中文題目：以免疫表現計分系統預測骨髓化生不良症候群病人之預後

英文題目：An Immune Signature-Based Scoring System Could Independently Predict the Prognosis of Myelodysplastic Syndrome Patients

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**Background**: Myelodysplastic syndromes (MDS) are clonal myeloid malignancies arising from hematopoietic stem cells. The clinical features and outcomes of MDS patients vary considerably, underscoring the importance of identifying molecularly and clinically distinct subgroups. Recently, a comprehensive collection of 160 gene-sets used for an extensive immunogenomic analysis of more than 10,000 tumors comprising 33 diverse cancer types was reported. However, the clinical impact of the immune microenvironment on MDS patients are not well defined yet.

**Method:** To address this question, we used single-sample gene-set enrichment analysis (ssGSEA) to score our 176 MDS patients with available microarray expression profiles. We constructed an immune signature-based scoring system focusing on 93 gene-sets which comprise 3 or more genes and correlated the scores with clinical features and prognosis of the patients. The diagnosis of MDS was based on the 2016 World Health Organization (WHO) classification; we excluded the patients with antecedent chemotherapy or hematologic malignancies.

**Results:** Forty-one (23.3%) patients had MDS with single lineage dysplasia (MDS-SLD), 22 (12.5%) had MDS with ring sideroblasts (MDS-RS), 36 (20.5%) had MDS with multilineage dysplasia (MDS-MLD), 32 (18.2%) had MDS with excess blasts-1 (MDS-EB1) and 44 (25%), MDS-EB2. The risk distribution of the cohort was very-high risk, 15.9%; high risk, 19.9%; intermediate risk, 23.3%; low risk 30.7%; and very-low risk 3.4%, according to the revised international prognosis scoring system (IPSS-R). We identified 3 immune signature sets (CD103, dendritic cells [DC] and natural killer cells with bright CD56, [NK CD56+]) whose scoresexpression were significantly correlated with overall survival (OS). An **MI-3 score** (MDS-immune-3) (0.562 x CD103 - 0.343 x DC -0.451 x NK CD56+) was constructed based on the weighted sums derived from Cox regression analysis. Higher MI-3 scores were associated with higher IPSS-R scores, and higher incidences of mutations of *N-RAS, RUNX1, ASXL1, SETBP1,* and *TP53*. High-score patients had significantly shorter leukemia-free survival (LFS, median, 36.1 months vs not reached, P<0.001, Figure 1A), and shorter OS (median, 19.9 months vs 69.9 months, P<0.001, Figure 1B). In subgroup analysis, MI-3 score could also well stratify MDS patients with either normal karyotype or unfavorable cytogenetic changes into different risk groups ($p$<0.001 and $p$=0.01, respectively). The prognostic significance of MI-3 scores for leukemia-free survival (LFS), AML transformation rate, and OS remained valid in both IPSS-R lower-risk (very low, low, and intermediate risk) subgroup (Figures 2A and 2B) and higher-risk subgroup (high and very high risk). In multivariate analysis, higher MI-3 score was an independent adverse risk factor for OS, irrespective of age, IPSS-R, and mutation statuses of *EZH2, SRSF2, ASXL1, ZRSR2,* and *TP53* (Table). We also validated the prognostic significance of the MI-3 scores in an independent cohort of 30 MDS patients (Figures 3A and 3B). To further compare the power between MI-3 score and IPSS-R in prognostic prediction, the time-dependent ROC curves were estimated by the inverse probability of censoring weighting (IPCW) method. As illustrated in Figure 4, MI-3 score had even better performance to predict both OS and LFS than IPSS-R. Interestingly, patients with higher MI-3 scores had a better OS if they received allogeneic hematopoietic stem cell transplantation than those who did not, suggesting that transplantation might compensate the unfavorable survival impact of high MI-3 scores.

**Conclusion:** In conclusion, through comprehensive analysis, we have created a simple and powerful MI-3 scoring system. By taking the immune factors of MDS patients' bone marrow microenvironment into account, the scoring system could serve as an independent prognostic predictor for this disease.

