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Original Study

Influence of Acute Myeloid Leukemia Progression on the Prognosis of 831 Patients With Myelodysplastic Syndromes From the Argentine Database

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Abstract

In our retrospective review of 831 patients with myelodysplastic syndromes, 158 developed progression with a very poor outcome (median survival after evolution, 3.5 months). The survival of patients with adverse karyotypes or with greater International Prognostic Scoring System-revised or World Health Organization-based Prognostic Scoring System risk was not affected when stratified by patients with and without evolution to acute myeloid leukemia. Our results could help in individualizing those patients who require more aggressive treatment.

Background: A large group of patients with myelodysplastic syndromes (MDS) will die of causes intrinsic to bone marrow failure. One third of patients will develop acute myeloid leukemia (AML), which is associated with an extremely poor outcome and a short survival. Our objectives were to analyze the prognostic variables and scoring systems in the attempt to determine the influence of progression on the overall survival of MDS patients. **Patients and Methods:** We performed a retrospective analysis of 831 MDS patients, including those from the Argentine Registry. **Results:** Of the 831 MDS patients, 158 (19.0%) experienced transformation, with a median overall survival of 17.9 months from diagnosis and 3.5 months after progression. The survival of patients with adverse karyotypes or greater risk, according to the International Prognostic Scoring System-revised (IPSS-R) or World Health Organization-based Prognostic Scoring System (WPSS) was not affected when stratified by patients with and without evolution to AML ($P > .05$). In contrast, the survival of lower risk patients was significantly reduced for those patients with progression to AML ($P < .001$) and those younger ($P = .024$) than those who died of non–AML-related causes. The intermediate-risk patients were heterogeneously distributed; however, an upgrade from a lower IPSS-R to a higher WPSS-hemoglobin risk category was associated with a worse outcome, not affected by progression ($P = .420$), with a median event-free survival of 16 months. **Conclusion:** The use of the IPSS-R and WPSS systems simultaneously might help in identifying those patients who require more aggressive treatment. Nevertheless, more efforts are needed to improve the identification of those lower risk patients whose survival is significantly reduced by progression to AML.

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Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders of hematopoietic stem cells with a substantial risk of transformation to acute myeloid leukemia (AML). Clonal evolution is associated with increasingly ineffective hematopoiesis, progressive impairment of cellular function, and worsening of the cytopenias of the peripheral blood elements.[1,2] Approximately two thirds of the patients with MDS will die of progressive bone marrow (BM) failure in MDS. Such dysfunction leads to bleeding, recurrent infections, and severe anemia. Therefore, a large proportion of the patients with this primary disorder will die of causes intrinsic to the disease and not from progression to AML. However, progression to AML is also associated with an extremely poor outcome and short survival.[1-8]

Patients with MDS exhibit great heterogeneity in biologic characteristics and disease severity at diagnosis. This variability includes, not only different dysplastic changes in ≥ 1 of the myeloid cell lines accompanied by peripheral cytopenias, but also various molecular, genetic, and cytogenetic changes.[1-6,9] A multiplicity of methods has been developed to allow risk stratification and aid in the timing and choice of therapy for patients with MDS.[3,4,10-12] The International Prognostic Scoring System (IPSS) sought to circumvent some of the heterogeneity obstacles by stratifying patients into 4 risk groups[3] and became the state-of-the-art method for predicting patient outcomes in MDS. The scientific evidence on the efficacy and safety of the currently available therapeutic modalities is derived from clinical studies adopting the IPSS score as the reference standard for including patients and analyzing results. Therefore, that stratification system is still recommended in recent guidelines for patient diagnosis, treatment, and follow-up.[13-15] However, the IPSS-revised version (IPSS-R),[4] in recognition of the limitations of the IPSS, is being used in many institutions. The inclusion of gender-specific hemoglobin thresholds in the World Health Organization-based Prognostic Scoring System-hemoglobin (WPSS-Hb) appeared to overcome the subjective criterion of transfusion dependency,[11,12,16] and current criteria for decision-making have validated that approach.[17] After the initial report regarding the usefulness of both systems, other studies have confirmed those findings and the corresponding improvements compared with the previous IPSS criteria.[18-21] Nevertheless, these revised systems have defined an intermediate-risk category, the classification of which is becoming a new challenge at the time of formulating risk-adapted therapies.

To the best of our knowledge, only 2 previous investigations have focused on patients with progression to AML from MDS. Shukron et al[7] sought to determine whether the risk of AML transformation was constant over time, and Okuyama et al[8] retrospectively evaluated the prognostic factors regarding the best supportive care or disease-modifying therapies. To individualize those patients requiring more aggressive treatment, we analyzed the prognostic variables and scoring systems with respect to the risk of evolution to AML and tested each variable and risk category in an attempt to access the differences in overall survival for patients with and without evolution to AML.

Patients and Methods

The present study was a multicenter retrospective analysis of 958 patients with MDS from Argentina. Of the overall population with MDS diagnosed from September 1981 to May 2014, 469 patients belonged to the MDS Registry (updated through October 2014), supported by the Argentine Society of Hematology. Into this database, 14 institutions from the cities of Buenos Aires, Haedo, Pilar, Córdoba, and La Plata have been inputting records from patients with an MDS diagnosis since 2007. The remaining patients belonged to a previous registry from the Genetic Department of the Argentine National Academy of Medicine. Hematologists from the participating institutions completed a standard registration form for each patient detailing the clinical and hematologic features at presentation and during the follow-up period. From the total records in the database, the data for 831 MDS patients were selected and evaluated using the IPSS criteria,[3] excluding those with secondary MDS (56 patients), proliferative chronic myelomonocytic leukemia with leukocyte counts $> 12{,}000/\mu L$ (40 patients), and oligoblastic AML (BM blast counts $> 20\%$ to $< 30\%$; 31 patients). The degree of cytopenias, BM blast percentages, and clonal cytogenetic changes were evaluated using the IPSS-R criteria.[4] According to our records, most patients received supportive care, 60 (7.2%) received various amounts of chemotherapy, 144 (17.3%) received hypomethylating agents, 16 (1.9%) received lenalidomide, and 30 (3.6%) underwent hematopoietic stem cell transplantation (HSCT).

Statistical Analysis

To compare differences in the baseline characteristics among the patients at presentation, we used the analysis of variance or Mann-Whitney U test for continuous variables and the χ^2 or Fisher exact test for categorical variables. The Kaplan-Meier method was used for univariate estimation of the survival time, calculated from the day of diagnosis until death or, for AML evolution, until the date of the first documentation of progressive disease, and whichever occurred first for event-free survival (EFS). Patients undergoing HSCT were censored at the time of the procedure. Each variable was analyzed using the log-rank test (Mantel-Cox) and Cox regression (enter method) to calculate the hazard ratio and 95% confidence intervals (CIs). The correspondence analyses were performed using version 1.1 of the Data Theory Scaling System Group (Faculty of Social and Behavioral Sciences, Leiden University, Leiden, The Netherlands). The threshold of statistical significance was fixed at $P = .05$. Analyses were performed with SPSS software, version 17.00 (IBM Corp, Armonk, NY).

