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ORIGINAL ARTICLE

Survival and risk factors for mortality in pediatric patients with acute myeloid leukemia in a single reference center in low–middle-income country

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Abstract

Despite advances in therapy and care for children with acute myeloid leukemia (AML), survival rates for children in low- and middle-income countries (LMICs) remain poor. We studied risk factors for mortality and survival in children with AML in a LMIC to develop strategies to improve survival for AML children in these countries. This retrospective cohort (2000–2014) analyzed newly diagnosed AML patients (age < 19 years) at a reference center in Brazil. Demographic and clinical variables were reviewed by AML subtype: acute promyelocytic leukemia (APL), AML with Down syndrome (AML-DS), and other AML subtypes. Cumulative hazard risk for early death (ED) until 6 weeks of treatment and risk factors for mortality were determined by the multivariate Cox hazard models. Survival was assessed for each AML subtypes. A total of 220 patients were diagnosed: APL 50 (22.7%), AML-DS 16 (7.3%), and other AML subtypes 154 (70.0%). The cumulative hazard function values for ED for all patients with AML were 12.5% (95% CI 8.5–18.4%); for each AML patients subtypes: APL, 21.7% (95% CI 11.7–40.5%); AML-DS, 6.2% (95% CI 0.9–44.4%); and other AML subtypes, 10.2% (95% CI 6.2–17.0%). White blood cell count (cutoff 10×10^9/L for APL and 100×10^9/L for other AML subtypes) and Afro-descendance were significant risk factors for mortality in APL and other AML subtypes, respectively. Overall survival for patients with APL, AML-DS, and other AML subtypes was 66.8%, 62.5%, and 38.0%, respectively. APL patients had the highest incidence of ED and those with other subtypes had increased relapse risk. We also observed high rates of death in complete remission mainly due to infection. Better risk classification and identification of risk factors for infection may improve the survival of these patients.

Keywords AML · Acute promyelocytic leukemia · Children · Risk factor · Low- and middle-income countries · Survival

Introduction

Acute myeloid leukemia (AML) comprises a heterogeneous group of disorders that account for approximately 20% of childhood leukemias, but is responsible for up to 50% of leukemia-related deaths in the Western world [1]. In developed countries, recent advances in chemotherapy, hematopoietic stem cell transplantation, and supportive care have increased long-term survival rates to up to 65% for children with AML [2]. However, most pediatric patients with AML in low- and middle-income countries (LMICs) have not benefited from these advances and continue to have survival rates lower than 40% [3, 4].

Outcomes of children with AML can vary by biological features; response to therapy; and host factors such as age at diagnosis, race, and socioeconomic status [5]. Current clinical trials for patients with newly diagnosed (de novo) AML are

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conducted by disease subtype: acute promyelocytic leukemia (APL), acute myeloid leukemia with Down syndrome (AML-DS), and other AML subtypes (no APL and no AML-DS).

Few studies have analyzed outcomes and risk factors for mortality in children with AML in LMICs. Brazil is an upper-middle-income country with wide socioeconomic variations by region. Recife is the capital and largest city of the state of Pernambuco in northeast Brazil. The mean per capita income in Pernambuco is below the national median (www.IBGE.gov.br). The annual median age-adjusted incidence rate of pediatric AML in Recife was 7.11 per million from 1998 to 2007 [6].

In this study, we describe our clinical experience of children with AML at Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), an oncology reference center in Recife. We conducted a retrospective analysis of patient characteristics, prognostic factors, survival rates, and risk factors for mortality in pediatric AML subtypes, with the goal of developing strategies to improve the survival of children with AML in LMICs.

Methods

Study design and participants

This retrospective cohort study was performed at IMIP from January 2000 to December 2014 included 220 patients (age < 19 years) with newly diagnosed de novo AML. IMIP is a pediatric oncology regional reference center in Recife exclusively dedicated to patients who are part of the Brazilian healthcare public system. Patients with myelodysplastic syndrome, biphenotypic leukemia, or treatment-related leukemia were excluded from the study. AML was diagnosed using clinical, morphological, immunological, and/or molecular methods. Informed consent was obtained for the patients who were followed up during the study period and consent was waived for patients who died. This study was approved by the IMIP local ethical committee (Approval Number: 3680-13).

