



## RESEARCH ARTICLE

# Distinctive Molecular Risk Factors Between MDS and MDS/AML Defined by ICC

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## ABSTRACT

Myelodysplastic syndromes/neoplasms (MDS) represent a heterogeneous group of clonal hematopoietic stem cell diseases with high risks of acute myeloid leukemia (AML) transformation. To emphasize the characteristics of AML transformation, the International Consensus Classification (ICC) has classified MDS with excess blasts (10%–19%) as MDS/AML. Recently, a clinical-molecular prognostic model International Prognostic Scoring System Molecular (IPSS-M) is developed, which improves the risk stratification of MDS. However, these molecular risk factors were analyzed in a cohort of highly heterogeneous patients with MDS including MDS/AML. Herein, we re-evaluated and compared the molecular risk factors in MDS (blasts <10%) and MDS/AML (blasts 10%–19%) defined by ICC. Notably, there is a significant difference in molecular landscape between MDS and MDS/AML. Importantly, most of the risk factors presented in MDS was not shown in MDS/AML except for TP53 aberrations and FLT3-ITD mutation. Since the IPSS-R and IPSS-M showed a poorly prognostic separation for MDS/AML patients, we further established a new prognostic model MDS/AML-IPSS-M and significantly improved its prognostic discrimination ability. Taking together, our research findings enhance the understanding of the molecular biology of MDS and can provide important guidance for the clinical identification of MDS/AML patients that might benefit clinical decision-making and therapeutic research.

Myelodysplastic syndromes/neoplasms (MDS) stand for a heterogeneous category of clonal hematopoietic stem cell diseases characterized by cytopenias, ineffective hematopoiesis, and high risks of transformation to acute myeloid leukemia (AML) [1, 2]. Naturally, approximately 30% of MDS patients, especially for high-risk MDS, will progress to AML over periods that vary from a few months to years [2]. In order to emphasize the characteristics of AML transformation in MDS, the International Consensus Classification (ICC) has classified MDS with excess blasts (10%–19%) as MDS/AML [3]. Identifying MDS patients at high risk of AML transformation

and providing intensive treatment could dramatically improve the clinical outcome of MDS. Recently, a clinical-molecular prognostic model, International Prognostic Scoring System Molecular (IPSS-M), was developed from 2957 patients with MDS profiled for mutations in 152 genes, which improves the risk stratification as well as AML transformation of MDS and designates a valuable tool for clinical decision-making [4]. However, these molecular risk factors were analyzed in a cohort of highly heterogeneous patients with MDS and myelodysplastic/myeloproliferative neoplasms overlap syndrome (MDS/MPN). Herein, we re-evaluated and compared the

**Abbreviations:** AML, acute myeloid leukemia; ICC, International Consensus Classification; IPSS-M, International Prognostic Scoring System molecular; LFS, leukemia free survival; MDS, myelodysplastic neoplasms/syndromes; MDS/MPN, myelodysplastic/myeloproliferative neoplasms; OS, overall survival; TCGA, The Cancer Genome Atlas.

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molecular risk factors in MDS (blasts <10%) and MDS/AML (blasts 10%–19%) defined by ICC.

The current study included 2421 MDS patients derived from cBioPortal datasets (<https://www.cbioportal.org/datasets>). Notably, patients diagnosed with MDS/MPN or MDS-RAEBt as well as MDS/AML with *NPM1* or *CEBPA* mutations were excluded. Clinical/laboratory features such as blood counts, blasts, karyotypic and molecular information, treatment, and survival of these patients were annotated [4]. A total of 52 MDS/AML patients from the Affiliated People's Hospital of Jiangsu University was also included as a validation cohort. Clinical/laboratory characteristics of these patients were given in Table S1. Targeted deep sequencing was performed on panels for myeloid neoplasms. Treatment for these patients was chemotherapy or hypomethylation agent-based regimen with and without allogeneic hematopoietic stem cell transplantation showed Table S1.

The total patients were reclassified as MDS ( $n = 2028$ ) and MDS/AML ( $n = 374$ ) based on ICC. Clinical and pathological features of these patients are summarized in Table S2. The most frequently mutated genes (mutation frequency over 10%) in MDS were *TET2* (30.2%), *SF3B1* (26.5%), *ASXL1* (24.9%), *SRSF2* (13.2%), *RUNX1* (11.2%), and *TP53* (10.7%), whereas gene mutation frequency over 10% in MDS/AML was *ASXL1* (31.6%), *TP53* (24.9%), *STAG2* (22.2%), *RUNX1* (21.7%), *TET2* (20.9%), *SRSF2* (20.9%), *SF3B1* (11.0%), and *BCOR* (10.7%) (Figure 1).

