

Application of different prognostic scoring systems and comparison of the FAB and WHO classifications in Korean patients with myelodysplastic syndrome

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We retrospectively studied 227 patients with MDS (1) to identify the prognostic factors of survival and acute leukemia evolution in Korean patients with MDS, (2) to apply different prognostic scoring systems to the same group of patients, and (3) to compare the FAB with the WHO classification. Six scoring systems were applied to the patients, and the FAB and WHO classifications were compared. The patients' median age was 57 years. The median survival time was 21 months, and age, dysgranulopoiesis and the IPSS cytogenetic groups were independent prognostic factors for survival. Acute leukemia occurred in 34 patients, and the cumulative incidence was 27.1% at 3 years. Marrow blast percentage was the only independent prognostic factor for acute leukemia evolution. Most scoring systems successfully discriminated risk groups for survival and acute leukemia evolution, but patient distribution into risk groups varied according to the scoring systems. Refractory cytopenia with multilineage dysplasia and RAEB II seemed to have different prognoses from RA or RARS and RAEB I, respectively. In summary, our MDS patients had different disease natures from those of Western countries regarding clinical features, prognostic factors and cytogenetic profiles. Although the WHO classification seems to improve the FAB classification, further studies are warranted to validate the utility of the WHO classification before it is accepted for routine clinical use. Our study has the limitations of retrospective analysis, and our results should be verified in future prospective studies.

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Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by ineffective hematopoiesis and peripheral cytopenias. The natural history of this syndrome ranges from more indolent forms of the disease spanning years, to those with a rapid evolution to acute leukemia. A prognostic classification of MDS is of great importance for a proper risk-based therapeutic choice. In 1982, the French–American–British (FAB) cooperative group proposed a classification system for MDS based on precise qualitative and quantitative morphologic criteria.¹ Despite being useful in clinical practice, it has limitations in evaluating clinical outcome for MDS patients.^{2–4} FAB classification is based on bone marrow and peripheral blood blast counts without considering clinical and biological variables such as cytogenetics and the degree and number of cytopenias. Furthermore, a wide range of marrow blasts (5 to 20%) is used for refractory anemia with excess of blasts (RAEB) and chronic myelomonocytic leukemia (CMML) subtypes. There are also significant differences in survival and leukemic risk among patients belonging to the

same FAB subtype. To resolve these problems, different scoring systems have been developed for predicting outcome in individual patients with MDS.^{4–10} Table 1 shows the most relevant and commonly used scoring systems. Each is based on various prognostic factors such as marrow blast percentage, bone marrow karyotype, cytopenia, age, and serum LDH level.

The World Health Organization (WHO) proposed a revised classification of MDS in 1999.¹¹ Subtypes of refractory anemia (RA) and RA with ringed sideroblasts (RARS) were defined only when the presence of dysplastic features were restricted in erythroid lineage only. CMML and RAEB in transformation (RAEBT) were eliminated from the subtypes of MDS. New subtypes of refractory cytopenia with multilineage dysplasia (RCMD), 5q– syndrome and MDS unclassifiable were added to the classification. Some investigators have suggested further discrimination of RAEB into RAEB I and RAEB II according to marrow blast percentage (5–10% and 11–20%, respectively).^{12,13}

This study was conducted (1) to identify prognostic factors of survival and acute leukemia evolution in a series of Korean patients diagnosed as having MDS in a single institute, (2) to apply different prognostic scoring systems to the same group of patients, and (3) to compare the FAB with WHO classifications.

Materials and methods

Patients

Two hundred and twenty-seven patients who were diagnosed as having MDS at the Asan Medical Center, Seoul, Korea during the period between August 1989 and June 2001 were included in the study. The diagnosis and classification of MDS were based on the FAB proposal.¹ Four patients with secondary MDS were not excluded. We retrospectively reviewed medical records of the patients. We obtained clinical, laboratory and cytogenetic data at diagnosis of MDS, and data of clinical outcomes such as survival and acute leukemia evolution. Acute leukemia evolution was defined by the presence of more than 30% of blasts in the bone marrow or peripheral blood. Cytogenetic analysis of bone marrow samples was performed at diagnosis in 119 patients as followings: Bone marrow cells were collected in heparin tubes and cultured for 24 or 48 h in RPMI1640 medium with 10% fetal bovine serum at 37°C under 5% CO₂. No mitotic stimulants were used. Colcemid (0.01 mg/ml) was added to the cultures for 30 min. Cells were treated with hypotonic KCl (0.075 M) for 20 min at room temperature and fixed with four changes of 3:1 ratio of absolute methanol and glacial acetic acid solution. Chromosomes were identified by Trypsin-Giemsa banding. Whenever possible, we analyzed at least 20 metaphases. The definition and description of clonal abnormalities followed the

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Table 1 Different prognostic scoring systems for patients with MDS

