

## Prognostic Factors and Life Expectancy in Myelodysplastic Syndromes Classified According to WHO Criteria: A Basis for Clinical Decision Making

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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### A B S T R A C T

#### Purpose

The aim of this study was to evaluate the prognostic value of the WHO proposal, to assess the role of the main prognostic factors in myelodysplastic syndromes (MDSs) classified into WHO subgroups, and to estimate mortality (standardized mortality ratio [SMR]) and life expectancy in these groups as a basis for clinical decision making.

#### Patients and Methods

Four hundred sixty-seven patients who were diagnosed as having de novo MDS at the Division of Hematology, University of Pavia (Pavia, Italy), between 1992 and 2002, were evaluated retrospectively for clinical and hematologic features at diagnosis, overall survival (OS), and progression to leukemia (leukemia-free survival).

#### Results

Significant differences in survival were noted between patients with refractory anemia (RA), refractory cytopenia with multilineage dysplasia, RA with excess blasts, type 1 (RAEB-1), and RAEB-2. The effect of demographic factors on OS was observed in MDS patients without excess blasts (age,  $P = .001$ ; sex,  $P = .006$ ), as in the general population. The mortality of RA patients 70 years or older did not differ significantly from that of the general population (SMR, 1.62;  $P = .06$ ). Cytogenetics was the only International Prognostic Scoring System variable showing a prognostic value in MDS classified into WHO subgroups. Transfusion-dependent patients had a significantly shorter survival than patients who did not require transfusions ( $P < .001$ ). Developing a secondary iron overload significantly affected the survival of transfusion-dependent patients ( $P = .003$ ).

#### Conclusion

These data show that the WHO classification of MDSs has a relevant prognostic value. This classification, along with cytogenetics, might be useful in decisions regarding transplantation. MDS with isolated erythroid lineage dysplasia identifies a subset of truly low-risk patients, for whom a conservative approach is advisable.

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### INTRODUCTION

Myelodysplastic syndromes (MDSs) are a heterogeneous group of disorders clinically characterized by peripheral cytopenia, followed by a progressive impairment in the ability of myelodysplastic stem cells to dif-

ferentiate and an increasing risk of evolution into acute myeloid leukemia (AML).<sup>1</sup> The natural history of MDS, ranging from indolent conditions spanning years to forms rapidly progressing to leukemia, complicates clinical decision making regarding therapeutic modalities and timing of intervention.

In 1982, the French-American-British (FAB) cooperative group proposed a classification of MDS based on morphologic criteria.<sup>2</sup> For the last two decades this classification has been the gold standard for patient management and clinical investigations. However, significant heterogeneity has been noted within FAB subgroups.<sup>3-6</sup> Various prognostic systems have been proposed with the aim of improving the ability to predict survival and progression in MDS patients, based on clinical variables, including age, peripheral cytopenias, bone marrow blast count, lactate dehydrogenase level, and cytogenetic pattern.<sup>7-10</sup> In 1997, an International MDS Risk Analysis Workshop defined the International Prognostic Scoring System (IPSS), based on bone marrow blast percentage scored into four ranges, number of peripheral cytopenias, and karyotype categorized in three groups.<sup>11</sup> Despite some discrepancies,<sup>12</sup> the IPSS has been extensively validated in independent patient populations,<sup>13,14</sup> and has become a benchmark for clinical trials and clinical decision making.

Recently, the WHO has formulated a new proposal for the classification of MDSs. This new classification is based on variables that had the demonstrated ability to stratify survival and leukemia progression in MDS patients, such as uni- or multilineage hematopoietic involvement, blast count split into narrower ranges, and peculiar cytogenetic abnormalities.<sup>15</sup> The clinical utility of this proposal is now under investigation,<sup>16-18</sup> and attempts are being made to refine the stratification of MDS classified according to the WHO criteria, based on clinical and morphologic criteria.<sup>19</sup>

The aim of this study was to evaluate the prognostic value of the WHO classification in a series of 467 patients with de novo MDS from our institution, to assess the role of the main prognostic factors in MDS patients classified in the WHO subgroups, and to estimate mortality rates and life expectancy of these groups as groundwork for evidence-based clinical decision making.

## PATIENTS AND METHODS

### Patient Characteristics and Clinical Procedures

All patients who were diagnosed as having de novo MDS at the Division of Hematology, University of Pavia Medical School, Istituto di Ricovero e Cura a Carattere Scientifico, Policlinico San Matteo (Pavia, Italy), between 1992 and 2002, were retrospectively evaluated for clinical and hematologic features at diagnosis, survival, and progression to leukemia. The procedures followed were in accordance with the ethical standards of the Institutional Committee on Human Experimentation and with the Helsinki Declaration of 1975, as revised in 1983. The cytologic diagnosis of MDS was initially made according to the FAB criteria<sup>2</sup>; all patients were then reclassified according to the WHO classification.<sup>15</sup>

Four hundred sixty-seven patients entered the analysis. Two hundred eighty-eight were male and 179 were female. The median age at diagnosis was 66 years (range, 22 to 97 years). According to the FAB criteria,<sup>2</sup> 187 patients were classified as having refractory

anemia (RA; 40%), 53 were classified as having RA with ringed sideroblasts (RARS; 11.3%), 131 were classified as having RA with excess of blasts (RAEB; 28.1%), 43 were classified as having RAEB in transformation (9.2%), and 53 were classified as having chronic myelomonocytic leukemia (11.3%).

