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Myeloid sarcoma, spectrum of clinical characteristics, prognostic impact, and treatment outcome

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Abstract

Background Acute leukemia may present with extramedullary (EM) tissues. Myeloid sarcoma (MS) and leukemia cutis (LC) are considered extramedullary diseases. This study aims to evaluate the incidence, clinical characteristics, and prognostic factors affecting the outcome of pediatric patients with myeloid sarcoma at the pediatric oncology center from July 2007 to December 2017. Radiological imaging was used to stage the tumor, biopsy was done for pathological diagnosis, and bone marrow aspirate for morphology, flow cytometry, cytogenetics, and molecular analysis. Patients received chemotherapy protocols based on those used by the Children's Cancer Group for acute myeloid leukemia (AML).

Result The study included 91 (13.2%) of 687 pediatric patients with acute myeloid leukemia, with a male-to-female ratio of 1.9 to 1. Prognostic factors that improved the patient's 5-year overall survival (OS) were age > 5 years old, molecular and cytogenetic detection of t (8; 21), inv 16, presence of a single and small size lesion < 5 cm, negative CNS lesion, and achieved radiological response in isolated disease or radiological and marrow complete remission in disseminated disease post induction 1 with significant *P* value. Relapse, particularly early relapse, worsens the OS and EFS by 10% and 7.7%, respectively.

Conclusion Patients over five with low-risk disease based on cytogenetics, a small, single, negative CNS lesion, and a complete response post induction 1 had better outcomes, with no significant difference between those with isolated extramedullary disease and those with marrow dissemination. Early relapse harms the outcome. The study group's 5-year OS and EFS rates are 51.4% and 49.4%, respectively.

Keywords Pediatric, Myeloid sarcoma, Chloroma, Granulocytic sarcoma, Extramedullary myeloid cell tumor, Isolated disease

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1 Background

Myeloid sarcoma (MS) is called chloroma, granulocytic sarcoma, and extramedullary myeloid cell tumor. It is a pathological diagnosis characterized by the presence and proliferation of one or more myeloid blast lineages in the extramedullary space, which affects the normal architecture of the infiltrated tissue with or without dissemination to the bone marrow [1].

Myeloid sarcoma (MS) and leukemia cutis (LC) are considered extramedullary manifestations [2]. There are insufficient available data about the impact of MS on prognosis. Some studies indicate that extramedullary illness may be associated with poor results [3].

Others note that the survival rate for MS patients is 20–30%, which is similar to the prognosis of acute myeloid leukemia (AML) in general. The prognostic value of diagnosing cytogenetic alterations with MS is debatable, but the presence of cytogenetic translocation t (8; 21) is associated with a better outcome when treated with traditional AML protocols consisting of intensive induction followed by intensive consolidative chemotherapy.

It remains unclear whether this favorable prognosis and outcome in extramedullary disease are due to this translocation as there are contradictory study results [4, 5].

The work aims to evaluate the incidence, clinical characteristics, prognostic factors, and treatment lines affecting the outcome of children with myeloid sarcoma at the pediatric oncology center from July 2007 to December 2017.

2 Patients and methods

This retrospective study included all patients under 18 years old with myeloid sarcoma who received acute myeloid leukemia regimen as first-line chemotherapy at the pediatric oncology center from July 2007 to December 2017.

2.1 Inclusion criteria

Age less than 18 years, established pathological diagnosis as myeloid sarcoma, received acute myeloid leukemia protocol as first-line chemotherapy. All patients underwent a physical examination, imaging for staging using computed tomography (CT), magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET CT), a biopsy from the tumor for pathology, and immunohistochemically staining, flow cytometry, cytogenetic and molecular analysis of the tissue is needed for the isolated lesion. Bone marrow aspirate was done for morphological examination, flow cytometry for immunophenotyping, cytogenetic and molecular analysis, and cerebrospinal fluid was analyzed. Response evaluation was performed following the Children's Cancer Group (COG) protocol, as patients received protocol adopted from the AAML 0531-COG protocols, which were given to all AML patients from 2007 to 2013, and the AAML 1031-COG protocols, which were given to all AML patients from 2014 to 2017, respectively. Supplemental Figs. 1 and 2 provide detailed information about each protocol. The patients received intensified treatment cycles that included two cycles of cytarabine-based induction chemotherapy, followed by two or three cycles of high-dose chemotherapy after remission (Supplementary Figs. 1, 2).

2.2 Methodology

Prognostic factors such as patient age and gender, extramedullary lesion site, number, and size (< or > 5 cm) at diagnosis, initial CNS or/BM infiltration (FAB classification, molecular and cytogenetic findings in infiltrated bone marrow), and early response at the end of induction 1 were evaluated using computed tomography, magnetic resonance imaging, or FDG-PET CT. The sort of chemotherapy utilized as the initial treatment was investigated.

