Prognosis in Pre-Fibrotic Primary Myelofibrosis

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The 2016 WHO classification recognized pre-fibrotic primary myelofibrosis (pre-PMF) as a distinct entity. Nevertheless, a prognostic model specific for pre-PMF is still lacking.

primary myelofibrosis | pre-fibrotic | prognosis | scoring system | IPSS | DIPSS

1. Introduction

As a matter of fact, the 2016 WHO-revised classification of MPNs recognized pre-fibrotic PMF (pre-PMF) as a distinct clinical entity from both overt fibrotic PMF (overt PMF) and essential thrombocythemia (ET) [1][2]. Indeed, while the initial presentation of pre-PMF is often an isolated thrombocytosis, thereby mimicking ET, its course may be symptomatic in a non-negligible number of cases [3]. Pre-PMF patients typically have higher leukocytes and platelets, lower hemoglobin, higher lactate dehydrogenase (LDH), and more frequent splenomegaly than ET [3]. Furthermore, pre-PMF may show a progressive clinical course with worsening of constitutional symptoms, increased bone marrow fibrosis (BMF) grade, and the appearance of high-risk cytogenetic or molecular abnormalities. However, it should be remembered that pre-PMF patients generally belong to lower prognostic risk categories at diagnosis. Conversely, overt PMF patients are enriched in higher-risk categories, not only at diagnosis but also during follow-up, thus suggesting a greater propensity for disease progression than pre-PMF. Importantly, median survival is significantly reduced in overt PMF vs. pre-PMF (7.2 vs. 17.6 years) [3], thereby reinforcing the appropriateness of making this distinction in clinical practice.

2. Diabetes and Second Neoplasia Impact

The revised 2016 WHO classification of myeloid malignancies dictated distinct criteria for pre- and overt PMF [1], which are mainly based on bone marrow morphology and the degree of fibrosis with BMF grade of 0 and 1 included in the pre-PMF category. In addition, peripheral blood leukoerythroblastosis is a minor diagnostic criterion for overt PMF, whereas anemia, leukocytosis, increased LDH, and palpable splenomegaly may be present in both diseases [1].

The existence of pre-PMF as a separate entity, and its differentiation from strictly WHO-defined ET, has been debated for several years [4], sometimes with conflicting results [5][6]. Low interobserver agreement in the application of WHO-based histopathological criteria for pre-PMF has been questioned by some experts [7], while

others have clearly delineated their reproducibility and the clinical relevance of adopting the diagnostic concept of pre-PMF [8]. In the largest multicenter study reported in the literature so far, 1104 ET patients underwent a central re-review of their diagnostic biopsies. The diagnosis of ET was then confirmed in 891 (81%) patients, while 180 (16%) were reclassified as pre-PMF, with important prognostic implications. Indeed, when compared with ET, the 10-year (76% vs. 89%) and 15-year survival rates (59% vs. 80%), leukemic transformation rates at 10 (5.8% vs. 0.7%) and 15 years (11.7% vs. 2.1%), as well as the progression rates to overt PMF at 10 (12.3% vs. 0.8%) and 15 years (16.9% vs. 9.3%) were all significantly worse in pre-PMF patients. Multivariable analysis confirmed these results and identified age > 60 years, leukocyte count > 11 × 10^9/L, anemia, and history of thrombosis as additional risk factors for survival, further underscoring the importance of differentiating pre-PMF from ET, particularly with regards to pre-PMF patients with absent fibrosis [9].

In this context, the appropriateness of a reappraisal of IPSS has been questioned; in fact, it was originally developed using PMF patients [10] that differed at least in part from the two categories of pre- and overt PMF currently identified by the 2016 revised WHO criteria [1]. In this regard, Guglielmelli et al. found that, although IPSS predicted overall survival, it largely failed to accurately distinguish between intermediate-1 and intermediate-2, and intermediate-2 and high-risk patients, respectively, in pre- and overt PMF, as well as in the individual groups according to the degree of fibrosis [11]. These observations may have importance in the settings of the decision-making process for stem cell transplantation, which is currently indicated in intermediate-2/high risk, as well as in selected intermediate-1 risk PMF patients [12], with a non-negligible percentage of subjects being inappropriately exposed to such a risky procedure.