Scoring systems/Ref.	Points					Risk group	Score
	0	0.5	1	1.5	2		
IPSS ⁸							
Marrow blasts (%)	<5	5–10		11–20	21–30	Low	0
Karyotype ^a	Good	INT	Poor			INT-1	0.5–1
Cytopenias ^b	0 or 1	2 or 3				INT-2	1.5–2
Lille ⁷						High	2.5–3.5
Marrow blasts (%)	<5		5–10		11–30	Low	0
Karyotype ^c	Good		Poor			INT	1 or 2
Platelets ($\times 10^3/\mu\text{l}$)	>75		<75			High	3 or 4
Bournemouth ^{4,10}							
Hemoglobin (g/dl)	>10		≤ 10				
Neutrophils ($\times 10^3/\mu\text{l}$)	>2.5–16		≤ 2.5 , >16			Low	0 or 1
Platelets ($\times 10^3/\mu\text{l}$)	>100		<100			INT	2 or 3
Marrow blasts (%)	>5		>5			High	4
Spanish ⁵							
Marrow blasts (%)	<5		5–10		11–30	Low (A)	0 or 1
Platelets ($\times 10^3/\mu\text{l}$)	≥ 100		51–100		≤ 50	INT (B)	2 or 3
Age (years)	≤ 60		>60			High (C)	4 or 5
Goasguen ⁹							
Hemoglobin (g/dl)	>10		≤ 10			Low	0
Platelets ($\times 10^3/\mu\text{l}$)	>100		≤ 100			INT	1 or 2
Marrow blasts (%)	<5		>5			High	3
Düsseldorf ⁶							
Marrow blasts (%)	<5		≥ 5				
Platelets ($\times 10^3/\mu\text{l}$)	>100		≤ 100			Low (A)	0
Hemoglobin (g/dl)	>9		≤ 9			INT (B)	1 or 2
LDH (U/l)	≤ 200		>200			High (C)	3 or 4

INT intermediate.

^aGood, normal, del(5q) only, del(20q) only, xY only; Poor, very complex (>2) abnormalities, chromosome 7 abnormalities; intermediate, other abnormalities.

^bHemoglobin level <10 g/dl, platelet count <100 $\times 10^3/\mu\text{l}$, neutrophil count <1.8 $\times 10^3/\mu\text{l}$.

^cGood, normal, single abnormalities; Poor, complex (>2) abnormalities.

recommendations of the International System for Human Cytogenetic Nomenclature (ISCN).¹⁴ The patients were placed into one of three prognostic groups according to the International Prognostic Scoring System (IPSS):⁸ (1) good risk group: -Y, del(5q) or del(20q) as a single aberration or normal karyotype; (2) poor risk group: chromosome 7 abnormalities or complex karyotypes (\geq three aberrations); or (3) intermediate risk group: other abnormalities. Cytopenia was also defined by the IPSS as following: a hemoglobin level of less than 10 g/dl, an absolute neutrophil count of less than 1800/ μl , or a platelet count of less than 100 000/ μl .

Prognostic scoring systems

Six scoring systems were applied to our patients to determine scoring systems' discriminative abilities for assessing disease outcomes. The Bournemouth score was calculated by marrow blast percentage, hemoglobin level, platelet count, and absolute neutrophil count;^{4,10} the score of the system proposed by the Spanish group was by age, marrow blast percentage and platelet count;⁵ the Goasguen score was by hemoglobin level, platelet count, and marrow blast percentage;⁹ and the Düsseldorf score was by marrow blast percentage, platelet count, hemoglobin level, and serum LDH level.⁶ The calculation of the IPSS score (calculated by marrow blast percentage, number of cytopenias, and karyotype)⁸ and the Lille score (calculated by marrow blast percentage, karyotype, and platelet count)⁷ required the results of cytogenetic analysis at diagnosis.

The WHO classification

All patients were reclassified according to the WHO proposals. RAEBT with bone marrow blasts more than 20% and CMML were eliminated for the WHO classification. RA or RARS with multilineage dysplasia belonged to the subtype of refractory cytopenia with multilineage dysplasia (RCMD). Multilineage dysplasia was defined as the presence of dysplastic features in two or more cell lines. RA (with or without ringed sideroblasts) was defined as a disorder involving the erythroid line only. RAEB was divided into RAEBI and RAEBII according to marrow blast percentage (5–10% and 11–20%, respectively). Cases that showed one of the following AML type cytogenetic abnormalities such as t(8;21), inv(16), or t(15;17) were excluded for the WHO classification. 5q- syndrome was defined as dysplastic features in the erythroid lineage only, an isolated interstitial deletion of the long arm of chromosome 5, and bone marrow blasts less than 5%.

Statistical analysis

Categorical variables were analyzed using the chi-square test. The actuarial probability of survival and cumulative risk of acute leukemia evolution were computed according to the Kaplan-Meier method, and differences were compared by the log-rank test. Patient survival was measured as the interval between diagnosis and death due to any cause. Time to acute leukemia evolution was measured from diagnosis to the occurrence of acute leukemia. Prognostic variables with

$P < 0.1$ by univariate analysis were entered into a Cox proportional hazards model, which was used to determine the effects of prognostic variables on survival and acute leukemia evolution. Differences were considered significant when the P value was < 0.05 .

