Clinico-pathological Analysis of Myelodysplastic Syndromes According to French-American-British Classification and International Prognostic Scoring System

LG Lau,[1]*MBBS, MRCP (UK)*, WJ Chng,[1]*MBChB, MRCP (UK)*, TC Liu,[2]*MBBS, MRCP (UK), FRCPath (UK)*, LK Tan,[2]*MBBS, MRCP (UK), MRCPath (UK)*, KH Ong,[1]*MBBS, MRCP (UK)*, BMF Mow,[1]*MBBS, ABIM*, YK Kueh,[3]*MD, FRCP (C)*

Abstract

Introduction: The aim of this study was to analyse the clinico-pathological features of a cohort of patients with myelodysplastic syndromes (MDS). Materials and Methods: The clinical and pathological data of 43 MDS patients over a 3-year period were reviewed. Survival analysis was performed according to the French-American-British (FAB) classification and International Prognostic Scoring System (IPSS) using the Kaplan-Meier method. Selected published studies for comparison were identified from MEDLINE search. Results: The patients were followed up for a median duration of 175 days (range, 2 to 1044 days). The median survival for refractory anaemia (RA) and refractory anaemia with ringed sideroblasts (RARS) has not been reached, but that for refractory anaemia with excess blasts (RAEB), refractory anaemia with excess blasts in transformation (RAEB-T) and chronic myelomonocytic leukaemia (CMML) was 250 days, 49 days and 44 days, respectively. The median survival for the low-risk and intermediate-1 IPSS categories has not been reached, while that for the intermediate-2 and high-risk categories was 58 days and 49 days, respectively. The survival analyses, according to the FAB classification and IPSS system, were statistically significant (P <0.05). Comparison of our data with those from neighbouring and Western countries revealed both similarity and disparity. We also noted different cytogenetic information in our cohort of patients. Conclusions: We found distinctly unique cytogenetic and clinico-pathological characteristics in our MDS patients. However, whether true biological differences exist among MDS patients in different geographies and populations with different genetic and environmental backgrounds require further large multi-national study.

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Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of acquired clonal haemopoietic stem cell disorders characterised by ineffective haematopoiesis and peripheral cytopenia. The natural history ranges from the indolent forms spanning years to those with rapid evolution to blast transformation.[1,2] The management of MDS is hampered by both its heterogeneous nature and variable clinical course. It is, thus, useful to find ways to predict the clinical course using available clinico-pathological data and to apply tailored management strategy to maximise therapeutic benefits.

Over the past 2 decades, several classification and prognostication systems have been published to help predict the clinical outcomes of MDS. The first and most widely used was that defined by the French-American-British (FAB) co-operative group on the basis of cellular morphology and percentages of peripheral and bone marrow (BM) blasts.[3,4] It divides MDS into 5 subgroups: refractory anaemia (RA), refractory anaemia with ringed sideroblasts (RARS), refractory anaemia with excess blasts (RAEB), refractory anaemia with excess blasts in transformation (RAEB-T) and chronic myelomonocytic leukaemia (CMML). This classification was followed by numerous

[1] Department of Haematology-Oncology
[2] Department of Laboratory Medicine
[3] Department of Medicine
National University Hospital, Singapore
Address for Reprints: Dr Lee Gong Lau, Department of Haematology-Oncology, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.
Email: LauLeeGong@nuh.com.sg

scoring systems which used diverse clinico-laboratory parameters such as age, peripheral counts, serum lactate dehydrogenase (LDH) and histopathologic features, in addition to the percentage of BM blasts.[5-8] With increasing recognition of the prognostic significance of cytogenetics,[9,10] subsequent systems included this important variable.[11-13] In 1997, the International MDS Risk Analysis Workshop incorporated 3 prognostic factors — number of cytopenia, percentage of BM blasts and cytogenetics — into the International Prognostic Scoring System (IPSS).[14] It classifies MDS into 4 distinct prognostic groups: low-risk, intermediate-1, intermediate-2 and high-risk. Recently, the World Health Organisation (WHO) classification of myeloid and lymphoid malignancies has further improved on the original FAB classification by incorporating new entities (e.g. del(5q) syndrome) and eliminating (e.g. RAEB-T) and reorganising (e.g. RAEB to RAEB I and RAEB II) some old subgroups.[15] The clinical significance of the WHO classification awaits further studies.[16,17]

Due to difficulties in diagnosis and complex classification, there is a lack of reliable epidemiological and clinico-pathological data on MDS, especially in Asia. These data would be invaluable as they form the basis for clinical management planning. We report the clinico-pathological characteristics of a cohort of Singaporean patients with MDS, accrued over a 3-year period, using the FAB classification and IPSS system.

