The Evolving Understanding of Prognosis in Post–Essential Thrombocythemia Myelofibrosis and Post–Polycythemia Vera Myelofibrosis vs Primary Myelofibrosis

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Abstract: Myelofibrosis (MF) is the most aggressive of the classic Philadelphia chromosome–negative myeloproliferative neoplasms (MPNs). In some patients with essential thrombocytopenia or polycythemia vera, which are relatively benign MPNs, MF develops as a natural evolution of their disease, resulting in post–essential thrombocythemia myelofibrosis (PET-MF) or post–polycythemia vera myelofibrosis (PPV-MF). Presenting with the same clinical features, including debilitating symptoms and signs of bone marrow failure, PET/PPV-MF has traditionally been considered akin to primary myelofibrosis (PMF). However, recent observations that PET/PPV-MF may be a distinct clinical entity from PMF have triggered efforts to improve prognostication in these diseases. Novel predictive models that incorporate rapidly emerging clinical and molecular data are being developed to improve outcomes in patients with PMF or PET/PPV-MF. This review focuses on the major clinical features and prognostic classification systems used in PMF and PET/PPV-MF.

Introduction

Myelofibrosis (MF) is one of the chronic Philadelphia chromosome–negative myeloproliferative neoplasms (MPNs). It is characterized by the clonal proliferation of myeloid cells, leading to extramedullary hematopoiesis, hepatosplenomegaly, constitutional symptoms (ie, fatigue, night sweats, weight loss, and fever), and cytopenia, along with bone marrow fibrosis and an increased risk for evolution into acute myeloid leukemia (AML). MF is the most aggressive of the MPNs. It may present as primary (ie, arising de novo) myelofibrosis (PMF) or evolve from essential thrombocythemia (ET) or polycythemia vera (PV); these forms are referred as PET-MF and PPV-MF, respectively. PET-MF and PPV-MF are both considered to be a natural evolution of ET and PV, with 15-year cumulative incidence rates varying between 5% and 19% for PV and between 4% and 11% for ET, according to different diagnostic criteria.[1-4]

Several clinical and molecular factors predictive of fibrotic transformation have been identified in various studies. The most frequently reported risk factors include advanced age; longer duration of disease; greater disease burden (eg, leukocytosis, thrombocytopenia, anemia, palpable splenomegaly); greater *JAK2* allele burden for PV; presence of *SRSF2, U2AF1,* and *ASXL1* mutations; bone marrow reticulin fibrosis of at least grade 1; and cytogenetic abnormalities (12p abnormality/acquired loss of heterozygosity of chromosome 1p).[5-12] The median time to transformation has been reported as approximately 11 years; it is longer in *CALR*-mutated ET than in *JAK2*-mutated ET and PV and triple-negative ET (median times of 12.1, 8.4, 11.0, and 8.2 years, respectively).[13,14] The prognosis of patients with MF varies, with overall survival (OS) ranging from a couple of months to many years. Owing to the fact that patients with PET/PPV-MF typically present with clinical symptoms related to complications of bone marrow failure and chronic inflammatory status, which are similar to the symptoms of patients with PMF, these entities were formerly considered to be the same. Prognostic models developed to predict the survival of patients with PMF were uniformly applied to all patients with MF, despite the unknown implications of their use in patients with PET/PPV-MF.

However, increasing evidence in recent years suggests that patients with PET/PPV-MF may differ from those with PMF, and that the performance of PMF-derived prognostic models may be suboptimal. Accurate prognostication in patients with PET/PPV-MF is essential for directing clinical decision making, especially regarding the use of high-risk but curative therapies, such as allogeneic stem cell transplant (SCT). For instance, official guidelines from the European LeukemiaNet and the European Society for Blood and Marrow Transplantation regarding SCT for patients with MF are currently restricted to those with PMF in light of the possible differences between PMF and PET/PPV-MF.[15]

