International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes

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Despite multiple disparate prognostic risk analysis systems for evaluating clinical outcome for patients with myelodysplastic syndrome (MDS), imprecision persists with such analyses. To attempt to improve on these systems, an International MDS Risk Analysis Workshop combined cytogenetic, morphological, and clinical data from seven large previously reported risk-based studies that had generated prognostic systems. A global analysis was performed on these patients, and critical prognostic variables were re-evaluated to generate a consensus prognostic system, particularly using a more refined bone marrow (BM) cytogenetic classification. Univariate analysis indicated that the major variables having an impact on disease outcome for evolution to acute myeloid leukemia were cytogenetic abnormalities, percentage of BM myeloblasts, and number of cytopenias; for survival, in addition to the above, variables also included age and gender. Cytogenetic subgroups of outcome were as follows: "good" outcomes were normal, −Y alone, del(5q) alone, del(20q) alone; "poor" outcomes were complex (ie, ≥3 abnormalities) or chromosome 7 anomalies; and "intermediate" outcomes were other abnormalities. Multivariate analysis combined these cytogenetic subgroups with percentage of BM blasts and number of cytopenias to generate a prognostic model. Weighting these variables by their statistical power separated patients into distinctive subgroups of risk for 25% of patients to undergo evolution to acute myeloid leukemia, with: low (31% of patients), 9.4 years; intermediate-1 (INT-1; 39%), 3.3 years; INT-2 (22%), 1.1 years; and high (8%), 0.2 year. These features also separated patients into similar distinctive risk groups for median survival: low, 5.7 years; INT-1, 3.5 years; INT-2, 1.2 years; and high, 0.4 year. Stratification for age further improved analysis of survival. Compared with prior risk-based classifications, this International Prognostic Scoring System provides an improved method for evaluating prognosis in MDS. This classification system should prove useful for more precise design and analysis of therapeutic trials in this disease.
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A MULTIPLICITY OF DISPARATE METHODS has been developed for evaluating the potential clinical outcomes for patients with myelodysplastic syndromes (MDSs). After the initial French-American-British (FAB) Morphology Group classification in 1982,[1] at least six additional risk classification systems have been used regarding prognostic classification of MDSs and their potential for survival and evolution to acute myeloid leukemia (AML).[2-7] These classification methods, in addition to the bone marrow (BM) morphological classification as used by the FAB group, have included clinical variables such as BM myeloblast percentage, BM biopsy features, specific cytopenias, age, lactate dehydrogenase level, and BM cytogenetic pattern.[1-9] A number of other cytogenetic classification methods have also been used to categorize patients with MDS.[8,10,11] However, imprecision associated with varying degrees of sensitivity and specificity persists with these classification systems regarding clinical outcomes.

To attempt to improve the clinical and prognostic use of these systems and to develop a consensus prognostic risk-based analysis system, an International MDS Risk Analysis Workshop was convened. In this workshop, cytogenetic, morphological and clinical data were combined and collated from patients with primary MDS from seven previously reported studies that used independent risk-based prognostic systems.[2-7,13] The combined data obtained from these patients were analyzed centrally, and a global analysis was performed. Critical prognostic variables were then re-evaluated using this data set to generate a prognostic system, in particular, using a more refined BM cytogenetic classification combined with relevant clinical parameters.

The goals of this study were (1) to obtain a database from a large representative group of well-defined untreated primary MDS patients with a prolonged follow-up period, (2) to refine the BM cytogenetic subgroups evaluated, (3) to combine statistically defined major clinical and cytogenetic parameters for evaluating clinical outcomes, (4) to define and weight prognostic risk categories utilizing multivariate analyses, (5) to generate an International Prognostic Scoring System (IPSS) for MDS based on these findings, and (6) to compare this IPSS with prior classification methods.

