Two Regression Models and a Scoring System for Predicting Survival and Planning Treatment in Myelodysplastic Syndromes: A Multivariate Analysis of Prognostic Factors in 370 Patients

By Guillermo F. Sanz, Miguel A. Sanz, Teresa Vallespi, M. Consuelo Cañizo, Marta Torrabadella, Sonia García, Dolores Irrigüe, and Jesús F. San Miguel

Therapy planning in patients with myelodysplastic syndromes (MDSs) is complicated by its high prognostic heterogeneity. Forty-one patient and disease characteristics at onset of 370 patients with MDS were analyzed to identify significant prognostic factors for survival and transformation to acute myeloblastic leukemia (AML), and to develop and validate a regression model for predicting survival. Multivariate regression analysis showed that the total bone marrow percentage of blast cells, age, platelet count, WBC count, and hemoglobin level were the characteristics more significantly associated with survival in the overall series. The bone marrow percentage of type I blast cells was the most important factor predicting transformation into AML. Proportional hazards regression analysis in a randomly selected training sample of 240 patients demonstrated that the combination of total bone marrow percentage of blast cells, platelet count, and age had the strongest predictive relation to survival length. The resulting regression models, continuous and categorized, were validated in the remaining test sample of 130 patients by demonstrating its capability of segregating patients into low-, intermediate-, and high-risk groups, with distinctively different survival curves ($P < .0001$). A scoring system derived from the categorized model also had a great prognostic value ($P < .0001$). These regression models and the simpler scoring system may be accurately used for decision-making regarding therapy in MDS patients.

The myelodysplastic syndromes (MDSs) constitute a heterogeneous group of hematologic disorders characterized by peripheral blood cytopenia(s) in the presence of hypercellular bone marrow with features of ineffective hematopoiesis involving one or more cell lineages, and an increased risk of transformation into acute myeloblastic leukemia (AML). MDSs are associated with a high mortality rate that results from bone marrow failure (infection and/or bleeding), whether or not AML supervenes. Because MDSs are particularly common in the elderly, the cause of death may be unrelated to the disorder.

In 1982, the French-American-British (FAB) cooperative group proposed a classification system for MDSs based on precise qualitative and quantitative morphologic criteria. Five MDSs were recognized: refractory anemia (RA), RA with ring sideroblasts (RARS), RA with excess of blast cells (RAEB), RAEB in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMML). Divisions between subtypes are somewhat arbitrary and there are numerous transitional forms. Although the prognostic usefulness of the FAB classification has been studied and demonstrated in some recent reports, its value is limited and in most studies only two groups could be clearly separated in terms of survival: RA plus RARS (good prognostic group) and RAEB plus RAEB-t (poor prognostic group). CMML was included in the low-risk group by some investigators or in the high-risk category by others. The great variability in survival among MDS, with some patients remaining symptom-free for many years, complicates decision-making regarding their therapy. The aim of some recent reports of prognostic factors in MDS has been to provide objective criteria for the selection of high-risk patients who should benefit from new therapeutic approaches. Only four of these studies have been carried out by multivariate methods, which take into account correlation between variables. This research has resulted in the publication of two scoring systems and a regression model for assessing prognosis in individual MDS patients. Assignment of patients to a risk-fitted treatment by using prognostic formulas has often been criticized due to the fact that their predictive value has not been demonstrated in an independent population.

The major aims of our work were as follows: (1) to identify by univariate and multivariate analysis significant prognostic factors of survival and AML transformation in a series of 370 patients diagnosed as having MDS according to the FAB criteria, (2) to develop a regression model for predicting survival in a randomly selected group of 240 patients (training sample), and (3) to validate the prognostic capability of the model in the remaining group of 130 patients (test sample).

Our study, the largest one until now on MDS, confirms the previously noted prognostic value of some patient and disease characteristics at diagnosis, recognizes new prognostic factors, and offers two validated regression models and a simple scoring system for accurately assessing prognosis and planning treatment in MDS patients. Our results also suggest that an extra cut-off point of 10% in the percentage of blast cells in bone marrow would add significant prognostic information to the accepted current FAB criteria for the stratification in terms of survival duration and AML transformation of MDS patients.
PATIENTS AND METHODS

Patients and Diagnostic Criteria

A total of 370 consecutive patients with the diagnosis of MDS according to the FAB criteria\textsuperscript{5} were included in the analysis. Patients were diagnosed at three different hospitals in Spain between 1971 and 1987. Cases with myelodysplasia secondary to vitamin B12 or folic acid deficiency were not considered. Patients with bone marrow (BM) dysmyelopoiesis satisfying FAB criteria but with concomitant hematologic malignancies or solid tumors were excluded. Nine patients with probable therapy-related MDS (previous exposure to chemotherapy or radiotherapy in three and six cases, respectively) were included.