Diagnosis of PMF and PET/PPV-MF

The diagnostic criteria for PMF from the World Health Organization (WHO) combine laboratory data with molecular and genetic findings, along with morphologic features of the bone marrow. According to revised WHO criteria from 2016, bone marrow biopsy has become critical for the diagnosis of MPNs, especially to differentiate ET from early prefibrotic MF (pre-MF; Table 1) and to reflect the recent recognition of pre-MF by several groups.[16-19] This represents a major improvement in efforts to diagnose and predict the prognosis of patients with these diseases, given that pre-MF behaves more aggressively than ET.[20]

The diagnosis of PET/PPV-MF has been widely

Table 1. Diagnostic Criteria for Primary Myelofibrosis and Prefibrotic Myelofibrosis

Primary Myelofibrosis		Prefibrotic Myelofibrosis
Major criteria (all required)		
1	Megakaryocytic proliferation and atypia, accompanied by reticulin and/or collagen fibrosis grade 2 or 3[17]	Megakaryocytic proliferation and atypia, without reticulin fibrosis grade >1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis
2	Not meeting WHO[16] criteria for ET, PV, *BCR-ABL1*+ CML, a myelodysplastic syndrome, or another myeloid neoplasm	
3	Presence of *JAK2, CALR,* or *MPL* mutation or, in the absence of these mutations, presence of another clonal marker[a] or absence of reactive myelofibrosis	
Minor criteria (≥1 required)		
1	Anemia not attributed to a comorbidity	
2	Leukocytosis (leukocyte level ≥11 × 10⁹/L)	
3	Palpable splenomegaly	
4	LDH increased to above upper limit of normal institutional reference range	
5	Leukoerythroblastosis	—

[a] In the absence of any of the 3 major clonal mutations, a search for the most frequent accompanying mutations (eg, *ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1*) is of help in determining the clonal nature of the disease; bone marrow fibrosis grading is according to the European classification.[17]

CML, chronic myeloid leukemia; ET, essential thrombocythemia; LDH, lactate dehydrogenase; PV, polycythemia vera; WHO, World Health Organization.

adapted from the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) expert consensus[21] (Table 2). Owing to the aforementioned misclassification of ET in the past (up to 20%-30% of patients with a diagnosis of ET may have had pre-MF[22]) and the difficulty of performing repeated bone marrow biopsies with fibrosis assessment in general clinical practice, PET/PPV-MF is often diagnosed on the basis of a combination of clinical features (minor criteria in Table 2).

Evolving Concepts in Understanding the Differences Between PMF and PET/PPV-MF, and Their Prognostic Relevance

Clinical Features

In evaluations of the largest cohorts of patients with PMF

Table 2. Criteria for Post–Polycythemia Vera Myelofibrosis and Post–Essential Thrombocythemia Myelofibrosis

Post–Polycythemia Vera Myelofibrosis	Post–Essential Thrombocythemia Myelofibrosis
Major criteria (all required)	
1 Documentation of a previous diagnosis of PV or ET as defined by WHO criteria[23]	
2 Bone marrow fibrosis grade 2-3 (on scale of 0-3)[24] or grade 3-4 (on scale of 0-4)	
Minor criteria (≥2 required)	
1 Anemia or sustained loss of requirement for either phlebotomy (in absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis	Anemia and decrease in hemoglobin level of >2 g/dL from baseline
2 —	Increased LDH (above reference level)
3 Leukoerythroblastosis	
4 Increasing splenomegaly, defined as either an increase in palpable splenomegaly of >5 cm (below left costal margin) or the appearance of newly palpable splenomegaly	
5 Development of >1 of 3 constitutional symptoms: >10% weight loss in 6 months, night sweats, and unexplained fever (>37.5°C)	

ET, essential thrombocytopenia; LDH, lactate dehydrogenase; PV, polycythemia vera; WHO, World Health Organization.

