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Advanced Molecular Diagnosis of Primary Myelofibrosis: A ReviewOlalere Fatai Dayo^{1,4}, Ufelle Silas Anayo², Olatunbosun Luqman Olayinka^{3,5}

Department of Medical Laboratory Sciences, Faculty of Health Sciences and Technology, College of Medicine, University of Nigeria, Enugu Campus, Nigeria¹, Department of Medical Laboratory Sciences, Faculty of Health Sciences and Technology, College of Medicine, University of Nigeria, Enugu Campus, Nigeria², Department of Haematology and Blood Transfusion Science, University of Ilorin Teaching Hospital, PMB 1459, Ilorin, Kwara State, Nigeria³, Department of Medical Laboratory Sciences, Faculty of Health Sciences, Al-Hikmah University, Ilorin, Nigeria⁴, Department of Medical Laboratory Sciences, Faculty of Health Sciences, Al-Hikmah University, Ilorin, Nigeria⁵

Author for Correspondence*: dayoolalereone@gmail.com/+234-805-583-3224

<https://dx.doi.org/10.4314/sokjmls.v10i3.31>**Summary**

Primary myelofibrosis (PMF) is a Philadelphia chromosome negative myeloproliferative neoplasm characterized by bone marrow fibrosis, splenomegaly, anaemia, constitutional symptoms, and extramedullary haematopoiesis. As a clonal haematopoietic stem cell disorder, it is often accompanied by a disease-initiating driver mutation and shortened survival. Diagnosis is often based on bone marrow findings. Diagnosis is supported by the presence of janus kinase 2 (JAK2), calreticulin (CALR), or thrombopoietin receptor protein (MPL) mutation, found in approximately 90% of patients, is supportive but not essential for diagnosis; these mutations are also prevalent in the closely related MPNs, namely polycythemia Vera (PV) and essential thrombocythemia (ET). Diagnosis of PMF is based upon the 2016 WHO criteria and includes a combination of clinical and laboratory findings. Patients with pre PMF often present with thrombocytosis (increased platelet count) and a lack of bone marrow fibrosis, thus they were often misdiagnosed as having ET. In ET patients, the differentiating bone marrow findings include granulocytic and erythropoietic cells that are in regular ratio with normal megakaryocytes. In Pre-PMF. Anaemia may be present, however tear-drop red blood cells (RBCs) are rare. The 2016 World Health Organization classification system distinguishes “prefibrotic” from “overtly fibrotic” PMF; the former might mimic ET in its presentation. Furthermore, approximately 15% of patients with ET or PV might progress into a PMF-like phenotype (post-ET/PV MF) during their clinical course.

Keywords: Myeloproliferative disorder, Philadelphia chromosome, Myelofibrosis, Neoplasm

Introduction

Primary myelofibrosis (PMF) is the least frequent Philadelphia chromosome negative (Ph negative) myeloproliferative neoplasm (MPN). PMF is an aggressive and chronic hematologic disease characterized by bone marrow fibrosis resulting in extramedullary haematopoiesis and splenomegaly. Primary myelofibrosis (PMF) is a BCR-ABL1-negative myeloproliferative neoplasm characterized by Additional disease features include anaemia, inflammatory cytokine production, constitutional symptoms, and transformation to acute leukaemia (Tefferi, 2021). Primary myelofibrosis (PMF) is one of four JAK2 mutation-prevalent myeloproliferative neoplasms (MPN), which also include polycythemia Vera (PV), essential thrombocythemia (ET), and MPN, unclassifiable (MPN-U). MPNs are included in the 2022 International Consensus Classification (ICC) category of myeloid neoplasms (Table 1), which also includes acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), the ICC differs from the World Health Organization (WHO) classification system, which was also revised in 2022 (5th edition); however, subclassification of MPN is similar between the two classification systems. The ICC subclassifies PMF into “Prefibrotic” /early primary myelofibrosis (pre-PMF) and “overtly fibrotic” PMF stages. (Barbui, et al, 2018). This subcategorization allows for distinction between “true” essential thrombocythemia (ET) and pre-

