Prospective validation of the WHO proposals for the classification of myelodysplastic syndromes

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Background and Objectives. The aim of this study was a prospective validation of the World Health Organization (WHO) proposals for the classification of myelodysplastic syndromes (MDS) with respect to their prognostic relevance.

Design and Methods. We classified 1095 patients with MDS diagnosed at our institution between November 1999 and December 2004 according to French-American-British (FAB) and WHO criteria by central morphologic review. The study was not population-based, but included all newly diagnosed patients from different regions in Germany. Patients were followed for survival and disease evolution to acute myeloid leukemia (AML) through December 31th, 2005.

Results. According to the WHO classification, there were 89 cases of refractory anemia (RA), 293 of refractory cytopenias with multilineage dysplasia (RCMD), 31 RA with ringed sideroblasts (RARS), 139 RCMD with ringed sideroblasts (RCMD-RS), 142 RA with excess blasts (RAEB) I and 149 RAEB II and 52 patients with 5q- syndrome. The median survival of patients with RA or RARS was not reached, the median survival of patients with RCMD was 31 months, that of patients with RCMD-RS was 28 months, that of 5q- patients was 40 months, of RAEB I 27 months and of RAEB II 12 months. The cumulative risk of AML evolution 2 years after diagnosis was 0% in RA and RARS, 8% in 5q-, 9% in RCMD, 12% in RCMD-RS, 13% in RAEB I and 40% in RAEB II. The number of high-risk karyotypes was lower in patients with RA/RARS than in those with RCMD/RCMD-RS and RAEB I/RAEB II. Karyotype findings were major prognostic variables.

Interpretation and Conclusions. The WHO classification is feasible and provides valuable prognostic information, even in a short–term prospective study. Together with cytogenetic data and other prognostic parameters, the WHO classification is very useful for clinical decision making.

Key words: myelodysplastic syndromes, prognosis, WHO-classification.

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In 1982, the French-American British (FAB) group introduced a system for classifying patients with primary myelodysplastic syndromes (MDS), which was based on cytomorphologic criteria as well as bone marrow and peripheral blast counts and the monocyte count in peripheral blood.[1] This classification system served as a gold standard for more than two decades not only because it provided widely accepted diagnostic definitions but also because of its prognostic power. In 1999, a working group of the World Health Organization (WHO) proposed a revised classification for MDS.[2] A detailed classification was published in 2000.[3] A final version with minor changes with regards to definitions of subtypes was established by the WHO working group.[4] Based on a retrospective study including 1600 patients with primary MDS,[5] who had been entered into the MDS Registry at the University of Düsseldorf, we demonstrated the prognostic relevance of the WHO classification. The same group of patients have now been followed up to November 2005, (Figure 1) showing that the differences in survival and evolution to acute myeloid leukemia (AML) between the WHO types did not change. Meanwhile, some other smaller retrospective reports on the prognostic value of the WHO proposals have been published[6-9] and have, at least in part, supported the WHO proposals. In the present study we aimed to validate the WHO proposals by means of a prospective study.

Design and Methods

Between November 1st, 1999 and December 31th, 2004, 1095 patients with MDS were diagnosed at our institution and included in the Düsseldorf MDS Registry. Only 17% of the patients included in the Registry live in the town district of Düsseldorf. The study was not population-based, but included all newly diagnosed MDS patients from different regions in Germany. The relative incidence of MDS types in our study was possibly influenced by referral patterns and recruiting patients into studies. The diagnostic procedures were exactly the same as used in our retrospective study. All blood and bone marrow smears were examined by the same investigator (*CA and/or UG*). The morphological diagnosis was made according to the proposals of the FAB[1] and WHO-Classification.[4] A differential white blood count was performed on 100 cells in the peripheral blood to determine the peripheral

