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Haematological Malignancy – Clinical

Comparison of severe aplastic anaemia and lower risk hypoplastic myelodysplastic neoplasms: Critical role of megakaryocyte count in distinguishing aplastic anaemia from myelodysplastic neoplasms

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Summary
Although genetic abnormalities are increasingly crucial for diagnosing and classifying haematopoietic diseases, dysplasia remains crucial for distinguishing myelodysplastic neoplasms (MDS) from aplastic anaemia (AA). Erythroid dysplasia may be observed in AA, complicating the differentiation between these conditions. In a previous study using the data from the Japan Idiopathic Myelodysplastic Syndrome Study Group's registry, we found that erythroid dysplasia does not affect the prognosis of AA. This current study was designed to compare the prognosis of patients with lower risk hypoplastic MDS (LR-hMDS), as determined by our review, and patients with severe AA (SAA), all enrolled concurrently, to validate our diagnostic approach. Stringent criteria were used to rule out MDS, considering bone marrow cellularity and megakaryocyte counts, with a confirmed AA diagnosis only following a reduced megakaryocyte count. The study comprised 39 severe cases extracted from a cohort of 100 AA patients previously reported and 41 patients with LR-hMDS. Significant differences in overall and leukaemia-free survival were observed between the two groups ($p < 0.0001$). Even among patients undergoing immunosuppressive therapy, a marked prognostic distinction became evident after 5 years, although their response to the therapy did not differ significantly. Therefore, the megakaryocyte count is pivotal in differentiating MDS from AA.

KEYWORDS
aplastic anaemia, hypoplastic MDS, megakaryocyte count, myelodysplastic neoplasms, survival

For affiliations refer to page 1696.

INTRODUCTION

Myelodysplastic neoplasms (MDS) are a heterogeneous group of clonal haematopoietic disorders resulting from abnormalities in bone marrow (BM) stem cells. The presence of genetic mutations, which influence the onset and progression of MDS, leads to diverse clinical manifestations.[1] This prognostic variability necessitates implementing risk-based treatment strategies to achieve optimal outcomes. Despite the recent shift from morphology-based to mutation-based diagnostic approaches,[2] there remain inherent limitations in relying solely on genetic mutations at diagnosis for treatment decisions, as these mutations can undergo dynamic changes during the disease.[3] Currently, the Molecular International Prognostic Scoring System, considered the most promising prognostic model, continues incorporating clinical findings as variables.[4] Furthermore, the widespread adoption of genetic testing in clinical settings encounters challenges, including high costs and complexities in interpretation.[5,6] A similar clinical challenge is the difficulty in the differential diagnosis between MDS and aplastic anaemia (AA), which is an important issue in MDS practice. Because both diseases affect the blood cell-producing system, accurate differentiation is essential for appropriate treatment. This is especially difficult in cases of BM hypoplasia.[7] MDS is characterized by dysplasia, but erythroid dysplasia can occur in patients with AA, as described in the UK guidelines for the diagnosis and management of adult AA.[8] We previously reported that erythroid dysplasia does not affect therapy response or survival in AA, supporting its inclusion in the diagnostic evaluation of AA in our cohort using a central morphological review system.[9] Our central diagnostic system prioritizes megakaryocyte counts in diagnosing AA and MDS.[10] Using a cohort contemporaneous with a prior report that validated erythroid dysplasia in AA, we reaffirmed our differential approach, focusing on megakaryocyte counts in the central diagnosis within a prospective case registry for AA and MDS. To validate our method, we compared the prognoses of patients with severe type AA (SAA) and lower risk hypoplastic MDS (LR-hMDS), both of which are diseases where treatment decisions have a significant impact on outcomes.

MATERIALS AND METHODS

Patients and database

This study utilized data from the Prospective Registration, Central Review, and Follow-up Study for Aplastic Anaemia and Myelodysplastic Syndromes conducted by the Japanese National Research Group on Idiopathic Bone Marrow Failure Syndromes, as described in a previous study.[9] The details of this registry system, including patient eligibility, data collection procedures and central review criteria, have been previously reported.[10] In brief, newly diagnosed patients with AA and MDS defined by the French–American–British classification,[11] as well as cases of cytopenia with unknown aetiology, were registered. Patients aged ≥16 years were enrolled from haematology departments across Japan. The study included patients registered from 26 July 2006 to 29 October 2020. No genetic testing was performed, and chromosomal karyotype data were only available from participating centres. Medical records were collected biannually, and patients found to have inconsistent diagnoses during follow-up could be excluded from the registry, even after central review.