Figure 1A. LFS in 176 patients stratified by MI-3 scores

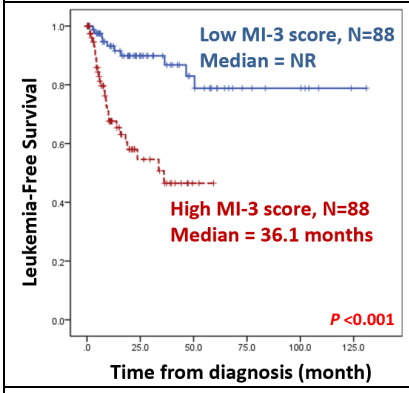



Figure 2A. LFS in IPSS-R lower-risk subgroup stratified by MI-3 score

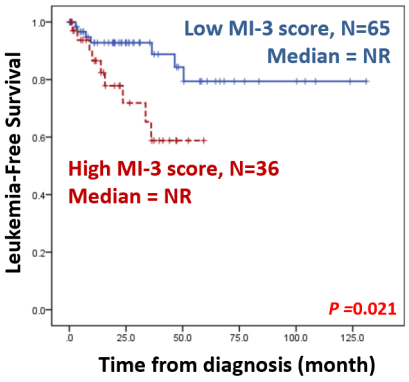



Figure 3A. LFS in validation cohort stratified by MI-3 score

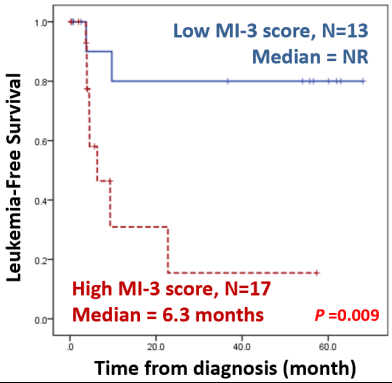



Figure 1B. OS in 176 patients stratified by MI-3 scores

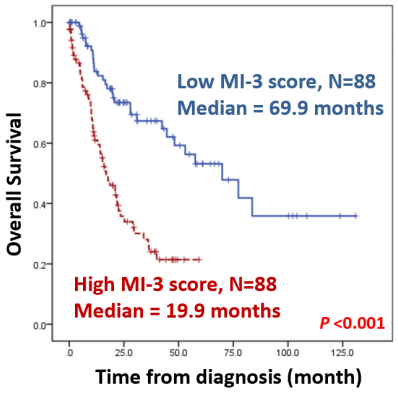



Figure 2B. OS in IPSS-R lower-risk subgroup stratified by MI-3 score

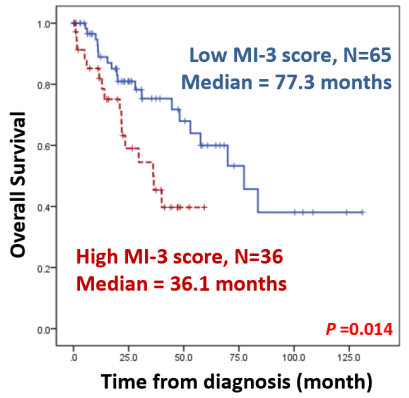



Figure 3B. OS in validation cohort stratified by MI-3 score

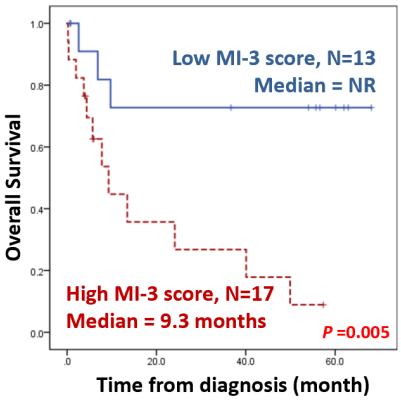
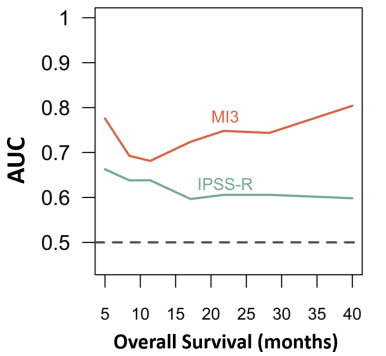



Figure 4. Time-dependent ROC curves showing MI-3 score had better predictive power for OS and LFS than IPSS-R



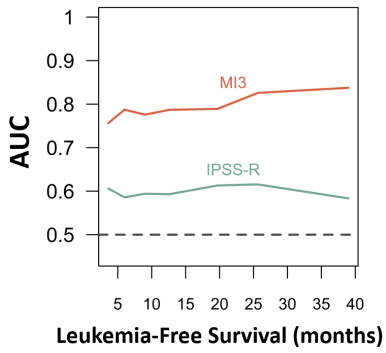




Table. Multivariable analysis for the OS in 164 MDS patients

| | OS | | | | LFS | | | |
|---|---|---|---|---|---|---|---|---|
| | | 95% CI | | | | 95% CI | | |
| Variable | OR | Lower | Upper | *P* | OR | Lower | Upper | *P* |
| Age[a] | 1.024 | 1.007 | 1.041 | **0.006** | 0.986 | 0.965 | 1.007 | 0.198 |
| IPSS-R[b] | 1.538 | 1.214 | 1.948 | **<0.001** | 1.596 | 1.135 | 2.244 | **0.007** |
| ***ASXL1*** | 1.180 | 0.548 | 2.542 | 0.673 | 3.854 | 1.541 | 9.636 | **0.004** |
| ***EZH2*** | 1.516 | 0.570 | 4.032 | 0.405 | 0.887 | 0.220 | 3.583 | 0.866 |
| ***SRSF2*** | 1.038 | 0.470 | 2.295 | 0.926 | 0.910 | 0.286 | 2.895 | 0.873 |
| ***TP53*** | 3.429 | 1.371 | 8.581 | **0.008** | 3.679 | 0.850 | 15.914 | 0.081 |
| ***ZRSR2*** | 1.417 | 0.673 | 2.983 | 0.359 | 0.602 | 0.179 | 2.018 | 0.411 |
| Higher MI-3 score[c] | 2.032 | 1.161 | 3.558 | **0.013** | 3.011 | 1.284 | 7.062 | **0.011** |

Abbreviations: RR, Relative Risk; CI, confidence interval.
*Statistically significant if *P*<0.05.
[a]Age, as a continuous variable
[b]IPSS-R lower-risk group (very low, low, intermediate) vs. higher-risk groups (high, very-high). Patients without chromosome data were not included in the analysis
[c]High vs. low MI-3 scores (median as cutoff)
[Note:] Only variables with P value less than or equal to 0.10 in univariate analysis were incorporated into the multivariate Cox proportional hazard regression analysis.