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There's Risk, and Then There's RISK: The Latest Clinical Prognostic Risk Stratification Models in Myelodysplastic Syndromes

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Abstract

Myelodysplastic syndromes (MDS) include a diverse group of clonal hematopoietic disorders characterized by progressive cytopenias and propensity for leukemic progression. The biologic heterogeneity that underlies MDS translates clinically in wide variations of clinical outcomes. Several prognostic schemes were developed to predict the natural course of MDS, counsel patients, and allow evidence-based, risk-adaptive implementation of therapeutic strategies. The prognostic schemes divide patients into subgroups with similar prognosis, but the extent to which the prognostic prediction applies to any individual patient is more variable. None of these instruments was designed to predict the clinical benefit in relation to any specific MDS therapy. The prognostic impact of molecular mutations is being more recognized and attempts at incorporating it into the current prognostic schemes are ongoing.

Keywords

Myelodysplastic syndrome; MDS; Prognostic scoring systems; Prognosis; Predictive biomarkers; Prognostic schemes; Risk stratification; IPSS; WHO; FAB

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Introduction

Myelodysplastic syndromes (MDS) comprise a diverse group of clonal hematopoietic malignancies with impaired myeloid differentiation leading to dysplastic morphologic changes and ineffective hematopoiesis which translates clinically into peripheral blood (PB) cytopenias and a variably increased risk of progression to acute myeloid leukemia (AML) [1, 2••, 3]. Despite the approvals of azanucleosides and lenalidomide for MDS treatment, allogeneic hematopoietic stem cell transplantation (AHSCT) remains the only potentially-curative modality [4]. Only a minority of patients undergo AHSCT due to advanced age and comorbidities [5]. Therefore, further therapeutic progress will likely hinge on better understanding of the genetic and biologic underpinnings of the disease that would allow development of targeted therapies [6]. While important discoveries occurred recently in exploring the genetic landscape of MDS, dissecting the biologic consequences and subsequent therapeutic translations has lagged behind [6–8].

Why Is Prognostication for Patients with MDS Important?

The wide heterogeneity in the clinical course of patients with MDS has long been appreciated. Therefore, attempts at subgrouping MDS patients into subsets with more uniform outcomes in terms of survival and leukemic progression started early in 1980s despite the absence of active therapies at the time [9–11]. The purpose of creating the prognostic schemes is to sum the collective effects of the most important prognostic variables in a weighted fashion to provide an evidence-based “gestalt” or a “composite” prognostic outlook for the patient [6]. Prognostication would, therefore, facilitate patient counseling and application of risk-adaptive therapeutic approaches. Over the last 25 years, several prognostication tools with improving capabilities of predicting the natural history of MDS have been developed [4, 12]. Still, none of the commonly-used prognostic schemes were designed to predict response to any particular therapeutic modality for MDS [4, 12]. Though not predictive, evidence-based precise disease-risk stratification would help place in context the risk/benefit ratio of any proposed therapeutic intervention such as AHSCT [4, 12, 13].

For therapeutic purposes, MDS is traditionally divided into two large prognostic categories, lower-risk (LR) and higher-risk (HR). In LR-MDS, treatment has been historically supportive with a focus on quality of life. In contrast, the goal of treatment for HR-MDS is to alter the natural history and prolong survival. Despite the “LR” designation, most patients with LR-MDS eventually die from the disease and its complications [14, 15]. As more effective therapies become available for MDS, better prognostication and redefining “LR” disease will be vital to improve outcomes by targeting “LR” patients with “increased risk” with early therapeutic trials or for clinical trial enrollment.

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Classification Systems and Clinical Prognostic Schemes for MDS

The French-American-British (FAB) Classification and the International Prognostic Scoring System (IPSS)

The first classification system for MDS was proposed in 1976 and expanded in 1982 by Bennett and colleagues in the French-American-British (FAB) working group [15–17]. The FAB classification is based on morphology, bone marrow (BM) and PB blast percentage, and PB monocytic count [17]. The FAB classification designates five categories: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), chronic myelomonocytic leukemia (CMML), and RAEB in transformation (RAEB-T). Although the FAB is a diagnostic classification, it has major prognostic relevance [9, 11].