Morphological analysis

Morphological assessments, including the calculation of the blast percentage and the evaluation of dysplastic cells in peripheral blood (PB) and BM using standard light microscopy and traditional glass slides, were conducted as previously described.[9] At least two haematologists independently examined PB and BM films based on the dysplasia evaluation according to the 2001 (third edition) World Health Organization (WHO) classification of Tumours of Haematopoietic and Lymphoid Tissues.[12] The cut-off threshold for dysplasia was set at 10%. In the current study, haematoxylin and eosin staining of clot and biopsy specimens was used to assess BM cellularity, the number of megakaryocytes and diagnoses. Normal BM cellularity was defined as 30%–60%. BM cellularity calculations considered age into account with 100% for newborns, 50% for those up to 30 years old and 30% for those over 70 years old considered normocellular. Values outside these ranges were deemed hyperplastic or hypoplastic, and the near-complete absence of BM cellularity was classified as aplasia.[13] The count of megakaryocytes was conducted using high-power fields (HPF) at objective ×400 magnification. A normal megakaryocyte count was defined as approximately 2/HPF, based on the mean count reported by Singal and Belliveau.[14] Counts below this threshold were deemed decreased. A pathologist evaluated BM cellularity and megakaryocyte counts. Clinical and laboratory data, including cytogenetic findings, were referenced for diagnoses.

In the event of a discrepancy in the morphological evaluation between the two morphologists, the final assessment was determined based on a consensus reached during the biannual joint review meeting described below.

AA criteria

Patients with BM hypoplasia and a low megakaryocyte count in biopsy or clot specimens were defined as AA after excluding non-haematological conditions causing cytopenia. Additionally, those for whom it was impossible to exclude MDS (as outlined in items 1–3 below) were excluded from AA.

1. Patients without a decrease in megakaryocyte count.
2. Patients with ≥10% granulocytic dysplasia and/or ≥10% megakaryocyte dysplasia.

3. Patients with chromosomal abnormalities are categorized as MDS according to the WHO classification.[15]

LR-hMDS criteria

MDS was defined according to the fourth WHO classification.[15] In this study, we defined hypoplastic MDS as LR-hMDS, characterized by either the absence or a very low percentage of blasts in the BM (<5%) and PB (<1%).

Review meeting

At the review meeting, patients with discordance among investigators were discussed. Additionally, for patients with a low megakaryocyte count where BM hypoplasia could not be clearly confirmed, the final diagnosis was determined during this meeting. Furthermore, patients more suggestive of MDS than AA, such as those showing abnormal localization of immature progenitor cells in the BM or those with less than 10% dysplasia but in whom evaluators judged the dysplasia to be evident in multiple haematopoietic lineages, were reviewed.

Comparison of responsiveness to immunosuppressive therapy (IST) between SAA and LR-hMDS

Responsiveness to IST was assessed using data from the Prospective Registration, Central Review and Follow-up Study for AA and MDS. Response criteria to IST were assessed based on the criteria proposed by Camitta.[16] The severity was assessed using the Camitta criteria.[17]

Comparison of overall survival (OS) and leukaemia-free survival (LFS) between SAA and LR-hMDS

OS and LFS were analysed using data from the Prospective Registration, Central Review and Follow-up Study for AA and MDS.

Statistical analysis

The data lock date for this analysis was set at 1 January 2022. Continuous variables underwent comparison using the Mann–Whitney *U*-test, whereas patient characteristics were analysed via Fisher's exact test. OS was delineated as the period from diagnosis to either death, haematopoietic stem cell transplantation or the last follow-up. Likewise, LFS was characterized as the duration until leukaemic transformation, death or the last follow-up. Moreover, OS and LFS estimates were derived using the Kaplan–Meier method, with subsequent comparisons conducted using the log-rank test. Statistical analyses utilized EZR version 1.68,[18] considering p-values less than 0.05 as statistically significant.

RESULTS

SAA and LR-hMDS

In total, 237 patients were included in the study, comprising 100 with AA and 137 with MDS, who were morphologically diagnosed through central review. Of the 100 evaluated patients with AA, 39 had SAA, 60 had non-severe type AA and one patient with AA was not evaluated for severity due to a lack of data. Similarly, among the 137 patients with MDS, 41 had LR-hMDS and 96 had MDS with non-hypoplastic BM and were not categorized as lower risk. Consequently, 39 patients with SAA and 41 patients with LR-hMDS were analysed. Our primary method centred on establishing a central morphological diagnosis using biopsy and film specimens. Where a biopsy was unobtainable, film specimens alone were considered adequate. Only one patient with normoplastic marrow with no chromosomal abnormalities indicative of MDS and an extremely low megakaryocyte count, diagnosed as AA during a review meeting, was included in this study.

Comparison of clinical features at diagnosis between SAA and LR-hMDS

A comparison of the clinical characteristics of SAA and LR-hMDS is summarized in Table 1. No significant differences in sex or BM erythroid-to-myeloid (E/M) ratio were observed between the two groups. In LR-hMDS, there was a significant increase in age, white blood cell count, neutrophil count, platelet count, BM blast ratio, reticulocyte count, lactate dehydrogenase (LDH) and proportion of abnormal karyotypes compared to SAA. Further details of the chromosome karyotypes, as per the accepted international guidelines,[19] in both groups are provided in Table S1. Compared to LR-hMDS, SAA showed a higher proportion of patients with paroxysmal nocturnal haemoglobinuria (PNH) clones, although the number of evaluable cases was limited. Additionally, SAA exhibited a significantly higher proportion of patients with a decreased megakaryocyte count. A weak association was observed in the mean corpuscular volume between the two groups ($p = 0.05$), which was borderline significant.