Results

Population and Clinical Data

We analyzed the data from the diagnosis of MDS in 831 patients from different Argentine hospitals and hematologic institutions (Table 1). Their median age was 70.5 years (range 17.0-94.9 years), with 74.6% aged > 60 years. The male-to-female ratio was 1.3 (466 males and 365 females).

During the follow-up period (median, 19.7 months), AML was diagnosed in 158 patients (19.0%), and 341 patients (41.0%) had died. Of those 158 patients with progression to AML, only 27 (17.1%) remained alive, including 9 who had undergone HSCT. The median time to transformation to AML was 9.8 months (95% CI, 8.4-11.2 months), the median overall survival from diagnosis was 17.9 months (95% CI, 14.8-21.0 months), and the median survival time after confirmation of progression was 3.5 months (95% CI, 2.9-4.1 months).

Table 1 Univariate Analysis of Prognostic Factors for Survival and Evolution to Acute Myeloid Leukemia Q6

Variable	Patients (n)	Survival			Evolution to AML		
		Events (n)	*P* Value[a]; Median (mo)	*P* Value[b]; HR (95% CI)	Events (n)	*P* Value[a]; 25% (mo)	*P* Value[b]; HR (95% CI)
Gender			<.001	<.001; 1.8 (1.4-2.3)		.004	.004; 1.6 (1.2-2.2)
Female	365	113	77.1		58	123.6	
Male	466	213	34.7		100	27.0	
Age (y)			.017	.017; 1.2 (1.0-1.3)		.006	.006; 0.8 (0.7-0.9)
<65	294	108	65.9		75	23.2	
≥65	534	216	44.4		81	53.1	
BM blasts (%)			<.001	<.001; 1.7 (1.6-1.9)		<.001	<.001; 2.4 (2.1-2.7)
0-2	494	147	77.3		41	123.6	
>2 but <5	91	30	65.9		17	50.0	
5-10	126	80	19.5		51	9.2	
>10	96	60	18.0		45	6.4	
Cytogenetic risk group			<.001	<.001; 1.9 (1.7-2.1)		<.001	<.001; 1.8 (1.5-2.2)
Very good	22	6	105.5		5	116.1	
Good	505	159	70.7		70	123.6	
Intermediate	118	63	33.6		28	31.6	
Poor	35	25	17.3		15	9.2	
Very poor	30	21	11.8		12	5.3	
Hb (g/dL)			<.001	<.001; 2.0 (1.6-2.4)		<.001	<.001; 2.4 (1.8-3.1)
≥10	364	109	82.5		41	116.1	
8-9.9	256	103	39.5		62	20.0	
≤8	170	90	21.4		44	14.6	
Hb by gender (g/dL)[c]			<.001	<.001; 2.4 (1.9-3.0)		<.001	<.001; 2.2 (1.6-3.1)
M ≥9; F ≥8	546	177	69.5		86	67.4	
M <9; F <8	244	125	21.5		61	14.6	
Platelet count (cells/μL)			<.001	<.001; 2.4 (1.8-3.2)		<.001	<.001; 2.7 (1.8-3.9)
≥100,000	512	166	64.3		76	71.7	
50-99,000	150	75	26.1		37	16.3	
<50,000	131	67	25.1		35	12.8	
Neutrophil count (cells/μL)			<.001	<.001; 4.1 (2.3-7.2)		<.001	<.001; 10.2 (5.0-20.7)
≥800	675	250	58.5		107	66.3	
<800	119	64	18.7		44	9.3	
LDH			<.001	<.001; 2.0 (1.5-2.6)		<.001	<.001; 2.6 (1.8-3.8)
Normal	449	153	63.6		62	116.2	
High	178	89	28.0		48	14.3	
Ferritin level (ng/mL)			<.001	<.001; 1.4 (1.2-1.6)		**.106**	**.108**; 1.2 (1.0-1.6)
≤350	249	65	121.2		29	NR	
>350	212	92	40.4		31	116.1	
IPSS			<.001	<.001; 2.4 (2.1-2.8)		<.001	<.001; 3.5 (2.9-4.3)
Low	278	55	105.5		8	NR	
Intermediate-1	289	125	44.1		64	39.1	
Intermediate-2	104	68	18.1		40	9.2	
High	30	21	13.6		16	4.0	
IPSS-R			<.001	<.001; 2.0 (1.8-2.2)		<.001	<.001; 2.4 (2.0-2.7)
Very low	165	27	121.2		6	NR	
Low	259	85	64.3		28	123.6	
Intermediate	84	40	42.7		25	18.8	
High	78	53	18.4		36	**6.3**	
Very high	55	37	12.3		21	**7.5**	

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Table 1 Continued

Variable	Patients (n)	Survival			Evolution to AML		
		Events (n)	*P* Value[a]; Median (mo)	*P* Value[b]; HR (95% CI)	Events (n)	*P* Value[a]; 25% (mo)	*P* Value[b]; HR (95% CI)
WPSS-Hb[c]			<.001	<.001; 2.1 (1.9-2.3)		<.001	<.001; 2.6 (2.1-3.1)
Very low	52	12	121.2		2	NR	
Low	233	48	125.8		14	123.6	
Intermediate	135	58	44.1		26	44.3	
High	126	73	17.5		46	9.0	
Very high	40	29	15.2		15	5.5	

Abbreviations: AML = acute myeloid leukemia; BM = bone marrow; CI = confidence interval; F = female; Hb = hemoglobin; HR = hazard ratio; IPSS = international prognostic scoring system; IPSS-R = revised IPSS; LDH = lactate dehydrogenase; M = male; NR = not reached; WPSS-Hb = World Health Organization-based Prognostic Scoring System-hemoglobin.
[a]Kaplan-Meier method and log-rank test (Mantel-Cox).
[b]Cox regression analysis.
[c]WPSS categorization revised according to Malcovati et al.[10]

Of the 326 patients (39% of 831 patients) who died during the follow-up period (excluding the 15 patients who died after HSCT), those patients who had previously developed AML (131 of 326; 40%) evidenced a greater percentage of BM blasts (6.0% vs. 1.0%; $P < .001$), younger age (median, 67 vs. 73 years; $P < .001$), and lower absolute neutrophil counts (1420 vs. 1872 cells/μL; $P = .001$). Moreover, of the patients developing AML, a greater percentage also exhibited elevated levels of lactate dehydrogenase (44% vs. 33%; $P = .072$), ferritin (≥ 170 ng/mL, 88% vs. 75%; $P = .062$), and abnormal karyotypes (57% vs. 42%; $P = .084$) and lower hemoglobin levels (9 vs. 9 g/dL; $P = .118$) and platelet counts (89,000 vs. 110,500 cells/μL; $P = .218$). Of the non–AML-related causes of death, 56 were from infection, 11 from bleeding or anemia severity, 30 from cardiovascular failure, 28 from comorbidities, 12 from progressions in blasts count without AML development, and 58 from unknown causes.

