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Extramedullary Infiltration in Pediatric Acute Myeloid Leukemia on Surveillance Magnetic Resonance Imaging and its Relationship With Established Risk Factors

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Purpose: Extramedullary infiltration (EMI) is a rare condition defined by the accumulation of myeloid tumor cells beyond the bone marrow. The clinical significance is still controversial. This study was aimed to evaluate the incidence, characteristics, and prognostic significance of EMI on complete magnetic resonance imaging (MRI) investigation in newly diagnosed pediatric acute myeloid leukemia (AML) patients who are asymptomatic without clinical evidence to suspect EMI.

Materials and Methods: Retrospective clinical and radiologic review of 121 patients with MRI examination at the time of initial diagnosis of AML without any clinical evidence suggestive of EMI was performed. Patients were divided into 2 groups according to the presence or absence of EMI, and the relationship between EMI and established risk factors was analyzed. Initial white blood cell count, the occurrence of an event (including relapse, death, and primary refractory disease), survival status, and detailed information on cytogenetic/molecular status was performed by a thorough review of electronic medical records system. All patients underwent full imaging evaluation with the contrast-enhanced whole body and some regional MRI at the time of initial diagnosis.

Results: The median age at diagnosis was 10.77 years (range, 0.37 to 18.83 y). Based on the risk stratification system of AML, 36, 45, and 40 patients are classified as low-risk, intermediate-risk, and high-risk groups, respectively. MRI at the time of the initial diagnosis of AML revealed 35 of 121 patients (28.9%) with EMI. The most common site of EMI was a skull, followed by the lower extremity bone and meninges of the brain. The median age at diagnosis was significantly younger in patients with EMI (7.87 vs. 11.08 y, $P = 0.0212$). Low incidence of *FLT3/ITD* mutation, low incidence of *AML-ETO* gene rearrangement, and the larger extent and more severe degree of bone marrow involvement was related with EMI. However, there was no significant prognostic difference in event-free survival and overall survival regardless of the presence of EMI in the overall patient population and each risk group. The location of EMI occurrence was also not related to prognosis.

Conclusions: Even if EMI symptoms are not evident, surveillance MRI scans at the initial diagnosis of pediatric AML patients are very helpful in detecting a significant number of EMIs. Younger age, some molecular features, and more severe bone marrow involvement of AML patients were related with EMI. However, there was no significant prognostic difference between patients with or without EMI regardless of risk group. Further prospective investigation is necessary to validate the prognostic effect of EMI in a larger group of patients with different risk groups.

Key Words: acute myeloid leukemia, extramedullary involvement, magnetic resonance imaging

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Pediatric acute myeloid leukemia (AML) accounts for about 5% of pediatric malignancies[1] and 15% to 25% of pediatric acute leukemia.[2–4] The reported cure rates range from 60% to 70% in the developed countries,[2,3] and the disease causes more than half of the leukemic deaths in children.[4] Although the prognosis of pediatric AML has been improved by risk group classification based on cytogenetics and early treatment response,[2,4] further investigations on risk factors to achieve better clinical outcomes are still ongoing.[1]

One of the potential, influential prognostic factors for investigation is extramedullary infiltration (EMI), the term used interchangeably with myeloid sarcoma, extramedullary myeloid tumor, and granulocytic sarcoma, is an accumulation of myeloid blasts, forming tumor mass with effacement of native tissue architecture at any extramedullary anatomic sites.[5–7] It may develop de novo in isolation or as part of the initial presentation of AML or presented at relapse.[5] The common sites of EMI are bone and periosteum, orbit, lymph nodes, skin and soft tissues, testes, gastrointestinal tract, and peritoneum,[5–10] and the published reports suggest that the specific involved sites have certain prognostic value.[8,9,11,12] It may occur at any age with no sex predilection.[6] The incidence of EMI in adults with AML is reported as 2% to 5%, while it is significantly more frequently found, about 7% to 49% in pediatric AML patients.[3,9–11,13]