Hematologic examinations were performed using standard methods. Initial peripheral blood (PB) and BM May-Grünwald-Giemsa and Prussian blue stained films were available in all cases. Marrow cell differential counts were performed on at least 500 cells. Criteria used for grading dyspoiesis (absent, mild, or marked) have been previously published elsewhere.\textsuperscript{14,15} All cases were reviewed independently by two observers and were allocated to the appropriate FAB subgroup. Five cases shared features common to different FAB subgroups. These were assigned to the subgroup that in theory had the worst prognosis (ie, a case with 2.5 x 10\textsuperscript{9}/L blasts and 20% BM ringed sideroblasts was classified as CMML). When there was a discrepancy between PB and BM percentage of blast cells affecting FAB classification, BM features were given priority (ie, a patient without circulating blasts and 7% BM blast cells was considered as RAEB).

Transformation to acute leukemia was defined as the presence of more than 30% blasts in BM, or more than 40% blasts in PB in the few cases where BM aspirates were not performed.

Three hundred and nine patients received only supportive treatment, while the remaining 61 patients were treated with different protocols generally based on single-agent chemotherapy in an attempt to control BM failure, hyperleukocytosis, or disease progression. The most commonly used drugs were low-dose cytosine arabinoside (18 cases), hydroxyurea (ten cases), and busulfan (eight cases). One patient with RAEB-t received an allogeneic bone marrow transplantation from an identical sibling. All patients were followed for survival and transformation into AML through September 1987.

Prognostic Factors

Forty-one patient and disease characteristics documented at initial evaluation were examined in the prognostic factor analysis to establish their relationship on survival and acute leukemic transformation. Basic demographic data and clinical characteristics at presentation included age, sex, year of diagnosis, previous chemotherapeutic agent(s) or radiation therapy (primary or therapy-related MDS), anemia symptoms, hemorrhages, infection, systemic symptoms (weakness, anorexia, and weight loss), interval between first symptom and diagnosis, and liver, spleen, and nodes enlargement. Serum biochemical parameters were blood urea nitrogen (BUN), creatinine, calcium, phosphorus, uric acid, bilirubin, glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), and lactate dehydrogenase (LDH). PB features included hemoglobin concentration and absolute reticulocyte, platelet, WBC, neutrophil, monocyte, lymphocyte, immature myeloid precursor, nuclelated RBCs, and blast cell counts. BM aspirate parameters evaluated were cellularity, degree of dyserythropoiesis, dysgranulopoiesis, and dysthrombopoiesis, type I, type II, and total (type I plus type II) blast cell proportions, and percentages of promonocytes, and ringed sideroblasts. In addition, FAB classification was also considered.

Statistical Analysis

The Kaplan-Meier product limit method was used to estimate the probability of survival and leukemic transformation.\textsuperscript{16} Survival was measured from hematologic diagnosis to death. All deaths, whether related or not to MDS, were considered as the endpoint of the follow-up interval. AML transformation was measured from diagnosis to AML development. Patients dying from any cause before developing AML were considered as censored data in the date of death for the calculation of AML transformation curves. Statistical comparisons between different actuarial curves were based on log rank tests or, if applicable, the test for trend, as recommended by Peto et al.\textsuperscript{17} Further multivariate analysis by means of the proportional hazards regression method developed by Cox was used in order to identify the most significant independent prognostic factors.\textsuperscript{18} Characteristics selected for possible inclusion in the Cox regression method were those for which there was some indication of a significant association with survival or AML transformation in univariate analysis (P < 0.10) or where prior studies had suggested a possible relationship. The forward stepwise regression procedure was stopped when the P value for entering an additional factor was above 0.1.

One of the major objectives of this work was to develop a regression model for accurately predicting survival and planning treatment in MDS patients. Criticism of prognostic regression models is sometimes based on the failure to identify an independent population in which the predictive capacity of the regression model can be validated.\textsuperscript{14} With this in mind, we randomly divided the 370 patients into training and test subsets containing 240 and 130 cases, respectively, so that we could identify important prognostic factors in one set of data and validate them in the other.

Using patient and disease characteristics selected in the multivariate analysis of survival in the global series, a proportional hazards regression procedure was carried out in the training sample.\textsuperscript{17} To identify the characteristics to be included, we used the forward stepwise selection approximation suggested by Peduzzi et al.\textsuperscript{18} Characteristics entered the model according to their level of significance until the P value for adding another characteristic exceeded 0.05. The data were then reanalyzed, with only the characteristics identified, using the more accurate maximum partial likelihood ratio statistics in the forward selection and stopping when the P value for adding an additional variable was above 0.1.

To assess the quality and predictive value of the regression model, we first calculated the hazard rate or relative risk of each case in the training sample and then divided the training set cases into three risk groups using these fitted hazard rates. Differences in the corresponding survival curves were statistically compared by means of the test for trend. The procedure was repeated for test set cases.

Finally, regression coefficients for the characteristics in the validated model were reestimated in the whole group of 370 patients to derive the final regression model.

