VOLUME 25 · NUMBER 23 · AUGUST 10 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Time-Dependent Prognostic Scoring System for Predicting Survival and Leukemic Evolution in Myelodysplastic Syndromes

Luca Malcovati, Ulrich Germing, Andrea Kuendgen, Matteo G. Della Porta, Cristiana Pascutto, Rosangela Invernizzi, Aristoteles Giagounidis, Barbara Hildebrandt, Paolo Bernasconi, Sabine Knipp, Corinna Strupp, Mario Lazzarino, Carlo Aul, and Mario Cazzola

From the Departments of Hematology and Medicine, University of Pavia & Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy; Departments of Hematology, Oncology, and Clinical Immunology and Human Genetics, Heinrich-Heine-University, Düsseldorf; and Department of Haematology, Oncology, and Clinical Immunology, St Johannes Hospital, Duisburg, Germany.

Submitted August 4, 2006; accepted May 9, 2007.

Supported by grants from Associazione Italiana per la Ricerca sul Cancro, Milan; Fondazione Cariplo, Milan; Fondazione Ferrata Storti, Pavia; and Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy (M.C.); from Kompetenznetz "Akute und Chronische Leukämien" des Bundesforschungsministerium (U.G.); Bundesministerium für Bildung und Forschung, Competence Network (C.A.); and from Piano Regionale Sangue 2006, Regione Lombardia, Milan, Italy (M.L.).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Mario Cazzola, MD, Department of Hematology, University of Pavia, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, 27100 Pavia, Italy; e-mail: mario.cazzola@unipv.it.

0732-183X/07/2523-3503/$20.00

DOI: 10.1200/JCO.2006.08.5696

ABSTRACT

Purpose
The aims of this study were to identify the most significant prognostic factors in myelodysplastic syndromes (MDS) taking into account both their values at clinical onset and their changes in time and to develop a dynamic model for predicting survival and leukemic evolution that can be applied at any time during the course of the disease.

Patients and Methods
We studied a learning cohort of 426 MDS patients diagnosed at the Department of Hematology, San Matteo Hospital, Pavia, Italy, between 1992 and 2004, and a validation cohort of 739 patients diagnosed at the Heinrich-Heine-University Hospital, Düsseldorf, Germany, between 1982 and 2003. All patients were reclassified according to WHO criteria. Univariable and multivariable analyses were performed using Cox models with time-dependent covariates.

Results
The most important variables for the prognostic model were WHO subgroups, karyotype, and transfusion requirement. We defined a WHO classification–based prognostic scoring system (WPSS) that was able to classify patients into five risk groups showing different survivals (median survival from 12 to 103 months) and probabilities of leukemic evolution ($P < .001$). WPSS was shown to predict survival and leukemia progression at any time during follow-up ($P < .001$), and its prognostic value was confirmed in the validation cohort.

Conclusion
WPSS is a dynamic prognostic scoring system that provides an accurate prediction of survival and risk of leukemic evolution in MDS patients at any time during the course of their disease. This time-dependent system seems particularly useful in lower risk patients and may be used for implementing risk-adapted treatment strategies.

J Clin Oncol 25:3503-3510. © 2007 by American Society of Clinical Oncology

INTRODUCTION

Myelodysplastic syndromes (MDS) are hematopoietic stem-cell disorders characterized by marrow failure and a substantial risk of progression into acute myeloid leukemia (AML). MDS occur mainly in older persons and show impressive clinical heterogeneity, from indolent conditions with a near-normal life expectancy to forms approaching AML.[1]

Following the proposal by the French-American-British cooperative group,[2] several studies have been performed to improve our ability to evaluate prognosis in MDS.[3-6] In 1997, Greenberg et al[7] developed the International Prognostic Scoring System (IPSS) based on marrow blasts, cytogenetic pattern, and number of cytopenias. The IPSS was derived from a multivariable analysis of hematologic characteristics of 816 patients at clinical onset, including also patients with 20% to 30% marrow blasts, who are now considered as having AML.

In 2002, WHO formulated a new classification of MDS based on unilineage or multilineage dysplasia, blast count, and cytogenetic features.[8] The prognostic relevance of this proposal was confirmed by several groups[9-13] and has been recently validated in a prospective study.[14] Among patients with MDS without excess blasts, the isolated involvement of the erythroid lineage is definitely associated with a better prognosis compared with multilineage dysplasia.[15]

In our previous study,[12] we found that the IPSS retains significance within the WHO subgroups. However, the two systems are redundant mainly

because the IPSS blast intervals have been substantially maintained by the WHO classification. Therefore, when accounting for blast percentage using WHO categories, the only other IPSS variable adding prognostic information was cytogenetics. We also found that transfusion dependency had a significant effect on survival in multivariable analysis and, hence, can be viewed as an independent indicator of the severity of the disease.

IPSS has been shown to be effective in also predicting the outcome of treatment after diagnosis.[16] However, the effectiveness of any treatment is usually assessed by comparing survival of patients whose IPSS score is calculated at the time of treatment with the expected survival of the corresponding risk group calculated at diagnosis. The fact that IPSS score was not designed to provide prognostic information at any time after diagnosis might introduce a bias.[17] In this study, we developed a dynamic prognostic model for predicting survival and leukemic evolution that can be applied to MDS patients at any time during their clinical course.

PATIENTS AND METHODS

Characteristics of the Patient Cohorts and Clinical Procedures

We retrospectively collected clinical and hematologic data of MDS patients diagnosed at the Department of Hematology, San Matteo Hospital, Pavia, Italy, and data of patients from the Düsseldorf MDS registry, Heinrich-Heine-University Hospital, Düsseldorf, Germany. The studies on MDS performed at these institutions were approved by the local ethics committees; the procedures followed were in accordance with the Helsinki Declaration of 1975, which was revised in 1983 and 2000.

The patients comprised a learning cohort, in whom investigations aimed at defining the variables to be included in the prognostic model, and a validation cohort, in whom we evaluated whether the prognostic value of the scoring system was confirmed. The learning cohort consisted of 426 patients with a diagnosis of de novo MDS made at the San Matteo Hospital between 1992 and 2004. The validation cohort consisted of 739 patients diagnosed with de novo MDS at the Heinrich-Heine-University Hospital between 1982 and 2003. The clinical features of the two cohorts at diagnosis are listed in Table 1.

