Detection of risk groups in myelodysplastic syndromes. A multicenter study

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Background and Objectives. Myelodysplastic syndromes (MDS) comprise a group of heterogeneous hematologic disorders with risk of leukemic evolution (LE). The *French-American-British* (FAB) cooperative group classifies them into five morphologic entities and the *International Prognostic Scoring System* (IPSS) proposes four groups of risk on the basis of clinical and cytogenetic variables. The aim of this study was to evaluate the application of the IPSS in our Argentine population, to test the prognostic value of its variables and to determine whether this score helps to associate prognostic subgroups of risk into FAB subtypes.

Design and Methods. Two hundred and thirty-four patients with primary MDS and a median follow-up of 28 months were evaluated using univariate analyses to determine median survival (SV) and the time to LE. The variables analyzed were FAB classification, IPSS, percentage of myeloblasts, cytogenetic groups of risk and number of cytopenias.

Results. Univariate analyses showed that all variables analyzed were predictive for SV and for LE in our MDS population. Application of the IPSS allowed discrimination into the 4 groups of risk and helped to identify prognostic subclasses among the FAB classification, associating 5%, 15% and 19% of cases with worse prognosis within the FAB classification of refractory anemia (RA), RA with ringed sideroblasts and RA with excess of blasts (RAEB), respectively. The IPSS was not informative for RAEB in transformation cases and would not be applied to patients with chronic myelomonocytic leukemia.

Interpretation and Conclusions. This score could be applied to our MDS population, showing no geographic differences. Stratification of FAB patients according to IPSS would be helpful to develop risk-adapted therapeutic strategies.

Key words: myelodysplastic syndromes, IPSS, prognostic variables, leukemic evolution.

Primary myelodysplastic syndromes (MDS) comprise a heterogeneous group of acquired bone marrow (BM) disorders characterized by ineffective and dysplastic hematopoiesis affecting one or more cell lines. The most prominent manifestations are varied degrees of cytopenias in the peripheral blood related to progressive BM failure despite its normal to increased cellularity. During the course of the disease, approximately 22-40% of patients undergo leukemic evolution (LE).[1-3] Although some patients die from complications related to cytopenias, others remain asymptomatic.

During the last 20 years, different methods have been published to predict the clinical outcome of these patients, but these methods have not been systematically used to make decisions regarding therapy. The first criteria for a systematic classification of MDS were defined in 1982 by the French-American-British (FAB) co-operative group on the basis of morphologic characteristics and percentage of BM blasts. The FAB group recognized five distinct morphologic entities: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB in transformation (RAEBt) and chronic myelomonocytic leukemia (CMML).[4] Later, different instrument-scoring systems for prognosis were developed taking into

account diverse parameters such as peripheral cell counts, enzyme levels, histopathologic features, in addition to the percentage of BM blasts.[5-7] In 1993, cytogenetic analysis was incorporated into the scores.[1,8] After that, in 1997, an International MDS Risk Analysis Workshop evaluated critical prognostic variables generating the International Prognostic Scoring System (IPSS). The conclusion of this workshop was that the major variables having an impact on LE were percentage of BM myeloblasts, cytogenetic abnormalities and number of cytopenias; and as regarding survival (SV), age and gender were also included. Using a multivariate analysis, the patients were separated into distinct subgroups of risk: low, intermediate-1 (Int-1), intermediate-2 (Int-2) and high.[9]

Chromosome abnormalities constitute a prognostic indicator in MDS[1,8,9] and they are found in 19-50% of the cases. The most frequent cytogenetic abnormalities are: -5 or del (5q), -7 or del (7q), +8, del (20q) and loss of the Y chromosome.[3,9-12]

The aim of this study was to evaluate the application of the IPSS in our Argentine population, to test the prognostic value of its variables and to determine whether this score helps to discriminate prognostic subgroups of risk within FAB subtypes.