Comparison of responsiveness to IST between SAA and LR-hMDS

As described, the treatment progress and prognostic data for all patients were confirmed through integration after the morphological diagnosis. Table 2 shows a comparison of

TABLE 1 Comparison of clinical features at diagnosis: SAA versus LR-hMDS.

	Total number (%)	SAA	LR-hMDS	*p*-value
Patients, no.	80 (100%)	39 (49%)	41 (51%)	
Females, no.		17 (44%)	20 (9%)	0.65
Age, years		51 (19–91)	67 (27–86)	0.004
WBC, $\times 10^9$/L		1.80 (0.49–6.14)	2.80 (1.40–6.50)	<0.0001
Neutrophils, $\times 10^9$/L		0.40 (0.04–1.47)	1.41 (0.39–3.62)	<0.0001
Haemoglobin, g/dL		6.8 (2.6–12.6)	9.6 (5.9–14.5)	<0.0001
MCV, fL		100 (75–118)	103 (76–134)	0.05
Platelets, $\times 10^9$/L		12 (0–59)	71 (6–279)	<0.0001
Reticulocytes, $\times 10^9$/L		14.2 (2.7–46.9)	43.5 (18.9–204)	<0.0001[a]
LDH, U/L		177 (126–342)	203 (141–1799)	0.03[b]
BM blasts, %		0.1 (0–1.3)	0.9 (0–4.9)	<0.0001
E/M ratio in BM		0.59 (0–3.20)	0.64 (0.11–5.80)	0.39
Abnormal karyotype, *N*/*N*		5/31 (16%)	23/41 (56%)	0.001[c]
PNH clone[d] positivity, *N*/*N*		21/26 (81%)	6/14 (43%)	0.001[e]
Megakaryocyte count (increased/normal/decreased/none)		0/0/4/34	3/16/15/6	<0.0001[f]

Abbreviations: BM, bone marrow; E/M, erythroid-to-myeloid; fL, femtolitre; L, litre; LDH, lactate dehydrogenase; LR-hMDS, lower risk hypoplastic myelodysplastic neoplasms; MCV, mean corpuscular volume; *N*, number; PNH, paroxysmal nocturnal haemoglobinuria; SAA, severe aplastic anaemia; U/L, units/litre; WBC, white blood cell.

[a]Results were limited to patients, excluding one in SAA and four in LR-hMDS, due to a lack of data.

[b]Results were limited to patients, excluding one in LR-hMDS, due to a lack of data.

[c]Results were limited to patients, excluding eight in SAA, due to a lack of testing or unsuccessful cytogenetics.

[d]Clone size >1%.

[e]Results were limited to patients, excluding 13 in SAA and 27 in LR-hMDS because of missing data due to a lack of testing.

[f]Results were limited to patients, excluding one in SAA and one in LR-hMDS, due to an inability to assess each cell density and megakaryocyte count.

TABLE 2 Comparison of responsiveness to IST within the initial 12 months of therapy initiation in SAA versus LR-hMDS.

	Number of patients[a] received IST (ATG + CsA)	Response to IST treatment		*p*-value	Number of patients[a] received ATG + CsA or CsA alone	Response to IST treatment, including CsA alone		*p*-value
		Yes	No			Yes	No	
SAA								>0.99
Total	13	7 (53.8%) CR 0 PR 7	6 (46.2%)	0.49	28	17 (60.7%) CR 1 PR 16	11 (39.3%)	
Severe[b]	11	6 (54.5%) CR 0 PR 6	5 (45.5%)		22	14 (63.6%) CR 0 PR 14	8 (36.4%)	
Very severe[b]	2	1 (50.0%) CR 0 PR 1	1 (50.0%)		6	3 (50.0%) CR 1 PR 2	3 (50.0%)	
LR-hMDS								
Total	2	2 (100%) CR 0 PR 2	0 (0%)		6	4 (66.7%) CR 1 PR 3	2 (33.3%)	

Abbreviations: ATG, anti-thymocyte globulin; CR, complete response; CsA, ciclosporin A; IST, immunosuppressive therapy; LR-hMDS, lower risk hypoplastic myelodysplastic neoplasms; PR, partial response; SAA, severe aplastic anaemia.

[a]Results excluding two in SAA and one in LR-hMDS where IST was administered, but the treatment response could not be assessed.