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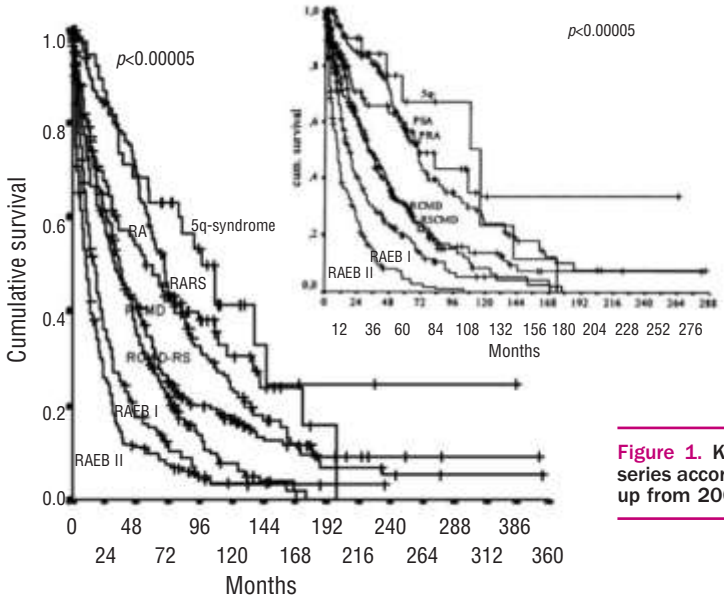

Figure 1. Kaplan Meier plots of survival of the retrospective series according to WHO classification (n=1157) with the follow up from 2005 and, in the small inlet, from 2000.

blast count and look for dysplastic features in the blood. A differential count was also carried out on 500 nucleated cells in the bone marrow to determine the proportion of bone marrow blasts and to diagnose MDS according to the proposed WHO classification. Dysmegakaryopoiesis was diagnosed if at least ten out of 25 megakaryocytes were micromegakaryocytes, mononuclear megakaryocates or if they had multiple widely separated nuclei. This definition differs slightly from the WHO proposals, but we decided to use exactly the same criteria as in our retrospective study. Dysgranulopoiesis was considered present if at least 10% of the granulopoietic cells showed signs of dysplasia including pseudo-Pelger cells and hypogranulated cells. Bone marrow cells were stained for myeloperoxidase (MPO) activity to assess MPO deficiency in the granulocytic lineage. We routinely used benzidine base staining for MPO (SIGMA diagnostics). A partial MPO defect was diagnosed if ten out of 100 mature granulocytes showed a negative or minimal reaction. An increase of bone marrow blasts above 30% was defined as evolution to acute myeloid leukemia (AML). Cytogenetic analysis was performed in 461 patients at diagnosis in the Institute of Human Genetics, Heinrich-Heine University, Düsseldorf. A minimum of ten metaphases were required for analysis and reporting. Cases with less than ten metaphases were excluded from the analysis. The median number of metaphases was 21.[10-28] Cytogenetic findings were documented according to the International System for Human Genetic Nomenclature.[10] They were classified following the International Prognostic Scoring System (IPSS) proposal (low-risk: 5q-, 20q, -Y, and normal karyotype: high-risk: aberrations of chromosome 7 and/or complex karyotypes, i.e. ≥3 abnormal chromosomes; intermediate risk: all other findings).[11] Patients were followed for survival and leukemic progression through to December 30, 2005. The patients were either regularly seen in our outpatient clinic, or their primary care physicians were contacted to gather pertinent information on the course of the disease. The Kaplan-Meier product limit method was used to estimate survival.[12] Prognostic factors were determined using the Mantel-Cox test and Cox's stepwise multivariate regression method.[13] Clinical and hematologic data of the patients at the time of diagnosis were compared using χ^2 and Wilcoxon's rank sum tests. For the survival calculations, patients who underwent allogeneic transplantation (n=28) or intensive chemotherapy (n=70) were excluded from the analysis.

Results

Clinical characteristics

The analysis was based on 1095 patients included in the study between November 1999 and December 2004. The entire group of patients had a median survival of 26 months. The Kaplan Meier estimates for survival for the entire retrospective series presented in 2000 and the prospective series are very similar (Figure 2). According to the FAB classification there were 428 patients with refractory anemia (RA) (39%), 176 with RA with ringed sideroblasts (RARS) (16%), 267 with RA with excess blasts (RAEB) (25%), 112 with RAEB in transformation (RAEB-T) (10%) and 112 with chronic myelomonocytic leukemia (CMML) (10%). The patients with RA according to the FAB classification were grouped following the proposals of the WHO as having RA in 21% (n=89), refractory cytopenia with multilineage dysplasia (RCMD) in 68% (n=293) and the 5q- syndrome in 11% (n=46). Taking the same approach for patients with RARS, 79% were allocated to the category of RCMD with ringed sideroblasts (RCMD-RS) (n=139), 18% to