To reclassify patients according to the WHO criteria,<sup>15</sup> two independent cytologists, who were blinded to the FAB classification, reanalyzed the marrow specimens morphologically. Five hundred bone marrow nucleated cells per sample were assessed. The evaluation of the erythroid lineage was based on the detection of megaloblastic changes, nuclear lobulation, multinuclearity, and cytoplasmic granules/inclusions. In the myeloid lineage, the following abnormalities were considered: bizarre nuclear shape, hypo- or agranularity, nuclear/cytoplasmic asynchrony, and pseudo-Pelger anomaly. Micromegakaryocytes, small binucleated megakaryocytes, megakaryocytes with small round separated nuclei, and megathrombocytes were considered signs of megakaryocytic dysplasia. A bone marrow lineage dysplasia was considered in the presence of 10% or more abnormal cells.

The concordance between the two reviewers of bone marrow morphology was evaluated using Cohen's  $\kappa$  test, which resulted in a 95% agreement ( $\kappa$ , 0.932;  $P < .001$ ). Discordant results were resolved by a joint review of the specimens. In this classification, 76 patients were given a diagnosis of RA (16%), 34 were given a diagnosis of RARS (7%), 80 patients were given a diagnosis of refractory cytopenia with multilineage dysplasia (RCMD; 17%), 13 patients were given a diagnosis of RCMD with ringed sideroblasts (RCMD-RS; 3%), 59 patients were given a diagnosis of RA with excess blasts, type 1 (RAEB-1; 13%), 72 patients were given a diagnosis of RAEB-2 (15%), 30 patients were given a diagnosis of MDS associated with isolated del(5q) (7%), and 10 patients were given a diagnosis of MDS unclassified (2%). Forty-six patients were classified as having chronic myelomonocytic leukemia (10%), whereas 47 patients were considered to have an AML from MDS (10%). The clinical and hematologic features of patients according to WHO subgroups are listed in Table 1.

Cytogenetic analysis was performed at diagnosis, using standard G-banding with trypsin-Giemsa staining,<sup>20</sup> and karyotypes were classified using the International System for Cytogenetic Nomenclature Criteria.<sup>21</sup> Cytogenetic data were available for 386 of the 467 patients, and clonal cytogenetic abnormalities were detected in 164 patients.

The IPSS was calculated according to Greenberg et al.<sup>11</sup> The score could be assessed in 310 of 374 patients diagnosed as having MDS according to the WHO criteria: 106 were classified as low risk (34%), 120 were classified as intermediate 1 (39%), 53 were classified as intermediate 2 (17%), and 31 were classified as high risk (10%).

### Statistical Analysis

Numerical variables were summarized by their median and quartiles or range. Categorical variables were described by counts and relative frequencies. Actuarial probability of survival and leukemia-free survival (LFS) were estimated using the Kaplan-Meier product limit method. Overall survival (OS) was defined as the time between diagnosis and death (as a result of all causes) or end of follow-up (censored observations). LFS was calculated from diagnosis to progression to acute leukemia or end of follow-up. Patients dying as a result of any cause before leukemic evolution were considered as censored at the time of death. Twenty patients who underwent allogeneic stem-cell transplantation, as well as 14 patients who received AML-like chemotherapy after

**Table 1.** Clinical and Hematologic Features of Patients at Diagnosis, According to WHO Subgroups

WHO Subgroups	RA	RARS	RCMD	RCMD-RS	RAEB-1	RAEB-2	MDS del(5q)	MDS-U
No. patients	76	34	80	13	59	72	30	10
Age, years								
Median	67	66	67	67	65	65	65	71
Range	28-93	46-83	24-90	50-91	22-87	22-86	47-85	46-86
Sex								
Male	41	16	47	8	43	55	15	
Female	35	18	33	5	16	17	15	6/4
Hb, g/dL								
Median	9.0	9.0	9.7	9.0	9.4	9.0	9.0	11.5
Range	5.3-13.2	6.4-11.2	4.8-15.0	5.0-11.0	4-17	5.6-14	6-15	7.3-15.5
MCV (fL)								
Median	101	102	95	95	99	94	101	98
Range	64-117	67-119	69-125	76-111	79-115	69-119	64-122	84-110
ANC, × 10 <sup>9</sup> /L								
Median	2.43	2.76	1.47	1.97	1.12	0.96	1.63	2.21
Range	0.52-8.74	0.16-9.73	0.1-4.32	0.10-3.71	0.06-25.52	0.04-26.60	0.18-7.58	0.31-3.42
Plt, × 10 <sup>9</sup> /L								
Median	179	285	82	90	54	67	219	83
Range	27-735	86-769	17-480	4-538	7-561	9-512	46-797	9-177
BM blasts, %								
Median	3	3	4	4	7	15	4	3
Range	0-4	0-4	0-4	1-4	5-9	10-19	2-4	2-4
IPSS subgroup, % (low/int 1/int 2/high)	65/28/7/0	74/23/3/0	30/59/11/0	20/80/0/0	0/68/32/0	0/8/41/51	67/33/0/0	20/60/20/0
Peripheral cytopenia, % (0/1/2/3)	25/53/13/7	17/62/14/7	5/49/32/14	8/42/34/17	11/30/42/17	3/26/46/25	7/62/31/0	10/50/40/0
Cytogenetic group, % (good/int/poor)	62/21/17	80/13/7	54/25/21	54/46/0	54/32/14	52/10/38	100/0/0	25/50/25

Abbreviations: RA, refractory anemia; RARS, RA with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RS, ringed sideroblasts; RAEB-1, refractory anemia with excess blasts, type 1; MDS, myelodysplastic syndrome; U, unclassified; Hb, hemoglobin; MCV, mean corpuscular volume; ANC, absolute neutrophil count; Plt, platelets; BM, bone marrow; IPSS, International Prognostic Scoring System; int, intermediate.

progression to leukemia, were censored at the time of therapeutic procedure. Comparisons between Kaplan-Meier curves were carried out by the Gehan's Wilcoxon test. Uni- and multivariate analyses were performed by means of Cox proportional hazards regression to identify the most significant independent prognostic factors affecting survival.