[b]According to the criteria proposed by Camitta et al.[17] The response to IST among severe/very severe AA patients was evaluated according to the response criteria described by Camitta.[16]

responsiveness to IST between SAA and LR-hMDS. Treatment response data were available for 28 of the 30 patients with SAA who received IST, including anti-thymocyte globulin (ATG) + ciclosporin A (CsA) in 13 patients and CsA alone in 15 patients. Of the 41 patients with LR-hMDS, only seven received IST, with CsA alone administered to four of the six

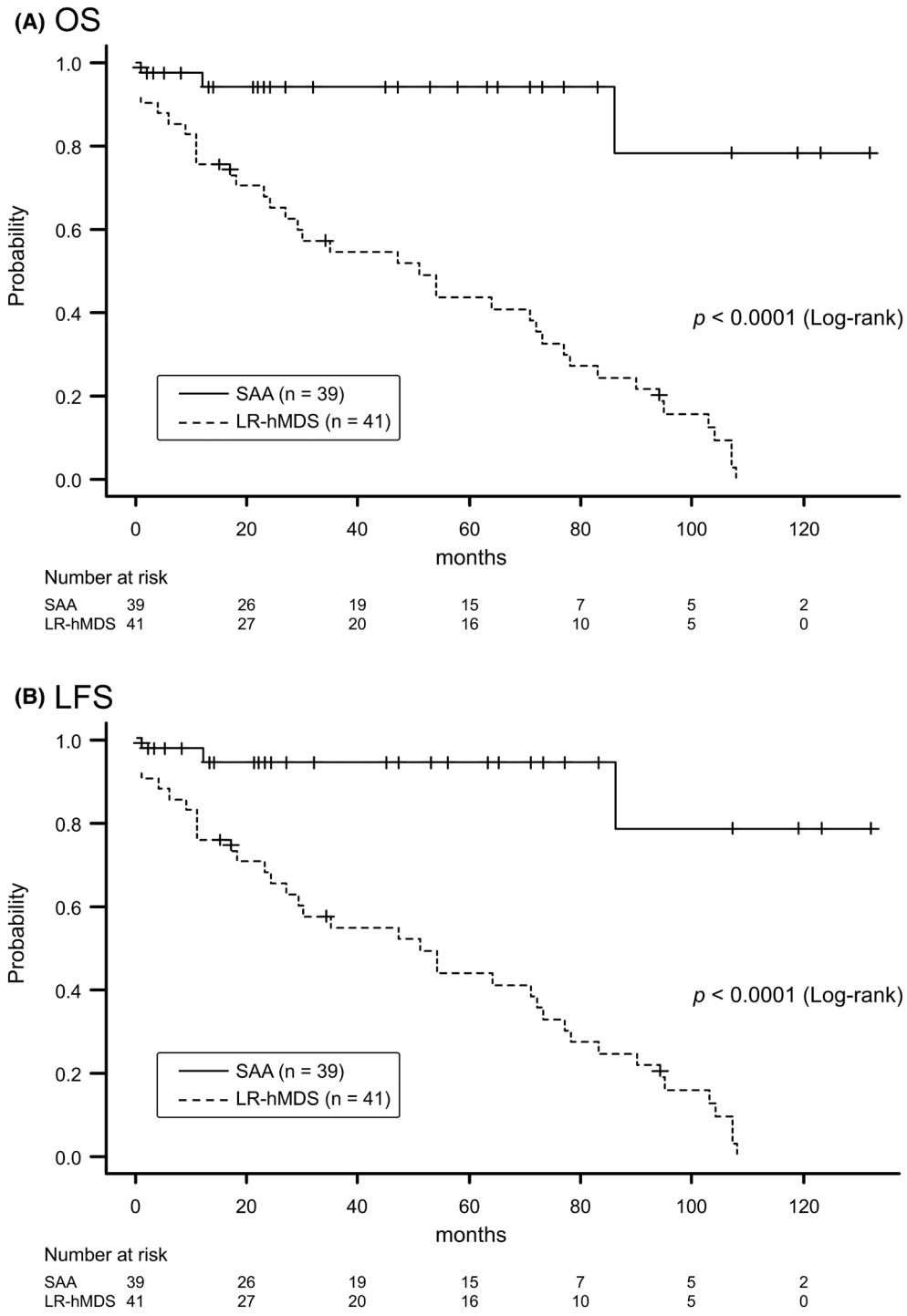

FIGURE 1 Kaplan–Meier survival analysis of OS and LFS: A comparison between SAA and LR-hMDS. (A) OS and (B) LFS in patients with SAA and those with LR-hMDS. A significant difference in OS and LFS was observed between SAA and LR-hMDS (both, $p < 0.0001$). LFS, leukaemia-free survival; LR-hMDS, lower risk hypoplastic myelodysplastic neoplasms; OS, overall survival; SAA, severe aplastic anaemia.

patients in whom analysis was feasible; moreover, only two patients received ATG + CsA. This assessment was completed within 12 months of IST initiation, including CsA alone. No significant difference was noted in treatment responses to IST between SAA and LR-hMDS (complete response [CR] + partial response [PR] rate: 60.7% and 66.7%, $p > 0.99$). Extending the assessment to 18 months revealed no significant differences, as confirmed using Fisher's exact test ($p = 0.64$; Table S3).

