Artificial intelligence-based Myelodysplastic Syndromes Score, 2022 classifications, and the Molecular International Prognostic Scoring System: a perfect match

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid neoplasms, characterized by ineffective hematopoiesis leading to cytopenias, dysplastic features in bone marrow and by progression to acute myeloid leukemia in about a third of patients.[1] The latest World Health Organization (WHO) classification and International Consensus Classification (ICC) have confirmed the importance of molecular biology in characterizing these diseases, particularly MDS with *SF3B1* and *TP53* mutations.[2,3] As the course of these diseases is very diverse, it is essential to stratify patients, and the International Prognostic Scoring System-Revised (IPSS-R) classification was used for more than a decade.[4] However, this classification only took into account hematological and cytogenetic data without formally integrating molecular biology, which have since shown its importance in understanding the pathophysiology of MDS but also in assessing prognosis.[5,6] This oversight was rectified and in 2022 the IPSS-molecular (IPSS-M) was published, based on an initial cohort of 2,957 patients and then validated on an external cohort of 754 patients.[7] Briefly, this score uses hematological parameters, cytogenetic abnormalities and somatic mutations in 31 genes to classify patients into six risk categories. However, this score does not include flow cytometry data. The role of multiparametric flow cytometry (MFC) in the diagnosis of MDS is not clearly defined. Several scores have been previously defined like the Ogata score focusing on progenitor cells or the RED score analyzing nucleated red blood cells[8,9] but the use of these different tools is limited by the lack of standardization. Previously, we published an article in Haematologica on the use of artificial intelligence (AI) on flow cytometry data to improve the diagnosis of MDS.[10] After selecting the most relevant parameters using a Boruta algorithm on a cohort of 191 patients, we developed a score, thanks to an Elasticnet model, that greatly improved the sensitivity of the Ogata score, enabling MDS to be diagnosed with a sensitivity of 91.8% and a specificity of 92.5%. Briefly, this score uses several parameters from the Ogata score like the granulocyte/lymphocyte side scatter (SSC) peak channel ratio, the percentage of B-cell and CD34 myeloid progenitors. This score has also been validated on an external cohort of 89 patients but only its diagnostic value had been evaluated.

We thought it might be interesting to compare our MFC score based on AI with the IPSS-M score, which is the current gold standard for prognostic classification of MDS, particularly regarding the diagnosis of low- and high-risk forms of progression.

We obtained data from 119 patients with complete molecular and MFC characteristics distributed over three different centers, 49 from Cochin Hospital (Assistance

Table 1. Global cohort characteristics.

Characteristics	Global cohort
Parameters, mean (SD)	
Age in years	77.1 (11.3)
Leukocytes x10^9/L	5.72 (4.9)
ANC x10^9/L	3.11 (3.3)
Hemoglobin g/dL	10.45 (1.85)
Platelets x10^9/L	165 (129.9)
Score MDS	2.02 (2.98)
WHO 2022, N (%)	
LB	55 (46)
IB1	21 (18)
SF3B1	18 (15)
IB2	12 (10)
Bi-*TP53*	8 (7)
5q	5 (4)
ICC 2022, N (%)	
MLD	29 (24)
EB	21 (18)
SF3B1	18 (15)
NOS	15 (13)
SLD	11 (9)
MDS/AML	11 (9)
TP53	9 (8)
Del 5q	5 (4)
IPSSM, N (%)	
Low	44 (37)
Moderate high	17 (14)
Moderate low	16 (13.5)
Very low	16 (13.5)
High	14 (12)
Very high	12 (10)

SD: standard deviation; ANC: absolute neutrophils count; MDS LB: myelodysplastic syndromes with low blasts; MDS *SF3B1*: MDS with low blasts and *SF3B1* mutation (World Health Organization [WHO])/MDS with *SF3B1* mutation (International Consensus Classification [ICC]); MDS del5q: MDS with low blasts and isolated 5q deletion (WHO)/MDS with del(5q) (ICC); MDS-IB1: MDS with increased-blasts 1; MDS-IB2: MDS with increased-blasts 2; MDS MLD: MDS with multilineage dysplasia; MDS SLD: MDS with single lineage dysplasia; MDS/AML: MDS/acute myeloid leukemia; IPSSM: International Prognostic Scoring System Molecular; MDS bi-*TP53*: MDS with biallelic *TP53* inactivation; MDS EB: MDS with excess blasts; MDS NOS: MDS not otherwise specified.