All analyses were performed by using DM, 1L, and 2L programs from the Biomedical Data Package (BMDP) statistical library\textsuperscript{19} run on an IBM PC AT microcomputer (IBM, Danbury, CT). The BMDP special function RNDU was used for the random assignment of cases to the training and test samples.

RESULTS

There were 207 males (56%) and 163 females (44%). The mean age was 68 years (range, 20 to 94). One hundred seventy-six patients (48%) were above 70 years of age, and only 15 (4%) were under 40 years of age. Eighty-five patients had RA (23%), 58 had RARS (16%), 119 had RAEB (32%), 38 had RAEB-t (10%), and 70 had CMML (19%).
The median survival of the 370 MDS patients was 15 months. At the time of the analysis, 82 patients were still alive 1+ to 116+ months from diagnosis. The actuarial probability of survival at 2 and 5 years was 37 ± 2% and 14 ± 2%, respectively. Complete responses (disappearance of cytopenias and normalization of BM blast count) were attained in only six of the 61 treated patients. Four of them had received aggressive combination chemotherapy, one low-dose cytosine arabinoside (LODAC) and the remaining one a bone marrow transplantation. With the exception of the transplanted patient, who was disease-free 36+ months after the transplantation procedure, responses were short-lived, all patients having relapsed within 1 year. Median survival for the 309 untreated, 61 treated, and 18 LODAC-treated patients were 16, 14, and 13 months, respectively. The outcome of these three groups was not significantly different (P = .48).

Due to insufficient follow-up data, the exact cause of death could only be properly ascertained in 216 (75%) of the 288 patients who died during the study. Upon analyzing the causes of death in this subset of 216 cases, 189 patients (88%) died from bone marrow failure (infection and/or hemorrhage). This later group included 60 patients (28%) who died after AML transformation had occurred. Complications secondary to hemochromatosis were the sole cause of death in three patients, and the remaining 26 (12%) died from MDS apparently nonrelated causes.

Sixty patients (16%) developed AML during the study period. The overall actuarial median of AML transformation has not been reached. The actuarial cumulative risk of leukemic transformation was 13 ± 2% and 32 ± 4% at 1 and 5 years, respectively.

Univariate Analysis of Survival Prognostic Factors

The univariate analysis of survival prognostic factors is illustrated in Table 1.

Clinical characteristics. Younger patients (<60 years of age) had a significantly longer survival. Male sex and the presence of bleeding and systemic symptoms at diagnosis were all associated with shorter survival. A progressive increase in survival was also noted the longer the interval between first symptom and diagnosis. The year of diagnosis and the presence of symptomatic anemia, infection, hepatosplenomegaly, and lymphadenopathy did not significantly influence survival. The median survival of the nine patients with therapy-related MDS (one RA, five RARS, two RAEB, and one CMML) (9 months) was somewhat shorter than for primary MDS (15 months) but the corresponding survival curves did not differ significantly (P = .53).

Serum biochemical parameters. Creatinine, uric acid, bilirubin, and LDH levels demonstrated a strong correlation with survival. Abnormally high levels of these parameters were associated with shorter survival. The serum level of all other characteristics studied failed to show any significant relationship with survival.

Hematologic features in peripheral blood. Excluding absolute reticulocyte, monocyte, and lymphocyte counts, all the other characteristics evaluated were closely related to survival. The hemoglobin levels, platelet counts, and absolute neutrophil counts were directly associated with survival whereas intermediate WBC counts were related to improved survival. The presence of blast cells, immature myeloid cells, and nucleated RBC in PB adversely affected survival.

Hematologic features in bone marrow. BM type I, type II, and total blast cell percentages had a strong inverse influence on survival length. The effect of the total percentage of blast cells in BM on survival is shown in Fig 1. A statistically significant difference was observed when comparing the survival curve of patients with <5% blasts with that of patients with 5% to 10% (P = .0004). The difference was also significant between patients with 5% to 10% of blasts and patients with 11% to 30% (P < .0001). However, no clear cut differences in survival were evident within the group of patients with >10% of blasts. The median survival for patients with 11% to 20% blasts and for patients with 21% to 30% was 5 months in both groups (P = .82). Dysmyelopoitic features were also associated with survival. A distinct stepwise relationship was noted between the degree of dysgranulopoiesis and survival but not between the degree of dyserythropoiesis or dysthrombopoiesis. The cellularity and the percentages of monocytes and sideroblasts failed to demonstrate any correlation with survival.

FAB classification. MDS subtype was a strong prognostic factor of survival (Fig 2). Significant differences in survival were present when comparing RA and CMML (P < .01), RA and RAEB (P < .0001), RA and RAEB-t (P < .0001), RARS and CMML (P = .009), RARS and RAEB (P < .0001), RARS and RAEB-t (P < .0001), CMML and RAEB-t (P = .0007), and RAEB and RAEB-t (P = .011). No statistical significance was found in comparisons of survival curves of RA and RARS, and of CMML and RAEB (P = .60 and .13, respectively).