Results

Patient characteristics

A total of 227 patients, 143 males (63%) and 84 females (37%), were analyzed in the study. The median age of the patients was 57 years (range, 15 to 86 years). Thirty-eight patients (16.7%) received various regimens of chemotherapy: low-dose cytarabine in 13 and combination chemotherapy in 25. Allogeneic bone marrow transplantation (BMT) was performed in 10 patients (4.4%). According to the FAB classification, 82 patients (36%) had RA, 19 (8%) RARS, 90 (40%) RAEB, 27 (12%) RAEBT, and nine (4%) CMML. Among the 119 patients in whom the results of cytogenetic analyses were available, 52 (44%) showed karyotypic abnormalities at diagnosis. The cytogenetic abnormalities found were trisomy 8 in seven cases (5.9%), del(9) in four (3.4%), t(8;21) in three (2.5%), loss of Y chromosome only in three (2.5%), del(5q) only in two (1.7%), and dup(1) and chromosome 7 abnormalities in two (1.7%) (Table 2). Eighteen patients (15%) had complex abnormalities (\geq three aberrations). Seventy-two patients (60%) were placed in the good risk group defined by the IPSS, 27 (23%) in the intermediate risk group, and 20 (17%) in the poor risk group.

Survival

The median follow-up duration of surviving patients was 38.7 months (range, 3.5 to 147.5). Seventy-nine patients (35%) are still alive and median survival of all patients was 21 months. The actuarial probabilities of survival at 3, 5 and 7 years were 37.8%, 28.2% and 27.1%, respectively (Figure 1). Univariate analysis of the prognostic factors for survival showed that age ≥ 60 years, serum albumin < 3.3 g/dl, marrow cellularity $\geq 60\%$, higher percentage of marrow blasts, presence of marrow fibrosis, presence of dysgranulopoietic or dysmegakaryopoietic features, and abnormal karyotypes of poor risk group

Table 2 Results of cytogenetic analysis in 119 patients

Results of cytogenetic analysis	No. of patients (%)
Good risk group ^a	72 (60.5)
Normal karyotype	67 (56.3)
Del(5q) only	2 (1.7)
Loss of Y chromosome only	3 (2.5)
Intermediate risk group ^a	27 (22.7)
Trisomy 8	7 (5.9)
Del(9)	4 (3.4)
t(8;21)	3 (2.5)
Dup(1)	2 (1.7)
Miscellaneous	11 (9.2)
Poor risk group ^a	20 (16.8)
Chromosome 7 abnormalities	2 (1.7)
Complex abnormalities	18 (15.1)

^aEach group is defined according to IPSS.

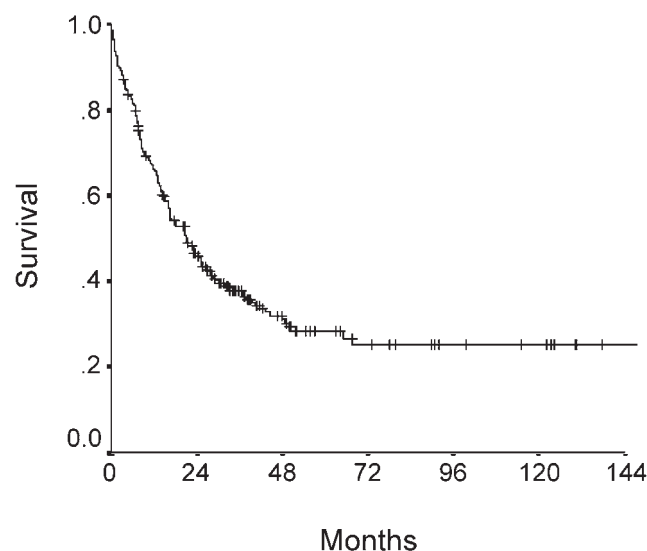


Figure 1 Actuarial probabilities of survival.

were significant adverse prognostic factors for survival (Table 3). Sex and the number or degree of cytopenia defined by the IPSS had marginal significance ($P = 0.080$ and $P = 0.068$, respectively). When significant prognostic factors for survival by univariate analysis were entered into the Cox proportional hazards model, age ($P = 0.001$), dysgranulopoietic features ($P = 0.012$), and IPSS cytogenetic groups ($P < 0.001$ for the high risk group) were independent prognostic factors for survival (Table 4).

Acute leukemia evolution

Acute leukemia occurred in 34 patients (15%); acute myelogenous leukemia in 33 and acute lymphoblastic leukemia in one. The median time to acute leukemia evolution was 6 months (range, 0.7 to 25.8 months). The cumulative incidence of acute leukemia evolution was 16.6% at 1 year, 25.6% at 2 years, and 27.1% at 3 years (Figure 2). Serum LDH level, presence of peripheral blood blasts, bone marrow cellularity, marrow blast percentage, and dysgranulopoietic features were significant risk factors associated with acute leukemia evolution by univariate analysis (Table 3). The number or degree of cytopenia and cytogenetic groups defined by the IPSS were not significant for acute leukemia evolution. Multivariate analysis using a Cox proportional hazards model demonstrated that marrow blast percentage was the only independent prognostic factor for acute leukemia evolution (Table 4). Patients with marrow blasts $> 10\%$ had a significantly higher risk of acute leukemia evolution.