AML subtypes and treatment

Pediatric patients with AML were classified into three groups according to clinical or molecular characteristics: APL or AML (PML-RARA), AML-DS, and other AML subtypes. Chemotherapy comprised two induction cycles (daunorubicin, cytarabine, etoposide) and two consolidation cycles (high-dose cytarabine plus mitoxantrone or etoposide). Patients with AML-DS received two cycles of induction chemotherapy followed by low-dose cytarabine [7]. Patients with APL (French–American–British classification M3) received all-*trans* retinoic acid (ATRA), which has been used as conventional chemotherapy since 2000 [8]. Patients with other AML subtypes received prophylactic antibiotic therapy [9–11].

Data collection

Although the study design was retrospective, the study's lead author (M.M.L) was part of the clinical staff monitoring these patients during the study period. Data were collected from medical record by characteristics of diagnosis: (1) demographic variables (i.e., age, gender, race, place of residence, time period of treatment, human development index (HDI), which includes life expectancy, education, and per capita income indicators) and (2) clinical variables (i.e., AML subtype, white blood cell (WBC) count and selected genetic markers). Patient age was categorized as < 10 years or ≥ 10 years, and the self-reported race was categorized as Afro-descendant or other. Place of residence was analyzed to consider the effect of access to healthcare and was classified as Recife and Metropolitan region or other. Different time periods were analyzed according to therapeutic strategies used: (1) for APL, period 2000–2006, when we started ATRA plus chemotherapy but without standardization and period 2007–2014, when we used ATRA according to ICC-APL study 01; (2) for other AML subtypes, before 2000–2011 and after 2012–2014 routine prophylactic antibiotics, with ciprofloxacin plus vancomicyn, started in the first day of chemotherapy until CAN > 500 and fluconazol started after 24 h of chemotherapy. As a proxy indicator of socioeconomic level, HDI of the patient's residence was classified as low, middle, or high [12]. Baseline WBC count was initially categorized into four groups and then recategorized according to AML subtype: cutoff 10×10^9/L for APL and 100×10^9/L for other AML subtypes.

Definitions and statistical analyses

Outcome events were relapse, death, and secondary malignancy. Early death (ED) was defined as death within 6 weeks of treatment and subclassified as ED within 7 days from the start of treatment, ED during and after the first therapy cycle (< 15 days of treatment), or ED in aplasia between days 15 and 42 of treatment before remission [13, 14].

Complete remission (CR) was defined according to the Cancer and Leukemia Group B criteria [15]. Patients still alive but not achieving CR after the second cycle of induction chemotherapy were considered as having refractory disease. The Nelson–Aalen method was used to estimate cumulative hazard risk of death until 6 weeks after diagnosis for all patients.

Patients with CR were followed until they had one of the three abovementioned outcomes or were censored at the date of the last contact within the first 5 years of diagnosis.

The univariate and multivariate Cox hazards models were used to study the association among characteristics at diagnosis and risk factors for mortality. Children with AML-DS were excluded from this analysis due to the small number of cases. The Kaplan–Meier method was used to estimate patient survival, and the log-rank test was used to compare patient survival among groups. Event-free survival (EFS) was either calculated from diagnosis until the first event (i.e., death, relapse, or secondary malignancy) or censored. The overall survival (OS) was calculated from the date of diagnosis until death (failure) or censored (at last contact or 5 years of surveillance). The level of significance was set at $P < 0.05$. The 95% confidence intervals (95% CIs) were calculated for study outcomes. All analyses were conducted by using Stata 13 software (StataCorp).

Results

Patient characteristics

Table 1 gives demographic and clinical characteristics of the 220 study participants. Patients with APL (50 [22.7%]) had a median age 12.2 years, a male/female ratio of 0.9:1, and a median baseline WBC count of 18.5×10^9/L. Patients with AML-DS (16 [7.3%]) had a median age of 1.6 years, a male/female ratio of 1.28:1, and a median baseline WBC count of 5.9×10^9/L. Patients with other AML subtypes (154 [70%]) had a median age 6.4 years, a male/female ratio of 1.7:1, and a median baseline WBC count of 23.5×10^9/L.

