Rapid Communication

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Comparison of the Molecular International Prognostic Scoring System (IPSS-M) and Revised International Prognostic Scoring System (IPSS-R) in predicting the prognosis of patients with myelodysplastic neoplasms treated with decitabine

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Abstract

Background: Molecular International Prognostic Scoring System (IPSS-M) is a newly developed prognostic model for myelodysplastic neoplasms (MDS), but has not yet been used widely. In this study, we aimed to compare the IPSS-M with the traditional Revised International Prognostic Scoring System (IPSS-R) in predicting the prognosis of decitabine treated-MDS patients.

Patients and methods: This retrospective cohort study was conducted on 19 newly diagnosed MDS patients who were examined for 51 gene mutations and received decitabine treatment. The survival analysis, including overall survival (OS), progression-free survival (PFS), and leukemia-free survival (LFS), was performed using the Kaplan–Meier method. Comparisons between the risk groups were carried out according to the IPSS-R and IPSS-M models.

Results: Among the 19 MDS patients, 12 (63.2 %) showed myeloid gene mutations, with the highest frequency of mutations in *ASXL1*, *RUNX1*, *SRSF2*, *TET2*, and *TP53* (15.8 %). Survival analysis found that the OS was significantly different between the risk groups of both IPSS-R and IPSS-M models, but the PFS and LFS showed significant differences between the risk groups in only the IPSS-M model. The PFS of the moderate, high, and very high-risk groups were 34.66, 25.00, and 15.33 months (p=0.031); respectively. The LFS of the moderate, high, and very high-risk groups were 39.20, 25.00, and 18.37 months, (p=0.039); respectively.

Conclusions: Our results found that IPSS-M was better than IPSS-R in predicting the PFS and LFS of decitabine-treated MDS patients, IPSS-M may be superior to IPSS-R in predicting the prognosis of MDS patients.

Keywords: myelodysplastic neoplasms (MDS); Molecular International Prognostic Scoring System (IPSS-M); prognosis; progression-free survival (PFS); leukemia-free survival (LFS); decitabine

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Introduction

Myelodysplastic neoplasms (MDS), previously named myelodysplastic syndromes, are a heterogeneous group of hematopoietic clonal disorders characterized by ineffective hematopoiesis, cytopenia, bone marrow dysplasia, and an increased risk of leukemic transformation [1]. According to the 2022 World Health Organization (WHO) criteria, 'myelodysplastic syndromes' was renamed 'myelodysplastic neoplasms' (MDS) to emphasize the neoplastic

nature, as well as the ability to transform into acute myeloid leukemia [2]. In addition, WHO 2022 proposed a new classification system, which classified MDS into two groups based on genetic and morphological abnormalities. This reclassification system aimed to emphasize the importance of genetic factors in hematopoietic clonal disorders [2]. These changes in terminology and the classification system have raised the question of whether a prognostic system like the Revised International Prognostic Scoring System (IPSS-R), which is based only on morphology and cytogenetics, is sufficient for predicting the prognosis of MDS patients.

Many studies have been conducted on the role of myeloid gene mutations in the prognosis of MDS [3–6]. Based on the association between myeloid gene mutations and MDS prognosis, a new prognostic model Molecular International Prognostic Scoring System (IPSS-M) has been proposed, which combines the traditional IPSS-R with molecular data (31 genes) [7]. A few studies have investigated the superiority of the IPSS-M model compared to the IPSS-R model [8–14]; however, a complete consensus has not yet been reached. Baer et al. evaluated the importance of individual genes in the IPSS-M for risk prediction [12]. Zamanillo et al. and Aguirre et al. confirmed that the IPSS-M model can be used for therapeutic decision-making [8, 9]. Maurya et al. and Sabile et al. found that the IPSS-M model is superior in stratifying patients than the IPSS-R model [10, 11]. In contrast, Wu et al. suggested that the IPSS-M model is better than the IPSS-R model only in classifying patients aged ≥60 years [13]. Sauta et al. found that the IPSS-M model showed a significant improvement in predicting the overall survival (OS) and leukemia-free survival (LFS) of post-transplant patients, but not of hypomethylating agent (HMA)-treated patients [14].

However, the screening of 31 genes makes the application of the IPSS-M model more complicated, especially due to the lack of consensus over its superiority over the IPSS-R model. In this study, we aimed to compare the IPSS-M model with the traditional IPSS-R model in predicting the prognosis of MDS patients treated with decitabine (an HMA).

