Impact of Age and Comorbidity in Myelodysplastic Syndromes

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Myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal hematopoietic stem cell disorders characterized by a variable clinical course, ineffective hematopoeisis, and a tendency to transition to acute myeloid leukemia (AML). Based on morphologic features, including bone marrow blast cell percentage, MDS are classified according to the French-American-British Cooperative Study Group or World Health Organization (WHO) proposal.² Because the survival time varies considerably among patients with MDS, even within morphologic subgroups, much attention has focused on identifying additional prognostic factors.

The International Prognostic Scoring System (IPSS) was a milestone and has become the gold standard for risk assessment in patients with primary MDS treated with supportive care only.³ The IPSS has improved risk stratification in clinical trials and is used for decision-making in clinical practice. Several attempts have been made to refine the IPSS, including the integration of additional parameters such as serum lactate dehydrogenase⁴ or dynamic aspects such as transfusion requirements.⁵,⁶ Thus, a WHO classification-based prognostic dynamic scoring system (WPSS) was described recently, based not only on initial findings but also on evolution over time and response to treatment.⁷

In Western countries, the older population is expanding progressively. Because 60% of malignancies occur in patients older than 65 years, the demand for antineoplastic treatment in the elderly is increasing progressively, paralleled by an increased demand for treatment of comorbid conditions.⁸ MDS are diseases typical of the elderly. The median age at diagnosis is 70+ years in epidemiologic studies (72 years in the Düsseldorf⁹ and 76 in the Tyrol¹⁰ registry). Moreover, incidence increases rapidly with advanced age, displaying age-specific incidences of 8.7, 24.5, and 31.3/100,000/year for the groups aged 60 to 70 years,
Age in MDS

Several studies have focused on the development of prognostic scores in MDS. Although chronologic age has been incorporated in most of these analyses, the prognostic value of age in a given patient with MDS often remains controversial. The Spanish Sanz Score established advanced age (≥ 60 years) as a risk factor for overall survival (Table 1). Remarkably, this is the only score that included age in the final prognostic model, along with the medullary blast cell percentage and platelet count. Although the latter 2 variables reflect a high probability of transformation to AML and the degree of bone marrow failure, age was assumed to be a host-related prognostic factor and a surrogate marker for comorbidity and organ dysfunction.

The analysis from Düsseldorf and a subsequent analysis by the German-Austrian MDS study group considered age of 70 years or older an independent adverse prognostic factor for survival in univariate and multivariate analyses. The Karnofsky Index was also a significant independent prognostic variable. The French Lille Score, the first to establish cytogenetic parameters as a key prognostic factor, also showed the importance of advanced age. The IPSS is currently the gold standard in clinical decision-making in primary MDS, and is based on cytogenetic risk categories in combination with the medullary blast count and number of cytopenias in peripheral blood.

During development of the IPSS, additional prognostic factors were examined, including age. In univariate and multivariate analyses, age of 70 years or older was significantly correlated with shorter survival. However, age was not formally included in the final IPSS because it had a weaker significance than the 3 variables ultimately defining the score. The recently developed WPSS classifies patients into 5 risk groups with different survivals and probabilities of leukemic evolution based on WHO subgroup, karyotype, and transfusion requirements. Age had a significant negative impact on overall survival in this series. Considering WHO subgroups, age was statistically relevant among patients who had refractory anemia with or without ringed sideroblasts (P = .001) and those who had refractory cytopenia with multilineage dysplasia with or without ringed sideroblasts (P = .002), whereas it was not significant among subgroups with refractory anemia with excess blasts, types 1 and 2.

In general, the relevance of age in prognosis is more pronounced in patients with good-risk than in those with high-risk disease as defined by the IPSS or WHO classification. Host-related parameters, such as performance status and comorbid conditions, predominantly impact the clinical outcome of low-risk MDS by influencing therapy tolerance and susceptibility to bone marrow failure. This is of special importance, because most MDS patients have low-risk MDS in clinical practice. In contrast, the clinical outcome in high-risk MDS is determined mainly by the unfavorable biology of the disease.

