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Survival analysis and AML development in patients with de novo myelodysplastic syndromes: comparison of six different prognostic scoring systems

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Abstract A number of prognostic scoring systems for patients with myelodysplastic syndromes (MDS) have been introduced in the past. In the present study, survival and AML evolution were analyzed retrospectively in a total of 180 patients with de novo MDS (observation period: 1989–1999; median age: 71; range 27–93; f/m ratio: 1/1.2). Diagnoses were established according to FAB criteria (RARS, n=37; RA, n=53; RAEB, n=50; RAEB-t, n=19; CMML, n=21). Six different multiparameter scoring systems (the Mufti, Aul, Sanz, Morel, and Toyama scores, and the international prognostic scoring system [IPSS]) were applied. The Aul, Sanz, and Mufti scores were applied to all 180 patients, Morel and Toyama scores to 109 patients, and the IPSS to 102. As assessed by multivariate analysis, the percentage of bm-blasts, hemoglobin, platelet count, neutrophil count, LDH, and karyotype were found to be independent single variables for survival, and bm-blasts, neutrophil count, platelet count, and karyotype for AML evolution. All prognostic scoring systems applied appeared to be highly predictive for survival and AML development ($P<0.001$). The highest predictive values were found for the Aul, Sanz, and Toyama scores for overall survival, and the IPSS, Toyama, and Morel scores for AML-free survival. In summary, our data show that scoring systems are useful for predicting overall and AML-free survival in patients with MDS. Karyotype-based multiparameter systems appear to be particularly effective in defining MDS patients who are at high risk of transforming to leukemia.

Keywords MDS · Scoring system · AML transformation · Survival

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Introduction

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal hematologic malignancies characterized by a profound defect in myeloid stem cells resulting in bone marrow (bm) failure with dysplasia in one or more cell lines, and occurrence of cytopenia(s) [6, 8, 23]. Traditionally, the MDSs are categorized according to the proposal of the French-American-British (FAB) cooperative study group [4]. Five major categories have been proposed by the FAB group: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with an excess of blasts (RAEB), RAEB in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMML) [4, 5]. In patients with RARS and RA the median survival amounts to several years with a low incidence of AML transformation. RAEB patients have a significantly shorter survival and an increased probability of transforming to secondary AML. The worst prognosis is found in the RAEB-t group [4]. Thus, survival and

AML-transformation rates vary significantly among FAB groups. However, patients in one particular FAB category also vary concerning survival and AML transformation and it may be difficult to predict the clinical course for individual patients [14].

To better predict survival and AML transformation in MDS patients, several prognostic scoring systems have been established in the past [1, 2, 20, 21, 22, 24]. These scoring systems are based on multiple prognostically important parameters, such as bone marrow blasts, karyotype, and LDH levels. In 1997, the International MDS Risk Analysis (IMRA) Workshop proposed the international prognostic scoring system (IPSS) [15]. This novel scoring system is based on bone marrow blasts, the number of peripheral cytopenias and karyotypes. A number of recent studies have confirmed the predictive value of the IPSS [3, 11, 19]. However, only a few studies have directly compared the various prognostic scoring systems with each other and with the IPSS. In the present study, a cohort of 180 patients diagnosed and followed up at a single center were analyzed to evaluate and compare the predictive values of the IPSS and five other prognostic scoring systems for survival and AML development.

Materials and methods

Patient characteristics

A total number of 180 patients with primary (de novo) MDS were analyzed retrospectively. The patients were diagnosed between 1989 and 1999 at the University Hospital of Vienna. The median age was 71 years (range 27–93; 81 females and 99 males; f/m ratio 1:1.2). Diagnoses were established according to FAB criteria [4, 5]. Patient characteristics are shown in Table 1. Patients who had previously been treated with chemotherapy or radiation were excluded.