Multivariate Analysis of Survival Prognostic Factors

The best combination of patient and disease characteristics selected by means of the Cox proportional hazards regression method in the overall group of patients is given in Table 2, where variables are listed in the order entered by the forward stepwise modeling procedure. The only five characteristics selected were the BM total percentage of blasts, age, platelet count, WBC count, and hemoglobin concentration.

Prognostic Factor Analysis of Acute Leukemia Transformation

The results of the prognostic factors analysis of leukemic transformation are presented in an abbreviated form in Table 3. Several clinical and laboratory characteristics were associated with AML transformation on univariate analysis: age, bleeding, systemic symptoms, platelet counts, WBC counts, absolute neutrophil counts, blast cells in PB, BM percentages of type I blasts and total BM percentages of blast cells, and FAB classification. Younger patients evolved more frequently to AML, as did those presenting hemorrhages and systemic symptoms. The presence of blasts in PB and the percentages of type I and total blasts in BM were directly related to the development of AML whereas the
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Category</th>
<th>No. of Patients</th>
<th>Median Survival (mo)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>≤40</td>
<td>15</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41 to 50</td>
<td>15</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>51 to 60</td>
<td>53</td>
<td>27</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>61 to 70</td>
<td>111</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 70</td>
<td>176</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>207</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>163</td>
<td>22</td>
<td>0.0016</td>
</tr>
<tr>
<td>Previous chemo/radiotherapy</td>
<td>No</td>
<td>361</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>9</td>
<td>9</td>
<td>0.53</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td>1976 to 1981</td>
<td>166</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1982 to 1987</td>
<td>184</td>
<td>18</td>
<td>0.22</td>
</tr>
<tr>
<td>Anemia symptoms</td>
<td>Yes</td>
<td>243</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>111</td>
<td>19</td>
<td>0.17</td>
</tr>
<tr>
<td>Hemorrhages</td>
<td>Yes</td>
<td>71</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>274</td>
<td>17</td>
<td>0.0094</td>
</tr>
<tr>
<td>Infection</td>
<td>Yes</td>
<td>64</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>277</td>
<td>17</td>
<td>0.30</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>Yes</td>
<td>130</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>222</td>
<td>19</td>
<td>0.017</td>
</tr>
<tr>
<td>Interval first symptom to diagnosis (mo)</td>
<td>&lt;1</td>
<td>67</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 to 6</td>
<td>159</td>
<td>14</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>&gt; 6</td>
<td>112</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Liver enlargement (cm)</td>
<td>&lt; 2</td>
<td>255</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 to 5</td>
<td>86</td>
<td>15</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>&gt; 5</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Spleen enlargement (cm)</td>
<td>&lt; 2</td>
<td>305</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 to 5</td>
<td>30</td>
<td>13</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>&gt; 5</td>
<td>15</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Yes</td>
<td>49</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>305</td>
<td>16</td>
<td>0.17</td>
</tr>
<tr>
<td>Serum biochemical parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>≤20</td>
<td>76</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>260</td>
<td>14</td>
<td>0.88</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>≤1.4</td>
<td>271</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1.4</td>
<td>50</td>
<td>8</td>
<td>0.0020</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>≤10</td>
<td>299</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>2</td>
<td>6</td>
<td>0.68</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>≤4.5</td>
<td>255</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;4.5</td>
<td>35</td>
<td>10</td>
<td>0.24</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>≤7</td>
<td>266</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;7</td>
<td>60</td>
<td>10</td>
<td>0.034</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>≤1</td>
<td>264</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>62</td>
<td>8</td>
<td>0.0027</td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>≤40</td>
<td>294</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;40</td>
<td>36</td>
<td>14</td>
<td>0.18</td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>≤55</td>
<td>299</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;55</td>
<td>23</td>
<td>21</td>
<td>0.082</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>≤225</td>
<td>140</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>226 to 400</td>
<td>77</td>
<td>11</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>&gt;400</td>
<td>48</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Hematologic features in blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>&lt;7</td>
<td>101</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 to 10</td>
<td>201</td>
<td>14</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>66</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Reticulocytes (× 10^9/L)</td>
<td>&lt;25</td>
<td>104</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 to 75</td>
<td>91</td>
<td>15</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>&gt;75</td>
<td>42</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>
Table 1. MDS. Survival Univariate Analysis (Cont'd)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Category</th>
<th>No. of Patients</th>
<th>Median Survival (mo)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets (x 10^9/L)</td>
<td>&lt;25</td>
<td>50</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 to 50</td>
<td>38</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>51 to 75</td>
<td>31</td>
<td>13</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>76 to 100</td>
<td>39</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;100</td>
<td>203</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>WBC (x 10^9/L)</td>
<td>&lt;2.5</td>
<td>63</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.6 to 10</td>
<td>233</td>
<td>21</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>70</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Neutrophils (x 10^9/L)</td>
<td>&lt;0.5</td>
<td>30</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6 to 1</td>
<td>49</td>
<td>11</td>
<td>.0027</td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>283</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Monocytes (x 10^9/L)</td>
<td>≤1</td>
<td>291</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>72</td>
<td>10</td>
<td>.26</td>
</tr>
<tr>
<td>Lymphocytes (x 10^9/L)</td>
<td>≤1.5</td>
<td>168</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1.5</td>
<td>196</td>
<td>15</td>
<td>.76</td>
</tr>
<tr>
<td>Immature myeloid precursors</td>
<td>Yes</td>
<td>131</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>232</td>
<td>18</td>
<td>.012</td>
</tr>
<tr>
<td>Nucleated RBC</td>
<td>Yes</td>
<td>271</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>85</td>
<td>8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Blast cells (x 10^9/L)</td>
<td>No</td>
<td>269</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1 to 1</td>
<td>71</td>
<td>6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>24</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Hematologic features in bone marrow

