and physician discretion. Cytoreduction with Hydroxyurea was offered to all intermediate and high-risk patients with PMF patients with predominant features of myeloproliferation including raised white cell count and platelet count and symptomatic visceromegaly. All high risk and some low-risk patients with high-risk cytogenetics were referred to transplant section, if matched related donor was available and Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) score was low. All MF patients presenting with or who had high MPN-SAS-TAF score or symptomatic splenomegaly were offered ruxolitinib based on affordability, platelet count and exclusion of major infections. For symptomatic anemia in MF, erythropoietin stimulating agents (ESA) in patients with low Nordic score and synthetic androgens or immunomodulatory drugs with steroids were used in those with high Nordic score or unresponsive to ESA. Figure 1 and 2 shows the treatments offered and the response to the treatment.

Table I: Demographics of the patients presenting with PMF.

			N	%
Mean age of the patients ± S.D: 53.14 ± 16.6 years				
Age group of the Patients				
1-15 Years			9	4.3
15-30 Years			12	5.7
30-50 Years			57	27.1
>50 Years			132	62.9
Gender of the Patients				
Male			63	30
Female			147	70
Risk Stratification of the Patients as per DIPPS* classification				
Low Risk			42	20.0
Intermediate 1 Risk			70	33.3
Intermediate 2 Risk			79	37.6
High Risk			19	9.0
Presenting Symptoms				
Bleeding			17	8.1
Bruising			9	4.3
Pallor			54	25.7
Weakness			112	53.3
Fever			41	19.5
Infection			13	6.2
Abdominal Discomfort			63	30.0
Plethora			4	1.9
History of Thrombosis			5	2.4
On Examination				
			Mean Size ± SD	
Hepatomegaly	71	33.8	6.1 ± 4.6	
Splenomegaly	139	66.2	10.6 ± 6.5	
Bone Marrow Aspiration and Trephine Biopsy Diagnosis at Presentation				
Pre-Fibrotic Phase of PMF			38	18.1
Overt Fibrotic Phase of PMF			143	68.1
Post PV-MF**			18	8.6
Post ET-MF***			8	3.8
PMF transformed to AML****			3	1.4
Grade of Fibrosis				
Reticulin Unremarkable			8	3.8
Reticulin 1			24	11.4
Reticulin 2			64	30.5
Reticulin 3			80	38.1
Reticulin 4			34	16.2
Driver Mutations				
JAK2 (V617F)[i]			115	54.8
cMPL[ii]			7	3.3
CALR[iii]			31	14.7
JAK2 exon 12			1	0.5
Triple Negative			56	26.7
Transformed Disease				
Pre-fibrotic transformed to overt phase PMF			17	8.0
PMF transformed from AML			8	3.8
Not Transformed			185	88.0

*DIPPS: Dynamic International Prognostic Scoring System
**PV: Polycythaemia Vera
***ET: Essential Thrombocythemia
****AML: Acute Myeloid Leukaemia
i JAK2: Janus Kinase 2
ii cMPL: Myeloproliferative Leukaemia
iii CALR: Calreticulin Gene

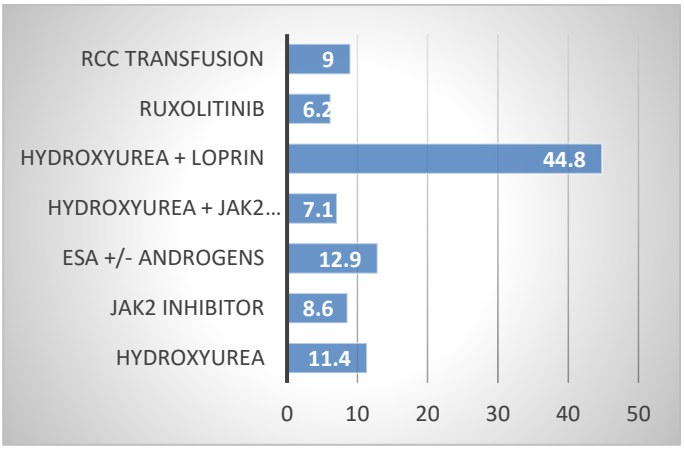


Figure I. Different treatment offered to patients presenting with PMF.