Prognostic parameters

The following parameters were recorded at presentation: age, gender, number of bm-blasts (Wright-Giemsa stained bm smears), FAB-subgroup, cytogenetics, LDH activity, complete blood picture, and differential count. In 109 of the 180 patients, cytogenetic analysis was done. Karyotyping was performed on unstimulated (24 h) bone marrow cells according to standard techniques [12]. Karyotypes were classified and described according to criteria provided by the International System for the Human Cytogenetic Nomenclature (ISCN) [16]. Cytogenetic groups in the IPSS were classified into three categories. (1) good: normal, -Y, del(5q), or del(20q); (2) poor: complex (≥3) or chromosome 7 anomalies; (3) intermediate: all other anomalies [15]. Progression to AML was defined by the presence of more than 30% blasts in the bone marrow or a blast cell percentage of more than 30% in the peripheral blood when no bm-smears were available. Informed consent was given by each patient before blood donation or bm biopsy. Patients were analyzed according to the Mufti score (bm-blasts, hemoglobin, platelets, granulocyte count), the Sanz score (bm-blasts, platelets, age), the Aul score (bm-blasts, hemoglobin, LDH, platelets), the Morel score (bm-blasts, platelets, karyotyping) and the Toyama score (bm-blasts, hemoglobin, platelets, granulocyte count, karyotyping), as well as the international prognostic scoring system [IPSS] (number of cytopenias, bm-blasts, karyotype) [1, 2, 15, 20, 21, 22, 24]. The criteria of the Aul, Mufti, and Sanz scores were applied in all 180 patients. The Morel and Toyama scores could only be applied in 109 patients (in 71 patients [39%] no karyotypes were available). Of the 109 patients, 7 with CMML could not be included in IPSS calculations since the WBC was >12,000/µl and consequently their disease was considered to be of the proliferative type according to the IPSS criteria.

Statistical analysis

Uni- and multivariate analysis were done by Cox regression [10]. The product limit method of Kaplan and Meier was applied to analyze the probability of survival and AML-free survival [17]. To calculate the significance of differences between risk groups, the log rank test was applied. For analysis of overall survival, only patients lost for follow-up were censored. For analysis of AML-free survival, patients who died or received intensive chemotherapy before AML transformation were also censored. Uni- and multivariate Cox regression analysis was performed to evaluate the prognostic value of single parameters (i.e. bm-blasts, ANC, platelets, hemoglobin, LDH, age, and karyotype [according to the IPSS criteria]) as well as the predictive potency of the different scoring systems (the IPSS, Mufti, Toyama, Aul, Sanz and Mufti scores). To compare scoring systems with and without inclusion of karyotyping, the Aul, Sanz and Mufti scores were also applied to the subgroup of patients with available karyotypes. Correlations between scoring systems and FAB groups were done by chi-square test. Differences were considered to be significant when the *P* value was <0.05.

Results

Follow-up and survival

Survival and AML-free survival were analyzed in 180 patients (82 females and 98 males) with primary MDS.

Table 1 Patient characteristics

FAB subtype	*n*	Median age (range)	Hb		ANC		Platelets		LDH		bm-blasts Median %
			Median g/dl	<10 g/dl	Median cells/µl	<1,500 cells/µl	Median cells/µl	<100,000 cells/µl	Median U/l	≥300 U/l	
RARS	37	72 (56–88)	9.7	70%	2,223	19%	211,000	8.1%	173	0%	1
RA	53	72 (37–87)	8.9	77%	1,999	43%	125,000	39%	193	8%	3
RAEB	50	72 (27–93)	9.1	69%	1,115	74%	75,500	58%	208	18%	10
RAEB-t	19	65 (27–84)	9.5	74%	571	79%	64,000	68%	206	26%	25
CMML	21	69 (47–86)	9.9	57%	5,399	19%	109,000	47%	233	38%	3
all MDS	180	71 (27–93)	9.4	70%	1,690	47%	115,500	42%	196	14%	4

Hb hemoglobin, *ANC* absolute neutrophil count, *bm* bone marrow

Table 2 Survival and AML-free survival in various FAB groups

FAB	Median survival[a] P=0.001[b]	Median AML-free survival, (ranges)[a] P<0.0001[b]	% of patients developing AML	Cumulative risk of AML evolution at 12 months
RARS	53.1 (0.2–89.6)	nr[c]	0%	0%
RA	36.8 (1.4–110.8)	nr (6.4–110.8)	11.3%	5%
RAEB	15.8 (0.1–50.0)	20.7 (1.2–47.3)	30.0%	26%
RAEB-t	11.6 (0.6–34.0)	7.0 (0.1–34.0)	36.8%	54%
CMML	14.6 (0.7–57)	16.5 (0.2–57.6)	23.81%	11%

