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Original Article

Demographic, clinical profile and survival outcome of relapsed pediatric acute myeloid leukemia

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تحليل الخصائص الديموغرافية والسريرية مع دراسة متوسط نسبة الشفاء من مرض انتكاسة سرطان الدم النخاعي الحاد لدى الأطفال

واصل جستنية
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الملخص العربي

الهدف:تحليل الخصائص الديموغرافية والخصائص السريرية و متوسط نسبة الشفاء من مرض انتكاسة سرطان الدم النخاعي الحاد لدى الأطفال الذين عولجوا في مركز الأميرة نورة للأورام بمدينة الملك عبدالعزيز الطبية، جدة، المملكة العربية السعودية.

الطرق:مراجعة استعادية على 86 طفلا تم تشخيصهم بسرطان الدم النخاعي الحاد حديثا وعلى التوالي من أغسطس 1986 إلى أبريل 2012، منهم 25 مريضا أصيب بانتكاسة وتأهل للدراسة الحالية.

النتائج:كان متوسط العمر عند التشخيص 3 سنوات (النطاق من 1 - 14) مع نسبة الذكور إلى الإناث (1.5:1) . وكانت الانتكاسة أكثر شيوعا في المرضى: الذين تتراوح أعمارهم بين 2 إلى 10 سنوات (58٪)، والذين تقل عدد كريات الدم البيضاء عندهم عن 100 (64%)، والذين يخلو سائل النخاع الشوكي عندهم من الخلايا السرطانية (84%)، وسرطان الدم النخلي ذو النمط الظاهري فصيلة M7 (24%). الانتكاسة النخاعية كانت الأكثر شيوعا بنسبة 80%, في حين كانت الانتكاسة في الجهاز العصبي المركزي بنسبة 4%. كان متوسط احتمالية البقاء على قيد الحياة لمدة 5 سنوات 12%. تباينت هذه النسبة اعتمادا على عمر المريض والشذوذ الكروموسومي في الخلايا السرطانية.

الخلاصه:المتغيرات الديموغرافية والسريرية تلعب دورا هاما في مرض انتكاسة سرطان الدم النخاعي الحاد لدى الأطفال. هذه الدراسة تثبت صعوبة شفاء انتكاسة مرض سرطان الدم النخاعي الحاد والحاجة الماسة لمزيد من الدراسات لاكتساب المزيد من المعرفة عن هذا المرض الصعب.

ABSTRACT

Objective: To analyze the demographic characteristics, clinical features and survival outcome of relapsed pediatric acute myeloid leukemia (AML) patients treated at the Princess Norah Oncology Center, King Abdulaziz Medical City, Jeddah, Saudi Arabia.

Methods: This is a retrospective review of 86 newly diagnosed children with AML treated consecutively from August 1986 to April 2012. A total of 25 relapsed patients qualified for the study.

Results: The median age at presentation was 3 years (range 1 - 14) with male to female ratio of 1.5:1. Relapse was more common in patients: aged 2 to 10 years (58%), with WBC less than $100x10^9$/L (64%), CSF negative (84%) and M7 phenotype (24%). Bone marrow was the most common site of relapse (80%) and isolated CNS relapse occurred in 4% of patients. The 5-year probability of post relapse overall survival (OS) was 12±6.5%. The OS varied significantly depending on patient's age (log-rank test, 7.072; *P = 0.029*) and cytogenetic risk group (*P = 0.019*).

Conclusion: Demographic and clinical variables play important role in relapsed pediatric AML. Our findings confirm that survival outcomes of relapsed pediatric AML were poor and there is a need for further studies to gain more insight on this challenging disease.

***Keywords*:** Relapsed AML, Pediatric, Demographic, Clinical Profile, Survival Outcome

INTRODUCTION

Over the past two decades, substantial improvements in the outcome for children diagnosed with acute myeloid leukemia (AML) have been made to reach as high as 70%[1]. The underlying reason for the success has been generally attributed to intensification in induction therapy and better supportive care [2-3]. Despite the current success, almost half of these children relapse and die from their disease [4]. Relapse remains the leading cause of treatment failure and accounts for about 40% of patients who achieved complete remission (CR) posing challenges to pediatric oncologists [5].