(N=1054, IPSS[25]; N=805, MIPSS70[26]), PET/PPV-MF (N=781, MYSEC-PM[27]), and both (N=1099/755 PMF, Masarova and colleagues[28]; N=1209/61% PMF, Barbui and colleagues[29]; N=918/585 PMF, Hernández-Boluda and colleagues[30]), as well as other studies,[31-33] both PMF and PET/PPV-MF appear to affect chiefly older people (median age, 64 years), with a slight male predominance (52%-58%). The basic clinical parameters appear largely similar in PMF and PET/PPV-MF. Major significant differences include the following: increased proliferation, a higher number of symptoms, more frequent leukocytosis and splenomegaly, and a higher incidence of thromboembolic events in PPV-MF (PPV-MF vs PET-MF, 3.2 vs 2.3 per 100 person-years, respectively)[27]; less frequent thrombocytopenia in PET-MF; and more frequent transfusions of packed red blood cells (PRBCs) in PMF.[28]

Since the first attempts at prognostication in patients with MF, multiple negative prognostic clinical factors have been identified in those with PMF. The most frequent are age older than 65 years, hemoglobin level below 10 g/dL, leukocyte level above 25 × 10⁹/L, increase in circulating blasts of more than 1%, presence of constitutional symptoms and/or splenomegaly, PRBC dependence, and platelet count less than 100 × 10⁹/L.[25,34-39] In patients with PET/PPV-MF, Hernández-Boluda and colleagues[40] confirmed the significance of age older than 65 years, hemoglobin level less than 10 g/dL, and increased percentage of circulating blasts as predictors of inferior OS, and they identified treatment with hydroxyurea as an additional negative predictor. Tefferi and colleagues[41] recently confirmed the predictive value of all factors used in patients with PMF, except for constitutional symptoms and leukocytosis. Masarova and colleagues[28] found that age older than 65 years, hemoglobin level less than 10 g/dL, and constitutional symptoms were predictive of PPV-MF, and that hemoglobin level less than 10 g/dL, platelet count less than 100 × 10⁹/L, peripheral blast percentage of at least 1%, and constitutional symptoms were predictive of PET-MF. Passamonti and colleagues[9] reported the relevance of a hemoglobin level less than 10 g/dL, platelet count less than 100 × 10⁹/L, and leukocyte count greater than 30 × 10⁹/L as factors predictive of PPV-MF. In another study,[27] they identified older age, hemoglobin level less than 11 g/dL, circulating blast percentage of at least 3%, platelet count less than 150 × 10⁹/L, and constitutional symptoms as predictive of both PET-MF and PPV-MF. Recently, Masarova and colleagues observed a particularly detrimental effect of severe thrombocytopenia (platelet count <50 × 10⁹/L) in patients with PET-MF[42] and of a blast percentage greater than 5% in all patients with PET/PPV-MF.[43] Barraco and colleagues[44] recently reported a gender effect on phenotype in patients with PET/PPV-MF, and they concluded that the disease phenotype is more indolent (higher platelet count, smaller spleen, and lower percentage of circulating blasts) in females than in males, with slower progression and longer survival.

Molecular Signatures and Karyotype

The Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway, which is caused by somatic "driver" mutations in approximately 90% of cases, is considered the hallmark of the pathophysiology behind MF. Molecular distribution of these driver mutations is similar in patients with PMF and those with PET-MF: 55% to 60% carry the *JAK2* (V617F) mutation, 25% to 30% carry the *CALR* (*CALR* type 1 > *CALR* type 2) mutation, 10% carry the *MPL* mutation, and 6% to 9% test negative for all 3 mutations (triple negativity).[13,28,45,46] Patients with PPV-MF carry exclusively the *JAK2* mutation.

The predictive value of driver mutations in MPN phenotype, survival, and transformation to AML appears to be similar in PMF and PET/PPV-MF. Patients who

