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Journal

ISSN

Authors

Jonas, Brian A
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Publication Date

DOI

Copyright Information

Peer reviewed

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MDS prognostic scoring systems — Past, present, and future

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The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal myeloid haemopathies characterized by defective differentiation of haematopoietic cells and expansion of the abnormal clone. This leads to bone marrow failure with the resulting peripheral blood cytopenias and evolution to or toward acute myeloid leukaemia that characterize MDS clinically. The clinical heterogeneity of MDS has led several groups to analyze patient and clinical characteristics to develop prognostic scoring systems yielding estimates of overall and leukaemia-free survival to guide clinical decision-making. These models have evolved over time as our understanding of the pathogenesis, natural history, and treatment of MDS has improved. Rapid advances in flow cytometric analysis, adjuncts to standard metaphase cytogenetics, and gene mutation analysis are revolutionizing our understanding of MDS pathogenesis and prognosis. Despite the existence of multiple well-validated prognostic scoring systems, further refinements of current models with these new sources of prognostic data are needed and are described herein.

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Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous spectrum of clonal haematopoietic stem cell (HSC) disorders characterized by defective maturation of haematopoietic precursors resulting in bone marrow (BM) failure and peripheral blood (PB) cytopenias and variable tendency of the abnormal clone to expand leading to progression to acute myeloid leukaemia (AML). The pathogenic phenotype is typified by dysplasia in one or more myeloid lineages, and the mechanisms of pathogenesis relate to a wide array of molecular and biological changes that are reflected in the clinical heterogeneity of MDS.

The current clinical management of MDS focuses on assessing disease risk at diagnosis by assaying clinical and patient characteristics and using established prognostic scoring systems to estimate survival and risk of evolution to AML. This information is used to guide therapeutic recommendations for patients, which range from watchful waiting to palliation of symptomatic cytopenias to disease-altering treatments, such as chemotherapy and potentially curative allogeneic haematopoietic cell transplantation.

This chapter reviews the most widely used current MDS prognostic scoring systems and the growing cadre of additional prognostic variables that are emerging as our molecular and biological understanding of MDS improves. Many of these new features are refining our understanding of MDS prognosis and are or will be making their way into ever-evolving MDS prognostic models.

Current MDS prognostic scoring systems and risk models

After the initial French-British-American (FAB) Morphology Group classifications of MDS were published in 1982, and considering the well-recognized clinical heterogeneity of MDS, several prognostic scoring systems and risk models have been proposed and are summarized in Table 1 [1–7]. These models were generated using several validated prognostic features, acting as surrogates for the underlying disease biology and patient host characteristics, to generate weighted scoring systems that divide patients into defined risk categories.

International prognostic scoring system (IPSS)

In an effort to improve upon initial prognostic models developed after publication of the FAB classification of MDS, an International MDS Risk Analysis Workshop was convened, and cytogenetic, morphologic, and clinical data were combined from primary untreated MDS patients from seven previously reported studies using independent risk-based prognostic scoring models to generate the IPSS [1]. Multivariate analysis identified BM blast percentage, number of cytopenias, and cytogenetic subgroup (good, intermediate, and poor) as the most significant independent variables for both overall survival (OS) and AML evolution. Weighted risk scores for each variable were used to generate the IPSS

Table 1
Prognostic classification systems for MDS and CMML.[a]

System	Blasts	Cyto	Hgb	Plts	ANC	Age	RBC txn	PS
IPSS	+	+	+	+	+	+		
WPSS	+[b]	+	+				+[c]	
MDA-LR	+	+	+	+		+		
MDAS	+	+	+	+	+[d]	+	+	+
FPSS	+(PB)	+					+	+
CPSS[e]	+	+	+		+[d]		+[c]	
IPSS-R[f]	+	+	+	+	+	+		+

[a] Table adapted from Refs. [1–7].
[b] WHO MDS subtype.
[c] RBC transfusion dependency can be substituted by haemoglobin (Hgb) level.
[d] Leucocytosis.
[e] CMML: FAB and WHO MDS subtypes.
[f] Plus other variables: LDH, ferritin, b2-microglobulin, fibrosis.

which stratified patients into four distinctive risk groups for both OS and AML evolution (low, intermediate-1, intermediate-2 and high). Age greater than 60 had a negative effect on OS for low and intermediate-1 risk patients, and female gender prolonged survival in the low risk group.