Even with the current risk assessment strategy, intensive frontline therapy and supportive care; treatment of relapsed pediatric AML patients remains unsatisfactory. Survival outcome following relapse is poor ranging from 10 to 33% [5-8]. Thus, there is a need to understand the underlying demographic factors, clinical profile and patterns of relapsed AML to gain further knowledge that may help improve outcome for these patients.

Studies addressing role of clinical and biological variables on survival outcome in relapsed pediatric AML are limited, and to our knowledge there are no published studies specifically addressing these issues in Saudi Arabia. The primary objective of the present study was to bridge this knowledge gap by describing the demographic, clinical profile and survival outcome of relapsed pediatric AML in a single institution, the Princess Norah Oncology Center, King Abdulaziz Medical City, Jeddah.

MATERIAL AND METHODS

Patients: This is a retrospective review of the records of 86 newly diagnosed children with AML treated consecutively between August 1986 and April 2012 at the Princess Norah Oncology Center, King Abdulaziz Medical City, Jeddah, Saudi Arabia (excluding AML-M3 patients). A total of 25 patients relapsed and qualified for the study. Data collected from hospital records include: age, gender, white blood cell count (WBC), cerebrospinal fluid (CSF), site of relapse, phenotype, cytogenetics, and the dates of diagnosis, relapse, last follow up, and death.

Chemotherapy Protocol

Patients with relapsed AML were treated with reinduction chemotherapy using two cylces of fludarabine, cytarabine and granulocyte colony-stimulating factor (G-CSF) followed by high dose cytarabine and l-asparaginase. Cycle 1 started with G-CSF (400 microgram/m^2) intravenously (IV) from day -1 until neutrophil count recovers to above 1 x 10^9/L, fludarabine (30 mg/m^2; maximum 50 mg) IV over 30 minutes daily for 5 days starting day 0 to day 4, and cytarabine (2000 mg/m^2) IV starting 4 hours after fludarabine and given as a 4 hour infusion daily for 5 days from day 0 to day 4. Cycle 2 started with G-CSF (400 microgram/m^2) IV from day 1 until neutrophil count recovers to above 1 x 10^9/L, fludarabine (30 mg/m^2; maximum 50 mg) IV over 30 minutes daily for 4 days starting day 0 to day 3, and cytarabine (2000 mg/m^2) IV starting 4 hours after fludarabine and given as a 4 hour infusion daily for 4 days from day 0 to day 3. Cycle 3 was given if the patient was not in remission or if hematopoietic stem cell transplant was delayed and consisted of cytarabine (3000 mg/m^2/dose) given IV over 3 hours every 12 hours on days 1, 2, 8, and 9 for a total of 8 doses, and l-asparaginase (6000 IU/m^2/dose) given intramuscularly 3 hours after the last cytarabine dose is completed on days 2 and 9.

Supportive care measures included pneumocysitis prophylaxis with spetrin, antifungal prophylaxias with fluconazole or itraconazole, irradiated blood products, antiemetic therapy using granisetrone, and steroid eye drops given every 6 hours beginning immediately before the first dose of cytarabine and continuing until 24 hours after the last dose. Patients who achieved remission following cycle 2 or 3 were referred for hematopoietic stem cell transplant if a match donor was available.

Definition of Risk Groups

Patients were stratified according to published cytogenetic risk profiles: low, intermediate and high risk groups[9]. High risk (HR) AML group was defined as patients with monosomy 7, monosomy 5, deletions of 5q, 3q rearrangements, complex cytogenetic abnormalities, and/or more than 5% blasts after the first course of chemotherapy, or patients with secondary AML. Low risk (LR) AML group was defined as patients with the favorable cytogenetic subtypes: inv(16) (p13q22) and t(8;21) (q22;q22). Intermediate risk (IR) AML group was defined as patients with all other aberrations not classified as low or high. Unknown risk (UR) AML group was defined to include patients with failed cytogenetics or were not done.

Statistical Methods

Relapse was defined as greater than 5% blasts in the bone marrow (BM) and/or the presence of 5% or more leukemic blasts per microliter in the CSF [10]. Time to treatment relapse (TTR) was calculated from the date of first remission until the date of relapse. Patients were categorized into three relapse groups: early, intermediate and late relapse depending on whether TTR was less than six months, 6 to 18 months or greater than 18 months. OS was measured from the time of diagnosis of first relapse to death from any cause or until the last follow-up date for surviving patients. OS was computed for the entire study population as well as for patients stratified by age group: less than 2 years, 2 to 10 years and greater than 10 years.