The definition in terms of accepted inclusion criteria and prognostic role of EMI is still controversial,[7,10,14,15] and there is even more limited information in the pediatric population.[2] There is a lack of consensus in various studies whether hepatosplenomegaly and lymph node involvement should be considered as EMI,[3,15,16] some arguing that those findings should not be regarded as EMI since they are a manifestation of organ infiltration by myeloblasts rather than discrete mass formation.[16] Some of the reports in the literature demonstrated the presence of EML is related with

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a worse prognosis,[1,8,10,11,17] while others argue that there is no association between EMI and prognosis.[1,15,18]

The diagnosis of EMI is possible based on clinical presentation, radiologic studies, and biopsy and histopathologic examination.[2,5,11] Although pathologic confirmation is the most accurate method of EMI diagnosis, noninvasive imaging examination in clinically suspected patients to have associated EMI is much more often performed, playing an essential role in diagnosis of EMI. However, routine surveillance for EMI is not usually included in the initial workup for newly diagnosed AML, making underestimation of the incidence of EMI inevitable.[8]

In the current study, the incidence and other features of EMI based on radiologic examination as well as its association with of well-known cytogenetic/molecular risk features are investigated in pediatric patients, who are asymptomatic and have no clinical evidence to suspect EMI, with screening magnetic resonance examinations at the initial workup of AML.

MATERIALS AND METHODS

Patients and Data Acquisition

This was a retrospective, observational, descriptive study approved by the institutional review of board. A total of 172 patients between 0 and 18 years old who were diagnosed with AML from December 2009 and October 2018 were included in this study. The patients were classified into 3 risk groups according to cytogenetic and molecular features (Table 1) and treated accordingly. Among the patients, 22 and 14 patients were excluded as cytogenetic and molecular analysis and imaging study was not performed, respectively. Thus, 136 patients remained, of which 15 with symptoms were excluded, and finally, 121 patients were included in the analysis.

Initial white blood cell (WBC) count, the occurrence of an event (including relapse, death, and primary refractory disease), survival status, and detailed information on cytogenetic/molecular status was performed by a thorough review of electronic medical records system. The last follow-up date was December 1, 2020, and the event-free survival (EFS) was defined as the time of diagnosis or remission to the date of the event, and the overall survival (OS) was defined as the time between diagnosis and death or the last follow-up.

Among the 121 patients, all patients underwent full imaging evaluation with contrast-enhanced whole-body magnetic resonance imaging (MRI) at the time of initial diagnosis, except for 3 patients with brain MRI and 1 patient with whole-spine MRI. The presence of EMI was assessed by a board-certified radiologist with 10 years of experience on picture archiving and communication system (PACS), searching for abnormal finding showing hypointensity or isointensity on T1-weighted image isointensity or hyperintensity on T2-weighted image, with contrast enhancement.[9] The presence of hepatosplenomegaly and lymph node enlargement were evaluated by not being included as EMI in this study. In addition, the extent of marrow abnormal signal intensity, manifested as hypointensity on T1-weighted image, hyperintensity on T2-weighted image, with contrast enhancement, was assessed and classified into 4 groups according to the extent of involvement: (1) focal, confined around metaphysis; (2) < 50% of bone marrow; (3) diffuse by confined within the bone marrow; (4) extensive, with periosteal infiltration.

TABLE 1. Risk Stratification Based on Cytogenetic/Molecular Status

Risk Group	Features
Low	inv(16), t(16;16), t(8;21) and *c-kit* mutation (−)
	Normal karyotype with *NPM1* (+) or *CEBPA* (+) and *FLT3/ITD* (−)
Intermediate	Normal karyotype, 11q23 abnormalities except t (6;11) and t(10;11)
	7q−, other noncomplex
	CBF leukemia with *c-kit* mutation (+)
High	−5, 5q−, −7, 3q abnormalities, complex (> 3 abnormalities), t(8;16), t(6;9), t(16;21), t(6;11), t(10;11), *MLL* abnormalities
	FLT3/ITD (+)