Comparative analysis of OS and LFS between SAA and LR-hMDS

Patients with LR-hMDS showed significantly inferior OS and LFS compared to those diagnosed with SAA (both, $p < 0.0001$; Figure 1). Among patients who underwent IST, those with LR-hMDS exhibited a survival rate comparable to or slightly higher than did those with SAA before

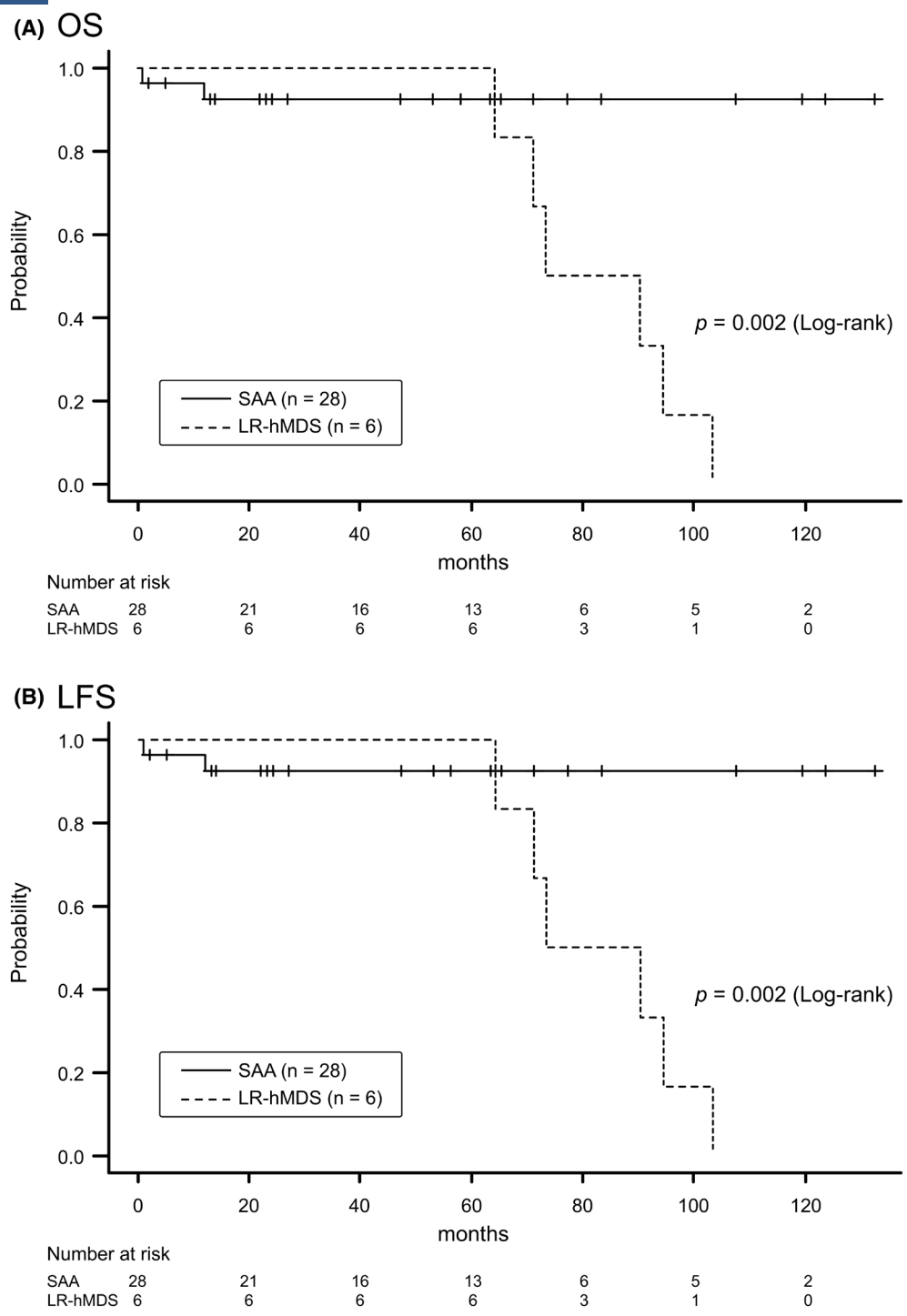

FIGURE 2 Kaplan–Meier survival analysis of OS and LFS in patients treated with IST: A comparison between SAA and LR-hMDS. (A) OS and (B) LFS in patients with SAA and LR-hMDS who received IST. IST included anti-thymocyte globulin combined with CsA and CsA alone, with 28 patients in the SAA group and 6 in the LR-hMDS group. A significant difference in OS and LFS was noted between SAA and LR-hMDS ($p = 0.002$). CsA, ciclosporin A; IST, immunosuppressive therapy; LFS, leukaemia-free survival; LR-hMDS, lower risk hypoplastic myelodysplastic neoplasms; OS, overall survival; SAA, severe aplastic anaemia.

approximately 60 months. However, beyond this time point, the prognosis for LR-hMDS significantly worsened (both, $p = 0.002$; Figure 2). Moreover, similar results were obtained when analysing patients who exhibited a treatment response to IST (both, $p = 0.001$; Figure 3).