Time and site of relapse, whether single or multiple, the existence of bone marrow or central nervous system infiltration at the time of relapse, responsiveness to second-line salvage chemotherapy, and allogeneic stem cell transplantation offered to the relapsed patient were all investigated.

Overall, event-free and disease-free survival rates were calculated, and patients with isolated myeloid sarcoma were compared to those with myeloid sarcoma with bone marrow dissemination.

2.3 Definitions

- Myeloid sarcoma (MS) is defined as chloroma due to its green color because of the enzyme myeloperoxidase, granulocytic sarcoma, and extramedullary myeloid cell tumor. It is a pathological diagnosis for an extramedullary appearance and proliferation of the myeloid blasts destroying the normal architecture of the affected tissue [6].
- Isolated myeloid sarcoma is defined as the presence of extramedullary myeloid tissues with the absence of leukemia or myelodysplastic syndrome (MDS) history and the deficiency of actual bone marrow infiltration [6].
- Combined disease is defined as the presence of bone marrow (BM) infiltration by myeloid blasts > 5%, and diagnosed as acute myeloid leukemia or myelodysplastic syndrome with the presence of extramedullary myeloid cell tumor [7].
- Complete remission (CR) is defined as no more evidence of malignant disease after treatment, and the bone marrow had < 5% blasts in the aspirate.

- Refractory disease (RD) is defined as the persistent presence of bone marrow blasts > 5% after two induction cycles.
- Disease relapse is defined as the coming back of disease after remission, and recurrent has more than 5% blast cells diagnosed by bone marrow aspirate.
- Early induction deaths are defined as the patient having died within 30 days of the first induction and prevaluation at the end of induction 1 chemotherapy.
- Overall survival (OS) is defined as the survival rate percentage of the proportion of patients in a study or treatment group still alive at a given period after diagnosis.
- Event-free survival (EFS) is defined as the survival rate percentage of the proportion of patients in a study or treatment group with progression of diseases or death of any cause from the time of diagnosis.
- Disease-free survival (DFS) is defined as the survival rate percentage of patients in a study or treatment group who have not died from a specific disease or experienced recurrence/relapse in a defined period after complete remission achieved from that specific disease.

2.4 Statistical analysis

Data from protocol adopted from COG AAML 0531-COG and AAML 1031-COG protocols were analyzed from July 2007 till the end of December 2017. Clinical features, cytogenetic abnormality by karyotyping or FISH, and molecular positivity by PCR were analyzed and compared in patients with myeloid sarcoma and subgroups by the sample *T*-test and the Pearson Chi-square test. Survival rates were calculated by the method of Kaplan and Meier and compared with the log-rank test to calculate the *P* value. Overall survival (OS) was defined as the duration from the date of initial diagnosis to death or the last follow-up date. EFS was known as the time which starts treatment post initial diagnosis to relapse, death, or lost follow-up date. Disease-free survival (DFS) was considered as the time from a complete response to relapse, death from any cause, or lost follow-up date. To clarify the prognosis associated the myeloid sarcoma with acute myeloid leukemia with bone infiltration. Both univariable and multivariable analyses were then used to determine the correlation between the clinical and cytogenetic findings and the outcome after the effect of chemotherapy for AML protocol treatment. The software application IBM-SPSS Statistics 20 for Windows (SPSS, Inc., Chicago, IL) was used to perform the statistical analyses.

3 Results

It is a retrospective study that included all patients of pediatric age who had myeloid sarcoma and received acute myeloid leukemia (AML) protocol as first-line chemotherapy at the pediatric oncology center between July 2007 and December 2017. Approximately 687 people were diagnosed with AML during the study period, with 91 (13.2%) diagnosed and treated with myeloid sarcoma. Of the patients included in the current study, 60 (66%) were male, with a male/female ratio of 1.9:1 with no significant *P* value (0.802) (Table 1). The median age was four years. At diagnosis, 54 (59.3%) patients were < 5 years old, with a 5-year overall survival (OS) of 42.6%. Thirty-seven (40.6%) patients were > 5 years old, with a 5-year OS of 64.3%, with a significant *P* value of 0.031. However, 14 (15%) patients were above 10 years old, with no significant *P* value (Table 1, Supplementary Fig. 3).

Bone marrow aspirates were collected for morphological, flow cytometry, cytogenetic, and molecular analysis, and FLT3-ITD was shown to be mutated in three (3%) patients, with no significant *P* value (Table 1). Molecular analysis was positive in 38 (41.7%) patients and negative in the remaining patients with 5-year OS (67.8% and 39.6%, respectively), with a significant *P* value of 0.005 (Table 1, Supplementary Fig. 4).

Translocation (8; 21) was discovered in 33 (36%) patients with 5-year OS 67.8%, and inv 16 was detected in 5 (5.5%) patients with 5-year OS 80%, compared to patients with normal karyotype who had 5-year OS 50%, with a significant *P* value of 0.005, Table 1, Supplementary Fig. 5.