have *CALR* mutations are younger, with higher platelet counts, less anemia, lower white blood cell counts, and less splenomegaly than patients who have *JAK2* mutations.[27,46] In PMF, patients with *JAK2* mutations have been noted to have a higher incidence of thrombosis,[13] but the results in PET-MF are conflicting.[27,33] The longest survival in patients with *CALR* mutations has consistently been observed in those with PMF (median, not reached to 17.7 years),[28,46] as well as in those with PET-MF (median, not reached to 14.3 years).[13,28] Although the survival advantage of *CALR* type 1 vs type 2 is somehow conflicting in PMF,[47-51] the distinction appears to play no role in patients with PET-MF.[27] With regard to *JAK2* mutations, OS was similar in *JAK2*-mutated PMF, PET-MF, and PPV-MF (median OS was 4.2, 5.4, and 4 years, respectively).[28] Patients with triple-negative PMF and PET/PPV-MF have the worst OS, with median OS times of 1.2 to 3.2 years and 4.8 years, respectively.[28,33,45] The incidence of AML is increased in patients who have PMF or PET/MF with either *JAK2* mutations or triple negativity.[13,52] However, the effect of a lower *JAK2* mutation allele burden on the rate of progression to AML was reported only in patients with PMF,[52-54] not in those with PET/PPV-MF.[28,33,55]

Whereas driver mutations seem to play similar roles in predicting outcomes in PMF and PET/PPV-MF, subclonal gene mutations do not appear to predict survival in patients with PET/PPV-MF in a meaningful way. In PMF, mutations in *ASXL1*, *EZH2*, *SRSF2*, *IDH1*, and *IDH2* (high-molecular-risk mutations, identified in about 25% of patients) have been associated with shorter survival and more frequent transformation to AML.[45,56,57] Although the frequency of these gene mutations seems roughly similar in PET/PPV-MF (25%-36%), they have not been shown to predict prognosis or leukemic transformation, with the exception of *SRSF2* mutations in patients with PET-MF.[33] The number of high-molecular-risk mutations in PMF (0 vs 1 vs 2+) has been found to be highly significant in terms of median OS (12.3 vs 7 vs 2.6 years, respectively).[58] The data for patients with PET/PPV-MF are scanty. Patel and colleagues,[59] however, observed a higher incidence of 3+ mutations in patients with PMF than in those with PPV-MF (in 10 of 12 with PMF), which directly correlated negatively with spleen response to the JAK2 inhibitor ruxolitinib (Jakafi, Incyte).

Regarding cytogenetic features, abnormal karyotype is seen in approximately one-third of all patients (PMF, 30%-45%[60]; PET/PPV-MF, 30%-35%[9,29,33,61]), with one small report showing abnormalities in up to 63% of patients with PPV-MF.[62] In both entities, the most frequent cytogenetic abnormalities are single abnormalities of chromosomes, such as 20q–, 13q–, +8, +9, and 1q+.[60,63] Interestingly, the presence of a sole chromosome

17 abnormality has been reported only in PMF.[28] In contrast, the occurrence of 2 or 3 abnormalities (referred to as complex karyotype) seems to be more frequent in patients with PPV-MF. Among patients with cytogenetic abnormalities, complex karyotype has been reported in up to 20% of those with PMF and in up to 32% of those with PPV-MF.[28,60,62] Patients with cytogenetic abnormalities and complex karyotype tend to be older with an advanced phenotype, characterized by, for example, a higher frequency of leukopenia, anemia, transfusion dependency, and thrombocytopenia; a higher blast percentage; a larger spleen; and more symptoms.[60,63,64] The correlation of unfavorable cytogenetics with inferior survival and more frequent transformation to AML in patients with PMF is largely known.[65,66] Unfavorable cytogenetics in PMF have long been known to include abnormalities of –7 or 7q–, –5 or 5q–, i(17q), +8, inv(3), 12p–, and 11q23 and complex karyotype, associated with a median survival of 2 years,[65] as well as monosomal karyotype (2 autosomal monosomies or a single monosomy with at least 1 additional structural abnormality), associated with a median survival of 0.6 year.[67] Recently, Tefferi and colleagues[60] redefined cytogenetics in 1002 patients with PMF, reporting a group of patients with highly unfavorable cytogenetics: monosomy 7, inv3 or 3q21, i(17q), 12p– or 12p11.2, 11q– or 11q23, and single or multiple trisomies other than trisomy 9 or 8, associated with a median survival of 1.2 years. This study suggested that complex karyotype or monosomal karyotype without the presence of one of the aforementioned abnormalities may not necessarily mean a poor outcome. The definition of unfavorable cytogenetics in PET/PPV-MF is still ongoing, largely owing to smaller patient samples in each subgroup. Our group[61] found that patients who have PET/PPV-MF (N=321) with chromosome 5, 7, 12p, or 11q abnormalities, complex karyotype, or monosomal karyotype have the worst OS (1.2 years). Mora and colleagues[63] (N=781, PET/PPV-MF) showed that those with complex karyotype or monosomal karyotype have the shortest OS, with median OS times of 2.7 years for complex karyotype and 2 years for monosomal karyotype. A group from the Mayo Clinic[68] (N=31) reported an OS of 2.9 years in patients who had PET/PPV-MF with cytogenetic abnormalities other than 20q– and 13q–.