Statistical Analysis

The statistical analysis was performed using SPSS, version 21.0 (SPSS Inc., Chicago, IL) and MedCalc, version 19.0.7 (MedCalc Software, Mariakerte, Belgium). The continuous variable was expressed as median ± interquartile range, and the significance of numeric variables in different groups were performed using the Mann-Whitney test. The χ^2 test or Fisher exact test was used for categorical variables. A 2-sided P-value < 0.05 was assumed to indicate statistical significance. The Kaplan-Meier method was used to determine EFS and OS in patient groups with or without EMI, and differences in EFS and OS were compared according to the presence or absence of EMI between risk groups using a 1-side log-rank test.

RESULTS

Overall Patient Characteristics

The median age at diagnosis was 10.77 years (range, 0.37 to 18.83 y). Among the included 121 patients, 78 patients were male, and 43 patients were female. Based on the risk stratification system by Lee et al,[19] 36, 45, and 40 patients are classified as low-risk, intermediate-risk, and high-risk groups, respectively. The median of initial WBC count of patients was 16.82×10^9/L (range, 0.72 to 339.03×10^9/L). At the time of analysis, 95 patients were alive while 26 patients were dead, and 45 patients experienced an event.

A thorough evaluation using the whole body, and some regional, MRI at the time of the initial diagnosis AML was performed and the findings from image analysis are summarized in Table 2. MRI at the time of the initial diagnosis of AML revealed 35 of 121 patients (28.9%) with EMI. The most common site of EMI was skull, followed by the lower extremity bone and meninges of the brain. In addition, hepatomegaly, splenomegaly, and lymph node enlargement were seen in 69, 51, and 27 patients, respectively.

The median EFS was 42.0 months (range, 0.7 to 130.0 mo) and the median OS was 65.0 months (range, 0.7 to 130.0 mo). There was no significant difference in EFS and OS regardless of the presence of EMI in the overall patient population and each risk group (Figs. 1, 2). The location of EMI occurrence was not related to prognosis.

Patient Characteristics Stratified by Presence of EMI

Table 3 shows a comparison of patient characteristics according to the presence or absence of EMI. The median age at diagnosis was significantly younger in patients with

TABLE 2. Incidence of Extramedullary Infiltration Based on the Involved Sites and Number of Patients With Organomegaly

Involved Sites	n (%)
Head and neck	22 (18.2)
Meninges of brain	6
Periorbital region	4
Sinus	5
Mastoid air cells	4
Parotid gland	1
Nasopharynx	2
Trunk	12 (10.0)
Paraspinal region	3
Spinal canal (epidural space)	4
Liver	3
Kidney	2
Musculoskeletal system	35 (28.9)
Skull	15
Pelvic bones	2
Upper extremity bone	1
Lower extremity bone	12
Upper extremity muscle	2
Lower extremity muscle	3
Total	63
Hepatomegaly	69 (57.0)
Splenomegaly	51 (42.1)
Lymph node enlargement	27 (22.3)

Note: All lesions in all patients were recorded.

EMI (7.87 vs. 11.08 y, $P = 0.0212$). There was no significant difference in sex ratio, survival and event status, median initial WBC count, and distribution of risk features whether the patients had EMI or not.

Cytogenetic and molecular features of the patients along with bone marrow involvement assessed based on MRI are shown in Table 4. Cytogenetic abnormalities are detected without significant difference whether the patients had EMI or not ($P = 0.1139$), and complex cytogenetic abnormality was present without significant difference between the 2 groups ($P = 0.1586$). *FLT3/ITD* mutation and *AML-ETO* gene rearrangement was significantly more frequently noted in patients without EMI. The incidence of *c-kit* mutation, *NPM1* mutation, *CEBPA* mutation, inv(16), *MLL* mutation in patients with or without EMI did not differ significantly.

