Prognostic impact of age and gender in 897 untreated patients with primary myelodysplastic syndromes

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Background: The International Prognostic Scoring System (IPSS) is the golden standard to assess prognosis in myelodysplastic syndromes (MDS). The aim of this analysis was to study age and gender as interacting variables for individualized prognostication.

Patients and methods: In all, 897 patients with primary MDS treated with supportive care only were examined in a retrospective multicenter study. A Cox model was developed to determine the prognostic impact of age and gender on survival and to examine their modulating influence on IPSS results. Based on main effects and interactions of these variables, we established an individualized age- and gender-adapted scoring system to improve prognostication in MDS.

Results: While the risk of a patient in the IPSS is best represented by the values 0 (low), +1 (intermediate-1), +2 (intermediate-2), and +3 (high), these values were found to vary between −1.9 and +3.5 in the same patients when including age and gender. Whereas in low-risk MDS, male patients were found to have a less favorable survival, a particularly high risk (+3.5) was found in younger (≤66 years) high-risk female patients.

Conclusion: The inclusion of age and gender and their respective interactions contribute to improved and individualized prognostication in MDS.

Key words: age, gender, IPSS, MDS, prognosis

Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of hematologic stem-cell disorders characterized by ineffective hematopoiesis. Morphological features and the bone marrow blast cell percentage classify these disorders according to the French–American–British (FAB) [1] or to the World Health Organization (WHO) [2] proposal. In addition, an international working group published recently new standards in the diagnosis of the MDS [3]. Because survival times vary considerably among patients with MDS, even within morphological subgroups, much attention has been focused on identifying additional prognostic factors. The International Prognostic Scoring System (IPSS) [4], introduced in 1997, has become the gold standard for risk assessment in patients with primary MDS, improving risk stratification in clinical trials and decision making in clinical practice. The IPSS includes three cytogenetic risk categories, medullary blast count and number of cytophenias in the peripheral blood. Although the IPSS has also been validated for the WHO classification [5], there is room for improvement, as proposed by us [6] and others, most recently by an Italian–German group presenting the so-called WHO classification-based Prognostic Scoring System (WPSSF), a new score, based on WHO classification, cytogenetics and red blood cell transfusion requirement [7].

Already in the original IPSS publication, age and gender were analyzed and discussed. Their additional predictive importance was stated, but not quantified in the scoring system [4]. The analysis indicated that not only age but also gender are significant prognostic factors for survival and acute myelogenous leukemia (AML) evolution in MDS patients, but somewhat weaker than the variables finally included in the IPSS. Moreover, earlier studies evaluating age and/or gender as prognostic factors had yielded significant results [8–10]. Although age and gender were of significant importance, even in multivariate analysis, they were not recognized as variables in the different prognostic proposals,
except the Spanish score, established in the precytogenetic era [10]. The other scoring systems favored disease-related variables over host-associated ones.

In a retrospective multicenter analysis, using a large German and Austrian database of 897 completely documented patients with primary MDS, treated exclusively with supportive care, the modulating impact of age and gender on the IPSS was studied, to improve risk assessment. The major aim of this study was to individualize the risk prediction of the IPSS for single-MDS patients by a model accounting for the observed heterogeneities within each IPSS subgroup regarding age and gender. This approach leaves the IPSS, as the best established prognostic tool and as common reference, unchanged. At the same time, it offers a way for further differentiation, as required for individual prognosis.

patients and methods

patients

From 1976 to 2002, 1157 patients with primary MDS and available cytogenetic analysis were diagnosed by the German and Austrian MDS study group, excluding cases of secondary MDS. In all, 897 patients who received only supportive treatment were subjected to this retrospective analysis. Supportive care was defined by transfusion therapy, growth factors, antibiotics when needed, and iron chelation. Patients were categorized according to the IPSS [4], evaluated for clinical features as well as for blood and bone marrow parameters at the time of diagnosis and followed for survival and leukemic progression. Overall survival duration was the primary end point; data for leukemic evolution were collected similarly.