To compare the molecular risk factors between MDS and MDS/AML, the impact of the genetic mutations detected over 1% of the total population on overall survival (OS) and leukemia free survival (LFS) was evaluated by Cox regression analysis. Firstly, the univariate analysis was performed to screen the risk factors among clinical features (IPSS-R and age) and genetic mutations in MDS and MDS/AML patients for the two clinical end points, and presented in Tables S3 and S4. We next conducted multivariate analysis to identify independent molecular risk factors correlated with the two clinical end points in MDS and MDS/AML patients. Adjusting for age and IPSS-R, mutations in *ASXL1*, *RUNX1*, monoallelic *TP53* (*TP53*<sup>mono</sup>), biallelic *TP53* (*TP53*<sup>bi</sup>), *STAG2*, *U2AF1*, *NF1*, *NRAS*, *MGA*, *MLL-PTD*, *NOTCH2*, *WT1*, *PPM1D*, *RAD21*, *GNB1*, *EZH2*, and *FLT3-ITD* served as independent risk factors for OS in MDS patients, whereas *TP53*<sup>mono</sup>, *TP53*<sup>bi</sup>, *NOTCH1*, *DDX41*, *SMG1*, *ATRX*, *FLT3-ITD*, *KDM5C*, and *SH2B3* mutations acted as independent risk factors for OS in MDS/AML patients (Table S5). Moreover, the independent molecular risk factors for LFS between MDS and MDS/AML were presented in Table S6.

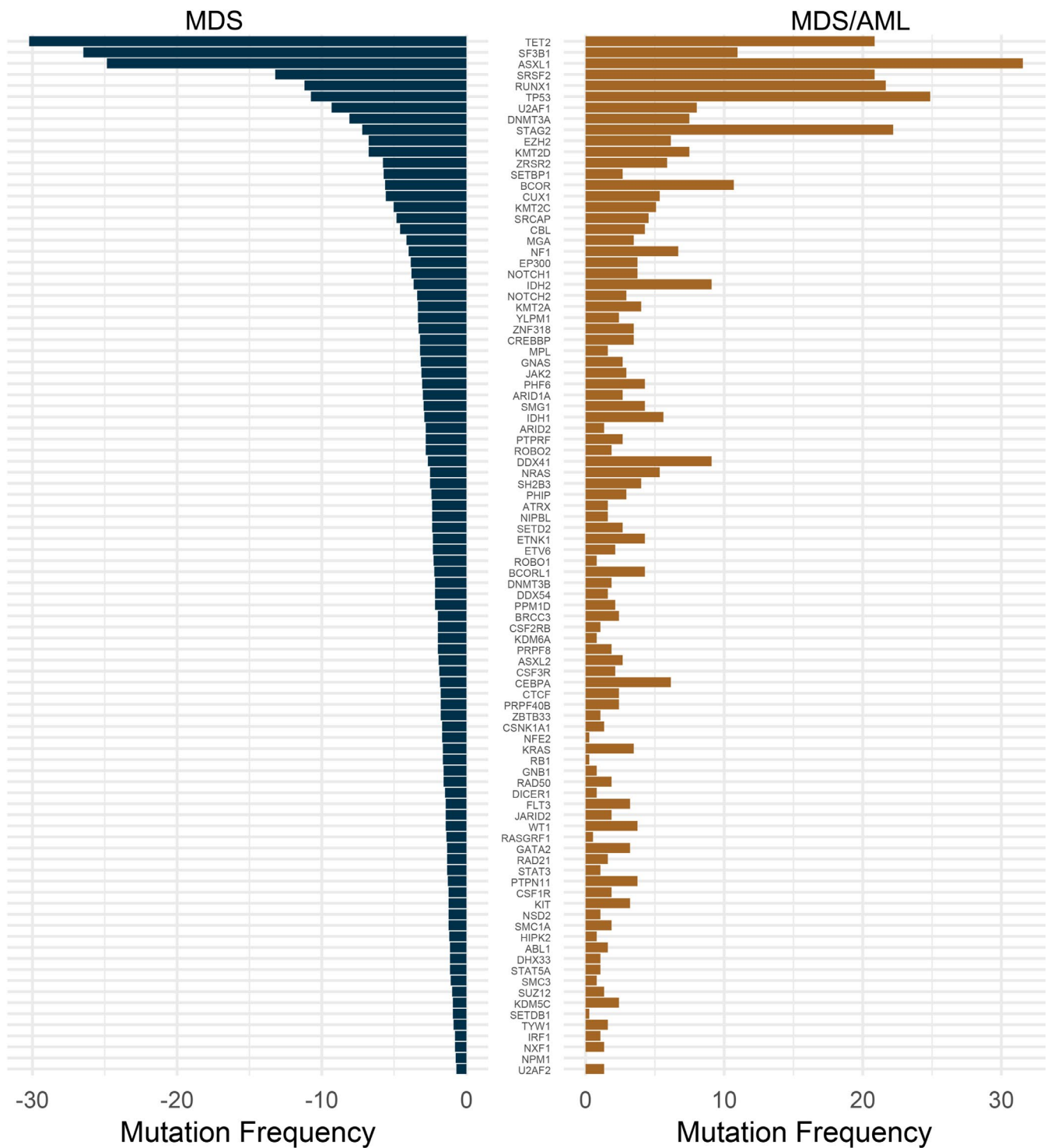
Since the distinctive molecular risk factors between MDS and MDS/AML, we re-evaluated the IPSS-R and IPSS-M in risk stratification of MDS and MDS/AML respectively. Although the IPSS-R and IPSS-M still presented a strongly prognostic separation in MDS patients, it showed a poorly prognostic discrimination for MDS/AML patients (Figure S1). Therefore, we established a new prognostic model for MDS/AML on the basis of a linear combination of these gene mutation multiplied by a regression coefficient ( $\beta$ ) derived from the multivariate Cox regression model of each gene. The prognostic risk score model was calculated by the following formula: Risk score =  $0.403 \times \text{IPSS-R} + 0.634 \times \text{TP53}^{\text{mono}} + 1.102 \times \text{TP53}^{\text{bi}} - 0.676 \times$