Survival seems to be better in patients with PET-MF than in those with PMF or PPV-MF, as reported by Masarova and colleagues (median OS times for PET-MF, PPV-MF, and PMF of 6, 4, and 3.75 years, respectively; *P*<.001)[28]; Vannucchi and colleagues (COMFORT pooled analysis; OS times for PET/PPV-MF vs PMF; hazard ratio [HR], 0.66; 95% CI, 0.47-0.94)[39]; and Passamonti and colleagues (median OS times for PET-MF vs PPV-MF, 14.5 vs 8.1 years; *P*=.05).[27]

Evolution of Prognostic Models in PMF and PET/PPV-MF

In the last decade, several prognostic models for PMF have been developed and are currently being used for treatment decision making. Table 3 lists the variables included in all models, along with the weight assigned to each variable and estimated survival. The first Lille scoring system, published in 1996, recognized anemia (hemoglobin level <10 g/dL) and a low (<4 × 10⁹/L) or high (>30 × 10⁹/L) leukocyte count as adverse factors for OS. It included both PMF and PET/PPV-MF, however.[27]

The real milestone in MPN prognostication was the development of more robust clinically based models: the International Prognostic Scoring System (IPSS),[25] used at diagnosis, and the Dynamic International Prognostic Scoring System (DIPSS),[35] used at any time during the disease course. Both assessed the significance of older age, anemia, leukocytosis, increased peripheral blood blasts, and constitutional symptoms to identify 4 risk categories, each with a distinct OS (Table 3) and risk for transformation to AML.[31] Growing evidence about cytogenetics and the effects of thrombocytopenia and PRBC dependence was later incorporated into the DIPSS plus model.[36] In recent years, the identification of various genetic and molecular prognostic factors (eg, presence or absence of driver mutations or high-molecular-risk mutations) and their effects on outcome in PMF made possible the development of new scoring systems that more precisely predict prognosis: the mutation-enhanced international prognostic scoring system (MIPSS),[69] the mutation-enhanced international prognostic scoring system for transplant-age patients (MIPSS70),[26] the karyotype-enhanced MIPSS70 (MIPSS70+),[26] the MIPSS70+ version 2.0,[70] and the genetically inspired prognostic scoring system (GIPSS; Table 3).[71]

A major barrier to the consistent use of all the prognostic scores developed for PMF stems from assessments based on retrospective studies and limited validation in patients with PET/PPV-MF. Several authors have shown that their predictive power decreases in patients with PET/PPV-MF. Hernández-Boluda and colleagues[40] (N=115 PET-MF, 61 PPV-MF) demonstrated that the IPSS was able to distinguish only patients with high-risk disease (median OS, 3.1 years) from all others with similar OS times (median OS times in Int-2, Int-1, and low-risk disease were 8.5 years, 10 years, and not reached, respectively). The same results were shown by Barbui and colleagues in the ERNEST study (Towards a Better Understanding of Epidemiology, Survival and Treatment in Myeloproliferative Neoplasms; N=1209, 19% PPV-MF).[29] Masarova and colleagues[28] (N=181 PPV-MF, 163 PET-MF) confirmed the inability of the IPSS to distinguish between PET-MF with low risk and PET-MF