In an analysis of bone marrow signal intensity using MRI, the extent of bone marrow involvement was broader in patients with EMI ($P = 0.0001$), and remarkably, periosteal infiltration was only demonstrated in patients with EMI ($P < 0.0001$).

DISCUSSION

Many studies have been conducted on EMI in AML patients, but there are still controversy and limited information on the topic, especially in the pediatric population.[2] Moreover, only few reports on EMI are published regarding

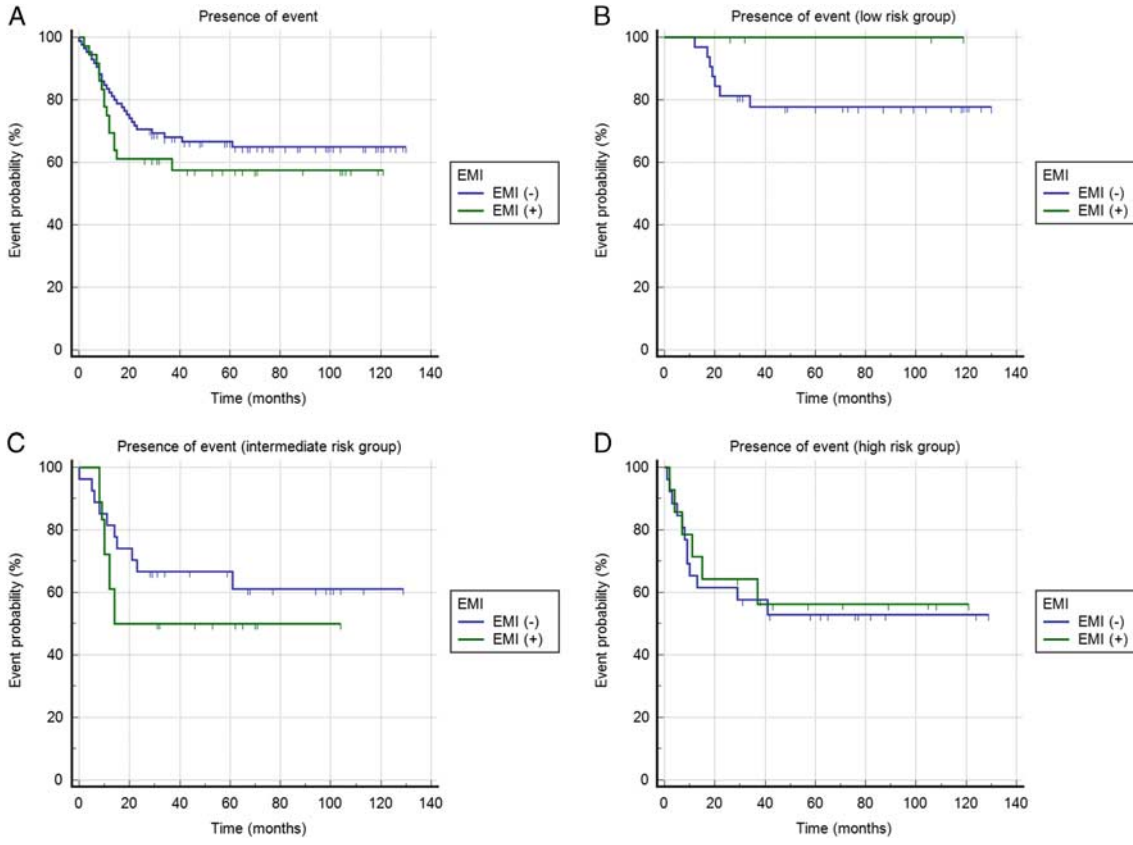

FIGURE 1. Differences in event-free survival with respect to absence of presence of extramedullary infiltration (EMI) in the overall patient population (A), low-risk group (B), intermediate-risk group (C), and high-risk group (D) patients.

