Improved Risk Stratification of MDS Patients with IPSS-M: A single institution experience

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Background

- International Prognostic Scoring System-Revised (IPSS-R) is the most common model used in clinical decisions and risk stratification of patients with myelodysplastic syndrome (MDS).
- Recently, IPSS-Molecular (IPSS-M), which integrates somatic mutations, has been reported to improve the risk stratification of patients with MDS.

Design

- Patients diagnosed with MDS between 2016 and 2023 with available NGS were identified.
- IPSS-R and IPSS-M were calculated.
- Because IPSS-M was heavily weighted by the presence of the rare *KMT2A* partial tandem duplication (PTD), which was unavailable in 61% of patients using identified NGS panels, we used the "mean" version of the probabilistic IPSS-M prediction.
- Overall survival (OS) was calculated from the date of MDS diagnosis until death or censoring.
- Groups were compared using log-rank test.
- The OS discrimination of IPSS-R and IPSS-M was evaluated using the Harrell's C concordance statistic from a Cox survival model.

Results

- We identified 123 patients with MDS.
- Their clinicopathologic findings are summarized in Table1.
- Changes in MDS risk categories for patients according to IPSS-R and IPSS-M are shown in Table 1 and Figure 1.
- The mutational profile of MDS cases is illustrated in the heatmap (Figure 2).
- For high-risk molecular signature, 17 (27%) patients had multi-hit *TP53* mutation, *KMT2A*-PTD was observed in 1/26 (4%) tested patients , and no patient had *FLT3* mutation.

Results

Figure 1

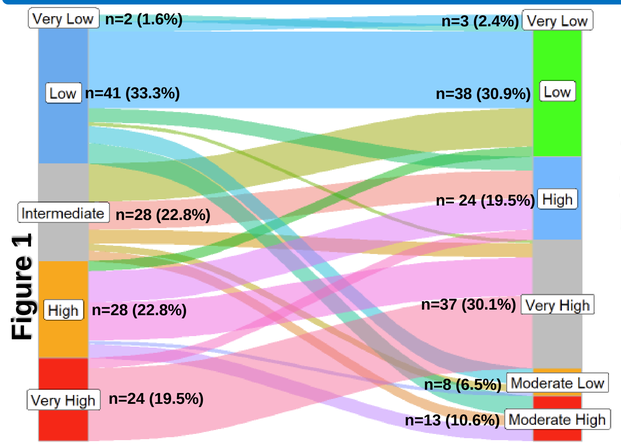


Table 1

Age	Gender	Median absolute neutrophil count	Median hemoglobin	Median platelet count	Median bone marrow blast count	Cytogenetic risk group	IPSS-R category	IPSS-M category-mean
74 years (13 to 94 years)	Female: 47 (38%) Male: 76 (62%)	1.7 x 10^9/L (0.1 to 11.4 x 10^9/L)	9.0 g/dL (5.9 to 14.7 g/dL)	99 x 10^9/L (7 to 814 x 10^9/L)	5% (0.2 to 18.8%)	very good: n=3 (2.4%) Good: n=72 (58.5%) Intermediate: n=16 (13.0%) Poor: n=10 (8.1%) very poor: n=22 (17.9%)	very low: n=2 (1.6%) Low: n=41 (33.3%), intermediate: n=28 (22.8%) High: n=28 (22.8%) very high: n=24 (19.5%)	very low: n= 3 (2.4%) Low: n=38 (30.9%) moderate low: n=8 (6.5%) moderate high: n=13 (10.6%) high: n=24 (19.5%) very high: n=37 (30.1%)

Figure 2

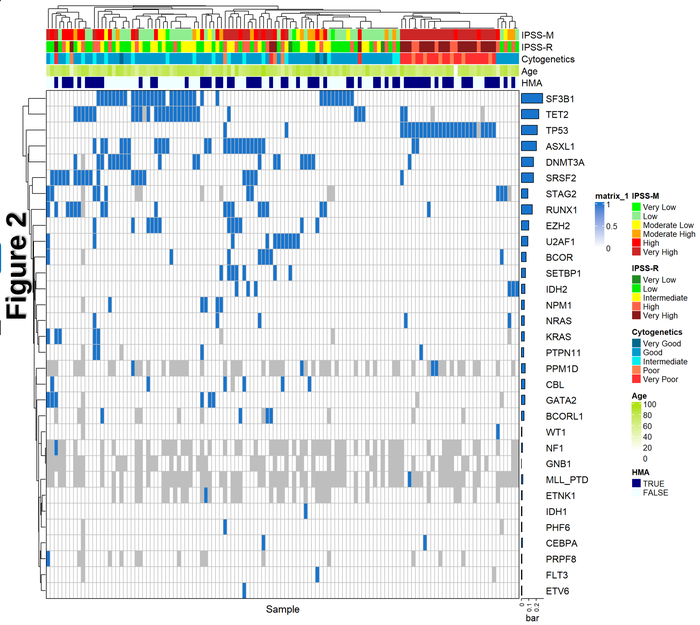


Figure 3

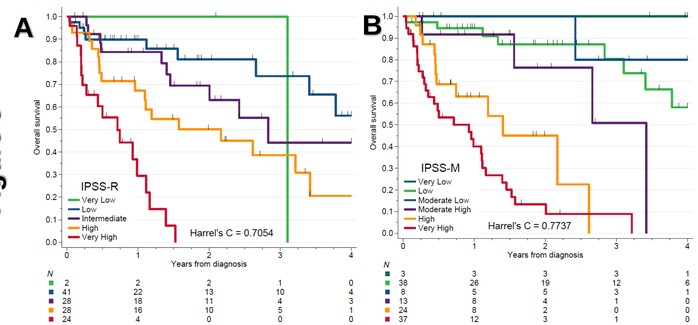
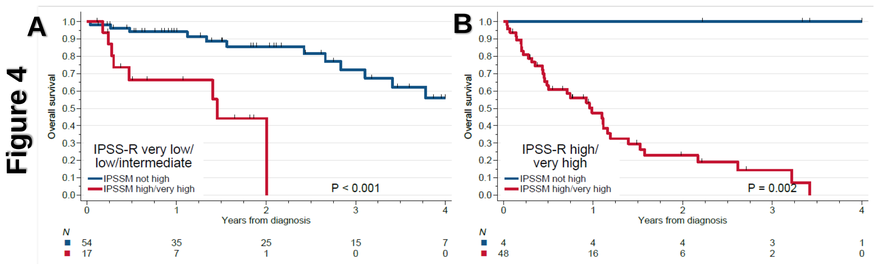


Figure 4



Results

- IPSS-R
  - Median OS ranged from 4.6 years (95%CI, 3.1 to not reached [NR]) for Very Low/Low groups to 0.7 years (95% CI, 0.2-1.1) for Very High group (Figure 3A).
- IPSS-M
  - Median OS ranged from 4.6 years for the Very Low/Low group (95% CI, 3.4-NR) to 0.9 years for Very High (95% CI, 0.3-1.1) (Figure 3B).
  - IPSS-M demonstrated superior OS discrimination than IPSS-R (Harrell's C=0.77 versus 0.68).
  - Lack of *KMT2A*-PTD did not compromise this improvement, with probabilistic Harrell's C ranging from 0.74 to 0.77.
  - Among patients with lower-risk IPSS-R (Very Low/Low/Intermediate), 24% (17 of 71 patients) were reclassified as high-risk (High/Very High) by IPSS-M, and the reclassified cases had significantly worse OS (2 years OS 42% for IPSS-M high-risk versus 86% for low-risk; P<0.001) (Figure 4A).
  - Among patients with high-risk (High/Very High) IPSS-R, 8% (4 of 52 patients) were reclassified as low-risk (Very Low/Low/Moderate Low) by IPSS-M, and these patients had excellent prognosis (2y OS, 100% vs. 23%, *P*=0.002) (Figure 4B).

Conclusions

- Even using widely available NGS panels which do not identify *KMT2A*-PTD, IPSS-M showed higher prognostic accuracy than IPSS-R in our cohort.
- In cases of discrepant risk classification, IPSS-M significantly improved prognostic assessment, particularly for high-risk IPSS-R cases with a low-risk mutational profile.

Reference

Bernard, E., et al., Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. NEJM Evid, 2022. 1(7): p. EVIDoa2200008.