Two hundred seventy-one patients in the learning cohort and 193 patients in the validation cohort were assessable for repeated measures during follow-up and were used for the time-dependent analysis. The median follow-up time was 27 months (range, 2 to 178 months) in the learning cohort and 30 months (range, 1 to 330 months) in the validation cohort.

The diagnosis before 2002 was made according to the French-American-British criteria[2]; all patients were reclassified according to the WHO classification,[8] as previously reported.[12] Patients with MDS unclassified, patients with chronic myelomonocytic leukemia, and patients with $\geq$ 20% marrow blasts, who were considered as having AML, were excluded from the analysis. Thus, the following categories were considered: refractory anemia (RA), RA with ringed sideroblasts (RARS), refractory cytopenia with multilineage dysplasia (RCMD), RCMD with ringed sideroblasts (RCMD-RS), RA with excess of blasts-1 (RAEB-1), RA with excess of blasts-2 (RAEB-2), and MDS with isolated del(5q) and marrow blasts less than 5%.

Karyotypes were classified using the International System for Cytogenetic Nomenclature Criteria.[18] The IPSS was calculated according to Greenberg et al.[7]

RBC transfusion therapy was administered according to evidence- and consensus-based guidelines.[19,20] Transfusion dependency was defined as having at least one RBC transfusion every 8 weeks over a period of 4 months.

Statistical Analysis

The cumulative probability of survival and risk of progression to leukemia were estimated using the Kaplan-Meier method. Patients undergoing stem-cell transplantation or receiving AML-like chemotherapy were censored at the time of the procedure; therefore, our studied cohorts consist of essentially untreated patients, excluding any potential source of bias as a result of differential treatment. Survival analyses were performed using Cox models

Table 1. Clinical and Hematologic Features of the Italian and German Cohorts of MDS Patients Classified According to the WHO Criteria

WHO Subgroups	Patients		Sex (No. of patients)		HgB (g/dL)		ANC ($\times 10^9$/L)		PLT ($\times 10^9$/L)		Cytogenetic Risk Group (% of patients)			RBC Transfusion (% of patients)	
	No.	%	Male	Female	Median	Range	Median	Range	Median	Range	Good	Intermediate	Poor	No	Yes
Learning cohort: Pavia, Italy															
RA	87	20	45	42	9.8	5.3-15.4	2.45	0.12-8.74	185	22-735	69	17	14	69	31
RARS	43	10	19	24	9.0	6.4-11.2	2.81	0.16-9.74	290	86-769	82	15	3	70	30
RCMD	114	27	74	40	9.7	4.8-15.0	1.46	0.1-4.32	83	7-561	58	27	15	64	36
RCMD-RS	17	4	10	7	9.4	5.0-11.0	2.35	0.1-4.8	101	4-538	67	33	0	59	41
RAEB-1	61	14	44	17	9.2	4-12.5	1.10	0.1-25.52	92	7-561	60	27	13	63	37
RAEB-2	70	17	53	17	9.0	5.4-14	0.93	0.04-26.6	66	9-512	50	13	37	54	46
MDS del(5q)	34	8	17	17	9.0	6-15	1.63	0.18-7.58	174	46-797	100	0	0	71	29
Validation cohort: Düsseldorf, Germany															
RA	51	7	24	27	9.9	4.6-14.6	2.3	0.3-15.7	112	20-840	68	20	12	66	34
RARS	28	4	13	15	10.1	5.6-11.7	3.0	0.5-8.5	307	116-999	86	10	4	75	25
RCMD	213	29	143	70	9.3	5.0-16.9	1.7	0.2-20.2	102	7-999	66	18	16	49	51
RCMD-RS	91	12	46	45	8.9	3.9-13.9	2.7	0.2-12.0	198	15-1,007	54	19	27	40	60
RAEB-1	117	16	71	46	9.0	4.8-14.9	1.3	0.1-9.5	82	7-778	55	17	28	49	51
RAEB-2	160	21	92	68	9.2	4.8-15.0	0.9	0.1-88.0	69	3-630	52	20	28	47	53
MDS del(5q)	79	11	28	51	8.9	3.0-12.2	2.4	0.6-9.3	286	28-1,540	100	0	0	40	60

Abbreviations: MDS, myelodysplastic syndrome; HgB, hemoglobin; ANC, absolute neutrophil count; PLT, platelets; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RAEB-1, refractory anemia with excess of blasts-1; RAEB-2, refractory anemia with excess of blasts-2; MDS del(5q), myelodysplastic syndrome with isolated del(5q) and marrow blasts less than 5%.

with time-dependent covariates to assess the effect of the variables of interest on overall survival (OS) and disease progression.

To decide which parameterization of the covariates (categoric, with indicator variables, *v* continuous, with a single parameter) was preferable, we carried out likelihood ratio tests, all of which were not significant. Therefore, we decided to treat all covariates as continuous variables, for simplicity in the presentation of the results.

Standardized mortality ratios (SMR) were calculated to compare the patients' mortality with the mortality of the general population in Italy. The Italian mortality rates by age, sex, and calendar year were provided by the Italian Institute of Statistics. All analyses were performed using Statistica software 6.0 (Statsoft, Tulsa, OK) and STATA 9 software (STATA Corp, College Station, TX).

RESULTS

Analysis of Disease-Related Prognostic Factors by Cox Regression With Time-Dependent Covariates

We performed univariable and multivariable analyses on the learning cohort by applying Cox regression with WHO category, cytogenetics, and RBC transfusion requirement as time-dependent continuous covariates. These variables had been previously demonstrated to be the main disease-related prognostic factors in MDS patients grouped according to the WHO criteria in a multivariable Cox exploratory analysis including the following fixed covariates: age, sex, blast count, unilinear versus multilinear dysplasia, cytogenetics, absolute neutrophil count, platelets, lactate dehydrogenase, and transfusion dependency. Patients with RA, RARS, and MDS with isolated del(5q) who did not show significant differences in survival were grouped into a single category, as were patients with RCMD and RCMD-RS.[12] Therefore, the following WHO subgroups were analyzed: RA/RARS/5q–, RCMD/RCMD-RS, RAEB-1, and RAEB-2. Cytogenetic abnormalities were scored according to the IPSS criteria.[7] Patients were classified into two categories according to the development of transfusion need during the course of their disease.