PMF (Tefferi, 2021). Additionally, myelofibrosis can follow a diagnosis of ET and polycythemia vera (PV) and is known as post-ET/post-PV MF (or secondary myelofibrosis), which distinguishes from other myeloid diseases and have the poorest prognosis. In 1951, haematologist William Dameshek included PMF among a group of diseases that he termed myeloproliferative disorders (Gangat and Tefferi, 2020). In the past, PMF has several names including agnogenic myeloid metaplasia, chronic idiopathic myelofibrosis, and myelofibrosis with myeloid metaplasia with the latest being primary myelofibrosis (Gangat and Tefferi, 2020). The 2008, 4th edition of the World Health Organization (WHO) Classification of Tumors of Haematopoietic and Lymphoid Tissues modified the term myeloproliferative disorders to myeloproliferative neoplasms. The disease named chronic idiopathic myelofibrosis was replaced with PMF (Michelle *et al.*, 2021). In addition, MPNs were classified based on bone marrow morphology, clinical features, and genetic information (Michelle *et al.*, 2021). In 2016, the WHO revised the 4th edition resulting in changes to the classification of MPNs. As described above, the classification of MPNs are still based on bone marrow morphology, clinical features and genetics, yet the revised edition has more integration of molecular genetic data due to the discovery of new somatic mutations. (Barbui *et al.*, 2018). In addition, there are several non-driver mutations associated with PMF patients that are believed to contribute to disease development and transformation into acute leukaemia (Table 1) (Gangat and Tefferi, 2020).

Epidemiology

The annual incidence rate of PMF is approximately 1 per 100,000 based on reports in Australia, Europe, and North America making it the least frequent Ph negative MPN (Michelle *et al.*, 2021) The prevalence rate of PMF ranges from 1.76 to 4.05 per 100,000.11 PMF has been reported in all ages, yet it is most often found in middle aged and elderly patients with the

majority of patients greater than 50 years old at diagnosis. (Liu and Hao, 2018, Takenaka *et al.*, 2018) Some studies have indicated that men are affected more frequently than women, however other studies indicate that both genders are nearly equally affected (Liu *et al.*, 2018). In general, median overall survival for PMF is 5-7 years post diagnosis with primary causes of death including leukemia transformation, vascular events, and infections (Liu and Hao, 2018; Mascarenhas, *et al.*, 2018).

Etiology and Pathogenesis

The majority of PMF patients have one of three disease-initiating driver mutations that over-activate the janus kinase 2 and signal transducer and activator of transcription (JAK2-STAT) pathway resulting in unregulated myeloproliferation. Approximately 50-65% of PMF patients have a mutation in the JAK2 gene, specifically the JAK2V617F exon 14 mutation. (Gilani *et al.*, 2019; Lee and Godfrey, 2020; Rumi *et al.*, 2020). These patients are associated with older age, higher haemoglobin levels and white blood cell (WBC) counts, and lower platelet counts. A mutation in the calreticulin (CALR) gene is found in 20-30% of PMF patients and associated with younger patients, lower haemoglobin and WBC counts with a higher platelet count (Gilani, *et al.*, 2019, Lee and Godfrey, 2020, Rumi *et al.*, 2020). The least frequent driver mutation, found in about 10% of PMF patients, is a mutation in the myeloproliferative leukaemia (MPL) gene (Gilani *et al.*, 2019; Lee and Godfrey, 2020; Rumi *et al.*, 2020). An estimated 10% of PMF patients do not have any of the three driver mutations and are known as “triple negative” cases. (Lee and Godfrey, 2020; Rumi *et al.*, 2020). Triple negative PMF patients can be difficult to distinguish from other myeloid diseases and have the poorest prognosis. In addition, there are several non-driver mutations associated with PMF patients that are believed to contribute to disease development and transformation to acute leukaemia (Table 1).

