Post-ET and Post-PV Myelofibrosis: Updates on a Distinct Prognosis from Primary Myelofibrosis

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Abstract
Purpose of Review The purpose of this review is to help doctors in the management of patients with post-polycythemia (PPV) and post-essential thrombocythemia (PET) myelofibrosis (MF) facing diagnostic criteria, prognostication, and treatment possibilities.

Recent Findings Diagnostic criteria of primary myelofibrosis (PMF) have been recently updated from the WHO classification. A clear-cut distinction between pre-fibrotic and overt PMF has been done. Concerning PPV and PET MF, the criteria come from 2008. Prognostication of PMF has been well established on clinical criteria, but recent molecular acquisitions will improve the strategy. For PPV and PET MF, the new MYSEC-PM is helpful for prediction of survival. JAK2-inhibitors and stem cell transplant are the two critical therapeutic approaches in myelofibrosis.

Summary Differences between PMF and SMF substantiate the efforts underway to adequately stratify SMF patients with ad hoc prognostic tools and to use such categorization to evaluate available treatment modalities.

Keywords Polycythemia · Thrombocythemia · Myelofibrosis · Prognosis · JAK2 · Survival

Introduction
In this review, we will describe the known main differences between primary myelofibrosis (PMF) and post-polycythemia vera (PPV) and post-essential thrombocythemia (PET) myelofibrosis (MF). Criteria for diagnosis of the two conditions are different as well as the expectation of life. All the information collected serve to a better risk stratification of patients and treatment approach to PET MF and PPV MF.

Diagnosis of PMF and SMF
MF is a chronic myeloproliferative neoplasm (MPN) characterized by megakaryocytic proliferation and atypia, variable degrees of bone marrow (BM) fibrosis, extramedullary hemopoiesis with splenomegaly, frequent anemia, peripheral blood leukoerythroblastosis, and a high burden of symptomatology. MF can appear as a de novo disease (primary myelofibrosis, PMF) or following a previously known diagnosis of ET or PV [1]. Both PMF and post-ET/post-PV MF negatively affect patients’ life expectancy and can transform into blast phase (BP) [2].

The 2017 World Health Organization (WHO) diagnostic criteria for PMF encompass new evidence collected in the last years, most notably the discovery of CALR mutations, the identification of additional clonal markers with an impact on survival, and the clear distinction between ET and pre-fibrotic/early PMF (pre-PMF) lacking significant fibrosis [3]. The 2017 WHO diagnostic criteria for ET, pre-PMF, and overt...
PMF are listed in Table 1. ET and pre-PMF can be indistinguishable with regard to clinical presentation, which is often characterized by prominent thrombocytosis (84.1% of pre-PMF cases present with a platelet count ≥ 450 × 10^9/L at diagnosis) [4]. Furthermore, driver mutations are overlapping [5, 6] and 48% of ET patients present at least one of the minor criteria required to diagnose pre-PMF [4]. The recognition of pre-PMF, which thus rests greatly on histopathologic features, is however compulsory as patients have a higher risk of evolution to overt MF or BP and an inferior survival with respect to ET patients [7, 8]. On the other hand, the presence of grade 2 and 3 reticulin fibrosis seems to imply an inferior survival in PMF [9]. Patients with overt PMF more often belong to higher risk categories and more frequently harbor one or more prognostically detrimental mutation (e.g., mutations in ASXL1 and EZH2) with respect to pre-PMF [8]. While recognizing the essential role of BM morphology, the WHO classification seeks to complement histopathological information with phenotypic and genotypic data, reflecting the complexity of MPNs and possibly limiting the impact of the subjective nature of BM morphology interpretation, often resulting in variable consensus among pathologists [3].