Design and Methods

Patients

This is a multicenter retrospective analysis of 234 MDS patients evaluated from 1984 to 2000 proceeding from Argentinian hematologic centers: *Instituto de Investigaciones Hematológicas* (IIHEMA); Hospital Privado de Córdoba, Hospital General de Agudos *Dr. Carlos G. Durand*, Hospital General de Agudos *José María Ramos Mejía* and others. A diagnosis of MDS was made after inspection of peripheral blood (PB) and BM to document the requisite dysplastic cytologic features. Trephine biopsy, cytogenetic studies, cytochemical and iron stains, immunophenotyping and, in some cases, ferrokinetics studies were performed to provide confirmatory diagnosis. All patients were categorized according to FAB criteria;[4,13] all had primary MDS without documented preceding radio- or chemotherapy. Most patients received supportive care, such as transfusion or polyvitamin therapy; only a minority received varying amounts of chemotherapy. Infections, bleeding, BM failure and LE were considered as MDS-related causes of death. The IPSS was applied according to Greenberg *et al.*[9] Table 1 provides a summary of the patients' clinical data. BM blasts, cytopenias, cytogenetic groups, FAB and IPSS classifications are presented in percentages and in absolute numbers, at the time of diagnosis. For each of these variables, the estimated median SV and the time to 25% of patients evolving to LE are also given.

Table 1. Clinical variables of MDS patients related to SV and LE.

Variables	*Pts (%)*	*Median SV (mos.)*	*SV # events*	*25 % LE (mos.)*	*LE # events*
FAB	n= 234	*p < 0.001		*p < 0.001	
RA	108 (46)	108	25	-	7
RARS	21 (9)	-	7	-	2
RAEB	55 (23)	37	34	9	20
RAEBt	25 (11)	10	17	5	18
CMML	25 (11)	28	16	25	7
BM Blasts	n= 234	*p < 0.001		*p < 0.001	
< 5 %	144 (62)	80	43	-	10
5-10 %	37 (16)	31	20	17	13
11-20%	27 (12)	36	17	9	13
> 20 %	26 (11)	9	19	3	18
Cytopenias	n= 234	*p < 0.001		*p < 0.001	
0 - 1	124 (53)	77	39	-	15
2 – 3	110 (47)	31	60	9	39
Cytogenetic groups	n= 198	*p = 0.013		*p < 0.001	
Good	126 (64)	60	46	46	16
Intermediate	41 (21)	34	24	19	11
Poor	31 (15)	28	18	5	14
IPSS	n= 198	*p < 0.001		*p < 0.001	
Low	60 (30)	-	10	-	2
Int-1	76 (38)	42	38	45	11
Int-2	32 (16)	33	18	25	8
High	30 (15)	14	22	5	20

*LE: leukemic evolution; SV: survival; mos: months; *: log-rank test.*

Cytogenetic pattern

Chromosome analyses of 198 patients with MDS were performed in BM samples, according to standard procedures of our laboratory. Inclusion in the study required the analysis of ≥ 11 metaphase cells per patient. Chromosome identification and karyotype designation were made taking into account the *International System for Human Cytogenetic Nomenclature*.[14]

Statistics

The Kaplan-Meier method was used for the univariate estimation of SV time and LE calculated from the day of diagnosis. Each variable was analyzed using the log–rank test. The level of statistical significance was fixed at 0.05.

Results

Patients

The clinical, demographic and cytogenetic findings are summarized in Table 1. At the time of diag-