Table 1: Frequent Non-driver Somatic Mutations in PMF

Mutation	Mutational Frequency
TET2 (TET oncogene family member 2)	~17%
SRSF2 (Serine/arginine-rich splicing factor 2)	~17%
U2AF1 (U2 Small Nuclear RNA Auxiliary Factor 1)	~16%
ASXL1 (Additional Sex Combs-Like 1)	~13%
EZH2 (Enhancer of zeste homolog 2)	~7%
DNMT3A (DNA cytosine methyltransferase 3a)	~7%
SF3B1 (Splicing factor 3B subunit 1)	~7%
IDH1/IDH2 (Isocitrate dehydrogenase 1 and 2)	~4%
TP53 (Tumor protein p53)	~4%

(Tefferi, 2021).

These non-driver mutations play a role in DNA methylation (TET2, DNMT3A, and IDH1/IDH2), RNA splicing (SF3B1), chromatin modifications (ASXL1, EZH2), and DNA repair (TP53). In triple negative patients, the presence of one or more of these non-driver mutations may be useful in diagnosis and often indicate a poorer prognosis (Gilani *et al.*, 2019). The overexpression of haematopoietic cytokines and growth factors associated with the over-activation of the JAK2-STAT pathway lead to megakaryocyte hyperplasia ultimately resulting in the classic features of PMF – bone marrow fibrosis and abnormal megakaryocytes. Abnormal megakaryocytes and other bone marrow cells release cytokines promoting bone marrow fibrosis. Extramedullary haematopoiesis is associated with the extensive bone marrow fibrosis which contributes to the splenomegaly seen in PMF patients. (Massimo *et al.*, 2022)

Clinical and Diagnostic Findings

The clinical manifestations in PMF vary, however most patients present with anaemia, constitutional symptoms (fatigue, fever, and night sweats), and splenomegaly. Splenomegaly is a hallmark finding in PMF patients and it often seen in approximately 90% of patients (Tefferi *et al.*, 2021). Splenomegaly results from extramedullary haematopoiesis leading to abnormalities in splenic architecture and increased presence of megakaryocytes. It is often a debilitating symptom and a contributing factor in morbidity. Other findings include changes in platelet counts, bleeding, bone pain, headache, hepatomegaly (40-70% of patients), thrombosis, and weight loss. (Tefferi *et al.*, 2021) Symptoms are often due to the production of cytokines during disease progression. Clinical findings may vary and approximately 30% of patients are asymptomatic at diagnosis.

Risk Factors for Myelofibrosis

Risk factors for Myelofibrosis may include:

- **Age** - The disease usually develops slowly in people over 50. Although it can occur at any age, it is most commonly diagnosed between the ages of 50 and 70.
- **Blood disorders** - Some people with leukaemia, lymphoma, essential thrombocythaemia (increased platelets) or polycythaemia vera (increased blood counts) develop PMF
- **Chemicals** - PMF has been linked to exposure to certain industrial chemicals such as benzene and toluene
- **Radiation exposure** - People exposed to high levels of radiations and radioactive contrast material like Thorotrast have an increased risk of developing PMF.

Symptoms of Primary Myelofibrosis (PMF)

Living with Primary myelofibrosis (PMF) is different for every person. No matter how myelofibrosis affects the individual, it is important to monitor and keep track of any symptoms. This will help the health care team both treat and manage any symptoms the patient may experience.

Symptoms of PMF might include:

- Abdominal pain
- Fatigue
- Fever
- Night sweats
- Bone/muscle pain
- Easy bruising or bleeding
- Pain under the left ribs
- Early feeling of fullness

Table 2: 2016 WHO Diagnostic Criteria for PMF (Diagnosis requires meeting all 3 major criteria and at least 1 minor criterion that is confirmed in 2 consecutive determinations)