Publique des Hôpitaux de Paris, APHP), 16 from Ambroise Paré Hospital (APHP), and 54 from Amiens Hospital. This study was approved by the local institutional review board and was conducted according to the Declaration of Helsinki. We obtained in this cohort an average age of 77.1 years, with a standard deviation (SD) of 11.3 years. Regarding biological parameters at diagnosis, the white blood cell (WBC) count was evaluated at 5.72x10^9/L on average (SD: 4.9x10^9/L), absolute neutrophil count (ANC) at 3.11x10^9/L (SD: 3.3x10^9/L), hemoglobin at 10.45 g/dL (SD: 1.85 g/dL), and platelets at 165x10^9/L (SD: 129.9x10^9/L). Among the 119 patients, according to the World Health Organization (WHO) 2022 classification, we obtained 55 MDS with low blast (46%), 21 with increased blasts 1 (18%), 18 with *SF3B1* mutation (15%), 12 with increased blasts 2 (10%), eight with a biallelic *TP53* inactivation (7%), and five with a 5q deletion (4%). We could also describe the cohort by the ICC of myeloid neoplasms, with 29 MDS with multilineage dysplasia (24%), 21 excess blasts (18%), still the 18 patients with mutated *SF3B1* (15%), 15 not otherwise specified (13%), 11 with single-lineage dysplasia (9%), 11 (9%) with an excess of blasts greater than 10% in bone marrow representing the MDS/AML category, nine with multi-hit *TP53* (8%), and still the five patients with a 5q deletion (4%). Concerning the IPSS-M, we obtained a majority of low-risk score with 44 patients (37%), 17 moderate high (14%), 16 moderate low (13.5%), 16 very low (13.5%), 14 high (12%), and 12 very high (10%).

We observed a mean of 2.02 (SD: 2.98) for the MDS score and a mean of -0.30 (SD: 1.27) for the IPSS-M score in the overall cohort. Taking into account the IPSS-M classification, we obtained for the AI-based MDS score for patients in the very-low group a mean of 0.8 (SD: 1.4, max: 2.58, min: -1.62), for the low group a mean of 0.82 (SD: 1.9, max: 5.2, min: -2.1), for the moderate low group a mean of 1.69 (SD: 1.93, max: 6.2, min: -1.3), for the moderate high group a mean of 2.41 (SD: 2.91, max: 11, min: -2.9), for the high group a mean of 4.6 (SD: 3.5, max: 12, min: -0.6), very high group at 4.9 (SD: 4.39, max: 15.5, min: 1.55).

We then conducted a mean comparison test between the IPSS-M groups and the AI-based MDS score obtained for each patient, resulting in a *P* value <0.001. *Post hoc* Tukey tests corrected by the Bonferroni method were performed (Table 2) between the different classes and found a significant difference between the low and high (difference: 3.8; adjusted *P*< 0.001), the low and very high (difference: 4.1; adjusted *P*<0.001), the moderate low and high (difference: 2.9; adjusted *P*=0.02), the moderate low and very high (difference: 3.2; adjusted *P*=0.01), the high and very low (difference: -3.8; adjusted *P*=0.001), and very high and very low groups (difference: -4.1; adjusted *P*<0.001). The results are presented in Figure 1, with the mean and 95% confidence interval for each IPSS-M group and clearly show a significant positive association between the AI-based MDS score and the IPSS-M score.

We then conducted another comparison between the WHO 2022 groups and the AI-based MDS score, which show a significant difference (*P*<0.001). The *post hoc* tests found significant differences between the MDS increased blasts 1 and low blast groups (3.39 *vs*. 0.82, adjusted *P*=0.001), the increased blasts 2 and low blast (4.1 *vs*. 0.82; adjusted *P*<0.001), the biallelic *TP53* inactivation and low blast (6.18 *vs*. 0.82; adjusted *P*<0.001), the increased blasts 2 and the *SF3B1* mutated (4.1 *vs*. 1.25; adjusted *P*=0.03), the biallelic *TP53* inactivation and SF3B1 mutated (6.18 *vs*. 1.25; adjusted *P*<0.001) and finally between the biallelic *TP53* inactivation

Table 2. *Post hoc* tests characteristics.