With regard to the diagnosis of post-ET/post-PV MF (also referred to as secondary MF, SMF), the criteria remain unchanged since 2008 and are listed in Table 2 [10]. However, since a preceding diagnosis of ET or PV is required, the 2017 WHO-based modifications in the diagnostic criteria of these diseases indirectly impact SMF diagnosis. Most notably, the lowering of the hemoglobin threshold for the diagnosis of PV (i.e., > 16.5 g/dL in men, > 16.0 g/dL in women, or hematocrit > 49% in men, > 48% in women) has brought to the diagnostic reallocation, bearing therapeutic implications, of a proportion of JAK2V617F-positive ET patients [3, 11]. The diagnosis of SMF requires the presence of grade 2 or 3 BM fibrosis and thus mandates a BM histopathological exam [12]. In routine clinical practice BM, biopsies are generally not performed on a regular basis in ET and PV unless clinical features suggest a disease evolution. Such features include, but are not limited to, the minor criteria for SMF diagnosis (i.e., development of constitutional symptoms, increasing splenomegaly, development of anemia or loss phlebotomy/cytoreduction requirement, increased serum LDH, and development of leukoerythroblastosis). Lastly, it is worth mentioning that MPNs can occur as sporadic diseases or have a familial clustering in around 7–11% of cases [13–16]. Phenotype, driver mutations, and disease evolution, comprising a possible evolution to SMF, are shared by both forms.

Predictive Factors of SMF Evolution at the Time of PV and ET

Fibrotic transformation in PV and ET occurs in a variable rate of 12–21% and 9–10%, respectively [17]. Several clinical parameters have been evaluated to investigate their potential role as predictors of SMF evolution. In PV, the presence of leukocytosis (white blood cell count > 10 or 15 × 10^9/L) [18], palpable splenomegaly at diagnosis [19] or during follow-up [20, 21], bone marrow reticulin fibrosis equal to or higher than grade 1 [22–24], resistance/intolerance to hydroxyurea, in terms of development of cytopenia and failure to reduce massive splenomegaly [21], and a long disease duration [25] have been associated with a higher risk of evolution into SMF. A large international study highlighted the prognostic relevance of distinguishing diagnosis of pre-fibrotic PMF from ET, in terms of risk to overt MF transformation (higher in pre-fibrotic PMF), identifying advanced age and anemia as risk factors for fibrotic progression to MF [7].

Among genetic risk factors, retrospective studies have identified that patients bearing homozygous JAK2V617F mutations [20, 26] and highest values for mutant allele burden (> 50%) are more likely to progress to post-PV MF [18], while JAK2-mutated ET patients have a lower risk of fibrotic transformation [27]. Concerning MPL mutations, the acquired copy-neutral loss of heterozygosity (CN-LOH) of chromosome 1p has been demonstrated to represent a molecular mechanism of fibrotic transformation in MPL-mutated MPNs [28], whereas CALR mutation and its variants did not appear to influence MF evolution [29]. More recently, a next-generation sequencing study identified the prognostic relevance of adverse variants/mutations and in particular of SRSF2 and U2AF1 on MF evolution in PV and ET patients, respectively [6]. A Mayo Clinic study on 196 PV patients has recently highlighted the detrimental effect of abnormal cytogenetic in MF evolution [30].

Clinical Features in PMF and SMF

Information on the clinical presentation of PMF and SMF mainly came from the largest datasets of patients as the IPSS (International Prognostic scoring System) for PMF [2, 31] and the MYSEC (myelofibrosis secondary to PV and ET) for SMF [32••]. Besides, a recent MD Anderson Cancer Center (MDACC) study focused on the different features between the two MF subtypes [33].

As for the IPSS cohort (N = 1054 PMF) [2, 34], the median age at diagnosis was 64 years; 17% of patients were younger than 50 years and 5% younger than 40. A majority of patients were males. Similar demographics data were obtained from the recent MDACC analysis (755 PMF and 344 SMF) [33] and from the MYSEC study (N = 781 SMF) [32••]. In the latter, the median age at time of SMF evolution was higher for PPV MF than for PET MF. Males represented 52% of the MYSEC population.

In the IPSS dataset, 89% of PMF patients presented with splenomegaly, 27% with constitutional symptoms, and 36%
with peripheral blood blasts. The incidence of thrombosis in PMF was $2.2 \times 100$ patients/year at 10 years [35]. As for the MYSEC study [32], 44% of SMF patients reported constitutional symptoms, 88% had splenomegaly, and 29% peripheral blood blasts. Subjects with PPV MF had higher values of white blood cells and hemoglobin, larger spleen size, and lower platelet count compared with PET MF cases. Patients with PPV MF had significantly higher frequency of constitutional symptoms and history of prior thrombosis than those with PET MF. Median incidence of thrombosis was $2.3 \times 100$ patients/year in PET MF and $3.2 \times 100$ patients/year in PPV MF. Masarova et al. [33] recently showed also that PMF patients were more likely RBC transfusion dependent than the SMF counterpart. Causes of death, known in 278 out of 517 PMF patients, in the DIPSS cohort were transformation to BP (31%), PMF