Analysis of prognostic factors excluding patients who received intensive treatments

Of the 227 patients included in the study, 32 patients received combination chemotherapy (25 patients) and/or bone marrow transplantation (10 patients). Because these treatments might influence the results of prognostic analysis, we also analyzed the prognostic factors excluding 32 patients who had received intensive treatments. By univariate and multivariate analyses, the prognostic factors for survival and acute leukemia evol-

Table 3 Univariate analysis of prognostic variables for survival and acute leukemia evolution

Variables	No. of patients (%)	5-Y survival (%)	P value	5-Y cumulative incidence of acute leukemia evolution (%)	P value
Sex					
Male	143 (63)	24.0	0.080	24.2	0.259
Female	84 (37)	35.5		31.4	
Age, years					
<60	131 (58)	46.5	<0.001	31.1	0.287
≥60	96 (42)	5.3		19.8	
Albumin, g/dl					
<3.3	54 (24)	17.8	0.011	24.0	0.981
≥3.3	168 (76)	31.0		27.2	
LDH U/l					
≤420	50 (29)	28.0	0.615	14.3	0.025
>420	121 (71)	29.4		37.4	
Hemoglobin (g/dl)					
<10.0	184 (83)	26.5	0.089	26.6	0.820
≥10.0	39 (17)	39.9		24.9	
ANC (μ l)					
<1800	132 (61)	28.9	0.821	25.0	0.517
≥1800	84 (39)	30.7		29.0	
Platelets ($\times 10^3/\mu$ l)					
<100	164 (74)	26.3	0.145	26.2	0.914
≥100	59 (26)	35.4		25.0	
Peripheral blood blasts					
Absent	175 (78)	31.4	0.057	16.1	<0.001
Present	48 (22)	18.4		59.3	
No. of cytopenia					
0 or 1 lineage	41 (19)	45.8	0.068	19.4	0.532
2 or 3 lineages	175 (81)	26.5		58.7	
Marrow cellularity (%)					
<60	102 (48)	38.5	0.015	15.4	0.015
≥60	112 (52)	20.7		36.1	
Marrow blasts (%)					
<5	98 (45)	45.9	<0.001	2.7	<0.001
5–10	56 (26)	22.7		37.8	
11–20	47 (21)	8.8		63.2	
21–30	17 (8)	9.5		37.8	
Marrow fibrosis					
Absent	175 (88)	32.1	0.005	24.3	0.059
Present	23 (12)	9.3		59.4	
Dyserythropoiesis					
Absent	14 (7)	12.8	0.241	29.9	0.126
Present	190 (93)	30.2		25.6	
Dysgranulopoiesis					
Absent	66 (32)	39.4	0.005	12.7	0.010
Present	138 (68)	23.9		33.3	
Dysmegakaryopoiesis					
Absent	77 (38)	37.7	0.018	20.5	0.272
Present	127 (62)	23.4		31.2	
Dyspoietic feature					
1 lineage	51 (40)	37.7	0.015	13.5	0.089
2 or 3 lineages	153 (16)	26.0		31.1	
IPSS cytogenetic groups					
Good risk	72 (60)	30.4	<0.001	20.2	0.664
Intermediate risk	27 (23)	39.3		36.7	
Poor risk	20 (17)	8.0		14.9	

ution in these patients were not different from those in the whole patients (data not shown).

Application of prognostic scoring systems

We applied six different prognostic scoring systems to our patients (Table 5). The Bournemouth, Spanish, and Goasguen scoring systems could be applied to all patients. The IPSS and

the Lille scoring system could be applied to only 115 patients whose karyotypes of bone marrow were examined at diagnosis. The application of the Düsselldorf scoring system was possible in 170 patients in whom serum LDH level was determined at diagnosis. Patient distribution into risk groups varied according to the scoring systems. The proportion of patients who were allocated to the low risk group was 29% in the Spanish system, whereas it was only 2% in the Goasguen and the Düsselldorf systems. The proportion of patients

Table 4 Multivariate analysis of prognostic factors for survival and acute leukemia evolution

Variables	Odd ratio (95% CI)	P value
<i>Multivariate analysis for survival</i>		
Age, years		
<60	1.00	0.001
≥60	3.10 (1.55–6.20)	
Dysgranulopoiesis		
Absent	1.00	0.012
Present	2.25 (1.19–4.23)	
IPSS cytogenetic groups		
Low risk group	1.00	
Intermediate risk group	1.12 (0.52–2.45)	0.770
High risk group	3.98 (1.84–8.57)	<0.001
<i>Multivariate analysis for acute leukemia evolution</i>		
Marrow blast percentage (%)		
<5	1.00	
5–10	4.72 (0.89–25.08)	0.069
11–20	20.60 (4.47–94.95)	<0.001
21–30	7.58 (1.01–56.96)	0.049

groups showed similar curves for both survival and acute leukemia evolution in the Lille system (Figure 3b). The Spanish system was able to meaningfully stratify patients into three distinct groups with significant discriminative power (Figure 3c).