We assessed the effect on survival of developing transfusion dependency and of the onset of secondary iron overload by applying Cox models with time-dependent covariates. Standardized mortality ratios (SMRs) were calculated to compare the patients' mortality with the mortality of the general population in Italy. The SMR is the ratio between the number of deaths observed and the number of deaths expected in the study group according to a set of reference mortality rates. The Italian population mortality rates by age, sex, and calendar year were provided by the Italian Institute of Statistics. An SMR > 1 indicates a higher mortality rate than that expected in the general population. SMR values were tested by means of the score test; a *P* value lower than .05 indicates that the SMR is statistically significantly different from 1. All analyses were performed using Statistica software version 6.0 (1995; Statsoft Inc, Tulsa, OK) and Microsoft Excel 2000.

## RESULTS

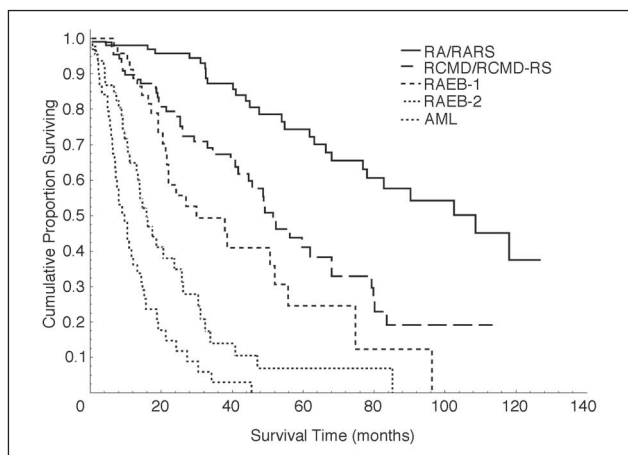
### Survival Analysis of WHO Subgroups

There was a significant difference in OS between patients with RA and those with RCMD; the median survival

of patients with unilineage dysplasia was 108 months, whereas it was 49 months in patients with RCMD (*P* < .001; Fig 1). Patients with RA also showed a significantly longer LFS (*P* = .005; Fig 2).

No significant difference in either OS or LFS was noted between patients with RA and those with MDS with isolated del(5q) (*P* = .94 and *P* = .89, respectively). We tested the effects of RS on survival in RA and RCMD. No significant differences were noted when the analysis was limited between RA and RARS (*P* = .64 and *P* = .19, respectively), or between RCMD and RCMD-RS (*P* = .12 and *P* = .23, respectively). To maximize the number of patients entering the analysis, we also compared patients with refractory cytopenia without ringed sideroblasts (including together RA and RCMD) versus refractory cytopenia with ringed sideroblasts (RARS and RCMD-RS). No significant differences were found in OS and LFS between the two groups (*P* = .09 and *P* = .95, respectively).

A nonsignificant difference in OS was observed between patients with RCMD and those with RAEB-1 (*P* = .06), but the difference in LFS between these two groups was statistically significant (*P* = .005). Significant differences in both OS and LFS were observed between patients with RAEB-1 and RAEB-2 (*P* < .001). Finally, a significant difference in



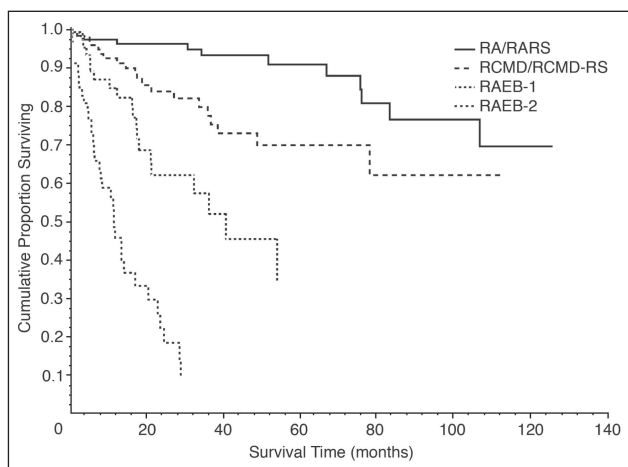
**Fig 1.** Overall survival of myelodysplastic syndrome (MDS) patients according to the WHO criteria ( $P < .001$ ). Patients with refractory anemia (RA) and RA with ringed sideroblasts (RARS), as well as those with refractory cytopenia with multilineage dysplasia (RCMD) and RCMD with ringed sideroblasts (RS), are plotted together in two groups identified as RA/RARS and RCMD/RCMD-RS, respectively. Acute myeloid leukemia (AML) group identifies patients with 20% to 30% bone marrow blasts, formerly classified as refractory anemia with excess blasts in transformation according to French-American-British criteria.

OS was noted between patients with RAEB-2 and AML from MDS ( $P = .004$ ).

### Demographic Prognostic Factors in MDSs Classified According to WHO Criteria

Cox proportional hazards regression was applied to assess the effects of age and sex on OS and LFS of our series of patients.