DISCUSSION

We had previously confirmed in a central diagnostic system cohort of patients with AA and MDS that erythroid dysplasia does not affect the prognosis of AA. Therefore, it is crucial

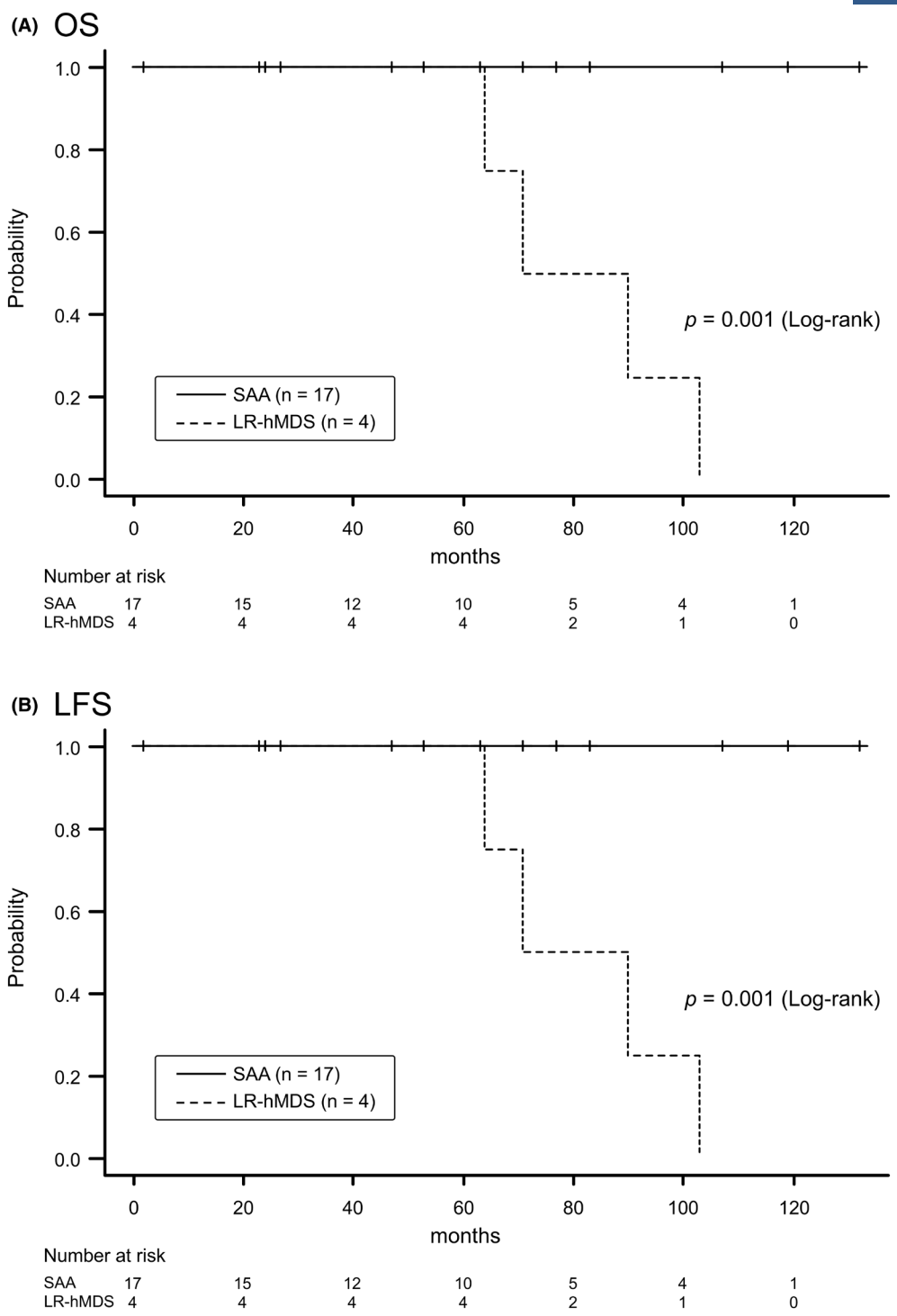

FIGURE 3 Kaplan–Meier survival analysis of OS and LFS in patients responding to IST: A comparison between SAA and LR-hMDS. (A) OS and (B) LFS in patients with SAA and LR-hMDS who responded to IST. IST treatment responses observed up to 12 months were used. The treatment responses include complete responses and partial responses, with details provided in Table 2. A significant difference in OS and LFS was observed between SAA and LR-hMDS ($p = 0.001$). IST, immunosuppressive therapy; LFS, leukaemia-free survival; LR-hMDS, lower risk hypoplastic myelodysplastic neoplasms; OS, overall survival; SAA, severe aplastic anaemia.

to determine whether there is a difference between AA and MDS that cannot be distinguished based solely on erythroid dysplasia. In particular, we must investigate whether differences exist between SAA and LR-hMDS, both being diseases in which treatment decisions significantly impact outcomes, and develop a method to distinguish between them. Comparing the clinical features of AA and MDS further validates our diagnostic approach.