[a] Median survival is expressed in months
[b] Differences in survival among FAB groups was significant as assessed by log rank test
[c] No patient developed secondary AML
nr not reached

Table 3 Prognostic factors for MDS (multivariate analysis)

Parameter		*n*	Survival *P* value	AML transformation *P* value
Blast cell count	<5	102	<0.05	<0.05
	≥5	78		
Hb	<10.0	119	<0.05	n.s.
	≥10.0	61		
ANC	≤1,500	86	<0.05	<0.05
	>1,500	94		
Platelets	<100,000	76	<0.05	<0.05
	≥100,000	104		
Karyotype (IPSS)	Good	62	<0.05	<0.05
	Intermediate	15		
	Poor	32		
LDH	<300	154	<0.05	n.s.
	≥300	26		
Gender	F	81	n.s.	n.s.
	M	99		
Age	≤60	28	n.s.	n.s.
	>60	152		

n.s. not significant

Table 4 Survival and AML-free survival according to different scoring systems

Scoring system risk groups	*n*	Survival[a]			AML-free survival[a]		
		75%	50%	25%	75%	50%	25%
Mufti's score							
A	54	15.1	89.6	nr	nr	nr	nr
B	103	10.1	24.7	47.3	17.0	nr	nr
C	23	5.0	9.7	32.7	18.0	nr	nr
Sanz score							
1	78	22.2	77.0	nr	nr	nr	nr
2	66	6.4	18.4	36.8	16.5	36.0	nr
3	36	4.2	11.9	32.7	7.0	nr	nr
Aul score							
A	36	26.3	89.6	nr	nr	nr	nr
B	86	10.7	27.4	nr	22.1	nr	nr
C	58	5.2	11.9	32.7	10.0	nr	nr
Morel score							
Low	35	27.4	89.6	nr	nr	nr	nr
Int	46	9.7	20.4	44.5	20.1	nr	nr
High	28	5.1	12.5	28.0	6.0	15.0	18.2
Toyama score							
L	56	27.4	89.6	nr	nr	nr	nr
M	34	6.4	11.9	20.3	22.1	nr	nr
H	19	4.3	18.4	32.7	7.0	15.0	20.7
IPSS							
LOW	23	77.0	89.6	nr	nr	nr	nr
INT-1	42	10.7	20.4	nr	nr	nr	nr
INT-2	20	6.4	22.2	35.0	6.4	18.6	nr
HIGH	17	4.3	12.5	28.0	6.0	15.0	17.0

[a] The cumulative percentage of survival is expressed as months; differences in survival among the risk groups in each of the scoring systems were significant as assessed by log rank test (P<0.005)
nr, not reached;

The median observation period was 11.3 months. Of the 180 patients, 62 are alive, and 33 were lost for follow-up. Eighty-five patients have died. Of these 85 patients, the majority (63.5%) died from disease-related morbidity (severe infections n=34; bleeding n=12) or leukemia (n=8), and 26.5% from non-disease-related morbidity. In 8 patients intensive chemotherapy for high-risk MDS was administered. The median survival of all patients was 26.3 months. Thirty-four patients (19%) developed secondary AML after a median time of 7.0 months (range 0.6–36 months). When analyzing the patients according to the FAB system, significant differences concerning survival and AML transformation were found among MDS subtypes with a P value of 0.001 and 0.0001, respectively (Table 2).