Materials and Methods

The data of patients >15 years old diagnosed with suspected MDS between January 1999 and December 2001 were analysed. The peripheral blood films (Wright's stain) and BM smears (May-Grunwald-Giemsa and Perl's stains) of each patients were re-evaluated, based on the cytomorphologic and histologic methods described in the FAB classification.[3] Most patients also had BM cytogenetic study done at the time of diagnosis. This was performed using short-term culture in Rosewell Park Memorial Institute (RPMI) media supplemented with fetal calf serum. Harvesting was performed according to standard protocol and chromosome banding was achieved by the trypsin-Giemsa-banding technique. A minimum of 20 metaphase spreads were analysed under oil immersion whenever possible. Karyotypes were designated according to the International System for Human Cytogenetic Nomenclature.[18]

All confirmed cases of MDS were classified according to the FAB system and assigned an IPSS score, based on published criteria.[3,14] The following clinical data were collected on each patient: age, gender, race, baseline blood counts, BM blast percentage, BM cellularity (on trephine biopsy), karyotype, initial presentation, management and eventual outcome. Infections (due to neutropenia), bleeding (due to thrombocytopenia), BM failure and leukaemic transformation were considered as MDS-related causes of death. The status of all patients lost from follow-up was ascertained via telephone on 31 March 2002. The overall survival (OS) and progression free survival (PFS) of the entire cohort and the different FAB subtypes and IPSS categories were assessed using the Kaplan-Meier method and log-rank tests.[19] These were performed using the SPSS software, version 11.0 (SPSS Inc., Chicago, Illinois, USA). A P value of <0.05 was considered statistically significant.

For comparison of data, selected published studies in the English language on the epidemiological pattern, clinico-pathological and cytogenetic characteristics of MDS from other countries were identified from a MEDLINE search.[5,6,14,17,20-24] The salient features were summarised and compared with our study.

Results

Fifty patients with a definite diagnosis of MDS were identified. However, 7 patients were excluded from the study as their case files could not be traced. Of the remaining 43 patients, 8 (18.6%) had drug-induced MDS and the rest de novo or primary MDS. As the mortality of patients with drug-induced MDS was comparable to that of the entire cohort (37.5% vs 44.2%), data for all 43 patients were analysed together. These are summarised in Table 1.

The 43 patients comprised 26 (60%) males and 17 (40%) females. There were 35 (81.3%) Chinese, 5 (11.6%) Malays, 2 (4.7%) Indians (4.7%) and 1 (2.3%) other race; the racial distribution reflects local demographic pattern and demonstrates a lack of racial preponderance. The mean age at presentation was 64 years (range, 15 to 89 years). Fifty-eight per cent of the patients were >60 years and only 9.3% were <40 years old, comparable to <10% reported in the British and Spanish series.[5,6] About half of our patients required blood product support and about one third of them did not require any specific management.

At presentation, the median white blood cell count was 5.61 x 10^9/L (range, 1.12 to 38.11 x 10^9/L), neutrophil count was 2.83 x 10^9/L (range, 0.31 to 17.16 x 10^9/L), haemoglobin was 7.7 g/dL (range, 3.2 to 13.4 g/dL), platelet count was 101 x 10^9/L (range, 14 to 547 x 10^9/L), and BM blast percentage was 0% (range, 0 to 26%). BM trephine biopsy showed 8 (20%) hypocellular, 9 (22.5%) normocellular (22.5%) and 23 (57.5%) hypercellular marrows. The percentage of hypoplastic MDS in our series was comparable with the 17% observed in another series.[25] The majority of patients with RAEB, RAEB-T and CMML had hypercellular marrows, while all hypocellular marrows were of the RA subtype. Two (25%) of the 8 patients with hypoplastic MDS had died as compared to 44.2% for the

whole cohort. Hence, the clinical course of MDS patients in our series with hypoplastic marrow seemed to be similar to that of normocellular and hypercellular MDS, a finding that is compatible with that reported in other series [26].