As the association between disease and patient characteristics with outcomes became evident in the 1980s, prognostic scores were developed to incorporate the pertinent parameters [10, 11, 18–20]. The early prognostic schemes did not gain wide clinical acceptance due to significant variations in the included parameters and differences in the relative weighting of the parameters that resulted from using relatively small databases [9]. To overcome these limitations, the International Prognostic Scoring System (IPSS) was developed [21].

The IPSS was derived from an international database of 816 untreated patients with de novo MDS (Table 1). Based on three criteria (BM blast proportion, cytogenetics, and PB cytopenias), four prognostic groups were defined: low-risk, intermediate-1 (INT-1), intermediate-2 (INT-2), and high-risk. The median OS for these four groups was significantly different at 5.7, 3.5, 1.2, and 0.4 years, respectively [21]. Because of its relative simplicity, the IPSS gained wide clinical acceptance and is still the most commonly used prognostic scheme. In addition to prognostication, the IPSS is used to inform medical decision-making, determine clinical trial eligibility, and to recommend timing of AHSCT [22–24]. The IPSS was also adopted in clinical guidelines and in FDA labeling of therapies [23, 25••]. The IPSS has also prognostic significance after diagnosis, including prediction of AHSCT outcomes [26, 27].

Several shortcomings of the IPSS became apparent. The IPSS excluded therapy-related (t)-MDS, proliferative CMML, and MDS/myeloproliferative neoplasms (MPN) overlap phenotypes. The IPSS did not account for important prognostic parameters such as red blood cell (RBC) transfusion-dependence, severity of cytopenias, and multilineage dysplasia, and underweighted the prognostic importance of karyotype relative to BM blasts [28–30]. The IPSS was developed for use only at the time of diagnosis for untreated patients and not validated as a dynamic tool [30]. The IPSS included patients with 20 – 30 % BM blasts who are currently classified as AML in the World Health Organization (WHO) classification. Lastly, it has been realized that the IPSS underestimates the poor outcome of a significant subgroup of patients classified by the IPSS as low or INT-1 who actually have an aggressive disease course with worse shorter survival than predicted by the IPSS [31–33].

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The WHO Classification and the WHO Classification-Based Prognostic Scoring System (WPSS)

Shortly after the IPSS was published, the WHO proposed a new morphology-based classification for myeloid malignancies which was subsequently revised in 2008 [34, 35]. In comparison to the FAB, the WHO classification divided the RAEB into two separate groups based on blast percentage (RAEB-1 and RAEB-2) and eliminated the RAEB-T category by classifying cases with ≥20 % BM blasts as AML. The WHO classification also added three new entities: refractory cytopenia with multilineage dysplasia (RCMD), MDS with isolated 5q- (5q- MDS), and MDS-unclassifiable (MDS-U). The WHO classification was found to be prognostic for outcomes including in the AHSCT setting [28, 36–38].

To capitalize on the prognostic capacity of the WHO classification and overcome some of the limitations of the IPSS, the WHO Classification-Based Prognostic Scoring System (WPSS) was developed from an Italian cohort of 426 patients and validated in a German cohort of 739 patients with primary MDS (Table 1) [30]. The WPSS assigns points for the WHO classification categories, therefore, accounting for the negative prognostic impact of multilineage dysplasia in addition to BM and PB blast percentages. It also replaced the number of cytopenias in the IPSS with RBC transfusion-dependence but maintained the IPSS cytogenetic prognostic grouping. Based on these three parameters, the WPSS separates patients into five prognostic subgroups.