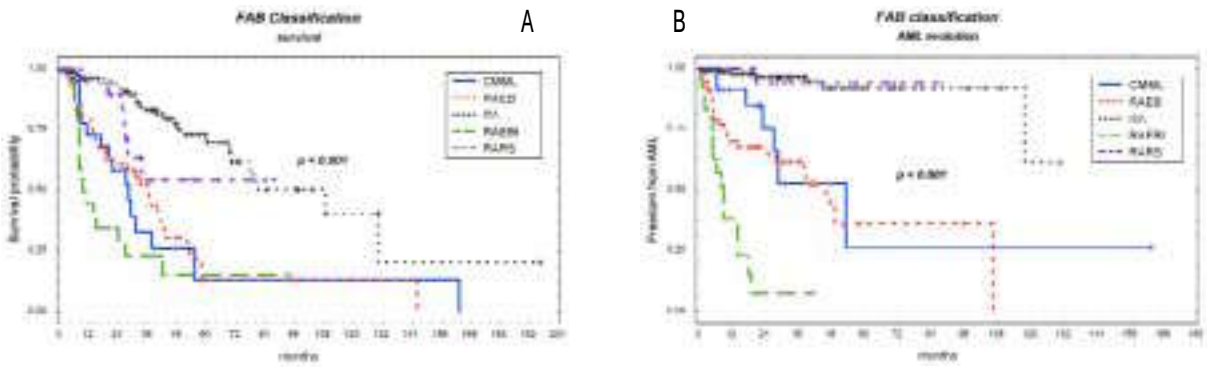

Figure 1. Survival (A) and freedom (B) from AML evolution of 234 MDS patients related to their FAB classification subgroup (Kaplan-Meier curves).

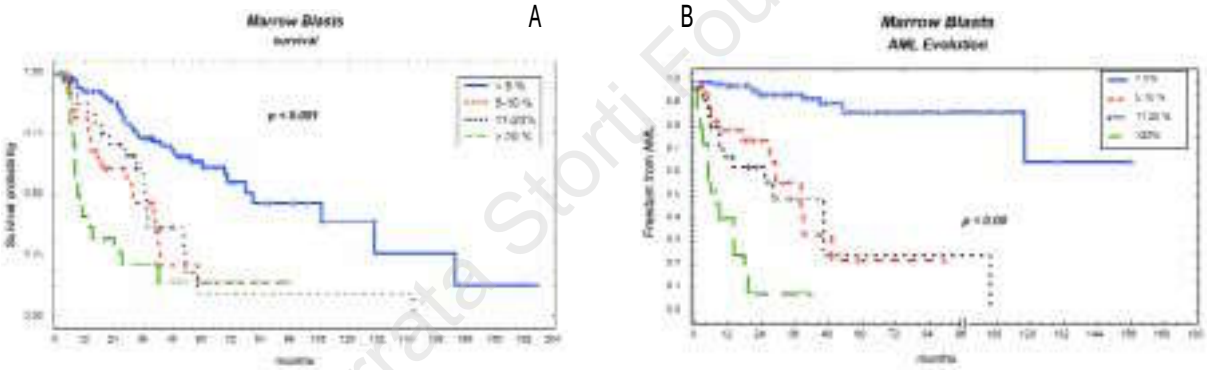

Figure 2. Survival (A) and freedom (B) from AML evolution of 234 MDS patients related to their percentage of BM blasts (Kaplan-Meier curves).

nosis 234 patients were classified thus: 108 (46%) with RA, 21 (9%) with RARS, 55 (23%) with RAEB, 25 (11%) with RAEBt and 25 (11%) with CMML. Thirty-six (15%) patients had no available metaphases for cytogenetic study, so only 198 were subtyped, according to the IPSS, into the following risk groups: 60 (31%) low, 76 (38%) Int-1, 32(16%) Int-2 and 30 (15%) high. The patients' median age was 64 years, ranged between 17 to 90 years and 57% were >60 years old. There were 127 males and 107 females with a M/F sex ratio of 1.2/1. The median follow-up time was 28 months and ranged between 1 to 196 months. Of the 234 patients analyzed, 54 (23%) underwent LE and 99 (42%) patients died of MDS-related causes, including 40 patients who underwent LE.