Cytogenetic study was performed in 40 patients at diagnosis: 21 (52.5%) had normal karyotype, 7 (17.5%) had single chromosome abnormality or translocation, 4 had double chromosome abnormality or translocation and 8 (20%) had complex chromosome abnormality. The Kaplan-Meier analysis did not show any difference (log-rank, P >0.2) in the overall survival among the different subgroups of cytogenetic abnormalities (data not shown). In terms of individual chromosome abnormality, complete or partial loss of chromosome 5 occurred in 6 (15%) patients: 3 with 5q- and 3 with monosomy 5. Interestingly, however, all the chromosome 5 anomalies in our series occurred as complex chromosome abnormality, rather than singly as reported in other series.[14,27,28] Other chromosome abnormalities included trisomy 8 and monosomy Y, which occurred in 4 (10%) patients each. Complete or partial loss of chromosome 7, one of the most common chromosome abnormalities in many other series,[13,14,27-29] occurred only in 3 (7.5%) patients in our series. On the other hand, del(4q), complete or partial loss of chromosome 18, monosomy 17 and monosomy 13, which were rarely reported in MDS,[27-29] also occurred in 3 (7.5%) patients each. There was no correlation between any specific chromosome abnormality and a particular FAB subtype. Table 1 summarises the frequency and percentage of common individual chromosomal abnormality in our cohort. The 40 patients with available cytogenetic data were each accorded with an IPSS score, as shown in Table 2.

The patients were followed up for a median duration of 175 days (range, 2 to 1044 days). There were 19 (44.2%) deaths, 4 (9.3%) transformations and 20 (46.5%) survivors. Of the 19 deaths, 13 (68.4%) were related to the underlying MDS. As expected, patients with more advanced MDS (RAEB and RAEB-T) and those with higher IPSS scores (intermediate-2 and higher) had higher mortality rates (Table 2).

The median OS (and PFS) of our MDS patients has not been reached (Fig. 1). The median OS for patients with RA and RARS was also not reached, but those for patients with RAEB, RAEB-T and CMML were only 250 days, 49 days and 49 days, respectively (Fig. 2). The median OS for patients in the IPSS low-risk and intermediate-1 categories was not reached, while those for the intermediate-2 and high-risk categories were only 58 days and 49 days, respectively (Fig. 3). The median OS according to FAB subtypes and IPSS categories were significantly different (P <0.0001 and P = 0.003, respectively). The Kaplan-Meier analyses for PFS were similar to those for OS (data not shown). Hence, the FAB classification and IPSS system have prognostic importance in our series of patients. Both systems will be helpful in developing risk-adapted therapeutic strategies in future patients with MDS.

Tables 3 and 4 compare our data with those from selected Asian and Western countries. This showed similar

Table 1. Demographics and Clinical and Cytogenetic Data of the MDS Patients

Variable	No. of patients (%)
FAB subtype (n = 43)	
RA	25 (58.1)
RARS	6 (14)
RAEB	7 (16.3)
RAEB-T	3 (7)
CMML	2 (4.7)
Age group (n = 43) (y)	
11-40	4 (9.3)
41-70	21 (48.8)
>70	18 (41.9)
Clinical presentation (n = 43)*	
Symptomatic anaemia	26 (60.5)
Bleeding manifestation	6 (14)
Infection	11 (25.6)
Incidental finding	12 (27.9)
Individual chromosome abnormality (n = 40)	
-5 or del(5q)	6 (15)
+8	4 (10)
-Y	4 (10)
-7 or del(7q)	3 (7.5)
-18 or del(18q)	3 (7.5)
-13	3 (7.5)
-17	3 (7.5)
Del(4q)	3 (7.5)
-16	2 (5)
Translocations [one each of t(1;19), t(3;21), t(7;11), t(8;20) and t(9;22)]	5 (12.5)
IPSS (n = 40)	
Low	10 (25)
Intermediate-1	17 (42.5)
Intermediate-2	10 (25)
High	3 (7.5)
Management (n = 43)†	
No specific management	14 (32.6)
Blood support	19 (44.2)
Haematinics	8 (18.6)
Erythropoietin	12 (27.9)
Steroid	3 (7)
AML-type chemotherapy	2 (4.7)
Thalidomide	2 (4.7)