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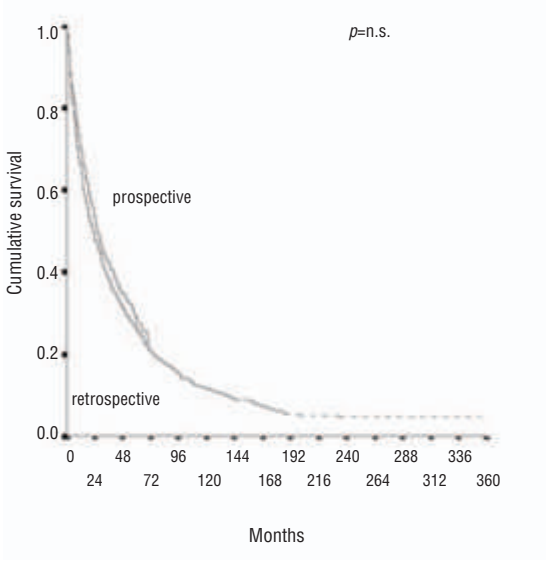

Figure 2. Survival plots of the whole retrospective (n=1600) and prospective (n=1095) groups of patients.

RARS (n=31) and 3% of the patients had a 5q-syndrome (n=6). Of the 267 patients with RAEB according to the FAB classification, 132 were allocated in the WHO classification to RAEB I (49%) and 135 to RAEB II in 51%. In addition, 14 patients with RAEB-T were classified as having RAEB II since they had less than 20% bone marrow blasts but more than 10% peripheral blasts or Auer rods (Table 1). Patients with RAEB-T and more than 20% bone marrow or peripheral blasts as well as in patients with CMML were not considered as having MDS according to the WHO proposals. The patients formerly classified as having RAEB-T remained separately in the analysis in order to allow a direct comparison with those classified as having RAEB II. The hematologic characteristics of the patients grouped into the different WHO types are shown in Table 2. Their median age was 70 years (range, 17-96). The degree of cytopenia, blast counts in blood and marrow and lactate dehydrogenase (LDH) activity increased from RA to advanced types of MDS.

AML evolution

The cumulative risk of the MDS evolving to AML by 5 years after diagnosis was less than 2% in patients with RA or RARS, whereas it was about 10% in patients with RCMD, RCMD-RS or the 5q- syndrome. Patients with RAEB II had a 40% risk of AML evolution as compared to 11% in patients with RAEB I and 84% in patients with AML (RAEB-T) (Figure 3).

Survival

Within the study period, 26 patients with RA (30%), 8 patients with RARS (26%), 117 patients with RCMD (40%), 58 patients with RCMD-RS (42%), 23 patients with 5q- (45%), 57 patients with RAEB I (43%) and 77 patients with RAEB II (52%) died. The median survival was not reached in RA and RARS patients, whereas it was 31 months for patients with RCMD, 28 months for RCMD-RS patients and 40 months for 5q- patients (Figure 4). The median survival of RAEB I patients was 27 months and that of RAEB II patients was 12 months; the former RAEB-T group had a median survival of 7 months (p=0.0005).

Table 1. Comparison between FAB and WHO diagnoses.

FAB n (%)	*WHO*	*n (%)*
RA 428 (39%)	RA	89 (21%)
	RCMD	293 (68%)
	5q-	46 (11%)
RARS 176 (16%)	RARS	31 (18%)
	RCMD-RS	139 (79%)
	5q-	6 (3%)
RAEB 267 (24%)	RAEB I	132 (49%)
	RAEB II	135 (51%)
RAEB-T 112 (10%)	RAEB II	14 (12.5%)
	AML	98 (87.5%)
CMML 112 (10%)	MPD/MDS	