with Int-1 risk; they also showed that the DIPSS failed to discriminate between high risk and Int-2 risk (median OS times in PPV-MF were 3.6 and 3.3 years, respectively, and in PET-MF were 3 and 5 years, respectively). Recently, Tefferi and colleagues[41] (N=79 PPV-MF, 46 PET-MF) demonstrated the inability of the IPSS, DIPSS, and DIPSS plus to distinguish between patients with Int-1 risk and low risk, as well as between those with Int-1 risk and Int-2 risk (median OS times for Int-2, Int-1, and low risk with IPSS were 5.6, 4.8, and 1.3 years; with DIPSS, 5.7, 2.4, and 0.8 years; and with DIPSS plus, 6, 4.9, and 0.9 years, respectively).

The obvious need for better prognostication in patients with PET/PPV-MF was first approached by Passamonti and colleagues.[9] In their dynamic PPV-MF model (N=647 PV, 68 PPV-MF), the development of a hemoglobin level less than 10 g/dL, platelet count less than 100 × 10⁹/L, and leukocyte count greater than 30 × 10⁹/L at any time after a diagnosis of PPV-MF resulted in a 4.2-fold increase in the risk for death. A comparison of this score with the DIPSS by Gowin and colleagues[72] (N=44 PPV-MF, 61 PET-MF) showed a concordance rate of only 12.5% to 24%.

In the latest model specifically designed for patients with newly diagnosed PET/PPV-MF, the Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM), Passamonti and colleagues[27] (N=685 PET/PPV-MF) incorporated 6 independent predictors of inferior OS: 2 points for a hemoglobin level less than 11 g/dL, a circulating blast percentage of at least 3%, and an unmutated *CALR* genotype; 1 point for a platelet count less than 150 × 10⁹/L and constitutional symptoms; and 0.15 point for any year of age. The score identified 4 risk groups: low (n=133; score <11), Int-1 (n=245; score ≥11 to <14), Int-2 (n=126; score ≥14 to <16), and high (n=75; score ≥16), with median OS times of not reached, 9.3 years, 4.4 years, and 2 years, respectively (P<.0001). The prognostic utility of MYSEC-PM was superior to that of IPSS (C-coefficient, 0.78 for MYSEC-PM and 0.71 for IPSS).

Since its publication, multiple researchers have validated the MYSEC-PM model and confirmed its superior predictive power for patients with newly diagnosed PET/PPV-MF. Hernández-Boluda and colleagues[73] applied the MYSEC-PM model to 262 patients with PET/PPV-MF and separated them into 4 risk groups with distinct OS times of not reached, 9.3 years, 3.4 years, and 1.7 years for those at low, Int-1, Int-2, and high risk, respectively (P<.001). MYSEC-PM outperformed the IPSS model, which failed to differentiate between Int-2 and high risk (OS times of 4.9 and 3.1 years, respectively). Our group[74] (N=178 PET/PPV-MF) showed similar results; MYSEC-PM defined 4 categories with distinctive OS times (long