In the time-dependent analysis, we included 271 patients from the learning cohort who had repeated measures during their follow-up. To exclude potential selection bias, we compared the repeated-measures cohort and patients evaluated at diagnosis only. There was no statistically significant difference in the characteristics at diagnosis and in OS ($P = .39$). The median frequency of bone marrow examinations was two per year (range, one to five examinations). The percentage of patients who experienced a change in the time-dependent covariates was 55% for WHO category (median time to first change, 19 months; interquartile range, 9 to 40 months), 11% for cytogenetic risk group (median time to first change, 26 months; interquartile range, 13 to 47 months), and 30% for transfusion need (median time to change, 23 months; interquartile range, 11 to 42 months).

In univariable analysis, WHO category, cytogenetic risk, and transfusion dependency significantly affected both OS (hazard ratio [HR] = 2.27; 95% CI, 1.95 to 2.60; HR = 1.92; 95% CI, 1.58 to 2.35; HR = 2.08; 95% CI, 1.50 to 2.85, respectively; $P < .001$) and risk of AML (HR = 4.3; 95% CI, 3.50 to 5.28; HR = 1.93; 95% CI, 1.52 to 2.38; HR = 2.69; 95% CI, 1.87 to 3.87, respectively; $P < .001$). In a multivariable analysis stratified by WHO subgroups, cytogenetics and transfusion requirement significantly affected both OS (HR = 1.48; 95% CI, 1.20 to 1.83; HR = 2.53; 95% CI, 1.71 to 3.75, respectively; $P < .001$) and risk of AML (HR = 1.3; 95% CI, 1.01 to 1.67; $P = .04$; HR = 2.4; 95% CI, 1.49 to 3.88; $P < .001$, respectively).

WHO Classification–Based Prognostic Scoring System

We defined a WHO classification–based prognostic scoring system (WPSS), including WHO subgroups (RA/RARS/5q–, RCMD/RCMD-RS, RAEB-1, and RAEB-2), karyotype abnormalities categorized according to IPSS, and transfusion requirement. We assigned the same weight to each variable based on the similar regression coefficients from the proportional hazards model, as follows: HR = 2.1 (95% CI, 1.8 to 2.5; $P < .0001$), HR = 1.5 (95% CI, 1.2 to 1.8; $P = .0002$), and HR = 1.8 (95% CI, 1.2 to 2.5; $P = .0017$) for WHO category, cytogenetics, and transfusion requirement, respectively (Table 2).

By applying WPSS, patients were classified into the following five risk groups: very low (score = 0), low (score = 1), intermediate (score = 2), high (score = 3 to 4), and very high (score = 5 to 6; Table 3). We then estimated the probability of survival and leukemic evolution in WPSS risk groups at diagnosis. Patients in the five risk groups showed significantly different OS ($P < .0001$), with the median survival time ranging from 103 to 12 months (Fig 1A). WPSS groups also had significantly different risks of AML ($P < .0001$; Fig 1B).

Time-Dependent Analysis of Prognostic Scoring Systems

As a first step, we assessed the prognostic value of IPSS at diagnosis (Figs 2A and 2B). We then evaluated changes in time of IPSS on the 271 patients in the learning cohort who were assessable for repeated measures. A score progression was observed in 37% of patients with a low or intermediate IPSS (the proportion of patients with progressive disease was 57% when including patients with high IPSS and accounting for leukemic evolution). When analyzing OS with a Cox regression analysis with IPSS as a time-dependent covariate, we obtained an HR

Table 2. WHO Classification–Based Prognostic Scoring System for MDS

Variable	0	1	2	3
WHO category	RA, RARS, 5q–	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	—
Transfusion requirement†	No	Regular	—	—

NOTE. Risk groups were as follows: very low (score = 0), low (score = 1), intermediate (score = 2), high (score = 3 to 4), and very high (score = 5 to 6).
Abbreviations: MDS, myelodysplastic syndrome; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; 5q–, myelodysplastic syndrome with isolated del(5q) and marrow blasts less than 5%; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RAEB-1, refractory anemia with excess of blasts-1; RAEB-2, refractory anemia with excess of blasts-2.
*Karyotype was as follows: good: normal, –Y, del(5q), del(20q); poor: complex (≥ three abnormalities), chromosome 7 anomalies; and intermediate: other abnormalities.
†RBC transfusion dependency was defined as having at least one RBC transfusion every 8 weeks over a period of 4 months.

Table 3. Clinical Features at Diagnosis, Survival, and Risk of Leukemia Progression of WPSS Risk Groups in the Italian (Learning) and German (Validation) Cohorts

WPSS Risk Groups	Patients		HgB (g/dL)		ANC (× 10^9/L)		PLT (× 10^9/L)		WHO Subgroup (% of patients)				Cytogenetic Risk Group (% of patients)			RBC Transfusion (% of patients)		Median OS (months)	AML Progression (cumulative probability)	
	No.	%	Median	Range	Median	Range	Median	Range	RA, RARS, MDS del(5q)	RCMD, RCMD-RS	RAEB-1	RAEB-2	Good	Intermediate	Poor	No	Yes		2 Years	5 Years
Learning cohort																				
Very low	99	23	9.5	7.9-15.4	2.86	0.25-9.74	190	21-797	100	0	0	0	100	0	0	100	0	103	0.0	0.06
Low	119	28	9.6	5.2-14.1	1.92	0.18-10.5	140	7-787	45	55	0	0	86	14	0	69	31	72	0.11	0.24
Intermediate	79	19	9.7	4.8-13.4	1.48	0.1-12.61	133	10-973	21	50	29	0	49	38	13	74	26	40	0.28	0.48
High	100	23	9.0	5.4-14	1.10	0.04-25.52	82	10-502	2	28	30	40	42	31	27	54	46	21	0.52	0.63
Very high	29	7	8.6	7.2-14	0.54	0.08-11.0	63	9-512	0	0	5	95	0	5	95	67	33	12	0.79	1.0
Validation cohort																				
Very low	74	10	10.2	9.0-14.6	2.8	0.4-9.3	249	28-999	100	0	0	0	100	0	0	100	0	141	0.03	0.03
Low	162	22	9.8	3.0-16.9	2.1	0.3-20.2	166	10-1,054	42	58	0	0	96	4	0	63	37	66	0.06	0.14
Intermediate	170	23	9.0	4.9-14.9	1.8	0.1-15.2	117	7-999	6	72	22	0	79	19	2	39	61	48	0.21	0.33
High	244	33	9.0	3.6-15.0	1.2	0.1-24.6	91	5-630	1	37	24	38	44	26	30	42	58	26	0.38	0.54
Very high	89	12	8.0	2.7-14.5	0.8	0.1-88.0	64	3-1,007	0	0	24	76	0	23	77	16	84	9	0.80	0.84