Imaging was performed using computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose [FDG] positron emission tomography (FDG-PET CT) for staging, and a tumor biopsy was performed for pathological diagnosis. Immunohistochemical staining, flow cytometry, cytogenetic, and molecular analysis were performed on the isolated lesion, which was detected in 15 (16.5%) patients.

Orbital mass was detected in 45 (49.4%) patients, other common sites included CNS masses and paraspinal mass, with a *P* value of 0.40 (Table 1). Single lesions were present in 50 (55%) patients, while multiple lesions were identified radiologically in 41 (45%) patients, with 5-year OS of 63.8% and 36.4%, respectively, with a significant *P* value of 0.005, Table 1, Supplementary Fig. 6.

The presence of mass < or > 5cm in size was calculated radio logically with 5-year OS, 63%, 17.4%, with high significance, *P* value of 0.000 (Table 1, Supplementary Fig. 7). The 5-year overall survival, according to CNS infiltration or not, was 41.7% and 62.8%, respectively, with a *P* value of 0.022 (Table 1, Supplementary Fig. 8).

The 5-year OS, according to isolated myeloid sarcoma lesions or combined with bone marrow infiltration, was 46.7%, and 52.6%, respectively, with a *P* value of 0.721 (Table 1, Supplementary Fig. 9).

From 2007 to 2013, all AML patients with or without myeloid sarcoma underwent the AAML 0531-COG regimen, but the AAML 1031-COG protocol was given from 2014 to 2017. The response assessment followed the COG procedure. All patients received intensive chemotherapy in the form of two cycles of cytarabine-based induction chemotherapy, followed by post remission intensification of two or three cycles of high-dose chemotherapy (Supplemental Figs. 1, 2). Complete remission (CR) was achieved in 61 (68%) patients post induction 1, evaluated by radiological finding and bone marrow response, and partial response (PR), or persistent disease was detected in nine patients, with 5-year OS, 69.1%, 33.3%, respectively, with *P* value of 0.018, Table 1, Supplementary Fig. 10, while radiological response selectively was done and was with CR in 56 (61.5%) patients with 5-year OS 76.6%, with a significant *P* value of 0.000, Table 1, Supplementary Fig. 11.

Relapse occurred in 20 (22%) patients with poor 5-year OS, which was 10% (Table 1, Supplementary Fig. 12). Early relapse (< 1 year following remission) had a lower 5-year OS (7.4%) than late relapse (14.3%), with a *P* value of 0.046 (Table 1, Supplementary Fig. 13). All relapsed patients were given salvage chemotherapy consisting of two cycles of FLAG ± M (fludarabine, high-dose cytarabine, ± mitoxantrone), followed by hematopoietic stem cell transplantation (HSCT) if practicable. Only two patients with 100% 5-year OS underwent allogeneic bone marrow transplantation (allo-BMT), with no significant *P* value of 0.243 (Table 1). The study group's 5-year overall survival was 51.4% (Fig. 1), event-free survival was 49.4% (Fig. 2), and disease-free survival was 69.5% (Fig. 3).

A multivariate analysis of age > or < 5 years with other variables revealed that, according to FAB classification, M2 was common in the favorable group (> 5 years old) and M5 was common in the unfavorable group (< 5 years old), with significant *P* value, 0.000 (see Table 2). Low-risk t (8; 21) was detected in the favorable group (> 5 years old) with a significant *P* value of 0.000 (Table 2).

Single lesions were found to have a better 5-year OS than multiple lesions in the favorable group (> 5 years old), with a significant *P* value of 0.044 (see Table 2). Mutant FLT3-ITD was found to be associated with a myeloid sarcoma lesion (orbital, CNS mass, paravertebral, or other sites), isolated or combined with marrow infiltration, positive CNS disease or not, radiological ± bone