As central reviewers, we were particularly interested in the significantly poorer prognosis for LR-hMDS compared

to that for SAA. The incidence of MDS generally increases with age, and the higher average age of the LR-hMDS patient population compared to that of those with SAA aligns with typical MDS characteristics.[20] Additionally, MDS usually has a poor prognosis. Thus, our findings demonstrate that LR-hMDS has a poorer OS and LFS compared to SAA, which aligns with MDS characteristics. In this study, although there was a significant difference in the proportion of patients with PNH clones between SAA and LR-hMDS, there was no difference in response to IST between the two groups. A recent retrospective study examining prognostic differences between MDS and AA, with and without PNH clones detected by high-sensitivity cytometry, indicated that PNH positivity favourably impacts prognosis following IST in patients with MDS and AA, irrespective of clone size.[21] Therefore, the lack of difference in IST response may be due to the fact that only 14% of patients with LR-hMDS received IST. Although this study was a prospective registry, the institution decided to perform IST, as previously reported.[9] This decision was primarily based on the physician's judgement, especially when distinguishing between MDS and AA was challenging. This may also have led to unusually good IST responsiveness in LR-hMDS, yielding responses akin to those in SAA. As previously noted, IST response and prognosis in AA did not vary in terms of whether erythroid dysplasia was present or not. Thus, in the current study, we extracted the SAA and LR-hMDS groups undergoing IST and compared their prognoses. The long-term outcomes were distinctly different between the groups despite similar treatment responses. These findings confirm that SAA and LR-hMDS are distinct populations, as classified by our diagnostic criteria focusing on megakaryocyte counts. This suggests that megakaryocyte count is an important differentiator for diagnosing AA and MDS. In this study, platelet counts in SAA below 100×10^9/L are understood to derive from the pathological assessment that a low megakaryocyte count is indicative of AA. Nevertheless, current guidelines permit an AA diagnosis even if platelet counts exceed 100×10^9/L, provided neutrophil counts remain below 1.50×10^9/L and haemoglobin levels below 10 g/dL. This poses clinical challenges when administering IST to patients with BM failure who are mistakenly diagnosed with AA, particularly when the underlying pathophysiology is non-immune and intrinsically resistant to IST. We anticipate that our diagnostic method will help address this problem.

The current study has several limitations. First, of the 39 patients diagnosed as SAA, eight did not undergo BM biopsy. Similarly, 15 of the 41 patients diagnosed as LR-hMDS did not receive a biopsy. Consequently, BM cellularity in these patients was assessed using clot specimens, and it cannot be ruled out that some cases classified as normocellular or hypercellular might actually have been hypoplastic. Although LR-hMDS showed a high response to IST, OS was poor. The most common cause of death was infection, accounting for three patients, followed by exacerbation of secondary alveolar proteinosis attributed to MDS after stem cell transplantation, another malignancy, leukaemic transformation and an unknown cause, each accounting for one patient. Among all LR-hMDS cases, four were classified as treatment-related MDS; however, none of these cases were fatal. The reason for the apparent discrepancy between treatment response and poor outcome cannot be fully explained and may be attributed to the limited number of patients who received IST for LR-hMDS, as mentioned before. Alternatively, as indicated by the characteristic curve trends in Figures 2 and 3, the inability to sustain the therapeutic effect in LR-hMDS, compared to SAA, may be a contributing factor. Based on the clinical differences between LR-hMDS and SAA shown in Table 1, as well as the clinical differences limited to patients who received IST (Table S2), a subgroup analysis was performed to assess potential confounding factors, including age, LDH, BM blast percentage, abnormal karyotype and PNH clone positivity (Figure S1). As a result, none of these factors were determined to be significant confounders. Furthermore, the lack of genetic mutation data in this study presents a significant limitation, hindering a comprehensive analysis. Despite these limitations, validating the diagnostic concordance within the same cohort over the same period was considered important. Additionally, it concerns the objectivity of megakaryocyte counts, as the differentiation between the two diseases relied on pathological examination of these counts. Measuring serum thrombopoietin levels may enhance the objectivity of this differentiation method. Our results might support this finding, which was previously reported.[22]

In conclusion, despite the challenges in differentiating AA from MDS, particularly SAA from LR-hMDS, our results support the validity of our differential method. Although we observed no difference in response to IST between SAA and LR-hMDS based on our criteria, a significant prognostic difference in OS and LFS was observed. This highlights the crucial role of megakaryocyte count in distinguishing MDS from AA.

