**P1032 REAL-LIFE VALIDATION OF MIPSS70: A RETROSPECTIVE MULTICENTER AND NGS ANALYSIS FROM THE GEMFIN DATABASE**

**Topic:** 16. Myeloproliferative neoplasms - Clinical

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**Background:** Primary myelofibrosis (PMF) is a myeloproliferative neoplasm characterized by the presence of driver mutations (JAK2, CALR or MPL) in most of the patients. The development of next generation sequencing (NGS) has favored the incorporation of mutational information in novel prognostic scores. However, most of these risk stratification models also include cytogenetic information, which is only available for a fraction of patients with this disease, thus reducing their real-life applicability. Mutation-enhanced international prognostic scoring system for transplant-age patients (MIPSS70) is based on clinical and mutational risk factors and it is useful in the absence of cytogenetic information, but it has not been validated yet in a real-life clinical setting.

**Aims:** To validate MIPSS70 risk stratification model for transplant-age PMF patients from a multicenter database.

**Methods:** From the GEMFIN multicenter database, 668 myelofibrosis patients with enough information to calculate MIPSS70 were selected. As the score is intended for patients aged ≤70 years with PMF, the final analysis was carried out in 218 patients meeting these criteria. Patients who received allogeneic stem cell transplantation were censored on the date of transplantation.

**Results:** Median age was 61 years (range 18-70), 69% of patients were male and median follow-up time was 4.65 years. Regarding the presence of MIPSS70 variables at disease diagnosis, 45% of patients had constitutional symptoms, 43% had hemoglobin <100g/L, 15% leukocytes >25 (x10⁹/L) and 33% platelets <100 (x10⁹/L). Circulating blasts were ≥2% in 30% and most patients presented BM fibrosis grade ≥2 (74%). CALR type 1 mutation was detected only in 12%, while any high-molecular risk (HMR) mutation was present in 31% (8% for ≥2 HMR mutations). In brief, in comparison to MIPSS70 training cohort, the patients in the present series were older and presented a higher proportion of adverse risk factors (Figure 1A).
More than half of the patients were classified as high risk according to MIPSS70 (52%), while 35% were intermediate and 13% low risk. The 5-year overall survival (OS) was 44% (median 4.6 years), 77% (median 13 years) and 95% (median not reached) for high, intermediate and low risk patients respectively (p<0.001, Figure 1B). The 5-year leukemia-free survival (LFS) was 42%, 77% and 95% for high, intermediate and low risk groups (p<0.001).

Univariate analysis of each MIPSS70 variable on OS was carried out, with statistically significant differences being confirmed for all variables except fibrosis grade and HMR mutations. ASXL1 was mutated in 27%, but it did not impact OS in our patients (HR 0.96, p=0.89). SRSF2 was the only MIPSS70 mutated gene (8%) associated with inferior OS (HR 2.5, p=0.04), while EZH2 and IDH1/2 mutations were only present in 2.5% of patients each. However, the analysis of the complete NGS panel allowed the identification of other genes associated with shorter OS in our series: CBL (HR 3.7, p=0.014), SETBP1 (HR 4.9, p=0.034) and KRA5 (HR 4.6, p=0.041), with a tendency for U2AF1 (HR 2.3, p=0.061) and NRAS (HR 3.6, p=0.083).

Summary/Conclusion:

This study constitutes the first real-life validation of MIPSS70 in a multicenter analysis. The score was able to stratify our cohort in three categories with significant differences in OS and LFS. Of note, mutation on ASXL1 gene was not associated with shorter OS in our patients. By contrast, several other genes with potential prognostic significance were identified. Further cooperative studies are needed in order to unravel PMF mutational landscape and its prognostic implications.