Abbreviations: WPSS, WHO classification–based prognostic scoring system; HgB, hemoglobin; ANC, absolute neutrophil count; PLT, platelets; OS, overall survival; AML, acute myeloid leukemia; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; MDS del(5q), myelodysplastic syndrome with isolated del(5q) and marrow blasts less than 5%; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RAEB-1, refractory anemia with excess of blasts-1; RAEB-2, refractory anemia with excess of blasts-2.

of 3.17 (95% CI, 2.56 to 3.93; $P < .001$; Fig 2C); the HR for leukemic progression was 3.79 (95% CI, 3.00 to 4.78; $P < .001$; Fig 2D).

We then tested the prognostic value of WPSS by applying a Cox regression with time-dependent covariates. The time-dependent WPSS significantly predicted OS (HR = 2.58; 95% CI, 2.6 to 3.10; $P < .0001$; Fig 1C) and risk of AML (HR = 3.63; 95% CI, 2.78 to 4.74; $P < .0001$; Fig 1D). Finally, we analyzed the probability of progression to a higher WPSS risk group; patients in the five risk groups had significantly different probabilities of progression (HR = 1.48; 95% CI, 1.33 to 1.66; $P < .0001$).

Demographic Prognostic Factors Within WPSS Risk Groups

Cox regression with time-dependent covariates was applied to assess the effects of age on survival in MDS patients classified into WPSS risk groups. Age had a significant effect on OS in the very low– and low-risk groups ($P = .03$); the older the age was, the worse the prognosis. No effect of sex was observed within WPSS categories.

SMRs at diagnosis were significantly greater than 1 in all WPSS subgroups ($P < .001$). Stratifying patients by age, the life expectancy of patients in the very low WPSS group who were 70 years or older at the time of diagnosis (n = 31) was not significantly shorter than that of the general population (SMR = 1.5; 95% CI, 0.68 to 3.35; $P = .31$). When MDS patients were dynamically classified according to the time-dependent WPSS, the life expectancy of patients in the very low–risk group (n = 84) was not significantly shorter than that of the general population (SMR = 1.8; 95% CI, 0.94 to 3.46; $P = .07$). In patients with low, intermediate, high, and very high risk, SMR was 3.47 (95% CI, 2.38 to 5.07), 4.9 (95% CI, 3.16 to 7.59), 16.18 (95% CI, 12.99 to 20.14), and 30.55 (95% CI, 21.83 to 42.76), respectively ($P < .0001$).