diagnosis of MDS

Diagnosis was made by cytomorphological and histological methods according to the proposals made by the FAB group in 1982 [1]. It was not possible to apply the WHO classification for all 897 patients [2]. The medullary blast count was determined on the basis of at least 300 nucleated cells analyzed in bone marrow smears. A diagnosis of MDS required that cytopenia had to be present for at least 3 months. All MDS types according to the FAB classification were considered in the analysis. Furthermore, a central morphological review was carried out. AML evolution was defined by an increase of the medullary blast count to ≥30%.

cytogenetics

Cytogenetic analysis was carried out at the individual centers, and karyotypes were documented according to the 1995 International System for Human Cytogenetic Nomenclature recommendations [11, 12]. Results were reviewed centrally by DH. A minimum of 10 metaphases per patient were required. Whenever possible, ≥20 metaphases from each patient were analyzed in order to demonstrate the clonal nature of the aberrations. The median number of metaphases was 22 (range 10–71). Details of cultivation, banding procedure, and processing have been described elsewhere [13, 14].

statistical analysis

For basic data description counts, percentages, medians, confidence intervals and ranges are given. The prognostic impact of different characteristics and their interactions on survival were estimated by Kaplan–Meier product limit estimates and Cox proportional hazards model models [15, 16], inspecting the proportionality assumption by plots of scaled Schoenfeld residuals over time and the ZPH test and checking the linearity assumption regarding the IPSS.

Models of different complexity including all main effects and first-order interactions were considered.

In addition to parameter estimates and P values, estimated risk, rescaled to the original IPSS scale (0–3), and model-based median survival for each subgroup together with Schoenfeld’s V coefficient [17] (quantifying the explanatory power of the model) are given.

As level of significance, alpha = 0.05 (two sided) was used. By its nature, the study is explorative and therefore no adjustment for multiple testing was applied. All calculations were done by the open source statistical computing environment R [18].

results

evaluation of the MDS population

Source data from 897 patients with primary MDS were evaluated for risk assessment. The median age at diagnosis was 68 years (range 16–99 years), the male : female ratio was 1.3 : 1, and the median survival for the whole population was 47 months, with a median follow-up of 56 months. Patient numbers, percentages, and median survival of the IPSS risk groups are given in Table 1 and survival curves (together with expected curves of corresponding reference populations) in Figure 1A. The distribution of the whole population into different IPSS risk groups and survival data were in accordance with published data, especially the original publication of the IPSS [4].

individualized risk assessment

As the IPSS has a large risk range within its different groups, we tried to refine the individual prognostication by adding age and gender as covariables. To keep the additional results as traceable as possible, we based our proceeding largely on the framework within which the IPSS was developed. The IPSS was treated as a metric score [low = 0, intermediate-1 (int-1) = 1, intermediate-2 (int-2) = 2, high = 3] to represent a common scale of reference. This was justified because the risk ratios between subsequent levels are substantially constant (data not shown).

The additional predictive value of gender and age was first examined by separate models for IPSS × gender and IPSS × age, including main effects and orthogonal interactions. Then, after estimating a full model, containing all interactions, we arrived at the final model by deletion of one insignificant interaction.

comparison of male and female risk groups

Our data included 513 male and 384 female patients with median survival of 39 and 63 months, respectively, typical for large MDS populations.

For the IPSS risk groups subdivided by gender, patient numbers, percentages, median survival, and P values for within-risk group comparisons are given in Table 1 and survival curves in Figure 1B.

Comparing male and female MDS patients, significant shorter survival could be detected for men in the lower risk groups (P < 0.001 and 0.012, respectively), while in the higher risk groups, the median survival durations were similar (not significant), i.e. an interaction between IPSS and gender was present. Additionally, analyzing the favorable subgroups after exclusion of the patients with 5q-syndrome, known to have an outstanding good prognosis and being predominantly (68.9%) female, did not alter the survival results [19, 20]. Female good risk patients (without 5q-syndrome, n = 201) survived in
median 70 months and their 334 male counterparts 48 months. This difference was still highly significant \((P = 0.004)\). For 5q patients, the results were 107 months for female \((n = 51)\) and 35 months for male \((n = 23)\) patients \((P < 0.001)\).