In contrast to the IPSS, the WPSS is a dynamic prognostic scheme that can be utilized throughout the course and not only at the time of diagnosis [30]. The prognostic relevance of the WPSS was validated by other groups including in the AHSCT setting [37, 39]. Similar to the IPSS, the WPSS has not been validated in patients with t-MDS, CMML, or MDS/MPN overlap disorders. For proper application, both the WPSS and the WHO require substantial pathologic expertise in evaluation for multilineage dysplasia and might not be easily reproducible [40, 41]. Additionally, the WPSS does not account for the depth of neutropenia or thrombocytopenia.

The WPSS has also been criticized for using RBC transfusion-dependence since this is a subjective parameter which can be influenced by many factors depending on the country, the institution, and the clinical situation [42]. To address this last issue, the WPSS was refined to use anemia severity (with a cutoff of 9 and 8 g/dl for men and women, respectively) in lieu of RBC transfusion dependence [43]. For a variety of reasons, the WPSS is more widely used in Europe than the US [44].

The MD Anderson Prognostic Schemes

In order to expand applicability of prognostic schemes to all patients including those with t-MDS, those receiving active therapies, and patients with CMML and MDS/MPN overlap, the MD Anderson group analyzed a large database of 1915 patients [45]. The MD Anderson Global Prognostic Scoring System (MDAPSS) was published in 2008 (Table 1). The following parameters were used to construct the prognostic model: performance status (PS), age, platelet count, hemoglobin level, RBC prior transfusions, BM blasts percentage, white

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blood cell (WBC) count, and cytogenetics. The MDAPSS separated patients into four prognostic categories with significantly different outcomes.

The MDAPSS was found to refine the prognosis within each of the IPSS risk groups and to upstage a significant minority of patients. Although the MDAPSS was subsequently validated by other groups, shown to refine prognostic precision, and demonstrated to be complementary to the IPSS [40], the MDAPSS did not gain wide clinical use. The main reasons included its relative complexity related to use of eight different variables, the use of a high hemoglobin cutoff of 12 g/dl, the use of only two karyotypes (complex and chromosome 7 abnormalities), and the uncertainty of best therapeutic approach for the "upstaged" patients [13, 44, 46].

The MD Anderson group developed another model specifically designed as a secondary classifier to identify patients within the IPSS low and INT-1 groups who have worse outcomes than predicted by the IPSS (Table 1) [32]. The MD Anderson Lower-Risk Prognostic Scoring System (LRMDA-PSS) was developed from a database of 856 patients and used five parameters (cytogenetics, age, hemoglobin level, platelet level, and BM blast percentage). The LRMDA-PSS separated IPSS LR-MDS patients into three secondary prognostic subgroups with significantly different median OS, thereby identifying MDS patients with IPSS LR with inferior outcomes than predicted by the IPSS [32]. The LR-PSS was externally validated by other groups and found to upstage a significant number of patients [33, 47].

The Revised IPSS (IPSS-R)

As the shortcomings of the IPSS became evident, Greenberg and colleagues compiled one of the largest international databases to refine the prognostic precision of the original IPSS (n= 7,012 compared to 816 for the original IPSS) [25••]. This database, similar to the original IPSS database, included untreated patients with primary MDS with a BM blast up to 30 %. In the revised IPSS (IPSS-R), the BM blast percentage, cytopenias, and cytogenetic groups remained the basis of the model. Major revisions from the original IPSS included adoption of a new five-group cytogenetic system proposed (see below) [48••], splitting patients with <5 % BM blasts into two categories (0 – 2 % and >2 to <5 %), using the same score for BM blasts >10 – 30 %, and weighting the severity of the individual cytopenias instead of just their number. Using five parameters (cytogenetics, BM blast percentage, hemoglobin, platelet count, and neutrophil count), five prognostic classes were generated instead of the original four (very low, low, intermediate, high, and very high) with significantly different outcomes (Table 1) [25••].