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Criteria 1 (morphologic)</th>
<th>Bone marrow morphology</th>
<th>Megakaryocytic proliferation and atypia, without reticulin fibrosis $&gt; 1$ grade, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion 2 (clinical)</td>
<td>WHO criteria for BCR-ABL1+ CML, PV, ET, MDS, or other myeloid neoplasms</td>
<td>Not meeting</td>
<td></td>
</tr>
<tr>
<td>Criterion 3 (genetic)</td>
<td>JAK2, CALR, or MPL mutation, or Clonal marker*, or Reactive BM reticulin fibrosis**</td>
<td>Presence, if absence</td>
<td>Presence</td>
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<td>Minor criteria</td>
<td>Anemia not attributed to a comorbid condition</td>
<td>Presence</td>
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<td>Leukocyte count</td>
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<td>Spleen size</td>
<td>Palpable</td>
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<td>Serum LDH</td>
<td>Increased to above the upper normal limit of institutional reference range</td>
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<tr>
<th>Major criteria</th>
<th>Criteria 1 (morphologic)</th>
<th>Bone marrow morphology</th>
<th>Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3</th>
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<tr>
<td>Criterion 2 (morphologic)</td>
<td>WHO criteria for ET, PV, BCR-ABL1+ CML, MDS, or other myeloid neoplasms</td>
<td>Not meeting</td>
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<tr>
<td>Criterion 3 (genetic)</td>
<td>JAK2, CALR, or MPL mutation, or Clonal marker*, or Reactive BM reticulin fibrosis**</td>
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<td>Serum LDH</td>
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<td></td>
<td>Leukoerythroblastosis</td>
<td>Presence</td>
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*WHO, World Health Organization; CML, chronic myeloid leukemia; PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; MDS, myelodysplastic syndromes

**In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (e.g., ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease

***Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies
progression (18%), thrombosis and cardiovascular complications (13%), infection (10%) or bleeding (5%) out of the setting of BP, portal hypertension (5%), and other events including secondary cancers (4%) [31]. The MYSEC dataset reported BP in 66 (8.4%) and death in 220 (28%) SMF patients. The most frequent causes of death in SMF patients were non-clonal disease progression (35–40%), BP (20–25%), and infections (6–10%). Other fatal events (included organ failure, complications after SCT, secondary malignancies) happened each in less than 10% of cases.

Cytogenetics Relevance in PMF and SMF

Information on karyotype and its implications is widely detailed in PMF [36–39], but few studies focused on cytogenetic differences between PMF and SMF [33].

Table 2 The International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria for post-essential thrombocythemia and post-polycythemia vera myelofibrosis

<table>
<thead>
<tr>
<th>Criteria for post-essential thrombocytopenia myelofibrosis (PET MF)</th>
<th>Diagnosis of post-ET MF entails meeting both required criteria and at least two additional criteria</th>
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<tbody>
<tr>
<td>Required criteria</td>
<td>1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria</td>
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<tr>
<td></td>
<td>2. Bone marrow fibrosis grades 2–3 (on 0–3 scale)* or grades 3–4 (on 0–4 scale)**</td>
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<tr>
<td>Additional criteria</td>
<td>1. Anemia and a ≥ 2 g/dL decrease from baseline hemoglobin level</td>
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<td>2. A leukoerythroblastic peripheral blood picture</td>
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<td>3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly</td>
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<td>4. Increased LDH (above reference level)</td>
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<td>5. Development of ≥ 1 of three constitutional symptoms: &gt; 10% weight loss in 6 months, night sweats, unexplained fever (&gt; 37.5 °C)</td>
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<th>Diagnosis of post-PV MF entails meeting both required criteria and at least two additional criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required criteria</td>
<td>1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria</td>
</tr>
<tr>
<td></td>
<td>2. Bone marrow fibrosis grades 2–3 (on 0–3 scale)* or grades 3–4 (on 0–4 scale)**</td>
</tr>
<tr>
<td>Additional criteria</td>
<td>1. Anemia or sustained loss of requirement of either phlebotomy (in the absence of cytoreduceive therapy) or cytoreduceive treatment for erythrocytosis</td>
</tr>
<tr>
<td></td>
<td>2. A leukoerythroblastic peripheral blood picture</td>
</tr>
<tr>
<td></td>
<td>3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly</td>
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<td>4. Development of ≥ 1 of three constitutional symptoms: &gt; 10% weight loss in 6 months, night sweats, unexplained fever (&gt; 37.5 °C)</td>
</tr>
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LDH, lactate dehydrogenase