Comparison of the FAB and WHO classifications

For the WHO classification, 36 patients with RAEBT or CMML and two with AML type cytogenetic abnormalities were excluded. Thirteen patients with RA, RARS or RAEB by the FAB classification could not be reclassified because of the loss of bone marrow data. The distribution of the remaining 176 patients according to the WHO classification included 18 patients with RA, four with RARS, 65 with RCMD, 51 with RAEB I, 37 with RAEB II, and one with MDS unclassifiable. There were no cases of 5q- syndrome. Owing to the low number of patients, we put two subtypes of RA and RARS in the WHO classification together and excluded one unclassifiable patient for statistical analysis of survival and acute leukemia evolution.

The FAB and WHO classifications could discriminate risk groups for both survival and acute leukemia evolution with statistical significance (Table 6). Subtypes of the FAB classification could be grouped into low risk (RA/RARS) and high risk groups (CMML/RAEB/RAEBT) (Figure 4a). After reclassification according to the WHO proposals, patients with RCMD tended to have poorer survival than those with RA/RARS (Figure 4b). When RAEB was divided into two subtypes, RAEB I and RAEB II, according to the WHO classification, survival and acute leukemia evolution between the two subtypes tended to be different.

Discussion

The main purpose of our study was to identify prognostic factors of survival and acute leukemia evolution in Korean patients with MDS, which was diagnosed in a single institution over a period of 10 years. MDS is a clonal hematopoietic stem cell disorder characterized by stepwise genetic progression. The molecular events that lead to MDS are heterogenous and racial differences may be present. Disease natures of MDS such as clinical features, prognostic factors and cytogenetic profiles have been reported to be different between patients from Asian and Western countries. One of the major differences is the age of patients. The median ages in the reports from the Asian countries^{15–18} including our study were 55 to 60 years, whereas the large-scale studies from Western countries reported a median age of around 70 years.^{4–10} The survival of our patients is similar to that reported from other Asian studies, but it is somewhat shorter compared to that of Western patients. Although the lower survival rate of our patients might be related to supportive care given to the patients, it might suggest the different nature of disease between Asian and Western patients. There have also been considerable discrepancies regarding prognostic factors for survival and acute leukemia evolution between reports from Asian and Western studies. In several studies from Western countries prognostic factors, marrow blast percentage, cytogenetic pattern, and number and degree of cytopenias were considered the major prognostic factors for survival and acute leukemia evolution.^{5,8} Our results were somewhat different from the Western studies. Multivariate analysis in our study

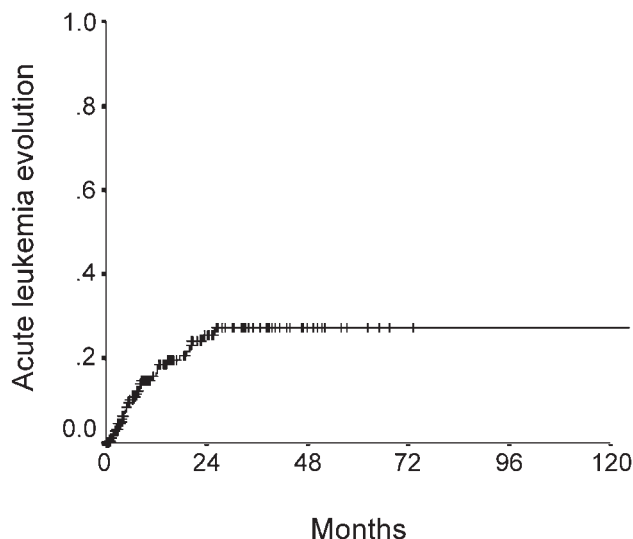


Figure 2 Cumulative risk of acute leukemia evolution.

allocated to the high risk group varied between 12% (IPSS) and 62% (Düsseldorf system).

All the systems successfully discriminated risk groups for survival. The median survival time of patients allocated to the low risk group ranged from 42.5 months to >50.0 months, and that of patients allocated to the high risk group ranged from 11.4 to 16.3 months. The Spanish scoring system ($P < 0.001$) showed the lowest P value for survival. For acute leukemia evolution, each prognostic scoring system separated our patients into different risk groups although the Bourne-mouth scoring system did not have statistical significance. The cumulative incidence of acute leukemia evolution at 5 years ranged from 0% to 10.9% in patients allocated to the low risk group, and from 43.1% to 56.7% in patients allocated to the high risk group.