Age had a significant effect on OS of the MDS population analyzed as a whole ( $P < .001$ ) and stratified by WHO



**Fig 2.** Leukemia-free survival (LFS) of myelodysplastic syndrome (MDS) patients according to the WHO criteria ( $P < .001$ ). Patients with refractory anemia (RA) and RA with ringed sideroblasts (RARS), who did not show a significant difference in LFS, are plotted together in a group identified as RA/RARS. Likewise, patients with refractory cytopenia with multilineage dysplasia (RCMD) and RCMD with ringed sideroblasts (RS) are plotted together in a group identified as RCMD/RCMD-RS.

subgroups ( $P < .001$ ): the older the age, the worse the prognosis. No significant influence was observed on the risk of progression to leukemia ( $P = .31$ ). If we focus the analysis on WHO subgroups, the effect of age was statistically relevant within RA and RARS patients ( $P = .001$ ), and RCMD and RCMD-RS patients ( $P = .002$ ), whereas it was not significant within RAEB-1 and RAEB-2 subgroups ( $P = .91$  and  $P = .52$ , respectively).

A significant influence of sex on OS of MDS patients was observed; male patients had the worse prognosis (hazard ratio [HR], 0.62;  $P = .006$ ). Focusing the analysis on WHO categories, the effect of sex was relevant in refractory cytopenias (RCs; HR = 0.58;  $P = .02$ ), but did not affect the outcome of MDS patients with excess blasts (HR = 1.2;  $P = .52$ ).

We calculated the SMR in MDS patients, comparing the observed mortality with the mortality of the general Italian population standardized by sex, age, and calendar year. Considering the entire MDS population, the SMR was 7.30, which is significantly higher than 1 ( $P < .001$ ). Male patients had a significantly lower SMR than did females (6.48 v 9.48;  $P = .008$ ).

If we focus the analysis on patients with RA, RARS, and MDS with del(5q) ( $n = 132$ ), the SMR was 2.6; again this value was significantly higher than 1 ( $P < .001$ ), and again the males had a significantly lower SMR than did the females (1.95 v 3.89;  $P = .04$ ). If we stratify patients by age, patients younger than 65 years ( $n = 68$ ) had an SMR of 6.55, indicating a higher mortality rate than among the general population ( $P < .001$ ). Patients from 65 to 70 years old ( $n = 22$ ) showed a global SMR of 3.02, significantly higher than 1 ( $P = .009$ ). Finally, the life expectancy of patients 70 years or older ( $n = 42$ ) was not significantly lower than that of the general population (SMR = 1.62;  $P = .06$ ).

Considering patients affected with RCMD and RCMD-RS, the SMR of these groups ( $n = 93$ ) was significantly higher than 1 (SMR = 6.12;  $P < .001$ ), as was that of the patients divided into age subgroups (patients younger than 65 years, SMR = 24.89,  $P < .001$ ; patients from 65 to 70 years, SMR = 5.99,  $P < .001$ ; patients 70 years or older, SMR = 3.60,  $P < .001$ ); there were no significant differences between sexes.

### Disease-Related Prognostic Factors in MDSs Classified According to WHO Criteria

A significant association between WHO categories and IPSS subgroups was observed ( $\chi^2$  test,  $P < .001$ ; Table 1). Cox proportional hazard models applied to both OS and LFS showed a significant effect of IPSS on both OS and LFS in MDS patients grouped according to the WHO criteria ( $P < .001$ ).

We then tested the prognostic value of IPSS variables via multivariate and univariate Cox regression analyses. Bone marrow blast count, cytopenia, and cytogenetic abnormalities were defined and scored according to IPSS

criteria. Patients with isolated del(5q) were excluded from the cytogenetic good-risk group because they constitute an autonomous entity in the WHO classification. Data on the incidence of peripheral cytopenias and karyotypic abnormalities within WHO subgroups are summarized in Table 1.

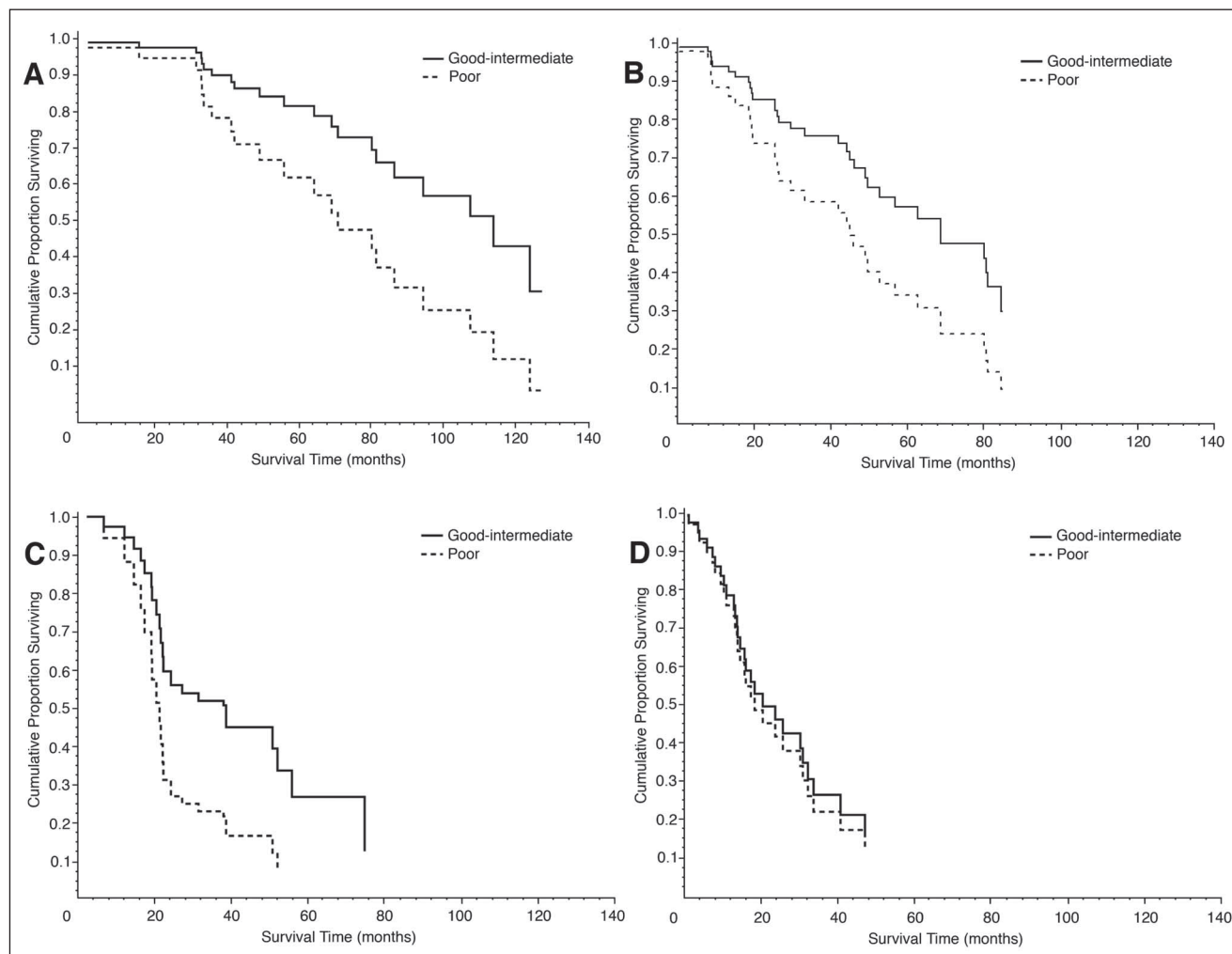
According to the multivariate analysis, blast count and cytogenetics showed a significant predictive value on both OS ( $P < .001$  and  $P = .03$ , respectively) and LFS ( $P < .001$  and  $P = .04$ , respectively) of MDS patients diagnosed according to WHO criteria, whereas peripheral cytopenia did not reach a statistical significance ( $P = .29$  and  $P = .27$  for OS and LFS, respectively).