PREFIBROTIC/EARLY PMF	OVERT PMF
MAJOR CRITERIA	
<p>BONE MARROW MORPHOLOGY:</p> <ol style="list-style-type: none"> 1. Megakaryocytosis with atypical features, lack of reticulin fibrosis > grade 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis 2. CLINICAL: Not meeting WHO criteria for BCR-ABL1+ CML, PV, ET, myelodysplastic syndromes or other myeloid neoplasms <p>GENETIC: Presence of JAK2, CALR, or MPL mutation or in the absence of these 3 major clonal mutations, presence of another clonal marker or absence of minor reactive bone marrow reticulin fibrosis</p>	<ol style="list-style-type: none"> 1. BONE MARROW MORPHOLOGY: Megakaryocytosis with atypical features, accompanied by either reticulin and/or collagen fibrosis (grade 2 or 3) 2. CLINICAL: Not meeting WHO criteria for BCR-ABL1+ CML, PV, ET, myelodysplastic syndromes or other myeloid neoplasms 3. GENETIC: Presence of JAK2, CALR, or MPL mutation or in the absence of these 3 major clonal mutations, presence of another clonal marker or absence of reactive myelofibrosis
MINOR CRITERIA	
<ul style="list-style-type: none"> • Anaemia not attributed to a comorbid condition • Leukocyte count • Palpable splenomegaly • Serum LDH level above the upper limit of limit of institutional reference range 	<ul style="list-style-type: none"> • Anaemia not attributed to a comorbid condition • Palpable splenomegaly • Serum LDH level above the upper institutional reference range <p style="text-align: center;">Leuko-erythroblastosis</p>

Key: WHO, World Health Organization; PMF, primary myelofibrosis; CML, chronic myeloid leukaemia; PV, polycythemia vera; ET, essential thrombocythemia; LDH, lactate dehydrogenase (Passamonti and Maffioli 2016 and Abner *et al.*, 2016).

Diagnosis of PMF is based upon the 2016 WHO criteria and includes a combination of clinical and laboratory findings (Table 2). Pre-PMF was integrated within the PMF category as a variant.

Table 3: WHO 2008 Criteria for Grading Reticulin Fibers

Grade	Description
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal bone marrow
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of collagen and/or focal osteosclerosis
MF-3	Diffuse and dense reticulin with extensive intersections and coarse bundles of collagen, often associated with osteosclerosis

Table adapted from Abner et al. (2016). **Key:** WHO - World Health Organization

Due to the hallmark of bone marrow fibrosis in overt PMF, successful bone marrow aspiration is often not achieved resulting in a dry tap requiring a trephine bone marrow biopsy. Bone marrow findings include significant collagen and/or reticulin fibrosis, patches of haematopoietic cellularity, and an increased number of abnormal mega-karyocytes often found in clusters (Tables 2 and 3.). Approximately 30%-50% of PMF cases demonstrate cytogenetic (karyotypic) abnormalities at diagnosis. (Michelle *et al.*, 2021) Cytogenetic analysis is important in the diagnosis and prognosis but it can be challenging due to bone marrow fibrosis. Some of the more common chromosomal abnormalities detected in PMF include deletions of the long arms of chromosomes 13 and 20, abnormalities of chromosomes 1, 7, and 9, and trisomy 8 and 9. Of these abnormalities, those associated with a favorable prognosis include deletions 13q and 20q, and trisomy 9. A normal karyotype is also associated with a favorable prognosis. Those associated with an unfavorable prognosis include deletions of 7q, trisomy 8, and complex karyotypes. These abnormalities are not specific for PMF as they are found in the other Ph negative MPNs and other myeloid malignancies

not specific to PMF as they are found in the other Ph negative MPNs and other myeloid malignancies. Since the discovery of the driver mutations in MPNs, genomic testing has become a critical component in diagnosis. Patients suspected of an MPN will have mutation analysis performed using next generation sequencing (NGS) methods. Myeloid gene sequencing panels can look for specific mutations in JAK2, CALR, and MPL genes (Lee *et al.*, 2020). Extended gene sequencing panels are used for identifying non-driver mutations assisting with prognostic information and therapeutic decisions. For example, PMF patients with mutations in serine and arginine rich splicing factor 2 (SRSF2), ASXL transcription regulator 1 (ASXL1), histone-lysine N-methyltransferase (EZH2), or isocitrate dehydrogenase 1/2 (IDH1/IDH2) have a shorter survival rate and increased risk of transformation to acute leukaemia. (Skov, 2020). NGS allows for the identification of patients that are at high risk for disease progression and transformation, and factors into treatment decisions. (Lee *et al.*, 2020; Skov 2020).