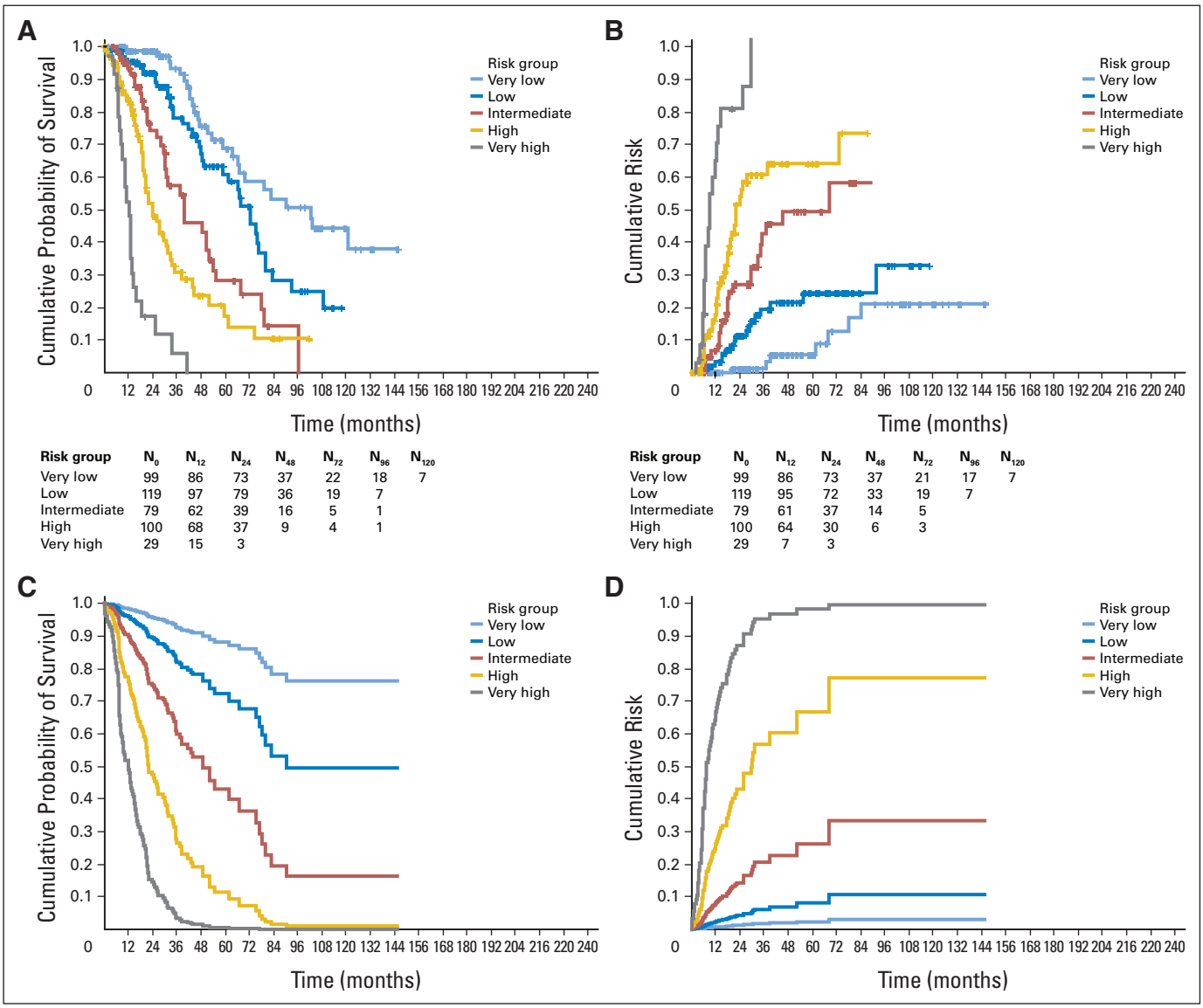
Validation of WPSS

The prognostic value of WPSS was tested in an independent cohort of 739 patients diagnosed at the Heinrich-Heine-University Hospital, Düsseldorf, Germany, between 1982 and 2003 (Table 1). When comparing clinical and hematologic features of the learning and validation cohorts, a significant difference was found in the frequency of WHO categories, with refractory cytopenias being more frequent in the German cohort ($P < .001$).

A significant difference was also noted in the proportion of transfusion-dependent patients at diagnosis ($P < .001$). In fact, different transfusion strategies were adopted. In Pavia, transfusions were administered to patients with severe anemia (hemoglobin [HgB] < 8 g/dL) and to patients with moderate anemia who were symptomatic because of cardiac and pulmonary comorbidities.[19] This strategy resulted in a pretransfusion median HgB level of 7.9 g/dL (range, 4 to 10.2 g/dL); in detail, all patients with HgB of less than 8 g/dL and 25% of patients with HgB of 8 to 10 g/dL received transfusion at diagnosis. In Düsseldorf, the transfusion regimen was tailored to the individual patient's needs.[20] This strategy resulted in a pretransfusion median HgB of 7.7 g/dL (range, 2.7 to 9.8 g/dL). All patients with HgB of less than 8 g/dL and 59% of patients with HgB of 8 to 10 g/dL received transfusion at diagnosis. The difference in proportions of transfused patients between the two cohorts decreased with time; 52% of Italian patients with HgB of 8 to 10 g/dL at diagnosis later on met the criteria for transfusion according to the Italian guidelines.

WPSS was calculated in the validation cohort based on features at diagnosis (Table 3). Patients in the five WPSS categories showed significantly different OS ($P < .0001$), with the median survival time ranging from 141 to 9 months (Fig 3A), and a significantly different risk of AML ($P < .0001$; Fig 3B). No significant differences were observed between the learning and the validation cohorts.

In the Düsseldorf cohort, 193 patients had repeated measures during their follow-up. The median time to first change since diagnosis was 24 months for WHO category (interquartile range, 9 to 51 months), 23 months for cytogenetic group (interquartile range, 10 to 58 months), and 25 months for transfusion need (interquartile range, 10 to 55 months). In a univariable analysis by Cox regression with time-dependent covariates, WHO subgroups, cytogenetics, and transfusion dependency significantly affected both OS (HR = 1.94; 95% CI, 1.59 to 2.36; $P < .001$; HR = 2.01; 95% CI, 1.59 to 2.50; $P < .001$; HR = 1.7; 95% CI, 1.14 to 2.65; $P = .01$, respectively) and risk of AML



Risk group	N_0	N_{12}	N_{24}	N_{48}	N_{72}	N_{96}	N_{120}
Very low	99	86	73	37	22	18	7
Low	119	97	79	36	19	7	
Intermediate	79	62	39	16	5	1	
High	100	68	37	9	4	1	
Very high	29	15	3				

Risk group	N_0	N_{12}	N_{24}	N_{48}	N_{72}	N_{96}	N_{120}
Very low	99	86	73	37	21	17	7
Low	119	95	72	33	19	7	
Intermediate	79	61	37	14	5		
High	100	64	30	6	3		
Very high	29	7	3				

Fig 1. Overall survival and risk of acute leukemia in the Italian cohort classified (A and B) into WHO classification–based prognostic scoring system (WPSS) groups at diagnosis and (C and D) into time-dependent WPSS groups. The number (N) of patients at risk at 0, 12, 24, 48, 72, 96, and 120 months is reported in the keys of panels A and B.

(HR = 3.02; 95% CI, 2.24 to 3.96; $P < .001$; HR = 2.59; 95% CI, 1.92 to 3.48; $P < .001$; HR = 1.74; 95% CI, 1.01 to 3.10; $P = .05$, respectively). In a multivariable analysis stratified by WHO subgroups, cytogenetics and transfusion dependency retained a significant effect on both OS (HR = 1.84; 95% CI, 1.44 to 2.34; $P < .001$; HR = 1.85; 95% CI, 1.18 to 2.89; $P = .007$, respectively) and risk of AML (HR = 2.27; 95% CI, 1.63 to 3.16; $P < .001$; HR = 2.25; 95% CI, 1.24 to 4.09; $P = .007$, respectively).

We then tested the prognostic value of WPSS by applying Cox regression with time-dependent covariates. The time-dependent WPSS significantly affected both OS (HR = 2.24; 95% CI, 1.83 to 2.73; $P < .0001$; Fig 3C) and risk of AML (HR = 3.71; 95% CI, 2.68 to 5.14; $P < .0001$; Fig 3D). Patients in the five risk groups also showed significantly different probabilities of progression to a higher WPSS category (HR = 1.42; 95% CI, 1.19 to 1.69; $P = .0001$). No significant differences were found when the HRs for survival, risk of AML, and risk of progression to a higher risk group were compared in the learning and the validation cohorts.

DISCUSSION

In this study, we identified WHO classification, cytogenetics, and transfusion requirement as the most significant prognostic variables in MDS patients classified according to the WHO criteria. By combining these variables, we developed the WPSS as a dynamic prognostic scoring system for predicting survival and leukemic evolution in MDS patients.