A Cox model including IPSS and gender showed significant main effects and IPSS-by-gender interaction effects (Figure 1C). Women had on average a 25% risk reduction \([\text{exp(coeff)} = 0.75, P = 0.003]\) compared with men. However, this reduction was not homogeneous over the IPSS risk groups, resulting in a significant interaction term \([\text{exp(coeff)} = 1.19, P < 0.001]\). The IPSS main effect was \([\text{exp(coeff)} = 1.74, P < 0.001]\), the coefficient of explained variation \(V = 0.16\). In Figure 1C, this shows up by markedly different slopes of the two lines. Women experienced much lower risk than men in the IPSS low-risk categories but similar risk in the high-risk categories. Consequently, the IPSS risk categories discriminate much better in women than in men. This model, if valid, implies that the risk ratios of women and men differ between IPSS risk categories rendering pairwise gender comparisons within IPSS risk categories substantially uninformative.

Comparison according to age. At diagnosis, 375 (41.8%) patients were 66 years of age or younger and 522 (58.2%) were above 66 years of age with median survival durations of 63 and 37 months, respectively. Sixty-six years as cut-off for age was chosen, representing the median age

<table>
<thead>
<tr>
<th>IPSS risk groups</th>
<th>Total ([n (%), \text{survival}])</th>
<th>Female ([n (%), \text{survival}])</th>
<th>Male ([n (%), \text{survival}])</th>
<th>(P) value (log-rank test)</th>
<th>(\leq 66) Years ([n (%), \text{survival}])</th>
<th>&gt;66 Years ([n (%), \text{survival}])</th>
<th>(P) value (log-rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>897 (100.0), 47 months</td>
<td>384 (42.8), 63 months</td>
<td>513 (57.2), 39 months</td>
<td>&lt;0.001</td>
<td>375 (41.8), 63 months</td>
<td>522 (58.2), 37 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>268 (29.9), 86 months</td>
<td>124 (32.3), 156 months</td>
<td>144 (28.1), 66 months</td>
<td>&lt;0.001</td>
<td>115 (30.7), 145 months</td>
<td>153 (29.3), 70 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>285 (31.8), 55 months</td>
<td>111 (28.9), 67 months</td>
<td>174 (33.9), 46 months</td>
<td>0.012</td>
<td>123 (32.8), 80 months</td>
<td>162 (31.0), 44 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>158 (17.6), 23 months</td>
<td>64 (16.7), 24 months</td>
<td>94 (18.3), 23 months</td>
<td>0.755</td>
<td>64 (17.1), 25 months</td>
<td>94 (18.0), 22 months</td>
<td>0.347</td>
</tr>
<tr>
<td>High</td>
<td>186 (20.7), 13 months</td>
<td>85 (22.1), 11 months</td>
<td>101 (19.7), 13 months</td>
<td>0.955</td>
<td>73 (19.4), 13 months</td>
<td>113 (21.7), 12 months</td>
<td>0.354</td>
</tr>
</tbody>
</table>

IPSS, International Prognostic Scoring System.
of the whole MDS cohort, including the 'treated' patients.

For the IPSS risk groups subdivided by age frequencies, percentages, median survival, and \( P \) values for within-risk group comparisons are given in Table 1 and survival curves in Figure 1D.

In the lower risk groups, younger patients had a longer median survival duration and in the higher risk groups, survival data were similar for both age subgroups (not significant) (see Table 1, Figure 1D).

Significant main effects \([\text{age} \leq 66 \text{ versus } >66]\) \(\exp(\text{coeff}) = 1.60, \ P \leq 0.001; \text{IPSS} \exp(\text{coeff}) = 1.72, \ P \leq 0.001\] and interaction \(\exp(\text{coeff}) = 0.92, \ P = 0.050\) were found in a Cox model \((V = 0.16)\) with these variables. The main effect of age was approximately the size of one step from one IPSS risk category to the next, while the interaction term was rather small, meaning that age had only little more importance in lower IPSS risk categories.