Patient outcomes

Of the 220 patients, 26 (11.8%) died before 6 weeks, 17 (7.7%) had refractory disease (all died), and 177 (80.4%) achieved CR. After CR 60/177 (33.8%) had relapse, 2 (1.1%) had secondary neoplasms. From all patients, 114 (51.8%) died. Figure 1 shows clinical outcomes of patients according to AML subtypes.

Among the 50 patients with APL, the majority of EDs occurred in the first week of diagnosis (Table 2). The patients were admitted with neurological symptoms, the main cause of ED was intracranial hemorrhage (9 of 10 patients), and the median WBC count was 60×10^9/L. Among the 16 patients with AML-DS, 1 patient had ED due to infection, 4 patients died later after CR, and 1 after relapse.

For 154 patients with other AML subtypes, the main cause of ED was sepsis. For the 123 patients admitted in the pre-antibiotic therapy period (2000–2011), 13 (10.6%) had ED, with 8 (61.5%) deaths due to sepsis. Among those patients who had complete remission, 14 died from infection at this first period. Of the 31 patients admitted during the post-antibiotic therapy period (2012–2014), there were 2 (6.5%) EDs due to leukostasis; none died from infection. Two other patients died from infection after complete remission. The differences were not significant among the patients who died with infection in the two study periods (data not shown).

The cumulative hazard function values for ED (Fig. 2) for all patients with AML were 12.5% (95% CI 8.5–18.4%); for patients with APL, 21.7% (95% CI 11.7–40.5%); for patients with AML-DS, 6.2% (95% CI 0.9–44.4%); and for patients with other AML subtypes, 10.2% (95% CI 6.2–17.0%).

Risk factors for mortality

Table 3 shows the results of univariate and multivariate analyses. For patients with APL, WBC count at baseline $\geq 10 \times 10^9$/L, Afro-descendant race, and treatment in the early ATRA period were significant risk factors for mortality in univariate analysis. In the multivariate analysis, only baseline WBC count of $\geq 10 \times 10^9$/L remained associated with mortality in the final model adjusted for the treatment period. For other AML subtypes, Afro-descendant race and the baseline WBC count of $\geq 100 \times 10^9$/L were significant risk factors in univariate analysis, and only Afro-descendant race remained a significant factor in the final model adjusted for WBC count.

EFS and OS

The 5-year EFS and OS for all pediatric AML patients were 39.3% (95% CI 32.4–46.1%) and 45.6% (95% CI 38.5–52.4%), respectively. For patients with APL, AML-DS, and other AML subtypes, the EFS values were 63.9% (95% CI 47.0–76.7%), 62.5% (95% CI 34.9–81.1%), and 30.8% (95% CI 23.5–38.4%), respectively. For patients with APL, AML-DS, and other AML subtypes, the 5-year OS rates were 66.8% (95% CI 50.2–79.0%), 62.5% (95% CI: 34.9–81.1%), and 38.0% (95% CI 30.0–46.0%), respectively (Fig. 3).

Discussion

This study evaluated outcomes and risk factors for mortality in 220 patients with AML treated at a single institution during a 15-year period. Among all patients with AML, 83.2% achieved CR and 11.8% experienced ED in the first 6 weeks after diagnosis. Compared with patients with AML-DS or other AML subtypes, those with APL had a higher risk for ED and a more than twofold cumulative hazard risk.

For childhood AML, differences in relative frequency of the APL subtype by geographic region and race group have been previously reported. APL accounts for approximately 10% of AML cases in the USA, compared with 21.6% in southern Spain, 34.0% in Costa Rica, and 31.3% in Cuba [16]. In a study (1997–2004) in Recife on 127 patients with AML, 16.6% of patients had APL [17].