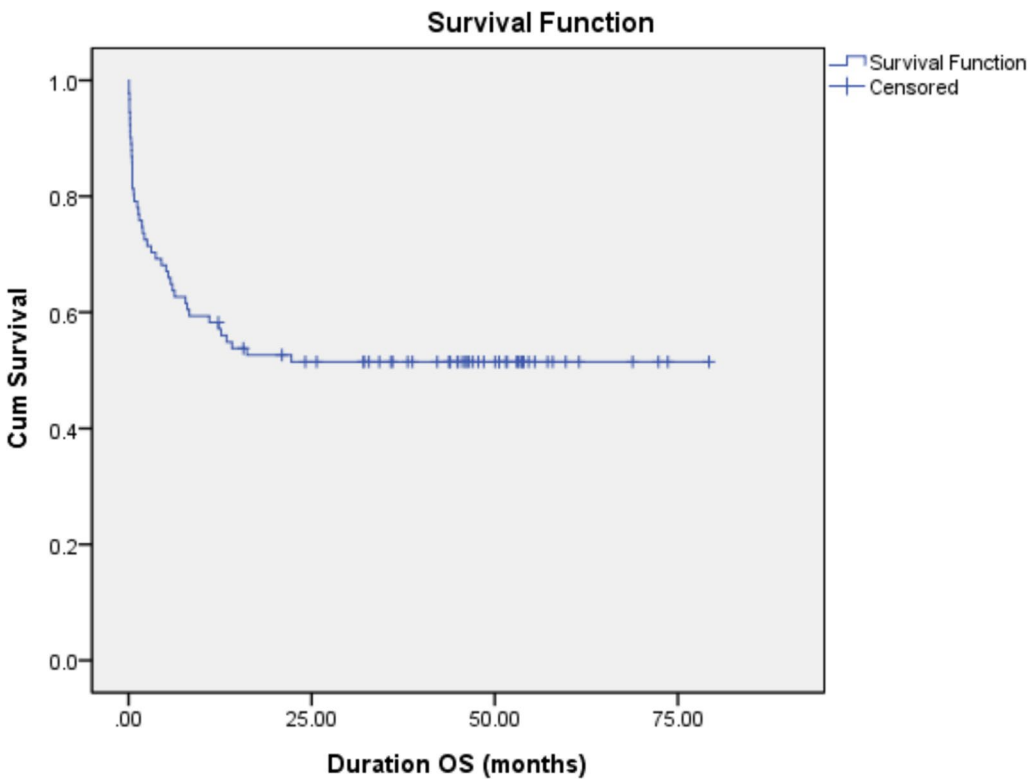

Fig. 1 5-year overall survival 51.4%, 3-year overall survival 52.6%

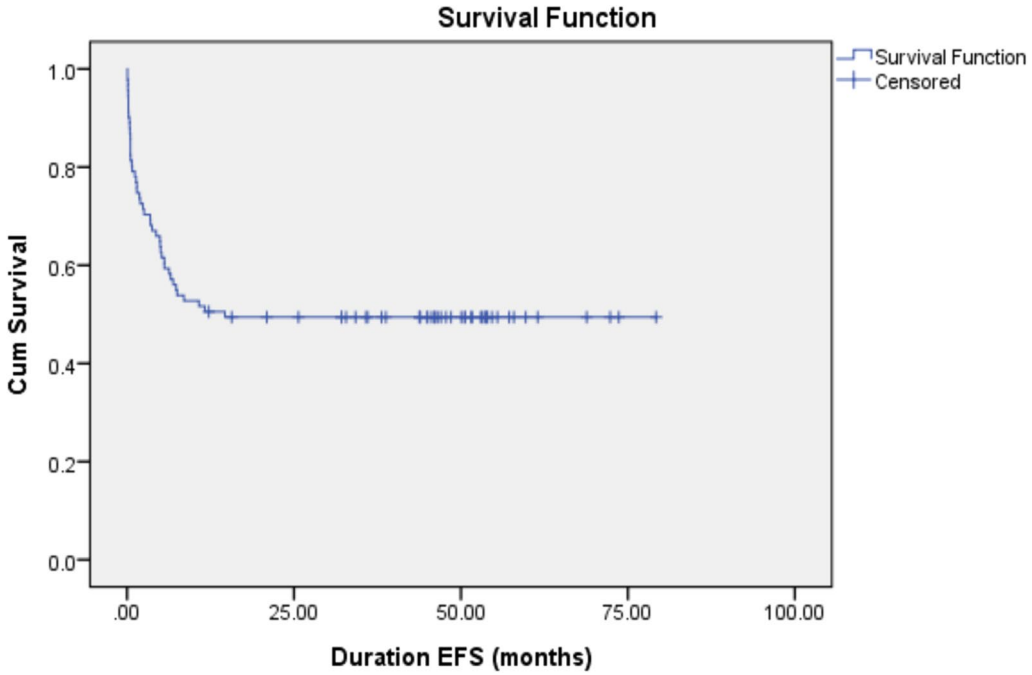

Fig. 2 5-year event-free survival 49.4%

marrow morphological remission post induction 1, early or late relapse, and no significant *P* value (Table 2).

Multivariate analysis for isolated myeloid sarcoma or mixed with bone marrow infiltration with other variables was performed, and it was discovered that FAB classification, M2, M4, and M5 were common in combined disease, with a significant *P* value of 0.000 (see Table 3). Molecular and cytogenetic detection of marrow low-risk t (8; 21) was prevalent in individuals with combined disease myeloid sarcoma, with a significant *P* value of 0.000 (Table 3).

The most common sites of infiltration were orbital and/or paraspinal lesions, whereas isolated disorders had a higher prevalence of positive CNS disease (*P* value = 0.004, Table 3). Table 3 shows that age, mutant FLT3-ITD, detection of single or multiple lesions, size of the mass (< or > 5 cm), site of the myeloid sarcoma lesion (orbital, CNS mass, paravertebral, or other sites), radiological and/or marrow morphological remission post induction 1, early or late relapse, and presentation with isolated myeloid sarcoma or with dissemination to bone marrow had no significant *P* value.