MATERIALS AND METHODS

Patients. Table 1 provides a summary of the clinical data obtained from 816 primary MDS patients evaluated in this study who had also been evaluated in prior individual risk-based studies regarding their clinical outcomes.[2-7,13] Of these patients, 759 individuals were also analyzed for AML evolution. Data are presented on demographic, clinical, and cytogenetic variables, including three of the most widely used MDS risk evaluation systems (ie, FAB, Spanish, and Lille).[1,3,5] For each of these variables, the number and percentages of patients in each category, as well as the estimated median

Table 1. Clinical Variables of MDS Patients Related to Survival and AML Evolution

Variable	No. of Patients	% of Patients	Median Survival (yr)	Log Rank	No. of Patients	% of Patients	25% AML (yr)	Log Rank
Cytogenetics*	816			99†	759			71†
Good	570	70	3.8		521	69	5.6	
Intermediate	112	14	2.4		107	14	1.6	
Poor	134	16	0.8		131	17	0.9	
Gender								
Female	325	40	3.9	15†	300	40	2.9	0.4‡
Male	491	60	2.5		459	60	3.1	
Age (yr)								
≤60	205	25	4.6	29†	187	25	2.6	0.3‡
>60	611	75	2.5		572	75	3.2	
FAB								
RARS	125	15	6.9	222†	109	14	10.1	202†
RA	294	36	4.2		272	36	4.7	
RAEB	208	26	1.5		198	26	1.4	
RAEB-T	61	8	0.6		60	8	0.2	
CMML§	126	15	2.4		118	16	2.9	
Cytopenia								
0	152	19	5.3	96†	140	18	7.6	39†
1	322	39	4.0		292	39	5.6	
2	224	27	1.6		213	28	1.6	
3	118	15	1.3		114	15	1.3	
Hb								
<10 g/dL	442	54	1.9	62†	409	54	2.1	17†
≥10 g/dL	373	46	4.5		349	46	4.4	
ANC								
<1.5 K/μL	366	46	2.5	4‡	379	50	2.1	12‖
≥1.5 K/μL	439	54	3.5		380	50	4.7	
Plts								
<100 K/μL	303	37	1.6	57†	289	38	1.6	14†
≥100 K/μL	512	63	3.9		469	62	3.8	
BM blasts								
<5%	483	59	4.4	220†	437	58	7.6	169†
5%–10%	183	22	2.1		178	23	2.1	
11%–20%	114	14	0.7		112	14	0.7	
21%–30%	36	5	0.6		35	5	0.2	
Lille								
Low	382	47	4.8	272†	565	75	5.5	172†
Intermediate	329	41	2.4		153	20	2.9	
High	100	12	0.5		39	5	0.2	
Total	811				757			
Spanish								
Low	391	48	4.9	226†	477	63	5.5	90†
Intermediate	311	38	2.4		161	21	1.6	
High	111	14	0.6		118	16	0.7	
Total	813				756			

Degrees of freedom for the log-rank χ^2 test are one less than the number of categories of the variable.

Abbreviations: Hb, hemoglobin level; ANC, absolute neutrophil count; Plts, platelet count; K, 1,000.

* Cytogenetic subgroups: Good, normal, del(5q) only, del(20q) only, −Y only; Intermediate, +8, single miscellaneous, double abnormalities; Poor, complex (ie, ≥3 anomalies) or chromosome 7 abnormalities.

† $P < .0001$.

‡ P value not statistically significant.

§ Excluding patients with WBC counts > 12,000/μL.

‖ $P < .0005$.

(time to 50%) survival and time to 25% of patients evolving to AML are given (Tables 1 and 2) using Kaplan-Meier analyses (see below, Statistics). These tables also include log-rank statistics with indications of statistical significance. Patients who had previously received intensive chemotherapy and those with secondary MDS were excluded from analysis. However, patients who had received prior short courses (ie, ≤3 months) of low-dose oral chemotherapy (43 patients) or hemopoietic growth factor exposure (20 patients) were included in the analysis. Investigators from the seven participating institutions completed a standard comprehensive registration form for each patient detailing the patients' clinical and cytogenetic features at presentation and clinical outcomes (ie, survival time from diagnosis and time until AML evolution). Cytopenias were defined as a hemoglobin level of less than 10 g/dL, an absolute neutrophil count of less than 1,500/μL, and a platelet count of less than 100,000/μL. These data were then submitted to the Workshop Central Statisti-