Univariate and multivariate analysis of single parameters

Single prognostic parameters included in established scoring systems (bm-blasts, hemoglobin, platelet count, absolute neutrophil count [ANC], LDH, age, and karyotype [IPSS-criteria]) were analyzed for survival and AML transformation by univariate analysis. All variables except the patients' age were found to be significant prognostic parameters for survival. Platelet count, LDH, ANC, and karyotype (IPSS criteria) were highly predictive for AML transformation. As assessed by mul-

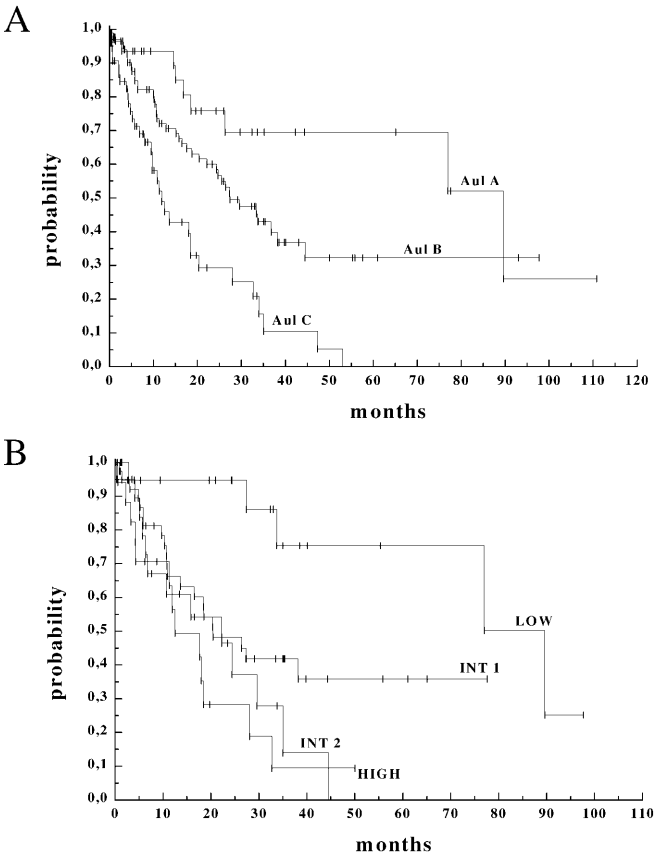

Fig. 1 Survival curves according to the Aul score (**A**) and the IPSS (**B**). Survival was calculated by Kaplan and Meier's product limit method. Differences in survival were analyzed by log rank test

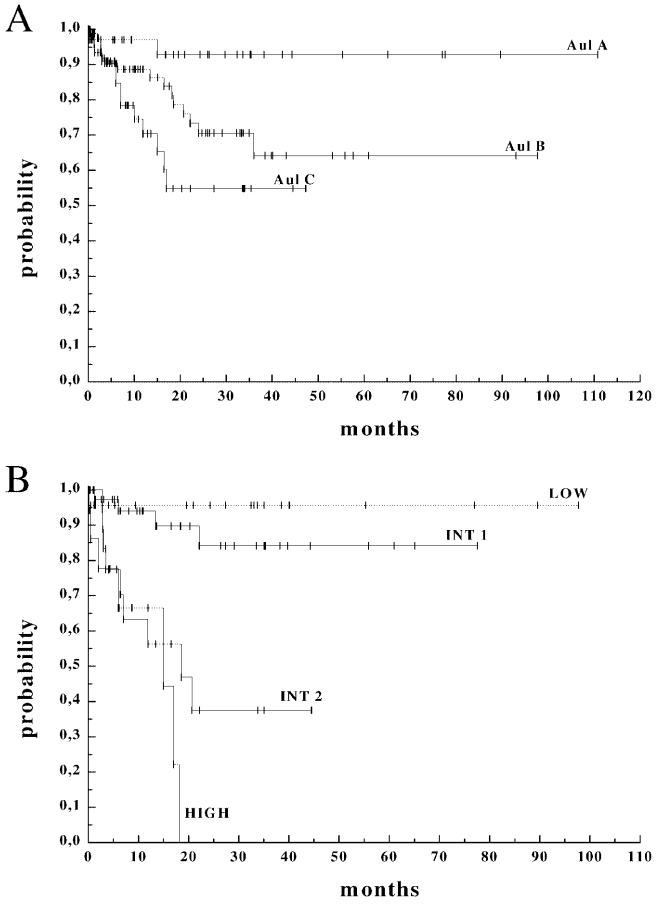

Fig. 2 AML-free survival according to the Aul score (**A**) and the IPSS (**B**). Survival was calculated by Kaplan and Meier's product limit method. Differences in survival were analyzed by log rank test

tivariate analysis, the percentage of bm-blasts, hemoglobin, platelet count, ANC, LDH, and karyotype were the major independent variables for survival, and bm-blasts, platelet count, and karyotype (according to the IPSS criteria) for AML evolution (Table 3). LDH was not an independent prognostic factor for AML transformation as assessed by multivariate analysis.