In the IPSS-R, age, PS, serum ferritin, serum LDH and serum beta-2-microglobulin levels were significant additive variables for survival but not for leukemic progression. Nonetheless, except for age, the effect of these parameters on survival was relatively minor. BM fibrosis was not independently prognostic. While age is not accounted for directly in the model, a formula was provided to adjust for age. The IPSS-R showed improved discriminatory power over the IPSS particularly by separating patients in the IPSS-LR INT-1 and INT-2 into all five IPSS-R categories. Among patients with IPSS low and INT-1, 27 % were upstaged in the IPSS-R, while 18 % of patients with IPSS INT-2 and high were

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downstaged in the IPSS-R. The IPSS-R was externally validated in an Austrian cohort of 200 untreated patients and by the Moffitt Cancer Center group [25••, 49]. The IPSS-R was found to be prognostic in patients receiving active MDS therapies including azacitidine [50–52]. An Italian group showed that the predictive power of the IPSS-R for leukemia-free survival and OS was significantly higher than that of the original IPSS and the WPSS [52].

The IPSS-R is relatively complex to apply, and similar to the IPSS, does not apply to CMML, treated patients, t-MDS, or MDS/MPN overlap disorders. Furthermore, the utility of the IPSS-R for making clinical decisions, especially for the intermediate risk group, and outcomes associated with various therapies in relation to different risk groups are yet to be determined [49].

An Update on Novel Prognostic Factors

New Insights into the Prognostic Value of Karyotypic Aberrations

Using traditional karyotyping (TK), chromosomal aberrations are detected in about half the patients with primary MDS and 80 % of patients with secondary MDS [53, 54]. The use of florescence in situ hybridization (FISH) has improved detection of cryptic lesions such as submicroscopic deletions [55]. The original IPSS used two prognostic categories to classify the six most commonly encountered cytogenetic profiles (Good: normal, isolated -Y, 5q-, 20q-; and poor: complex [at least three abnormalities] and any chromosome 7 abnormalities), while lumping all the other rare cytogenetic profiles into an intermediate category [21]. Therefore, the IPSS could cytogenetically classify only 86 % of patients and couldn’t assign an informed prognostic category to many of the rare chromosomal abnormalities [21, 29, 48••, 53, 56].

To address this issue, an effort led by the Austro-German group compiled an international database of 2,902 patients with de novo MDS treated with supportive care (SC) only to define 19 cytogenetic groups, thereby allowing cytogenetic classification of 91 % of patients [48••]. These novel cytogenetic groups were used to create a new cytogenetic classification with five prognostic categories: very good, good, intermediate, poor, and very poor with significantly different survivals (Table 2). One of the notable differences from the IPSS cytogenetic system was the assignment of intermediate prognosis to isolated 7q-while −7 maintained its poor prognostic assignment. The worse prognosis associated with very complex karyotype (more than three abnormalities) in comparison to complex karyotype (three abnormalities) was confirmed in this study [48••].

The new five-group cytogenetic scoring system was validated by other groups and incorporated in IPSS-R [25••, 57]. The five-group cytogenetic system is also predictive for AHSCT outcomes [58]. In contrast, the Mayo clinic group was not able to confirm the prognostic superiority of the IPSS-R very good karyotype or differentiate prognostically between the very good, intermediate and poor karyotypes [59]. Recent cytogenetic studies in MDS yielded conflicting results on whether monosomal karyotype is associated with worse outcomes beyond that of the poor-risk cytogenetics [59, 60]. Lastly, the number of adjunct chromosomal abnormalities in 5q- MDS was found to be associated with incrementally worse outcomes [61].

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Genome-Wide Techniques and Prognosis

Approximately 50 % of MDS patients have normal cytogenetics using TK, and even patients with similar karyotypic abnormalities can have significantly different disease course [2••, 53, 62]. As such, detection of genetic abnormalities beyond TK became a priority in MDS research not only to refine prognostic precision, but also to understand the pathophysiology of the disease and discover therapeutic targets. The use of genome-wide techniques such as array-based comparative genomic hybridization (aCGH), single-nucleotide polymorphism arrays (SNP-A), and DNA sequencing assays increased the percentage of demonstrable clonal aberrations and allowed discovery of new important somatic molecular mutations [55, 63, 64]. Both aCGH and SNP-Awere found to provide prognostic information beyond that of the traditional clinicopathological parameters [64–66].