Table 2. Major Multivariate Variables Related to Clinical Outcome in MDS Patients Using Proportional Hazards Regression Analysis: International MDS Risk Analysis Workshop

Variable	No. of Categories	χ^2 Values*	
		Survival	AML Evolution
BM blasts	4	97	102
Cytogenetics	3	63	70
Cytopenias	4	46	43
Age	2	38	31
Gender	2	24	19

Categories of variables are defined in Table 1 and text.

* $P < .0001$.

cal Analyst (C.C.) to provide a comprehensive database and to permit further analysis.

BM morphology. BM morphology was evaluated by each institution using the FAB classification system.[1] Patients had clinically stable MDS and cytopenias for ≥4 weeks for inclusion in the study. The FAB classification system defined MDS as showing BM dysplasia in at least two of the hemopoietic cell lines; patients with refractory anemia (RA) had less than 5% BM myeloblasts; those with RA with excess blasts (RAEB) had 5% to 20% blasts; and those with RAEB in transformation (RAEB-T) had 21% to 30% blasts. Patients with RA with ringed sideroblasts (RARS) had 15% of the erythroid cells with RS as well as less than 5% BM blasts. Patients were also subdivided into those with BM blasts less than 5%, 5% to 10%, 11% to 20%, and 21% to 30%. In our study, patients with chronic myelomonocytic leukemia (CMML), ie, with monocytosis of greater than 1,000/μL, were subdivided into ''proliferative'' and ''nonproliferative'' subtypes. Proliferative-type CMML (ie, patients with white blood cell [WBC] counts >12,000/μL) were excluded from this analysis, because these individuals were believed to predominantly represent myeloproliferative disorders (MPDs) rather than MDS.[14] Nonproliferative CMML patients had WBC counts ≤12,000/μL, as well as other features of MDS, and were included in this analysis. A representative proportion of slides from each center (35 cases, randomly selected) was separately reviewed by three members of the Workshop Morphology Committee (J.B., Chair; T.H. and T.V.). Highly significant ($P < .0004$) concordance between reviewers was found regarding the percentage of BM blasts enumerated, with blinded independent evaluations, as determined by correlation analysis.

Cytogenetic pattern. Cytogenetic analysis of BM specimens was performed at the individual centers; the results were reviewed and collated centrally by the Workshop Cytogenetics Committee (M.M.L., Chair). Inclusion in the study required the analysis of ≥10 metaphase cells per patient. The criteria defined by the International System for Human Cytogenetic Nomenclature, 1995[15] were used for identification of abnormal clones. For cytogenetic categorization, patients were divided into those with normal karyotypes or those with single recurring, double recurring, or complex (ie, ≥3 anomalies) recurring, or miscellaneous (nonrecurring) abnormalities. The individual cytogenetic abnormalities were classified according to 1 of 12 different cytogenetic categories. Subsequently, based on the outcome analyses indicated in Table 1 and shown below, the patients were placed into good, intermediate, and poor risk subgroups.

Statistics. Each clinical and cytogenetic variable was analyzed by the Workshop Statistical Committee (C.C., Chair) using Kaplan-Meier curves and log-rank tests (for univariate analysis, see Tables 1 and 2). P values less than .05 were considered statistically significant. The committee then generated information regarding multivariate analysis of the parameters evaluated, using proportional hazards regression analysis. The final set of risk variables for the prognostic

model was chosen on both statistical and clinical grounds. Weighting each of the prognostic variables (to express their relative importance) using regression coefficients from the proportional hazards regression analysis permitted generation of a categorical risk-scoring system. The numbers provided for the risk-scoring values were approximations to the nearest 0.5 unit. These scores were combined as explained below to create risk categories to develop the IPSS. The predictive power of this IPSS was also compared with those of the FAB, Spanish, and Lille classification systems for MDS.[1,3,5] Correlation analysis was performed for evaluation of concordance between morphological reviewers.