$\text{DDX41} + 1.753 \times \text{FLT3-ITD}$  (namely as MDS/AML-IPSS-M, If the gene was mutated defined as 1, if not defined as 0). According to the risk score, we divided the MDS/AML patients into four groups (Risk score  $\leq 0.5$ : Low;  $0.5 < \text{Risk score} \leq 1$ : Low-Intermediate;  $1 < \text{Risk score} \leq 1.5$ : High-Intermediate; Risk score  $> 1.5$ : High). By Kaplan–Meier analysis, the above risk categories resulted in improved prognostic discrimination across all risk groups in MDS/AML (Figure 2a,b), superior to both IPSS-R and IPSS-M (Figure 2c,d). Moreover, we applied the MDS/AML-IPSS-M to an independent cohort of 52 patients with MDS/AML from our institution. As expected, the MDS/AML-IPSS-M risk categories resulted in clearly separated OS time in patients with MDS/AML (Figure 2e), whereas IPSS-R and IPSS-M showed a poorly prognostic discrimination (Figure S2).

Based on the findings that there is no remarkable difference on OS and event free survival between AML and MDS with excess blasts (10%–19%) according to the 2016 WHO classification [5], an innovative change in the 2022 ICC is the segregation of MDS/AML from MDS. The importance of the introduction of this new subtype was elucidated based on the observation that MDS/AML patients had distinct clinical characteristics, genomic landscapes, and poor outcomes compared to patients with a blast percentage of <10% [6]. Herein, we focused on the mutational differences, and revealed the distinctive molecular risks between the MDS and MDS/AML. Although the previous study did not reveal the molecular risks for MDS and MDS/AML respectively, they observed that MDS/AML patients more frequently harbored *ASXL1*, *BCOR*, *RUNX1*, *SRSF2*, *STAG2*, and *TP53* mutations in accordance with our study [6]. Moreover, they also showed that patients with MDS/AML showed a higher mutation burden than those with MDS [6].