Considering these results, chronologic age emerges as a significant prognostic factor for overall survival in univariate and multivariate analyses (Table 1). However, age as a prognostic parameter is included in only one, namely the Spanish score, because other parameters achieve more statistical significance. Thus, including age per se in scoring systems remains controversial. Although the scoring systems established so far have clearly succeeded in defining disease-specific prognostic factors, patient-related factors such as functional capacities, comorbidities, including cardiac insufficiency, or tolerance to chemotherapy, are less well defined. Age has often been used as a surrogate marker to unite the latter factors in one parameter. However, the prognostic importance of factors...
such as transfusion requirements or ferritin levels\textsuperscript{5,6} showed that patient-related factors influence the outcome of this disease.

Results are complex regarding the relevance of chronologic age in leukemia transformation. The analysis by Sanz et al.\textsuperscript{13} and the IPSS Int-2 subgroup\textsuperscript{3} showed that the percentage of leukemia transformation was higher in younger persons. Although the time to AML evolution seemed shorter in elderly patients in the IPSS Int-1 subgroup (6.9 vs. 2.7 years in those aged ≤ 60 vs. > 60 years, respectively), advanced age was not defined as a risk factor for AML evolution in the whole IPSS study group.\textsuperscript{3}

Similarly, in most analyses, age and leukemia transformation were not correlated.\textsuperscript{4,7,9} A detailed analysis of the different age groups showed a significantly lower leukemia transition in cohorts aged 20 to 39 years and ≥ 80 years or older.\textsuperscript{17} These findings indicate that younger patients are offered chemotherapy or hematopoietic stem cell transplantation often before transformation occurs, whereas results in elderly patients may suggest a diagnosis bias. Postmortem examination and bone marrow aspiration, which is the cornerstone of AML diagnosis, are obviously performed less often in elderly patients. However, in patients aged 80 years, age-related median survival should be considered, which is more than 8 years in women and more than 6 years in men.\textsuperscript{19} Considering these survival estimates, diagnostic and therapeutic procedures should not be withheld in elderly patients with MDS based solely on age. As clinical outcome and life expectancy are clearly influenced by performance status and coexisting disorders, the latter parameters should be evaluated and integrated in current decision models.

### Relevance of Age-Adjusted Evaluation

Because shorter overall survival in elderly persons is logical, prognostication in the elderly should include an age-adjusted evaluation model. Parameters such as the standardized mortality rate (SMR) or age-adjusted survival must be considered and implemented. These factors compare the survival of a given patient with an age- and sex-matched population, contributing to the comprehensive understanding and decision-making for individual patients.\textsuperscript{20} Thus, the standardized mortality rate for a representative MDS cohort was 4.58, implying a 4.58-fold risk for death. Considering the different IPSS groups, the standardized mortality rate was 2.5 in low-risk; 3.83 in intermediate-1; 6.71 in intermediate-2; and 11.13 in high-risk patients.\textsuperscript{16} Addressing various age groups, younger patients had an SMR of 10.08 compared with 3.39 in elderly patients. Thus, even in elderly persons, MDS is a relevant disease displaying a threefold risk for death, resulting in a significant loss of life years in most prognostic subgroups.\textsuperscript{16,20} However, in a subgroup of elderly patients (≥ 70 years) with excellent prognosis, life expectancy is more than 8 years in women and more than 6 years in men.\textsuperscript{19}