* Some patients had >1 symptom

† Some patients received >1 treatment

AML: acute myeloid leukaemia; CMML: chronic myelomonocytic leukaemia; FAB: French-American-British; IPSS: International Prognostic Scoring System; MDS: myelodysplastic syndromes; RA: refractory anaemia; RARS: refractory anaemia with ringed sideroblasts; RAEB: refractory anaemia with excess blasts; RAEB-T: refractory anaemia with excess blasts in transformation

Table 2. Mortality in MDS Patients According to FAB Subtypes and IPSS Scores

Variable	No. of patients	No. of deaths (%)
FAB subtype (n = 43)		
RA	25	8 (32)
RARS	6	2 (33.3)
RAEB	7	5 (71.4)
RAEB-T	3	3 (100)
CMML	2	1 (50)
IPSS category (n = 40)		
Low	10	3 (30)
Intermediate-1	17	7 (41.2)
Intermediate-2	10	5 (50)
High	3	3 (100)

CMML: chronic myelomonocytic leukaemia; FAB: French-American-British; IPSS: International Prognostic Scoring System; MDS: myelodysplastic syndromes; RA: refractory anaemia; RARS: refractory anaemia with ringed sideroblasts; RAEB: refractory anaemia with excess blasts; RAEB-T: refractory anaemia with excess blasts in transformation

distribution of MDS in the different published series analysed according to the FAB classification and IPSS system. It also showed that while our lower-risk MDS (either by FAB subtypes or IPSS scores) patients had similar OS compared to other series, higher-risk MDS patients fared much poorer. This was most likely due to the small number of patients in our series and short follow-up (175 days). The short follow-up may also have contributed to the low transformation rate of 9% in our cohort.

Discussion

Histomorphologic complexity, variable classification schemes and evolving treatment strategies all contribute to the difficulty in interpretation and application of published data on MDS. More importantly, data from one country should not be extrapolated and generalised to local MDS patients. This is true when Western data are incorporated into the management of MDS patients in Asian populations. It would be most appropriate to identify the unique features that influence the clinical outcomes of local patients. These can then be taken into consideration in management planning in conjunction with other well-established prognostication systems.

We analysed the clinico-pathological features of MDS patients in our institution using the FAB classification and IPSS system[3,14] against those of selected published series.[5,6,14,17,20-24] We found similar distribution of MDS subgroups as these published series using both the systems. The median age of our patients straddle that from the Western and the Asian series,[5,6,17,20-22] and was very similar to the Argentine series.[24] Like the Western data, the proportion of patients <40 years in our series was <10%. This was in contrast to the other Asian series, which reported proportions ranging from 17% in the Japanese series to 50% in the Turkish series.[20,30] It is also interesting to note that the mean age of MDS patients from Turkey and Central Africa was only 44 and 58 years respectively.[30,31] Thus, in terms of age at presentation, our data were closer to those of the Western countries.

Table 3. Comparison of MDS Features According to FAB Classification in Different Series

Variable	Country							
	Japan[20]	Taiwan[21]	Thailand[22]	UK[5]	Spain[6]	Austria[17]	Argentina[24]	Singapore
No. of patients	838	68	117	141	370	431	234	43
Median age (y)	60	59	56	73	68	73	64	65
<40 years (%)	17	NA	32	7.8	4.0	NA	NA	9.2
Male:Female ratio	1.7:1	1.9:1	1:1	1.05:1	1.3:1	1:1	1.2:1	1.5:1
FAB distribution (%)								
RA	40	16	*	37.6	23	33	46	58.1
RARS	10	10	*	14.9	16	11	9	14.0
RAEB	33.9	32	23.1	17.7	32	21	23	16.3
RAEB-T	10	27	12.8	7.8	10	12	11	7.0
CMML	6.1	16	9.4	22	24	23	11	4.6
Median survival (mo)								
RA	65	38	†	32	24	66	108	NR
RARS	58	NR	†	76	34	73	NR	NR
RAEB	16	30	19.9	10.5	10	15	37	8.3
RAEB-T	10	9	8.7	5	6	9	10	1.6
CMML	20	16	10.7	22	24	24	16	1.5
Transformation rate (%)	NA	29	25	17	16	36	23	9