A total of 25 patients (11.9%) experienced disease transformation during the study period. Among these, 17 (68%) patients progressed to the overt phase of PMF, while 8 (32%) patients developed acute leukemia. Notably, 18 of the patients who transformed were initially diagnosed with PV, and 4 had ET. These patients presented at AFBMTC with already progressed disease, manifesting as PMF at their initial evaluation. The overall survival (OS) of patients diagnosed with PMF in our cohort is 65.6%, with a median follow-up duration of 36 months, is depicted in Figure 3. Progression-free survival (PFS) for the same cohort is calculate to be 84.4% illustrated in Figure 4.

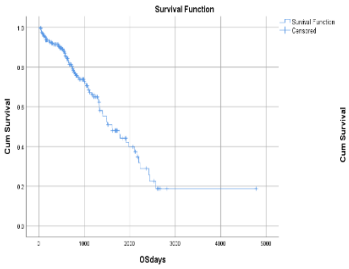


Figure 3. Overall survival (OS) of PMF.

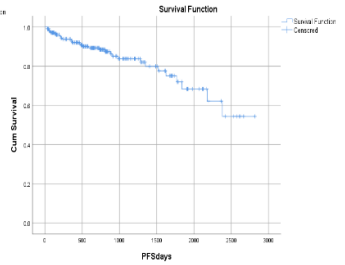
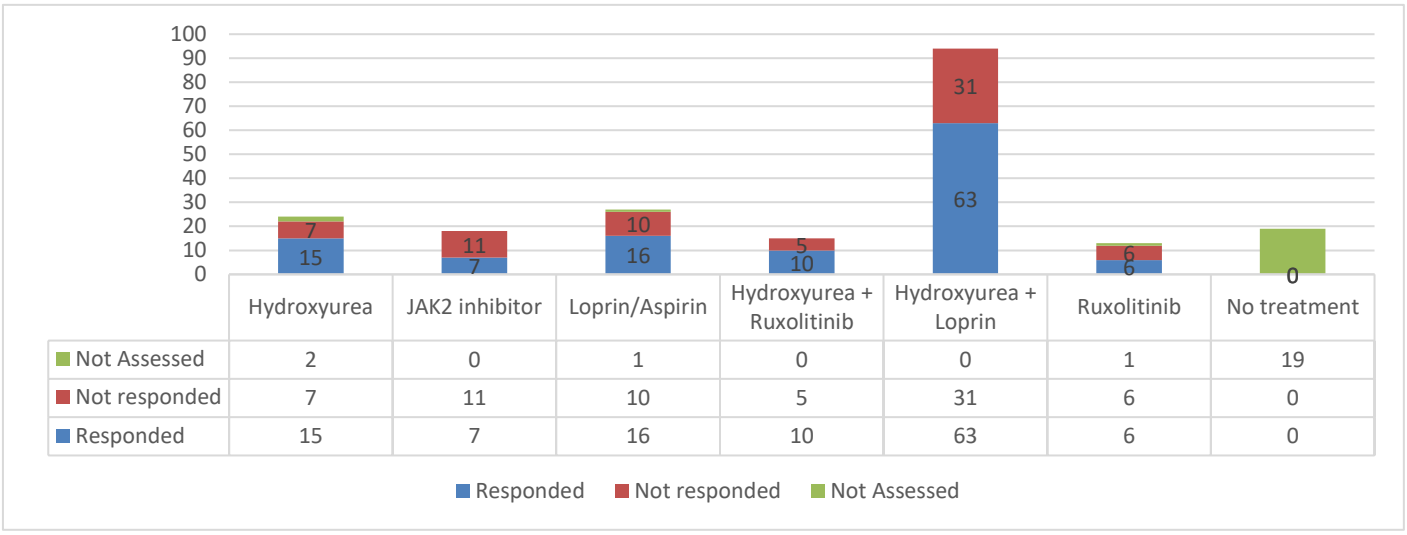


Figure 4. Progression Free Survival (PFS) of PMF.

Discussion

Primary myelofibrosis (PMF) is a rare clonal MPN associated with a relatively poor prognosis. PMF is primarily driven by three mutations—JAK2, CALR, and MPL, among these, JAK2 V617F is most prevalent, seen in approximately 50–60% of PMF cases globally. Our study findings align with the global data as 54% of the chorot had mutate JAK2 gene. A study conducted at Khyber Pakhtunkhwa (KP) reports a higher relevance rate of 77.8% of JAK2 mutations in PMF patients, highlighting its diagnostic and prognostic significance.[12] Regional data reports comparable results, as a study in India reported JAK2 positivity in 58.8% of patients.[13] while rates from other countries ranged from 40% in China.[14]

This study from KP also reports the mean age of patients was 48.9 years with a male predominance (71%).