Analysis of the age-related events (n = 351), including the patients who developed AML and remained alive (n = 27), indicated that mortality unrelated to previous AML progression increased with age from 37% in the patients < 50 years old to 64% in patients > 80 years old ($P < .001$; Table 2).

Influence of AML Progression on Survival

Univariate and Cox regression analyses were performed to evaluate the influence of individual prognostic factors and scoring systems on patient prognosis using the data from the 831 selected patients (Table 1). Univariate and Cox regression analyses were also performed to evaluate the influence of progression to AML on survival by stratifying the patients according to progression to AML (Table 3). Almost all the prognostic factors and scoring systems were found to be significant predictive variables in the population without AML, just as was observed for the entire population (Table 1). In contrast, gender and platelet count were not significant predictive variables for survival, and lactate dehydrogenase and ferritin levels merely indicated a tendency for those patients who had developed AML during the follow-up period (Table 3).

Each variable and risk group was then evaluated according to the development of AML, and univariate analyses were performed for each patient population to determine the influence of AML progression on survival. The vast majority of the parameters analyzed indicated that patients without evolution to AML experienced a longer median overall survival than those with progression to AML (Table 3). Nevertheless, the groups with greater blast counts (> 10%; $P = .344$) and worse cytogenetic findings (poor, $P = .807$; or very poor, $P = .674$; both, $P = .952$) and, correspondingly, greater IPSS scores (intermediate-2, $P = .419$; high, $P = .401$), IPSS-R (high, $P = .071$; very high, $P = .786$), and WPSS-Hb (high, $P = .053$; very high, $P = .850$) scores showed similar survival, regardless of their leukemic progression (Table 3; Supplemental Figure 1; in the online version).

IPSS-R and WPSS-Hb Cross-tabulation

Because the IPSS-R and WPSS-Hb define an intermediate-risk category, which is a new challenge in formulating risk-adapted therapy, we cross-tabulated the data from 562 patients who could be effectively stratified using both systems. Despite the significant concordance (Kendall's tau, 0.717) observed between the IPSS-R and WPSS-Hb, which mainly identified the lower and higher risk patients (Supplemental Table 1; in the online version), the distribution of intermediate-risk patients was more heterogeneous ($P < .001$; Figure 1) with differences in EFS (Figure 2A).

As expected, the survival of higher risk patients using both systems was unaffected by evolution to AML ($P = .442$; Figure 3B). Also, with a median EFS of 16 months (Figure 2B), 25% of patients with low or intermediate risk using IPSS-R but stratified as higher

Table 2 Age Range, Mortality, and AML Status at Death

Age Range (y)	AML Development		Death Without AML Development
	Alive	Dead	
<50	6 (16)	18 (48)	14 (37)
50 to <60	6 (11)	29 (54)	19 (35)
60 to <70	4 (5)	26 (35)	45 (60)
70 to <80	4 (4)	37 (33)	72 (64)
≥80	7 (10)	19 (27)	45 (63)
Total	27 (8)	129 (37)	195 (56)

Data presented as n (%).
Abbreviation: AML = acute myeloid leukemia.

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Table 3 Influence of AML Progression on Predictability of Prognosis

Variable	Evolution to AML			No Evolution to AML			Comparison Between Categories		
	Patients (n)	*P* Value[a]; OS (50%, mo)	*P* Value[b]; HR (95% CI)	Patients (n)	*P* Value[a]; OS (50%, mo)	*P* Value[b]; HR (95% CI)	*P* Value[a]	*P* Value[b]	HR (95% CI)
Gender		**.184**	**.185**; 1.3 (0.9-1.8)		<.001	<.001; 2.0 (1.5-2.7)			
Female	58	19.5		307	120.3		<.001	<.001	4.4 (3.0-6.4)
Male	100	16.8		366	58.6		<.001	<.001	3.0 (2.3-3.9)
Age (y)		.027	.028; 1.2 (1.0-1.5)		<.001	<.001; 1.3 (1.1-1.6)			
≥65	81	17.5		453	63.6		<.001	<.001	3.8 (2.8-5.0)
<65	75	20.0		219	125.8		<.001	<.001	4.0 (2.8-5.9)
BM blasts (%)		.037	.037; 1.2 (1.0-1.4)		<.001	<.001; 1.7 (1.5-2.0)			
0-2	41	16.7		455	120.3		<.001	<.001	4.2 (2.8-6.2)
>2 but <5	17	43.8		73	79.8		.002	.002	3.1 (1.5-6.4)
5-10	51	17.0		75	24.9		.038	.040	1.6 (1.0-2.5)
>10	45	**14.8**		60	**18.4**		**.170**	**.344**	1.3 (0.8-2.2) Q5
Cytogenetic risk group		.003	.008; 1.3 (1.1-1.6)		<.001	<.001; 2.1 (1.7-2.5)			
Very good[c]	5+	NA		17	NR		NA	NA	NA
Good[c]	70	20.4		435	94.8		<.001	<.001	3.8 (2.7-5.2)
Intermediate	28	21.5		90	39.9		.003	.004	2.2 (1.3-3.6)
Poor	15	**16.8**		20	17.6		**.807**	**.807**	0.9 (0.4-2.1)
Very poor	12	**17.3**		18	15.8		**.674**	**.674**	1.2 (0.5-2.9)
Hb (g/dL)		.002	.001; 1.6 (1.2-2.2)		<.001	<.001; 1.9 (1.5-2.4)			
≥10	41	32.0		323	121.2		<.001	<.001	3.3 (2.2-5.0)
8-9.9	62	13.2		194	64.3		<.001	<.001	4.5 (3.1-6.7)
≤8	44	13.9		126	33.4		<.001	<.001	2.2 (1.4-3.4)
Hb by gender (g/dL)[d]		.003	.004; 1.7 (1.2-2.5)		<.001	<.001; 2.7 (2.0-3.6)			
M ≥8; F ≥9	86	23.3		460	98.2		<.001	<.001	2.6 (1.8-3.8)
M <8; F <9	61	11.6		183	33.4		<.001	<.001	4.2 (3.1-5.7)
Platelet count (cells/μL)		**.075**	**.248**; 1.3 (0.8-2.0)		<.001	<.001; 2.8 (1.9-4.0)			
≥100,000	76	23.3		436	98.2		<.001	<.001	4.3 (3.2-6.0)
50-99,000	37	**11.5**		113	44.1		<.001	<.001	3.5 (2.2-5.6)
<50,000	35	**13.2**		96	28.7		.018	.020	1.8 (1.1-3.0)
Neutrophil count (cells/μL)		.017	.022; 2.5 (1.2-5.4)		**.063**	**.065**; 2.2 (1.0-5.2)			
≥800	107	19.8		568	79.8		<.001	<.001	3.3 (2.5-4.3)
<800	44	13.9		75	69.5		<.001	<.001	3.4 (2.0-5.7)