Table 1 Demographic and clinical characteristics of patients with AML by subtype (APL, AML-DS, and other AML subtypes) at IMIP, Recife, 2000–2014

Variable	Acute myeloid leukemia			
	Total [*N* (%)]	APL [*N* (%)]	AML-DS [*N* (%)]	Other AML subtypes [*N* (%)]
Number of patients	220 (100)	50 (22.7)	16 (7.3)	154 (70.0)
Age (years)				
< 10	134 (60.9)	16 (32.0)	16 (100)	102 (66.2)
≥10	86 (39.0)	34 (68.0)	0	52 (33.7)
Gender				
Female	90 (40.9)	26 (52.0)	7 (43.7)	57 (37.0)
Male	130 (59.1)	24 (48.0)	9 (56.2)	97 (62.3)
Race				
Black	17 (7.7)	6 (12.0)	0 (0.0)	11 (7.1)
Other	203 (92.3)	44 (88.0)	16 (100.0)	143 (92.9)
Place of residence				
Recife and Metropolitan region	93 (42.3)	23 (46.0)	9 (56.2)	61 (39.6)
Other	127 (57.7)	27 (54.0)	7 (43.7)	93 (60.4)
HDI				
Low	85 (38.6)	9 (18.0)	4 (25.0)	38 (24.7)
Middle	70 (31.8)	15 (30.0)	2 (12.5)	53 (34.4)
High	51 (23.2)	22 (44.0)	9 (56.2)	54 (35.0)
Missing	14 (6.4)	4 (8.0)	1 (6.2)	9 (5.8)
Time period of treatment for APL				
2000–2006	-	18 (36.0)	–	–
2007–2014	-	32 (64.0)	–	–
Time period of treatment of other subtypes				
2000–2011	–	–	-	123 (80.0)
2012–2014	–	–	-	31 (20.0)
WBC (baseline)				
$< 10 \times 10^9$/L	87 (39.5)	23 (46.0)	11 (68.8)	53 (34.4)
$10–50 \times 10^9$/L	65 (29.5)	13 (26.0)	5 (31.3)	47 (30.5)
$50–100 \times 10^9$/L	32 (14.5)	9 (18.0)	–	23 (14.9)
$\geq 100 \times 10^9$/L	30 (13.6)	3 (6.0)	–	27 (17.5)
Missing	6 (2.7)	2 (4.0)	–	4 (2.7)

AML acute myeloid leukemia, *AML-DS* AML with Down syndrome, *APL* acute promyelocytic leukemia, *ATRA* all-*trans* retinoic acid, *HDI* human development index, *IMIP* Instituto de Medicina Integral Prof. Fernando Figueira

In our study, 22.7% of 220 patients with AML diagnosed from 2000 to 2014 had APL. A hospital-based cancer registry study from 2001 to 2012 involving 239 oncologic centers in Brazil, with the majority located in the southeast region, reported APL frequencies of 6.4% for AML in children younger than 13 years of age and of 11.8% for children 13–21 years of age. However, the authors pointed out that for the same age ranges, the high percentage of AML, not otherwise specified, and no validation of AML classification may have led to the low number of patients with APL [18].

We found that gender distribution of patients diagnosed with APL was similar, which is consistent with the results from studies on a larger number of participants and with a recent review finding no evidence of male or female prevalence in patients with APL [18, 19]. Among children with other AML subtypes, the female/male ratio was consistent with that reported previously [20].

WBC count greater than 10×10^9/L is an important prognostic factor for APL [21]. WBC count greater than 20×10^9/L is associated with increased risk of death due to intracranial hemorrhage during induction chemotherapy [22]. In our study, the median WBC count was very close to that for the group at highest risk for intracranial hemorrhage, and among patients with APL, inductive failure mainly occurred due to this complication. Intracranial hemorrhage was observed in patients mainly in the early ATRA period, which is consistent