The WHO classification represents the basis of our prognostic model. The implementation of this classification requires skilled morphologists, but despite this, interobserver agreement may be scarce.[21] However, we believe that the WHO classification should be

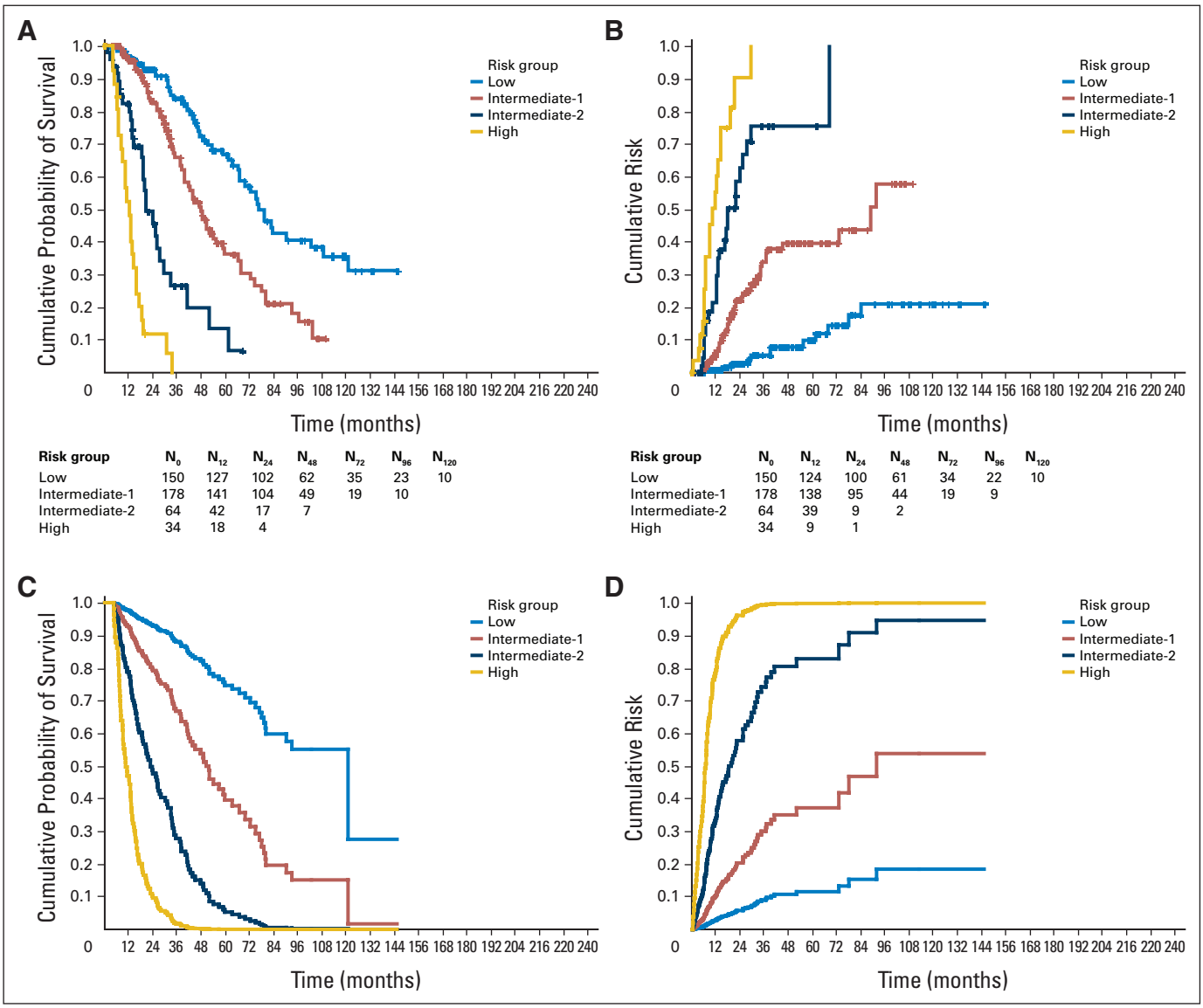


Fig 2. Overall survival and risk of acute leukemia in the Italian cohort classified (A and B) into International Prognostic Scoring System (IPSS) groups at diagnosis and (C and D) into time-dependent IPSS groups. The number (N) of patients at risk at 0, 12, 24, 48, 72, 96, and 120 months is reported in the keys of panels A and B.