Detailed discussion of the molecular aberrations and their prognostic impact is beyond the scope of this review, but the interested reader is referred to recent comprehensive reviews [54, 62, 67, 68]. Bejar et al. [2••] evaluated samples from 439 MDS patients and identified somatic mutations in 18 genes. Half of the patients had at least one mutation including 52 % of the patients who had normal cytogenetics by TK. The most commonly mutated genes were genes involved in epigenetic regulation including DNA methylation (*TET2* [20.5 %]) and chromatin posttranslational modifications (*ASXL1* [14.4 %], *EZH2* [6.4 %]), transcription regulation (*RUNX1* [8.7 %], *TP53* [7.5 %]), and signal transduction (*NRAS* [3.6 %], *JAK2* [3 %]). Some of these mutations were associated with clinical features such as cytopenias, blast percentage, and karyotypes. In a regression model including the IPSS, age, and other frequent mutations identified in the study, five mutations had independent negative prognostic significance for OS: *TP53* (HR, 2.48; 95 %CI, 1.60 – 3.84), *EZH2* (HR, 2.13; 95 %CI, 1.36 – 3.33), *ETV6* (HR, 2.04; 95 %CI, 1.08 –3.86), *RUNX1* (HR, 1.47; 95 %CI, 1.01 – 2.15), and *ASXL1* (HR, 1.38; 95 %CI, 1.00 – 1.89). Incorporating these mutations in the IPSS improved its prognostic discrimination by upstaging patients who had any of these five mutations to the next-highest IPSS risk-group [2••].

In another study focusing on LR-MDS, samples from 288 patients were examined for mutations in 22 genes including regulators of the spliceosome (*SF3B1*, *SRSF2*, *U2AF1*) and the epigenetic modulator *DNMT3A* [33]. The authors validated the MD Anderson LR-PSS model and found that mutations in four genes (*EZH2*, *RUNX1*, *TP53*, and *ASXL1*) were associated with negative prognostic impact on OS independent of the LR-PSS. Interestingly, the mutations associated with a poor prognosis were enriched in the highest-risk LR-PSS group. Only mutations in *EZH2* were associated with prognostic significance in a multivariable model that included LRMDA-PSS and other mutations (HR, 2.90; 95 %CI, 1.85 –4.52). The researchers were able to improve the discriminatory power of the LR-PSS prognostic scheme by assessment of the *EZH2* mutational status, thereby identifying 29 % of patients with IPSS LR-MDS who had worse-than-expected prognosis [33].

The adverse prognosis associated with *TP53* mutations appear to persist in patients treated with azacitidine or AHSCT [69, 70]. Recent data suggest that *TP53* mutations confer an independent negative prognosis in patients with 5q-MDS and might be the main driver of the poor outcomes in MDS patients with complex karyotypes [2••, 69, 70]. Nonetheless,

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before molecular aberrations can be used in routine clinical practice, the laboratory assays will require standardization, further validation, and resolution of logistic issues. The best way to incorporate these mutations into current prognostic schemes and how to use this data clinically will also need to be defined.

Comorbidities and Prognosis in MDS

Although the majority of MDS patients have medical comorbidities that affect outcomes including survival, none of the commonly used prognostic schemes accounts for co-morbidity [71–73]. Several comorbidity scales including the Charlson comorbidity index, the Hematopoietic Stem Cell Transplantation-Specific Comorbidity Index, and the Adult Comorbidity Evaluation-27 scale (ACE-27) were all found to be prognostic for OS in MDS even after accounting for age and the IPSS, especially in lower-risk patients [71–75].

The Italian group developed a time-dependent MDS-specific comorbidity index (MDS-CI) that separated patients into three groups with different OS [76]. Diseases of the heart, liver, lungs, kidneys, and history of solid tumors were all independently prognostic. The MDS-CI was validated in German and Italian cohorts including azacitidine-treated patients [75–77]. Tobacco smoking and chronic pulmonary obstructive disease were also associated with increased mortality in MDS patients [78, 79].