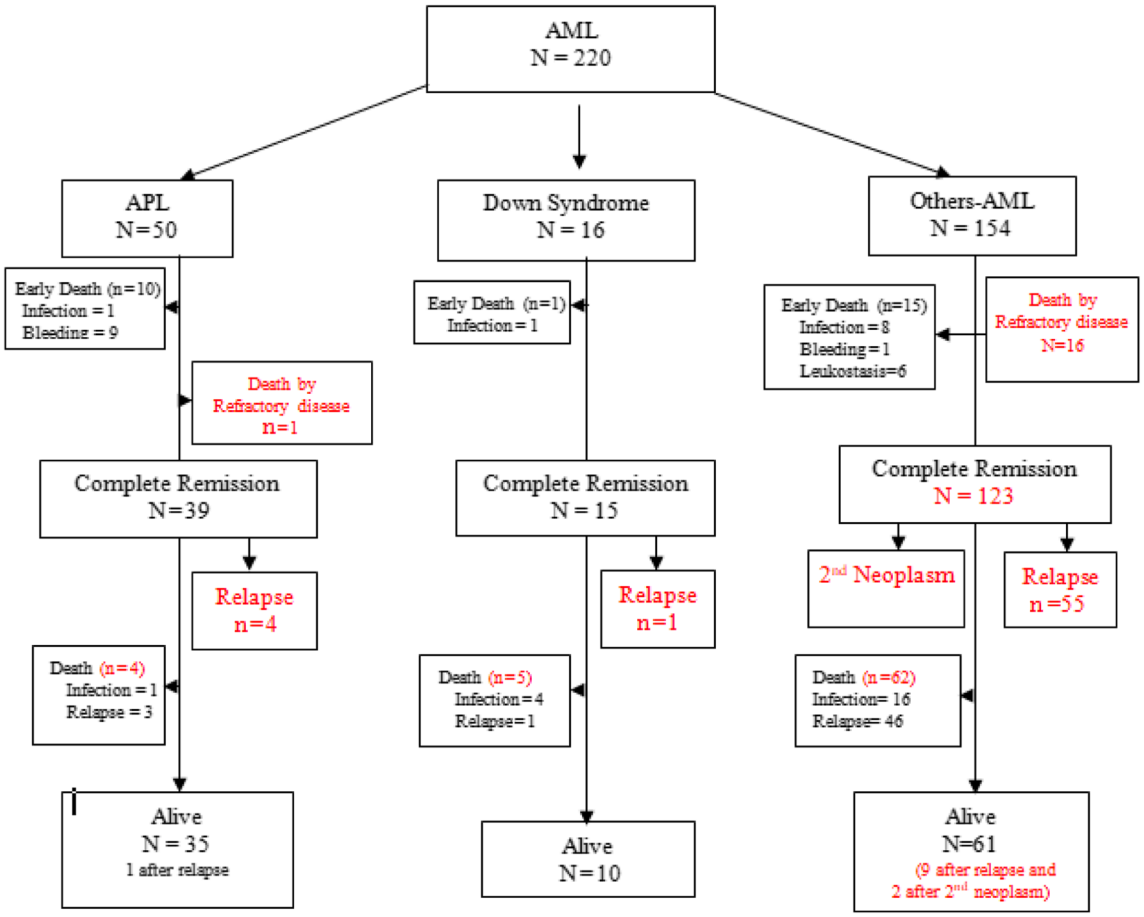

Fig. 1 Flow chart showing clinical evolution of children with acute myeloid leukemia (AML) by subtype APL (acute promyelocytic leukemia), Down syndrome, and other AML (non APL and non-Down); IMIP, Recife, 2000–2014

with a previous study in Brazil [23]. The percentage of relapse for children with APL was low, highlighting that ED is a major concern during treatment.

For other AML subtypes, Afro-descendant race was significantly associated with death, which is consistent with previous studies [4]. Differences in survival by race for children with leukemia could be attributed to social differences, difficulty in accessing medical care, genetic factors, and variations in treatment response [24]. In Brazil, race is a confusing topic because there is a lot of racial diversity and

Table 2 Distribution of deaths of children with acute myeloid leukemia according to time periods and refractory disease or after remission status—IMIP (Instituto Medicina Integral Prof. Fernando Figueira) 2000–2014

Period	APL $n = 50$ (%)	AML-DS $n = 16$ (%)	Other AML $n = 154$ (%)	TOTAL $n = 220$(%)
Early death (≤ 6 weeks)	10 (20.0)	1(6.2)	15 (9.7)	26 (11.8)
≤ 7 days	9 (18)	1 (6.2)	6 (3.9)	16 (7.2)
8–15 days	1 (2)	–	2 (1.3)	3 (1.4)
16–30 days	–	–	4 (2.6)	4 (1.8)
31–42 days	–	–	3 (1.9)	3 (1.4)
Death after 6 weeks until 5 years	5 (10.0)	5 (31.3)	78 (50.6)	88 (40.0)
Refractory disease*	1 (2.0)	0	16 (10.4)	17 (7.7)
After complete remission	4 (8.0)	5 (31.3)	62 (40.2)	71 (32.3)
After relapse	3	1	46	50
In complete remission	1	4	16	21
Total	15 (30.0)	6 (37.5)	93 (60.3)	114 (51.8)