Descriptive statistics were used to describe demographic and clinical variables (gender, age, WBC, CSF, site of relapse and phenotype).The Fisher exact test was used to test for association between categorical variables. OS probabilities were calculated by the Kaplan-Meier method. The log-rank test was used to compare survival probabilities between age groups as well as between relapse categories. In all evaluations, *P*-values below 0.05 were considered significant. All statistical computations were performed using SPSS software package (SPSS Inc., Chicago Il. USA) and R software (version 2.13.2).

RESULTS

Demographic Characteristics

The diagnostic characteristics of relapsed patients are reported in Table 1. In total, 25 out of 86 (29%) pediatric AML patients experienced relapse between August 1986 and April 2012. The median age of these patients was 3 years (range 1 - 14) of which 15 (60%) were male and 10 (40%) female. Relapse by age group revealed that children aged 2 to 10 accounted for 56% of total relapse followed by children aged less than two years with 36% and children older than 10 years with 8%.

Of the 25 patients, 16 (64%) had WBC less than $100x10^9$/L and 6 (24%) greater or equal to$100x10^9$/L. The median leukocyte count was 36.6×10^9/L (range, 5.5 to 390×10^9/L). Patients with CSF negative status at diagnosis experienced more frequent relapse (84%) compared to patients with CSF positive results (16%).

Table 1. Characteristics of relapsed acute myeloid leukemia patients

Characteristic	No. (%)

Gender	
Male	15 (60.0)
Female	10 (40.0)
Age (years)	
<2	9 (36.0)
2-10	14 (56.0)
>10	2 (8.0)
WBC (x 10^9/L)	
< 100	16 (64.0)
≥ 100	6 (24.0)
Not available	3 (12.0)
CSF	
Positive	4 (16.0)
Negative	21 (84.0)
Site of Relapse	
Bone Marrow	20 (80.0)
CNS	1 (4.0)
Combined	3 (12.0)
Extramedullary	1 (4.0)
Phenotype	
M0	3 (12.0)
M1	2 (8.0)
M2	4 (16.0)
M4	3 (12.0)
M5	3 (12.0)
M7	6 (24.0)
Not available	4 (16.0)
Risk Groups	
Low	3 (12.0)
Intermediate	6 (24.0)
High	5 (20.0)
Unknown	11 (44.0)

White blood count (WBC), Cerebrospinal fluid (CSF)

Relapse by Risk Group

Risk based outcome revealed that 20% (5/25) of relapses occurred in HR: monosomy 7, abn(3q), and complex cytogenetics (one each); 24% (6/25) in IR: normal cytogenetics (n = 3) and other translocation (n = 3); and 12% (3/25) in LR: t(8;21) (q22;q22). None of the patients in the relapse group had inv(16) (p13q22). Cytogenetics were unknown in 11 patients.

Relapse by Phenotype

Relapse incidence grouped by French-American-British (FAB) classification for childhood AML showed 6 patients (24%) with subtype M7 experienced relapse followed by 4 patients (16%) with FAB subtype M2. Patients with FAB subtype M0, M4 and M5 each accounted for 12% (3/25) of relapse while FAB M1 had only 8% (2/25).

Site of Relapse

In the present study, BM relapse occurred in 20 children and accounted for 80% of relapse. Combined (BM+CNS) relapse occurred in 3/25 (12%), isolated CNS relapse in 1/25 (4%) and extramedullary in 1/25 (4%) patients. CNS relapse (isolated or combined) occurred in 4/25 (16%) children. The CSF status at diagnosis was negative in 3/4 (75%) patients and positive in one patient. The patient with positive CSF had simultaneously experienced a combined relapse.

Mortality

The overall mortality rate in the present study was 88% (22/25). Table 2 depicts factors associated with mortality. Mortality by risk group was statistically significant (P = 0.019). The mortality rate was 100%, 83%, and 33% for HR, IR, and LR group patients; respectively. The median TTR for the 25 patients was 7 months (range: 2 to 36 months). However, 11 of these patients had early relapse, 9 intermediate relapse and 5 late relapse. Early relapse patients had high incidence of death 91% (10/11) followed by intermediate 89% (8/9) and late relapse 80% (4/5). Similarly, all patients with phenotype M0, M5 and M7 had 100% mortality rate while M1, M2 and M4 had 50%, 75% and 67%; respectively (P = 0.314). Age, gender, WBC, CSF, and site of relapse, did not influence mortality with P values: 0.425, 0.250, 0.532, 1.00, and 0.257, respectively.