Materials and methods

Patients

The retrospective cohort study was conducted at the National Institute of Hematology and Blood Transfusion (NIHBT, Hanoi, Vietnam). All the newly diagnosed MDS patients who were treated with decitabine from January 2018 to June 2021 were enrolled in the study. The Review Board of the NIHBT approved the study (no. 939/QĐ-HHTM) and waived informed consent as it was a retrospective observational study. All the patient records were de-identified to protect patient privacy.

Cytogenetic and gene mutation analysis

We analyzed the bone marrow samples of the MDS patients obtained at the time of diagnosis. The karyotypes were determined based on the results of G-band staining. Fluorescence *in situ* hybridization was used to detect del(5q). Next-generation sequencing was performed to detect the 51 myeloid gene mutations, including mutations in the DNA methylation, chromatin modification, RNA splicing, cohesin complex, transcription, cytokine receptor/tyrosine kinase, RAS signaling, checkpoint/cell cycle, and DNA repair gene groups. Although there were 51 gene mutations were tested, 7 of the 31 genes listed by IPSS-M were lacking. They were *BCORL1*, *ETKN1*, *GNB1*, *PHF6*, *PPM1D*, *PRPF8*, and MLL^{PTD}.

Treatment

The patients received a 3 h infusion of 15 mg/m^2 decitabine every 8 h for 3 consecutive days. Patients received 4 to 9 treatment cycles, and each cycle was repeated every 6 weeks.

Definition

MDS diagnosis was conducted according to the newly proposed minimal diagnostic criteria for MDS [15], and MDS classification was based on the 2022 WHO criteria [2]. Risk stratification was conducted according to the IPSS-R and IPSS-M models [7, 16, 17]. The OS was calculated from the time of diagnosis to death or the last follow-up. The progression-free survival (PFS) was calculated from the start of treatment to relapse or death, whichever happened first. The LFS was calculated from the beginning of treatment to leukemic transformation.

Statistical analysis

The IPSS-R and IPSS-M were scored in all patients. Survival analyses, including the OS, PFS, and LFS, were performed using the Kaplan–Meier method. Comparisons between the IPSS-R and IPSS-M risk groups were carried out. The $p^{Log\text{-}rank}$ value<0.05 was considered statistically significant. Statistical analysis was performed using SPSS 25 software.

Bias was controlled because there was no missing data. Our study conforms to the STROBE guidelines [18].

Results

Patient characteristics

A total of 19 patients were retrospectively analyzed in this study. Among these, 12 were male (63.2 %) and 7 were female (36.8 %) with a median age of 64 years (28–81 years). According to the WHO 2022 criteria, the majority of patients (n=10; 52.6 %) were classified into MDS-IB1 type, while only one patient (5.3 %) was diagnosed with MDS-bi *TP53*, the rest were classified into MDS-IB2 (n=8; 42.1 %), (Table 1). The results of the cytogenetic analysis and the cell indices are presented in Table 1.

Table 1: Patients' characteristics.

Classification		n, %
MDS subtypes (n, %)	MDS-bi *TP53*	1 (5.3 %)
	MDS-IB1	10 (52.6 %)
	MDS-IB2	8 (42.1 %)
Cytogenetics category (n, %)	Very good	0 (0 %)
	Good	15 (78.9 %)
	Intermediate	0 (0 %)
	Poor	2 (10.5 %)
	Very poor	2 (10.5 %)
IPSS-R (n, %)	Very low	0 (0 %)
	Low	0 (0 %)
	Intermediate	6 (31.6 %)
	High	10 (52.6 %)
	Very high	3 (15.8 %)
IPSS-M (n, %)	Very low	0 (0 %)
	Low	0 (0 %)
	Moderate low	3 (15.8 %)
	Moderate high	7 (36.8 %)
	High	5 (26.3 %)
	Very high	4 (21.1 %)

Cell indices	Mean	Min–max
Hemoglobin, g/L	82.58	47–105
Total neutrophil count, $\times 10^9$/L	2.21	0.11–18.86
Platelet count, $\times 10^9$/L	145.47	15–472
Peripheral blood blast, %	4.47	0–18
Total bone marrow cell count, $\times 10^9$/L	74.25	5.8–448
Bone marrow blast, %	9.79	5–17

Gene mutation analysis

In this study, we detected a total of 14 myeloid gene mutations in MDS patients. Among the 19 MDS patients, 12 (63.2 %) showed myeloid gene mutations, with the number of mutations ranging between 1 and 7 per patient with a mean value of 2.5. The highest frequency of mutations was observed in the following genes: *ASXL1*, *RUNX1*, *SRSF2*, *TET2*, *TP53* (15.8 %), (Table 2).