### Table 1 Age as a Risk Factor for Survival and Leukemia Transformation in MDS

<table>
<thead>
<tr>
<th>Score</th>
<th>Survival Univariate Analysis (Risk Factor; P Value)</th>
<th>Survival Multivariate Analysis (Risk Factor; P Value)</th>
<th>Leukemia Transformation Univariate Analysis (Risk Factor; P Value)</th>
<th>Leukemia Transformation Multivariate Analysis (Risk Factor; P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spanish Sanz Score\textsuperscript{14}</td>
<td>≥ 60 y.; .018</td>
<td>≥ 60 y.; .0001</td>
<td>&lt; 60 y.; .0004</td>
<td>NS</td>
</tr>
<tr>
<td>Düsseldorf Score\textsuperscript{9}</td>
<td>≥ 70 y.; .002</td>
<td>≥ 70 y.; .008</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>French Lille Score\textsuperscript{15}</td>
<td>≤ 50, 50–60, Age; .0001</td>
<td>&gt; 60 y.; &lt; .0001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>IPSS\textsuperscript{3}</td>
<td>&gt; 60 y.; .0001</td>
<td>&gt; 60 y.; &lt; .0001</td>
<td>NS</td>
<td>&gt; 60 y.; &lt; .0001 25% AML</td>
</tr>
<tr>
<td>IPSS-LDH\textsuperscript{4}</td>
<td>≥ 70 y.; &lt; .00005</td>
<td>≥ 70 y.; &lt; .00005</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>WPSS\textsuperscript{5,7}</td>
<td>Advanced age; &lt; .001</td>
<td>NR</td>
<td>NS</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; IPSS, International Prognostic Scoring System; IPSS-LDH, International Prognostic Scoring System, with serum lactate dehydrogenase as a prognostic variable; MDS, myelodysplastic syndromes; NR, not reported; NS, not significant; WPSS, WHO classification-based Prognostic Scoring System.

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expectancy was not different from that of the general population, indicating the relevance of age-matched prognostic scoring systems for designing age- and risk-adapted treatment strategies.

**Concept and Dimension of Comorbidity in Geriatric Oncology**

Advanced age is not only associated with a growing incidence of MDS, but also an increase in illnesses and health problems. Comorbidity is defined as "any distinct clinical entity that has existed or may occur during the clinical course of a patient who has a condition under study." Comorbidities are essential in overall prognosis and treatment decision-making in elderly patients. They clearly complicate and influence diagnostic approaches and treatment concepts and are associated with reduced life expectancy and treatment tolerance.

The presence of comorbidities, such as diabetes (odds ratio [OR], 2.0; 95% CI, 1.8–2.3), lung disease (OR, 4.9; 95% CI, 4.0–6.0), heart failure (OR, 5.5; 95% CI, 4.4–7.0), or coronary artery disease (OR, 2.0; 95% CI, 1.7–2.2), has been shown to be correlated with an increased mortality rate in older adults. Compared with patients who had no comorbid conditions, patients with breast cancer who had 2 of 7 selected comorbid conditions had a twofold higher rate of 3-year mortality, and those with 3 or more comorbidities had a fourfold higher rate, supporting the cumulative relevance of comorbidities.

The relevance of comorbidities is underlined by the frailty index, which defines the personal biologic age of an elderly person and consists of the chronologic age and comorbidity of that person. The frailty index is a strong predictor of survival. Implementing comorbidity in clinical plans is a mainstay of geriatric oncology, which, by definition, begins "when the health status of patients begins to interfere with oncological decision-making guidelines."

Because comorbidity is a multidimensional variable, including diseases that influence function, survival, or tolerance to treatment, several scoring systems addressing distinct aspects have been developed. Multiple comorbidity scales are used, each offering advantages and disadvantages. Several instruments have been developed to classify various comorbid diseases and quantify the severity of the overall comorbid condition. None of the instruments were specifically designed for patients with cancer, but they have been used to classify comorbidity in several types of cancer (Table 2).