Survival results and comparison of different scoring systems

Six different prognostic scoring systems were applied (the IPSS, Morel, Toyama, Aul, Sanz and Mufti scores). All scoring systems were found to distinguish three or four (IPSS) distinct risk groups for survival (Table 4, Fig. 1) and AML transformation (Table 4, Fig. 2) in our patients. The results obtained by all scoring systems applied were found to be highly significant ($P<0.001$). To further analyze the prognostic value of the scoring systems applied, Cox regression analysis was performed. The predictive value of all scoring systems was highly significant for both survival and AML development (Table 5). For overall survival, the Aul, Sanz and Toyama scores had the highest predictive value. When the calculation was performed only for patients with available karyotyping, the Toyama, Morel and Aul scores appeared to be most predictive. Analyzing AML transformation, the scoring systems that included karyotypes disclosed the most significant results. In particular, the IPSS, Morel, Toyama scores were found to be most effective in defining MDS patients who are at high risk of transforming to AML.

Correlation between scoring systems and FAB groups

The FAB groups were correlated with the IPSS. As expected, the majority of our RARS patients were found within the LOW-risk group, while most of the RA and RAEB patients were in the INT-1- and INT-2-risk groups of the IPSS, respectively. RAEB-t patients were primarily found in the HIGH-risk group (Table 6). CMML patients were included in the INT-1 and INT-2 groups. The correlation between the IPSS and the FAB classification was significant as assessed by the chi square test. Similar significant results were obtained when FAB groups were correlated with other prognostic scoring systems as shown for Aul's score (Table 7).

Table 5 Prognostic values of scoring systems in our patients as assessed by multivariate Cox regression

Scoring system	Survival		AML-free survival	
	P value, all patients[a] *n*=180	*P* value, patients with cytogenetics[a] *n*=109	*P* value, all patients[a] *n*=180	*P* value, patients with cytogenetics[a] *n*=109
Aul	0.000002	0.000202	0.001544	0.007345
Sanz	0.000007	0.001176	0.001085	0.004715
Mufti	0.000024	0.000396	0.000104	0.002073
Toyama	–	0.000008	–	0.000132
Morel	–	0.000046	–	0.000008
IPSS	–	0.000302	–	0.000003

[a] *P* values were calculated by Cox regression

Table 6 Correlation between FAB and IPSS[a]

FAB groups	LOW	INT-1	INT-2	HIGH
RARS	64%	36%	0%	0%
RA	30%	60%	10%	0%
RAEB	0%	33%	43%	24%
RAEB-t	0%	0%	18%	82%
CMML	33%	50%	17%	0%

[a] $P<0.0005$ as assessed by chi square test

Table 7 Correlation between FAB and Aul's score[a]

FAB groups	A	B	C
RARS	49%	46%	5%
RA	25%	58%	17%
RAEB	0%	48%	52%
RAEB-t	0%	47%	53%
CMML	14%	53%	33%

[a] $P<0.0005$ as assessed by chi square test

Discussion

Myelodysplastic syndromes are clonal hematologic disorders characterized by abnormal differentiation and maturation of myeloid cells, bone marrow failure, and a genetic instability that predisposes for progression to AML [13]. Survival of MDS patients and the period to AML transformation range from months to years [14]. Variability in survival and/or progression of disease is observed among different FAB groups, but also among patients within the same FAB group [4, 5]. Therefore, several prognostic scoring systems have been established in order to identify high-risk MDS patients [1, 2, 15, 20, 21, 22, 24]. These scoring systems are based on the bm morphology and other prognostic parameters such as the number of cytopenias, karyotype, LDH, or age. In the present study a larger group of MDS patients was analyzed using six different prognostic scoring systems. Our data show that all prognostic scoring systems are useful for the prediction of survival and AML transformation. With regard to AML evolution, the karyotype-based, multiparameter scoring systems may be superior.