In the IPSS, the intermediate-1 risk group and the intermediate-2 risk group overlapped the low risk group and the high risk group, respectively, for both survival and acute leukemia evolution (Figure 3a). Similarly, the low and intermediate risk

Table 5 Application of six different prognostic scoring systems to the patients with MDS

Prognostic systems	No. of patients (%)	Median survival (months)	5-Y survival (%)	P value	5-Y cumulative incidence of acute leukemia evolution (%)	P value
IPSS						
Low risk	6 (6)	42.5	40.0	0.010	0.0	0.023
Intermediate-1 risk	60 (52)	37.6	43.2		10.7	
Intermediate-2 risk	35 (30)	13.1	16.0		49.1	
High risk	14 (12)	11.4	26.9		55.6	
Lille						
Low risk	17 (15)	42.5	0.0	0.041	6.7	0.029
Intermediate risk	70 (60)	30.1	42.1		18.2	
High risk	28 (25)	16.1	11.0		56.7	
Bournemouth						
Low risk	18 (9)	48.5	49.6	0.006	6.7	0.224
Intermediate risk	133 (64)	21.0	32.1		24.3	
High risk	58 (28)	16.3	17.3		43.1	
Spanish						
Low risk	62 (29)	48.5	40.8	<0.001	10.9	0.019
Intermediate risk	100 (46)	23.1	36.3		29.7	
High risk	54 (25)	13.2	2.8		44.1	
Goasguen						
Low risk	5 (2)	48.5	50.0	0.004	0.0	0.015
Intermediate risk	132 (61)	28.2	38.1		19.6	
High risk	79 (37)	16.1	13.9		44.2	
Düsseldorf						
Low risk	3 (2)	>50.0	100.0	0.017	0.0	0.013
Intermediate risk	61 (36)	42.5	36.9		12.7	
High risk	106 (62)	15.3	24.1		44.5	

showed that age, the presence of dysgranulopoietic features, and IPSS cytogenetic group were independent risk factors for survival, and marrow blast percentage was the only independent risk factor for acute leukemia evolution. Regarding the presence of dysgranulopoietic features, a Japanese study also found it to be an important prognostic factor for survival.¹⁵ The number and degree of cytopenia (hemoglobin <10 g/dl, ANC <1800/ μ l, platelets <100 \times 10³/ μ l) defined by the IPSS were not major factors for survival or acute leukemia evolution in our patients, and this finding is similar to the results of other reports from Asian countries.^{15,16} In general, variables representing qualitative abnormalities had higher prognostic significance than variables representing quantitative abnormalities in Asian patients with MDS.¹⁵ Although these discrepancies of clinical features and prognostic factors between Asian and Western countries remain to be clarified, genetic disparity and/or environmental factors might be involved. The molecular events leading to MDS may be different among different ethnic groups. Results of cytogenetic studies also showed differences between Asian and Western patients. For example, chromosome 5 abnormalities are common in Western patients, but they are relatively rare in Asian patients.¹⁷ This genetic disparity may explain the different clinical features and prognosis between Asian and Western patients. In addition, environmental factors may also be involved. According to the intensity of exposure to chemical and environmental pollutants, sequential occurrence of mutations, which are probably required for the full development of the MDS phenotype, may be accelerated. The effects of genetic disparity and/or environmental factors on clinical feature or disease course in MDS patients should be elucidated.

The cytogenetic risk group defined by the IPSS was an independent prognostic factor for survival, but not for acute leukemia

evolution in our study. The overall incidence of cytogenetic abnormalities in our study was 44%, a figure similar to other reports.¹⁹⁻²² Although the prognostic importance of cytogenetic findings in patients with MDS has been reported in several studies,^{7,23,24} using cytogenetic abnormalities as a prognostic indicator has some pitfalls. Even in specialized centers, cytogenetic results are not available in almost 30 to 50% of patients, and some of the single chromosomal abnormalities that are classified at present as having an intermediate prognosis may well prove to be of good or poor prognosis when a large number of cases are analyzed.¹⁹ As mentioned above, patterns of cytogenetic abnormalities might also be different according to ethnic groups. To define a more accurate prognostic role of cytogenetic abnormalities in MDS patients, it is necessary to undertake a very large cooperative study and to use more improved techniques of cytogenetic analysis such as fluorescence *in situ* hybridization.

Although there were differences in age distribution and some prognostic factors, the distribution of FAB subtypes in our patients were comparable to those in patients of Western countries. The limitations of the FAB classification, which has been a standard for categorizing MDS patients since 1982, have led to the development of various prognostic scoring systems. To develop a consensual, prognostic, risk-based analysis system, the International MDS Risk Analysis Workshop was convened in 1997. In the Workshop, cytogenetic, morphological and clinical data were combined and collated from a large group of patients with MDS, and the IPSS was proposed.⁸ Although the IPSS and other scoring systems are useful in predicting clinical outcomes of Western patients with MDS, the use of prognostic scoring systems based on Western patients may be misleading in decision-making for patients of Asian countries.^{15,16} In our study, most scoring systems successfully discriminated risk groups for survival and acute leukemia