APL acute promyelocytic leukemia, *AML-DS* Down syndrome, and other AML (non APL and non-Down)

*Refractory disease or primary resistant disease = patient without complete remission after 6 weeks of treatment

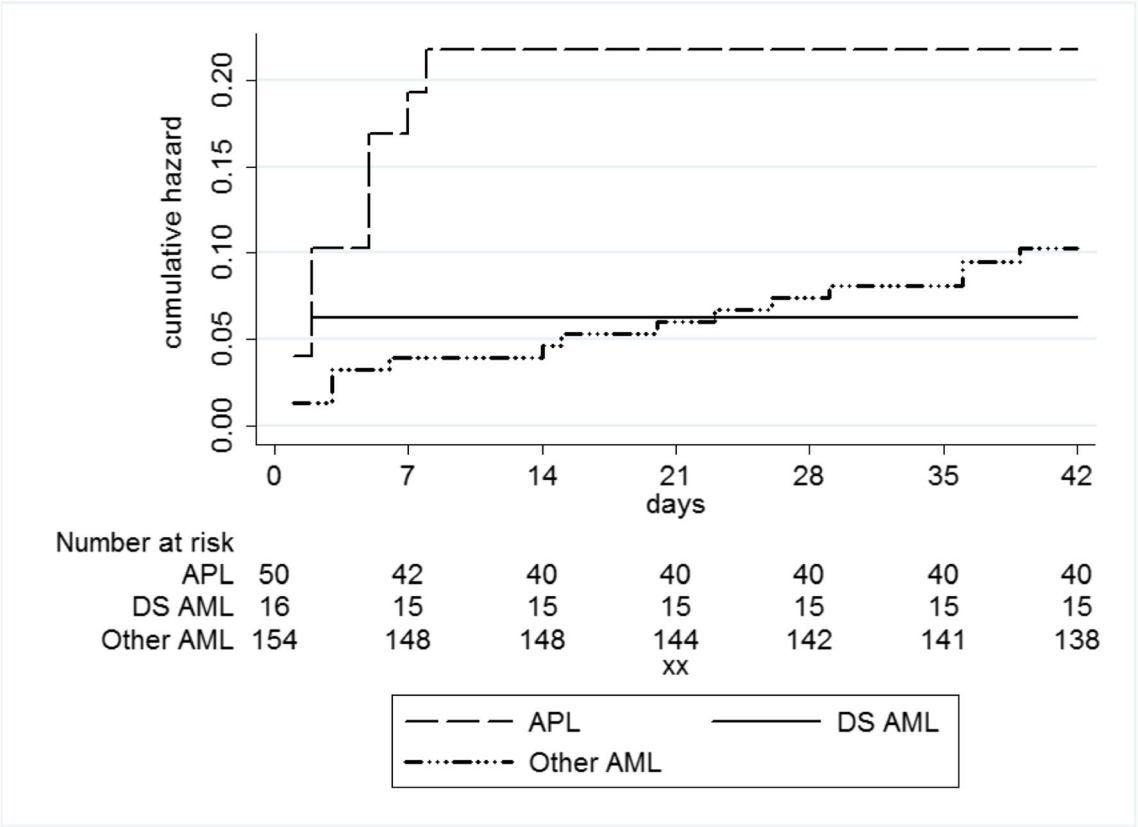

Fig. 2 Cumulative hazard risk of death until 6 weeks after diagnosis among children with AML, APL, AML-DS, and other AML subtypes at IMIP, Recife, 2000–2014. AML, acute myelocytic leukemia, APL acute promyelocytic leukemia, AML-DS AML with Down syndrome, IMIP Instituto de Medicina Integral Prof. Fernando Figueira

certainly, Afro-descendance in our study was underestimated. Among Afro-descendants, it is not so easy to separate race from socioeconomic problems. After controlling for social indicators such as HDI and access to health services, Afro-descendant race persisted as a risk factor for mortality, which suggests the presence of other genetic factors and differences in therapy response.