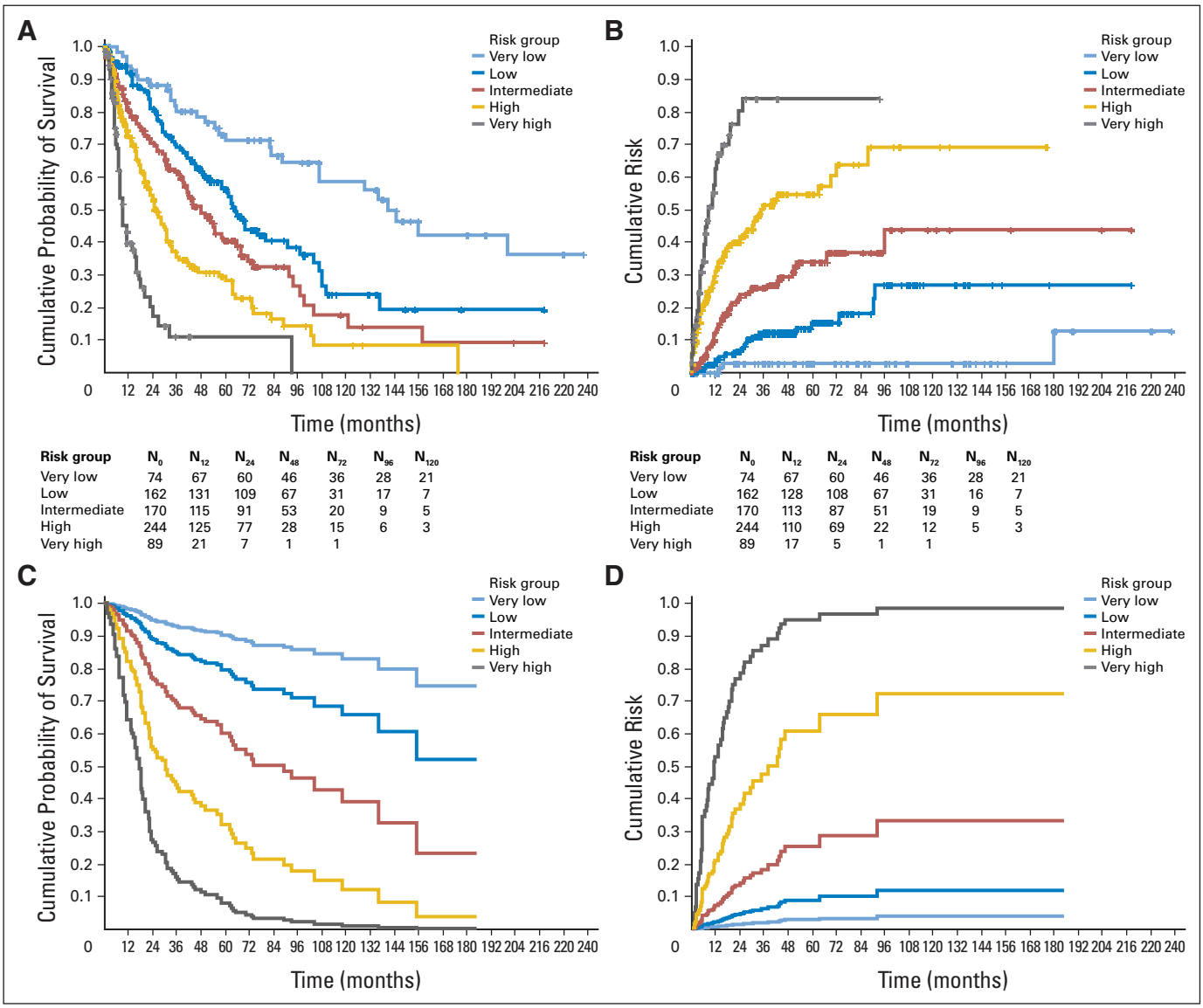
considered as a framework to accommodate more reliable parameters in the future, such as flow cytometric immunophenotyping data[22,23] and, hopefully, molecular markers.[24]

Cytogenetic pattern according to IPSS was proven to add prognostic information to the WHO subgroups.[12] Although several attempts have been made to refine the composition of IPSS cytogenetic subgroups,[25,26] the original one still remains a widely accepted and validated reference.[7]

Transfusion dependency was shown to be an independent prognostic factor in MDS patients[1,12] and can be considered as a reliable indicator of the severity of the disease, partly reflecting the presence of comorbidities.[27] Although different transfusion strategies were adopted in the two participating institutions, both strategies eventually converged towards the identification of similar patient populations.

As compared with the four groups defined by the IPSS, WPSS was able to identify five risk groups of MDS patients with different survival and risk of AML. The most relevant improvement in prognostic ability was observed among MDS without excess blasts and was mainly a result of the strong impact of lineage involvement and transfusion dependency. WPSS was also able to identify a group of patients with an extremely poor outcome, despite the lower marrow blast cutoff introduced by the WHO to define AML.[8]

A crucial point in clinical decision making, particularly in indolent conditions such as low-risk MDS, is the ability to assess the effectiveness of treatments administered at any time after diagnosis. To this purpose, we developed and validated a time-dependent scoring system that can be used at any time after diagnosis. According to this dynamic model, a patient is classified into a risk group at diagnosis and stays in the same group as long as the score remains unchanged. If the patient experiences progression, he/she will change risk category according to the resulting score and will be subsequently followed up in the new risk group. The survival curves resulting from such a model are unquestionably different from traditional survival curves.



Risk group	N_0	N_{12}	N_{24}	N_{48}	N_{72}	N_{96}	N_{120}
Very low	74	67	60	46	36	28	21
Low	162	131	109	67	31	17	7
Intermediate	170	115	91	53	20	9	5
High	244	125	77	28	15	6	3
Very high	89	21	7	1	1		

Risk group	N_0	N_{12}	N_{24}	N_{48}	N_{72}	N_{96}	N_{120}
Very low	74	67	60	46	36	28	21
Low	162	128	108	67	31	16	7
Intermediate	170	113	87	51	19	9	5
High	244	110	69	22	12	5	3
Very high	89	17	5	1	1		

Fig 3. Overall survival and risk of acute leukemia in the German cohort classified (A and B) into WHO classification–based prognostic scoring system (WPSS) groups at diagnosis and (C and D) into time-dependent WPSS groups. The number (N) of patients at risk at 0, 12, 24, 48, 72, 96, and 120 months is reported in the keys of panels A and B.

Non–time-dependent curves give an estimate of survival and risk of AML based on data at diagnosis, irrespective of any further evolution of the disease. In contrast, time-dependent survival curves provide a risk estimate based on the actual clinical features.

A recent study has shown that aggressive treatment approaches should rarely be recommended to younger MDS patients belonging to the lower risk groups.[28] In addition, a decision analysis demonstrated that life expectancy of patients with low-risk MDS who have HLA-identical siblings was higher when transplantation had been delayed but performed before the development of AML.[17] In this regard, a time-dependent prognostic scoring system is essential to obtain a reliable estimate of the potential benefit of the therapeutic procedure.

We used the dynamic risk groups also to compare the mortality in each WPSS subgroup with that of the general population. Interestingly, the mortality of the very low–risk group was not significantly different from that of the general population. In both the Italian and the German cohorts, approximately 60% of the very low–risk patients did not show any sign of disease progression during follow-up. These patients are likely to benefit from delayed treatment strategies.

It must be acknowledged that there might be a potential source of bias in this retrospective study. In fact, bone marrow and cytogenetic examinations were likely to have been performed according to individual patient's clinical needs, which can vary considerably. However, considering clinical characteristics and outcome, patients included in the time-dependent model did not differ significantly from patients whose data were available at diagnosis only.