<table>
<thead>
<tr>
<th>Cellularity</th>
<th>Decreased</th>
<th>30</th>
<th>12</th>
<th>.71</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal or increased</td>
<td>327</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Dyserthropoiesis</td>
<td>Absent</td>
<td>87</td>
<td>11</td>
<td>.028</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>174</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marked</td>
<td>103</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Dysgranulopoiesis</td>
<td>Absent</td>
<td>109</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>134</td>
<td>15</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>Marked</td>
<td>120</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Dysthrombopoiesis</td>
<td>Absent</td>
<td>64</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>132</td>
<td>21</td>
<td>.0065</td>
</tr>
<tr>
<td></td>
<td>Marked</td>
<td>157</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Type I blast cells (%)</td>
<td>≤5</td>
<td>208</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 to 10</td>
<td>86</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 to 20</td>
<td>51</td>
<td>5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>25</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Type II blast cells (%)</td>
<td>≤5</td>
<td>346</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;5</td>
<td>24</td>
<td>5</td>
<td>.0009</td>
</tr>
<tr>
<td>Total blast cells (%)</td>
<td>≤5</td>
<td>174</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;5</td>
<td>24</td>
<td>5</td>
<td>.0009</td>
</tr>
<tr>
<td></td>
<td>5 to 10</td>
<td>100</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 to 20</td>
<td>58</td>
<td>5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>21 to 30</td>
<td>38</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Promonocytes (%)</td>
<td>≤5</td>
<td>296</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;5</td>
<td>46</td>
<td>15</td>
<td>.89</td>
</tr>
<tr>
<td>Sideroblasts (%)</td>
<td>0</td>
<td>171</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 to 15</td>
<td>61</td>
<td>14</td>
<td>.41</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>87</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>FAB classification</td>
<td>RA</td>
<td>85</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RARS</td>
<td>58</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMML</td>
<td>70</td>
<td>12</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>RAEB</td>
<td>119</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAEB-t</td>
<td>38</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
Fig 1. Survival according to total percentage of blast cells in bone marrow in all patients.

Fig 2. Survival according to FAB classification in all patients.
Table 2. MDS. Multivariate Analysis: Characteristics Related to Survival

<table>
<thead>
<tr>
<th>Characteristics and Order of Entrance in the Regression</th>
<th>Log Likelihood</th>
<th>Chi-Square</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total BM blasts (%)</td>
<td>-1427.339</td>
<td>56.632</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>-1419.272</td>
<td>15.501</td>
<td>.0001</td>
</tr>
<tr>
<td>Platelets ($x10^3/L$)</td>
<td>-1412.722</td>
<td>13.102</td>
<td>.0003</td>
</tr>
<tr>
<td>WBC ($x10^9/L$)</td>
<td>-1406.979</td>
<td>11.485</td>
<td>.0007</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>-1401.311</td>
<td>11.336</td>
<td>.0008</td>
</tr>
</tbody>
</table>

Unfavorable characteristics include increasing total proportion of BM blasts, increasing age, decreasing platelet count, increasing WBC count, and decreasing hemoglobin level.

Table 3. MDS. Characteristics Related to Acute Leukemia Transformation: Summary of Prognostic Factor Analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariate Analysis (P Value)</th>
<th>Multivariate Analysis (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.0004 NS</td>
<td></td>
</tr>
<tr>
<td>Hemorrhages</td>
<td>.023 NS</td>
<td></td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>.036 NS</td>
<td></td>
</tr>
<tr>
<td>SGPT</td>
<td>.065 NS</td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>.0018 NS</td>
<td></td>
</tr>
<tr>
<td>WBC count</td>
<td>.0005 NS</td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>&lt;.0001 NS</td>
<td></td>
</tr>
<tr>
<td>Absolute blast count in PB</td>
<td>&lt;.0001 NS</td>
<td></td>
</tr>
<tr>
<td>Proportion of type I blasts in BM</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total proportion of BM blasts in BM</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>FAB classification</td>
<td>&lt;.0001 NI</td>
<td></td>
</tr>
</tbody>
</table>

Unfavorable characteristics include younger age, presence of hemorrhages and systemic symptoms, decreasing platelet count, decreasing WBC and absolute neutrophil counts, increasing absolute blast count in PB, and increasing proportion of type I and total BM blasts. For FAB classification, see text.