Risk stratification

The IPSS-R model classified 31.6 , 52.6, and 15.8 % of the MDS patients into intermediate, high, and very high-risk groups; respectively. In contrast, the IPSS-M model reclassified 15.8, 36.8, 26.3, and 21.1 % of the MDS patients into moderate low, moderate high, high, and very high-risk groups; respectively (Table 1).

Table 2: Frequency of gene mutations in MDS patients.

Pathway/function	Gene	n, %
Chromatin modification	*ASXL1*	3 (15.8)
Cohesin complex	*STAG2*	2 (10.5)
Transcription	*RUNX1*	3 (15.8)
	BCOR	2 (10.5)
RNA splicing	*SF3B1*	2 (10.5)
	SRSF2	3 (15.8)
	U2AF1	1 (5.3)
DNA methylation	*TET2*	3 (15.8)
	IDH2	2 (10.5)
	DNMT3A	2 (10.5)
Cytokine receptor/tyrosine kinase	*CSF3R*	1 (5.3)
	KIT	1 (5.3)
RAS signaling	*NRAS*	2 (10.5)
Checkpoint/cell cycle	*TP53*	3 (15.8)

Survival analysis

The OS analysis showed a significant difference between the risk groups in both the IPSS-R and IPSS-M categories. There was a significant difference between the intermediate, high, and very high-risk groups of the IPSS-R model and the moderate, high, and very high-risk groups of the IPSS-M model (p=0.005 and 0.043; respectively). This difference was more clearly observed between the very high-risk group and the remaining groups (Table 3). However, the PFS and LFS analysis found a significant difference between the risk groups in only the IPSS-M category. The PFS of the moderate, high, and very high-risk groups were 34.66, 25.00, and 15.33 months (p=0.031); respectively. The LFS of the moderate, high, and very high-risk groups were 39.20, 25.00, and 18.37 months, (p=0.039); respectively, (Table 4; Figures 1 and 2).

Discussion

Since its proposal in 2012, IPSS-R has become the primarily used prognostic system for MDS patients. It has also been used for therapeutic decision-making for MDS patients of different risk groups. For instance, the provision of supportive care and erythropoiesis-stimulating agents for low-risk patients (including very-low and low), HMA for high-risk patients (including high and very high), and varying treatments (erythropoiesis-stimulating agents or HMA) for intermediate-risk patients based on their status

Table 3: OS according to IPSS-R and IPSS-M.

Risk		n	Months	p-Value	Risk		n	p-Value
IPSS-R	Intermediate + high	16	36.50	**0.002**	IPSS-R	Intermediate	6	**0.005**
	Very high	3	12.00			High	10	
						Very high	3	
IPSS-M	Moderate + high	15	38.19	**0.016**	IPSS-M	Moderate (low and high)	10	**0.043**
	Very high	4	20.50			High	5	
						Very high	4	

Bold values represent values <0.05.

Table 4: PFS and LFS according to IPSS-R and IPSS-M.

Risk		n	PFS		LFS	
			Months	p-Value	Months	p-Value
IPSS-R	Intermediate	6	25.50	0.368	27.83	0.211
	High	10	32.74		39.30	
	Very high	3	12.00		13.00	
IPSS-M	Moderate (low and high)	10	34.66	**0.031**	39.20	**0.039**
	High	5	25.00		25.00	
	Very high	4	15.33		18.37	

Bold values represent values <0.05.

[16, 17, 19]. However, MDS pathogenesis is associated with genetic mutations [20], and with the development of genetic techniques, it is vital to add molecular data to the prognostic system. Some studies that supported this improvement [8–11]. In addition, there are still some opinions that need further consideration. Since the IPSS-M online calculator can still assess risk even if data of some gene mutations are missing, it is not clear if it is essential to identify all 31 genes. Baer et al. suggested that *TP53*, $FLT3^{ITD}$, and $KMT2A^{PTD}$ (MLL^{PTD}) mutations are especially necessary for risk stratification in MDS patients [12]. However, in a study by Wu et al. $KMT2A^{PTD}$ (MLL^{PTD}) mutation was not detected in 852 MDS patients [13]. Therefore, in this study, we did not include $KMT2A^{PTD}$ (MLL^{PTD}), similar to the study by Zamanillo et al. [8]. Sauta et al. defined a minimum set of 15 essential genes for IPSS-M classification [14]. Therefore, the selection of genes to evaluate IPSS-M must be considered for their high efficiency and cost savings.