Prognostic factors

Cytogenetic aberrations were less frequent in RA and RARS than in RCMD and RCMD-RS. The frequency of chromosomal aberrations did not, however, differ between RAEB I and II patients. We also looked for prognostic parameters other than WHO types within our prospective series of patients. As expected, cell counts, age, LDH concentration and cytogenetic categories had prognostic impacts on survival as well as on the risk of AML evolution (Table 3). We then applied the IPSS[11] and Düsseldorf score[14] to our WHO patients, bearing in mind that these scores were built on data from patients with MDS including RAEB-T and CMML. The Düsseldorf-Score, as well as the IPSS and the refined IPSS-LDH[15] were able to separate risk groups in the entire group of patients, as well as within the WHO types. However, the high-risk group of the IPSS shrank from 20% to 7.5 % due to the lack of patients fulfilling the most important risk criterium within the IPSS, a bone marrow blast count of more than 20%. The high-risk group according to the Düsseldorf score lost only 33 % of its patients and comprised 22 % of the entire patients. Looking at the prognostic impact of transfusion need, we found that, within all subtypes except RA/RARS/5q-, transfusion dependency at the time of diagnosis was associated with a worse prognosis (*data not shown*).

Multivariate analyses

In order to assess the relative prognostic value of the different WHO categories (RA/RARS/5q- vs. RCMD/RCDM-RS vs RAEB I vs RAEB II), we performed a regression

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Table 2. Hematologic, cytogenetic and clinical characteristics according to the WHO types.

	RA	*RARS*	*RCMD-RCMD*	*RS*	*RAEB I*	*MDS RAEB II*	*AML del(5q)*	*(RAEB-T)*
Number patients (%)	89	31	293	139	142	149	52	98
Sex								
Male	42	16	172	70	90	84	17	55
Female	47	15	121	69	42	65	35	43
Age								
Median	69	73	71	72	68	68	65	70
Range	19-90	45-86	17-94	31-93	34-105	27-93	32-87	29-91
Hemoglobin g/dL								
Median	8.7	9.15	9.3	8.7	9.1	9.2	9.2	9.0
Range	3.4-13.3	5.9-11.7	4.1-16.9	2.2-13.8	2.7-16.9	4.8-14.5	3-11.9	5.2-15.2
WBC/μL								
Median	5000	5800	4200	4400	3000	2800	4400	2700
Range	900-3200	3400-15100	500-36200	900-20300	900-17800	700-139000	1900-12610	800-139000
ANC/μL								
Median	2990	3032,5	2376	2183	1493,5	899	2685	800
Range	327-18144	1400-10541	50-20272	160-17255	40-10854	38-88960	1064-9290	30-87000
Platelets/μL								
Median	164	334	120,5	207	79	73	303	55
Range	2-1190	60-718	5-1900	5-2101	6-1408	5-630	14,5-1540	3-448
LDH U/L								
Median	212	160	204	188.5	221	230	181.5	237
Range	106-1551	109-354	75-2500	90-599	82-584	45-1112	103-369	102-875
Number of peripheral cytopenia, defined by IPSS (%)								
0	11	26	17	15	11	7	13	1
1	52	63	42	47	21	26	59	24
2	26	11	26	33	46	37	23	34
3	11	0	15	5	22	30	5	41
Peripheral blasts								
Median	0	0	0	0	0	0	0	0
Range	0-1	0-1	0-1	0-1	0-8	0-15	0-1	0-29
Bone marrow blasts								
Median	1	1	1	1	8	15	2	25
Range	0-5	0-3	0-5	0-5	1-10	1-20	0-5	20-29
Abnormal Karyotype (%)	53	25	49	56	61	62	100	72
Chromosomal risk groups (%)								
0	68	88	70	62	60	58	100	44
0.5	18	12	14	16	15	16	0	13
1	14	0	16	22	25	26	0	43
IPSS (%)								
0	20	60	29	41	0	0	70	0
1	70	40	59	45	64	8	30	0
2	10	0	12	14	34	55	0	7
3	0	0	0	0	2	37	0	93
Düsseldorf score (%)								
0	11	30	21	22	0	0	29	0
1	82	70	73	74	65	42	68	42
2	7	0	6	4	35	58	3	58
AML (%)	1	0	10	8	16	32.2	15.7	75