Abbreviations: NS, nonstatistical significance (P > .01); NI, not included.

forward stepwise regression analysis resulted in the selection of the total BM percentage of blasts, platelet count, and age in the order listed (Table 4). Hazard rates were calculated for each patient in the training set by using the regression model. The training sample was divided into three risk groups (low, intermediate, and high risk) according to the fitted hazard rates, using cut-off points of 0.7 and 1.3. Survival curves for these risk groups are plotted in Fig 5A. Median survival was 39, 20, and 5 months for the low-, intermediate-, and high-risk groups, respectively (chi-square, 54.49; P < .00001). The regression model obtained in the training set was validated by demonstrating its capacity in identifying risk groups in the test sample. The survival curves for the risk groups in the test set (Fig 5B) differed significantly (chi-square, 24.15; P < .0001).

The regression coefficients for the three characteristics in the model were reestimated using only the cases in the test sample. Comparable estimates to those of the training sample were obtained, further validating the quality of the model. Reestimation of these regression coefficients in the total population of 370 MDS patients was performed to derive the final estimates used in the continuous regression model offered in Table 4. Survival curves by risk score in all MDS patients were notably different (chi-square, 75.06; P < .00001).

Development of a Simplified Model and a Scoring System

A simplified alternative model, more convenient for routine clinical use, was examined. This categorized model, with total BM percentage of blasts coded 0 if <5, 1 if 5 through 10, and 2 if >10, with platelet count coded 0 if ≥100, 1 if 51 through 100, and 2 if ≤50, and age coded 0 if ≤60 and 1 if >60, was as effective as the continuous model in identifying three risk groups (chi-square, 96.82; P < .00001) (Fig 6). The new regression equation was as follows: ln[h(t)/h0(t)] = 0.62 (total BM percentage of blasts code) + 0.36 (platelet count code) + 0.53 (age code). A numerical scoring index was devised using the same code system as the categorized regression model, ranging the score for each patient between 0 and 5. The survival curves of patients scoring 0 or 1 (group A), 2 or 3 (group B), and 4 or 5 (group C) are shown in Fig 7A. The differences in survival for the three groups were highly significant (chi-square, 102.82; P < .00001). As is outlined in Fig 7B, the scoring system could also segregate patients with ≤5% BC in BM into three risk groups with a median survival of 51 months (score 1), 15 months (score 2 or 3), and 4 months (score 4 or 5), respectively (chi-square, 51.08; P < .00001).

Given that the Bournemouth scoring system for predicting outcome in MDS patients seems to have obtained wide acceptance in recent years,26 we decided to examine its predictive capacity in our series. The scoring system had considerable prognostic value in the whole group of patients. The survival curves for group A (median survival, 34 months), group B (median survival, 14 months), and group C (median survival, 4 months) highly differed (chi-square, 43.42; P < .0001). This scoring system was less effective in predicting survival for patients with a BM percentage of blasts ≥5%. Only two risk groups (low risk, score 1 to 3; and
Fig 3. Cumulative probability of acute leukemic transformation according to FAB classification in all patients.

Fig 4. Cumulative probability of acute leukemic transformation according to percentage of type I blast cells in bone marrow in all patients.
high risk, score 4) were identified. The median survival (9 and 4 months, respectively) and the corresponding survival curves were only marginally different (chi-square, 5.38; P = .02).

Regression Models in Untreated Patients With Primary MDS

The present series included nine patients with therapy-related MDS and 61 patients that had received some form of chemotherapy during the MDS phase or after AML had occurred. Survival for these groups of patients was not clearly different from that observed for primary or untreated MDS patients, respectively. However, to insure that the results of the study were not biased, the data were reanalyzed on the 301 primary untreated MDS patients. The prognostic factors and the regression models remained unchanged except for minor variations in the values of the regression coefficients for the characteristics (total BM percentage of blasts, platelet count, and age) entering the models (data not shown). These values remained within the confidence intervals of the regression coefficients for the characteristics in the models derived from the whole group of 370 patients. They further confirmed the validity of the previously derived regression models.