Table 3 Continued

Variable	Evolution to AML			No Evolution to AML			Comparison Between Categories		
	Patients (n)	*P* Value[a]; OS (50%, mo)	*P* Value[b]; HR (95% CI)	Patients (n)	*P* Value[a]; OS (50%, mo)	*P* Value[b]; HR (95% CI)	*P* Value[a]	*P* Value[b]	HR (95% CI)
LDH		**.074**	**.076**; 1.5 (1.0-2.3)		<.001	<.001; 1.9 (1.3-2.6)			
Normal	62	15.6		387	98.2		<.001	<.001	4.0 (2.8-5.6)
High	48	15.3		130	44.1		<.001	<.001	3.2 (2.0-4.9)
Ferritin level (ng/mL)		**.066**	**.069**; 1.3 (1.0-1.8)		.002	.002; 1.3 (1.1-1.6)			
≤350	29	21.5		220	121.2		<.001	<.001	4.6 (2.7-7.8)
>350	34	15.3		178	62.5		<.001	<.001	3.9 (2.5-6.1)
IPSS		.015	.004; 1.3 (1.1-1.5)		<.001	<.001; 2.6 (2.1-3.2)			
Low[c]	8+	NA		270	121.2		NA	NA	NA
Intermediate-1[c]	64	23.3		225	80.0		<.001	<.001	3.4 (2.5-4.7)
Intermediate-2	40	**17.9**		64	**18.6**		**.418**	**.419**	1.2 (0.8-2.0)
High	16	**13.6**		14	**17.3**		**.397**	**.401**	0.7 (0.3-1.7)
IPSS-R		.001	<.001; 1.4 (1.2-1.6)		<.001	<.001; 2.0 (1.7-2.3)			
Very low+[c]	5+	NA		160	135.8		NA	NA	NA
Low[c]	28	31.5		231	76.6		<.001	<.001	3.3 (2.1-5.2)
Intermediate	25	15.1		59	63.0		.004	.005	2.5 (1.3-4.8)
High	36	**17.5**		42	19.7		**.068**	**.071**	1.7 (1.0-2.9)
Very high	21	**12.2**		34	15.1		**.785**	**.786**	1.1 (0.6-2.1)
WPSS-Hb[d]		**.144**	.042; 1.1 (1.0-1.4)		<.001	<.001; 2.3 (1.9-2.7)			
Very low+[c]	2+	NA		50	135.8		NA	NA	NA
Low[c]	14	30.0		219	125.8		<.001	<.001	5.5 (3.0-9.9)
Intermediate	26	19.5		109	63.0		.001	.001	2.5 (1.4-4.3)
High	46	**15.1**		80	**19.7**		**.050**	**.053**	1.6 (1.0-2.5)
Very high	15	**14.8**		25	**15.8**		**.850**	**.850**	0.9 (0.4-2.0)

Abbreviations: AML = acute myeloid leukemia; BM = bone marrow; CI = confidence interval; F = female; Hb = hemoglobin; HR = hazard ratio; IPSS = international prognostic scoring system; IPSS-R = revised IPSS; LDH = lactate dehydrogenase; M = male; NA = not applicable; NR = not reached; WPSS-Hb = World Health Organization-based Prognostic Scoring System-hemoglobin.

[a]Kaplan-Meier method and log-rank test (Mantel-Cox).

[b]Cox regression analysis.

[c]Data combined for statistical purposes for patients who developed AML.

[d]WPSS categorization according to Malcovati et al.[10]

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risk using the WPSS-Hb (n = 46) can be expected to die within 12 months, with or without AML ($P = .420$; Figure 2C).

However, leukemic evolution did affect survival when other combinations were analyzed. Patients with concordant intermediate risk (n = 33) displayed a median EFS of 33 months (Figure 3A); however, those with evolution to AML had a median overall survival that decreased significantly to 4 months ($P = .014$; Figure 3B). The EFS of these concordant intermediate-risk patients was similar to that of the 89 patients with a discordant lower IPSS-R and intermediate WPSS-Hb score ($P = .127$; Figure 2A). The outcomes of this merged intermediate group (Figure 2B) were also affected by leukemic evolution (16 vs. 63 months; $P < .001$; Figure 2C). They also tended to be younger (65 vs. 75 years; $P = .007$) and to present more frequently with neutrophil counts < 800 cells/μL (38% vs. 9%; $P = .014$) compared with those who died of non−AML-related causes. The outcomes of the concordant lower risk patients (n = 265) were also influenced by AML progression, with a median survival time of 30 months ($P < .001$; Figure 3B). These patients also were more frequently < 60 years old (39% vs. 9%; $P = .024$) and tended to present with more cytopenias (46% vs. 19%; $P = .067$). No other parameter showed statistical significance between those patients who died with and without AML evolution.

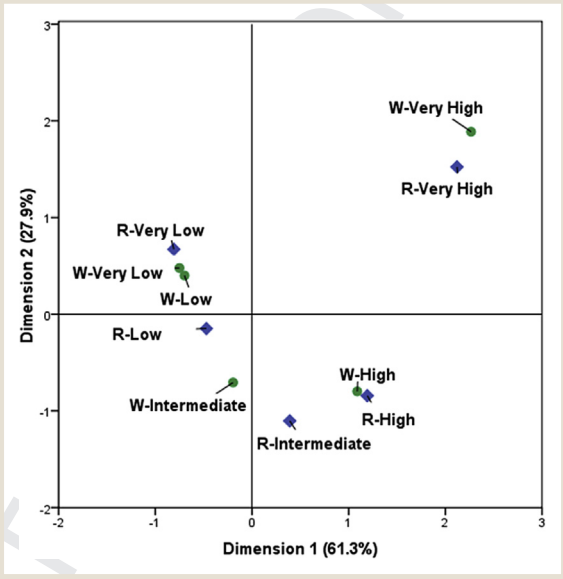
Discussion

In the present study, the prognosis of patients who underwent transformation from MDS to AML proved to be very poor, with a median survival of 3.5 months after progression. Only 11.4% (18 of 158) of our patients (with the exclusion of those who underwent HSCT) were still alive at the end of the follow-up period, in agreement with previously published data.

As stated, to the best of our knowledge, only 2 previous studies have focused on patients who developed AML from MDS.[7,8] In agreement with their data, in our population, almost all the prognostic variables and scoring systems were significantly associated with AML development. Almost none of those parameters or scoring systems assessed at initial diagnosis, however, was associated with the survival time after progression to AML in our series (Supplemental Table 2 and Supplemental Figure 2; in the online version). Only the cytogenetic findings, as interpreted using the criteria of the IPSS-R,[4] showed a prognostic tendency, with patients with karyotypes corresponding to very poor cytogenetic groups of risk showing a median survival of < 2 months ($P = .061$), reflecting the aggressiveness of the particular malignant clone involved.