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analysis. The results show that the risk rises from the level of 1 set from RA/RARS/5q-, to 1.62 in RCMD/RCDM-RS, to 1.97 in RAEB I and to 3.64 in RAEB II. The same was true for the cumulative risk for AML evolution. This risk rises from the level of 1 set in RA/RARS/5q- to 2.51 in RCMD/RCDM-RS, to 3.71 in RAEB I and to 15.34 in RAEB II. The results of multivariate regression analysis aimed at identifying prognostic parameters for survival and AML evolution are presented in Table 4. The most important parameter for predicting survival and AML evolution were karyotype and WHO type. This reflects the multilineage dysplasia as well as bone marrow blast count, both defining parameters of the WHO classification which have strong prognostic impact not only on survival but also on the risk of AML evolution. Other parameters that showed a prognostic impact in the univariate analysis

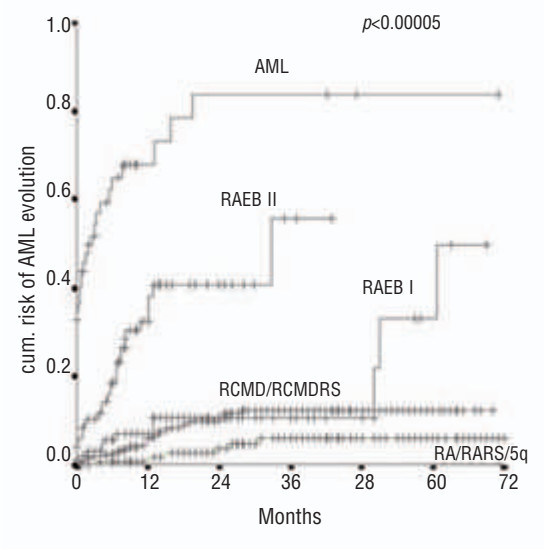

Figure 3. Kaplan Meier plots of the risk of AML in the prospective series.

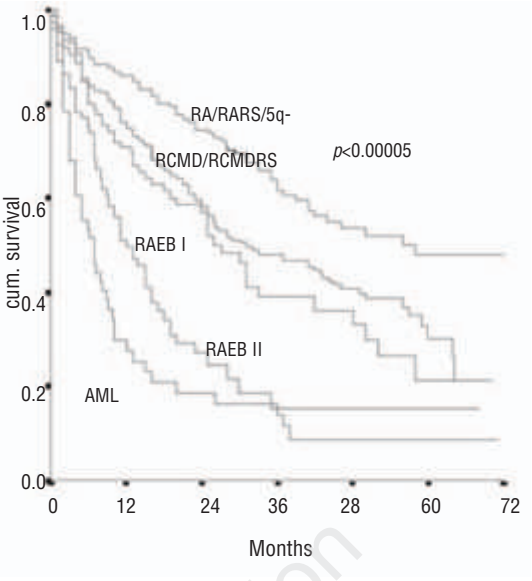

Figure 4. Kaplan Meier plots of survival of the prospective series.

failed to do so in the multivariate tests. We then repeated the multivariate analysis also entering those patients who had not been karyotyped at diagnosis. As the median survival of this group was not different from those with an intermediate risk karyotype (26 months), they were entered together with this group. The only difference in the regression analysis was that elevated LDH and a hemoglobin concentration of less than 10 g/dL were shown to be independent prognostic factors for survival as well as for AML evolution.

Finally, we assessed, whether the presence of a high-risk karyotype influences the prognosis within the WHO groups. Figure 5 (A-D) shows that within all WHO groups with the exception of the RA/RARS group, a high-risk karyotype was associated with an adverse prognosis. This is true even for the former RAEB-T group.

Discussion

In the present study we showed that the WHO classification of patients with primary myelodysplastic syndromes enables a clear distinction between the different types of MDS and in addition provide with a significant prognostic information. Patients with the newly defined MDS types differ in terms of survival duration, AML evolution, cytogenetic features and hematologic characteristics. Our data may help to overcome the extremely controversial debate about the significance of this classification, which began shortly after its introduction.[16,17] Our findings on the prognostic relevance of the WHO classification presented here are in line with those of an earlier retrospective study from our institution,[5] as well as several other smaller retrospective studies.[18-29] Now, after prospectively using the FAB and WHO classifications in parallel for 6 years, we have validated the WHO proposals in a large morphologic laboratory. Despite the shorter observation time in the prospective series than in the retrospective one, the relevant prognostic characteristics of the WHO subtypes were confirmed.