4 Discussion

Data about the prognostic effect of myeloid sarcoma on outcomes are limited, then the work aims to evaluate the incidence, clinical characteristics, prognostic factors, and treatment lines affecting the survival outcomes of patients of pediatric age with myeloid sarcoma at the pediatric oncology center from June 2007 to December 2017.

During the study period, a total of 687 patients were diagnosed with acute myeloid leukemia; of these, 91(13.2%) were diagnosed and treated with myeloid sarcoma and included in the current study, which was conducted in collaboration with Magdalena S et al., who reported that the overall incidence of myeloid sarcoma in pediatric patients is approximately 10–15% of patients with AML [8–10].

In the current study, the male-to-female ratio was 1.9:1 with no significant *P* value, and the median age was 4 years, whereas Fanghua Ye et al. reported an 8:3 male-to-female ratio and a median age at diagnosis of 7 years [11]. Others stated that 55–75% of MS patients were male [12–14]. At the time of diagnosis, 54 patients (59.3%) were under the age of five, whereas 37 (40.6%) were older than five. The 5-year OS was 43% and 65%, respectively, with a significant P value. However, 14 (15%) of the patients were older than ten years old, which had no significance.

Aspirates of bone marrow were collected for morphological, flow cytometry, cytogenetic, and molecular investigation. FAB classification, M2, M4, and M5 were all prevalent, with a significant *P* value of 0.000. By cytogenetic, t (8; 21) was discovered in 33 (36%) patients, with 5 years OS 67%, and inv 16 was detected in 5 (5.5%) patients, with 5 years OS 80%, in comparison with patients with normal karyotype, which had

Table 1 Myeloid sarcoma patient's characteristics and overall survival

Initial variables	Count	Number of events (death)	Overall survival (5 years)	*P* value with OS
Gender	91		51.60%	0.802
Female	31	16	48.40%	
Male	60	28	53.30%	
Age group	91	44	51.60%	0.031
< 5	54	31	42.60%	
> 5	37	13	64.90%	
Age group	91	44	51.60%	
< 10	77	37	51.90%	0.813
> 10	14	7	50.00%	
FLT3-ITD	60			0.065
Mutant AR < 0.4	1	2	33.30%	
Mutant AR > 0.4	2	22	61.20%	
Wild	57			
Initial molecular	91		51.60%	0.005
Positive	38	12	68.40%	
Negative	53	32	39.60%	
Cytogenetic	87		51.70%	0.005
Inv 16	5	1	80%	
t(8;21)	33	11	66.70%	
MLL gene + ve	16	8	50.00%	
Complex cytogenetic	8	7	12.50%	
t(1;22)	4	3	25.00%	
Normal	16	8	50.00%	
Others abnormalities	5	4	20.00%	
Initial site of myeloid sarcoma	91	44	51.60%	0.4
Orbital	45	18	59.90%	
CNS mass	9	4	55.60%	
Paraspinal lesion	17	9	47.10%	
Others	20	13	34.30%	
Number of lesions	91	44	51.60%	
Single	50	18	63.80%	0.005
Multiple	41	26	36.40%	
Myeloid sarcoma lesion size	91	44	51.60%	0
> 5 cm	23	19	17.40%	
< 5 cm	68	25	63.00%	
CNS infiltration	91	44	51.60%	0.022
Yes	48	28	41.70%	
No	43	16	62.80%	
Myeloid sarcoma	91	44	51.60%	0.721
Isolated	15	8	46.70%	
Combined with BM infiltration	76	36	52.60%	
Response to induction 1	71	25	64.80%	0.018
CR	62	19	69.10%	
PR or persistent disease	9	6	33.30%	
Radiological response post ind 1				0
CR	56	13	76.80%	
PR	13	9	30.80%	
Persistent disease	1	1	0.00%	

Table 1 (continued)

Initial variables	Count	Number of events (death)	Overall survival (5 years)	*P* value with OS
Relapse	89	42	52.80%	0.002
Yes	20	18	10%	
No	69	24	65.20%	
Time of relapse	20	18	10%	
Early < 1 year post remission	13	12	7.40%	0.046
Late > 1 year post remission	7	6	14.30%	
Bone marrow transplantation				0.243
Yes	2	0	100%	
No	89	44	50.60%	
State of life				
Alive	45			
Dead	44			
Lost follow-up	2			

Median age = 4, Range: 0.1–17.8, Mean: 5.229, Std. deviation: 4.6762, Median follow-up duration = 71.1 (time on months)