Classification	Group 1	Group 2	Mean difference	*P*
ICC	MDS EB	MDS MLD	-2.544	0.0108
ICC	MDS EB	MDS NOS	-3.2773	0.0034
ICC	MDS EB	MDS/AML *TP53*	6.1632	0.0022
ICC	MDS MLD	MDS/AML	3.4489	0.0032
ICC	MDS MLD	MDS/AML *TP53*	8.7072	<0.0001
ICC	MDS NOS	MDS/AML	4.1822	0.001
ICC	MDS NOS	MDS/AML *TP53*	9.4405	<0.0001
ICC	MDS *SF3B1*	MDS/AML	3.0514	0.0342
ICC	MDS *SF3B1*	MDS/AML *TP53*	8.3098	<0.0001
ICC	MDS SLD	MDS/AML *TP53*	7.88	0.0001
ICC	MDS *TP53*	MDS/AML *TP53*	5.7774	0.0269
ICC	MDS del5q	MDS/AML *TP53*	8.8601	0.0001
ICC	MDS/AML	MDS/AML *TP53*	5.2583	0.03
WHO	MDS IB1	MDS LB	-2.5786	0.0016
WHO	MDS LB	MDS-IB2	3.2854	0.0011
WHO	MDS LB	MDS-bi*TP53*	5.3631	<0.0001
WHO	MDS *SF3B1*	MDS-IB2	2.8534	0.0335
WHO	MDS *SF3B1*	MDS-bi*TP53*	4.9311	0.0001
WHO	MDS del5q	MDS-bi*TP53*	5.4814	0.0029
IPSSM	Low	High	3.8206	0.0001
IPSSM	Low	Very high	4.0906	0.0001
IPSSM	Moderate low	High	2.9457	0.0277
IPSSM	Moderate low	Very high	3.2157	0.0182
IPSSM	High	Very low	-3.8287	0.0013
IPSSM	Very high	Very low	-4.0988	0.0009

MDS: myelodysplastic syndromes; MDS LB: myelodysplastic syndromes with low blasts; MDS *SF3B1*: MDS with low blasts and *SF3B1* mutation (World Health Organization [WHO])/MDS with *SF3B1* mutation (International Consensus Classification [ICC]); MDS del5q: MDS with low blasts and isolated 5q deletion (WHO)/MDS with del(5q) (ICC); MDS-IB1: MDS with increased-blasts 1; MDS-IB2: MDS with increased-blasts 2; MDS MLD: MDS with multilineage dysplasia; MDS SLD: MDS with single lineage dysplasia; MDS/AML: MDS/acute myeloid leukemia; IPSSM: International Prognostic Scoring System Molecular; MDS bi-*TP53*: MDS with biallelic *TP53* inactivation; MDS EB: MDS with excess blasts; MDS NOS: MDS not otherwise specified.