In particular, the extremely important value of the distinction between unilineage and multilineage dysplasia in the RA and RARS groups were confirmed in the prospective series. Dysmegakaryopoiesis was diagnosed if at least 10 out of 25 megakaryocytes were micromegakaryocytes, mononuclear megakaryocates or if they had multiple widely separated nuclei This definition differs slightly from those used in the WHO proposals, and could possibly lead to an over-diagnosis of RA and RARS. This issue should be analyzed in detail in further studies. The differentiation between unilineage and multilineage dysplasia is also supported by molecular and clinical findings. Rong *et al.*[30] showed that ras mutations can be found in bone marrow samples of patients with RCMD-RS but not in those from patients with RARS. Similarly, Cermak *et al.*[31] demonstrated that clonality of CD3 and CD14 cells was found frequently in patients with RCMD, but in only a few with RA. There are also some differences in treatment outcome. Data from the Nordic group[32] showed that patients with unilineage dysplasia had better responses to erythropoietin. The same held true for antithymocyte globulin[33,34] and valproic acid.[35] The degree of lineage involvement also has an impact on decision making in allogeneic stem cell transplantation.[36] One particular concern of WHO critics has not been sufficiently addressed yet. There is still a lack of minimal diagnostic criteria for making the diagnosis of RA. In some cases only repeated bone marrow examinations during follow-up may ulti-

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Table 3. Univariate analysis of prognostic factors.

Variable	%	Median survival/months	Log-rank	p	Cumulative AML evolution (%) 2 years	5 years	Log-rank	p
WHO-types								
RA	10	n.r.	114.37	<0.00005	0	2	93.3	<0.00005
RARS	3	n.r.			0	0		
RCMD	31	31			6	12		
RSCMD	15	28			5	9		
RAEB I	13	27			9	11		
RAEB II	14	12			23	40		
5q-	6	40			2	8		
RAEB T	8	7			68	84		
Gender								
Male	51	22	20.52	<0.00005	13	18	1.08	n.s.
Female	49	41			12	16		
Age								
<60	17	n.r	31.34	<0.00005	5	8	11.0	0.0009
>60	83	25			13	19		
Hemoglobin level (g/dL)								
<10	66	23	13.87	0.0002	6	11	2.15	n.s.
≥10	34	41			13	14		
<8	24	19	8.5	0.0035	11	14	0.01	n.s.
≥8	76	31			13	14		
Platelets/μL								
<100,000	42	17	35.32	<0.00005	7	10	28.7	<0.00005
≥100,000	58	41			21	27		
WBC/μL								
≥2500	23	16	10.98	0.0009	19	27	15.6	0.0001
≥2500	77	31			10	14		
ANC/μL								
<1,800	36	21	8.91	0.0028	10	12	14.3	0.0002
>1,800	64	33			17	24		
Number of cytopenias (according to IPSS)								
0	15	nr	45.21	<0.00005	2	6	36.4	<0.00005
1	40	35			7	11		
2	30	20			16	22		
3	15	12			30	32		
Transfusion need at the time of diagnosis								
no	48	46	19.65	<0.00005	12	33	1.78	n.s.
yes	51	20			18	28		
Medullary blast count								
<5%	69	41	26.23	<0.00005	8	11	38.38	<0.00005
>5%	31	18			24	43		
Medullary blast count								
<10%	85	37	41.50	<0.00005	6	13	81.24	<0.00005
≥10%	15	12			41	55		
LDH (U/L)								
Normal	63	31	22.30	<0.00005	11	14	10.6	0.0011
Elevated	37	14			20	26		
Peripheral blasts (%)								
Yes	11	12	19.55	<0.00005	12	15	3.4	n.s.
No	89	36			23	26		
Karyotype								
good	68	52	58.31	<0.00005	12	15	42.4	<0.00005
intermediate	15	30			18	42		
high	17	11			44	56		
AML progress								
Yes	15	14	56.99	<0.00005				
No	85	37						
IPSS								
Low	25	n.r.	75.33	<0,00005	4	6	175.0	<0.00005
Intermediate I	41	31			4	14		
Intermediate II	119	21			28	40		
High	15	8			76	94		
Düsseldorf-Score								
Low	13	59	93.59	<0.00005	0	0	58.9	<0.00005
Intermediate	66	31			10	14		
High	21	9			33	38		
Low a	73	n.r.	6.25	0.01	7	7	0.05	n.s.
Low b	27	36			5	10		
Intermediate I a	71	31	4.7	0.02	7	11	0.03	n.s.
Intermediate I b	29	18			9	25		
Intermediate II a	55	23	0.03	n.s.	76	94	1.2	n.s
Intermediate II b	45	25			68	68		
High a	37	15	19.83	0.0002	60	75	1.35	n.s.
High b	62	5			90	100		