The effect of cytogenetic status on prognostic accuracy is well-known, and our data confirm its predictive ability for overall survival, the lag time before AML progression, and patient survival after AML development.[3,4,7,11,12,20] In addition, the outcomes of our patients with cytogenetic findings associated with poor risk were similar in terms of patient survival with and without AML development. Among the various definitions of higher risk patients according to the Grupo Español de Síndromes Mielodisplásicos (Spanish Myelodysplastic Syndrome Group), the presence of such poor cytogenetic findings in patients in an intermediate-risk category point to a worse prognosis.[22] Although multiple mutations have been identified in association with the progression of MDS to AML, and some of those abnormalities have been correlated with worse outcomes,[9,23] they have not been widely included in clinical practice.

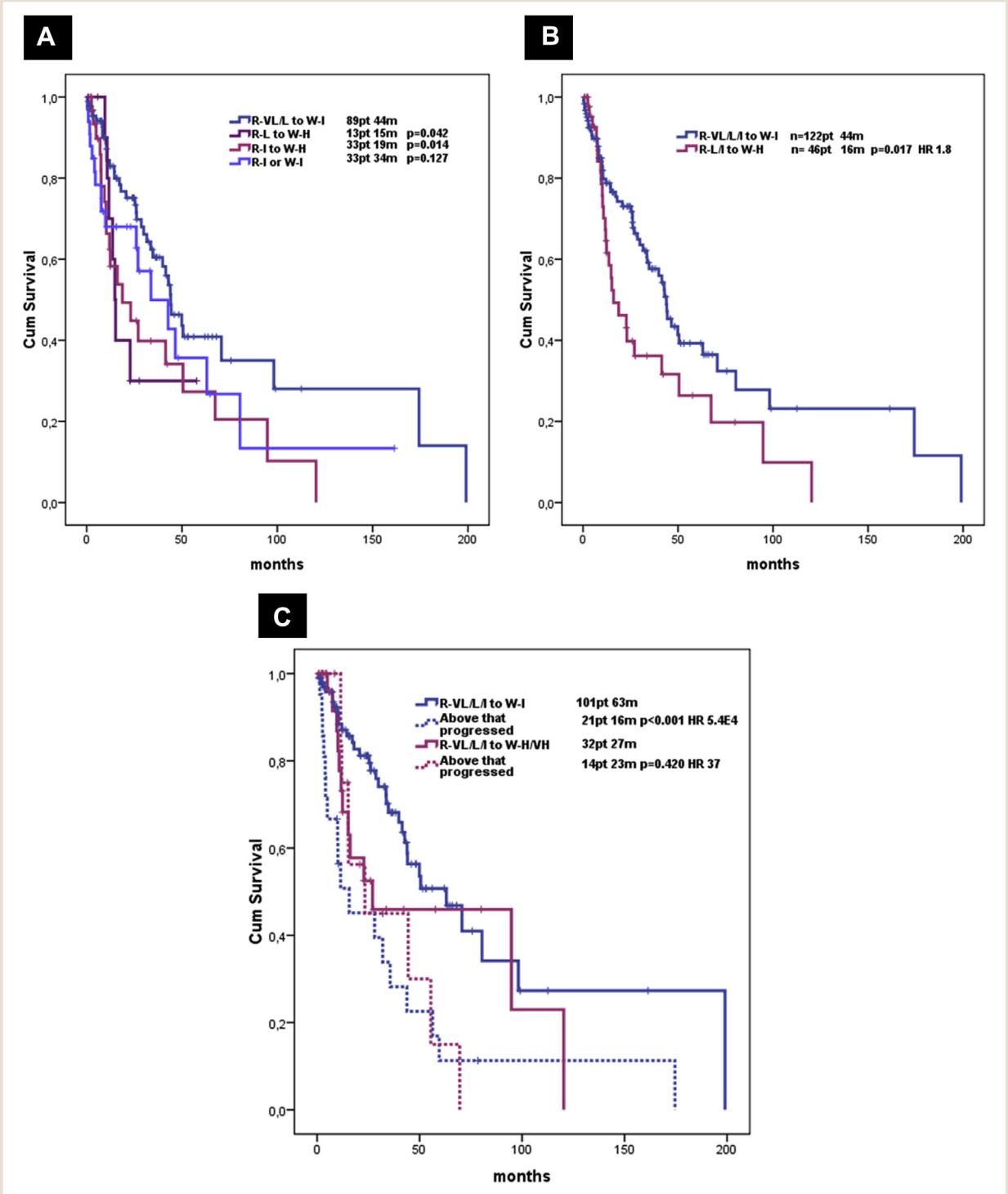
Figure 1 Correspondence Analyses. Graphs Showing Distribution of Patients According to the Revised International Prognostic Scoring System (R) and World Health Organization Classification-based Prognostic Scoring System-hemoglobin (W) Risk Groups. Dimension 1 (Abscissa) Accounted for 61.3% of the Difference and Dimension 2 (Ordinate) for 27.9%. The Distribution of Patients in Both Intermediate-risk Groups Accounted for the Differences Observed in the First Dimension and in Both Low-risk Groups for the Differences Observed in the Second Dimension



The significant concordance between the IPSS-R and WPSS-Hb to individualize higher and lower risk patients shows that such patients require more aggressive treatment. In this context, the finding that the baseline parameters, such as greater blast percentages, worse cytogenetic findings, and correspondingly greater IPSS, IPSS-R, and WPSS-Hb groups of risk, did not affect survival between patients with and without AML evolution is highly relevant. Our clinical findings are consistent with previous reports reporting that the expansion of genetically and epigenetically abnormal precursors can lead to the development of multilineage cytopenias.[24] Thus, these high-risk patients will die of causes intrinsic to the disease and directly related to BM failure.

The distribution of the intermediate-risk patients using both systems, however, was more heterogeneous. Whether IPSS-R intermediate-risk patients should be reclassified into the low-risk or high-risk categories varies according to "certain circumstances" in the different clinical practice guidelines.[17,22,25] Della Porta et al[26] suggested that the clinical choice of the prognostic system should be determined by the differences in the concept of the IPSS-R and the WPSS and the specific clinical need. We would add that the use of both systems simultaneously might help to more exactly risk stratify intermediate-risk patients. We found that stratification of patients from an IPSS-R lower risk to a WPSS higher risk category was associated with worse outcomes, with and without AML evolution. Thus, such patients have a greater risk, with a median EFS of 16

Figure 2 Kaplan-Meier Curves. (A) Median Event-free Survival for Patients From Intermediate-risk Group and Patients Whose Prognostic Categories Were Discordant Between the Revised International Prognostic Scoring System and Revised World Health Organization Classification-based Prognostic Scoring System-hemoglobin (WPSS-Hb). Patients Belonging to the Revised International Prognostic Scoring System "Very Low-risk/Low-risk—Revised World Health Organization Classification-based Prognostic Scoring System Intermediate-risk" (R-VL/L to W-I) Group Were Considered the Category of Reference for Comparisons. (B) Median Event-free Survival for Merged Categories of Discordant Patients With Risk at Intermediate or With a Shift to a Higher WPSS-Hb. (C) Influence of Acute Myeloid Leukemia Progression on Survival of Patients With Discordant Risk Group



Abbreviations: Cum = cumulative; H = high; HR = hazard ratio; m = months; Pt = patient; V = very high.