The Charlson Comorbidity Index (CCI), established by Mary Charlson in 1987, was based on 1-year mortality in internal medicine in an inpatient setting. The CCI is a chart-based scoring system using 19 items, including various diseases, which are weighted, and is validated for several types of tumors. An age-adjusted composite version has been developed and adds an extra point for each decade starting at 50 years of age. Although it is simple and can be easily and retrospectively implemented from the charts, limitations include the lack of rating (e.g., for dementia or coronary heart disease) and deficiency of relevant health problems, such as hematopoietic insufficiency or decreased lung function, which might be present in the elderly. In contrast, AIDS is included as a parameter, but is rarely encountered in elderly patients with MDS. Working from these limitations, newer indices based on the CCI have been developed.

The Cumulative Illness Rating Scale (CIRS) comprehensively assesses comorbid diseases in a particular patient. Severity of comorbidities is rated similarly to the Common Toxicity Criteria grading from 0 to 4 (0, no problem; 1, mild; 2, moderate; 3, severe; 4, extremely severe). This scale can be presented as the number of categories endorsed, total score achieved, and number of categories displaying a grade 3 or 4 severity. Based on needs in the elder population, the Cumulative Illness Rating Scale for Geriatricians (CIRS-G) was established and includes the dimension hematopoietic. Applying the sophisticated CIRS-G requires more experience than the CCI. Parameters of the CCI can be extracted from the CIRS.

Satariano and Ragland determined the effect of comorbidity on survival in patients with breast cancer. Based on an overall 3-year survival of 85%, 3 or more comorbid ailments resulted in a 20-fold higher rate of mortality than no comorbidity. The effects of comorbidity were observed independently of age, race, tumor stage, histologic type, type of treatment, or social/behavioral factors.

Application of comorbidity scales shows increasing comorbidity with age. However, outcomes and clinical prognoses of elderly patients are determined multidimensionally. Clinical outcome is determined by functional capacities, cognition, and quality of life, including depression and social support, in addition to
Furthermore, ample evidence shows that comorbidity and performance scales each independently predict outcome. Based on this, indices have been developed that combine comorbidity and functional predictors for a more comprehensive evaluation. For example, the composite Kaplan-Feinstein Scale (KFS) is based on 12 ailments rated on a scale of 0 to 3; in addition, the functional aspect is addressed by applying the item “impairment of locomotion.” Similarly, the Index Of Coexisting Disease integrates diseases and functional domains.

A prognostic index that includes comorbid conditions and functional capacities to predict survival in the elderly was recently described. It is based on the parameters age, sex, self-reported comorbid conditions, and functional capacities. It is easy to use with no need to analyze medical records or laboratory testing. It helps identify older patients with low-risk disease who may benefit from diagnostic and therapeutic strategies, and estimates life expectancy. An 85-year-old woman with excellent functional capacities and lack of comorbid conditions is thus characterized by an 88% probability of 4-year survival, identifying her as a candidate for diagnostic and therapeutic strategies.

The table below summarizes various comorbidity scales in geriatric oncology:

<table>
<thead>
<tr>
<th>Index</th>
<th>Items</th>
<th>End Point</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson Comorbidity Index (CCI)</td>
<td>19 conditions, weighted 1–6</td>
<td>1-y mortality in hospitalized internal medicine patients</td>
<td>Simple, most widely used in oncology; underdetects significant ailments, such as anemia and decreased lung function</td>
</tr>
<tr>
<td>CCI age</td>
<td>Each decade after 50 years of age, add 1 point</td>
<td>5-y mortality in surgery patients</td>
<td>Composite index</td>
</tr>
<tr>
<td>Cumulative Illness Rating Scale (CIRS)</td>
<td>13 organ systems, weighted 0–4</td>
<td>Detailed and comprehensive list of diseases</td>
<td></td>
</tr>
<tr>
<td>Cumulative Illness Rating Scale-Geriatric (CIRS-G)</td>
<td>14 organ systems, rated 0–4 (weighted)</td>
<td>Geriatric outpatients</td>
<td>Adapted for elderly</td>
</tr>
<tr>
<td>Satariano and Ragland</td>
<td>Myocardial infarction, types of heart disease, diabetes, other forms of cancer, and respiratory, gallbladder, liver conditions</td>
<td>3-y survival in 936 breast cancer patients based on SEER registry</td>
<td>Simple, qualitative valuation</td>
</tr>
<tr>
<td>Kaplan and Feinstein</td>
<td>12 ailments weighted, including functional activity (locomotive impairment), alcohol, and miscellaneous</td>
<td>5-y survival in diabetes mellitus</td>
<td>Composite index</td>
</tr>
<tr>
<td>Index Of Coexisting Disease</td>
<td>Includes 14 diseases (0–4) and a functional index of 12 conditions (0–2)</td>
<td>2-y survival in breast cancer patients</td>
<td>Composite index</td>
</tr>
<tr>
<td>Prognostic Index</td>
<td>Composite index based on 12 items (e.g., age, sex, self-reported comorbidity, functional measures)</td>
<td>4-y mortality established in community-dwelling U.S. adults</td>
<td>Not yet validated in oncology patients</td>
</tr>
</tbody>
</table>