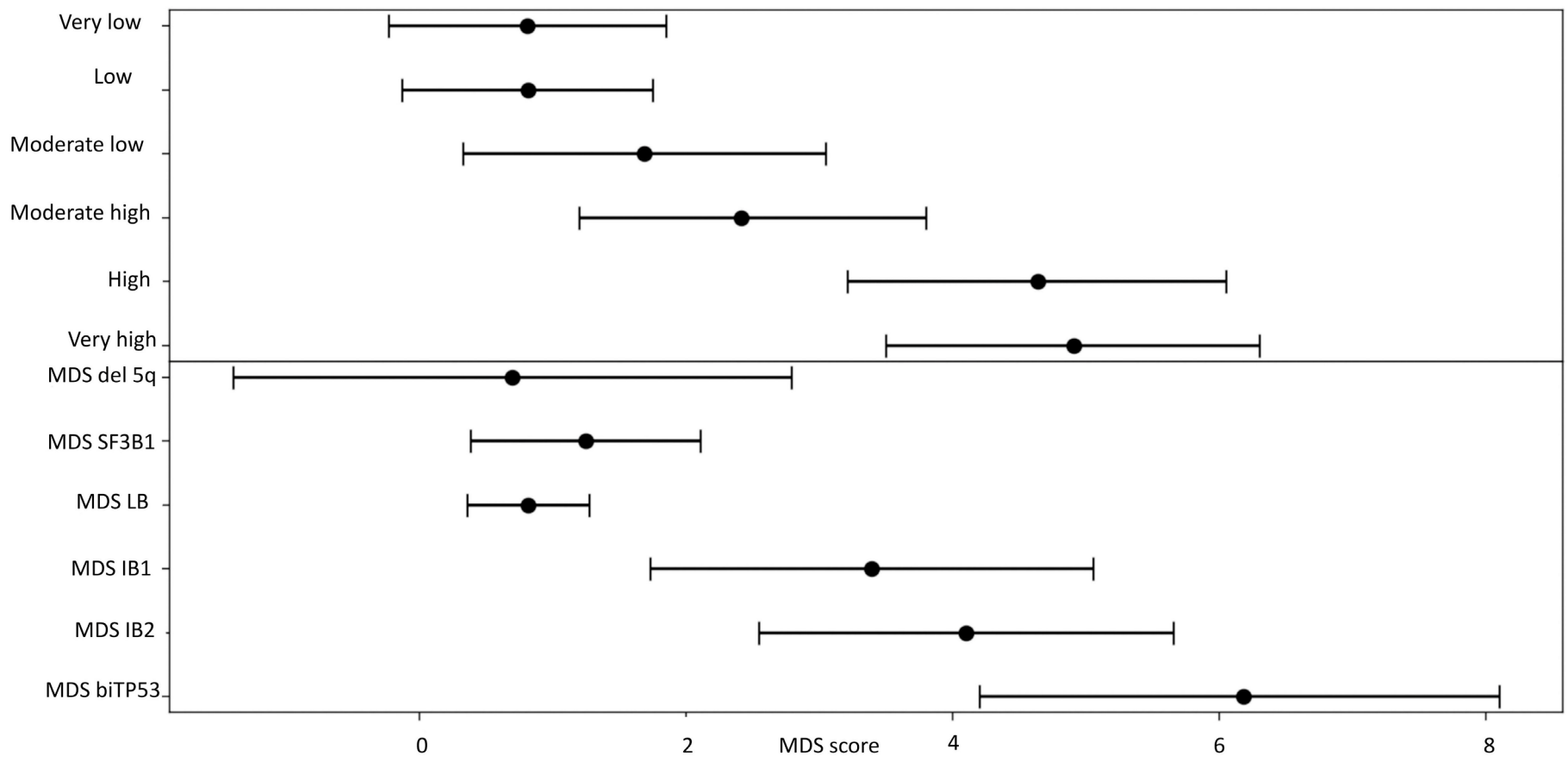

Figure 1. Distribution of Myelodysplastic Syndromes Scores from the elasticnet algorithm across the different Molecular International Prognostic Scoring System groups and the 2022 World Health Organization classification. The range corresponds to the 95% confidence interval. It shows a significant positive association between the Artifical Intelligence-based Myelodysplastic Syndromes score and the Molecular International Prognostic Scoring System Score. MDS: myelodysplastic syndromes; LB: low blast; IB1: increased blast between 5 and 9%; IB2: increased blast >9%; *bi-TP53*: *TP53* bi-allelic abnormalities.

and the 5q deletion groups (6.18 *vs*. 0.69; adjusted *P*=0.002). Finally, we compared ICC 2022 and the MFC score, with another significant difference (*P*<0.001). The most significant ones were between MDS SLD and MDS/AML *TP53* (1.7 *vs*. 9.5; *P*<0.001), the 5q deletion and MDS/AML *TP53* (0.7 *vs*. 9.5; *P*<0.001), MDS NOS and MDS/AML (0.1 *vs*. 4.3; *P*=0.001), MDS-EB and MDS/AML *TP53* (3.4 *vs*. 9.5; *P*=0.003) and between MDS MLD and MDS/AML *TP53* groups (0.84 *vs*. 9.5; *P*=0.003).