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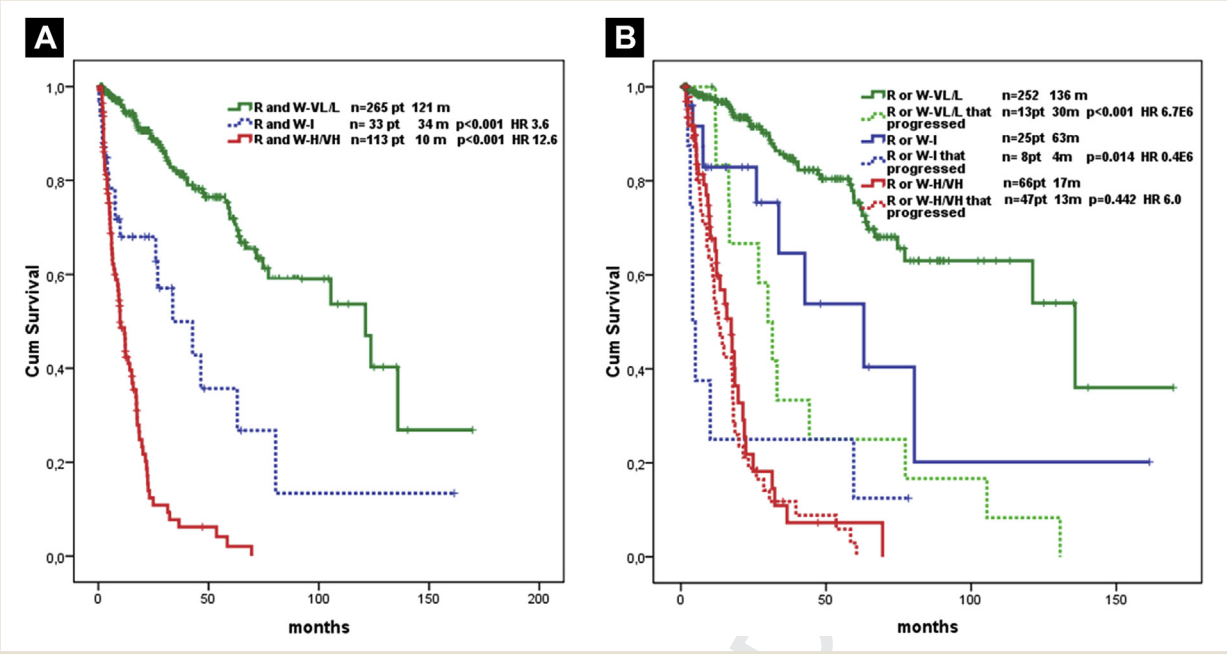
Figure 3 Kaplan-Meier Curves for Patients Whose Prognostic Categories Were Concordant Between the Revised International Prognostic Scoring System and Revised World Health Organization Classification-based Prognostic Scoring System-hemoglobin. (A) Median Event-free Survival. (B) Influence of Acute Myeloid Leukemia Progression on Survival



Abbreviations: H = high; HR = hazard ratio; I = intermediate; L = low; R = Revised International Prognostic Scoring System; VH = very high; VL = very low; W = Revised World Health Organization Classification-based Prognostic Scoring System-hemoglobin.

months. The EFS of patients within the intermediate-risk category using other combinations was > 40 months; however, survival was significantly reduced for those with AML progression. A similar effect was observed among lower risk patients stratified using both systems, with their median survival decreasing to 30 months. When clinical characteristics were analyzed, those with AML progression were younger than those who had died without evolution. Furthermore, analysis of age-related causes of death in our series demonstrated that the events associated with AML progression decreased with age from 64% in patients < 60 years old to 36% in patients > 80 years old. These observations might indicate that the risk of developing AML declines with age or that this decline in risk results from either a lower tolerance to cytopenia-related complications or the tendency for older patients with MDS to die of various age-related diseases before AML transformation occurs.

At present, HSCT, although highly toxic, is the only potentially curative treatment. Okuyama et al[8] suggested that younger patients with progression from MDS to AML should consider HSCT as the premier treatment option at progression because of the longer survival than any other patient groups in their study. The survival of patients with progression after failure with hypomethylating agents has not improved with available treatments or investigational agents.[27] Therefore, we must improve our prognostic systems to detect those patients with a short life expectancy with or without evolution whose survival might be improved by HSCT until new agents have been tested and approved.

Owing to the retrospective nature of our study, we recognize certain limitations, including the merger of data from 2 databases and that 35% of cases were diagnosed before 2007, accounting for the heterogeneity in treatment among the patients. Second, our sample size was limited, which reduced our power to assess some associations in our analyses. Despite these limitations, we believe we studied a relevant cohort for this disease and that the findings from this and other epidemiologic studies can serve as important comparison data for future studies.

Conclusion

AML transformation is associated with extremely poor outcomes and short survival and is the main cause of death in younger MDS patients. The worst outcome of the higher risk patients is intrinsic to their BM failure, with or without leukemic evolution. However, the survival of lower risk patients decreases significantly with AML progression. The use of IPSS-R and WPSS-Hb systems simultaneously might help risk stratify intermediate-risk patients with more accuracy when making critical treatment decisions.

Clinical Practice Points

- For patients with progression from MDS to AML, the outcome is very poor, with a median survival of 3.5 months after progression.
- AML progression is the main cause of death for patients aged < 60 years.
- The use of IPSS-R and WPSS-Hb systems simultaneously might help in identifying those patients requiring more aggressive treatment.
- The survival of patients with adverse karyotypes or with greater risk was not affected when stratified by evolution to AML.

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- A shift from a lower IPSS-R category to a higher WPSS-Hb category was associated with worse outcomes.
- The survival of patients within the lower risk group was significantly influenced by AML progression, and the patients with AML progression were younger than those who died of non–AML-related causes.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figures and tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clml.2017.06.024.