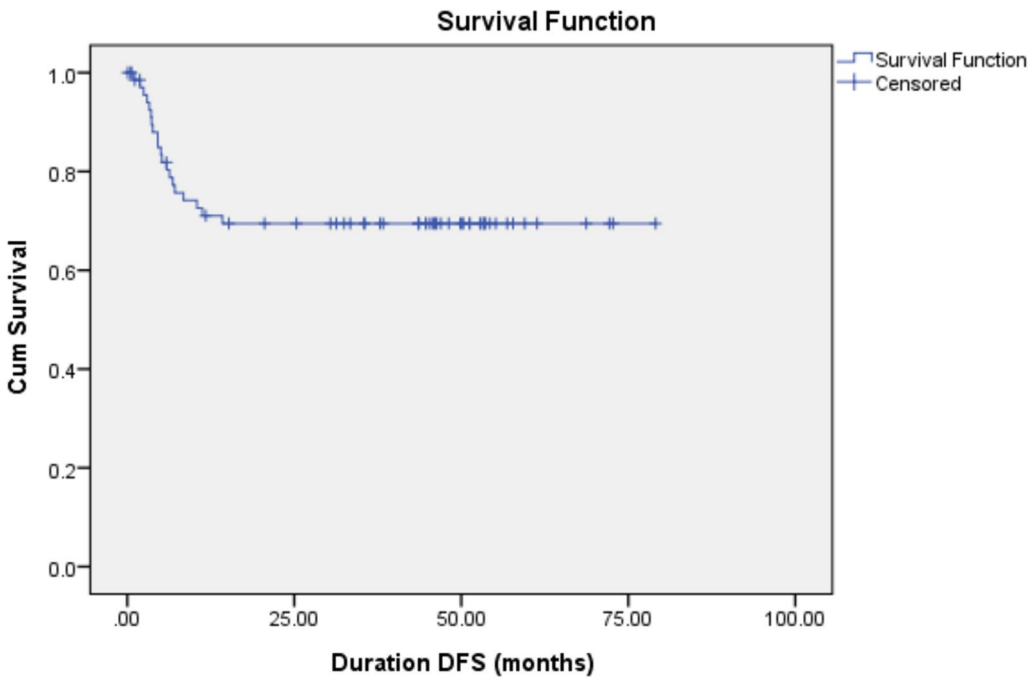

Fig. 3 5-year disease-free survival 69.5%

5 years OS 50.0%, with *P* value of 0.005, that was with Zhou et al. [15].

Imaging for staging was performed using computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET CT), In addition, tumor tissue was used for pathological diagnosis and immunohistochemical staining.

Common presenting sites include the skin, orbit, bone, periosteum, lymph nodes, gastrointestinal tract, soft tissue, central nervous system, and testis [8]. In the current study, orbital mass was the most common site and was discovered in 45 (49.4%) patients; yet, positive CNS disease was common in isolated illness; however, the 5-year OS differed according to CNS infiltration or not, with 42% and 63%, respectively (*P* value = 0.022). Single lesions

Table 2 Multivariate analysis age > or < 5 years with other variables

	Variables				***P* value**
	WHO classification (AML NOS)	WHO classification (myeloid sarcoma)	FAB(M0)		0
Age group					
Age < 5	0	8	3		
Age > 5	1	7	0		
	FAB(M1)	FAB(M2)	FAB(M4)		
Age group					
Age < 5	1	10	8		
Age > 5	2	24	2		
	FAB(M5)	FAB(M6)	FAB(M7)		
Age group					
Age < 5	12	6	6		
Age > 5	1	0	0		
	Molecular (negative)	Molecular: t(8;21)	Molecular: inv 16		0
Age group					
Age < 5	4	8	3		
Age > 5	10	25	2		
	Cytogenetic inv(16)/t(16;16)	Cytogenetic	Cytogenetic		0
		t(1;22)	Complex		
Age group					
Age < 5	3	4	8		
Age > 5	2	0	0		
	Cytogenetic	Cytogenetic	Cytogenetic		
	Normal	Other abnormalities	t(8;21)		
Age group					
Age < 5	11	4	8		
Age > 5	5	1	25		
	FLT3-ITD mutant (< 0.4 AR)	FLT3-ITD mutant (> 0.4 AR)	FLT3-ITD wild		0.093
Age group					
Age < 5	0	0	32		
Age > 5	1	2	25		
	Single lesion	Multiple lesions			0.044
Age group					
Age < 5	25	29			
Age > 5	25	12			
	Lesion size < 5 cm	Lesion size > 5 cm			0.863
Age group					
Age < 5	40	14			
Age > 5	28	9			
	Site of lesion (CNS)	Site of lesion (orbital)	Site of lesion (others)	Site of lesion (paraspinal)	0.677
Age group					
Age < 5	6	27	13	8	
Age > 5	3	18	7	9	
	Combined	Isolated			0.604
Age group					
Age < 5	46	8			
Age > 5	30	7			
	CNS negative	CNS positive			0.83

Table 2 (continued)