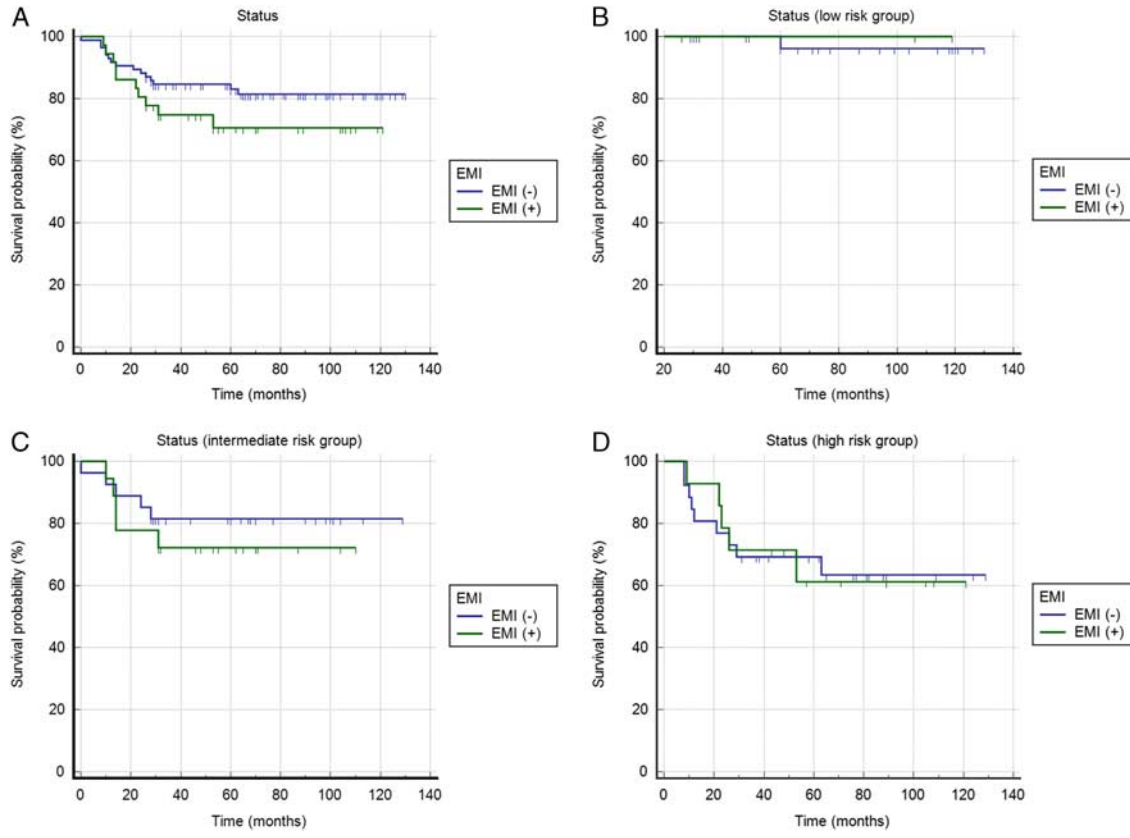

FIGURE 2. Differences in overall survival with respect to absence of presence of extramedullary infiltration (EMI) in the overall patient population (A), low-risk group (B), intermediate-risk group (C), and high-risk group (D) patients.

image diagnosis despite of its usefulness.[20,21] Imaging studies, especially MRI, is noninvasive diagnostic tool with high sensitivity that can be used to assess location and extent of disease as well as treatment response.[8,9,11,22] EMI in AML patients can be diagnosed when extramedullary masses with abnormal bone marrow signal intensity on MRI, even before peripheral blood abnormalities appear.[9] Diagnosing EMI solely based on clinical manifestation is often underestimated as it is possible only with high suspicion,[8] more aggressive use of MRI may be helpful in diagnosing EMI in pediatric patients. To our knowledge, this study was the first investigation focusing on EMI diagnosed by routine initial screening MRI in de novo pediatric AML patients.