The best way to incorporate comorbidities in the current prognostic schemes has not been determined. The Italian groups found that the MDS-CI can better define the life expectancy of MDS patients stratified according to the WPSS [75, 76]. The MD Anderson group developed a new prognostic scheme that included age, IPSS, and the ACE-27 scale which separated patients into three groups with different OS (43.0, 23.0, and 9.0 months, respectively) [74]. Other investigators proposed using the “Multidimensional Geriatric Assessment” which accounts for the functional status, the cognitive and nutritional states, and geriatric syndromes in addition to comorbidity for decision-making along with the IPSS [80].

Other Prognostic Factors

Komrokji and colleagues found that serum albumin level was independently associated with OS after accounting for the IPSS, age, serum ferritin level and RBC transfusion-dependence [81]. Similarly, serum ferritin level and iron overload were found to be associated with worse prognosis, especially in LR-MDS (reviewed in [8]). The Italian group reported that BM fibrosis and CD34+ cell clusters were both independent negative prognostic factors for OS and leukemia-free survival, and that BM fibrosis upstaged patients within the IPSS and the WPSS prognostic groups by one step [82]. Nonetheless, the analysis of the large database used to create the IPSS-R showed that serum ferritin had a relatively minor independent prognostic effect on OS, while BM fibrosis was not independently prognostic [25••].

An increasing number of reports indicate a diagnostic and prognostic potential for flow cytometric evaluation in MDS, and flow cytometric prognostic scores were developed [83–85]. Mailloux and colleagues [86] found that expansion of the effector memory regulatory

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T-cells was independently associated with inferior survival in patients with LR-MDS after accounting for the IPSS components and for comorbidities. The authors proposed that expansion of this subset might be associated with changes in the BM microenvironment that are conducive to leukemic progression by facilitating immune escape of the malignant cells [86].

Predictive Schemes for Specific Therapies

As active MDS therapies became available, the focus has been shifting from prognostic schemes to predictive tools than can predict objective clinical responses and survival benefit in relation to specific interventions [3]. Development of predictive models would allow selection of patients with higher likelihood to respond to a certain intervention, therefore, avoiding other therapies with their toxicities and cost, and saving important time that might be lost in a “trial and error” approach [6, 12]. Unfortunately, the creation of predictive models has met little success, save for the development of models that predict responses to immunosuppressive agents and erythropoiesis-stimulating agents which performed variably [87–90]. Therefore, decisions on using and sequencing MDS therapies, including AHSCT, to date are still guided by prognostic, rather than predictive, factors.

The French group retrospectively developed a scheme, the French Prognostic Scoring System (FPSS), which predicted clinical responses and survival with azacitidine therapy for patients with IPSS HR-MDS [91, 92]. The FPSS measures four parameters: PB blast percentage, RBC transfusion requirements, IPSS cytogenetic risk group, and the PS. Based on these parameters, patients were separated into three groups with significantly different median OS (32.1, 15.0, and 6.1 months). The FPSS was retrospectively validated in a cohort from the AZA001 trial and in smaller cohorts from other institutions in Europe [77, 93]. The FPSS will require prospective validation of utility for clinical decision-making before it can be recommended for routine use in clinical practice.

Another area of active research is the identification of predictive biomarkers that can predict objective responses and survival to different MDS therapies. The commonly used predictive biomarkers in clinical practice are the 5q- abnormality in LR-MDS to guide lenalidomide use, and the serum erythropoietin level to guide the use of erythropoiesis-stimulating agents [3]. An erythroid differentiation gene expression signature and a polymorphism in the gene that codes for the ubiquitin ligase cereblon were reported to predict response to lenalidomide therapy in patients with LR-MDS who did not have the 5q-abnormality [94, 95]. The French group reported that mutations in *TET2* predicted response to azacitidine therapy in patients with HR-MDS [96]. Mutations in *TET2*, *DNMT3A*, *IDH1*, and *IDH2* were found to be predictive of achievement of CR in patients with HR-MDS who received azacitidine and lenalidomide combination therapy [97]. All these proposed predictive biomarkers require further validation and standardization before they can be recommended for routine clinical use to guide therapy selection.