In a first step of our study, univariate and multivariate analysis were applied to identify single prognostic parameters in our cohort of patients. Univariate analysis showed that the major single prognostic parameters for both survival and AML evolution were bm blasts, hemoglobin, ANC, platelets, karyotypes, and LDH. These parameters were also found to be independent prognostic factors for survival as assessed by multivariate analysis. However, concerning transformation to AML, the LDH was not an independent prognostic parameter. All in all, these data are in line with previous results [1, 2, 14, 15, 20, 21, 22, 24]. However, although age has also been described as a predictive factor for survival in MDS in previous studies [15, 22], age was not a significant prognostic parameter in the current study. This discrepancy may be caused by the relatively high median age of our population (only 16% of the patients were under 60 years of age).

To better predict the prognosis of MDS patients, several prognostic scoring systems have been introduced in the past [1, 2, 15, 20, 21, 22, 24]. In the present study, six different multi-parametric prognostic scoring systems were applied, and their predictive values for survival and AML development were analyzed. In these analyzes, highly significant results were obtained for both survival and AML-free survival with all prognostic scoring systems applied, and overall, the results of our study confirmed the data published previously [1, 2, 15, 19, 20, 21, 22, 24]. However, when comparing various studies with regard to survival in certain risk groups (in individual scoring systems), slight to marked differences were found [3, 11, 19]. Likewise, the published median survival times for patients in the IPSS LOW-risk group were 68 months [15], 45 months [19], 41 months [3], and 25 months [11], and thus lower as compared to the survival found in our study (89 months). A similar variability was also found in all other IPSS risk groups and also for AML-free survival [3, 11, 15, 19]. The reason for this variability is not known, however. Explanations could be a heterogeneity in the patient's median age or differences in co-morbidity (non-leukemic mortality). In this regard it is noteworthy that the median age in our patient groups were rather high, and that the (unexpectedly) low survival rate in our IPSS INT-1 group (as opposed to a relatively low AML-transformation rate) was apparently due to a high rate of non-leukemia-related mortality. All in all, however, most of the results obtained in this study were found to be comparable with

previous analyzes, and the actual survival curves were found to fit well with published data [1, 2, 3, 11 15, 19, 20, 21, 22, 24].

All the different scoring systems applied in our population were highly predictive for both survival and progression to AML. However, concerning survival, the Aul, Sanz, and Toyama scores had slightly lower *P* values compared to the other scoring systems, whereas the IPSS, Morel, Toyama scores were superior concerning AML transformation. The differences in the scoring systems on single prognostic parameters included may contribute to these slight differences. Likewise, LDH is an independent prognostic parameter for survival. Thus, the inclusion of this parameter in Aul's score may provide additional information concerning survival. In fact, this scoring system appears to identify many high-risk patients (more than other scoring systems) also in the RA and RARS groups of MDS. In contrast, karyotyping may contribute to the predictive potency of the IPSS (as well as to that of the Morel and Toyama scores) for progression to AML. Nevertheless, as stated above, significant results were achieved with all scoring systems applied.

Applying scoring systems seems to contribute to estimating the probability of AML development [3, 11, 15, 19]. With all the scoring systems applied in our study significant results were obtained concerning AML-free survival. However, prognostic scoring systems including karyotyping, especially the IPSS, had the lowest *P* values and thus are slightly superior compared to other scoring systems. This may indicate the value of cytogenetics and the IPSS for improved decision-making in this complex disease. Whether modifying the categorization of cytogenetic aberrations as has been recently presented [18, 23] or new parameters as provided by molecular biology [9, 7] would further improve the prognostic value remains to be determined.

In summary, our results show that of the use of scoring systems may be helpful in estimating the probability of AML transformation as well as survival in MDS. The best results concerning AML development were obtained with the IPSS.

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