FAB criteria

SV and LE curves according to FAB subgroups were significantly different ($p<0.001$). The median SV was not achieved in the RARS group while in

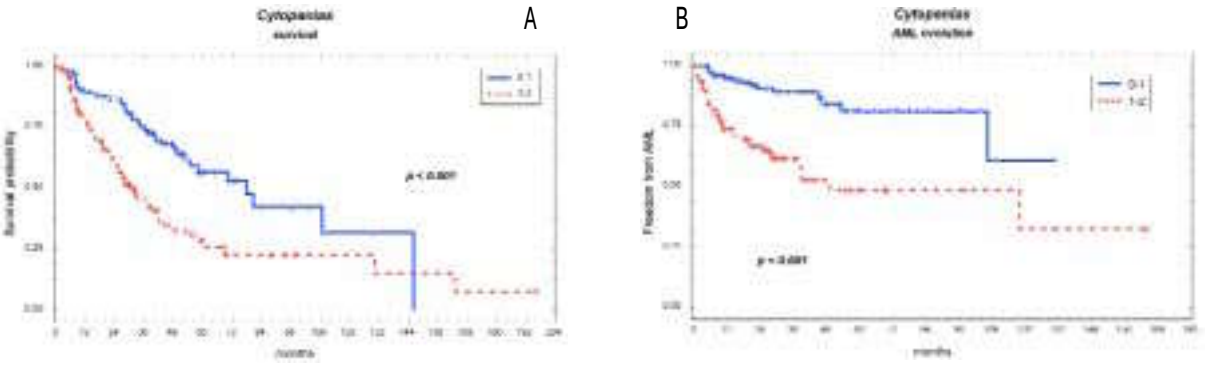

Figure 3. Survival (A) and freedom (B) from AML evolution of 234 MDS patients related to their number of cytopenias (Kaplan-Meier curves).

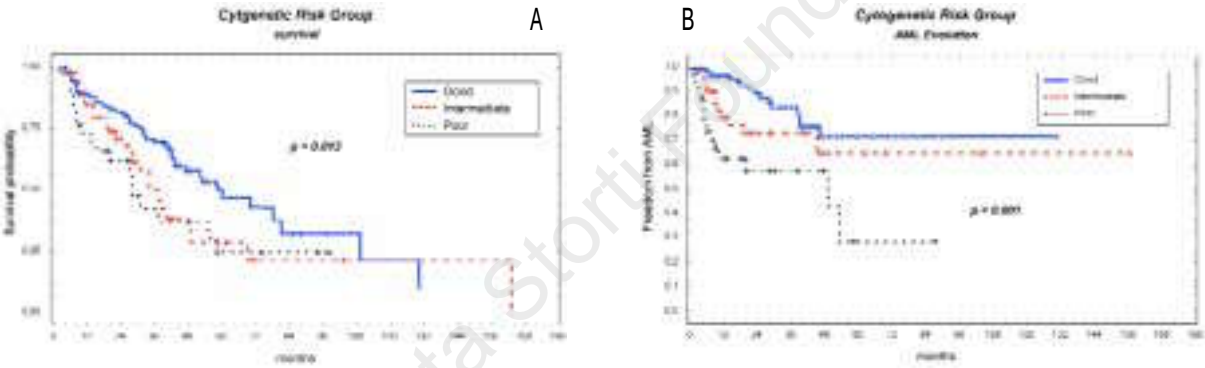

Figure 4. Survival (A) and freedom (B) from AML of the 3 groups of patients based on initial cytogenetic findings (Kaplan-Meier curves).

the RA, RAEB, RAEBt and CMML groups it was 108, 37, 10 and 28 months, respectively. A 25% rate of LE was not achieved in the RA and RARS groups, while for the RAEB, RAEBt and CMML groups, it was reached at 9, 4 and 25 months, respectively (Figure 1, Table 1).

Percentage of BM myeloblasts

SV and LE curves for groups divided according to IPSS cut-off of blast percentage were significantly different (p<0.001). The median SV was 80 months and the LE (25%) was not achieved in the group with <5% blasts; while, for the groups with 5-10%, 11-20% and >20% blasts the median SV and LE (25%) were 31 and 17; 36 and 9; 9 and 3 months, respectively. However, no differences were observed between the group with 5-10% blasts and that with 11-20% regarding SV (p=0.225) and LE (p=0.085). (Figure 2, Table 1).