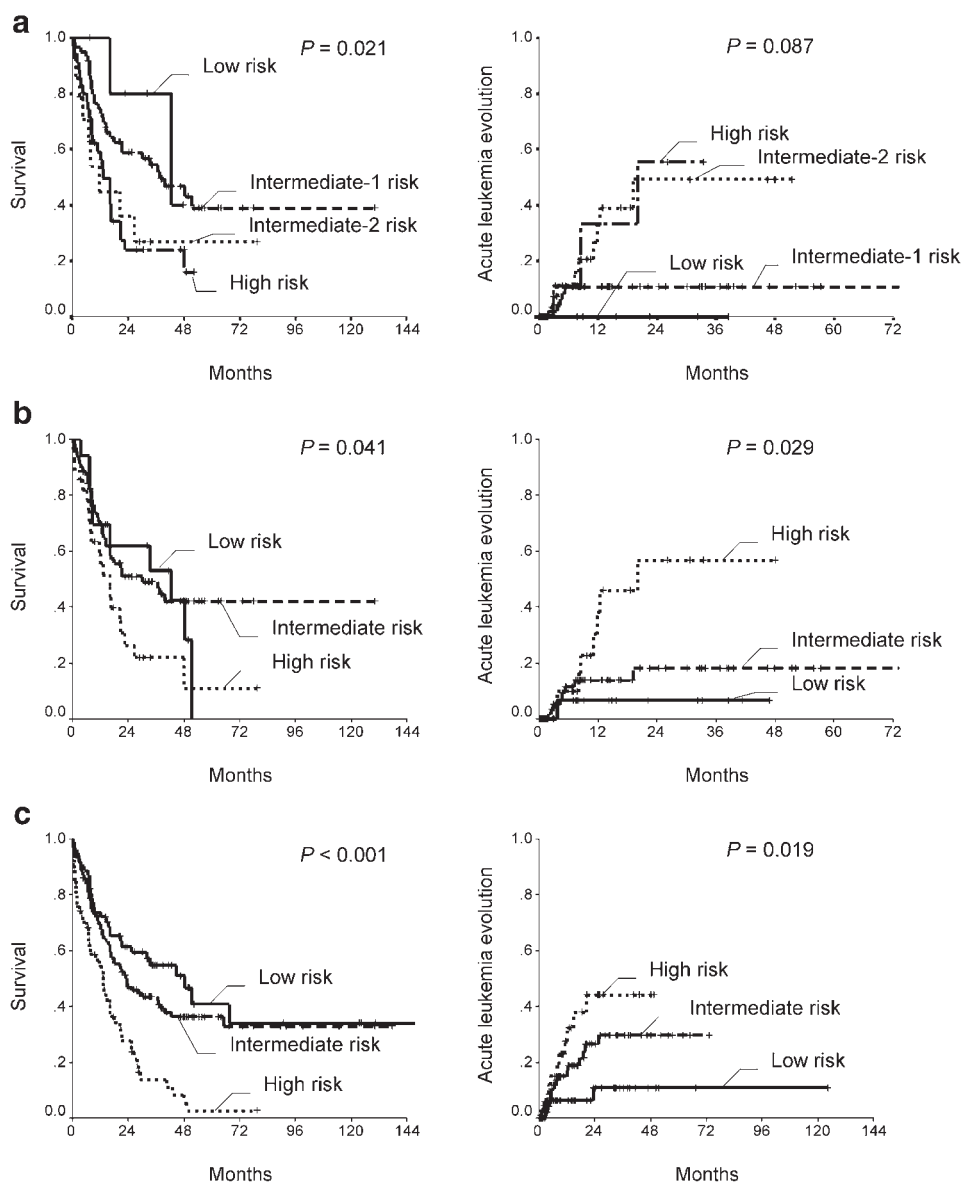


Figure 3 Actuarial probabilities of survival and cumulative risk of acute leukemia evolution according to the IPSS (a), the Lille system (b) and the Spanish system (c).

Table 6 Comparison of the FAB and WHO classifications

Classifications	No. of patients (%)	Median survival (months)	5-Y survival (%)	P value	5-Y cumulative incidence of acute leukemia evolution (%)	P value
FAB classification						
RA	82 (36)	42.5	46.5	<0.001	3.2	<0.001
RARS	19 (8)	33.2	36.5		0.0	
CMMML	9 (4)	8.4	11.1		25.0	
RAEB	90 (40)	16.4	13.6		48.0	
RAEBT	27 (12)	13.8	22.4		50.2	
WHO classifications						
RA/RARS	22 (12)	51.4	46.0	0.002	0.0	<0.001
RCMD	65 (37)	23.2	43.5		4.3	
RAEB I	51 (29)	16.7	18.7		40.2	
RAEB II	37 (21)	16.4	9.0		59.8	
Unclassifiable	1 (1)					