Collectively, these findings should promote efforts to critically reassess current prognostic scores and ultimately develop separate risk scores for pre- and overt PMF that include the most relevant clinical, histological, molecular, and cytogenetic variables.

The present multicenter study identifies two clinical variables to integrate prognostic information from the two well-known prognostic models for PMF, i.e., IPSS and DIPSS, and refine the prognosis in pre-PMF patients.

In this specific context, even though the degree of BMF (MF-0/1 vs. MF-2/3) has already been shown to play a crucial role in better defining PMF prognosis [13], neither BMF grade (MF-0 vs. MF-1) nor driver mutation status seems to exert any significant impact on the outcome. The first of these two observations further confirms the importance of a correct diagnosis of pre-PMF vs. overt PMF because, from a histological point of view, the main prognostic risk factor is represented by a BMF degree ≥ 2, as it has already been reported in the two most recent prognostic models developed for PMF, namely MIPSS70 and MIPSS70+ version 2.0 [14][15].

However, it should be underlined further that a prognostic model specific for pre-PMF is still lacking.

Interestingly, in the series, the strongest association with outcome was documented for the two models that included a common cardiovascular risk factor, like diabetes, and the occurrence of secondary malignancies, either

hematological or not.

A similar observation of the impact of comorbidities on prognosis and outcome in cancer patients has already been made for other hematological malignancies. In 2011, Naqvi et al. conducted a retrospective cohort study of 600 consecutive patients with myelodysplastic syndromes (MDS), applying the Adult Comorbidity Evaluation-27 (ACE-27) scale to evaluate comorbidities [16]. Considering patients with no, mild, moderate, or severe comorbidities, median survival progressively decreased from 31.8 to 16.8, 15.2, and 9.7 months, respectively ($p < 0.001$), regardless of age and IPSS risk groups; accordingly, a thorough assessment of comorbidity severity can help predict survival in MDS patients.

Similarly, in 2014, Newberry et al. evaluated the frequency and severity of comorbidities in 349 consecutive PMF patients [17]. As expected, comorbidities had a significant negative impact on survival ($p < 0.001$), with subjects suffering from severe comorbidities having double the risk of death compared to those without comorbidities. However, this study only considered patients who were diagnosed between 2000 and 2008, i.e., using the 2008 WHO criteria with no distinction between pre- and overt PMF.

Being aware of the limitation of the present study, represented mainly by its retrospective design, it can be hypothesized that disease progression (whether overt PMF or acute myeloid leukemia) represented the final cause of death only in a minority of cases (28/107, 26.2%), while a leading role is played by other events, including thrombo-hemorrhagic complications (13/107, 12.1%), or due to other neoplasia or related treatments (21/107, 19.6%), thus confirming how pre-PMF may represent a chronic disease with possible multiorgan involvement.

In such a context, it should still be remembered that pre-PMF patients have approximately a two times greater risk of cardiovascular events, including major thromboses and hemorrhages, compared to the reference age-matched population [18]. Indeed, in a paper [18], Guglielmelli et al. demonstrated that the risk of total thromboses in pre-PMF can be accurately predicted by the IPSET score, originally developed for ET [19], corresponding to 0.67, 2.05, and 2.95% patients/year in the low-, intermediate-, and high-risk categories, thus representing the basis for individualized management aimed at reducing the increased risk of major cardiovascular events in this specific subgroup of PMF patients.

Furthermore, in addition to an inherent risk of thrombo-hemorrhagic events, studies have consistently reported that MPNs are also prone to developing second cancers (SC) [20], and the latter can have a negative impact on MPN outcome; in particular, in a recent large international study including 1881 cases [21], patients were grouped into two prognostic classes based on the five-year relative survival from cancer diagnosis, with a “poor prognosis” SC group including cancers in the stomach, esophagus, liver, pancreas, lung, ovary, head-and-neck, nervous system, osteosarcomas, multiple myeloma, aggressive lymphoma, and acute leukemia [22]. In addition, MPN patients with SC have already shown to be exposed to an increased risk of arterial thromboses; indeed, thrombotic events after MPN and before SC were higher in cases than in controls without a history of SC (11.6% vs. 8.1%; $p = 0.013$), due to a higher rate of arterial thromboses (6.2% vs. 3.7%; $p = 0.015$) [11].

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