Table 2. Factors associated with mortality in relapsed acute myeloid leukemia

Factors	Alive	Dead

	n (%)	n (%)	*P-Values*
Age (median; range)	2.5 years; (1:10)	3.0 years; (1:14)	
Gender			
Male	3 (20%)	12 (80%)	0.250
Female	0 (0%)	10 (100%)	
WBC (median; range)	118 x 10^9/L (13.7:390)	32.6 x 10^9/L (5.5:360)	
CSF			
Positive	0 (0%)	4 (100%)	1.000
Negative	3 (14%)	18 (86%)	
Site of Relapse			
BM	2 (10%)	18 (90%)	0.257
CNS	1 (100%)	0 (0%)	
Combined	0 (0%)	3 (100%)	
Extramedullary	0 (0%)	1 (100%)	
TTR			
Early	1 (9%)	10 (91%)	1.000
Intermediate	1 (11%)	8 (89%)	
Late	1 (20%)	4 (80%)	
FAB:			
M0	0 (0%)	3 (100%)	0.301
M1	1 (50%)	1 (50%)	
M2	1 (25%)	3 (75%)	
M4	1 (33%)	2 (67%)	
M5	0 (0%)	3 (100%)	
M7	0 (0%)	6 (100%)	
Risk group			
HR	0 (0%)	5 (100%)	0.019
IR	1 (17%)	5 (83%)	
LR	2 (67%)	1 (33%)	
UR	0 (0%)	11 (100%)	

White blood count (WBC), cerebrospinal fluid (CSF), bone marrow (BM), central nervous system (CNS), time to relapse (TTR), French-American-British (FAB), high risk (HR), intermediate risk (IR), low risk (LR), unknown risk (UR).

Survival Outcome

The median post relapse survival was 3 months (range: 0 to 140 months). The 5-year probability of post relapse OS rate for all patients was 12%±6.5% as shown in (Figure 1). The OS by age-groups was statistically significant (log-rank test, 7.072; P = 0.029) as shown in (Figure 2). The OS for children less than 2 years was 11.1%±10.5% compared to 21.4%±11%

and 50%±35.4% for patients aged 2 to 10 years and for patients older than 10 years; respectively. The OS for early, intermediate and late relapsed patients were 9±9%, 11±10% and 20±18%; respectively (Figure 3). However, these OS rates were not statistically significant (log-rank test, 1.074; P = 0.584). Similarly, the 5 year OS by risk groups was 66.7%±27.2% for LR and 16.7%±15.2% for IR, however, the OS for HR and UR group patients was not achieved (log-rank test, 3.778; P = 0.286). Survival outcome by phenotype was not statistically different (log-rank test, 10.663; P = 0.099).

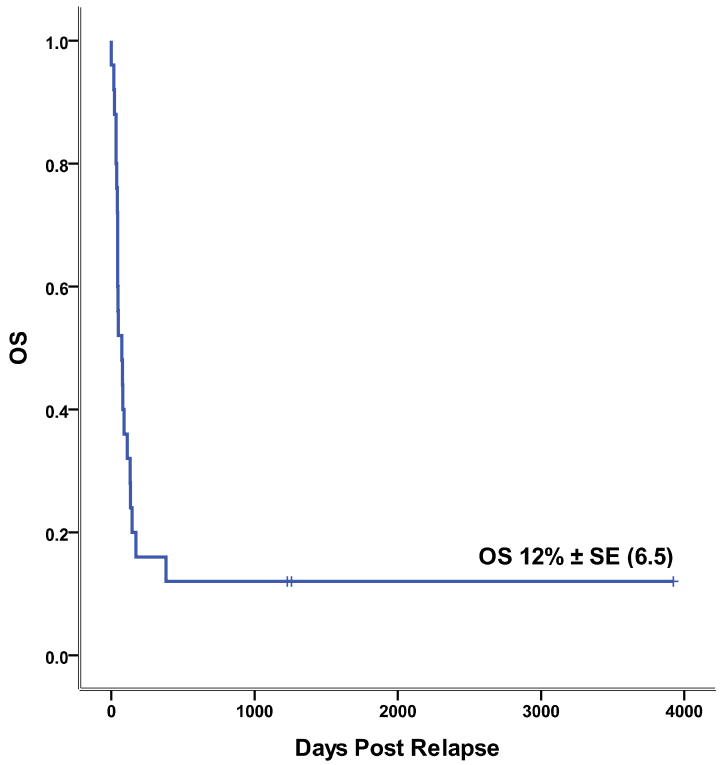

Figure 1: Five-year overall survival (OS) of relapsed pediatric acute myeloid leukemia.