RESULTS

Univariate analyses. The proportion of patients in this study with FAB classification subtypes was 15% RARS, 36% RA, 26% RAEB, 8% RAEB-T and 15% CMML. The median age of the patients was 69 years (range, 16 to 96 years). The male:female ratio was 1.5:1; 25% of the patients were ≤60 years of age, and 55% were ≤70 years of age (Table 1). The median follow-up time for these patients was 1.9 years (range, 0.1 to 17 years). Tables 1 and 2 indicate the factors determined by univariate analysis to be relevant for survival and AML evolution in the MDS patients studied. This analysis showed that the major variables predictive of outcome for survival were FAB classification, percentage of BM blasts, cytogenetic pattern, age, gender, and number of cytopenias. The major features predictive of AML evolution were FAB classification, percentage of BM blasts, cytogenetic pattern, and number of cytopenias.

Survival and AML evolution times for patients are shown as they related to their initial FAB classification (Fig 1), BM blast percentages (Fig 2), and the number of cytopenias (Fig 3). These clinical outcomes as they related to individual cytogenetic subgroups are shown in Figs 4A and 4B. These data showed relatively poorer prognoses for patients with RAEB or RAEB-T, greater than 10% BM blasts, and 2 to 3 cytopenias and for those with complex cytogenetic abnormalities or chromosome 7 anomalies. Table 2 provides detailed information regarding survival and AML evolution as they related to BM cytogenetic subcategories and indicates the proportion of patients with various cytogenetic abnormalities. A normal karyotype was found in 60% of the patients. The most common single abnormalities were del(5q) and trisomy 8 (≈5% to 6% for each).

Based on the univariate analysis, the patients were separated for both survival and AML evolution into three prognostic subgroups related to their BM cytogenetic pattern: good, intermediate, or poor (Table 1). Patients with BM karyotypes that were normal, del(5q), del(20q) and −Y had relatively good prognoses (70%), whereas relatively poor prognoses were present in patients with complex abnormalities (ie, ≥ 3 anomalies) or chromosome 7 or chromosome anomalies (16%). The remaining patients were intermediate in outcome (14%). Of the 66 patients in the ''complex'' category, 63 patients had chromosome 5 and/or 7 abnormalities in addition to other anomalies (33, abnormalities of chromosome 5; 7, abnormalities of chromosome 7; 23, abnormalities of both chromosomes). The median survival times of patients within these three cytogenetic subgroups groups were 3.8, 2.4, and 0.8 years, respectively, and the times for

FAB Classification

A

Survival

	RARS	125 pts
	RA	294 pts
	CMML	126 pts
	RAEB	208 pts
	RAEB-T	61 pts

B

AML Evolution

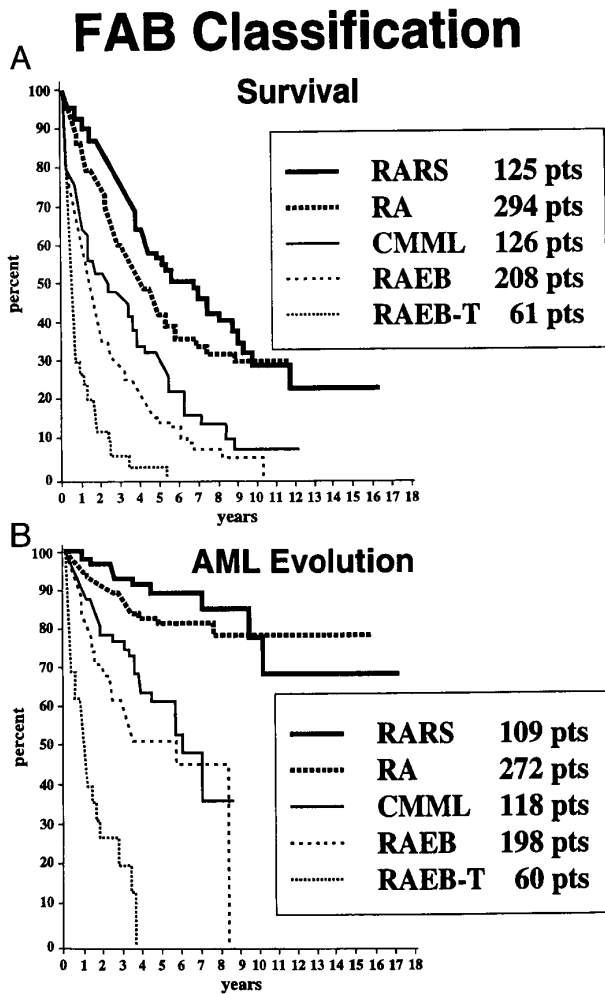|	RARS	109 pts
	RA	272 pts
	CMML	118 pts
	RAEB	198 pts
	RAEB-T	60 pts