The IPSS that emerged from this large multinational FAB-defined MDS patient population with detailed information on the natural history of MDS became a standard for clinical MDS prognostication and trial design. It has been validated in independent studies [8–10]. The IPSS used a more refined cytogenetic classification and breakdown of BM blasts than prior systems, demonstrated importance of age-related stratification, and was simple to calculate since it relies on information obtained in the standard MDS diagnostic work-up. It also showed that mortality from complications of BM failure and comorbid conditions played a more prominent role in lower-risk patients while evolution to AML was most prominent in higher-risk patients [1]. More recent work has shown that IPSS can be used to predict transplant outcomes for MDS patients [11–13].

Despite its utility, limitations with the IPSS have become apparent and have led to the several additional attempts at refining MDS prognostic scoring systems described in the following sections and in Table 1. Because of the way the model was created, it was not a dynamic model that can provide serial prognostication, did not offer prognostic information for patients with treated or secondary MDS or proliferative CMML (WBC >12 K/mm^3), did not consider depth of cytopenias, and potentially had a bias related to survival times being calculated from time to presentation to a tertiary care centre.

World Health Organization prognostic scoring system (WPSS)

In 2002, the WHO formulated a new proposal for the classification of *de novo* MDS based on bone marrow cell morphology, blast count, number of lineages affected, and a unique MDS subtype defined by del(5q) [14]. An Italian group evaluated the prognostic value of the new WHO classification and showed that WHO morphologic subgroups, IPSS cytogenetic categories, and red blood cell (RBC) transfusion-dependency each had prognostic value in MDS [15]. They also showed that RBC transfusion-dependence with development of secondary iron overload had a worse prognosis in multivariate analysis.

These workers extended this analysis to evaluate significant prognostic factors taking into account changes over time to develop the WPSS, a dynamic MDS prognostic model that stratified patients into five risk groups [2]. In multivariate analysis, the most important variables were WHO subgroups, IPSS karyotype, and transfusion requirement. Age had an effect on survival in the lower risk groups. Subsequently the latter parameter was replaced by haemoglobin (Hgb) level, changing the transfusion-dependency variable to Hgb <9 g/dL for males and <8 g/dL for females [16]. The WPSS was also validated and pre-transplant score shown to have prognostic value in the post-transplantation outcomes of patients with MDS [17].

The main advantage of the WPSS was the ability to be used for serial prognostication. It had similar limitations as the IPSS and did not account for degree of cytopenias, excluded RAEB-T patients, and relied on detailed morphologic analysis (e.g., dysplasia) to determine WHO subtype that has not been universally discernable.

M.D. Anderson lower-risk MDS prognostic scoring system (MDA-LR)

In an effort to further characterize the prognosis of lower-risk IPSS patients, patients with IPSS low or INT-1 risk disease referred to the M.D. Anderson Cancer Center (MDACC) were evaluated for characteristics that predicted shorter survival [3]. Multivariate analysis of clinical characteristics demonstrated that unfavourable cytogenetics, Hgb, platelet (Plt) count, and BM blasts percentage were significantly associated with survival. These variables were weighted and used to develop the MDA-LR which stratified patients into three risk groups. This analysis also included patients with CMML and secondary MDS (sMDS). Limitations were similar to the IPSS and WPSS.

Global M.D. Anderson risk model score for MDS (MDAS)

The group at MDACC also evaluated prognostic features in MDS patients referred at any time in their disease course in an attempt to improve upon the IPSS [4]. Multivariate analysis identified several

independent adverse factors as continuous and categorical values including Eastern Cooperative Oncology Group (ECOG) performance status, older age, thrombocytopaenia, anaemia, increased BM blasts, leucocytosis, chromosome 7 or complex abnormalities, and prior transfusions. These disease and host factors were weighted and used to develop the MDAS model which stratified patients into four risk categories. The model's prognostic significance did not change when the WHO-defined AML patients were excluded, and importantly, the model was able to stratify CMML and sMDS patients into the four risk categories similar to the general population studied. This model was validated at another institution [18]. The MDAS was more complex compared to the simpler IPSS score and the impact of prior therapy on the analysis of prognosis in this patient population was unclear. The overall advantages of this model were the inclusion of patient populations not included in the prior IPSS or WPSS models, ability of this model to be used for dynamic prognostication, and identification of lower-risk IPSS patients with higher risk features.