	Variables			*P* value
Age group				
Age < 5	26	28		
Age > 5	17	20		
	Radiological response post induction 1 (CR)	Radiological response post induction 1 (PR)	Radiological response post induction 1 (stationary)	0.523
Age group				
Age < 5	31	8	1	
Age > 5	25	5	0	
	Bone marrow response post ind 1 (CR)	Bone marrow response post ind 1 (persistant)	Bone marrow response post ind 1 (PR)	0.166
Age group				
Age < 5	34	3	3	
Age > 5	28	0	3	
	Relapse (yes)	Relapse (no)		0.573
Age group				
Age < 5	13	40		
Age > 5	7	29		
	Time of relapse (< 1 yr from CR)	Time of relapse (< 1 yr from CR)		0.591
Age group				
Age < 5	9	4		
Age > 5	4	3		
	Clinical status (alive)	Clinical status (dead)	Clinical status (lost FU)	0.113
Age group				
Age < 5	22	31	1	
Age > 5	23	13	1	

survive better than multiple lesions with 5-year OS 64% and 36%, respectively, with a *P* value of 0.005. Masses larger than 5cm showed a worse 5-year survival rate (17% vs. 63%), with a significant *P* value. On the other hand, we did not find a significant difference between isolated myeloid sarcoma lesions and myeloid sarcoma with bone marrow infiltration, as the 5-year OS was 46.7% and 52.6%, respectively, with a *P* value of 0.721, but Reinhardt D discovered that remission was achieved in isolated myeloid sarcoma with an increased risk of relapse, this could be due to the unique biology of the isolated myeloid sarcomas, as well as delayed or insufficient treatment [16].

In the current study, patients were given protocols adapted from COG protocols, specifically AAML 0531-COG and AAML 1031-COG. The response assessment followed the COG procedure. Complete remission (CR) was achieved in 61 (68%) patients after induction 1, as assessed by radiological findings and bone marrow response, while radiological response was selectively performed for all myeloid sarcoma lesions and was associated with CR in 56 (61.5%) patients with a 5-year OS of 76.8%, with a significant *P* value of 0.001, but relapse occurred in 20 (22%) patients with a very poor 5-year OS of 10%, as with. [17]Early relapse (< one year from remission) had worse 5-year OS, which accounted for 7.7%, than those who had late relapse, which was calculated at 14.3%, which needed aggressive salvage treatment followed by hematopoietic stem cell transplantation (HSCT). In Mareike Rasche et al. initial high-risk features and early relapse remain the most prognostic factors [18]. Achieving second complete remission (CR2) before HSCT was related to improving outcomes ($P < 0.01$). Reinduction therapy after relapse was advised using either etoposide, cytarabine, and mitoxantrone (ECM) or fludarabine, cytarabine, and granulocyte colony-stimulating factor (FLAG) regimens ($P < 0.01$) [18].

Good prognostic indicators include core binding factor-AML, t (8;21), and inv (16) ($P < 0.01$). A genomic investigation also found that FMS-like tyrosine kinase 3 (FLT3)-internal tandem duplication is a poor predictive predictor ($P = 0.04$). Recent molecular focused

Table 3 Multivariate analysis isolated or combined myeloid sarcoma with other variables

	Variables				***P* value**
	Age < 5 y	Age > 5 y			0.604
Combined	46	30			
Isolated	8	7			
	WHO classification (AML NOS)	WHO classification (myeloid sarcoma)	FAB(M0)		0
Combined	1	0	3		
Isolated	0	15	0		
	FAB(M1)	FAB(M2)	FAB(M4)		
Combined	3	34	10		
Isolated	0	0	0		
	FAB(M5)	FAB(M6)	FAB(M7)		
Combined	13	6	6		
Isolated	0	0	0		
	Molecular (negative)	Molecular: t(8;21)	Molecular: inv 16		0.004
Combined	38	32	5		
Isolated	14	1	0		
	Cytogenetic inv(16)/t(16;16)	Cytogenetic t(1;22)	Cytogenetic Complex	Cytogenetic t(8;21)	0.004
Combined	5	3	7	32	
Isolated	0	1	1	1	
	Cytogenetic MLL gene + ve	Cytogenetic normal	Cytogenetic Other abnormalities		
Combined	15	9	5		
Isolated	1	7	0		
	FLT3-ITD mutant (< 0.4 AR)	FLT3-ITD mutant (> 0.4 AR)	FLT3-ITD wild		0.839
Combined	1	2	51		
Isolated	0	0	0		
	Single lesion	Multiple lesions			0.066
Combined	45	31			
Isolated	5	19			
	Lesion size < 5 cm	Lesion size > 5 cm			0.218
Combined	55	21			
Isolated	13	2			
	Site of lesion (CNS)	Site of lesion (orbital)	Site of lesion (others)	Site of lesion (paraspinal)	0.392
Combined	6	40	16	14	
Isolated	3	5	4	3	
	CNS negative	CNS positive			0.004
Combined	41	35			
Isolated	2	13			
	Radiological response post induction 1 (CR)	Radiological response post induction 1 (PR)	Radiological response post induction 1 (stationary)		0.568
Combined	49	10	1		
Isolated	7	3	0		
	Bone marrow response post ind 1 (CR)	Bone marrow response post ind 1 (persistant)	Bone marrow response post ind 1 (PR)		0.42
Combined	55	3	4		
Isolated	7	0	2		
	Relapse (no)	Relapse (yes)			0.329