Number of cytopenias

SV and LE curves drawn according to the number of cytopenias defined by the IPSS were significantly different (p<0.001). The median SV was 77 months and the LE (25%) was not achieved in patients with 1 or no cytopenia; while, for those patients having 2 or 3 cytopenias the median SV was 31 months and LE had occurred in 25% by 9 months (Figure 3, Table 1).

Table 2. Correlation between outcome according to cytogenetic group and IPSS classification.

Cytogenetic risk subgroups	*IPSS Low*	*Int-1*	*Int-2*	*High*	*Total*
Good (%)	60 (48)	46 (36)	13 (10)	7 (6)	126 (64)
Normal karyotype (%)	56 (48)	43 (37)	12 (11)	5 (4)	116 (59)
Abnormal karyotype					
del (5q)	2	1	1	1	5
del (20q)	2	2	0	0	4
lost Y	0	0	0	1	1
Intermediate (%)	0	25 (61)	6 (14)	10 (24)	41 (21)
Trisomy 8	0	6	0	0	6
Misc. single karyotypes	0	17	4	5	26
Misc. double karyotypes	0	2	2	5	9
Poor (%)	0	5 (16)	13 (42)	13 (42)	31 (15)
-7/ del (7q) (Non Complex karyotypes)	0	2	2	5	9
All Complex karyotypes	0	3	11	8	22
Total	60	76	32	30	198

Misc.: miscellaneous; Complex: ≥ 3 abnormalities.

Cytogenetic findings

A total of 198 cases could be successfully analyzed since no metaphases were available from 36 (15%). An abnormal karyotype was observed in 82 (41%) patients at diagnosis. The most common cytogenetic abnormalities were: -7 or del(7q) [9 patients], +8 [6 patients], del(5q) [5 patients], del(20q) [4 patients] and del(12p) [4 patients]. Less common abnormalities included del(6q) [2 patients], i(17q) [2 patients], and +13 [2 patients]. Twenty-two patients showed complex karyotypes (Table 2).

Cytogenetic findings were subdivided according to IPSS into 126 (64%) good, 41 (21%) intermediate and 31 (15%) poor and the SV and LE curves according to these subdivisions showed significant differences (p=0.013 and p<0.001). The median SV and the times to 25% of patients undergoing LE were 60 and 46, 34 and 19, 28 and 5 months in the groups with good, intermediate and poor cytogenetic findings, respectively (Figure 4, Table 1).

We observed that the proportion of normal karyotypes decreased according to worsening prognostic IPSS subgroup, since 48% of cases with normal karyotypes were present in the IPSS low risk group while only 4% of them were in the IPSS high risk group. The correlation between cytogenetic subgroups and IPSS showed that 84% of patients belonging to the good risk cytogenetic group were in low (48%) and Int-1 (36%) IPSS risk groups; 61% of patients with an intermediate cytogenetic risk group were in the Int-1 IPSS group; whereas, 84% of patients with poor cytogenetic findings were in Int-2 (42%) and high (42%) IPSS risk groups. These data show the importance of cytogenetic parameters (Table 2).

IPSS

SV and LE curves plotted according to IPSS stratification were significantly different (p<0.001). The median SV and the LE (25%) were not achieved in the low risk group but were 42 and 45; 33 and 25; 14 and 5 months for the Int-1, Int-2 and high risk groups, respectively (Figure 5, Table 1).