French prognostic scoring system (FPSS)

The Groupe Francophone des Myelodysplasies (GFM) evaluated IPSS INT-2 or high risk patients treated with 5-azacitidine (AZA) for prognostic factors affecting response and survival [5]. Multivariate analysis showed that ECOG performance status, IPSS cytogenetic risk, presence of circulating blasts, and RBC transfusion dependency were prognostic for survival. In addition, achievement of any type of haematological improvement (HI) in patients without complete or partial remission was associated with improved OS. Combining and weighting those factors affecting OS led to development of the FPSS, which discriminates three prognostic groups. This score was validated in an independent set of patients from the AZA-001 trial and retained its prognostic significance in longer follow-up of the same patient cohort [19,20]. However in a recent ECOG study, analysis indicated no improvement in OS prediction for the FPSS over the IPSS-R in AZA-treated patients [21].

Chronic myelomonocytic leukaemia (CMML) prognostic scoring system (CPSS)

Like MDS, CMML is a heterogeneous group of diseases with significant clinical variability, survival, and risk of transformation to AML. Previous MDS prognostic models differ with respect to CMML. The IPSS excluded MPN-like CMML (WBC >12 K/mm^3) and the WPSS excluded all CMML patients, whereas the MDAS included both MDS-like CMML (WBC <12 K/mm^3) and MPN-like CMML [1,2,4]. Considering the lack of a prior consensus model, a multinational European study recently described a new prognostic system for CMML, the CPSS [6]. In 2011, a CMML-specific cytogenetic risk stratification scheme had been developed and was used in this study [22]. Multivariate analysis revealed that the most important variables predicting OS and progression to AML were FAB and WHO CMML subtypes, CMML-specific cytogenetic risk classification, and RBC-transfusion dependency. These factors were statistically weighted to generate the CPSS, which stratified patients into four risk groups. Changing the RBC transfusion dependency variable to an Hgb level <10 g/dL offered nearly identical prognostic efficacy. Overall, the model confirmed the prognostic importance of the FAB and WHO CMML subtypes and CMML-specific cytogenetic classification and recognized the importance of RBC transfusion in these patients.

Revised international prognostic scoring system (IPSS-R)

The various newer prognostic models described in the preceding sections, in addition to several reports suggesting modifications of the original IPSS variables and new prognostic factors, argued for the need for a refinement of the IPSS, which had become the clinical and research standard since its description in 1997. Importantly, a new cytogenetic classification scheme for MDS was proposed to replace the original risk groups proposed in the IPSS [23]. This new cytogenetic classification defined 16 specific cytogenetic abnormalities that were grouped into five prognostic categories. Other features including age [24], depth of cytopenias [25,26], LDH [27], ferritin [15], beta-2 microglobulin [28], BM fibrosis [29], and performance status [30] were also shown to have prognostic significance in MDS.

To evaluate these new findings and refine the IPSS, the International Working Group for Prognosis in MDS (IWG-PM) project coalesced databases from multiple international institutions [7]. Data from 7012 patients with primary MDS and a median age of 71 years was collected and analyzed. Patients were classified by both FAB and WHO criteria and patients with RAEB-T, non-proliferative CMML, and isolated del(5q) were included. Cytogenetics was classified according to the new MDS classification proposed by Schanz et al. [23].

Modelling of risk was based on multivariate analysis of OS and time to AML transformation and developed following a hierarchical approach that built upon and further confirmed the original IPSS variables. The analysis revealed five main features, including cytogenetics (five categories), BM blast percentage (≤ 2, 3–4, 5–10, and >10%), and depth of cytopenias [Hgb (≥ 10, 8–<10, and <8 g/dL), Plt (≥ 100, 50–99, and <50 K/mm^3), and ANC (≥ 0.8 and <0.8 K/mm^3)], as having statistically significant prognostic impact on OS and time to AML transformation. These features were weighted and used to develop the final IPSS-R model, which stratified patients into five risk categories (very low, low, intermediate, high, and very high) with significantly different median OS (8.8, 5.3, 3, 1.6 and 0.8 years, respectively) and median time to 25% AML evolution (not reached, 10.8, 3.2, 1.4, and 0.7 years, respectively).

Age was also a major prognostic factor for OS, but not AML evolution, and had the most significant impact on the lower-risk groups. Additionally, differentiating features such as performance status, serum ferritin, LDH, and beta-2 microglobulin were prognostic for OS but not for AML evolution. Ferritin may be a reflection of both clinical (transfusion burden) and biological (degree of ineffective erythropoiesis and inflammation) features of MDS, so the impact of these features on OS illustrated the importance of variables outside of the main five used to calculate the IPSS-R. These factors could shift a patient to a higher or lower category based on dichotomized values although their effect was less significant compared to the five main prognostic features.