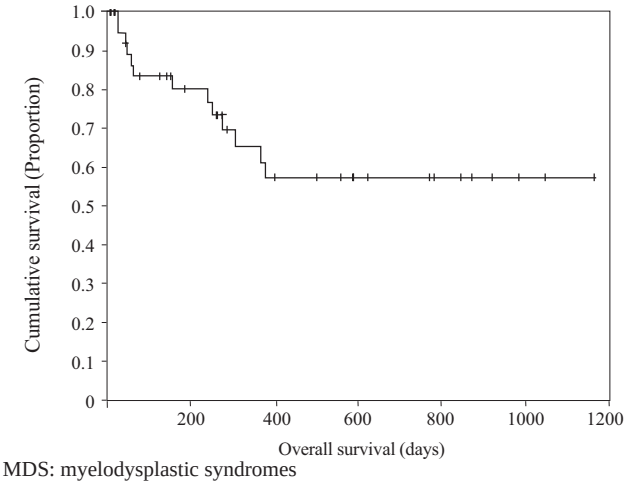
*%RA/RARS, 54.7; †median survival for RA/RARS, 58.4 months

CMML: chronic myelomonocytic leukaemia; FAB: French-American-British; MDS: myelodysplastic syndromes; NA: not available; NR: not reached; RA: refractory anaemia; RARS: refractory anaemia with ringed sideroblasts; RAEB: refractory anaemia with excess blasts; RAEB-T: refractory anaemia with excess blasts in transformation

Table 4. Comparison of the Median Overall Survivals According to IPSS Scores with Other Series

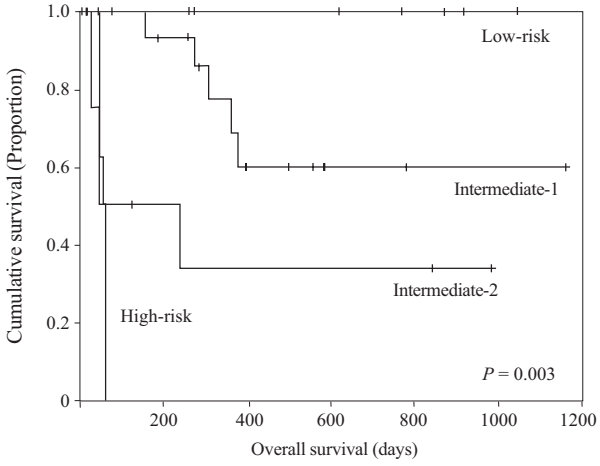
IPSS score	International Workshop[14] (n = 816)		Argentina[24] (n = 234)		MD Anderson[23] (n = 219)		Singapore (n = 43)	
	No. of patients (%)	Median survival (y)	No. of patients (%)	Median survival (y)	No. of patients (%)	Median survival (y)	No. of patients (%)	Median survival (y)
Low	267 (33)	5.7	60 (30)	NR	29 (13)	2.1	10 (25)	NR
Intermediate-1	314 (38)	3.5	76 (38)	3.5	89 (41)	1.2	17 (42.5)	NR
Intermediate-2	176 (22)	1.2	32 (16)	2.75	66 (30)	0.7	10 (25)	0.16
High	59 (7)	0.4	30 (15)	1.17	35 (16)	0.4	3 (7.5)	0.13

IPSS: International Prognostic Scoring System; NR: not reached



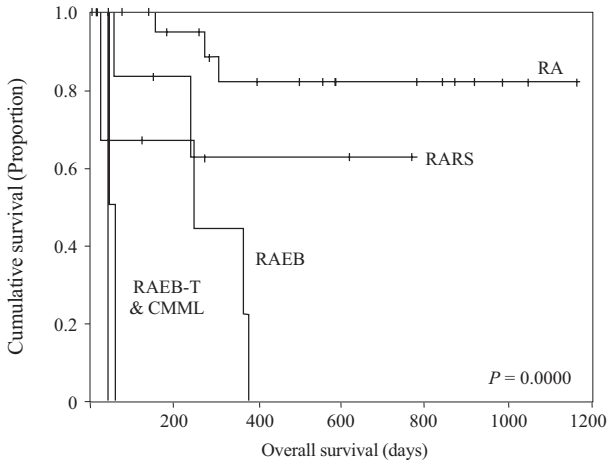
MDS: myelodysplastic syndromes

Fig. 1. Kaplan-Meier overall survival curve of the MDS patients.