	Hydroxyurea	JAK2 inhibitor	Loprin/Aspirin	Hydroxyurea + Ruxolitinib	Hydroxyurea + Loprin	Ruxolitinib	No treatment
Not Assessed	2	0	1	0	0	1	19
Not responded	7	11	10	5	31	6	0
Responded	15	7	16	10	63	6	0

Figure II. Response to the treatment.

Another study from Peshawar, Pakistan reports a male predominance (68%), with a median age of 50.60 years.[15] This is contrast to our observation as the mean age of our cohort was 53 years, slightly younger than international reports.[16] However, these findings are

consistent with data from Germany and Sweden, where the reported median ages were 57 and 55 years, respectively.[17] A Malaysian study reports the median age at diagnosis was 59 years[18], which coincides with our findings. The relatively lower median age, as compared to international studies, in our study as well in local data may reflect the lower life expectancy in Pakistan. Our study also reports significant gender disparity having male predominance that reproduce the finding of international studies. A study conducted in Thailand document a notable male predominance in and a younger median age at diagnosis as compared to Western cohorts, suggesting potential environmental or genetic influences in Asian populations.[19]

Among patients presented to AFBMTC, approximately 80% of patients were symptomatic at diagnosis, with constitutional symptoms—particularly easy fatigability and progressive pallor being the comments symptoms. Upon clinical examination splenomegaly was present in 66.2% of patients, a rate similar to other international studies.[20] Study conducted in Thailand also reports thrombotic events were common, approximately 21% patients presented with arterial thrombosis, particularly ischemic stroke being the most frequent complication (64.2% of arterial events). Similar findings were documented in a meta-analysis published in 2019.[21] While in our cohort no significant history of prior thrombotic event was documented, only 9 patients have thrombotic episodes (ischemic CVA being commonest). We also document no major bleeding events in our cohort, contrasting with the 6.2% hemorrhagic complication rate noted in the meta-analysis.

Most patients in our study were diagnosed with Intermediate to high-risk myelofibrosis (MF), likely due to delayed presentation and limited disease awareness among clinicians—an issue seen across many centers in our region. The reported prevalence and incidence rates is based on hospital-based data and patients with available bone marrow findings, potentially underestimating actual disease burden, as many patients declined invasive procedures and majority centers lack the facility of bone marrow trephine biopsy. The Bone marrow reticulin grading revealed that majority of the patients have grade 2-4, the study from KP, Pakistan reports similar finding i.e. 60% had MF-2 and 34% had MF-3, with only 6% presenting with MF-1.[22] Despite being majority of the cohort had intermediate to high-risk disease none of patients underwent allogeneic stem cell transplantation (HSCT). Factors that limits transplant includes the age of the patients, lack of matched sibling donor and cost of transplant.

Hydroxyurea was the most commonly used therapy in our population, even though ruxolitinib has shown superior efficacy in symptom control and survival outcomes in our cohort.[23] This aligns with real-world data from the United Kingdom.[24] Early initiation of ruxolitinib shows improve survival outcomes and would be preferable if resources allowed.[25] The reasons for not preferring JAK2 inhibitor could be the affording capabilities of patients, drug availability and healthcare policies in our country.

The overall survival of our patients was recorded 65.6% with a median follow up of 36 months which is comparable to the survival outcomes globally i.e. a five-year OS is 67.7% in PMF, reflecting the more aggressive nature of PMF as compared to other subtypes of MPN.

Limitations of the Study: Our study has several limitations. Firstly, it is a single center study and our management practice has grown enormously and changed significantly over period of time. Our study does not specifically address separate issues in MPNs particularly fertility and pregnancy outcomes, associated CV risk factor assessments, lack of resources for better risk stratification and response assessment as per IWG guidelines. The limited sample size reduces the statistical power of the findings, highlighting the importance of establishing a nationwide registry to more accurately capture data on MF and enhance patient care strategies.

Conclusion

This study offers a real-world perspective on MF patients in a developing region, shedding light on critical gaps in clinical care. This study highlights the demographics, presentation, treatment patterns and outcomes of MPNs from a low income country. This study also highlights the reduced risk of transformation in MPNs in our population. Further prospective research is needed to explore the full disease spectrum and to compare the effectiveness of different treatment approaches. Given the regional disparities in presentation and mutation prevalence, as JAK2 V617F was the most prevalent mutation in our population, there is a need for further large-scale studies to better understand PMF in diverse populations. Overall, our findings underscore the clinical and prognostic

relevance of JAK2 mutations in PMF, particularly in resource-limited settings.

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