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Conclusion

While several commonly used prognostic schemes function well to predict the natural course of MDS and inform choice of therapeutic approaches, none of these instruments was designed to predict the clinical benefit in relation to any specific therapy. The prognostic schemes divide patients into subgroups with similar prognosis, but the extent to which the prognostic prediction applies to any individual patient is more variable [6, 12]. Therefore, therapeutic decisions should be guided by these prognostic estimates but not completely depend on them. Also, the most widely used schemes do not have account for comorbidities which are important to consider for clinical decision-making.

Despite significant improvements in the prognostication for MDS, there is a clear need for the scientific community to agree on one unified, validated, and robust prognostic scheme that can be easily used in the community [44]. This scheme would ideally incorporate some of the prognostic biomarkers and exhibit a predictive precision for outcomes in relation to specific therapies. While several genetic parameters were studied to help “individualize” the prognostic estimation or as predictive biomarkers, none has been formally incorporated into prognostic schemes or validated to inform clinical decision-making in a risk-adaptive fashion. The biomarkers whose independent prognostic effect is not reflected in other prognostic clinicopatholgoic features will probably be the most valuable to add to the existing prognostic schemes (e.g. *EZH2* mutations) [2••].

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Table 1

The most widely used prognostic schemes for myelodysplastic syndromes (MDS): the International Prognostic Scoring System (IPSS) (reference 21), the revised IPSS (IPSS-R) (reference 25••), the World Health Organization (WHO) Classification-Based Prognostic Scoring System (WPSS) (reference 30), the MD Anderson Global Prognostic Scoring System (MDAPSS) (reference 45), and the MD Anderson Lower-Risk Prognostic Scoring System (LR-MDAPSS) (reference 32)

IPSS, 1997			IPSS-R, 2012			WPSS, 2007			MDAPSS, 2008			LR-MDAPSS[%], 2008		
Parameter	**Score**		**Parameter**	**Score**		**Parameter**	**Score**		**Parameter**	**Score**		**Parameter**	**Score**	
BM blasts %			BM blasts %			WHO Class			PS >2	2		Cytogenetics***		
<5 %	0		≤2 %	0		RA, RARS, 5q-	0		Age (years)			Unfavorable	1	
5 – 10 %	0.5		>2 to<5 %	1		RCMD, RCMD-RS	1		60–64	1		Age (years)		
11 – 20 %	1.5		5 – 10 %	2		RAEB-I	2		≥ 65	2		≥ 60	2	
21 – 30 %	2.0		> 10 %	3		RAEB-II	3		Platelets (× 10^9/L)			Hb		
Cytogenetics*			Cytogenetics**			Cytogenetics*			<30	3		< 10 g/dL	1	
Good	0		Very Good	0		Good	0		30 – 49	2		Platelets		
Intermediate	0.5		Good	2		Intermediate	1		50 – 199	1		< 50 ×10^9/L	2	
Poor	1.0		Intermediate	4		Poor	2.0		Hb <12 g/dL	2		50 – 200 × 10^9/L	1	
			Poor	6		RBC Transfusion††			BM blasts %			BM blasts %		
			Very poor	8		Yes	1		5 – 10 %	1		≥ 4 %	1	
Cytopenias†			Hb	≥ 10 g/dL	0	No	0		11 – 29 %	2				
0/1	0			8 – <10 g/dL	1				WBC >20×10^9/L	2				
2/3	0.5			< 8 g/dL	1.5				Cytogenetics					
			ANC (× 10^9/L)	≤ 0.8	1				Chromosome 7 Abn	3				
			Platelets (×10^9/L)	≥ 100	0				Complex ≥ 3	3				
				50 – 100	0.5				RBC Transfusion	1				
Risk Group	Score	OS (Y)	Risk Group	Score	OS (Y)	Risk Group	Score	OS (M)	Risk Group	Score	OS (M)	Risk Group	Score	OS (M)
Low	0	5.7	Very good	0 – 2	8.8	Very Low	0	141	Low	0 – 4	54	Cat-1	0 – 2	80
INT-1	0.5 – 1	3.5	Good	3 – 5	5.3	Low	1	66	INT-1	5 – 6	25	Cat-2	3 – 4	27
INT-2	1.5 – 2.0	1.1	INT	6 – 7	3.0	INT	2	48	INT-2	7 – 8	14	Cat-3≥514		
High	≥ 2.5	0.4	Poor	8 – 9	1.6	High	3 – 4	26	High	≥ 9	6			