*Grades 2–3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain); or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain)

**Grades 3–4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis; or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

About one third of PMF patients presented chromosomal abnormalities [2, 33, 36]. In the MYSEC study, abnormal karyotype (AK) was present in 34% of SMF patients, with higher frequency in the PPV MF subgroup (40%) (Mora et al., in press). These findings were similar to those of the MDACC SMF dataset [40].

In large cohorts of MF patients, sole abnormalities were the most represented cytogenetic alterations: 68% of PMF [39] and 57% of SMF. In PMF, the most frequent individual abnormalities were 20q− (23%), 13q− (18%), +8 (11%), +9 (10%), chromosome 1q+ (9.5%), and 7q− (7%) [39, 41]. Chromosome 17 abnormalities seem specific for PMF, as relatively rare in SMF [33]. The MYSEC study showed that the most prevalent single chromosomal alterations in SMF were, as in PMF, 20q−, 13q−, +8, and +9 (< 10% each) (Mora et al., in press). Similar results have been reported in PV [30] and—even if in a smaller frequency—in ET [42]. As suggested by recent sequential data on cytogenetics in PV and PPV MF, chromosomal individual alterations could
be a consequence of a pre-existing PV/ET phase rather than being involved in SMF pathogenesis [43]. As for PMF, double abnormalities and complex karyotype (CK) were present in 17 and 11% [39], while in 8 and 5% in another cohort [33]. The MYSEC and the MDACC studies showed a higher rate of double abnormalities (17%) and CK (20%, including 8.5% monosomal—MK) in SMF. On the contrary, less than 5% of PV/ET cases showed two or more cytogenetic alterations [23, 43]. Therefore, multiple chromosomal alterations could be more related to evolution in SMF.

Looking for karyotype-phenotype associations in PMF, Wassie et al. [39] showed that AK correlated to leukopenia, anemia, and thrombocytopenia; besides, the CK subgroup was more frequently characterized by younger age and lower platelet count. In the same study, specific phenotypic parameters were associated with single chromosomal abnormalities: leukopenia with 20q−, + 8, and 7q−; thrombocytopenia with 20q− and 7q−. As for SMF, AK clustered with a more advanced phenotype: lower platelets, larger spleen size, higher frequency of symptoms, and more peripheral blood blasts (Mora et al., in press). Preliminary data in SMF showed also an association between CK and more severe bone marrow fibrosis grade [33].

Associations between genotype and karyotype have been detailed in PMF, as the case of 13q− and CALR mutation, + 9 and JAK2 mutation, 20q− with SRSF2 mutation, ASXL1 and normal karyotype [39]. On the contrary, no definitive associations between driver mutations and karyotype were found in SMF.

In the MYSEC study, chromosomal abnormalities did not impact on risk of thrombosis, while CK was a predictor of blast phase evolution (Mora et al., in press). Same prognostic value of CK was suggested in other cohorts, which included also PMF patients [33]. Considering PMF outcome, single or double chromosomal abnormalities including + 8, 7q−, i(17q), inv[3], 5q−, 12p−, rearrangement 11q23, CK, and MK were associated with an unfavorable outcome [36]. Tefferi et al. [44] showed that MK, inv[3], and inv(17q) were “very high risk” cytogenetic categories, associated with an extremely severe prognosis (median estimate, 9 months). Survival of SMF patients with AK reflected an aggressive disease (median estimate, 6.1 years) and very detrimental impact had CK (median estimate, 2.7 years) or MK (median estimate, 2 years) (Mora et al., in press). Among all the chromosomal aberrations, only MK showed independent prognostic value from the MYSEC-PM stratification. Besides, AK was significantly associated with higher MYSEC-PM risk categories.