**Integrative model—IPSS, gender, and age.** The abovementioned results indicated to extend the prognostic model of the IPSS by formal differentiating by gender and age. Age was included categorized as \(\leq 66\) versus \(>66\) (age 66). All main effects and orthogonal interactions of these parameters were considered. The final model chosen included all main effects (IPSS, gender, and age) and all significant interactions, all of them with \(P < 0.01\) and a global \(P\) value \(<0.001\). The results are best displayed and explained in Table 2. The estimated survival risks associated with the original IPSS levels can well be expressed by the numbers 0–3 for 'low risk', 'int-1', 'int-2', and 'high risk', respectively, because the risk ratios between subsequent levels are substantially constant \((\sim 1.7)\), i.e. a step of one IPSS risk level corresponds to \(\sim 70\%\) hazard increase (data not shown).

These risk levels are valid for each total IPSS subgroup, without taking into account the age and gender of the concerned patient.

Formal consideration of the age and gender of a patient in risk estimation is done by first calculating the IPSS level of the patient in the usual way [4], and then choosing the appropriate line of Table 2 according to the age and gender of the patient. The number found in the respective IPSS column represents the estimated risk for the concerned patient on a common 'IPSS scale'.

To give an example, a male patient aged \(>66\) years with an IPSS level int-1 has an estimated risk of 1.9 (see Table 2). This is almost equal to the average risk of IPSS level int-2, i.e. taking the age and gender of this patient into account would change his risk estimate from an average int-1 risk to an average int-2 risk.

On the other hand, a female patient aged \(\leq 66\) years with an IPSS level int-1 would be assigned \(-0.1\), i.e. a little lower than the average IPSS 'low-risk' category. This patient would be assigned an average low risk on the IPSS scale.

An essential fact expressed by this model is that the risk ratios between adjacent IPSS levels are not constant over age-by-gender subgroups. The highest risk ratios between IPSS levels were observed in the female \(\leq 66\) years subgroup \((\sim 2.6)\), while the lowest risk ratios between adjacent IPSS levels were estimated for the male \(\leq 66\) years subgroup \((1.4)\) (see Figure 2A—on a log scale).

Therefore, the observed effects of age and gender and their interactions cannot be expressed by adding constants to the IPSS.

Usually, one would prefer to use Table 2 but the entries in the table can also be calculated according to the following formula for a prognostic index \((PI)\):

\[
P_1 = \text{IPSS} \times 0.59 + \text{sex} \times -0.31 + \text{age} \times 0.51 + (\text{IPSS} : \text{sex}) \times 0.42 + (\text{IPSS} : \text{age} \leq 66) \times -0.23 + (\text{IPSS} : \text{sex} : \text{age} \leq 66) \times -0.58.
\]

This model has substantially (45\%) higher predictive power (Schemper's \(V = 0.193\)) than the 'IPSS-only model' (Schemper's \(V = .133\)) [17].

**Table 2.** Individualized prognostic model based on the modulating impact of age and gender on the IPSS

<table>
<thead>
<tr>
<th>PI values</th>
<th>Low</th>
<th>Intermediate-1</th>
<th>Intermediate-2</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.0</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Male, (\leq 66) years</td>
<td>0.4</td>
<td>1.0</td>
<td>1.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Female, (\leq 66) years</td>
<td>-1.9</td>
<td>-0.1</td>
<td>1.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Male, (&gt;66) years</td>
<td>1.2</td>
<td>1.9</td>
<td>2.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Female, (&gt;66) years</td>
<td>0.3</td>
<td>1.2</td>
<td>2.1</td>
<td>3.0</td>
</tr>
</tbody>
</table>

PI, prognostic index; IPSS, International Prognostic Scoring System.