The IPSS-R had multiple refinements beyond the IPSS including the new marrow blast categories, refined cytogenetic risk groups (five versus three groups and 16 vs seven specific cytogenetic categories), evaluation of depth of cytopenias, inclusion of differentiating features (for survival), and five instead of four risk categories. The IPSS-R was able to upstage 27% of IPSS lower-risk patients and downstage 18% of IPSS higher-risk patients, confirming its improved predictive power compared to the IPSS, particularly for INT-1 and INT-2 patients. The model also confirmed that the main cause of death for higher-risk patients was leukaemia while BM failure complications and patient comorbidities played a more significant role in lower-risk patients.

Overall, the IPSS-R had several strengths and some limitations. It improved on the original IPSS for primary untreated MDS with consideration of depth of cytopenias and improved classification of BM blasts and cytogenetics. Online calculators have been developed to help apply the IPSS-R (http://www.ipss-r.com and http://www.mds-foundation.org/calculator/advanced). The model has been validated by several groups and was extended to and validated in treated patients and at times other than at diagnosis [31–37]. Furthermore, the IPSS-R was shown to be an improvement over the IPSS as a classification method for predicting outcomes after standard or reduced-intensity allogeneic haematopoietic cell transplant [38]. Additionally, the IWG-PM database was recently evaluated to address the potential attrition of prognostic power from the time of diagnosis, which has been a problematic issue for all prognostic scoring systems [39]. Evaluating several prognostic systems, analysis showed that the IPSS-RA (IPSS-R with age normalization) retained the most prognostic power over time, followed by the IPSS-R and WPSS, which were better than the IPSS. Retention of prognostic power over time was greater for lower risk patients than for higher risk patients, in part related to patient mortality in the latter patient group. Although patients with secondary MDS were excluded from the IPSS-R dataset, in a subsequent study the IPSS-R was shown to have prognostic significance in a series of patients with therapy-related MDS and therapy-related oligoblastic AML [40].

Additional prognostic features

A number of other potentially relevant prognostic approaches in MDS will be reviewed in the following sections. In particular, data from the emerging fields of flow cytometry, cytogenetic adjuncts,

and molecular analysis will most likely form the basis of the next iteration of the IPSS-R and other MDS prognostic models [41].

Flow cytometry

Several groups have reported on flow cytometry-based scoring systems that have both diagnostic and prognostic value in MDS. The flow cytometric scoring system (FCSS) was developed by comparing BM cells from MDS patients to other disorders and healthy donors [42]. This model was based on myeloid and monocytic cell immunophenotypic aberrancies and divided patients into three categories (normal/mild, moderate, and severe) that correlated with IPSS risk. The FCSS had diagnostic and prognostic value and was subsequently validated and found to have prognostic value for post-transplantation outcome and response to MDS therapy [43–45]. The European LeukemiaNet Working Group consortium also developed and validated a flow cytometric score (FCM-score) based on four weighted factors including myeloblast-related cluster size, B-progenitor-related cluster size, lymphocyte to myeloblast CD45 ratio, and granulocyte to lymphocyte side scatter ratio [46]. These factors can be assayed with only forward scatter, side scatter, CD45, CD13, and CD33 parameters required. The FCM-score was shown to be both sensitive and specific for diagnosis of the often difficult to diagnose low-grade MDS cases and provided additive prognostic power to the IPSS-R [47,48]. Another study showed that the number of CD34+/CD13 + cells added prognostic value to the IPSS-R [37]. To date, none of the major prognostic scoring systems have included flow cytometry variables including lineage infidelity and aberrant antigen expression.

Cytogenetics adjuncts

Approximately 50–55% of MDS patients have a normal karyotype, but conventional metaphase cytogenetics (MC) analysis is limited by the sensitivity of the assay and cannot detect copy neutral loss of heterozygosity (CN-LOH) from acquired uniparental disomy [23]. Newer cytogenetic adjuncts, such as single-nucleotide polymorphism array (SNP-A) and array comparative genomic hybridization (aCGH), have emerged as diagnostic adjuncts with prognostic significance. Combination of SNP-A and MC improved the diagnostic yield of chromosome defects from 44% to 74%, and the presence and number of new lesions detected by SNP-A had independent prognostic significance [49]. SNP-A analysis of either BM or PB cells was also able to detect chromosomal abnormalities in 50% of patients with unsuccessful MC and these correlated with IPSS-R risk groups [50]. Array CGH was used to study CD34 + cells from lower-risk MDS patients and showed that maintenance of genomic integrity with <3 megabases total disruption of the genome resulted in better OS and lower leukaemia transformation risk [51]. Further refinements, including accessibility of the technique and controlling for germline changes, will be required before their use can become generalized.