TABLE 3. Patient Characteristics Regarding EMI in the Pediatric Acute Myeloid Leukemia Patients

	EMI (+)	EMI (−)	*P*
n (%)	35 (28.9)	86 (71.1)	
Median age at diagnosis	**7.87**	**11.08**	**0.0212**
Sex (male/female)	23/12	54/32	0.7628
Status (alive/dead)	25/10	70/16	0.2281
Event (yes/no)	20/15	56/30	0.4125
Initial WBC, median (range) ($\times 10^9$/L)	15.2 (1.01-287.06)	16.8 (0.72-339.03)	0.8325
Risk features			**0.0124**
Low-risk group (n = 36, 29.8%)	4	32	
Standard-risk group (n = 45, 37.2%)	18	27	
High-risk group (n = 40, 33.1%)	14	26	

Bold values indicate statistical significance ($P < 0.05$).
EMI indicates extramedullary infiltration; WBC, white blood cell.

In the current study, the prognostic effect of EMI itself, as well as its relationship with the known risk factors in the previously published literature, was investigated. The prognostic role of EMI is still on the debate as different results are reported in the literature, some showing poorer prognosis in patients with EMI,[1,8,10,11,17] while others revealing no significant relationship between EMI and prognosis.[1,15,18] There was no significant difference in EFS and OS regardless of the presence of EMI in the overall patient population and each risk group in our study. Various prognoses have been reported according to the location of EMI[8,9,11,12] but there was no relationship between the location of EMI and the prognosis in this study.

There are several established prognostic factors of AML, and based on the relationship between these known AML prognostic factors and EMI, it might be possible to infer the effect of EMI on the prognosis. Creutzig et al[13] reported the most important factors are genetic abnormalities and treatment response. A high WBC count at initial diagnosis ($> 100\times 10^9$/L) is generally associated with a worse prognosis.[3,10,11] Some cytogenetic findings including t(8;21), t(15;17), inv(16), *AML1-ETO, CEBPA, NPM1*, and trisomy 21 are associated with favorable prognosis,[8,15] whereas *MLL* rearrangements and *c-kit* mutation are related with poor prognosis.[2,3,11,13]

TABLE 4. Cytogenetic/Molecular and Magnetic Resonance Imaging–based Bone Marrow Involvement Characteristics of Study Population Stratified by Extramedullary Infiltration (EMI) Status

	All Patients (N = 121), n (%)	EMI (+) (n = 35)	EMI (−) (n = 86)	*P*
Cytogenetic status				0.1139
Normal	32 (26.4)	6	26	
Abnormal	89 (73.6)	30	59	
Complex (≥ 3)	30 (24.8)	12	18	0.1586
C-kit mutation				0.3601
Positive	18 (14.9)	7	11	
Negative	103 (85.1)	29	74	
FLT3/ITD mutation				**0.046**
Positive	20 (16.5)	5	15	
Negative	101 (83.5)	31	70	
NPM1 mutation				0.0773
Positive	7 (5.8)	0	7	
Negative	114 (94.2)	36	78	
CEBPA mutation				0.1874
Positive	4 (3.3)	0	4	
Negative	117 (96.7)	36	81	
inv(16)				0.1967
Positive	8 (6.6)	4	4	
Negative	113 (93.4)	32	81	
MLL mutation				0.2341
Positive	11 (9.1)	5	6	
Negative	110 (90.9)	31	79	
AML-ETO gene rearrangement				**0.0424**
Positive	32 (26.4)	5	27	
Negative	89 (73.6)	31	58	
Bone marrow involvement				**0.0001**
Focal, around metaphysis	11 (9.1)	2	9	
< 50% of bone marrow	54 (44.6)	11	43	
Diffuse but confined to bone marrow	48 (39.7)	15	33	
Periosteal infiltration	8 (6.6)	8	0	**< 0.0001**

Bold values indicate statistical significance ($P < 0.05$).