In approximately 20% of pediatric AML patients with baseline WBC counts greater than 100×10^9/L, pulmonary leukostasis, central nervous system ischemia, hemorrhage, and ED are common [25]. In our study, 17.3% of patients with other AML subtypes had WBC counts more than 100×10^9/L, with leukostasis being the second-leading cause of ED in 30.8% of patients. Leukostasis is an important risk factor for both ED and morbidity in patients with AML. In our study, patients did not achieve CR mainly due to ED (9.7% of patients), with the main cause being sepsis, followed by leukostasis (diagnosed by clinic parameters when a patient presents with acute myeloid leukemia, WBC > 100.000, with respiratory or neurological distress without evidence of infection).

For other AML, ED dropped from 10.6% in the first therapy period (2000–2011) to 6.4% in the last therapy period (2012–2014). The difference between deaths in both periods was not significant, perhaps because we only have 31 patients in the second period. Improvements related to supportive care, physicians' clinical experience, and discussion of cases with specialists from other centers in Brazil and other countries, through our collaboration with St. Jude Children's Research Hospital, may have led to this decrease in ED in the last therapy period. The ED rate in our study is similar to that recently reported in Argentina for children with AML treated with different Berlin–Frankfurt–Muenster protocols from 1990 to 2013 [26]. ED in the Argentine study declined from 15.0 to 7.4% [26], but a German study had already reported an ED rate of 3.5% in 1998 [13].

We found that survival rates of patients with APL before and at beginning of the ATRA administration period (2000–2006) were the same as those for patients with other AML subtypes, with rates of ED and relapse being high. Risk classification, improved management of patients receiving ATRA, and better guidelines for blood support might contribute to improved survival of patients with APL. However, survival rates for our patients remained lower than for patients in high-income countries (HICs). In addition to ATRA use, factors specific to LMICs, such as access to healthcare and the time elapsed from initial symptoms to diagnosis, might have contributed to ED.

Table 3 Crude and adjusted risk of death by the Cox regression analysis for patients with APL and other AML subtypes according to demographics and clinical characteristics. IMIP, Recife, 2000–2014

Variable	AML							
	APL ($N = 50$)				Other AML subtypes ($N = 154$)			
	HR (95% CI)				HR (95% CI)			
	Crude	p	Adjusted	p	Crude	p	Adjusted	p
Age (years)		0.64				0.48		
< 10	1.00				1.00			
≥ 10	1.31 (0.42–4.14)				0.85 (0.55–1.33)			
Gender		0.51				0.50		
Female	1.0				1.00			
Male	0.71 (0.25–1.99)				0.19 (0.56–1.31)			
Race		< 0.01				< 0.01		< 0.01
Afro-descendants	4.51 (1.53–13.22)				2.50 (1.29–4.84)		2.83 (1.40–5.69)	
Other	1.00				1.00		1.00	
HDI*		0.61				0.32		
Middle or high	1.00				1.00			
Low	1.40 (0.38–5.20)				0.77 (0.47–1.28)			
Place of residence		0.61				0.86		
RMR	1.00				1.00			
Other	1.30 (0.46–3.67)				0.96 (0.63–1.46)			
Time periods of treatment								
APL		0.01		0.06				
2000–2006	3.86 (1.31–11.35)		2.99 (0.97–9.24)		–	–		
2007–2014	1.00				–	–		
Other AML subtypes						0.94		
2000–2011	–	–			0.99 (0.57–1.74)			
2012–2014	–	–			1.00			
WBC count (cells/L)								
APL		0.01		0.01				
$< 10 \times 10^9$	1.00		1.00					
$\geq 10 \times 10^9$	13.76 (1.79–10.07)		12.72 (1.65–98.28)					
Other AML subtypes	–					< 0.01		0.35
100×10^9	–				1.00		1.00	
$\geq 100 \times 10^9$					1.96 (1.19–3.24)		1.18 (0.83–1.68)	

AML acute myeloid leukemia, *AML-DS* acute promyelocytic leukemia, *CI* confidence interval, *CR* complete remission, *HR* hazard ratio, *IMIP* Instituto de Medicina Integral Prof. Fernando Figueira, *RMR* Recife Metropoliton Region, *WBC* white blood cell

For patients with other AML subtypes who achieved remission, the risk of relapse was higher than the risk of death due to toxicity. These results agree with those from previous studies in both LMICs and HICs [25, 26].