A number of studies have validated the prognostic accuracy of the IPSS-M in patients with MDS [7–10], even in MDS redefined by ICC [11]. However, the performance of IPSS-M in MDS/AML remains poorly determined. Although Huber et al. reveal that the IPSS-M is superior to AML European LeukemiaNet risk classification in MDS/AML overlap patients defined by ICC [12], it did not show strong prognostic discrimination for MDS/AML patients. Moreover, Kwag et al. also report a poor performance of IPSS-M risk stratification in MDS-IB2 defined by WHO2022 [13]. In our study, as far as we know, we for the first time established and validated a new prognostic model for MDS/AML with strong prognostic discrimination power. Eventually, the classification and separation of MDS/AML patients may let these poor-risk patients receive more intensive treatments and have more chances to be enrolled in clinical trials to improve their outcomes.

Notably, the prognostic model incorporates the *DDX41* mutation, which is likely a germline mutation and characterized by unique clinical-molecular characteristics and prognosis. Although a recent work shows that current prognostic tools (IPSS-R/M and ELN 2017/22) are not able to adequately assess leukemic evolution and survival outcomes in *DDX41*-mutant myeloid neoplasia [14], several studies have reported higher response rates with favorable outcomes in MDS, especially treated with an azacitidine-based regimen [15, 16]. In this study, we also demonstrated *DDX41* mutations as a slightly beneficial mutated gene, in accordance with previous studies. Thus, we included