Abbreviation: SEER, Survey of Epidemiology and End Results.
for tailored approaches; or 3) frail patients with complex comorbidity or major functional impairment who benefit mainly from palliative treatment and symptom management.\textsuperscript{8,19,38}

### Comorbidity in MDS: Status Quo and Future Directions

The impact of comorbidity on survival and leukemia transformation in MDS is still poorly understood and evaluated.\textsuperscript{39} The WPSS transfusion frequency parameter reflects MDS biology that results in anemia. In addition, comorbidity is partially addressed, because transfusion frequency is clearly determined by cerebrovascular, cardiac, and pulmonary diseases and performance status. Preliminary analyses indicate that the CCI might represent a prognostic parameter independent from IPSS.\textsuperscript{40} However, available data are mainly from the structured evaluation of patients with MDS as part of a cohort treated with high-dose strategies.

Nonmyeloablative hematopoietic cell transplantation (HCT) regimens and improvements in supportive care result in more patients of advanced age or with more severe comorbidities, for whom allogeneic HCT is considered. Therefore, scores were developed to quantify comorbidity and predict mortality and survival (Table 3).

#### Table 3 Application of Comorbidity Scores in MDS

<table>
<thead>
<tr>
<th>Test</th>
<th>Items</th>
<th>End point</th>
<th>Comment</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson Comorbidity Index (CCI)</td>
<td>Score based on CCI</td>
<td>Different end points, such as toxicity, survival, and mortality</td>
<td>Adapted CCI applied in HCT. High pretransplantation comorbidity scores predict higher NRM</td>
<td>Sorror et al.\textsuperscript{41} Diaconescu et al.\textsuperscript{42}</td>
</tr>
<tr>
<td></td>
<td>CCI</td>
<td>Overall survival</td>
<td>Prognostic factor independent from IPSS in MDS</td>
<td>Pelz et al.\textsuperscript{40}</td>
</tr>
<tr>
<td>HCT-Specific Comorbidity Index (HCT-CI)</td>
<td>Modified, weighted score based on CCI</td>
<td>2-y NRM and survival in validation set of 347 HCT patients</td>
<td>Median age 44.8 y More sensitive and better predictor of survival than CCI</td>
<td>Sorror et al.\textsuperscript{43} Sorror et al.\textsuperscript{44}</td>
</tr>
<tr>
<td></td>
<td>• New items obesitas, psychiatric, or infectious problems</td>
<td>Overall survival</td>
<td>Was used for risk stratification in induction therapy in elderly AML patients</td>
<td>Giles et al.\textsuperscript{45}</td>
</tr>
<tr>
<td></td>
<td>• Refined definitions in several items like cardiac, pulmonary, or hepatic function</td>
<td>Early death rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretransplantation Assessment of Mortality Score (PAM)</td>
<td>8 weighted items, including age, donor type, disease risk, conditioning regimen, renal, hepatic, pulmonary function</td>
<td>2-y all-cause mortality for allogeneic HCT</td>
<td>Age is an item Pulmonary function must be tracked</td>
<td>Parimon et al.\textsuperscript{46}</td>
</tr>
<tr>
<td>CCI Kaplan-Feinstein Scale (KFS) ECOG Performance Status (PS)</td>
<td>Parallel evaluation of 2 comorbidity and 1 function scales</td>
<td>TRM in 105 RIC-HCT patients</td>
<td>Combination scale of KFS and PS</td>
<td>Artz et al.\textsuperscript{47}</td>
</tr>
<tr>
<td>MDS-specific comorbidity index (MDS-CI)</td>
<td>Adapted from HCT-CI</td>
<td>NLD Overall survival</td>
<td>Retrospective analysis of 840 consecutive MDS patients</td>
<td>Della Porta et al.\textsuperscript{48}</td>
</tr>
</tbody>
</table>