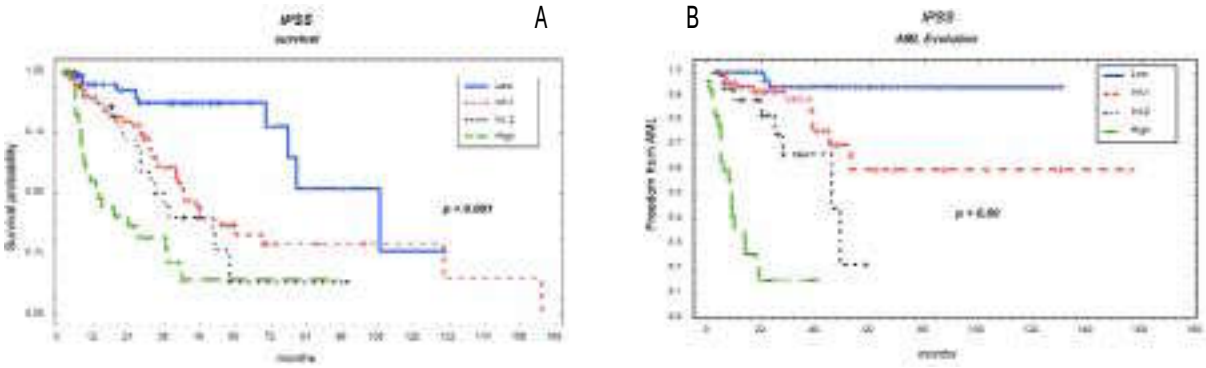

Figure 5. Survival (A) and freedom (B) from AML of the 4 groups of patients related to their IPSS group of risk (Kaplan-Meier curves).

Table 3. Correlation between IPSS and FAB classifications.

	FAB classification					
IPSS	*RA (%)*	*RARS (%)*	*RAEB (%)*	*RAEBt (%)*	*CMML (%)*	*Total(%)*
Low	50 (53)	4 (31)	0 (0)	0 (0)	6 (25)	60 (30)
Int-1	40 (42)	7 (54)	13 (30)	0 (0)	16 (67)	76 (38)
Int-2	**5 (5)**	**2 (15)**	22 (51)	1 (5)	2 (8)	32 (16)
High	0 (0)	0 (0)	**8 (19)**	22 (95)	0 (0)	30 (15)
Total	95	13	43	23	24	198

Bold numbers indicate patients with a worse prognosis within the FAB classification in relation to their IPSS risk.

IPSS vs. FAB subtyped patients

The correlation between IPSS and FAB classifications identified patients with RA (5%) and RARS (15%) within the Int-2 group and those with RAEB (19%) within the high risk group as having worse prognosis (Table 3). The additon of number of cytopenias to an adverse cytogenetic risk group not only increased the risk of LE, but also predicted a short SV.

The IPSS was not informative about RAEBt because the patients had an uniformly poor outcome in relation to their high blast count. With respect to CMML, it was too favorable because all patients (92%) were included in the low and Int-1 risk groups.

Discussion

In this study we evaluated the IPSS and its prognostic variables in a large group of patients with FAB-classified primary MDS over the past sixteen years. The median SV for our patients according to their FAB subtype was similar to those previously reported,[1,8,15] although it was slightly higher for patients with RAEB. The longest median SV and time to undergo LE was observed in RA and RARs cases while RAEBt patients showed the shortest median SV and time for 25% to undergo LE.

From our studies and others,[1,6,7] it is clear that the number of cytopenias, including severity of Hb level, platelet and neutrophil counts, show a direct relation with worse prognosis for SV and LE. The main causes of death in MDS patients are infections and/ or bleeding,[5] and the majority of patients die before overt acute leukemia occurs.[16] This clinical pattern was observed in 60% of our patients, while the remaining 40% developed leukemia before dying.

The karyotype of BM at diagnosis coincided strongly with chromosome alterations reported in other large series.[3,9,10] We observed that the proportion of normal karyotypes decreased according to worsening prognostic IPSS subgroup and the increase of chromosome abnormalities was evident in them, showing the importance of cytogenetic results. Different chromosome aberrations were observed in a few cases; however we noted that del(5q) may be associated with a favorable outcome when it is the sole abnormality and not associated with an excess of blasts.[9,17-19] When this abnormality was found in patients belonging to high risk groups, their poor outcome was not modified. There has been lively comment on the clinical significance of cases with del(20q) and trisomy 8.[3,9,15,18,20] In our study, only one of four patients with del(20q) and one of six patients with trisomy 8 underwent LE before dying; more patients would be necessary to determine the statistical impact of these aberrations. In our series 31 patients showed chromosome 7 alterations and complex karyotype. This group of patients with poor risk cytogenetic findings was associated with a worse prognosis, having a shorter median SV and time to LE than the other cytogenetic groups.