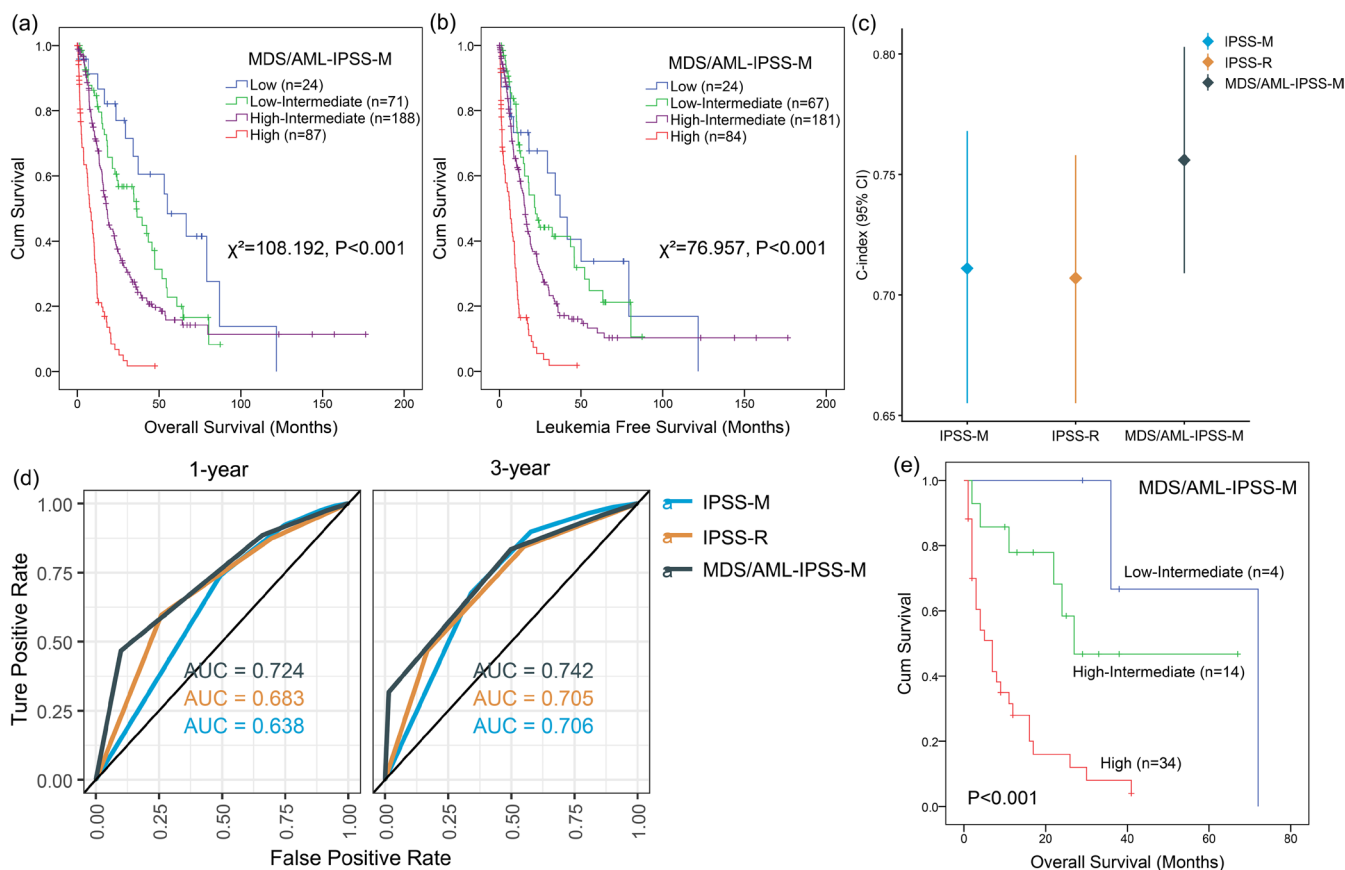


**FIGURE 1** | Comparison of mutation frequencies between MDS and MDS/AML. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ajh.70296)]

*DDX41* mutation in the MDS/AML-IPSS-M model and showed better prognostic separation than that without *DDX41* mutation. Certainly, a larger cohort of MDS patients harboring *DDX41* mutations is required to validate our model.

It should also be noted that this study has several limitations. First, the sample size of the validation cohort is relatively small, which may compromise the statistical power and generalizability of the findings. Second, this is a single-center study; thus, the

results may not be directly applicable to other clinical settings with different patient populations and practice patterns. Third, elderly patients with higher IPSS-R/IPSS-M risks account for a predominant proportion of the enrolled subjects, leading to a potential selection bias and limiting the extrapolation of the conclusions to total groups. These limitations should be taken into consideration when interpreting the study results, and future multicenter research with larger, more age-diverse validation cohorts is warranted to verify and expand on the present findings.



**FIGURE 2** | Construction and validation of a new prognostic model for MDS/AML. (a) Kaplan–Meier probability estimate of leukemia free survival (LFS) is presented across MDS/AML-IPSS-M risk categories. (b) Kaplan–Meier probability estimate of overall survival (OS) is presented across MDS/AML-IPSS-M risk categories. (c) C-index hazard ratios are provided for the MDS/AML-IPSS-M risk categories compared with that for IPSS-R and IPSS-M risk categories. (d) Time-dependent ROC curves of the MDS/AML-IPSS-M for 1-, 3-, and 5-year OS compared with that for IPSS-R and IPSS-M. (e) Validation of the MDS/AML-IPSS-M risk categories in MDS/AML from our research center. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

Taking together, our research findings enhance the understanding of the molecular biology of MDS and can provide important guidance for the clinical identification of MDS/AML patients that might benefit clinical decision-making and therapeutic research.

#### Author Contributions

**T.Z.:** data curation, formal analysis, investigation, methodology, funding acquisition, writing – original draft. **Y.Z.:** data curation, formal analysis, investigation, methodology. **Z.X.:** formal analysis, software. **J.Q.:** data curation, resources, funding acquisition. **J.Z.:** conceptualization, methodology, funding acquisition, validation, writing – review and editing. All authors have read and agreed to the published version of the manuscript.

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#### Ethics Statement

The present study was approved by the Ethics Committee of the Affiliated People's Hospital of Jiangsu University. The procedures used are consistent with the principles of the Helsinki Declaration.

#### Consent

Written informed consents were obtained from all enrolled individuals prior to their participation.

#### Conflicts of Interest

The authors declare no conflicts of interest.

#### Data Availability Statement

Data is provided within the manuscript or [Supporting Information](#) files.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Kaplan–Meier probability estimates of overall survival and leukemia free survival are presented across IPSS-R and IPSS-M risk categories among MDS and MDS/AML. **Figure S2:** Kaplan–Meier probability estimates of overall survival are presented across IPSS-R and IPSS-M risk categories in MDS/AML of validation cohort. **Table S1:** Clinic-pathologic characteristics of MDS/AML patients in validation cohort. **Table S2:** Clinic-pathologic characteristics of MDS and MDS/AML patients. **Table S3:** Comparative of molecular risk factors for overall survival between MDS and MDS/

AML evaluated by Cox regression univariate analysis. **Table S4:** Comparative of the molecular risk factors for leukemia free survival between MDS and MDS/AML evaluated by Cox regression univariate analysis. **Table S5:** Comparative of the molecular risk factors for overall survival between MDS and MDS/AML evaluated by Cox regression multivariate analysis. **Table S6:** Comparative of the molecular risk factors for leukemia-free survival between MDS and MDS/AML evaluated by Cox regression multivariate analysis.