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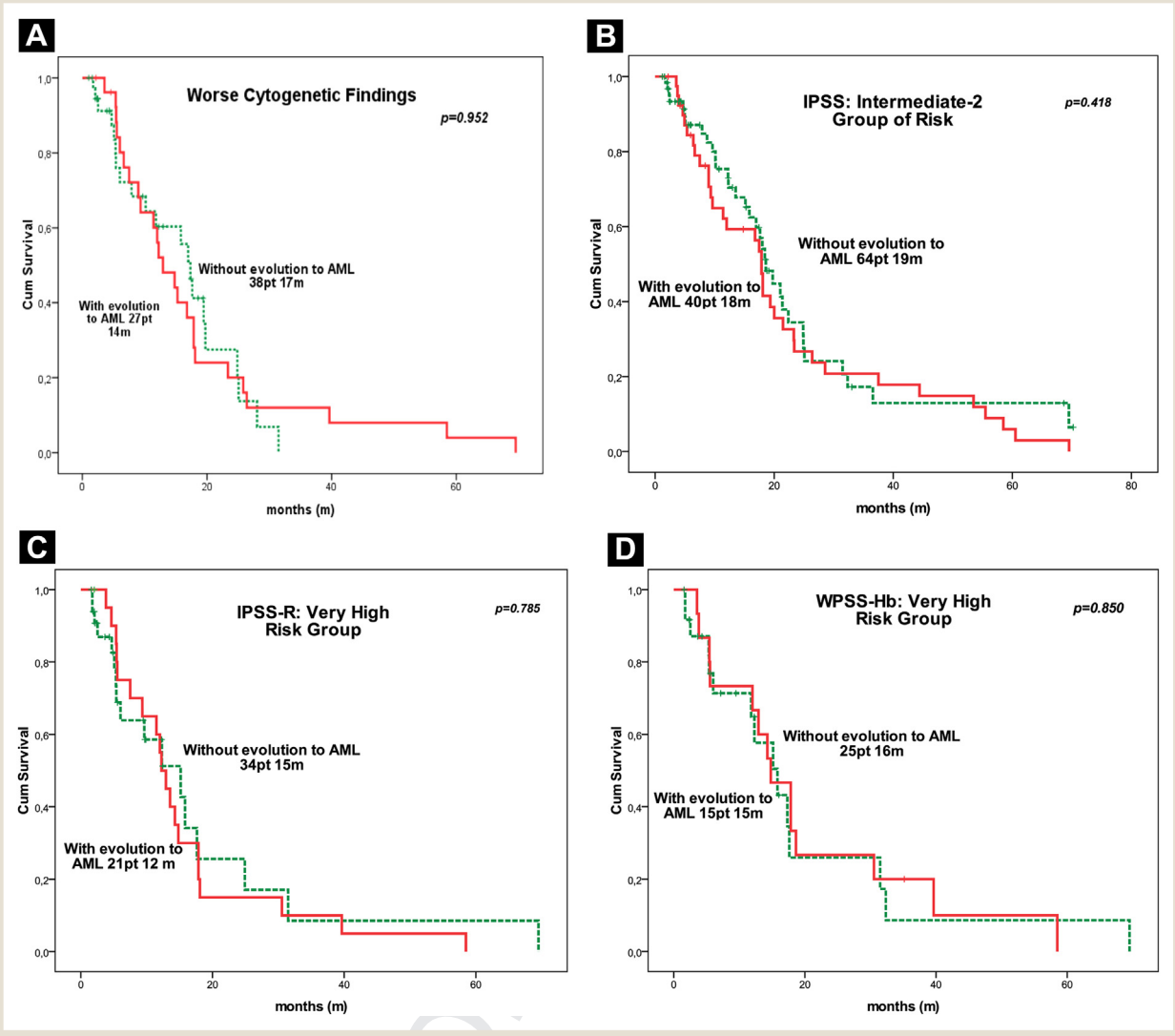
Supplemental Figure 1 Kaplan-Meier Curves of Baseline Factors Not Affecting Overall Survival Regarding Evolution to Acute Myeloid Leukemia (AML). (A) Worse Cytogenetic Findings; (B) International Prognostic Scoring System (IPSS) Intermediate-2 Risk Group; (C) Revised IPSS (IPSS-R) Very-high-risk Group; and (D) World Health Organization-based Prognostic Scoring System-hemoglobin (WPSS-Hb) Very-high-risk Group. Number of Patients (pt) and Median Survival (Months [m]) for Each Group Are Indicated. Red Indicates Patients Who Developed AML; Green, Patients Without AML



Abbreviation: Cum = cumulative.

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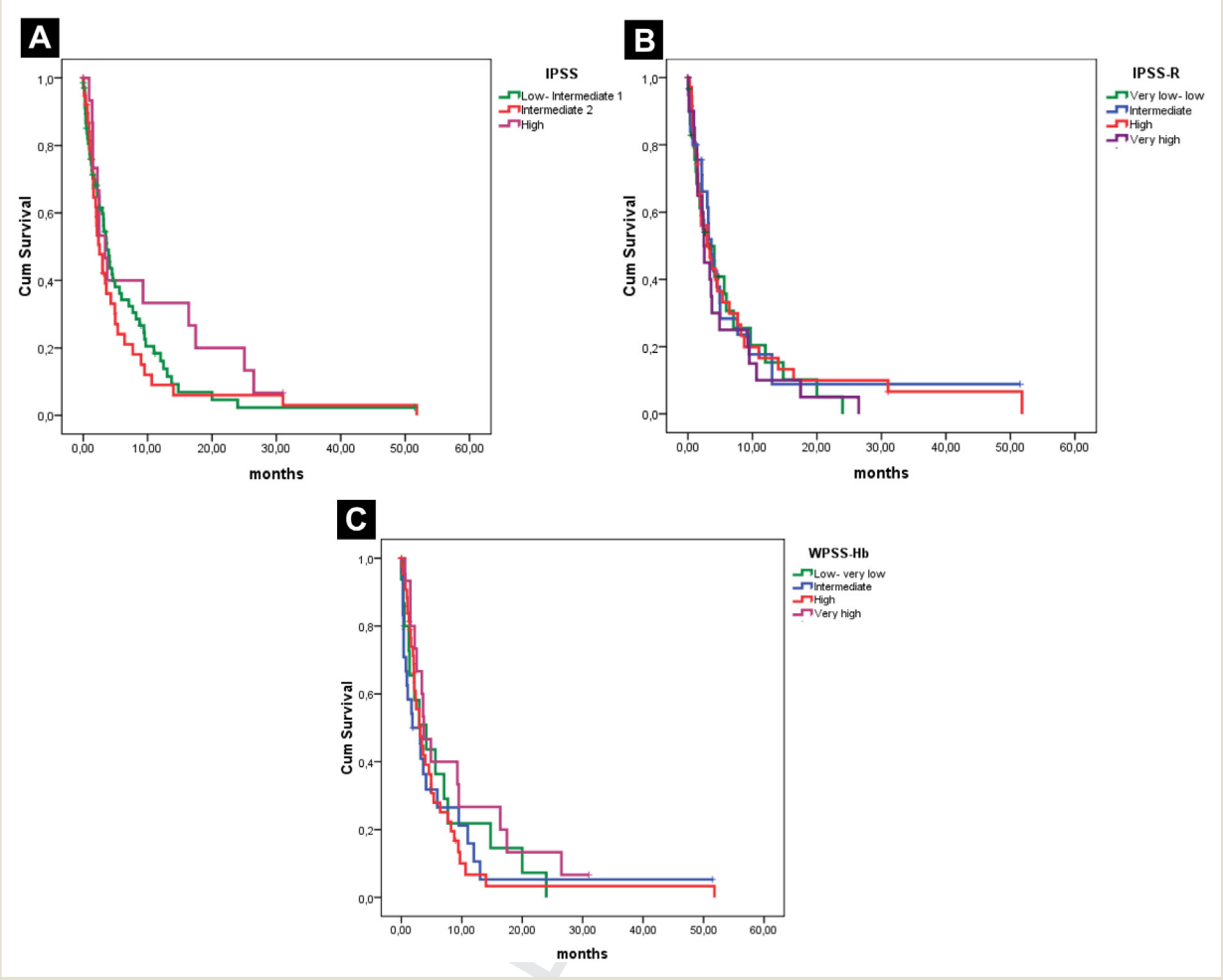
Supplemental Figure 2 Kaplan-Meier Curves of Groups of Risk at Baseline for Survival After Evolution to Acute Myeloid Leukemia. Kaplan-Meier Survival Curves After Development of Acute Myeloid Leukemia Regarding Groups of Risk at Baseline (Details Provided in Supplemental Table 2). (A) International Prognostic Scoring System (IPSS); (B) IPSS Revised Version (IPSS-R); and (C) World Health Organization-based Prognostic Scoring System-hemoglobin (WPSS-Hb), Revised According to Malcovati et al[10]