To assess the effect of IPSS variables within WHO categories, we performed a stratified multivariate analysis. The highly significant likelihood-ratio test ( $P < .001$ ) between the stratified and the pooled model indicated different effects of blast count and cytogenetics among WHO

subgroups. Hence, we performed separate analyses in each WHO category. Given that blast count categorization is similar in WHO classification and IPSS, we used the percentage of bone marrow blasts as a continuous covariate in the stratified analyses.

Karyotype significantly affected OS of both MDSs without blasts excess and RAEB-1 (HR = 1.43,  $P = .046$ ; HR = 2.79,  $P = .008$ , respectively), whereas in LFS the magnitude of this effect was maintained without achieving statistical significance. No effect of cytogenetics was noticed in RAEB-2. Qualitatively similar results were obtained after grouping patients with good (normal karyotype, del(20q), or -Y) and with intermediate cytogenetic risk according to IPSS (Fig 3). No blast count effect was found on OS and LFS in any WHO subgroup.

Finally, we tested the ability of the WHO classification to provide a substratification within IPSS subgroups.



**Fig 3.** Overall survival of WHO subgroups according to cytogenetic risk defined according to International Prognostic Scoring System [patients with good and intermediate risk were pooled; patients with isolated del(5q) were excluded from the good-risk group]. The prognostic value of cytogenetics is noticeable in (A) refractory anemia (RA) and RA with ringed sideroblasts (RARS); (B) refractory cytopenia with multilineage dysplasia (RCMD) and RCMD with ringed sideroblasts (RS); and (C) refractory anemia with excess blasts, type 1 (RAEB-1); whereas it is not relevant in (D) RAEB-2.

Patients with low IPSS risk were distributed within RA/RARS (58%), MDS del(5q) (21%), and RCMD/RCMD-RS (21%). The WHO classification significantly stratified OS of patients with a low IPSS risk (HR = 2.71;  $P = .01$ ). A trend was noticed also on LFS (HR = 2.19), but was not statistically significant ( $P = .28$ ).

Patients with intermediate 1 risk were distributed mainly within the RA/RARS (20%), RCMD/RCMD-RS (40%), and RAEB-1 (27%) groups. Patients in the WHO subgroups (RA/RARS, RCMD/RCMD-RS, and RAEB-1) showed a significantly different OS (HR = 2.06;  $P = .005$ ). There was a trend toward a difference in LFS, although this was not statistically significant (HR = 1.71;  $P = .06$ ); RA/RARS patients tended to have a longer LFS than did patients in the RCMD/RCMD-RS and RAEB-1 groups.

Patients with intermediate 2 risk were distributed within RCMD/RCMD-RS (13%), RAEB-1 (26%), and RAEB-2 (51%). No significant differences in OS or LFS were observed among patients with intermediate 2 risk grouped in RCMD/RCMD-RS, RAEB-1, and RAEB-2 (HR = 1.25,  $P = .35$ ; HR = 1.83,  $P = .06$ , respectively).