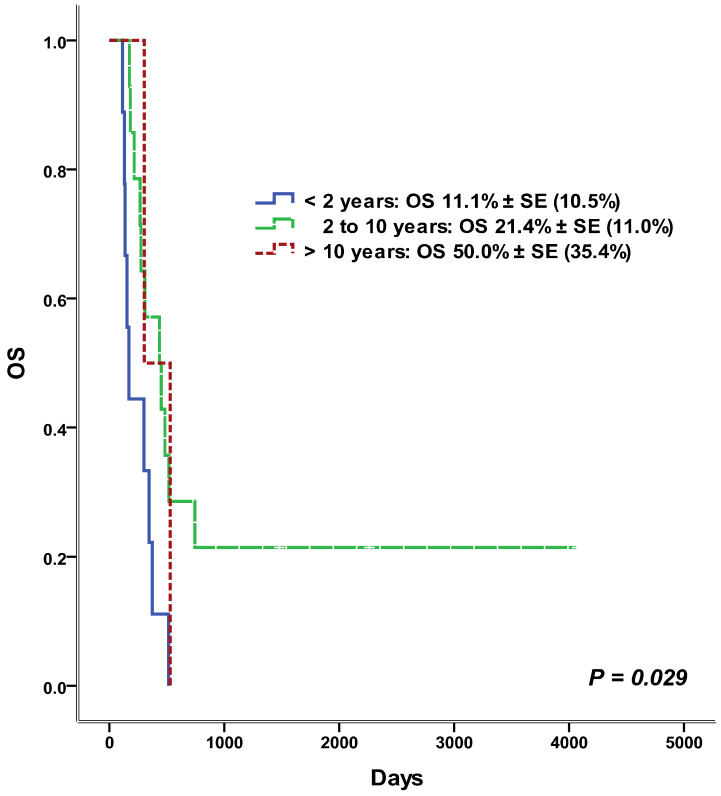

Figure 2: Overall Survival (OS) by age group.