**Distribution and Effects of Genotype in PMF and SMF**

Overall, 60% of PMF patients in the IPSS cohort carried the JAK2 (V617F) mutation [2]. After the discovery of CALR mutation, other studies clarified driver mutations’ distribution in PMF: for instance, out of 254 PMF patients, 58% harbored JAK2 (V617F), 25% CALR, 8% MPL mutations, and 9% were negative for all three mutations (TN) [45]. In the MYSEC study, all PPV MF patients carried the JAK2 (V617F) mutation. As for PET MF cases, the driver mutations’ distribution seems similar to that of PMF: 54% displayed JAK2 (V617F), 30% CALR, 9% MPL, 6% TN. Five PET MF patients had more than one driver clone [46]. Corresponding data were obtained in a recent study on 165 PET MF patients [40], while mutations’ distribution was different in another smaller cohort (MPL in 0%, CALR in 42%) [47].

Considering CALR mutated cases, CALR type 1 mutations were more frequent (60–70%) than CALR type 2 (15–25%) either in PMF or in SMF [48, 49]. Actually, some studies on ET reported that CALR type 1 mutation is preferentially associated with a higher risk of evolution to PET MF [50]. CALR mutations showed an association with younger age, higher platelet count, lower risk of anemia, or leukocytosis in PMF. JAK2 mutated PMF had higher incidence of thrombosis than CALR [51]. Also in the MYSEC cohort, when compared to JAK2, CALR-mutated patients were younger, with lower white blood cells and smaller spleen size. CALR type 1/type 1-like and CALR type 2/type 2-like were similar in terms of clinical presentation and outcome. In another study, JAK2-positive SMF cases resulted more symptomatic and with a higher risk of thrombosis [40]. In PMF, additional mutation impacting survival (so-called high molecular risk, HMR) was described in 25% of patients: ASXL1 (31%), EZH2 (6%), IDH 1-2 (4%), SRSF2 [52]. On the contrary, HMR mutations had no implication on SMF outcome prediction, with the exception of SRSF2 mutations, which correlated with reduced survival [40].

Looking at PMF outcome, CALR mutations had a favorable impact on survival, while unfavorable factors were CALR(−)/ASXL1(+) and TN cases [53] or SRSF2. In the MYSEC cohort, JAK2 mutated and TN cases showed a significantly higher incidence of BP compared with CALR-mutated patients, even after adjusting for age and IPSS risk category [46]. To note, in PET MF, CALR type 1-mutated patients had a lower rate of death. This was extensively explored in the MYSEC study: CALR-mutated cases had a significantly superior survival compared with JAK2-mutated PET and PPV MF, even adjusting for age and IPSS category [49].