Prognosis and Risk Stratification

Treatment decisions are often made based on overall survival and risk of transformation to acute leukemia. Thus, prognostic assessment of PMF (prognostic systems for pre-PMF have yet

to be developed) has evolved over the years as scientific knowledge has advanced. Early prognostic scoring models were primarily based on clinical and haematology findings (Table 4).

Table 4: Earlier Prognostic Models for PMF

	PSS - estimates survival at time of diagnosis	DIPSS – can be applied anytime during clinical course	DIPSS-plus – can be applied anytime during clinical course
		RISK FACTORS	
	Age >65 years (1 point)	Age >65 years (1 point)	Age >65 years (1 point)
	Constitutional symptoms (1 point)	<input type="checkbox"/> Constitutional symptoms (1 point)	Constitutional symptoms (1 point)
	Haemoglobin <10 g/dL (1 point)	Haemoglobin <10 g/dL (2 points)	<input type="checkbox"/> Haemoglobin <10 g/dL (2 points)
	WBC Count >25 x 10 ⁹ /L (1 point)	WBC Count >25 x 10 ⁹ /L (1 point)	WBC Count >25 x 10 ⁹ /L (1 point)
	Circulating (PB) blasts	Circulating (PB) blasts	Circulating (PB) blasts
			<input type="checkbox"/> RBC transfusion need (1 point)
			<input type="checkbox"/> Platelet count <100 x 10 ⁹ /L (1 point)
			<input type="checkbox"/> Unfavorable karyotype (1 point)
		RISK GROUPS	
Low	0 points (median survival 11.3 years)	0 points (median survival not reached)	0 points (median survival 15.4 years)
Intermediate 1	1 point (7.9 years)	1-2 points (14.2 years)	1 point (6.5 years)
Intermediate 2	2 points (4.0 years)	3-4 points (4.0 years)	2-3 points (2.9 years)
High	years)		

Key: IPSS, international prognostic scoring system; DIPSS, dynamic international prognostic scoring system; WBC, white blood cell count; PB, peripheral blood; RBC, red blood cell count; PMF, primary myelofibrosis.

One such system is the International Prognostic Scoring System (IPSS) developed in 2009 by the International Working Group for MPN Research and Treatment (IWG-MRT). The IPSS uses five risk factors (age > 65 years, haemoglobin < 10g/dl, WBC count > 25 x 10⁹/L, percentage of circulating blasts > 1%, and presence of constitutional symptoms), at diagnosis to predict survival. (Gangat and Tefferi, 2020; Rumi *et al.*, 2020; Tefferi, 2021). The IPSS prognostic model places patients into one of four risk groups: low, intermediate-1, intermediate-2, and high based on the number of risk factors present. (Gangat and Tefferi, 2020; Rumi *et al.*, 2020). The risk groups allow for better projections of median survival in years. One year later the IWG-MRT developed the dynamic IPSS (DIPSS) that utilizes the same risk factors as the IPSS; however it is applicable throughout the course of the disease (Tefferi, 2021). DIPSS was further developed to include three additional risk factors (unfavorable karyotype, platelet count < 100 x 10⁹/L, and the need for RBC transfusions) and is identified as the DIPSS-plus model. (Gangat, *et al.*, 2020).

Conclusion

Recent advances in molecular and genomic studies have contributed to the understanding of the pathogenesis and pathophysiology of PMF. Due to these advances, the diagnosis and prognostic models and therapeutic options for PMF have evolved to incorporate molecular and genetic findings. Despite the progress, pathophysiology is complex, and diagnosis can be challenging especially in differentiating pre-fibrotic PMF from ET. Two new prognostic systems for PMF have recently been introduced: GIPSS (genetically inspired prognostic scoring system) and MIPSS70+ version 2.0 (MIPSSv2; mutation- and karyotype-enhanced international prognostic scoring system). GIPSS is based exclusively on mutations and karyotype. MIPSSv2 includes, in addition, clinical risk factors. GIPSS features four and MIPSSv2 five risk categories.

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