Fig 1.　Survival (A) and freedom from AML evolution (B) of MDS patients related to their FAB classification subgroup (Kaplan-Meier curves).

25% of the patients to undergo AML evolution were 5.6, 1.6, and 0.9 years (Table 1 and Fig 5).

Multivariate analyses.　Using proportional hazards regression multivariate analysis, the most significant independent variables for determining outcome were BM blast percentage, number of cytopenias, cytogenetic subgroup (ie, good, intermediate, or poor), age, and gender (Table 2). The final set of risk variables used for the prognostic model were BM blast percentage, number of cytopenias, and cytogenetic subgroup (chosen on both clinical and statistical grounds, these were significant variables for both survival and AML evolution). Risk scores for each significant variable were generated with weighting relative to the statistical power (ie, using coefficients from the proportional hazards regression analysis), and an IPSS for MDS was developed. The risk scores for BM blast percentage, cytogenetic subgroup, and number of cytopenias were evaluated, and the weighted scores are shown in Table 3 (categories are defined in the text and Table 1). By combining the risk scores for these three major variables, patients were stratified into four distinctive risk groups regarding both survival and AML evolu-

tion, with their risk scores being: low, 0; intermediate-1 (INT-1), 0.5 to 1.0; INT-2, 1.5 to 2.0; and high, ≥ 2.5. Table 4 indicates the proportions of patients in each risk group, their median survival times, and times to 25% AML evolution. Figure 6 shows the Kaplan-Meier curves depicting survival and freedom from AML times for patients in these prognostic subgroups. Much less precise discrimination between the four subgroups occurred when either cytopenias or cytogenetic subtypes were omitted from the classification (data not shown).

Age- and gender-related effects.　Because age at diagnosis was shown to be an important variable for survival of these patients (but not for AML evolution in univariate analysis), the patients were stratified for this outcome for this parameter. Table 4 indicates the proportions of patients stratified by age in each risk group, their median survival times, and times to 25% AML evolution. As shown in Fig 7 and
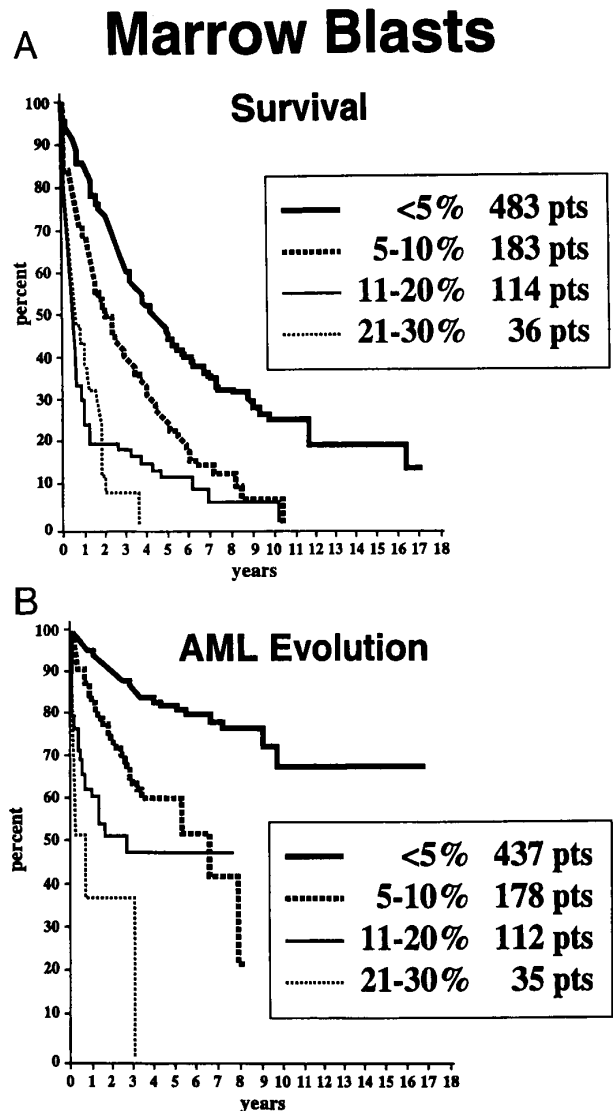
A