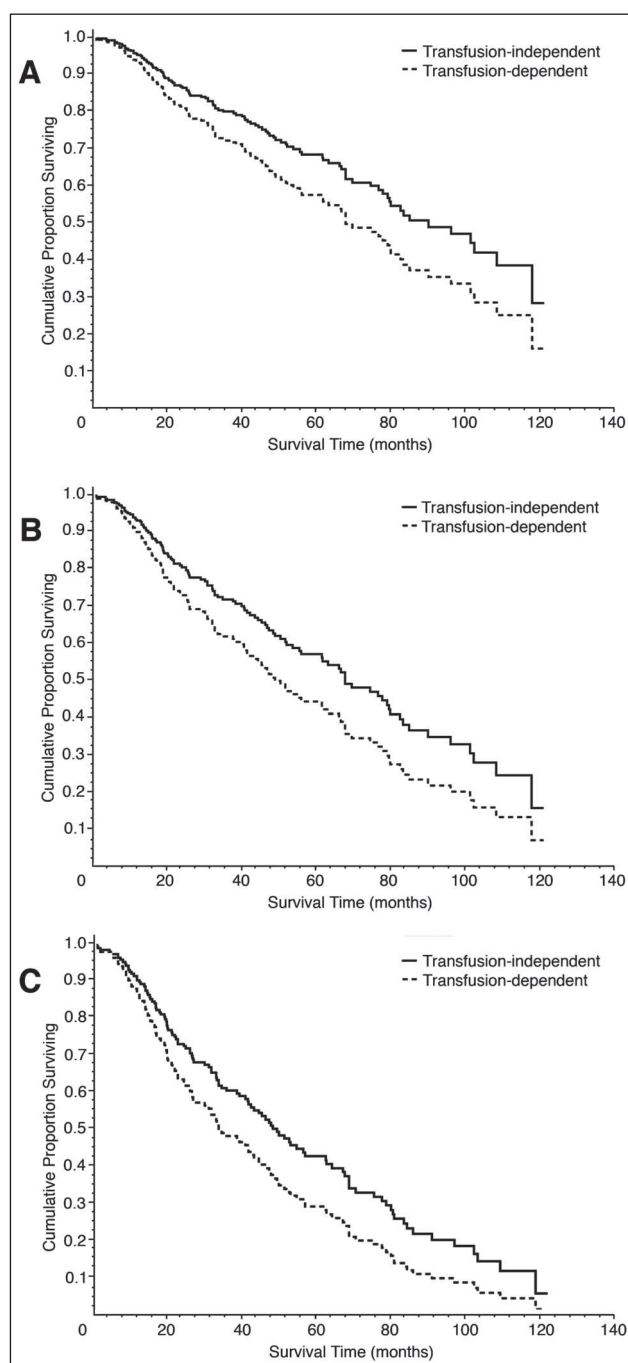
#### Survival and Life Expectancy in MDS According to Transfusion Dependency

We applied Cox regression with time-dependent covariates to evaluate the prognostic value of developing RBC transfusion dependency among patients with MDS. The OS of transfusion-dependent patients was significantly shorter than that of patients who did not develop a transfusion requirement (HR = 2.16;  $P < .001$ ). LFS of patients who developed transfusion dependency was also significantly worse than that of patients who did not need transfusions (HR = 2.02;  $P < .001$ ).

We then tested the effect of developing RBC transfusion dependency in a multivariate analysis with cytogenetics scored according to IPSS criteria, which was shown to be the only significant disease-related prognostic factor in WHO subgroups. Both karyotype and transfusion dependency showed a predictive value on OS (HR = 1.44,  $P = .001$ ; HR = 1.72,  $P = .007$ , respectively; Fig 4) and LFS (HR = 1.50,  $P = .003$ ; HR = 2.64,  $P < .001$ , respectively).

We then tested the effect on the survival of the transfusion burden via a Cox regression with time-dependent covariates. First, we grouped patients receiving less than 20, 20 to 40, or more than 40 RBC units during their clinical course. The number of transfusions affected both OS (HR = 1.21;  $P = .02$ ) and LFS (HR = 1.39;  $P < .001$ ).

However, because the total number of RBC units depends on the duration of follow-up since the onset of transfusion dependency, we also considered the effect of transfusion burden calculated as the number of transfusions per month. A significant effect was found on both OS (HR = 1.35;  $P < .001$ ) and LFS (HR = 1.75;  $P < .001$ ). These effects were maintained after accounting for cytogenetics.



**Fig 4.** Overall survival of myelodysplastic syndrome patients grouped according to cytogenetic risk, defined according to International Prognostic Scoring System [(A) good, (B) intermediate, (C) poor risk], and development of transfusion requirement. Patients with isolated del(5q) were excluded from the cytogenetic good-risk group. The survival curves in this graph do not account for time dependency of the transfusion requirement.

We then assessed the survival of transfusion-dependent and nontransfused patients via a Cox model with time-dependent covariates, considering nonleukemic death as an end point. These included mainly cardiac failure (51% of patients), infection (31% of patients), hemorrhage (8% of

patients), and hepatic cirrhosis (8% of patients). Among MDS patients without excess blasts who died as a result of nonleukemic causes, cardiac failure was significantly more frequent in transfusion-dependent patients ( $P = .01$ ). In the first 50 months of follow-up, transfusion-dependent patients had a significantly worse survival than those who did not require transfusions ( $HR = 1.98$ ;  $P = .01$ ), whereas no differences were noticed after this time period.

Table 2 shows the clinical and hematologic characteristics at diagnosis of patients within WHO subgroups, according to the development of transfusion requirement during their clinical course. Significant differences between patients who developed a transfusion dependency and those who did not were noticed in hemoglobin levels at diagnosis ( $P$  values ranging from .04 to  $< .001$ ), whereas no significant differences were noticed in cytogenetics.

The negative effect of developing a transfusion requirement on OS was observed both in patients with RA, RARS, or MDS with del(5q) ( $HR = 3.46$ ;  $P = .005$ ), and in those with RCMD or RCMD-RS ( $HR = 1.87$ ;  $P = .04$ ). In RAEB-1 patients, transfusion dependency had a borderline effect ( $HR = 2.34$ ;  $P = .09$ ); whereas it showed no effect on the survival of RAEB-2 patients ( $HR = 1.47$ ;  $P = .22$ ).

The total number of RBC units did not retain significance within WHO subgroups, whereas the transfusion burden calculated as number of RBC units per month significantly affected the survival of both patients with RA, RARS, or MDS with del(5q) ( $HR = 1.62$ ;  $P = .007$ ) and those with RCMD or RCMD-RS ( $HR = 1.51$ ;  $P = .02$ ).