The percentage of blasts in BM aspirates is one of the parameters with strong prognostic value. Several scoring systems have proposed different cut-offs[1,6,7] for this percentage besides the generally accepted one in the FAB criteria.[4] In our experience this variable was strongly predictive for SV and LE, although there were no significant differences between groups with 5-10% and 11-20% blasts. These data indicate that our patients with 5-20% blasts presented a similar behavior. However, when the blast percentage was analyzed together with cytogenetic pattern and number of cytopenias, its discriminative power was increased and it was possible to separate the four IPSS risk groups.

Considering that there were great variations in SV and LE among patients belonging to the same FAB subtype, this integration of IPSS and FAB criteria allowed identification of worse prognostic subgroups within patients with RA, RARS and RAEB. The score value for blast percentage was null in RA and RARS, but adding the increased number of cytopenias and a poor cytogenetic pattern demonstrated the worse prognosis for these cases. These variables also improved the subdivision of RAEB patients in addition to their division according to blast percentage.

CMML encompasses heterogeneous disorders, which seem to belong to a continuous spectrum of myelodysplastic and myeloproliferative diseases with a variable SV. Prognostic factors for these disorders are leukocyte and monocyte counts, lactate dehydrogenase levels, presence of immature precursors in BM and PB, splenomegaly and certain chromosomal anomalies.[7,15,19,21-24] Most of these clinical features were not taken into account in this score. Our data demonstrated that the majority of CMML patients were included in groups of better outcome at presentation. However, they showed a shorter SV and time to evolve LE than predicted by IPSS. For these reasons, another score for predicting prognosis for these patients must be developed.

Our univariate analyses showed that FAB classification, IPSS and its variables, percentage of blasts, cytogenetic pattern and number of cytopenias, were predictive for SV and LE. These results showed that Argentine MDS patients have a similar behavior to other MDS populations and that the stratification of patients according to IPSS taking into account FAB subtypes will be helpful in developing risk-adapted therapeutic strategies for MDS.

Contributions and Acknowledgments

CB and IL were responsible for the conception and design of the study, interpretation of its results and writing the manuscript. CB, SA, NR and IL performed the cytogenetic analyses. RB, GA, NW, JG, GF and SG selected the patients and provided clinical data. SA and RB critically revised the content of the manuscript. All authors gave significant contributions to drafting the article and approved the final version to be submitted. We thank Lic. Francisco Lastiri for performing the statistical analyses and the following Hematological Services for providing the patients' clinical data: Instituto de Investigaciones Hematológicas "Mariano R. Castex" (IIHEMA), Academia Nacional de Medicina, Hospital Privado de Córdoba, Hospital General de Agudos "Dr. Carlos G. Durand", Hospital General de Agudos "José María Ramos Mejía", Hospital Militar "Cosme Argerich", Hospital Italiano, and Hospital Francés.

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Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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PEER REVIEW OUTCOMES

What is already known on this topic

Prognostication is particularly relevant in myelodysplastic syndromes (MDS). The major challenge for a prognostic score is to demonstrate its prognostic accuracy in an independent population.

What this study adds

This study shows the International Prognostic Scoring System (IPSS) for MDS is also valuable in an Argentinian cohort of MDS patients. This is of interest as the IPSS did not include South American patients. These data reinforce the argument that the IPSS should be used for planning therapy in MDS.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Guillermo Sanz, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Sanz and the Editors. Manuscript received August 3, 2001; accepted November 6, 2001.

Potential implications for clinical practice

Identification of differents groups of risk is very important for clinical practice in myelodysplastic patients.

Guillermo F. Sanz, Associate Editor