Marrow Blasts

Survival

	<5%	483 pts
	5-10%	183 pts
	11-20%	114 pts
	21-30%	36 pts

B

AML Evolution

	<5%	437 pts
	5-10%	178 pts
	11-20%	112 pts
	21-30%	35 pts

Fig 2.　Survival (A) and freedom from AML evolution (B) of MDS patients related to the percentage of their marrow myeloblasts (Kaplan-Meier curves).
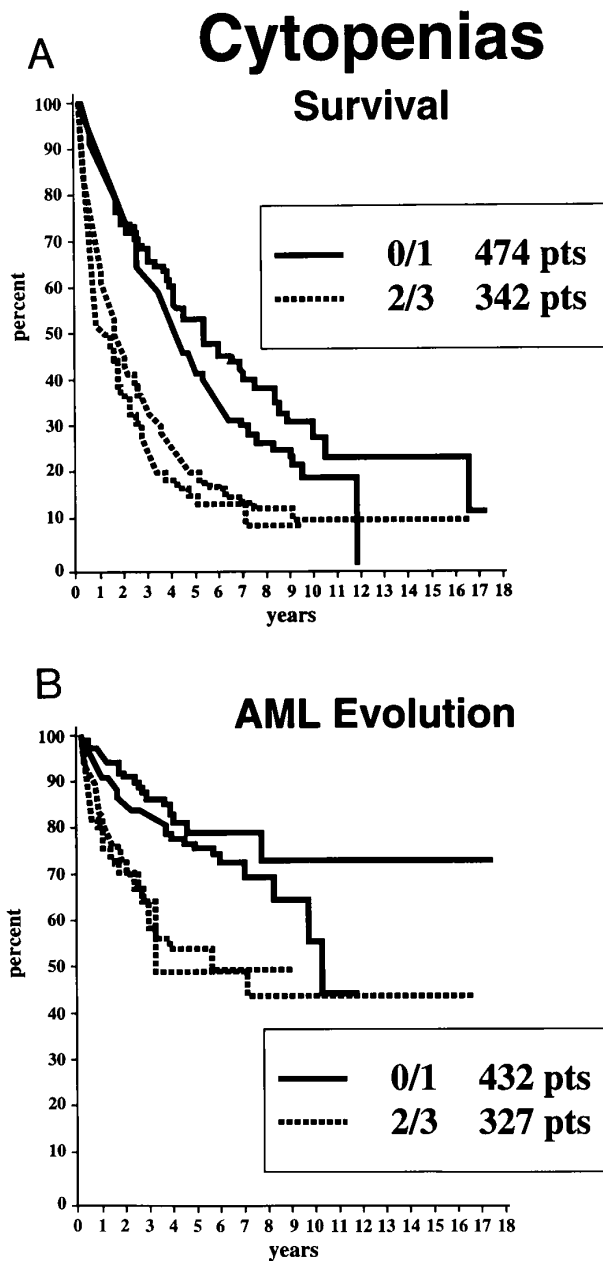
Fig 3. Survival (A) and freedom from AML evolution (B) of MDS patients related to the number of cytopenias initially present (Kaplan-Meier curves). The two solid lines in each graph indicate patients with 0 or 1 cytopenia; the two dashed lines indicate patients with 2 or 3 cytopenias, respectively.