Although its association with clinical outcome is unknown, EMI is known to be related with genetic abnormalities such as *c-kit* mutation, 11q23 abnormalities involving *MLL* gene, t(8;21), inv(16), and *NPM1*, in addition to several other factors such as <1 year, male sex, and central nervous system disease, whereas inconsistent relationship is seen between EMI and the recognized prognostic factors of AML including WBC counts at diagnosis and FLT3-ITD.[1,7,8] The results of the current study revealed patient group with EMI were significantly younger than those without EMI, with a median age of 7.87 and 11.08 years, respectively. There was no significant relationship between EMI and initial WBC count. Cytogenetic abnormality was present in 73.6% of patients in the current study, which was higher than that reported as 50% in previous studies.[5] The complexity of cytogenetic abnormality showed no significant difference regardless of the absence or presence of EMI. Among the abovementioned genetic abnormalities known to be related EMI, *FLT3/ITD* mutation, and *AML-ETO* gene arrangement were the only significant genetic factors, both of them being positive in a higher proportion in patients without EMI.

In addition to these previously investigated prognostic factors, the extent of abnormal bone marrow signal intensity on MRI was examined in the current study, speculated as another possible prognostic factor as in a previously published report that stated bone infiltration to be an independent risk factor for lower relapse-free survival in patients with EMI.[1] AML is one of the diseases with infiltration of bone marrow, demonstrating decreased marrow signal intensity on T1-weighted images due to infiltration of normal fatty marrow by tumor cells,[9,12,22] though marrow signals could be normal in very early in the disease course.[12] Bone and periosteum is one of the most common sites of EMI, which could be explained as direct spread from the adjacent infiltrated marrow.[6] The patients with EMI showed a significantly broader extent of bone marrow involvement, and periosteal infiltration was noted only in patients with EMI.

To summarize, younger of patients, low incidence of *FLT3/ITD* mutation and *AML-ETO* gene rearrangement, and the larger extent and more severe degree of bone marrow involvement was related with EMI. The Kaplan-Mayer analysis about EFS and OS showed no significant difference between patients with or without EMI regardless of risk group. It is an expected result since different treatments were performed according to the risk group, resulting in similar outcome in patients of various risk groups.

There are several limitations in this study. First, it was a retrospective study; thus, selection bias was inevitable. Second, this is a single-center study with limited sample size, and the study population during the 9-year of research period at our institution were treated according to 2 different protocols depending on the time of treatment, as described by Lee et al.[19] Third, data acquisition and analysis were mainly based on medial record, and radiologic reports, without histology and immunohistochemistry, included. Fourth, data on some of the cytogenetic/molecular factors were not only available in all patients, and as the data was available only in a small number of patients, there is a possibility that flaws may still exist despite careful analysis and interpretation of results.

The current study has significance in that it was the first study conducted in pediatric patients who underwent a surveillance MRI investigation in newly diagnosed pediatric AML patients who are asymptomatic without clinical evidence to suspect EMI. Even if EMI symptoms are not evident, surveillance MRI scans revealed a significant number of EMIs. This study revealed that younger age, some molecular features, and more severe bone marrow involvement of AML patients were related with EMI. However, the authors found no evidence that asymptomatic EMI lesions had a worse prognosis than AML without EMI. But the further prospective investigation is necessary to validate the prognostic effect of the presence or treatment response of EMI in a larger group of patients with different risk groups.

REFERENCES

1. Hu GH, Lu AD, Jia YP, et al. Prognostic impact of extramedullary infiltration in pediatric low-risk acute myeloid leukemia: a retrospective single-center study over 10 years. *Clin Lymphoma Myeloma Leuk*. 2020;20:e813–e820.