Analysis of gene expression, microRNAs, epigenetics, and telomeres

The prognostic role of gene expression changes in MDS has been studied for many years before the more recent advent of microarray-based gene expression profiling (GEP). For example, changes in expression of BCL2, MYC, WT1, MN1, ERG, BAALC, EVI1, and RPS14 have each been shown to have prognostic significance in MDS [52–55]. GEP in CD34 + cells from patients with MDS has confirmed the prognostic significance of deregulated gene pathways and RNA expression. GEP-based scores have been developed that build upon the IPSS and distinguish patients whose disease rapidly transformed to AML [56–58]. These studies have implicated pathways involving immunodeficiency, apoptosis, and chemokine signalling in early MDS and DNA damage response and checkpoint pathways in advanced MDS. Furthermore, profiling of microRNA (miR) expression has revealed that changes in expression of specific miRs play an important role in MDS pathogenesis and may have a prognostic impact for survival and treatment response [59].

Epigenetic changes, particularly DNA hypermethylation, are also important in the pathogenesis of MDS. Increased DNA hypermethylation has been shown to be associated with shorter OS and shorter time to AML evolution independent of IPSS risk category, although these changes did not predict

outcome to HMA therapy [60,61]. Finally, telomere dynamics and telomerase activity have been associated with MDS pathogenesis and prognosis [62].

Gene mutations

The discovery of recurrent mutations in MDS has increased dramatically since the development of next generation sequencing (NGS) approaches. Genes have been sequenced in several large series of MDS patients using targeted gene set approaches [63–65] or whole exome or genome sequencing [66]. These and other studies show that up to 80% of patients with MDS harbour a mutation of interest and subclone complexity increases with transformation to AML [65,66].

A summary of recurrent gene mutations found in at least 5% of *de novo* MDS patients across multiple studies and their prognostic impact is shown in Table 2 [63–67]. Among these mutations, TP53, TET2, DNMT3A, and SRSF2 are most frequently mutated in therapy-related MDS with TP53 showing the most negative prognostic impact [68]. For CMML, 93% of patients had mutations in at least one of TET2, SRSF2, ASXL1, RAS, RUNX1, CBL, EZH2, JAK2, and IDH1/2 [69]. U2AF1 and DNMT3A were associated with a poor prognosis in CMML patients [70].

Two studies used a cancer-targeted mutation screening approach to examine the presence and prognostic relevance of mutations in MDS [64,65]. Bejar et al. showed that 51% of patients had a mutation, including 52% of patients with a normal karyotype. Five genes retained negative prognostic significance independent of IPSS in multivariate analysis: TP53, EZH2, ETV6, RUNX1, and ASXL1. The presence of these gene mutations was found to upstage patients classified by IPSS by one risk category. Papaemmanuil et al. showed that MDS was characterized by oncogenic mutations in 43 genes with genes implicated in RNA splicing and DNA modification occurring early and chromatin regulation and cell signalling occurring later in the course of disease [65]. Fifty-one per cent of patients had an mRNA splicing pathway mutation and 43% had 2-3 total oncogenic mutations. Outcomes positively correlated with the number of oncogenic mutations, and driver mutations had equivalent prognostic significance whether they were clonal or subclonal. Incorporation of mutational data with the IPSS did not add significant prognostic power suggesting that clinical features may account for many effects of the mutations and that large datasets will be required to assess prognostic significance of mutations in MDS.

Most recently, Haferlach et al. screened MDS patients for known and putative mutations and deletions in 104 genes using targeted NGS and aCGH [63]. All WHO subtypes and IPSS-R risk categories were represented. They found that 90% of patients harboured at least one mutation and 92% of patients had either a mutation of copy number alteration. Univariate analysis revealed that 25 genes had an effect on survival. Cox regression analysis was used to create a novel prognostic model combining 14 genes (ASXL1, CBL, ETV6, EZH2, KRAS, LAMB4, NCOR2, NF1, NPM1, NRAS, PRPF8, RUNX1, TET2, and TP53) with clinical variables (age, sex, and IPSS-R variables including cytopenias, BM blasts, and cytogenetics) that separated patients into four risk categories. A gene-only model was similarly effective at stratifying risk, but was inferior to the model combined with the clinical IPSS-R categories. Notably, the combined model outperformed the IPSS-R alone.