Here, we compared the AI-based MDS score's performance with the latest classifications of hemopathies and the IPSS-M prognostic score and found a perfect correlation between the score and these different entities. Furthermore, as shown in Figure 1, the score illustrates the linear progression between low- and high-risk categories. In this way, it could be used as a prognostic score in patients for whom molecular biology cannot be performed, for cost reasons in particular, in order to propose the most appropriate treatment for their MDS. Indeed, flow cytometers are available in almost all hospitals and the Ogata score, which is required to calculate the AI-based score, costs around 90 euros (compared with 2,000 euros for targeted next-generation sequencing). The main limitation of this study lies in the cohort size, which is distributed across only three hospitals. While this is sufficient for a proof of concept, increasing the cohort size, especially in the less common molecular groups, seems necessary in the future. The use of MFC instead of molecular biology can be useful in certain situations, such as determining IGHV mutational status in CLL.[11] To our knowledge, the diagnostic and prognostic scores based on MFC have neither been compared with the latest classifications, nor with the IPSS-M score, unlike other prognostic classifications such as IPSS-R. In a real-world validation cohort, Sauta and colleagues showed that the IPSS-M provided a better prognostic classification than the IPSS-R, with 46% of patients falling within the risk group and a better selection of candidates for hematopoietic stem cell transplantation.[12] Therefore, it would be interesting to carry out this correlation, in order to highlight the performance of MFC scores, like the iFS score which is known for its excellent balance between sensitivity and specificity.[13] Other teams have developed fully automated systems using the FlowSOM algorithm with raw data preprocessing and then using a machine learning algorithm.[14] This process has considerably improved scores such as iFS and Ogata and would therefore be an ideal candidate for evaluation in the face of new prognostic tools such as IPSS-M.

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Contributions

TB and VC designed the research study and wrote the paper, which was approved by both authors.

Data-sharing statement

The authors confirm that the data supporting the findings of this study are available within the article.

References

1. Adès L, Itzykson R, Fenaux P. Myelodysplastic syndromes. Lancet. 2014;383(9936):2239-2252.
2. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719.
3. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
4. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. Blood. 2012;120(12):2454-2465.
5. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013;122(22):3616-3627.
6. Nazha A, Al-Issa K, Hamilton BK, et al. Adding molecular data to prognostic models can improve predictive power in treated patients with myelodysplastic syndromes. Leukemia. 2017;31(12):2848-2850.
7. Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognostic Scoring System for myelodysplastic syndromes. NEJM Evid. 2022;1(7):EVIDoa2200008.
8. Ogata K, Della Porta MG, Malcovati L, et al. Diagnostic utility of flow cytometry in low-grade myelodysplastic syndromes: a prospective validation study. Haematologica. 2009;94(8):1066-1074.
9. Mathis S, Chapuis N, Debord C, et al. Flow cytometric detection of dyserythropoiesis: a sensitive and powerful diagnostic tool for myelodysplastic syndromes. Leukemia. 2013;27(10):1981-1987.
10. Clichet V, Lebon D, Chapuis N, et al. Artificial intelligence to empower diagnosis of myelodysplastic syndromes by multiparametric flow cytometry. Haematologica. 2023;108(9):2435-2443.
11. Couillez G, Morel P, Clichet V, et al. Flow cytometry as a fast, cost-effective tool to assess IGHV mutational status in CLL. Blood Adv. 2023;7(17):4701-4704.
12. Sauta E, Robin M, Bersanelli M, et al. Real-world validation of molecular international prognostic scoring system for myelodysplastic syndromes. J Clin Oncol. 2023;41(15):2827-2842.
13. Cremers EMP, Westers TM, Alhan C, et al. Implementation of erythroid lineage analysis by flow cytometry in diagnostic models for myelodysplastic syndromes. Haematologica. 2017;102(2):320-326.
14. Duetz C, Van Gassen S, Westers TM, et al. Computational flow cytometry as a diagnostic tool in suspected-myelodysplastic syndromes. Cytometry A. 2021;99(8):814-824.