Table 4, the survival curves for patients aged 60 and under or greater than 60 years of age in the high-risk or INT-2–risk groups did not differ substantially whether patients were elderly or younger; however, in the low-risk and INT-1–risk groups, there were striking differences in survival times, with poorer survival times occurring in the relatively older subgroup. Similar findings for individuals in these risk groups were present in patients aged 70 and under or greater than 70 years of age (Table 4).

Moderate gender-related differences for survival were noted in the low-risk patients, with women having slightly more prolonged survival rates than men (6.3 *v* 5 years, respectively). These differences were less pronounced and less statistically significant than those that were age-related (Tables 1 and 2). Similar proportions of men versus women were represented within the four risk groups (low, 33% *v* 33%; INT-1, 37% *v* 40%; INT-2, 22% *v* 21%; and high, 8% *v* 6%). This similarity of representation within the risk groups was also present for patients aged 60 and under or greater than 60 years of age.

Leukemia-free survival (LFS). Patients were also analyzed for LFS to determine the impact of AML evolution on overall survival. Of the 759 patients analyzed for leukemic outcome, 492 patients (65%) died; of these individuals, 149 patients (30%) died with leukemia (20% overall; Table 5). As shown in Table 5, differences were noted in the proportion of these patients who died with leukemia in relation to their initial prognostic risk group. Of the patients who died, the proportions who died with leukemia in the low-risk, INT-1–risk, INT-2–risk, and high-risk groups were 19%, 30%, 33%, and 45%, respectively. The risk of death from AML in the low-risk group was less than that for the other combined groups ($P = .0001$). The median LFS time for the low-risk group was also longer than that for the remaining combined groups (5.7 *v* 1.9 years; $P < .0001$). The LFS times for these four patient risk groups were 5.7, 2.7, 0.95, and 0.3 years, respectively.

Comparison of prognostic systems. Patients were analyzed for clinical outcomes based on their categorization using the FAB (based on BM blast percentage),[1] Spanish (BM blasts, age, and platelet count),[3] and Lille (platelet count, BM blasts, and karyotype)[5] prognostic risk systems, in addition to the IPSS. The IPSS effectively discriminated between the defined subgroups of these other categorization systems. For patients classified by the FAB system, MDS patients with the RA subtype were separable into low-risk, INT-1–risk, and INT-2–risk subgroups, and RARS patients were separable into low-risk and INT-1–risk subgroups (proportions not shown). The RAEB patients were predominantly separated into INT-1– and INT-2–risk subgroups, with a low proportion in the high-risk group. Patients with RAEB-T were separated into INT-1–, INT-2–, and high-risk groups. CMML patients were present in all four risk groups. The Spanish and Lille systems had their high-risk patients distributed between the IPSS INT-1–, INT-2–, and high-risk groups. The intermediate groups in both of these systems were well-separated into the IPSS high-risk, INT-2–risk, INT-1–risk, and, to a lesser degree, low-risk patients; whereas the low-risk patients were separated into INT-1–, INT-2–, and low-risk groups. The IPSS had smaller *P* values after it and the three other prognostic systems were used to predict both survival ($P < .0001$ in all comparisons *v* $P = .001$ to $< .0001$) and AML evolution ($P < .0001$ in all comparisons *v* $P = .043$ to $< .0001$), indicating its greater discriminating power compared with that of the other systems.

DISCUSSION

We herein report the results of the IPSS for MDS regarding critical factors related to clinical outcome in a large

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