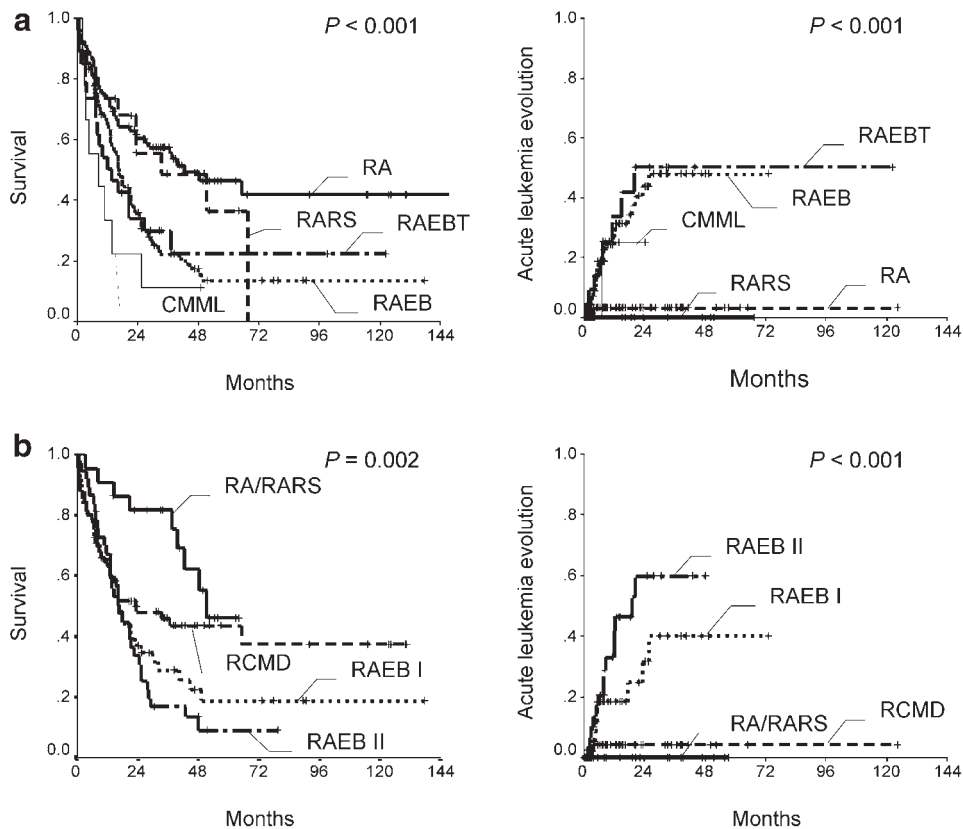


Figure 4 Actuarial probabilities of survival and cumulative risk of acute leukemia evolution according to the FAB classification (a) and the WHO classification (b).

evolution, but the distribution of patients into risk groups varied according to the scoring systems. Most scoring systems are not good enough to identify the small subset of very low risk patients who will rarely require treatment, and could not meaningfully stratify patients into three or four subgroups. The IPSS did not discriminate between the low risk and intermediate 1 risk group, and between the high risk and intermediate 2 group (Figure 3a). The Lille system showed similar findings to the IPSS. The Bournemouth system could not separate our patients into different risk groups for acute leukemia evolution with statistical significance. The Goasguen and Düsseldorf systems categorized only a few patients as low risk. The Spanish system was the most effective in terms of patient distribution into each risk group and discriminative power.

The WHO classification of MDS addresses several issues related to FAB classification.^{11–13} Patients with less than 5% of marrow blasts and multilineage dysplasia are considered a new subtype separated from RA or RARS. In our study, patients of this subtype showed a tendency of lower survival compared with those of the RA or RARS subtypes with erythroid involvement only ($P = 0.087$), without increased risk of acute leukemia evolution. The RAEB subtype in the FAB classification has too broad a range of marrow blast percentage, but several studies showed that a threshold of 10% had prognostic importance.^{5,7,8,24} RAEB remained unchanged at first in the WHO classification,¹¹ but later was divided into two subtypes.^{12,13} Our study also showed that marrow blast percentage was the only independent risk factor for acute leukemia evolution. Our study suggested that survival ($P = 0.435$) and acute leukemia evolution ($P = 0.112$) tended to be differ-

ent between RAEB I and RAEB II, and splitting RAEB by marrow blast percentage seemed to be reasonable. However, our data are not in definite support of the utility of the WHO classification because we could not demonstrate the statistically significant difference in outcome analysis between the WHO subtypes. The exclusion of CMML and RAEBT from MDS also raised some debate. A proportion of patients with CMML were similar to those with MDS in terms of prognosis,^{25,26} and RAEBT showed different prognosis from AML with dysplastic features.²⁵

In conclusion, our MDS patients showed lower age, lower survival rate, different prognostic factors and lower incidence of chromosome 5 abnormalities compared to Western countries. These findings might suggest different disease natures between Asian and Western patients. Although the WHO classification seems to improve the FAB classification, further studies are warranted to validate the utility of the WHO classification before it is accepted for routine clinical use. Our study has the limitations of retrospective analysis, and our results should be verified in the future prospective studies.

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