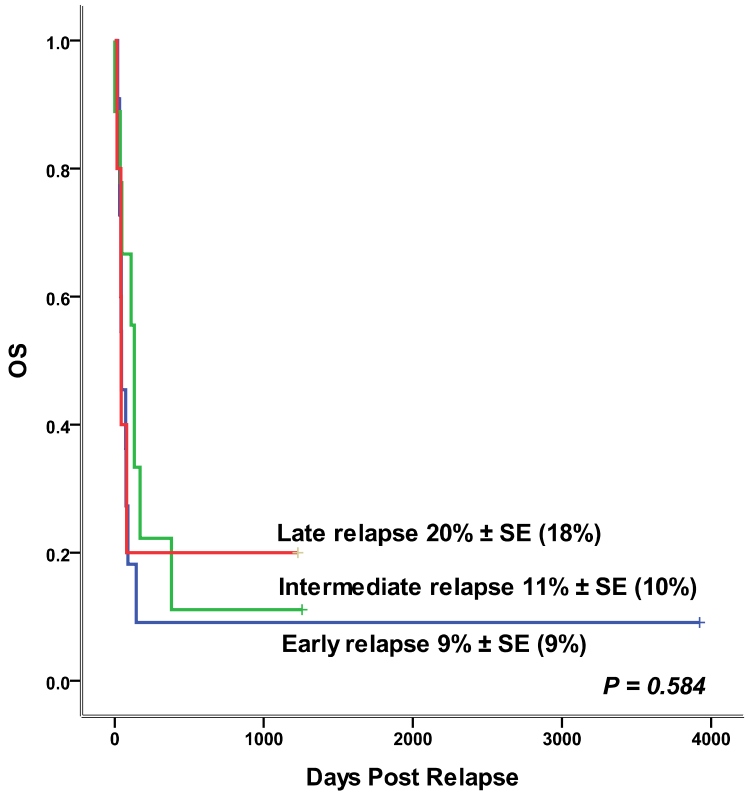

Figure 3: Overall Survival by time to relapse

DISCUSSION

Identifying factors that are related to poor outcome in relapsed pediatric AML patients is an effort to optimize treatment of these patients. The present study revealed demographic and clinical variability are associated with outcome of relapsed patients. The pattern of association that emerged from the analysis may help gain further understanding about the dynamics of relapse as well as recognizing patients who are at higher risk of treatment failure or may benefit from experimental therapies.

Demographic factors including gender and age have been associated with outcome in pediatric patients with AML[11]. The present study evaluated these variables in the context of relapsed AML patients and found that age at diagnosis did not influence risk of relapse but was found to be predictive of poor outcome. In particular, patients younger than 2 years of age had an inferior OS compared to other age groups.

In our study population, female patients were less likely to experience relapse compared to males and there was no statistically significant difference in mortality rates by gender. Despite this, the literature indicates that female patients have slight better outcome than males, however, this association was not strong enough to be included in therapeutic stratification[11]. The finding of the present study highlights the weakness of this association further.

Factors such as high WBC count (> 100,000 cells/ml), CNS disease at diagnosis and site of relapse have been associated with unfavorable outcome in pediatric AML patients [11-13]. The present study explored if these variables were associated with the incidence of relapse and did not find association between higher WBC at diagnosis and the risk of experiencing relapse.

Despite a high CSF positive rate at diagnosis, the most common site of relapse was the BM with an isolated CNS relapse rate of 4%. This finding is in line with the incidence of isolated CNS relapse range of 2% to 8.8% reported in the literature[14]. The incidence of any CNS relapse (isolated or combined) in our study was 16%. However, CSF positivity did not influence the risk of CNS relapse.

The present study revealed that Saudi Arabian pediatric AML patients with M7 phenotype were at higher risk of experiencing incidence of relapse. In comparison, patients with FAB subtype M1 had lower risk. Despite this, the mortality rates by phenotype were not significantly different.

Risk group using cytogenetics is considered as one of the most important significant prognostic factors in newly diagnosed AML[11]. Risk-based classification could have favorable and unfavorable outcomes in newly diagnosed AML. The present study evaluated the implication of risk-based classification with outcome in relapsed AML patients. It is worth noting that relapsed patients in LR group had a relatively low rate of relapse and a significantly lower mortality rate. This finding is indicative that risk-based stratification remains a significant prognostic factor in both relapsed and newly diagnosed AML patients.

In the present study, the OS of pediatric patients with relapsed AML remained poor. This finding is consistent with the outcomes reported in the literature[5-8]. However, post relapse OS rate was higher for late relapse patients followed by intermediate and early relapse. TTR has been well documented as a risk factor in pediatric acute lymphoblastic leukemia (ALL) and

its prognostic significance in influencing post relapse outcome is well established[2,10-12]. It is now possible to stratify relapsed ALL patients into different risk categories that would benefit from different treatment approaches. However, studies on the prognostic significance of TTR in pediatric AML are limited[2,6,10].

The present study was unable to demonstrate the prognostic significance of TTR in pediatric AML. However, given the retrospective design and the relatively small patient population of the study, the importance of TTR in determining the outcome of childhood AML cannot be ruled out. This highlights the need for further studies on prognostic variables that would help target improvement in therapeutic approach to this challenging disease.

CONCLUSIONS

Demographic, clinical and biological variables exist in relapsed pediatric AML and associated with important prognostic implications. The present study was able to demonstrate that the OS rate of relapsed pediatric AML treated in our institution is poor and within the range reported in the literature. In addition, age at diagnosis and risk group stratification was identified as factors significantly impacting survival in the present study. These findings are of potential relevance in individual treatment decisions as well as in improving the overall outcome of relapsed AML patients with poor-risk disease using risk-adapted treatment strategies.

The findings of the present single center study may not be generalized to all relapsed AML children in Saudi Arabia. However, conducting further multicenter studies that examine the significance of demographic factors, clinical characteristics and time to relapse may provide broader understanding of relapsed pediatric AML patients in the Kingdom. This in turn may improve the approach and management of this challenging disease.

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