Table 3 (continued)

	Variables			*P* value
Combined	56	18		
Isolated	13	2		
	Time of relapse (< 1 yr from CR)	Time of relapse (< 1 yr from CR)		0.646
Combined	12	6		
Isolated	1	1		
	Clinical status (alive)	Clinical status (dead)	Clinical status (lost FU)	0.657
Combined	38	36	2	
Isolated	7	8	0	

medicines, such as FLT3 inhibitors, may help to improve the result [19]. Improved supportive care after rigorous chemotherapy to enhance overall survival for relapsed patients. Because of the small number of transplanted patient groups in the current study, only two patients had allogeneic bone marrow transplantation (BMT) with a 5-year OS of 100%, with no significant P value of 0.243. Extramedullary recurrence is a serious complication that is more common in post-transplant patients than in those treated without allo-HSCT. It accounts for approximately 7–46% of all AML relapses. [17]

The study group had a 5-year overall survival rate of 51.4%, event-free survival of 49.4%, and disease-free survival of 69.5%.

5 Conclusion

Our findings revealed that FAB classification, M2, M4, M5, and cytogenetic identification of marrow low-risk t (8; 21) were prevalent among pediatric myeloid sarcoma patients. Orbital lesions were present in approximately 50% of patients with isolated myeloid sarcoma.

There was no significant difference in outcomes between patients with isolated extramedullary disease and those with marrow dissemination. Prognostic factors that improve overall survival (OS) for pediatric patients with myeloid sarcoma include age > 5 years, molecular and cytogenetic detection of t (8; 21), or inv 16, presence of negative CNS, single and small size lesion < 5 cm, and achieved radiological response in isolated disease or radiological and marrow complete remission in disseminated disease post induction 1 with significant *P* value.

The study group's 5-year OS is 51.4%, and their 5-year event-free survival (EFS) rate is 49.4%. Relapse, particularly early relapse, lowers OS and EFS by 10% and 7.7%, respectively, necessitating extensive salvage therapy followed by hematopoietic stem cell transplantation.

Abbreviations

EM	Extramedullary
MS	Myeloid sarcoma
LC	Leukemia cutis
COG	Children's cancer group
AML	Acute myeloid leukemia
OS	Overall survival
t	Translocation
inv	Inversion
CNS	Central nervous system
CT	Computed tomography
MRI	Magnetic resonance imaging
FDG	Fluorodeoxyglucose
FDG-PET CT	Fluorodeoxyglucose positron emission tomography
BM	Bone marrow
FAB	French-American-British
MDS	Myelodysplastic syndrome
CR	Complete remission
NED	No evidence of disease
RD	Refractory disease
EFS	Event-free survival rate
DFS	Disease-free survival rate
IBM-SPSS	International business machines—statistical package for the social sciences
FLT3-ITD	FLT3-Internal tandem duplication
HSCT	Hematopoietic stem cell transplantation

Supplementary Information

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Supplementary Material 1.

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Author contributions

Samah Fathy Semary: is the corresponding author, who writes the manuscript, and submits the manuscript to the journal. Mahmoud Hammad: did the design of the manuscript. Sonya Soliman: revised the collected data belonging to the morphology of bone marrow aspirate. Nayera Hamdy: revised the collected data belonging to molecular of bone marrow aspirate. Sherine Salem: revised the collected data belonging to cytogenetics. Iman zaky: revised the collected data belonging to the radiological investigations done for the patients as initial workup of follow-up radiology. Naglaa elkinaai: revised the collected data belonging to the initial diagnostic pathology. Nermeen Ezzat: is a clinical pharmacist who collects and revises the chemotherapy side effects and complications. Doaa Albeltagy: collected the data, analyzed of the data, and did the statistics of the results. Youssef Madany: helped in revision of the manuscript.

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Availability of data and materials
All authors agree to make the raw data and materials described in our manuscript freely available to any scientist wishing to use them for non-commercial purposes, as long as this does not breach participant confidentiality.

Declarations

Ethics approval and consent to participate
All authors confirm that we obtained approval from an ethical committee, it is a retrospective research article to evaluate the incidence, clinical characteristics, prognostic factors, and treatment lines affecting the outcome of pediatric patients with myeloid sarcoma in Children Cancer Hospital Egypt from July 2007 till the end of December 2017. We collected statistical data from the files of the patients who had written consent to follow the chemotherapy protocol for the treatment of myeloid sarcoma at Children Cancer Hospital Egypt. We confirm that all experiments on humans and/or the use of human tissue samples were performed according to relevant guidelines and regulations

Consent for publication
All authors confirm that the manuscript has been read and approved by all named authors for submission and publication.

Competing interests
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