Table 3. Prognostic Models in Primary Myelofibrosis

	Risk Categories[a]					
	Very Low	**Low**	**Int-1**	**Int-2**	**High**	**Very High**
IPSS[25] *1 point:* symptoms; age >65 y; Hgb <10 g/dL; WBC >25 × 10^9/L; PB blasts ≥1%	—	0	1	2	3+	—
	—	[11.25 y]	[7.9 y]	[4 y]	[2.25 y]	—
DIPSS[35] *1 point* for all in IPSS but *2 points* for Hgb <10 g/dL	—	0	1-2	3-4	5-6	—
	—	[NR]	[14.2 y]	[4 y]	[1.5 y]	—
DIPSS plus[36] *0-3 points:* DIPSS scores low to high *1 point:* UNF CG; plt <100 × 10^9/L; PRBC	—	0	1	2-3	4+	—
	—	[15.4 y]	[6.5 y]	[2.9 y]	[1.3 y]	—
MIPSS[69] *0.5 point:* Hgb <10 g/dL; symptoms; *JAK2; MPL; ASXL1; SRSF2* *1 point:* plt <200 × 10^9/L *1.5 points:* age >60 y; triple negativity	—	0-0.5	1-1.5	2-3.5	4+	—
	—	[26.4 y]	[9.7 y]	[6.4 y]	[1.9 y]	—
MIPSS70 (<70 y)[b,26] *1 point:* Hgb <10 g/dL; BM fibrosis 2+; PB blasts ≥2%; symptoms; ABS of *CALR* type 1; HMR *2 points:* WBC >25 × 10^9/L; plt <100 × 10^9/L; 2+ HMR	—	0-1	2-4		5+	—
	—	[27.7 y-NR]	[7.1-6.3 y]		[2.3-3.1 y]	—
MIPSS70+[b,26] *1 point:* Hgb <10 g/dL; PB blasts ≥2%; symptoms; HMR *2 points:* ABS of *CALR* type 1; 2+ HMR *3 points:* UNF CG	—	0-2	3	4-6		7+
	—	[20 y-NR]	[6.3-24.2 y]	[3.9-10.4 y]		[1.7-3.9 y]
MIPSS70+ version 2.0[70] *1 point:* Hgb 8-9.9 g/dL female or Hgb 9-10.9 g/dL male; PB blasts ≥2% *2 points:* Hgb <8 g/dL female or <9 g/dL male; symptoms; ABS of *CALR1*; HMR *3 points:* UNF CG; 2+ HMR *4 points:* VHR CG	0	1-2	3-4	5-8		9+
	[NR]	[16.4 y]	[7.7 y]	[4.1 y]		[1.8 y]
GIPSS[71] *1 point:* ABS of *CALR1*; *ASXL1; SRSF2; U2F1Q157*; UNF CG *2 points:* VHR CG	—	0	1	2	3+	—
	—	[26.4 y]	[8 y]	[4.2 y]	[2 y]	—

[a] Points appear in upper row; median overall survival appears in lower row in square brackets

[b] This study had validation and training cohorts, and table shows OS for both groups.

ABS, absence; BM, bone marrow; DIPSS, dynamic international prognostic scoring system; GIPSS, genetically inspired prognostic scoring system; Hgb, hemoglobin; HMR, high-molecular-risk mutations (*ASXL1, SRSF2, EZH2, IDH1,* and *IDH2,* plus *U2F1Q157* only for MIPSS70+ version 2.0); IPSS, international prognostic scoring system; MIPSS, mutation-enhanced international prognostic scoring system; NR, not reached; PB, peripheral blood; plt, platelet (count); PRBC, packed red blood cell dependence; UNF CG, unfavorable cytogenetics as defined by Caramazza and colleagues[65]; VHR CG, very high-risk karyotype as defined by Tefferi and colleagues[60]; WBC, white blood cell (count); y, years.

to short) of 14.25, 7.75, 4.9, and 1.25 years, respectively (*P*<.0001). The IPSS failed to distinguish between Int-1 and low risk (median OS times of 14.25 years and not reached, respectively), as well as between Int-2 and high risk (median OS times of 5 and 3.7 years, respectively).

Palandri and colleagues[32] evaluated MYSEC-PM in patients (N=421 PET/PPV-MF) treated with ruxolitinib and similarly showed 4 groups with distinct OS rates at 4 years: 100% (low), 91.4% (Int-1), 77.6% (Int-2), and 41.4% (high). In this study, IPSS showed similar OS

rates for all risk groups (low, Int-1, Int-2, and high) at 4 years: 87.8%, 85.5%, 85.2%, and 82.9%, respectively (P=.80).

Although the MYSEC-PM model demonstrated a greater predictive power for OS among patients with newly diagnosed PET/PPV-MF, attempts to determine its applicability at any time during the course of disease yielded conflicting results. In the aforementioned studies, our group[74] was not able to show a difference in OS between the Int-1 risk and Int-2 risk groups (median OS times of 4.9 and 6.8 years, respectively; P=.27) when the model was applied to all referred patients. However, Palandri and colleagues[32] showed a similar predictive power of the model when evaluating patients during the course of their disease at the start of treatment with ruxolitinib. MYSEC-PM created 4 distinct groups (low, Int-1, Int-2, and high risk) with OS rates at 2 years of 100%, 97%, 72.6%, and 35.1%, respectively (P <.001).