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Table 4. Multivariate analysis of different prognostic parameters for survival and AML evolution.

Parameter	Prognostic parameters for survival χ^2	p
High risk karyotype	14.01	<0.00005
WHO type	9.01	0.003
Platelets <100.000/µl	5.1	0.02

Parameter	Prognostic parameters for AML evolution χ^2	p
High risk karyotype	15.0	<0.00005
WHO type	38.2	<0.00005

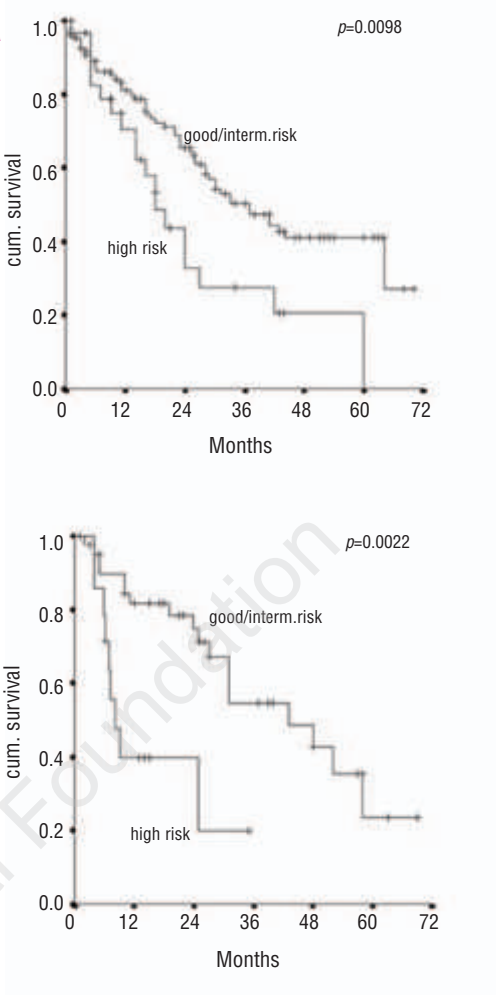

Figure 5. A. Cumulative survival of patients with RCMD/RCMDSRS divided according to whether they had a good/intermediate risk karyotype or high-risk karyotype. B. Cumulative survival of patients with RAEB I divided according to whether they had a good/intermediate risk karyotype or high-risk karyotype.

mately justify the diagnosis of MDS. New methods such as immunphenotyping,[37] genomics,[38-40] or proteomics[41] may help to separate MDS from secondary anemia.

Besides the groups with RA and RARS, patients with the 5q- syndrome constituted the third subgroup showing a superior survival in our analysis. Our data are in line with those of former studies.[42,43] As our data indicate, the good prognosis might be more easily appreciated when data from longer follow-ups are available. As for the degree of lineage involvement, clinical data seem to support the separation of 5q-syndrome from other MDS subtypes. List *et al.*[43,44] have shown a high response rate to treatment with lenalidomide in patients exhibiting the 5q- anomaly.