This study has limitations inherent to the retrospective study design. Because this study was on a rare disease from a single institution with few patients, some analyses were unfeasible. The follow-up duration for patients enrolled after 2009 was shorter than for those enrolled in earlier years. However, our study is important because although AML is the leading cause of death in children with cancer, few studies have focused on pediatric AML, especially in LMICs, where most children reside [27]. Our study identifies the main causes of treatment failure and highlights the need for multicenter and collaborative studies to improve the survival of children with AML in LMICs [28, 29].

Despite advances in supportive care and reduction of ED rates, recurrence rates for patients with AML continue to remain high, even in HICs [30, 31]. Collaboration between HICs and LMICs is crucial to improve risk group stratification, gain more knowledge about the genetic basis of AML, and identify molecular targets to develop effective therapies.

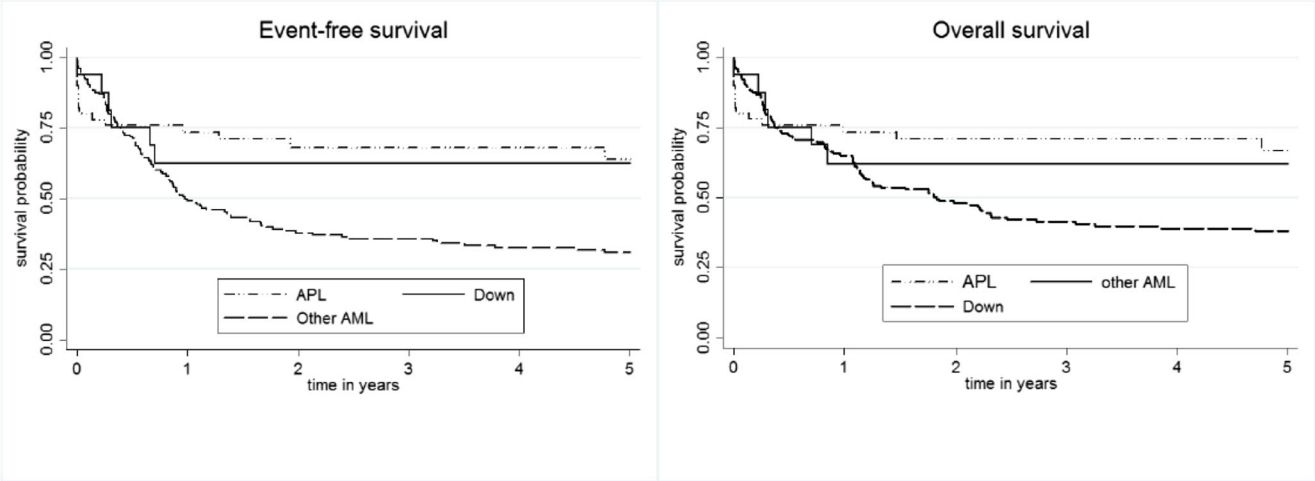

Fig. 3 The Kaplan–Meier analysis of 5-year event-free survival and overall survival in children with AML by subtype (APL, AML-DS, and other AML subtypes) in Recife, 2000–2014. AML acute myelocytic leukemia, APL acute promyelocytic leukemia, AML-DS AML with Down syndrome, IMIP Instituto de Medicina Integral Prof. Fernando Figueira

In conclusion, although the 5-year EFS and OS for patients with APL in LMICs have improved over the years; they remain lower than for patients in HICs. EDs due to hemorrhage and infection and leukostasis are the main causes of treatment failure for patients with APL and other AML subtypes, respectively. For patients with other AML subtypes, deaths in complete remission and relapse remain an important concern. Strategies for early diagnosis, better risk classification, improved supportive care mainly infection control, and development of risk-directed therapeutic protocols can help reduce early mortality and relapse rates in pediatric patients with AML in LMICs.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

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