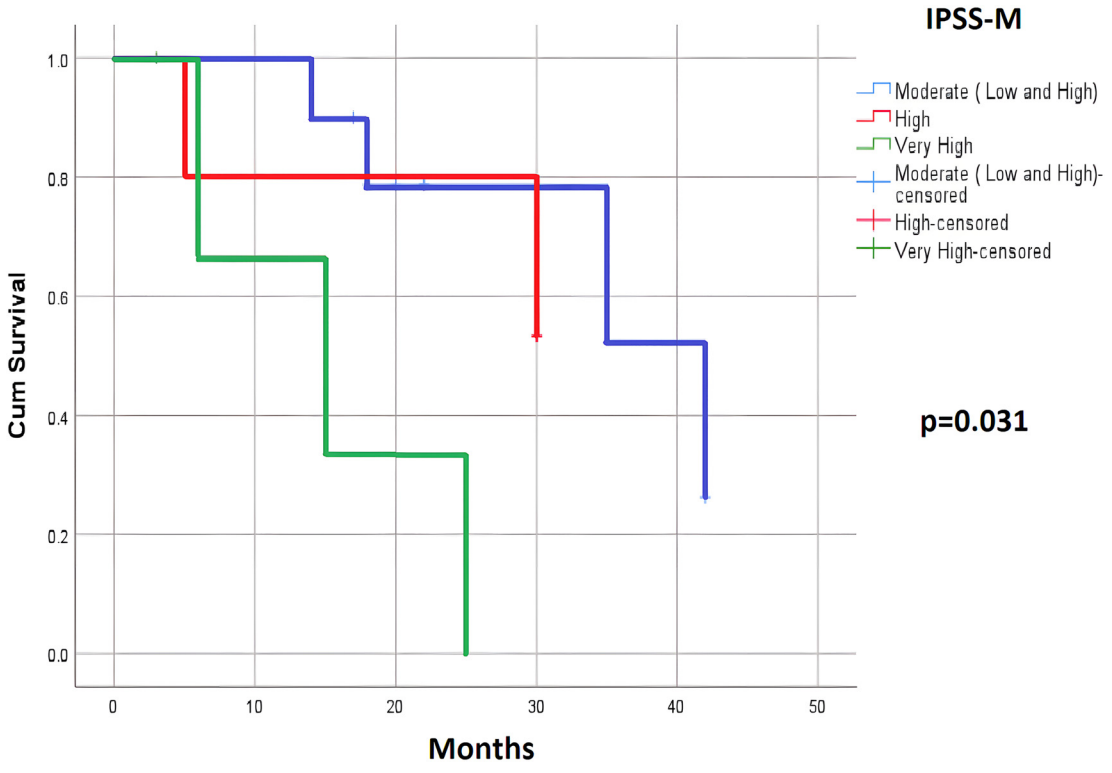

Figure 1: PFS according to the IPSS-M.