In all these validation studies, the distribution of risk scores was similar to the original distribution of Passamonti and colleagues, in which the majority of patients were in the intermediate-risk groups. MYSEC-PM mainly reduced the proportion of patients in the higher-risk categories, reclassifying about 40% of patients into a lower-risk group and only about 15% into a higher-risk group relative to IPSS. This finding is reflected in the low rate of concordance between the high-risk groups of the 2 models (25% in the study of Palandri and colleagues[32]). Hernández-Boluda and colleagues[73] also noticed a significantly higher number of older patients with high-risk scores when MYSEC-PM was used (patients >70 years in the Int-2 and high-risk groups with MYSEC-PM vs IPSS, 74% vs 55%; P=.002). These observations raised concerns that MYSEC-PM gave too much weight to age, thereby possibly substantially reducing the number of candidates for SCT, which is currently indicated for patients younger than 70 years with higher-risk disease.[15] The question of whether the MYSEC-PM could be used similarly to the IPSS, DIPSS, or DIPSS, as well as to establish an indication for SCT, would require further study in larger groups of patients. However, MF is a disease of older individuals with various comorbidities; therefore, the indication for SCT should not be based on age, or even on a single prognostic score at diagnosis, but rather on overall performance status and disease dynamics over time.

A risk-adapted strategy that uses the most accurate prognostic models is paramount for patients with PET/PPV-MF to optimize treatment decision making. The 2 most important treatment strategies that hold the potential for cure or at least longer survival in patients with MF—SCT and ruxolitinib—are offered only to symptomatic or higher-risk patients.[15,75,76] Only a few reports suggest that patients with PET/PPV-MF might have a better response to ruxolitinib[39] or derive longer benefit from therapy[59] than those with PMF. In the later study by Patel and colleagues,[59] the duration of therapy with ruxolitinib was significantly shorter in patients with PMF than in those with PPV/PET-MF (35% vs 60%, P<.01), and the time to treatment discontinuation was shorter (median times of 119 and 240 weeks for PMF and PPV/PET-MF, respectively; P=.006). However, a recent study by Palandri and colleagues[32] did not confirm this finding. Although the higher frequency of anemia, higher number of molecular mutations, and higher incidence of grade 2+ anemia observed in the patients with PMF on ruxolitinib[32] might partly explain this observation, larger studies with longer follow-up are needed to investigate the issue.

Conclusion

Risk stratification within PMF and PET/PPV-MF has become a fast-moving area of interest. As our biological and molecular understanding of MF has evolved over recent decades, so too have the prognostic classification systems. In light of these observations, recently proposed molecularly and genetically enhanced models for PMF (MIPSS, GIPSS) and PET/PPV-MF (MYSEC-PM) clearly represent superior tools for disease risk stratification. Yet, prognostication in patients with PET/PPV-MF is far from complete. Unlike in patients with PMF, information about disease course and molecular profiling and their prognostic value in those with PET/PPV-MF is quite scanty. Although the secondary nature of PET/PPV-MF is not in itself considered an adverse prognostic risk factor, given the long duration of antecedent ET/PV, one can naturally assume that these patients are older and have more comorbidities, and that they will present with a higher number of chromosomal and molecular abnormalities as a consequence of natural disease evolution. Available data indicate that these assumptions are incorrect. It is imperative to improve our understanding of the precise molecular mechanisms that define this disease, particularly those that lead to progression and transformation. It is hoped that the current enormous interest in defining the mutational landscape of these patients will shed more light on the topic. Also needed are predictive algorithms that can be universally and widely adopted in everyday clinical practice. The current prognostic models are limited in their ability to incorporate other important factors, such as the dynamic nature of MF, the comorbidities of most patients, and the prolonged time course of antecedent ET/PV. It is important to propose clinically relevant models that reflect underlying disease pathology and can help us identify proper therapies to alter disease outcome.

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