We confirmed the prognostic impact of splitting the large group of patients with RAEB into those with RAEB I and II, as already demonstrated in previous studies. The elimination of the RAEB-T category from MDS and its integration into AML is the subject of a long and still ongoing debate. Of interest, the median survival of patients with RAEB II was similar to that of patients with RAEB-T. This supports critics of the WHO proposals, who argue that the prognosis of patients and the distinction between MDS and AML is not only dependent on blast counts. The fact that AML evolution itself does not influence survival in patients with more than 10% marrow blasts further emphasizes the arbitrary feature of a classification relying on blast percentages. The WHO classification has taken this fact at least partially into account by introducing the new AML category of AML with multilineage dysplasia, a disease with a more indolent course, a higher frequency of poor risk cytogenetics, an early stem cell phenotype and overexpression of multidrug resistance proteins.

Despite the great value of the WHO classification, it should be noted that it did not take into account additional morphologic features. The prognostic relevance of myelofibrosis,[45,46] the presence of peripheral blasts,[47] and cellularity[48-50] are not incorporated in the current WHO classification. Patients with CMML[51,52] and patients with myeloproliferative disease plus ringed sideroblasts[53,54] are assigned to mixed myeloproliferative/myelodysplastic types by the WHO classification and no longer considered as MDS.

The IPSS score[11] has become essential for risk assessment in MDS. Our data on the application of different scoring systems such as the IPSS and a refined IPSS score[15] show that IPSS-based scores are still valid and useful for decision making despite having been developed on the basis of the FAB classification and having some shortcomings when applied to the WHO system. Thus an IPSS-based score adapted to the WHO classification is warranted. Considering the array of treatment options including epigenetic, immunomodulatory, anti-angiogenetic and molecular drugs, the traditional scores also need to be supplemented by drug-related predictive scores which are based on a better understanding of the molecular pathophysiology of the particular types of MDS.

In summary, the WHO classification of primary myelodysplastic syndromes provides a very good diagnos-

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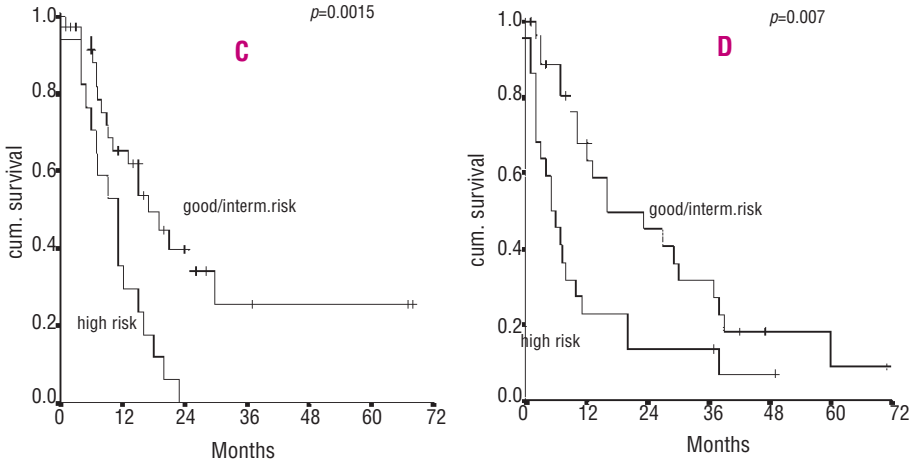

Figure 5. C. Cumulative survival of patients with RAEBII divided according to whether they had a good/intermediate risk karyotype or high-risk karyotype. **D.** AML (RAEB-T) divided according to whether they had a good/intermediate risk karyotype or high-risk karyotype.

tic tool, improves risk stratification and helps to identify patients for different treatment strategies. Some controversies, especially concerning minimal diagnostic criteria for RA and the best way of separating AML from MDS, still remain and need to be addressed in the future.

UG: provided concept and design, prepared the manuscript, performed morphologic examinations; CS: contributed clinical patient data, helped with data assembly; AK: assisted in preparing the manuscript, contributed clinical patient data, helped with data assembly; SI: contributed clinical patient data, helped with data assembly; SK: contributed clinical patient data, helped with data assembly; BH: performed cytogenetic analysis; AG: contributed clinical patient data, helped with data assembly; CA: provided concept and design, performed morphologic examinations; NG: critical review; RH: critical review. The authors declare that they have no potential confilct of interest. This work was supported by the "Kompetenznetzwerk akute und chronische Leukämien".

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