2. de Lima MC, da Silva DB, Freund AP, et al. Acute myeloid leukemia: analysis of epidemiological profile and survival rate. *J Pediatr (Rio J)*. 2016;92:283–289.
3. Morais RV, Souza MV, Silva KAS, et al. Epidemiological evaluation and survival of children with acute myeloid leukemia. *J Pediatr (Rio J)*. 2020;97:204–210.
4. Meshinchi S, Arceci RJ. Prognostic factors and risk-based therapy in pediatric acute myeloid leukemia. *Oncologist*. 2007; 12:341–355.
5. Magdy M, Abdel Karim N, Eldessouki I, et al. Myeloid sarcoma. *Oncol Res Treat*. 2019;42:224–229.
6. Singh A, Kumar P, Chandrashekhara SH, et al. Unravelling chloroma: review of imaging findings. *Br J Radiol*. 2017;90: 20160710.
7. Xu LH, Wang Y, Chen ZY, et al. Myeloid sarcoma is associated with poor clinical outcome in pediatric patients with acute myeloid leukemia. *J Cancer Res Clin Oncol*. 2020;146:1011–1020.
8. Solh M, Solomon S, Morris L, et al. Extramedullary acute myelogenous leukemia. *Blood Rev*. 2016;30:333–339.
9. Lee JY, Chung H, Cho H, et al. Clinical characteristics and treatment outcomes of isolated myeloid sarcoma without bone marrow involvement: a single-institution experience. *Blood Res*. 2017;52:184–192.
10. Kobayashi R, Tawa A, Hanada R, et al. Extramedullary infiltration at diagnosis and prognosis in children with acute myelogenous leukemia. *Pediatr Blood Cancer*. 2007;48:393–398.
11. Samborska M, Derwich K, Skalska-Sadowska J, et al. Myeloid sarcoma in children—diagnostic and therapeutic difficulties. *Contemp Oncol (Pozn)*. 2016;20:444–448.
12. Hwang S, Panicek DM. Magnetic resonance imaging of bone marrow in oncology, part 2. *Skeletal Radiol*. 2007;36:1017–1027.
13. Creutzig U, van den Heuvel-Eibrink MM, Gibson B, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. *Blood*. 2012;120:3187–3205.
14. Bakst RL, Tallman MS, Douer D, et al. How I treat extramedullary acute myeloid leukemia. *Blood*. 2011;118:3785–3793.
15. Bisschop MM, Révész T, Bierings M, et al. Extramedullary infiltrates at diagnosis have no prognostic significance in children with acute myeloid leukaemia. *Leukemia*. 2001;15: 46–49.
16. Ganzel C, Manola J, Douer D, et al. Extramedullary disease in adult acute myeloid leukemia is common but lacks independent significance: analysis of patients in ECOG-ACRIN Cancer Research Group Trials, 1980-2008. *J Clin Oncol*. 2016;34:3544–3553.
17. Paydas S, Zorludemir S, Ergin M. Granulocytic sarcoma: 32 cases and review of the literature. *Leuk Lymphoma*. 2006;47:2527–2541.
18. Lan TY, Lin DT, Tien HF, et al. Prognostic factors of treatment outcomes in patients with granulocytic sarcoma. *Acta Haematol*. 2009;122:238–246.
19. Lee JW, Kim S, Jang PS, et al. Prognostic role of postinduction minimal residual disease and myeloid sarcoma type extramedullary involvement in pediatric RUNX1-RUNX1T1 (+) acute myeloid leukemia. *J Pediatr Hematol Oncol*. 2020;42:e132–e139.
20. Kim JY, Im SA, Lee JH, et al. Extramedullary relapse of acute myeloid and lymphoid leukemia in children: a retrospective analysis. *Iran J Pediatr*. 2016;26:e1711.
21. Yoon HM, Kim JR, Jung AY, et al. Whole body MR imaging: a useful imaging modality in the management of children with acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2017; 17:231–237.
22. Yoshikawa T, Tanizawa A, Suzuki K, et al. The usefulness of T1-weighted magnetic resonance images for diagnosis of acute leukemia manifesting musculoskeletal symptoms prior to appearance of peripheral blood abnormalities. *Case Rep Pediatr*. 2016; 2016:2802596.