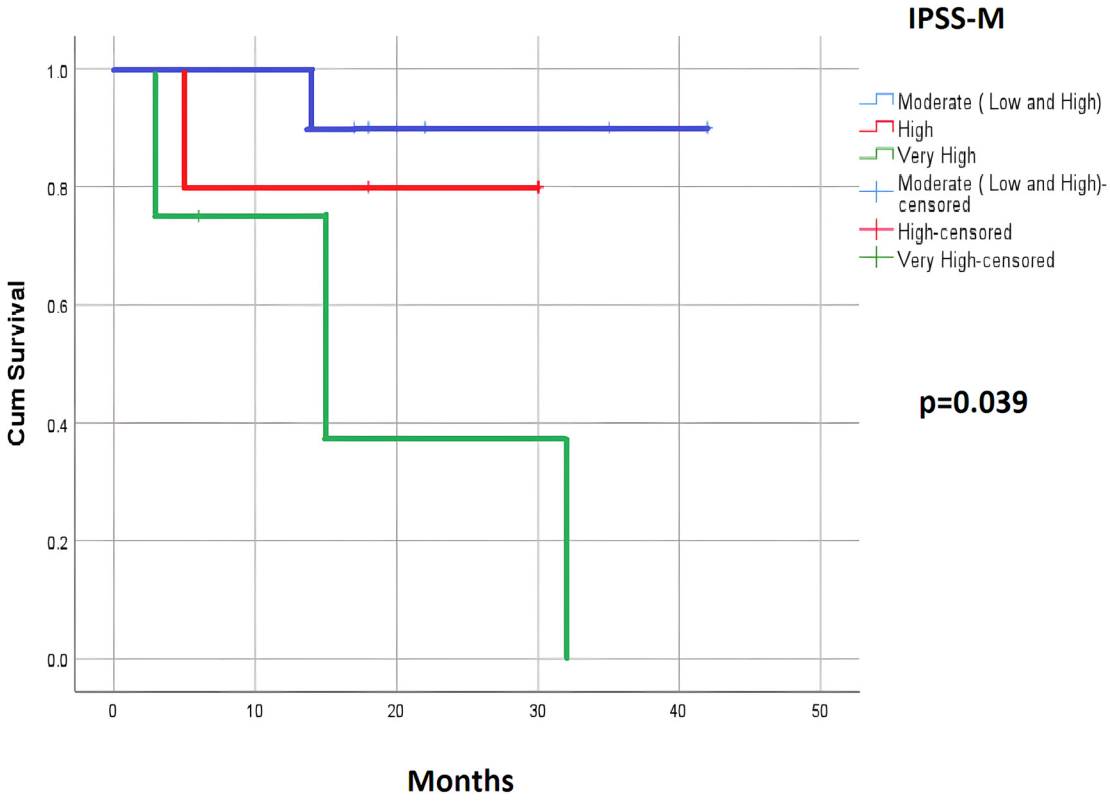

Figure 2: LFS according to the IPSS-M.

Wu et al. found that the IPSS-M was superior to the IPSS-R in the classification of MDS patients aged ≥60 years [13]. Wu et al. also suggested that the distinctive genetic factors of ethnic specificities affected the accuracy of IPSS-M risk categories [13]. Several studies showed that cytogenetic characteristics are associated with ethnicity [21–24]. However, there are no studies on the frequency of myeloid gene mutations according to ethnic groups.

Sauta et al. suggested that IPSS-M improves MDS stratification and may be more effective in allotransplantation choice; however, IPSS-M could not effectively predict the prognosis of HMA-treated patients [14]. This may be attributed to the effect of HMA on some key genes in the DNA methylation group, such as *DNMT3A* and *TET2*. In contrast to the results reported by Sauta et al., our study found that compared to IPSS-R, IPSS-M could effectively predict the PFS and LFS of MDS patients treated with decitabine. In general, studies support the superiority of IPSS-M over IPSS-R; however, there are some inconsistencies between the target groups.

Some of the limitations of our study are that this was a small-scale study with a limited number of patients, and we presented an initial report of our analysis as a short communication. Therefore, further analysis is required on the IPSS-M based on the age, ethnicity, and treatment regimen of the patients, as well as the cost-effectiveness.

Conclusions

Our study found that compared to IPSS-R, IPSS-M could predict the PFS and LFS of decitabine-treated MDS patients more accurately, IPSS-M may be a better prognostic system than IPSS-R for predicting the prognosis of MDS patients.

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Research ethics: The Review Board of the NIHBT approved the study (no. 939/QĐ-HHTM) and waived informed consent as it was a retrospective observational study.

Informed consent: The Review Board of the NIHBT waived informed consent as it was a retrospective observational study.

Author contributions: Minh Phuong Vu and Quang Hao Nguyen conceived the study. Minh Phuong Vu and Quang

Hao Nguyen designed the study. Quang Hao Nguyen, Tuan Anh Tran, Quoc Chinh Duong and Duc Binh Vu participated in data collection and processing. Minh Phuong Vu, Quang Hao Nguyen, Tuan Anh Tran, Quoc Chinh Duong, Duc Binh Vu, Ha Thanh Nguyen and Quoc Khanh Bach participated in data analysis and interpretation, as well as in the literature search, wrote the manuscript. All authors have read and approved the final manuscript.

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Data availability: Data can be obtained from the corresponding author upon resonable request.

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