In conclusion, we have defined a prognostic scoring system that provides an accurate prediction of survival and of risk of leukemic evolution in MDS patients at any time during the course of the disease. This time-dependent system may be used for implementing risk-adapted treatment strategies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Luca Malcovati, Ulrich Germing, Mario Cazzola
Provision of study materials or patients: Luca Malcovati, Ulrich Germing, Andrea Kuendgen, Matteo G. Della Porta, Rosangela Invernizzi, Aristoteles Giagounidis, Barbara Hildebrandt, Paolo Bernasconi, Sabine Knipp, Corinna Strupp, Mario Lazzarino, Carlo Aul, Mario Cazzola
Collection and assembly of data: Luca Malcovati, Ulrich Germing, Andrea Kuendgen, Matteo G. Della Porta, Cristiana Pascutto, Rosangela Invernizzi, Aristoteles Giagounidis, Mario Cazzola
Data analysis and interpretation: Luca Malcovati, Ulrich Germing, Cristiana Pascutto, Mario Cazzola
Manuscript writing: Luca Malcovati, Cristiana Pascutto, Mario Cazzola
Final approval of manuscript: Luca Malcovati, Ulrich Germing, Andrea Kuendgen, Matteo G. Della Porta, Cristiana Pascutto, Rosangela Invernizzi, Aristoteles Giagounidis, Barbara Hildebrandt, Paolo Bernasconi, Sabine Knipp, Corinna Strupp, Mario Lazzarino, Carlo Aul, Mario Cazzola

REFERENCES

1. Cazzola M, Malcovati L: Myelodysplastic syndromes: Coping with ineffective hematopoiesis. N Engl J Med 352:536-538, 2005
2. Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 51:189-199, 1982
3. Mufti GJ, Stevens JR, Oscier DG, et al: Myelodysplastic syndromes: A scoring system with prognostic significance. Br J Haematol 59:425-433, 1985
4. Sanz GF, Sanz MA, Vallespi T, et al: Two regression models and a scoring system for predicting survival and planning treatment in myelodysplastic syndromes: A multivariate analysis of prognostic factors in 370 patients. Blood 74:395-408, 1989
5. Aul C, Gattermann N, Heyll A, et al: Primary myelodysplastic syndromes: Analysis of prognostic factors in 235 patients and proposals for an improved scoring system. Leukemia 6:52-59, 1992
6. Morel P, Declercq C, Hebbar M, et al: Prognostic factors in myelodysplastic syndromes: Critical analysis of the impact of age and gender and failure to identify a very-low-risk group using standard mortality ratio techniques. Br J Haematol 94:116-119, 1996
7. Greenberg P, Cox C, LeBeau MM, et al: International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 89:2079-2088, 1997
8. Vardiman JW, Harris NL, Brunning RD: The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 100:2292-2302, 2002
9. Germing U, Gattermann N, Strupp C, et al: Validation of the WHO proposals for a new classification of primary myelodysplastic syndromes: A retrospective analysis of 1600 patients. Leuk Res 24:983-992, 2000
10. Nosslinger T, Reisner R, Koller E, et al: Myelodysplastic syndromes, from French-American-British to World Health Organization: Comparison of classifications on 431 unselected patients from a single institution. Blood 98:2935-2941, 2001
11. Howe RB, Porwit-MacDonald A, Wanat R, et al: The WHO classification of MDS does make a difference. Blood 103:3265-3270, 2004
12. Malcovati L, Della Porta M, Pascutto C, et al: Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: A basis for clinical decision-making. J Clin Oncol 23:7594-7603, 2005
13. Matsuda A, Germing U, Jinnai I, et al: Difference in clinical features between Japanese and German patients with refractory anemia in myelodysplastic syndromes. Blood 106:2633-2640, 2005
14. Germing U, Strupp C, Kuendgen A, et al: Prospective validation of the WHO proposals for the classification of myelodysplastic syndromes. Haematologica 91:1596-1604, 2006
15. Malcovati L, Della Porta MG, Cazzola M: Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. Haematologica 91: 1588-1590, 2006
16. Sierra J, Perez WS, Rozman C, et al: Bone marrow transplantation from HLA-identical siblings as treatment for myelodysplasia. Blood 100:1997-2004, 2002
17. Cutler CS, Lee SJ, Greenberg P, et al: A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: Delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood 104:579-585, 2004
18. Standing Committee on Human Cytogenetic Nomenclature: ISCN: An International System for Human Cytogenetic Nomenclature—Report of the Standing Committee on Human Cytogenetic Nomenclature. Birth Defects Orig Artic Ser 21:1-117, 1985
19. Alessandrino EP, Amadori S, Barosi G, et al: Evidence- and consensus-based practice guidelines for the therapy of primary myelodysplastic syndromes: A statement from the Italian Society of Hematology. Haematologica 87:1286-1306, 2002
20. Bowen D, Culligan D, Jowitt S, et al: Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. Br J Haematol 120:187-200, 2003
21. Vardiman JW: Hematopathological concepts and controversies in the diagnosis and classification of myelodysplastic syndromes. Hematology Am Soc Hematol Educ Program 199-204, 2006
22. Malcovati L, Della Porta MG, Lunghi M, et al: Flow cytometry evaluation of erythroid and myeloid dysplasia in patients with myelodysplastic syndrome. Leukemia 19:776-783, 2005
23. Della Porta MG, Malcovati L, Invernizzi R, et al: Flow cytometry evaluation of erythroid dysplasia in patients with myelodysplastic syndrome. Leukemia 20:549-555, 2006
24. Pellagatti A, Cazzola M, Giagounidis AA, et al: Gene expression profiles of CD34+ cells in myelodysplastic syndromes: Involvement of interferon-stimulated genes and correlation to FAB subtype and karyotype. Blood 108:337-345, 2006
25. Pfeilstocker M, Reisner R, Nosslinger T, et al: Cross-validation of prognostic scores in myelodysplastic syndromes on 386 patients from a single institution confirms importance of cytogenetics. Br J Haematol 106:455-463, 1999
26. Sole F, Luno E, Sanzo C, et al: Identification of novel cytogenetic markers with prognostic significance in a series of 968 patients with primary myelodysplastic syndromes. Haematologica 90: 1168-1178, 2005
27. Deschler B, de Witte T, Mertelsmann R, et al: Treatment decision-making for older patients with high-risk myelodysplastic syndrome or acute myeloid leukemia: Problems and approaches. Haematologica 91:1513-1522, 2006
28. Kuendgen A, Strupp C, Aivado M, et al: Myelodysplastic syndromes in patients younger than age 50. J Clin Oncol 24:5358-5365, 2006