In multivariate analysis with cytogenetics, the number of RBC transfusions per month retained a statistical significance on OS of both patients with RA, RARS, or MDS with del(5q) ( $HR = 1.54$ ;  $P < .001$ ) and those with RCMD or RCMD-RS ( $HR = 1.45$ ;  $P = .03$ ). A negative effect was also observed on LFS of both patients with RA, RARS, or MDS with del(5q) ( $HR = 1.44$ ;  $P = .05$ ), and those with RCMD or RCMD-RS ( $HR = 1.54$ ;  $P = .02$ ). In patients with excess blasts, transfusion dependency did not have a significant effect on LFS.

Finally, we applied the Cox model with time-dependent covariates to evaluate the prognostic value of patients with MDS developing iron overload during their follow-up. We chose a serum ferritin level of 1,000 ng/mL as a threshold that distinguishes between mild and clinically relevant iron burden.<sup>22</sup> Considering patients with transfusion needs, this threshold was reached after they received a median number of 21 RBC units (median time from development of transfusion requirement to onset of iron overload, 10.8 months). The development of secondary iron overload significantly affected the OS ( $P < .001$ ), with an HR of 1.36 every 500 ng/mL of increase in serum ferritin above the threshold. After we added the transfusion needs (number of packed red cell units per month) into the model, the effect of iron overload was maintained ( $HR = 1.30$ ;  $P = .003$ ). If we focus the analysis on WHO

subgroups, the effect of secondary iron overload was still present in patients with RA/RARS ( $HR = 1.51$ ;  $P < .001$ ), whereas it was not significant in those with RCMD/RCMD-RS ( $HR = 1.34$ ;  $P = .20$ ).

## DISCUSSION

Our results show that the WHO classification of MDSs has prognostic relevance. Among patients with MDS without excess blasts, isolated involvement of the erythroid lineage rather than bi- or trilineage marrow dysplasia is associated with a significantly better prognosis in terms of both OS and LFS. The definition of two categories of refractory anemia with excess blasts identifies two groups of patients with significantly different OS and LFS.

As reported in other studies,<sup>7,8,11,23</sup> the OS of male MDS patients is shorter than that of female patients. However, the SMR is significantly higher in female patients than in male patients. The effect of sex is noticeable in patients with RA and refractory cytopenia, whereas it disappears in those with MDS with excess blasts, in whom the more aggressive disease probably overwhelms demographic predictors of life expectancy.

With regard to age, we found that older patients had a shorter survival, as observed in other MDS cohorts.<sup>7,8,11</sup> However, as previously reported by Morel et al,<sup>23</sup> the SMR is significantly higher in younger patients than in older patients.

The difference between sex- and age-specific SMRs can be due to the predominance of disease-related mortality in the patients' cohort. It is a demographic fact that males have a shorter life expectancy than females of the same age group. Given that both male and female MDS patients experience a much higher mortality than the reference population, the higher SMR in females is due mainly to the lower reference mortality rates. The same mechanism may apply to the higher SMR observed in young people.

MDS with isolated erythroid lineage dysplasia identifies a subset of truly low-risk patients, whose survival is significantly affected by demographic variables rather than by disease features. The life expectancy of such patients aged 70 years or older is not significantly shorter than that of the general population.

IPSS has a significant prognostic value in MDS patients stratified into WHO subgroups. However, both the systems were based on similar criteria, in particular with regard to the ranking of bone marrow blast. When we tested the significance of the IPSS variables in the WHO subgroups, as expected bone marrow blast count failed to show a prognostic value. Likewise, the number of peripheral cytopenias did not show a significant predictive value on the outcome of either low- or high-risk MDS. Although one may assume that peripheral cytopenia is an expression of more severe lineage involvement, in our analysis this failed to show an

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**Table 2.** Clinical and Hematologic Features at Diagnosis of Patients According to the Development of Transfusion Requirement During Their Clinical Course