Table 2
Prognostic impact of recurrent (>5%) mutations in MDS.[a]

Function	Gene
Epigenetic/chromatin modifiers	TET2[b], DNMT3A[c], ASXL1[c], EZH2[c]
Splicing	SF3B1[b], SRSF2[c], U2AF1[c], ZRSR2[c]
Differentiation	RUNX1[c]
DNA damage response/apoptosis	TP53[c], BCOR[c]
Cohesin complex	STAG2[d]
Signalling	CBL[d]

[a] Table adapted from Refs. [63–67].
[b] Favourable prognostic impact.
[c] Negative prognostic impact.
[d] Neutral prognostic impact.

Gene mutations have a clear impact on MDS prognosis, but challenges remain before these studies can be widely applied to patients with MDS. Many of the prognostic effects of individual mutations differ by study arguing that adequate sample size is important and that changes in multiple gene pathways are likely to be critical to evaluate. It will be important to standardize testing methods, determine which mutations within a gene are prognostic, and the variant allele frequency level at which a gene mutation becomes prognostic before these assays can be used routinely. Further modifications of prognostic scoring systems factoring in gene mutations should become feasible for use in everyday practice. An international collaborative study by the IWG-PM is ongoing, working to coalesce a large molecular and clinical dataset to develop a further refinement of a next-generation MDS prognostic classification.

Comorbidities

Because of the advanced age of the MDS population, several groups have evaluated comorbidities as a prognostic factor in MDS. The Charlson comorbidity index (CI) and haematopoietic stem-cell transplantation-specific comorbidity index (HCT-CI) were both prognostic for OS in MDS [30,71]. The MDS comorbidity index (MDS-CI), consisting of cardiac, liver, renal, and pulmonary disease and solid tumours was developed and validated as a time-dependent tool for OS and non-leukaemic death prognostication in MDS [72,73]. Subsequent work has shown that the model may be additive to the IPSS, WPSS, and IPSS-R [72,74,75]. Another model, the Adult Comorbidity Evaluation-27 (ACE-27), was shown to add to the prognostic ability of both the IPSS and IPSS-R, with the most pronounced effect on prognosis in intermediate and higher-risk groups [76,77]. These studies have shown that future prognostic scoring systems may benefit from the additional inclusion of comorbid medical conditions.

Miscellaneous prognostic factors

A number of other features have been associated or correlated with prognosis in MDS, including BM microenvironment alterations [78–80], mean corpuscular volume [81], platelet mass [82], absolute lymphocyte count [83], basophilia and eosinophilia [84], hypoalbuminemia [85], and T-regulatory cells [86]. A separate risk model for hypocellular MDS has also been proposed [87].

Summary

The heterogeneous clinical and pathological nature of MDS has presented a challenge to clinicians managing this spectrum of diseases. Many groups have independently developed MDS prognostic scoring systems over the past few decades to account for this heterogeneity by providing treating physicians information about survival and leukaemia evolution to aid in clinical decision-making. Furthermore, these models have been incorporated in the clinical trials that have led to approval of new therapeutic agents in MDS. The IPSS-R has shown improved prognostic utility for assessing survival and leukaemia evolution compared to the IPSS and other prognostic scoring systems. This categorization was designed for everyday clinical use and for further aiding the design and analysis of future clinical trials for MDS.

However, as for all classification systems, it is becoming clear that further refinements in prognostic scoring systems are required as our understanding of MDS pathogenesis and prognosis rapidly evolves with recent advances in flow cytometric analysis, gene expression profiling, array-based genomics, and next-generation molecular sequencing-based mutational profiling. In addition, models addressing the role of comorbidities have been reported and will need incorporation. These new data need further refinement, study in larger patient cohorts, and standardization for use in routine clinical practice. Combination of advanced analyses of clinical, cytogenetic, and molecular variables should markedly enhance the ability of future models to improve prognostication in MDS.

Conflict of interest statement

Dr. Jonas has no conflicts of interest to disclose.
Dr. Greenberg has no conflicts of interest to disclose.

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