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Supplemental Table 1 Cross-tabulation of Patients Effectively Stratified Using IPSS-R and WPSS-Hb

WPSS-Hb	IPSS-R					Total
	Very Low	Low	Intermediate	High	Very High	
Very low			NA	NA	NA	
Patients (n)	25[a]	23[a]				48
Within WPSS-Hb (%)	52.1[a]	47.9[a]				
Within IPSS-R (%)	17.5[a]	10.3[a]				8.5
Low					NA	
Patients (n)	115[a]	102[a]	7	2		226
Within WPSS-Hb (%)	50.9[a]	45.1[a]	3.1	0.9		
Within IPSS-R (%)	80.4[a]	45.5[a]	9.6	2.8		40.2
Intermediate						
Patients (n)	3[b]	86[b]	33[a]	7	0	129
Within WPSS-Hb (%)	2.3[b]	66.7[b]	25.6[a]	5.4	0	
Within IPSS-R (%)	2.1[b]	38.4[b]	45.2[a]	9.9	0	23.0
High	NA					
Patients (n)		13[b]	33	55[a]	19[a]	120
Within WPSS-Hb (%)		10.8[b]	27.5	45.8[a]	15.8[a]	
Within IPSS-R (%)		5.8[b]	45.2	77.5[a]	37.3[a]	21.4
Very high	NA	NA	NA			
Patients (n)				7[a]	32[a]	39
Within WPSS-Hb (%)				17.9[a]	82.1[a]	
Within IPSS-R (%)				9.9[a]	62.7[a]	6.9
Total (n)	143 (25.4)	224 (39.9)	73 (13.0)	71 (12.6)	51 (9.1)	562 (100.0)

Data in parentheses are percentages.
Abbreviations: IPSS-R = revised international prognostic scoring system; NA = not applicable; WPSS-Hb = World Health Organization-based Prognostic Scoring System-hemoglobin (WPSS categorization revised according to Malcovati et al[10]).
[a]Patients who sustained their risk group.
[b]Patients who shifted from IPSS-R lower risk groups to WPSS-Hb higher risk groups.

Supplemental Table 2 Univariate Analysis of Baseline Prognostic Factors for Survival After Evolution to Acute Myeloid Leukemia

Variable	Patients (n)	Survival After AML Progression[a]		
		Events (n)	Median (95% CI) (mo)	*P* Value
Gender				.217
Female	58	46	4.1 (2.1-6.1)	
Male	99	84	3.0 (2.3-3.8)	
Age (y)				.178
≥65	81	70	3.2 (2.5-3.8)	
<65	74	58	3.7 (2.3-5.2)	
BM blasts (%)				.414
0-2	40	31	3.0 (2.3-5.2)	
>2 but <5	17	13	1.4 (0.7-5.2)	
5-10	51	44	3.6 (0.1-4.5)	
>10	45	39	3.4 (2.4-3.9)	
Cytogenetic risk group				.065
Very good+[b]	4+			
Good[b]	70	58	4.1 (2.7-5.6)	
Intermediate	28	23	3.2 (1.5-4.8)	
Poor	15	14	3.6 (1.0-6.2)	
Very poor	12	11	1.6 (0.1-3.2)	
Hb (g/dL)				.585
≥10	40	32	3.2 (1.0-5.3)	
8-9.9	62	52	3.2 (2.5-3.8)	
≤8	44	35	3.4 (2.6-4.2)	
Hb by gender (g/dL)[c]				.292
M ≥9; F ≥8	85	69	3.2 (2.5-3.9)	
M <9; F <8	61	50	3.4 (2.1-4.8)	
Platelet count (cells/μL)				.273
≥100,000	76	61	4.1 (2.3-5.9)	
50-99,000	37	32	2.2 (0.5-3.9)	
<50,000	34	28	3.4 (1.4-5.4)	
Neutrophil count (cells/μL)				.287
≥800	106	86	3.6 (2.8-4.2)	
<800	44	39	2.4 (0.8-4.0)	
LDH				.724
Normal	61	49	3.0 (1.9-4.0)	
High	48	39	3.6 (2.2-5.1)	
Ferritin level (ng/mL)				.431
≤350	24	20	4.1 (0.1-8.7)	
>350	33	29	2.2 (0.2-4.2)	
IPSS				.206
Low+[b]	7+			
Intermediate-1[b]	64	56	4.0 (2.7-5.2)	
Intermediate-2	40	35	2.5 (1.5-3.6)	
High	16	14	3.4 (2.0-4.8)	
IPSS-R				.852
Very low+[b]	4+			
Low[b]	28	24	3.1 (1.0-5.3)	
Intermediate	25	19	3.6 (2.5-4.8)	
High	36	31	3.0 (1.0-5.0)	
Very high	21	20	2.5 (2.1-2.8)	

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Supplemental Table 2 Continued

Variable	Patients (n)	Survival After AML Progression[a]		
		Events (n)	Median (95% CI) (mo)	*P* Value
WPSS-Hb[c]				.390
Very low+[b]	1+			
Low[b]	14	14	4.1 (0.6-7.6)	
Intermediate	26	21	3.1 (0.8-5.5)	
High	46	37	3.2 (1.8-4.5)	
Very high	15	14	3.7 (1.8-5.6)	

Abbreviations: AML = acute myeloid leukemia; BM = bone marrow; CI = confidence interval; F = female; Hb = hemoglobin; IPSS = international prognostic scoring system; IPSS-R = revised IPSS; LDH = lactate dehydrogenase; M = male; WPSS-Hb = World Health Organization-based Prognostic Scoring System-hemoglobin.
[a]Kaplan-Meier method and log-rank test (Mantel-Cox).
[b]Data combined for statistical purposes.
[c]WPSS categorization revised according to Malcovati et al.[10]

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