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IPSS, 1997		IPSS-R, 2012		WPSS, 2007			MDAPSS, 2008		LR-MDAPSS[%], 2008	
Parameter	**Score**	**Parameter**	**Score**	**Parameter**	**Score**		**Parameter**	**Score**	**Parameter**	**Score**
	Very poor	10 – 18	0.8	Very High	5 – 6	9				

[%]: The LR-MDAPSS is a secondary classifier that applies only to MDS patients who belong to the IPSS low and INT-1 risk groups. BM: Bone marrow, PS: Performance status, RA: refractory anemia, RARS: refractory anemia with ring sideroblasts, RCMD: Refractory cytopenia with multilineage dysplasia, RAEB: Refractory anemia with excess blasts, 5q-: interstitial deletion of long arm of chromosome 5, Hb: hemoglobin, g: Gram, L; Liter, dL: deciliter, ANC: absolute neutrophil count, RBC: red blood cells, Abn: Abnormality, OS: Median overall survival, Y: years, M: months. Cat: Category.

[*] Good: Normal, -Y, 5q-, 20q-; Poor: complex (≥ 3 abnormalities) or chromosome 7 abnormalities. Intermediate: Other karyotypic abnormalities;

[†] Hb<10 g/dL; ANC<1800/μL; platelets< 100,000/μL.

[**] Refer to Table 2 for cytogenetic groups used in the IPSS-R.

[††] RBC transfusion dependence: ≥ 1 RBC transfusion every 8 weeks over a period of 4 months.

[***] In this analysis, diploid and 5q were favorable cytogenetics, all others were considered as unfavorable cytogenetics

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Table 2

The new five-group comprehensive cytogenetic prognostic system for MDS developed by Schanz et al. (Adapted from reference 48••)

Prognostic Subgroup (% of patients)	Very Good (2.9 %)	Good (65.9 %)	Intermediate (20.7 %)	Poor (3.6 %)	Very Poor (7.0 %)
Cytogenetic abnormality					
Single	-Y	Normal	7q-	inv(3)	NA
	11q-	5q-	+8	t(3q)	
		12p-	i(17q)	3q-	
		20q-	+19	−7	
			Any other		
Double	NA	Including 5q-	Any other	Including −7 or 7q-	NA
Complex	NA	NA	NA	3	> 3
Outcomes					
Median OS (months) (95 %CI)	60.8 (50.3 – NR)	48.6 (44.6 – 54.3)	26.0 (22.1 – 31.0)	15.8 (12.0 – 18.0)	5.9 (4.9 – 6.9)
HR for OS (95 %CI)	0.5 (0.3 – 0.7)	1.0 (0.98 – 1.1)	1.6 (1.4 – 1.8)	2.6 (2.1 – 3.2)	4.2 (3.4 – 5.2)
Median time to leukemic progression (months) (95 %CI)	NR (121.2 – NR)	NR (189.0 – NR)	78.0 (42.6 – NR)	21.0 (13.4 – 42.2)	8.2 (6.4 – 15.4)
HR for leukemic progression (95 %CI)	0.5 (0.2 – 1.2)	1.0 (0.9 – 1.2)	2.2 (1.8 – 2.7)	3.4 (2.5 – 4.6)	4.9 (3.6 – 6.7)

NA: Not available, OS: Overall survival, CI: Confidence interval, HR: Hazard ratio, NR: Not reached