IPSS: International Prognostic Scoring System

Fig. 3. Kaplan-Meier overall survival curves for the different IPSS categories.



FAB: French-American-British; RA: refractory anaemia; RARS: refractory anaemia with ringed sideroblasts; RAEB: refractory anaemia with excess blasts; RAEB-T: refractory anaemia with excess blasts in transformation

Fig. 2. Kaplan-Meier overall survival curves for the different FAB subtypes.

In this report, we included 8 patients with possibly drug-induced MDS. We found that the presentations in terms of clinico-laboratory parameters, distribution of FAB subtypes and IPSS scores, clinical courses and mortality rates were comparable to de novo MDS. Others have reported distinctly poorer prognosis for patients with therapy-induced MDS, as they are more likely to have karyotypic abnormalities that are associated with a poor prognosis.[32] The disparity may be due to our smaller sample size and shorter follow-up.

Our study failed to show any significant differences in the overall survivals among the different subgroups of cytogenetic abnormalities while most studies reported worse prognosis among MDS patients with complex chromosome abnormality.[11,14,27-29] Although our sample size is small and follow-up is short, it is still possible that the types of cytogenetic abnormality seen in our cohort may have different prognostic implications. Indeed, a few unique features in terms of the types of chromosome abnormality were noted in the present series. Complete or partial loss of chromosome 5 only occurred in the setting of complex chromosome abnormality rather than as a single recurring anomaly as reported in other series.[14,27-29] It has been known that isolated chromosome 5 anomaly (as in the 5q- syndrome) is associated with long term survival,[33] and that this anomaly occurring in the setting of complex cytogenetic abnormalities loses the favourable prognostic implication.[14]

Whether the presence of chromosome 5 anomaly is able to modulate or modify the clinical course of MDS with complex cytogenetic abnormalities as might have occurred in some of our patients would require further studies. Complete or partial loss of chromosome 7 commonly reported in numerous other series,[11,14,27-29] occurred rarely in our cohort, while rare chromosome abnormalities such as del(4q), loss of chromosome 18, monosomy 17 and monosomy 13, were not uncommon in our series. All these different patterns of cytogenetic abnormalities may have influenced the clinical courses and outcomes of our patients. This can be confirmed or disproved as we accrue more patients in the coming years.

The median OS (and PFS) of our cohort and the lower-risk MDS patients (RA/RARS and low/intermediate-1 risk) had not been reached while those for the higher-risk MDS patients (RAEB/RAEB-T/CMML and intermediate-2/high-risk) were distinctly shorter compared to published series (Tables 3 and 4). Shorter median durations of survival were also reported in the MD Anderson series.[23] Several reasons could have accounted for these disparate results. These included sample size (our small sample size), patient inclusion criteria (we included drug-induced MDS) and treatment modalities. Barring all these potential confounding factors, whether there still exists true biological differences (as suggested by the different cytogenetic data) in MDS as they occur in different countries and different races with different genetic make-ups and environmental influences require confirmation by further multi-centre studies. However, knowing the poorer prognosis of our higher-risk MDS patients, we should, perhaps, in future use more aggressive and experimental therapies.[34,35] The recent good results with 5-azacytidine are particularly encouraging.[35]

The Kaplan-Meier analyses of the median OS and PFS according to the FAB subtypes and IPSS categories were significantly different. Hence, both these systems are able to distinguish prognostically different subgroups of MDS patients in our cohort. This is in broad agreement with that observed in other published series.[14,17,22-24] By assigning patients to different risk-groups, both systems are helpful in developing risk-adapted therapeutic strategies in future patients with MDS.

In conclusion, we detected both similarity as well as disparity when we compared clinico-pathological data of our MDS patients with those from selected Asian and Western countries. Part of the discrepancy may be due to the smaller sample size, shorter follow-up and different selection/inclusion criteria. Nonetheless, distinctly different cytogenetic information was observed in our series. Therefore, true biological differences may exist among MDS in different populations. Further large multi-national study is required to confirm this observation.

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