**Survival of PMF and SMF and Prognostication**

In the last decade, three clinical-derived prognostic models for PMF have been developed and are currently used in the treatment decision-making: (i) the IPSS [2], which is applicable at the time of initial diagnosis and includes five variables that independently impact on survival (age > 65 years, hemoglobin < 10 g/dL, leukocyte count > 25 × 10^9/L, circulating blasts...
transfusion need, platelet count $< 100 \times 10^9/L$, and unfavorable karyotype. Furthermore, the most comprehensive mutational landscape in PMF and its prognostic relevance allowed the development of scoring systems including both driver and other non-driver mutational status and cytogenetic information for transplant-candidate patients with PMF [55••]. The MIPSS70 identified the following as significant risk factors for survival: hemoglobin $< 10$ mg/dL, leukocytes $> 25 \times 10^9/L$, platelets $< 100 \times 10^9/L$, circulating blasts $\geq 2\%$, bone marrow fibrosis grade $\geq 2$, constitutional symptoms, absence of CALR type 1 mutation, presence of high molecular risk mutation (i.e., ASXL1, EZH2, SRSF2, IDH1/2), and presence of two or more high molecular risk mutations. Although, in the clinical practice, the management of PMF and SMF does not differ, there is evidence that the prognostic models IPSS and DIPSS are suboptimal in prognosis stratification of SMF patients [56, 57]. Recent studies have also illustrated a different prognostic molecular profile between PMF and SMF. Vannucchi et al. [52] defined the relevance of HMR in PMF (ASXL1, EZH2, SRSF2, and IDH1/2), whereas in SMF only SRSF2 mutations seem to be associated with reduced survival in PET-MF [40]. Masarova et al. [33] showed that patients with PET-MF have better survival than those with PMF and PPV-MF and that PPV-MF and PMF patients have similar survival. Age $> 65$ years, hemoglobin $< 10$ g/dL, and constitutional symptoms are associated with shorter survival for PPV-MF, while hemoglobin $< 10$ g/dL, platelets $< 100 \times 10^9/L$, peripheral blasts $\geq 1\%$, and constitutional symptoms were prognostic factors for those with PET-MF. Again, hemoglobin $< 10$ g/dL, platelet count $< 100 \times 10^9/L$, and leukocyte count $> 30 \times 10^9/L$ are independent risks of survival in PPV-MF [12]. Hernandez-Boluda et al. [58] identified age $> 65$, hemoglobin $< 10$ g/dL, increased peripheral blood blasts, and treatment with hydroxyurea at the time of transformation as independent factors for predicting worse survival in PMF. Furthermore, the authors demonstrated that the current prognostic scoring systems used in PMF (IPSS/DIPSS) are not effective for an adequate prognostic stratification of SMF. Also, a Mayo Clinic Study on 125 SMF patients provided evidence that IPSS, DIPSS, and DIPSS-plus are ineffective in SMF patients [59]. All these information emphasize the need of new models dedicated to SMF. Ultimately, Passamonti et al. [32••] developed on a cohort of 781 SMF the MYSEC-PM, in order to address the prediction of survival in patients with SMF. This prognostic model includes age, hemoglobin $< 11$ g/dL, platelet $< 150 \times 10^9/L$, circulating blasts $\geq 3\%$, CALR unmutated genotype, and constitutional symptoms (available at https://mysec.shinyapps.io/prognostic_model/). It allocated SMF patients into four risk categories with different survival: low (median survival NR; 133 patients), intermediate-1 (9.3 years, 95% CI 8.1-NR; 245 patients), intermediate-2 (4.4 years, 95% CI 3.2–7.9; 126 patients), and high risk (2 years, 95% CI 1.7–3.9; 75 patients). The MYSEC-PM has been recently validated [56, 60].

**Treatment of PMF and SMF: Are Differential Strategies Warranted?**

Treatment avenues for MF patients encompass potentially curative strategies, such as allogeneic stem cell transplant [61, 62••], and an array of non-disease eradicating options [5, 63, 64, 65•]. Available prospective and retrospective treatment-centered trials in MF include both PMF and SMF patients without differential approaches according to MF subtype. JAK-inhibitor-based clinical trials comprise a significant proportion (variable between 35 and 55%) of SMF patients [65••, 66, 67, 68••, 69, 70••, 71••, 72, 73••, 74••, 75] and the indication of the only currently approved JAK-inhibitor in MF (i.e., ruxolitinib) includes both PMF and SMF. However, as previously mentioned, PMF and SMF differ in clinical features bearing relevance in treatment outcomes. Transfusion-dependence [76–78]—more frequent in PMF [33]—may impact transplant and JAK-inhibitor treatment outcome, whereas constitutional symptomatology—prominent in post-PV MF—is a risk factor included in several transplant-specific prognostic scores [33, 79–81]. Furthermore, survival differences between PET MF and PMF may hamper the correct interpretation of clinical trial results [33]. When a risk-based treatment strategy is adopted, both in the transplant and in the non-transplant trial settings [61], patients are currently stratified according to scoring systems geared on PMF, such as the IPSS, DIPSS, or DIPSS-plus [2, 31, 54, 82, 83], regardless of their diagnosis (PMF vs. SMF). Since these models are inadequate for SMF prognostication [32••], this may lead to the selection of prognostically heterogeneous PMF and SMF patients biasing result assessment.

With regard to available JAK-inhibitor trial data, evidence of a differential response according to MF subtype derives from a multivariate analysis of COMFORT-2 suggesting a higher response to ruxolitinib in PET MF with respect to PMF. A pooled analysis of overall survival in COMFORT-1 and COMFORT-2 showed that SMF was associated with a better prognosis than PMF independently of treatment [84].
Conclusions

The aforementioned differences between PMF and SMF (summarized in Table 3) substantiate the efforts underway to adequately stratify SMF patients with ad hoc prognostic tools (such as the MYSEC-PM) and to use such categorization to evaluate available treatment modalities according to a SMF-specific risk assessment. In addition, future clinical trials gauging whether a differential clinical approach in PMF and SMF is of value are desirable. In the meanwhile, the most recent ELN guidelines must be adopted.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance


