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Impact of the updated IPSS-molecular prognostic scoring system for myelodysplastic syndrome in 10,283 real world samples

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1. Introduction

The International Prognostic Scoring System-Molecular (IPSS-M) is a validated prognostic method that incorporates molecular information to improve risk stratification for patients with myelodysplastic syndromes (MDS). The IPSS-M is a weighted sum of prognostic variables consisting of clinical, cytogenetic, and somatic mutation information used to generate a patient-specific risk score and associated risk category assignment[1]. The IPSS-M updates the revised IPSS (IPSS-R) to include molecular information from up to 31 genes. To assess the impact of combining additional molecular data into MDS prognosis, we retrospectively analyzed 10283 real world samples from patients who had been sequenced with a commercially available targeted next-generation sequencing (NGS) panel to determine the number of patients whose risk stratification could potentially be altered by the IPSS-M.

2. Methods

Next-generation sequencing was performed on 10283 samples using a panel capable of detecting and reporting single nucleotide variants and small indels across 50 genes. The IPSS-M uses 19 binary molecular features incorporating somatic mutation information from 31 genes, 27 of which are targeted by the NGS panel used. Whole blood or bone marrow samples from patients with cause-for-testing for MDS or peripheral blood cytopenias were submitted for analysis by a clinician. DNA was extracted and assayed by the targeted, NGS panel and sequenced on Illumina DNA sequencers (Illumina, San Diego, CA). Results were reviewed, orthogonally confirmed unless previously validated, and reported by clinical laboratory directors. Disease status or symptoms were abstracted from test requisitions for each patient. *TP53* loss of heterozygosity and *KMT2A* partial tandem duplications (*MLL*^{PTD}) are molecular features in the IPSS-M but could not be assessed in this study. Cytogenetics, bone marrow blast counts, and complete blood count data (platelets (10^3/µL) and hemoglobin (g/dL)) necessary to calculate the IPSS-M was available for a subset of 1712 of 10283 samples. Absolute neutrophil count (10^3/µL) was available for 1359 of 1712 samples allowing the calculation of the IPSS-R[2]. Cytogenetics, bone marrow blast counts and CBCs were performed up to 90 days before and 14 days after the associated targeted sequencing analysis. Samples with bone marrow blast counts >20% were excluded. IPSS-M risk scores were calculated using the R package ipssm V1.0.0.

3. Conclusions

- 45.6% (4689/10283) of samples had molecular findings that could allow for further clinical risk stratification using IPSS-M.
- 546 of 1359 (40.2%) patients were reclassified to a different risk category based on IPSS-M compared to IPSS-R.
- These findings show the benefit of targeting a broad panel of genes using NGS for accurate MDS prognosis and patient risk stratification.

References

1. Bernard, E. *et al*. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. *NEJM Evid*. 1, EVIDoa2200008 (2022).
2. Greenberg, P. L. et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. *Blood* 120, 2454–2465 (2012).

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Tables + Figures

Table 1. IPSS-M weighted sum of prognostic variables

Table shows clinical, cytogenetic and molecular variables required for IPSS-M risk score calculations. Table adapted from Bernard, E. *et al*. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. NEJM Evid. 1, EVIDoa2200008 (2022).
**TP53* LOH, *MLL*^{PTD}, *ETNK1*, *GNB1*, *PPM1D* and *PRPF8* were not assessed in his study. The IPSS-M accounts for missing values and generates a risk score under the best, worst and mean scenarios.

Clinical and cytogenetic feature	IPSS-M model weight	Description
Bone marrow blasts (%)	0.070	
Platelet count (10^3/µL)	-0.0022	
Hemoglobin (g/dL)	-0.171	
IPSS-R cytogenetic category	0.287	
Molecular feature	**IPSS-M model weight**	**Description**
TP53^{mult}	1.18	2 or more *TP53* mutations including *TP53* LOH*
MLL^{PTD}*	0.798	
FLT3	0.798	Internal tandem duplicate or tyrosine kinase domain mutation
SF3B1^{5q}	0.504	Co-mutation with del(5q)
NPM1	0.43	
RUNX1	0.423	
NRAS	0.417	
ETV6	0.391	
IDH2	0.379	
CBL	0.295	
EZH2	0.27	
U2AF1	0.247	
SRSF2	0.239	
DNMT3A	0.221	
ASXL1	0.213	
KRAS	0.202	
SF3B1$^{\alpha}$	-0.0794	*SF3B1* without co-mutation with *BCOR, BCORL1, NRAS, RUNX1, SRSF2 or STAG2*
Gene residuals ("Nres")	0.231	2 or more of *BCOR, BCORL1, CEBPA, ETNK1*, GATA2, GNB1*, IDH1, NF1, PHF6, PPM1D*, PRPF8*, PTPN11, SETBP1, STAG2*, and *WT1*

Figure 1. Patient indications and IPSS-M molecular features assessed in 10283 samples

(A) Indications of patient samples. A total 10283 samples were analyzed including 43.1% (4437 of 10263) with an indication for MDS. Patients with MDS symptoms were defined as those with leukopenia, neutropenia, pancytopenia, and thrombocytopenia. **(B) Number of IPSS-M molecular features observed per patient**. 45.6% (4689/10283) of samples had at least one of 17 IPSS-M molecular features assessed by the targeted sequencing panel. The mean number of features observed was 0.82 with a range 0-6. **(C) Frequency of IPSS-M molecular features per patient.** In the IPSS-M, multiple mutations in *TP53* have the strongest negative effect and this feature was observed in 2.3% of patients (236/10283). *SF3B1-α*, which provides the strongest positive effect, was observed in 6.5% (666/10283) of patients. The most common features were *ASXL1* (15.3%, 1571/10283), *DNMT3A* (11.7%, 1204/10283) and *SRSF2* (10.0%, 1030/10283

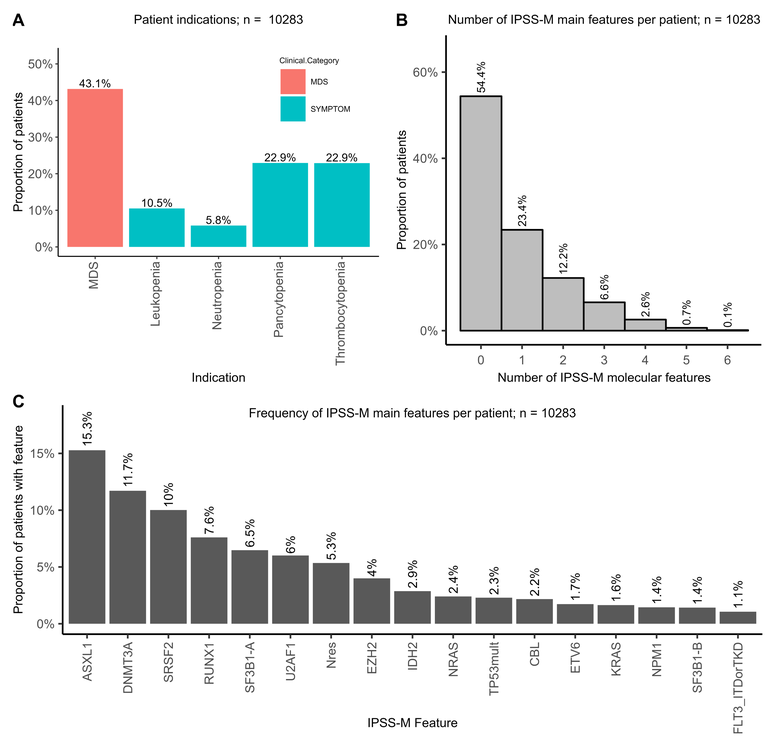
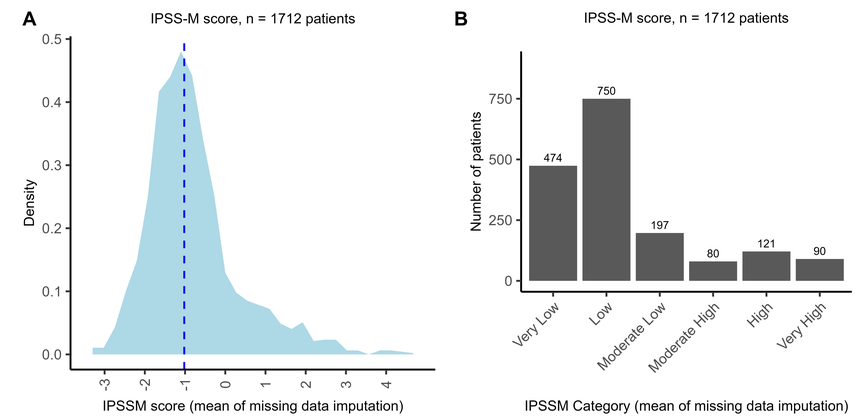


Figure 2. IPSS-M risk score and category for 1712 patient samples



Clinical, cytogenetic and molecular features necessary to calculate the IPSS-M were available for a subset of 1712 of the 10283 samples. 863 of 1712 (50.4%) had an indication of MDS. The median age was 72 years. (**A) Area plot of IPSS-M risk score**. Risk score plotted is the mean risk score for each patient taking into account missing values for *TP53* LOH, *MLL*^{PTD}, *ETNK1*, *GNB1*, *PPM1D* and *PRPF8*. Dashed blue line shows median IPSS-M risk score of-1.02. A risk score of 0 represents the average MDS patient suggesting the patients in this study have better outcomes than average. The median risk score was also lower than the published median risk score (-0.38) of the 2957 representative MDS patients used to build the IPSS-M model. Patients under 60 years (15.8%; 270/1712) had a better median IPSS-M risk score of-1.3 compared to-0.96 for those over 60 years (84.2%; 1442/1712). **(B) IPSS-M risk scores stratified into risk categories**. The average MDS patient is expected to show a "Moderate Low" or "Moderate High" risk category.

Figure 3. Re-stratification of 1359 patients from IPSS-R to IPSS-M

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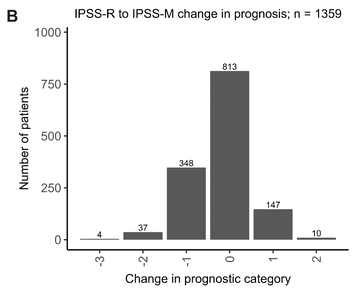
IPSS-R \ IPSS-M	Very Low	Low	Moderate Low	Moderate High	High	Very High
Very Low	333	232	20	4	4	0
Low	42	308	57	19	8	0
Intermediate	5	53	69	25	21	5
High	0	2	9	15	34	19
Very High	0	0	0	3	28	44



Clinical, cytogenetic and molecular features necessary to calculate both the IPSS-M and IPSS-R were available for a subset of 1359 of the 10283 samples. 645 of 1359 (47.5%) had an indication of MDS. **(A) Contingency table of IPSS-R risk category and corresponding IPSS-M risk category for 1359 patients**. IPSS-R category of "Intermediate" was encoded as "Moderate Low" or "Moderate High" for IPSS-M. 546 of 1359 (40.2%) patients were reclassified. **(B) Change in prognosis from IPSS-R to IPSS-M**. A negative change in prognostic category indicates a worse prognosis upon re-stratification. A positive change indicates an improved prognosis. 51 of 1359 (3.8%) showed a difference of at least 2 risk categories. Patients whose prognosis worsened by 2 or more categories had a mean number of 2.88 IPSS-M molecular features.