DISCUSSION

The MDS encompasses a heterogeneous group of primary hematologic disorders believed to result from neoplastic transformation at the level of the pluripotent stem cell. BM is usually hypercellular and may contain an increased number of immature myeloid cells. A variable degree of ineffective hemopoiesis is always present and results in characteristic morphologic abnormalities in both PB and BM, and in cytopenias in various combinations. Mortality in MDS is generally associated with AML transformation or complications derived from bone marrow insufficiency. In line with previous reports, our study confirms that bone marrow failure (infection and/or bleeding; 88% in this series) is the major cause of death in MDS, and that the number of patients dying from this cause is greater before than after the development of overt acute leukemia had supervened (60% vs 28%). There have been substantial differences in the reported incidence of progression to AML in MDS (16% in our series), ranging from 6% to 37% in those series classified according to the FAB proposals. Factors accounting for these variations between series are sample size, length of follow-up, differences in factors correlated with transformation into AML, and use of inappropriate statistical methodology, without using actuarial analysis and without considering deaths from any cause before transformation into AML as censored data. Overall survival in the present series (15 months) coincides closely with that currently accepted for MDS patients. Survival for RA and RARS patients was similar to that found by Tricot et al but shorter than reported in other series. Differences in the criteria used for computing survival time (ie, from BM aspiration as in our study, or from first evidence of anemia or onset of symptoms) may be responsible for these apparentlycontroverted results.

The wide variability in outcome of MDS patients complicates decision-making regarding their therapy. This has led us to identify through prognostic factor analysis those high-risk patients who could benefit from new treatment strategies. Our analysis of 370 MDS patients identified 23 characteristics strongly associated with survival duration. The study confirms the prognostic value of several patient and disease characteristics such as age, systemic symptoms, hemoglobin level, platelet count, absolute neutrophil count, presence of blasts and nucleated RBC in PB, degree of dyserythropoiesis, dysgranulopoiesis, and dysthrombopoiesis, type I, type II, and total blast cell proportions in BM, and FAB classification. The adverse prognosis for males, longer intervals between first symptom and hematologic diagnosis, hemorrhages, immature myeloid precursors in PB, and elevated serum creatinine, bilirubin, uric acid, and LDH levels had not previously been recognized. The development in recent years of new antibiotics and better transfusional support might have had a major impact in a series of MDS patients spanning 16 years. To test this hypothesis, we analyzed the influence of the year of diagnosis on the outcome. Clear-cut differences in survival were not observed, indicating the stability of the population course over this period of time. When correlation between covariates was taken into account by means of a multivariate regression analysis, only five characteristics retained a statistically significant independent prognostic weight (total percentage of blasts in BM, age, platelet count, WBC, and hemoglobin concentration).

While the importance of some BM biopsy findings, cytogentic, and the in vitro culture pattern of hemoopoietic progenitors has recently become apparent, these features where excluded from the present analysis in order not to reduce the sample size.

Apart from the well-known relationship between the FAB classification and AML transformation, age, bleeding, systemic symptoms, platelet counts, WBC counts, absolute neutrophil counts, blast cells in PB, type I and total BM proportion of blast cells were characteristics closely related to AML transformation on univariate analysis in our series.

### Table 4. MDS. Validation of the Continuous Regression Model for Predicting Survival by Multivariate Analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Training Set RC (SE)*</th>
<th>Testing Set RC (SE)</th>
<th>Total Series RC (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blasts in BM (%)</td>
<td>0.057 (0.0095)</td>
<td>0.052 (0.014)</td>
<td>0.055 (0.0077)</td>
</tr>
<tr>
<td>Platelets (x 10^7/L)</td>
<td>-0.0022 (0.0006)</td>
<td>-0.0011 (0.0008)</td>
<td>-0.0017 (0.0005)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>0.020 (0.0067)</td>
<td>0.026 (0.010)</td>
<td>0.022 (0.0055)</td>
</tr>
</tbody>
</table>

Regression model, in [ln(t/\(\tau_0\))] = 0.055 (total blasts in BM, eight) - 0.0017 (platelets - 173) + 0.022 (age - 68).

*Regression coefficients (RC) and standard errors (SE) of the RC for the characteristics entering the model.
Fig 5. Survival according to the hazard rate predicted by the continuous regression model. (A) in the training set, and (B) in the test set.

Excluding RA and CMML, and RARS and CMML, progression to AML differed distinctively between the FAB subtypes. There was a much higher rate of AML transformation for RAEB-t than for RAEB. A recent paper by the Morphologic, Immunologic, and Cytogenetic Cooperative Study Group (pooling data from 11 independent studies reported in the past 6 years, and including 1,081 patients with primary MDS) found a 44% and 60% leukemic progression rate for RAEB and RAEB-t, respectively. Using actuarial methodology, the present series reports statistically
significant differences in leukemic transformation rate between these two FAB subgroups. The proportion of BM type I blast cells had the strongest predictive weight for transformation into AML on multivariate analysis. There was a distinct stepwise relationship between type I blast counts in BM and leukemic transformation. The actuarial cumulative probability of evolving into AML was 100% for those patients with a type I blast count between 20% and 30% at 30 months from diagnosis, a fact that emphasizes that the accepted border between RAEB-t and AML is completely arbitrary. It is also worth noting that the proportion of type II blast cells in bone marrow did not have any relationship to AML development. This suggests that type II blasts are either more differentiated cells lacking leukemic transformation capability or that type I and type II blasts would derive from distinct progenitor clones.