AUTHOR CONTRIBUTIONS

JK, HKawa, TI, MS-U and AT-K organized the registry system and developed the study concept. TM, AK, HKawa, TH, TS, KS, KA, HKaya, KT and AM contributed to the morphological diagnosis of clinical samples as members of the central review. AO contributed to the statistical analyses. KU, NA and MN collected data. SC, SN and YM guided the study design. TM and AM performed data analysis and interpretation and drafted the original manuscript. This study was supervised by KO, SA, MK and KM. All authors critically reviewed and revised the manuscript draft and approved the final version for submission.

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CONFLICT OF INTEREST STATEMENT

TM received research funding from Chugai and Sumitomo and honoraria from Novartis, Nippon Shinyaku, Nippon Becton Dickinson, Pfizer, Otsuka, AbbVie, Amgen, Bristol-Myers Squibb, Janssen, Astellas, CSL Behring, Asahi Kasei and Daiichi Sankyo. AM received consulting fees from Kyowa Kirin, honoraria from Alexion, Nippon Shinyaku, Sumitomo, Novartis and Chugai, and serves on an advisory board for Kyowa Kirin. HKawa received honoraria from Nippon Shinyaku and Bristol-Myers Squibb. KS received honoraria from Astellas, Sysmex, Kyowa Kirin, Ishiyaku Publishers, Maruzen Publishing and Igaku Shoin and held leadership roles in several boards, including chairman of the Committee on Hematological Technology (JCLS), and Hematology subcommittees on Standardization of Blood Cell Morphology (JSLH). TH received grants or contracts from Sysmex. TS received honoraria from Novartis, Kyowa Kirin, Chugai, Nippon Shinyaku, Bristol-Myers Squibb and Sanofi, and is a member of advisory boards for Bristol-Myers Squibb. KU received grants or contracts from Astellas, AbbVie, Bristol-Myers Squibb, Janssen, Ono, Otsuka, Chugai, Aperis, Yakult, MSD, Amgen, Alxion, Incyte, Eisai, Kyowa Kirin, Sanofi, SymBio, Celgene, Daichi Sankyo, Sumitomo, Nippon Shinyaku, Novartis, Mundian and Takeda; consulting fees from Astellas, Amgen, Alnylam Japan, Alexion, Eisai, Otsuka, Kyowa Kirin, Sanofi, Sando, SymBio, Takeda, Chugai and Nippon Shinyaku; and honoraria from Novartis, AbbVie, Alexion, Incyte, Ono, Kyowa Kirin, Sanofi, Takeda, Nippon Shinyaku, Pfizer and Bristol-Myers Squibb. SC received grants or contracts from Eisai, Chugai, Astellas, Thyas, Kyowa Kirin and Bayer. SN received honoraria from Kyowa Kirin. MK received grants or contracts from AbbVie, Kyowa Kirin, Otsuka, Chugai, Nippon Shinyaku, Takeda, Sumitomo Dainippon Pharma, Asahi Kasei, Teijin, Shionogi and Daiichi Sankyo; consulting fees from Mochida, Nippon Shinyaku and Nippon Kayaku; and honoraria from BeiGene, MSD, Sebia Japan, AstraZeneca, AbbVie, Amgen, Alexion, Eisai, Gilead Sciences, Genmab, Novartis, Pharma Essentia, Pfizer, Bristol-Myers Squibb, Janssen, Kyowa Kirin, Sumitomo, Ono, Otsuka, Daiichi Sankyo, Chugai, Nippon Kayaku, Takeda, Asahi Kasei, Astellas, Sanofi and Mochida; and participated on advisory boards for AstraZeneca, Incyte and Daiichi Sankyo. AT-K received grants or contracts from AbbVie, Asahi Kasei, Chugai, DKS Co. Ltd., Eisai, Kyowa Kirin, Nippon Shinyaku, Ono, Otsuka, Pharma Essentia and Shionogi; consulting fees from Megakaryon Co.; and honoraria from AbbVie, AstraZeneca, Bristol-Myers Squibb, Chugai, Gilead Sciences Inc., Janssen, Novartis and Otsuka. KM received grants or contracts from Kyowa Kirin and Chugai; consulting fees from Kyowa Kirin and Bristol-Myers Squibb; honoraria from Kyowa Kirin, Chugai, Novartis, Bristol-Myers Squibb and Sanofi; support for attending meetings and/or travel from Kyowa Kirin; and served on advisory boards for Novartis and Bristol-Myers Squibb. All other authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL STATEMENT

This study was conducted according to the tenets of the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

All patients have signed written informed consent.

CLINICAL TRIAL REGISTRATION

The research protocol received approval from the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (approval no. R1057 and G1268) as well as the Ethics Committee of each participating institution.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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