**Figure 2.** Estimated risk levels, i.e. prognostic index \((PI)\) values (A) and estimated median survival times (B) for the International Prognostic Scoring System risk groups by combined gender \(\times\) age subgroups. Remark: estimated median survival for low : female : \(\leq 66\) is ‘not reached’ and therefore cannot be displayed in the figure (B).
Estimated median survival times for each subgroup based on the integrative model are displayed in Figure 2B.

**discussion**

This work’s main goal was to enhance the predictive power of the IPSS by inclusion of influential characteristics. As there was good evidence regarding gender and age [4], they were candidates for an extended model. Our choice of the final model was guided by clinical and practical considerations. The model should be reasonable, stable, in good agreement with clinical experience, easy to handle, and reliable. Therefore, we kept the IPSS unchanged, adapting only the score values for the different gender × age subgroups.

The ‘plain IPSS’ differentiates well (but not equally well) within each gender × age subgroup (data not shown). The presented ‘integrative model’ accounts for the considerable heterogeneity within each IPSS risk level, attributable to gender and age. It enhances substantially the precision of the risk estimation compared with the plain IPSS for specific patient subpopulations.

The IPSS discriminates better in lower risk subgroups, clearly evident for gender (with much better performance of the IPSS in female patients) resulting in a strong IPSS by gender interaction and less pronounced for age. This is essentially the meaning of the IPSS by gender-by-age interaction (given its dependence on model type and parametrization).

Indirectly, these results confirm a recent publication by the Düsseldorf group who focused on MDS patients <50 years of age, showing that younger good risk patients have a significant better prognosis than their elderly counterparts, while age at diagnosis has no impact on disease outcome in high-risk patients [21].

We limited this paper to results concerning overall survival as the main end point and postponed presentation of results for the preleukemic interval. Preliminary evaluations showed that the risk of transformation may be partially guided by other aspects than the risk of dying, still age and gender exhibit substantially similar, but weaker effects (data not shown). The preleukemic duration, although important in its own therefore does not appear to be a perfect surrogate end point for survival.

Our data further contribute to the validation of the IPSS, the gold standard in MDS prognostication for years [4]. Similarly, our findings require validation on independent data.

As many new specific treatment options for MDS patients appear on the horizon, large analyses of untreated MDS patients will be nearly impossible in the future [22–26]. We assume that this is the last time that such an analysis can be carried out on a large database.

Since the introduction of the IPSS in clinical routine, the WHO classification was established and recently new therapeutic options are available for this heterogeneous disease calling for evaluation of new prognostic systems. Recently, a new score called WPSS, based on the WHO classification, cytogenetics and red blood cell transfusion requirement at time of diagnosis, was presented [7].

Although it is very important to consider the WHO classification and the prognostic impact of multilineage dysplasia for a new prognostic instrument, it has to be shown in a prospective study if this approach is appropriate. The reproducibility of the WHO entities and the cytogenetic categories used in the IPSS and the WPSS have to be reevaluated and possibly refined.

Nevertheless we think that time has come for a new prognostic scoring system for MDS patients. As recently published by our study group, lactate dehydrogenase is one parameter to be recognized for reevaluating prognostication [6]. We showed in this analysis that also host-related factors play a major role in prognosis. Differentiating by age and gender made evident that an—on average—well working scoring system like the IPSS may have quite different prognostic impact in defined subgroups (in the present case, very strong impact for women ≤66 years and rather weak impact for men >66 years). This is an important aspect for individual prognostication and by far not limited to the IPSS (data not shown).

Since there is an ongoing transition regarding the categorization of MDS entities from FAB to WHO, we excluded these diagnostic systems from our final model, but we want to remind that a risk scoring system alone is no substitute for an etiologically sound categorization of subentities of MDS.

**conclusions**

In addition to the IPSS, gender and age significantly influence prognosis of MDS patients. Although they reflect characteristics of the general population, they have to be considered for individual estimation of prognosis. Our model allows an improved prognostication for MDS patients, by adding simple, host-related parameters to the IPSS. In the future, it should be validated on other untreated MDS patient cohorts and also be tested in the era of new therapeutic agents.

This analysis could be a starting point for a worldwide effort to refine prognosticatation in MDS.

**funding**

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