**Abbreviations:** AML, acute myeloid leukemia; HCT, hematopoietic cell transplantation; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; NLD, nonleukemic death; NRM, nonrelapse mortality; RIC-HCT, reduced-intensity conditioning hematopoietic cell transplantation; TRM, treatment-related mortality.
Impact of Age and Comorbidity in Myelodysplastic Syndromes

Because of the usefulness of the CCI in predicting outcome in patients with MDS undergoing HCT, the HCT-specific comorbidity index (HCT-CI) was developed. Incorporating laboratory data, new items were included and cardiac, pulmonary, and hepatic functions redefined. This new index was established in a training and validation set and proven to be more sensitive and more predictive of survival than the CCI. Even in a series of patients with AML, the HCT-CI better predicted early death and overall and event-free survival in patients 60 years or older treated with induction therapy. Parimon et al. developed another score for assessing comorbidity in HCT that includes age, unlike the HCT-IC.

An analysis by Artz et al. introduces the dimension of function in HCT risk-scoring. In assessing the ECOG Performance Status (PS) and the dimension of comorbidity using 2 indices (CCI, KFS) in parallel, this analysis provides a prognostic predictor combining the KFS and PS and distinguishing high- from low-risk patients based on transplant-related mortality.

In general, results of these studies are limited to patients who underwent HCT. Patients who did not qualify or were not referred to a transplant center were not analyzed. Thus, MDS patients who constitute the majority in clinical practice (i.e., those displaying complex comorbidities, an advanced age, or those with low-risk MDS) generally do not qualify for HCT and therefore were not included and evaluated. Applying comorbidity scores in these patients, particularly the CCI and HCT-CI, seems promising, but has only just begun. Based on the CCI, Pelz et al. from Düsseldorf showed that comorbidities were a relevant prognostic parameter for overall survival independent from IPSS. In a large cohort of consecutive patients with MDS from Italy, comorbidities were described in more than half, with cardiac disease the most relevant disorder. Comorbidities significantly affected risk for nonleukemic death and overall survival, whereas the risk for leukemic progression was not influenced. Based on these data, an MDS-specific comorbidity index was developed, identifying 3 distinct groups of patients with different probabilities of nonleukemic death and overall survival, and providing a new useful tool for clinical decision-making, particularly in patients with low-risk MDS.

Conclusions

Although treating patients with MDS has become more successful, it is also more complex because of new therapeutic options, including demethylating agents and immune modulating drugs, such as lenalidomide, and improvements in supportive care, including iron chelation. To choose appropriate treatment for individual patients, especially those who are elderly, algorithms must be established and implemented that integrate not only chronologic age but also age-adjusted life expectancy and comorbidity. Comorbidity scores have been developed, evaluated, and validated for high-dose strategies in MDS. Application of these scores to non-HCT MDS patients is in its infancy and provides preliminary evidence that integration of comorbidities improves prognostic scoring and risk stratification, particularly in low-risk MDS. The systematic evaluation and integration of aspects of comorbidity in MDS will improve individualized therapy-planning and outcome in clinical studies and medical practice.

References