WHO Subgroups	RA		RARS		RCMD		RCMD-RS		RAEB-1	
	Indep	Dep	Indep	Dep	Indep	Dep	Indep	Dep	Indep	Dep
Total patients										
No.	43	33	19	15	38	42	6	7	31	28
%	57	43	56	44	48	52	46	54	53	47
Age, years										
Median	61*	68*	62	69	67	67	70	66	62	66
Range	28-88	38-93	46-83	56-78	28-90	24-87	68-80	50-91	40-80	22-87
Sex										
Male	21	20	8	8	19	28	3	5	23	20
Female	22	13	11	7	19	14	3	2	8	8
Hb, g/dL										
Median	11.2*	8.6*	9.7	7.7	10.6*	8.7*	9.75	8.6	10.6*	8.5*
Range	7.9-13.2	5.3-13	7-11.2	6.4-11	8-15	5-12.4	7-11	5-11	7-17	4-12
ANC, × 10 <sup>9</sup> /L										
Median	2.09	2.90	2.30	2.76	1.52	1.64	1.97	2.59	0.96	1.39
Range	0.86-8.74	0.52-7.20	0.16-5.37	1.04-9.73	0.10-4.32	0.1-4.07	0.54-3.42	0.10-3.71	0.06-6.44	0.11-25.5
Plt, × 10 <sup>9</sup> /L										
Median	175	180	229	302	83	132	57	249	119	101
Range	55-503	27-735	86-769	111-698	20-263	17-480	40-397	4-538	11-561	7-393
BM blasts, %										
Median	4	3	3	4	3	4	4	3	7.5	7
Range	0-4	0-4	0-4	0-4	0-4	2-4	1-4	1-4	5-9	5-9
Peripheral cytopenia, % (0/1/2/3)	38/41/16/5*	10/70/10/10*	21/50/14/14	13/74/13/0	6/57/26/11	5/40/38/17	20/20/40/20	0/57/29/14	15/23/54/8	7/37/30/26
Cytogenetic group, % (good/intermediate/poor)	55/26/19	70/15/15	74/21/5	91/0/9	57/25/18	50/27/23	67/33/0	40/60/0	50/29/21	51/37/12
WHO Subgroups	RAEB-2		MDSdel (5q)		MDS-U					
	Indep	Dep	Indep	Dep	Indep	Dep				
Total patients										
No.	32	40	16	14	7	3				
%	44	56	53	47	70	30				
Age, years										
Median	67	63	64	70	60	78				
Range	25-81	22-86	47-79	50-86	46-84	71-86				
Sex										
Male	24	31	9	6	5	1				
Female	8	9	7	8	2	2				
Hb, g/dL										
Median	10.0*	8.5*	9.0	9.0	12.2*	7.4*				
Range	8-14	5.6-13.3	8-15	6-13	10.3-15.5	7.3-11				
ANC, × 10 <sup>9</sup> /Ld										
Median	0.92	1.24	3.02	1.57	2.21	2.32				
Range	0.13-26.6	0.04-11	0.22-7.58	0.18-4.8	0.31-3.42	2.1-2.55				
Plt, × 10 <sup>9</sup> /L										
Median	57	77	225	240	41	130				
Range	10-290	9-512	46-797	64-447	9-167	83-177				
BM blasts, %										
Median	13	15	4	3.5	3.5	3				
Range	10-19*	10-19*	1-4	1-4	2-4	1-4				
Peripheral cytopenia, % (0/1/2/3)	7/24/52/17	0/28/41/31	7/60/33/0	7/64/29/0	14/57/29/0	0/33/67/0				
Cytogenetic group, % (good/intermediate/poor)	65/8/27	41/11/48	100/0/0	100/0/0	34/50/16	0/50/50				

Abbreviations: RA, refractory anemia; RARS, RA with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RS, ringed sideroblasts; RAEB-1, refractory anemia with excess blasts, type 1; MDS, myelodysplastic syndrome; U, unclassified; dep, RBC transfusion dependent; indep, RBC transfusion independent; Hb, hemoglobin; ANC, absolute neutrophil count; Plt, platelets; BM, bone marrow.

\*The differences between transfusion-dependent and transfusion-independent patients were statistically significant within each WHO subgroup (P ranging from .04 to < .001).

independent prognostic significance. The only IPSS variable that maintains a prognostic value in MDS patients classified into the WHO subgroups is cytogenetics. In our analysis, the effect of karyotype abnormalities is noticeable in RA and RC as well as in RAEB-1, whereas it seems to be negligible in patients with more than 10% of blasts.

The development of transfusion dependency significantly worsens the survival of patients with MDS. Although most clinical features at diagnosis do not differ significantly between transfusion-dependent and transfusion-independent patients within WHO subgroups (Table 2), the significant effect of cytogenetics in multivariate analysis suggests that this might partly reflect the severity of bone marrow failure. However, development of secondary iron overload (defined as serum ferritin > 1,000 ng/mL) significantly worsens survival: after adjusting for transfusion burden, we obtained a 30% increase in hazard for every 500 ng/mL of increase in serum ferritin above the threshold.

The effect of iron overload was noticeable mainly among patients with RA, who have a longer survival and are therefore more prone to develop long-term toxicity of iron overload. In contrast, secondary iron overload did not affect the survival of patients with refractory cytopenia, who have a median survival of about 50 months. On the basis of these results, it seems possible to recommend adequate iron chelation therapy for patients with RA whose transfusion burden exceeds 20 to 25 RBC units.

The critical clinical decision in MDS is whether to perform allogeneic stem-cell transplantation, which is the only potential cure for these syndromes.<sup>24-26</sup> There is wide agreement on performing allogeneic transplantation in adult MDS patients with high, intermediate 2, or intermediate 1 IPSS risk, whereas consensus is less definite for patients with low risk scores.<sup>27</sup> A recent decision analysis suggested that a delayed transplantation strategy for low and intermediate 1 IPSS groups would maximize survival, despite the worse outcome of the transplantation procedure.

According to these results, in low-risk patients, transplantation should be performed in the presence of clinical events suggestive of disease progression.<sup>28</sup> Although such an approach reduces the relevance of predictive systems (given that the clinical decision is based on evidence of progression), individualized follow-up is essential to avoid progression to leukemia or nonleukemic events that could preclude transplantation. Our analysis shows that WHO classification is the most significant predictor of survival in patients with low-risk and intermediate 1 IPSS MDS, and can be used, in combination with cytogenetics, to guide the choice of whether to perform a transplantation procedure or, in the context of a delayed transplantation strategy, to define the follow-up schedule. In these patients, the onset of transfusion requirements is associated with an increased hazard of progression to leukemia. Moreover, among transfusion-dependent patients, the development of iron overload worsens survival. This might support the indication for transplantation in eligible patients with low-risk MDS and a transfusion requirement.

In summary, our data show that the WHO classification of MDSs has prognostic value. This classification, along with cytogenetics, seems to be relevant to the choice of whether to perform transplantation. In particular, MDS with isolated erythroid lineage dysplasia identifies a subset of truly low-risk patients, whose outcome seems independent of disease characteristics, and in whom a conservative approach seems to be advisable. The development of secondary iron overload significantly worsens the survival of these patients. Therapeutic approaches aimed at reducing transfusion needs and at preventing iron overload are warranted.

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### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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