One of the major aims of this study was to develop a regression model for stratifying patients according to prognosis for survival, allowing individual prognostication and providing a basis for risk-directed therapy. On the other hand, confirmation of the validity of a regression model seems essential for further clinical application. In our study the regression model, derived from a randomly selected training sample of two thirds of patients, was confirmed in the test sample of the remaining one third by demonstrating its capacity for identifying risk-groups according to the fitted hazard rates. The prognostic model containing only three characteristics (total proportion of blast cells in BM, platelet count, and age) divided patients into three separate low-, intermediate-, and high-risk groups. Two of the three variables included in the model (total percentage of blasts in BM and platelet count) may reflect the degree of BM failure and a high probability of transformation into AML. Age is host-related and is probably an indicator of organ dysfunction and other medical illnesses that may contribute to a worse tolerance of the consequences of marrow insufficiency (infection and bleeding).

Some investigators are reluctant to assign patients to risk groups using detailed regression models. They consider that their routine clinical use is uncomfortable and suggest the use of easier scoring systems. For this reason, we evaluated an alternative categorized model that was as good as the detailed one. A simple scoring system was derived from this categorized model. A score of 2 was assigned to BM blast cells >10% and platelet count ≤50 × 10⁹/L, and a score of 1 to BM blast cells between 5% and 10%, platelets between 51 and 100 × 10⁹/L, and age >60 years. Therefore, the score for each patient ranged between 0 and 5. Differences in outcome between group A (score 0 or 1), group B (score 2 or 3), and group C (score 4 or 5) were highly significant. The scoring system could also segregate patients with ≥5% blast cells in BM into three separate risk groups. Until now, there has been a lack of prognostic significance of a BM blasts count ≥5%, which has provoked speculation. Nevertheless, in this series, the differences in disease outcome as well as in leukemic transformation of patients with <5%, 5% to 10%, and 10% to 30% blast cells in BM were greatly significant. These data suggest that the addition of an extra cut-off point of 10% to the universally accepted 5% and 20% FAB criteria in the percentage of blasts in BM would make a notable contribution to prognostic information in MDS patients.

The recently published prognostic index by Mufti et al was valuable in the whole group of our MDS patients. Nevertheless, its prognostic use was minimal for patients.
Fig 7. Survival according to scoring system, (A) in all patients, and (B) in patients with ≥5% blast cells in bone marrow.

with ≥5% BC in BM. From our data, it appears that the Bournemouth score gives excessive prognostic importance to peripheral cytopenias, insufficient weight to the BM percentage of blasts, and does not take into account a host-related factor such as age, which may have a high value in a group of diseases characterized by its preponderance in the elderly. We could not evaluate the prognostic value of the scoring system proposed by Varela et al⁹ because of the differences in criteria for assessing dyshemopoiesis. The validity in our series of the regression equations for predicting survival in MDS patients developed by Garcia et al¹³ has been recently published.²⁸
Changes in therapeutic strategies over time may modify the natural history of a disease and also affect the relative importance of different prognostic factors. Therefore, the major shortcomings of analysis of prognostic factors in series that include patients studied over a long period and who have received multiple treatments are obvious. As indicated above, in this study there was no change in overall survival in time for the whole MDS population. Furthermore, the prognostic factors and the regression models remained unaltered after excluding those patients with therapy-related MDS or who received any form of chemotherapy during follow-up. This evidence supports the validity of the prognostic models derived.

The MDSs must be regarded as life-threatening disorders because of the risks associated with persistent and profound cytopenias, regardless of whether transformation to acute leukemia occurs. A sound knowledge of the natural history of MDS is crucial for planning therapy. Decision-making regarding therapy is complicated because most MDS patients are elderly, and all forms of treatment available at present may worsen an existing cytopenia and lead to unacceptable morbidity and mortality. \[1,2\] Our analysis of prognostic factors in MDS resulted in two regression models, continuous and categorized, and a scoring system with a high prognostic value. Although scoring systems are simpler to use, it must be remembered that they inevitably result in information losses and a greater chance of misclassification of patients. On the other hand, the use of detailed regression models in a computerized era should not be an obstacle to bed-side therapeutic decisions. In any case, the regression formulas and the scoring system derived from this study can be accurately used to estimate the individual prognosis of patients with MDS and should assist in the design and analysis of subsequent clinical trials.

ACKNOWLEDGMENT

The authors thank Ronald M. Cox for his help in manuscript translation.

REFERENCES

27. Third MIC Cooperative Study Group: Recommendations for
a morphologic, immunologic, and cytogenetic (MIC) working classification of the primary and therapy-related myelodysplastic disorders. Cancer Genet Cytogenet 32:1, 1988


Two regression models and a scoring system for predicting survival and planning treatment in myelodysplastic syndromes: a multivariate analysis of prognostic factors in 370 patients

GF Sanz, MA Sanz, T Vallespi, MC Canizo, M Torrabadella, S Garcia, D Irriguible and JF San Miguel